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### Review

### Original Papers

Review

# Public Health Implications of Adapting HIV Pre-exposure Prophylaxis Programs for Virtual Service Delivery in the Context of the COVID-19 Pandemic: Systematic Review

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## Abstract

**Background:** The novel coronavirus disease COVID-19 caused by SARS-CoV-2 threatens to disrupt global progress toward HIV epidemic control. Opportunities exist to leverage ongoing public health responses to mitigate the impacts of COVID-19 on HIV services, and novel approaches to care provision might help address both epidemics.

**Objective:** As the COVID-19 pandemic continues, novel approaches to maintain comprehensive HIV prevention service delivery are needed. The aim of this study was to summarize the related literature to highlight adaptations that could address potential COVID-19–related service interruptions.

**Methods:** We performed a systematic review and searched six databases, OVID/Medline, Scopus, Cochrane Library, CINAHL, PsycINFO, and Embase, for studies published between January 1, 2010, and October 26, 2021, related to recent technology-based interventions for virtual service delivery. Search terms included "telemedicine," "telehealth," "mobile health," "eHealth," "mHealth," "telecommunication," "social media," "mobile device," and "internet," among others. Of the 6685 abstracts identified, 1259 focused on HIV virtual service delivery, 120 of which were relevant for HIV prevention efforts; 48 pertained to pre-exposure prophylaxis (PrEP) and 19 of these focused on evaluations of interventions for the virtual service delivery of PrEP. Of the 16 systematic reviews identified, three were specific to PrEP. All 35 papers were reviewed for outcomes of efficacy, feasibility, and/or acceptability. Limitations included heterogeneity of the studies' methodological approaches and outcomes; thus, a meta-analysis was not performed. We considered the evidence-based interventions found in our review and developed a virtual service delivery model for HIV prevention interventions. We also considered how this platform could be leveraged for COVID-19 prevention and care.

**Results:** We summarize 19 studies of virtual service delivery of PrEP and 16 relevant reviews. Examples of technology-based interventions that were effective, feasible, and/or acceptable for PrEP service delivery include: use of SMS, internet, and smartphone apps such as iText (50% [95% CI 16%-71%] reduction in discontinuation of PrEP) and PrEPmate (OR 2.62, 95% CI 1.24-5.5.4); telehealth and eHealth platforms for virtual visits such as PrEPTECH and IowaTelePrEP; and platforms for training of health care workers such as Extension for Community Healthcare Outcomes (ECHO). We suggest a virtual service delivery model for PrEP that can be leveraged for COVID-19 using the internet and social media for demand creation, community-based self-testing, telehealth platforms for risk assessment and follow-up, applications for support groups and adherence/appointment reminders, and applications for monitoring.

**Conclusions:** Innovations in the virtual service provision of PrEP occurred before COVID-19 but have new relevance during the COVID-19 pandemic. The innovations we describe might strengthen HIV prevention service delivery during the COVID-19 pandemic and in the long run by engaging traditionally hard-to-reach populations, reducing stigma, and creating a more accessible health care platform. These virtual service delivery platforms can mitigate the impacts of the COVID-19 pandemic on HIV services, which can be leveraged to facilitate COVID-19 pandemic control now and for future responses.

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**KEYWORDS**

HIV; pre-exposure prophylaxis; COVID-19; virtual service delivery; HIV prevention; public health; systematic review; virtual service; health intervention; digital intervention; health technology; social media platform; telehealth; public health message

## Introduction

The novel coronavirus disease COVID-19 caused by SARS-CoV-2 threatens to disrupt global progress toward HIV elimination [1]. In response to the COVID-19 pandemic, many countries have employed nonpharmacologic interventions such as lockdowns, social distancing, and restrictions on gatherings to control the spread of SARS-CoV-2. However, other countries with a high burden of COVID-19 have not successfully and universally instituted these mitigation measures at a national level [2]. Countries with limited uptake of mitigation measures are seeing their health care infrastructure overwhelmed with the pandemic due to widespread community transmission, and are thus struggling to provide comprehensive clinical care for COVID-19 and for chronic diseases, including HIV [1,2]. Recent gains in HIV epidemic control may be lost if HIV prevention and treatment services are not maintained. Additionally, the morbidity and mortality of COVID-19 might be increased in the face of uncontrolled chronic diseases and HIV, although there have been conflicting reports among persons living with HIV [3,4].

COVID-19 and HIV both disproportionally affect socially disadvantaged and hard-to-reach populations [4]. Opportunities exist to leverage ongoing public health responses to mitigate the impacts of COVID-19 on HIV services, and novel approaches to care provision might help address both epidemics. For example, the US Ending the HIV Epidemic (EHE) initiative aims to overcome existing social and economic disparities by increasing access to HIV services for vulnerable populations in the United States [5]. In this regard, the aims of EHE to increase services for vulnerable populations align with approaches for controlling the COVID-19 pandemic, which has also exacerbated health inequities [6]. Globally, the public and private sectors have collaborated for years to address the HIV crisis using a public health approach. This has resulted in platforms for service delivery, a health workforce trained in HIV care and treatment, supply chains, and collaboration across a diverse group of stakeholders, including community leaders and governments, to ensure that marginalized populations receive the services they need. Efforts should be made to identify best practices and lessons learned from HIV prevention to lessen the impacts of COVID-19 on HIV programs [7]. The HIV community can sustain progress toward HIV epidemic control by rapidly employing innovations to maintain and extend HIV programming during the COVID-19 pandemic [8]. Additionally, COVID-19–specific education, testing, and vaccination could be integrated into HIV prevention programs, considering that these service delivery platforms are designed to reach vulnerable persons at risk of HIV and the general population.

To ensure that HIV prevention programs are improved to deliver services in the context of limited mobility and strained health systems, we reviewed the literature for adaptations of pre-exposure prophylaxis (PrEP) programs for HIV prevention both prior to and in the time of COVID-19. PrEP is vital to achieving HIV epidemic control and should be prioritized in the context of COVID-19 along with HIV treatment. We describe technological innovations for HIV prevention and PrEP service delivery, and propose a model for virtual PrEP service delivery to ensure HIV prevention interventions reach those most vulnerable during the implementation of COVID-19 mitigation measures.

## Methods

### Literature Search and Review

We performed a review of the literature to identify published peer-reviewed articles about virtual service delivery and related adaptations such as telemedicine (see Multimedia Appendix 1 for the detailed search strategy). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was used as a guide for this systematic review [9]. We searched the OVID/Medline, Scopus, Cochrane Library, CINAHL, PsycINFO, and Embase databases to identify human studies published between January 1, 2010, and October 26, 2021, to reflect the time period during which innovative technologies for health were introduced. Search terms included "telemedicine," "telehealth," "mobile health," "eHealth," "mHealth," "telecommunication," "social media," "mobile device," and "internet," among others (see Multimedia Appendix 1). The search was limited to articles published in English. We used EndNote X8 (Clarivate Analytics) to compile, clean, categorize, and assess citations. We assessed for risk of bias in a randomized controlled trial (RCT) using the Cochrane risk of bias tool [10].

### Ethics Considerations

This activity was reviewed by the US Centers for Disease Control and Prevention (CDC), and was conducted in compliance with applicable federal law and CDC policy. The activity was determined to meet the requirements of nonresearch and secondary data analysis for a public health response, as defined in 45 CFR 46.102(l). Thus, a protocol was not developed and registered.

### Study Selection

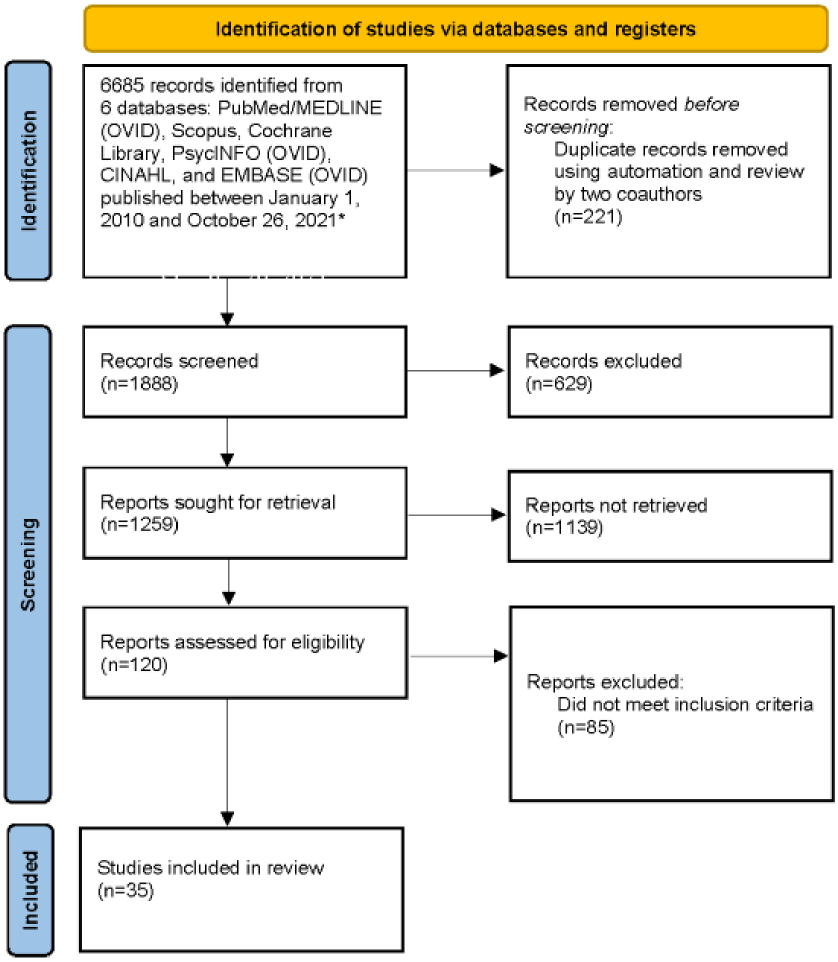
Two authors (PP and MK) screened the titles and abstracts of articles identified from our database search for references to HIV, PrEP, and virtual service delivery using filters in EndNote. Next, the same two authors (PP and MK) reviewed the selected articles' titles and abstracts to identify those reporting effective adaptations for virtual HIV service delivery, particularly related to PrEP, HIV prevention, and HIV testing, by reporting outcomes related to efficacy, feasibility, and/or acceptability. The full text of articles reporting relevant data and systematic reviews of virtual service delivery interventions were further reviewed. All systematic reviews about innovations of virtual HIV service delivery that focused on adherence and HIV testing were included because both have relevance to PrEP programs. Studies of interventions were included if they focused on innovations for HIV prevention service delivery, particularly PrEP. We thus included intervention studies that described the use of technology such as apps, use of the internet, SMS text messaging, telemedicine/telehealth, mobile health (mHealth), and eHealth for PrEP. We also included all reviews and meta-analyses of technology innovations pertinent to HIV prevention service delivery, as these data would inform the virtual service delivery model that we aimed to propose. We excluded studies that did not focus on virtual service delivery, focused on prevention of vertical mother-to-child transmission, described protocols, were not in English, or were not accessible (Table 1).

**Table 1.** Inclusion and exclusion criteria.

| Parameter | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Study topic | Technology innovations for HIV prevention and specifically pre-exposure prophylaxis service delivery, virtual service delivery | Focused on vertical mother-to-child transmission, did not focus on virtual HIV prevention service delivery |
| Study type | Randomized clinical trials, pre-postevaluations, mixed methods evaluations, surveys, reviews, meta-analyses | Protocols, viewpoints, editorials |
| Language | English | Language other than English |
| Time frame | Published after 2010 | Published before 2010 |
| Accessible | Able to retrieve publication | Publication was inaccessible |

Figure 1 details the study selection procedure. In addition, the references of papers that were selected were examined to identify other pertinent references. These selections and related data were confirmed by a second reviewer independent of the first reviewer. Studies with missing data were excluded.

**Figure 1.** Selection of studies regarding virtual service delivery and HIV. *See Multimedia Appendix 1 for more details.



### Other Considerations

The RCT was assessed for risk of bias using the Cochrane risk of bias tool [10] and some concerns were identified (Multimedia Appendix 2). Given the limited number of studies and the heterogeneity of studies and their outcomes, it was decided that we could not perform a robust meta-analysis of any given outcome. Thus, related analyses to explore causes of heterogeneity and certainty were not performed.

After reviewing the literature, we considered evidence-based interventions for PrEP service delivery in the time of COVID-19, and developed a virtual service delivery model for implementation to improve HIV prevention services now and in the future. We also suggest how to leverage this model for COVID-19 service delivery to maximize the use of vital health resources. All data and tools used are presented in this manuscript and are publicly available.

## Results

### Characteristics of Included Studies

Of the 6685 abstracts identified, 1888 were specific to virtual service delivery. Of those 1888 articles, 1259 focused on HIV, 120 of which were relevant for HIV prevention efforts; 48 pertained to PrEP and 19 of these focused on evaluations of interventions for virtual service delivery of PrEP; 16 were conducted in the United States and the other three were conducted in Kenya, India, and England [11-29]. One RCT was identified [19]. There were 16 systematic reviews related to virtual HIV care delivery [30-45], 3 of which were related to virtual PrEP delivery [30,42,45]. The remaining articles focused on aspects of care delivery, including telemedicine, use of SMS and the internet, mHealth, and eHealth. (Figure 1). These 16 papers were reviewed and examined for interventions that support virtual care delivery, which were evaluated for efficacy, feasibility, and/or acceptability and could be considered for PrEP service delivery in the time of COVID-19. Three systematic reviews provided pooled estimates [34,39,44].

### Summary of Pertinent Studies

We identified 19 papers [11-29] related to evaluations of interventions for PrEP virtual service delivery. These papers are summarized in Table 2. The primary aim of many of these interventions was to address barriers to PrEP delivery and uptake before the COVID-19 pandemic started in early 2020. For example, the interventions sought to reach people in rural areas or those who were not able to access facilities, as well as eliminating the stigma of PrEP and improving health literacy about many HIV prevention services, including HIV testing, condom use, PrEP, and testing for sexually transmitted infections (STIs). The data presented provide support for the use of social media, smartphone apps, text messaging, and the internet for service delivery and health communication. Two studies described successful PrEP initiation and monitoring using an online platform [17,27], and four studies found that telehealth for PrEP was feasible, acceptable, and effective [13,16,24,25]. Eight studies examined the use of apps [11,18,21,28] and SMS [15,19,22,26] for PrEP service delivery. Of note, only one study, the Enhancing PrEP in Community Settings (EPIC) study, presented results from an RCT [19]. One study described the successful use of the Extension for Community Healthcare Outcomes (ECHO) platform for training of PrEP providers [29]. ECHO, a distance telemonitoring program, has been extensively used to create communities of practice and deliver clinical mentorship to support remote health care provision, which has also been used for PrEP [29,41,46,47].

Of the 16 systematic reviews identified, three were specific to PrEP; one described successful PrEP delivery models, including community-based and home-based approaches [42], and two summarized novel interventions to use technology to improve PrEP availability, adherence, and uptake [41,45]. These include mobile apps that offer PrEP prescribing and preclude an in-person visit, distance mentorship of community PrEP providers, video teleconferencing for provider visits, electronic consults, and using text messaging and mobile/web platforms for PrEP initiation (Table 3) [41,45].

We also summarize systematic reviews that focus on technology innovations to improve HIV testing and adherence in Table 3, because these would also pertain to PrEP programs [30-45]. Most of these reviews focused on interventions to improve adherence to antiretroviral therapy (ART) [31-33,41,43,44]. Two studies reported pooled estimates for improved ART adherence, one for mHealth interventions (pooled odds ratio 2.15, 95% CI 1.18-3.91) and one for eHealth interventions (pooled Cohen *d*=0.25, 95% CI 0.05-0.46). All studies reported positive outcomes; however, the evaluation methods varied and thus have limited comparability.

**Table 2.** Summary of evidence-based interventions for HIV pre-exposure prophylaxis (PrEP) virtual service delivery.

| Author, year | Country | Intervention | Sample size | Study period | Study name | Evaluation | Results | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Biello et al [11], 2021 | United States | MyChoices app to increase HIV testing and PrEP uptake | 11 YMSM[a] | 2 months | University of North Carolina/Emory Center for Innovative Technology (iTech) | Baseline and 2-month postbaseline assessments | Mean System Usability Scale (SUS) score was 71 (SD 11.8); 80% (9/11) reported that app was useful | MyChoices app is acceptable to end users |
| Bond et al [12], 2019 | United States | Avatar-led eHealth video | 116 African American women aged 16-61 years | 6 weeks | PEP[b] and PrEP for Women | Cross-sectional web-based study with thematic analysis | 89% of participants rated the video as good or higher | Utilization of an avatar-led eHealth video fostered education about PEP and PrEP among African American women who have experienced insufficient outreach for biomedical HIV strategies |
| Chasco et al [13], 2021 | United States | Home specimen self-collection kits with central laboratory testing | 77 participants offered test kits (35 accepted and 42 refused) | 18 months | Iowa TelePrEP | Mixed methods evaluation | Compared to laboratory-site use, kit use was associated with higher completion of extragenital swabs (OR[c] 6.33, 95% CI 1.20-33.51 for anorectal swabs), but lower completion of blood tests (OR 0.21, 95% CI 0.06-0.73 for creatinine) | Telehealth PrEP programs should offer clients home kits and support clients with blood collection and kit completion |
| Farley et al [14], 2021 | United States | Community engagement and linkage with both virtual and face-to-face models; prepmaryland.org, PrEP telephone/text line, and PrEPme smartphone app | 2465 (24 prepmaryland.org; 60 phone line; 168 PrEPme app) | 4 years | N/A[d] | Observational programmatic evaluation | Overall success of: prepmaryland.org (4/24, 16.7%), phone line (18/60, 30%), PrEPme app (39/168, 23.2%) | Compared to face-to-face community outreach efforts, all virtual platforms reached lower total numbers, but had greater success in attendance at PrEP visits |
| Fuchs et al [15], 2018 | United States | Mobile health intervention (iText) to support adherence with bidirectional texting | 56 MSM[e] | 12-week pilot | iPrEx open-label extension study | Pre- and postintervention regression discontinuity analysis | 50% reduction in discontinuation of meds (95% CI 16%-71%; *P*=.008) | iText strategy was feasible and acceptable, and improved adherence to PrEP |
| Hoth et al [16], 2018 | United States | Pharmacist-led video visits | 186 referrals; 91% MSM | 18 months | Iowa TelePrEP | Results at 6 months | Retention was 61%, and 96% completed laboratory tests | Regional telehealth PrEP programs can be developed to offer PrEP widely |
| Hughes et al [17], 2021 | United States | Web-based PrEP service | 31 PrEP requesters | 5 months | Nurx | Electronic chart review and 90-minute semistructured interviews | Nurx eased barriers to PrEP access through the availability of knowledgeable, willing prescribers, and minimizing embarrassment and discrimination | Nurx produced satisfaction by achieving an acceptable balance between 2 client desires: efficiency and humanity |

| Author, year | Country | Intervention | Sample size | Study period | Study name | Evaluation | Results | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Liu et al [18], 2019 | United States | LYNX app to support HIV testing and PrEP uptake | 30 YMSM in focus group and 16 in open pilot | 2-month pilot | Adolescent Trials Network iTech U19 | SUS and focus groups | Median SUS score=72/100 | The LYNX app was feasible and acceptable; well-received, especially the sexual diary and gamification features (sex-positive badges) |
| Liu et al [19], 2019 | United States | Youth-tailored bidirectional text messaging intervention (PrEPmate) | 121 participants | 36 weeks | EPIC study | Randomized clinical trial (RCT) with some concerns of risk of bias[f] | Participants who received PrEPmate were more likely to attend study visits (OR 2.62, 95% CI 1.24-5.5.4) and have TDF-DP[g] levels consistent with >4 doses/week (OR 2.05, 95% CI 1.06-3.94) | An interactive text messaging intervention had high acceptability and significantly increased retention and adherence |
| McLaughlin et al [20], 2016 | United States | Tweets about PrEP on Twitter | 1435 tweets | 4 months | N/A | Poisson regression for propagation rate | Affective tone was a significant predictor of tweet propagation frequency (Wald $\chi^2_2$=30.997, $P$<.001) | PrEP-related tweets covered a wide range of issues, and affective tone in tweets is a critical factor in predicting propagation |
| Mitchell et al [21], 2018 | United States | Smartphone-based intervention (mSMART) | 10 YMSM | 4 weeks | mSMART open-label phase 1 trial | Real-time adherence assessment using a camera-based medication event–monitoring tool | Participants reported mean PrEP adherence rates of 91% via daily entries in mSMART | mSMART is feasible and acceptable |
| Mwonge et al [22], 2018 | Kenya | SMS-based surveys to collect data on sexual behaviors and adherence | 142 participants from serodiscordant partnerships | 24 months | Partners Demonstration Project | Questionnaires | 72% preferred SMS surveys to in-person visits | SMS surveys were acceptable and serve as reminders for adherence to PrEP and condom use |
| Patel et al [23], 2020 | India | Peer-delivered, internet-based messaging for HIV testing and condom use | 244 participants | 12 weeks | CHALO! Pilot | Pre-postsurveys | Increase in HIV testing | Online HIV prevention interventions are feasible and acceptable, and can improve HIV testing rates |
| Perlson et al [24], 2018 | United States | PrEP telenavigation program | 139 participants | 9 months | “At Distance” PrEP Navigation | Surveys | Increased knowledge of PrEP and linkage to HIV testing and prevention services | PrEP telemedicine can improve PrEP utilization |
| Refugio et al [25], 2019 | United States | Telehealth approach to PrEP initiation | 25 YMSM | 180 days | PrEPTECH | 2 online surveys | At least 75% felt PrEPTECH was confidential, fast, convenient, and easy to use | Telehealth PrEP programs increase access and eliminate barriers such as stigma |

| Author, year | Country | Intervention | Sample size | Study period | Study name | Evaluation | Results | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Shrestha et al [26], 2020 | United States | Text messages over a 4-week intervention period | 40 people enrolled in a methadone maintenance program | 10 months | Telerivet mobile messaging platform | An audio computer-assisted self-interview (ACASI) was used to assess all quantitative measures and qualitative interviews were semistructured | Mean adherence score of 87.6 (SD 18.6) for having taken PrEP in the past 30 days; mean acceptability (range 0-100) for the daily PrEP reminder was 75.0 (SD 11.7) | Preliminary evidence of the feasibility and acceptability of a text messaging–based approach as a potential tool for primary HIV prevention to improve PrEP adherence and HIV risk reduction among this underserved population |
| Wang et al [27], 2018 | England | Online generic PrEP and therapeutic drug monitoring | 293 individuals | 6 months | InterPrEP | Testing baseline and every 3-6 months | PrEP drug concentrations were above target; no creatinine elevations were seen; no cases of HIV, hepatitis B or C were noted | Online PrEP services with therapeutic drug monitoring are feasible |
| Weitzman et al [28], 2021 | United States | PrEP adherence mobile app (“Dot”); the Dot intervention combined with personalized pill reminders with positive psychology-based texts | 54 culturally diverse YMSM | 6 weeks | Dot app | Pre- and posttest evaluation of the impact of the Dot mobile app on self-reported PrEP adherence, PrEP treatment self-efficacy, PrEP knowledge, and intention to practice safe sex | Significant changes in the percentage of participants who reported perfect (100%) PrEP adherence from pre- to posttesting ($t_{53}$=4.458, *P*<.001); PrEP treatment self-efficacy ($t_{53}$=3.067, *P*=.003); and intention to follow safe sex and HIV testing guidelines ($t_{53}$=3.067, *P*=.003). | The Dot app was feasible and effective at improving PrEP adherence for supporting medication adherence among culturally diverse YMSM on PrEP |
| Wood et al [29], 2018 | United States | Project ECHO[h]–PrEP telemonitoring intervention | 69 medical providers | 2 years | Project ECHO | Pre- and postsurvey | Providers reported that Project ECHO participation helped them stay current on PrEP guidelines, improved knowledge, increased likelihood to prescribe PrEP, and addressed most concerns about prescribing PrEP | It is feasible to incorporate PrEP training into Project ECHO distance telementoring programs as a tool to educate community practitioners and support PrEP prescribing |

[a] YMSM: young men who have sex with men.

[b] PEP: postexposure prophylaxis.

[c] OR: odds ratio.

[d] N/A: not applicable.

[e] MSM: men who have sex with men.

[f] Risk of bias was assessed using the Cochrane risk of bias tool [10] (see Multimedia Appendix 2).

[g] TDF-DP: tenofovir diphosphate.

[h] ECHO: Extension for Community Healthcare Outcomes.

**Table 3.** Systematic reviews of technological innovations for improved HIV and pre-exposure prophylaxis (PrEP) service delivery.

| Author, year | Innovation(s) examined | Outcomes | Main findings |
|---|---|---|---|
| Catalani et al [30], 2013 | 62 articles summarizing the use of mobile health (mHealth) technology for HIV/AIDS | N/A[a] | Promising trend toward implementing mHealth innovations that are feasible and acceptable, but they are still in their early stages |
| Claborn et al [31], 2015 | Computer-delivered adherence intervention; 5 randomized controlled trials (RCTs) and 1 single-group pre-posttrial; 5 conducted in the United States and 1 in Canada | Adherence | Computer-delivered adherence interventions are feasible and acceptable among both HIV-positive adolescents and adults |
| Cooper et al [32], 2017 | mHealth interventions, mainly SMS-based. The 41 studies were conducted in 12 countries across North America, South America, Africa, Asia, Europe, and New Zealand | Adherence and health-related behaviors | Significant impacts on a range of outcomes, including adherence, viral load, mental health, and social support |
| Daher et al [33], 2017 | Digital innovations, classified into (1) mHealth-based (SMS/phone calls), (2) internet-based mHealth/eHealth (social media, avatar-guided computer programs, websites, mobile apps, streamed soap opera videos), and (3) combined innovations (including both SMS/phone calls and internet-based mHealth/eHealth). Reviewed 99 studies, 63 (64%) from America/Europe, 36 (36%) from Africa/Asia; 79% (79/99) were clinical trials; 84% (83/99) evaluated impact. Of innovations, 70% (69/99) were mHealth-based, 21% (21/99) were internet-based, and 9% (9/99) were combined. All digital innovations were highly accepted (26/31, 84%) and feasible (20/31, 65%) | Feasibility, acceptability, impact. mHealth-based innovations (SMS) significantly improved antiretroviral therapy (ART) adherence (pooled OR[b] 2.15, 95% CI 1.18-3.91) and clinic attendance rates (pooled OR 1.76, 95% CI 1.28-2.42); internet-based innovations improved clinic attendance (6/6), ART adherence (4/4), and self-care (1/1), while reducing risk (5/5); combined innovations increased clinic attendance, ART adherence, partner notifications, and self-care | Digital innovations were acceptable, feasible, and generated impact. A trend toward the use of internet-based and combined (internet and mobile) innovations was noted. Large scale-up studies of high quality, with new integrated impact metrics and cost-effectiveness are needed. Findings will appeal to all stakeholders in the HIV/STI global initiatives space |
| Hightow et al [34], 2015 | Synthesis of 66 relevant papers on HIV, technology, and youth | N/A | A growing number of technology-based interventions for HIV prevention and care have been published; however, the majority were published in the United States. Given the disproportionate burden of HIV among adolescents worldwide, there is a need for more broadly expanding eHealth and mHealth to youth globally |
| Horvath et al [35], 2020 | mHealth and other technology-based interventions for HIV testing: 6 efficacy trials and 12 pilot RCTs or quasiexperimental studies; 10 were conducted outside the United States, including countries in sub-Saharan Africa (n=4: Kenya, Tanzania, South Africa), China (n=3), Latin America (n=2: Brazil, Peru), and India (n=1) | Efficacy, feasibility, acceptability | All efficacy trials showed some evidence of efficacy. Most pilot RCTs demonstrated high levels of feasibility and acceptability. Technology-assisted HIV testing interventions may be an important strategy to reach national and global targets for HIV status awareness in the general population and for most at-risk groups |
| Labelle et al [36], 2020 | Summary of 22 papers on use of technology for HIV prevention and PrEP to inform an mHealth app development in Taiwan | N/A | Features identified from studies testing HIV prevention applications for PrEP, such as education and gamification, will be used to formulate features of an HIV prevention app in Taiwan |

| Author, year | Innovation(s) examined | Outcomes | Main findings |
|---|---|---|---|
| Maloney et al [37], 2019 | eHealth interventions for HIV care and prevention; 113 studies were included with 84 unique interventions. The majority (n=71, 85%) of interventions were developed for users in resource-rich countries. The remaining (n=13, 15%) were intended to address the unique cultural needs of specific communities in low- or middle-income countries | N/A | Robust collection of eHealth interventions in the published literature as well as unpublished interventions still in development. In the published literature, there is an imbalance of interventions favoring education and behavior change over linkage to care, retention in care, and adherence, especially for PrEP |
| Manby et al [38], 2021 | 25 RCTs that randomized a total of 15,343 participants: 2356 were randomized to interactive interventions, 5530 to noninteractive interventions, and 5808 to the control condition. Studies were from 10 countries in Africa: 8 in Kenya, 7 in Uganda, and 5 in South Africa; 6 studies reported outcomes related to HIV prevention behaviors | Meta-analyses show that eHealth interventions significantly improved HIV management behaviors (OR 1.21, 95% CI 1.05-1.40; *Z*=2.67; *P*=.008), but not HIV prevention behaviors (OR 1.02, 95% CI 0.78-1.34; *Z*=0.17; *P*=.86). There was no effect for HIV testing or biological outcomes (OR 1.17, 95% CI 0.89-1.54; *Z*=1.10; *P*=.27) compared with minimal intervention control groups | eHealth interventions can improve adherence to ART in sub-Saharan Africa, and serve as important tools to help reduce HIV-related morbidity and mortality as well as HIV transmission |
| Nelson et al [39], 2020 | 16 studies: 1 study was a fully powered RCT, 7 were single-arm pilots with pre-postassessments, 4 were pilot RCTs, and 4 tested public health campaigns with postassessments | N/A | All studies found that mHealth approaches were feasible and acceptable; however, most studies were small pilot trials |
| Schnall et al [40], 2014 | 13 studies: 5 targeted HIV testing behaviors and 8 focused on decreasing HIV risk behaviors with wed-based education modules, test messaging, chat rooms, social networking | N/A | eHealth has the potential to effectively reduce HIV risk behaviors and increase testing rates. Further evaluations are needed as there was wide variation in interventions and methodological quality |
| Touger et al [41], 2019 | Multiple models of telehealth innovations in the United States (8 studies): *provider to patient* (mobile apps for PrEP prescribing [nurx.com], videoconferencing for PrEP initiation [PrEPTECH, PrEPIOWA, plush-care.com], home-based PrEP [ePrEP]); *provider to provider* (distance learning for community providers [ECHO$^c$ Project], electronic consults for PrEP support) | PrEP dissemination and adherence | Technology-based intervention can address gaps in the PrEP care continuum and reach underserved populations; however, costs may impede progress. Platforms to share technology are needed as well as further research to assess scalability and sustainability |
| Vanhamel et al [42], 2020 | Scoping review of PrEP delivery models. The identified service delivery models showed that PrEP services mainly targeted people at high risk of HIV acquisition, with some models targeting specific key populations, mainly men who have sex with men | N/A | PrEP was often delivered centralized and in a clinical or hospital setting; yet, community-based as well as home-based PrEP delivery models were also reported. Providers of PrEP were mainly clinically trained health professionals, but in some rare cases community workers and lay providers also delivered PrEP. In general, in-person visits were used to deliver PrEP. More innovative digital options using mHealth and telemedicine approaches to deliver specific parts of PrEP services are currently being applied in a minority of the service delivery models in mainly high-resource settings. This reflects differentiation of care according to different contextual settings |

| Author, year | Innovation(s) examined | Outcomes | Main findings |
|---|---|---|---|
| Velloza et al [43], 2021 | Systematic review of adherence support interventions for adolescents. Fifteen oral contraceptive pill (OCP) articles and 26 ART, diabetes, and asthma systematic reviews were included. Interventions that improved medication adherence for OCPs, ART, asthma, and diabetes treatment included reminder text messages, computer-based and phone-based support, and enhanced counseling. Multimonth prescriptions and same-day pill starts also were found to improve OCP adherence and continuation. Adolescent-friendly clinics and peer-based counseling significantly improved ART adherence, and telemedicine interventions improved diabetes medication adherence | Adherence. Enhanced counseling (whether in groups, families, or computer-delivered) and phone-based support (eg, one-way and two-way text messages) improved ART adherence. Peer support interventions and adolescent-friendly services were effective for ART adherence | Interventions that improve medication adherence among youth include enhanced counseling, extended pill supply, adolescent-friendly services, and text message reminders. PrEP programs could incorporate and evaluate such interventions for their impact on PrEP adherence and continuation among at-risk adolescents |
| Wang et al [44], 2019 | eHealth interventions. Twenty-one trials: 8 trials from high-income countries and 13 trials from low- and middle-income countries | Adherence. eHealth interventions significantly improved ART adherence of people living with HIV (pooled Cohen $d$=0.25, 95% CI 0.05-0.46; $P$=.01) | Some of the eHealth interventions may be used as an effective method to increase the ART adherence of people living with HIV |
| Wong et al [45], 2020 | Four studies: one pilot study, three retrospective evaluations (Iowa TelePrEP, PrEPTech, Nurx, PlushCare) | Retention. The percentage of PrEP initiation after the first telehealth appointment ranges from 84% to 94%, and 6-month retention remains relatively high, in the range of 76%-99% | Success could be attributed to the ability of technology to address the barriers of geographic distance and social stigma faced by those who would otherwise have limited access to care. The use of telemedicine for PrEP is generally viewed by users as easy, fast, and convenient |

[a] N/A: not applicable.

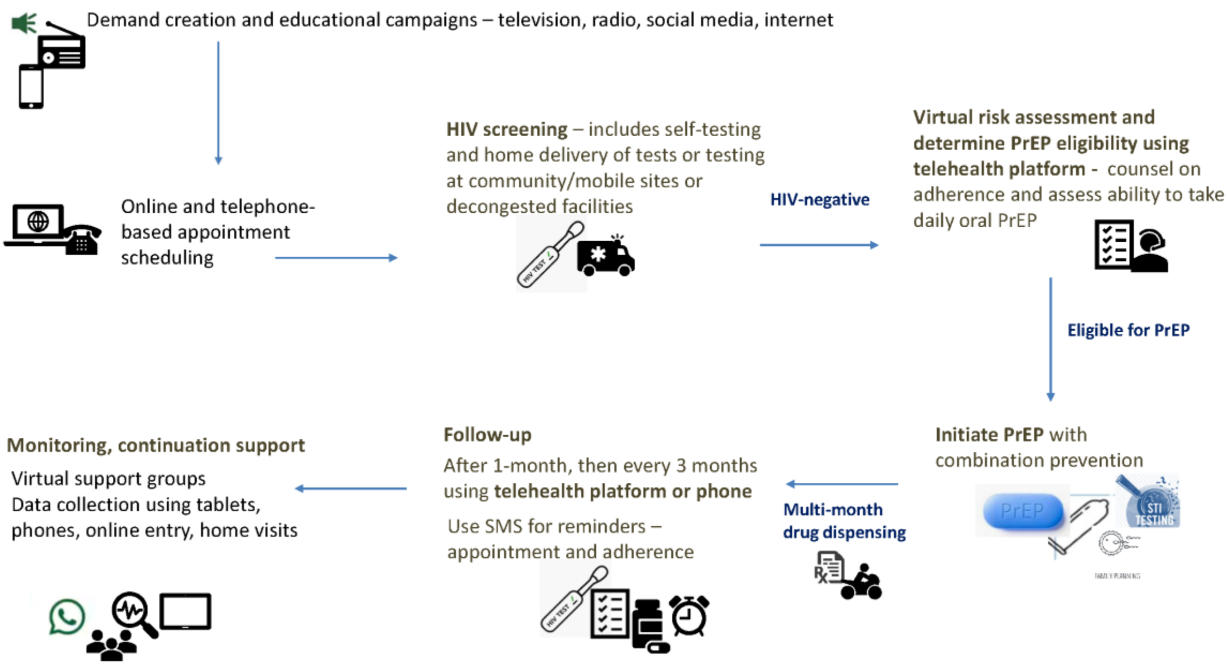
[b] OR: odds ratio.

[c] ECHO: Extension for Community Healthcare Outcomes.

## PrEP Virtual Service Delivery Model

According to the evidence-based innovations identified from the literature review and those implemented during the COVID-19 pandemic, we suggest a comprehensive model for virtual PrEP service delivery (Figure 2) that includes a combination of interventions such as internet for demand creation and risk assessment, telehealth platforms for visits and training, multimonth dispensing and medication delivery, community-based and self-testing for HIV, and smartphone apps for follow-up reminders and adherence support groups [11-45,48-51]. Regarding monitoring and follow-up, quarterly PrEP monitoring is acceptable and preferred with in-person follow-up but also with telehealth [52].

**Figure 2.** Model of differentiated virtual HIV pre-exposure prophylaxis (PrEP) delivery.



Demand creation: process of increasing the demand for a product or intervention using marketing techniques.

## Leveraging Adaptations for COVID-19 Service Delivery

Although our primary goal was to consider how innovative PrEP program delivery methods could be used to mitigate the impact of COVID-19 on PrEP services, it is also clear that these PrEP delivery methods have the potential for COVID-19 prevention and control (Table 4). Examples include: (1) demand creation using traditional (radio, television) and social media platforms for HIV prevention and COVID-19 messaging; (2) service delivery with decentralized care, moving from facility to community, including home-based and mobile delivery (for HIV and/or COVID-19 testing and multimonth PrEP prescription refills); virtual platforms for follow-up appointments (telehealth), such as risk assessment, lab assessment, and adherence counseling for PrEP; mental health counseling; using apps (eg, WhatsApp) for support groups and mobile device SMS for adherence reminders; (3) training and education with the use of web-based platforms for education and training of health care workers about HIV prevention (and developments in COVID-19 prevention and management) to promote task-shifting (eg, ECHO project); (4) monitoring and evaluation, involving web-based and app-based data entry using tablets and/or mobile devices of PrEP core indicators; and (5) supply chain vulnerabilities, involving working with governments to enact policies that allow for continued manufacturing of commodities and novel procurement and distribution platforms (electronic prescriptions, mail order, direct drug delivery).

**Table 4.** Leveraging adaptations to HIV pre-exposure prophylaxis (PrEP) service delivery in the time of COVID-19.

| PrEP program component | Adaptation | Evidence/reference | Contribution to COVID-19 response |
|---|---|---|---|
| Demand creation | Add web-based and social media platforms (TikTok videos, ads on Facebook and Instagram, pop-ups in apps like Tinder); continue campaigns and traditional methods (TV and radio) | [12,18-20,23,28] | Incorporate COVID-19 messaging, including information about social distancing and face masks, into the PrEP messaging and HIV education materials and campaigns |
| Service delivery | Decentralize care to decongest the clinics/facilities; virtual platforms for scheduling and appointments with maps for locations of mobile sites; use community and mobile delivery (eg, tests and medications); virtual risk assessment (using internet and/or apps); scale-up telehealth for consultation with PrEP provider for review of risk assessment and test results, adherence counseling for PrEP, and mental health counseling in general; support groups (eg, WhatsApp) and mobile device SMS for adherence and appointment reminders | [11-45,48,52] | Provide COVID-19 services as prevention and treatment modalities become available. This platform could be used to deliver the COVID-19 vaccine |
| Drug delivery | Multimonth prescriptions for PrEP, home delivery using postal service, mobile pharmacies | [13,16,24,25,27,49-51] | Delivery of pharmacologic interventions for COVID-19 |
| Testing | Home-based testing and self-testing, mobile testing sites (eg, drive-through sites), home delivery (postal service, health care workers), community delivery (eg, at pharmacies, faith-based centers, vending machines) | [13,16,17,25,35,41,45] | Delivery of COVID-19 testing |
| Training and education | Web-based platforms for education and training of health care workers about HIV prevention, particularly PrEP (eg, ECHO[a] Project) | [29,41,46,47] | Include developments in COVID-19 management to promote task-shifting so PrEP providers are knowledgeable about COVID-19 diagnostics, treatments, and prevention interventions |
| Monitoring and evaluation | Web-based and app-based data entry using tablets and/or mobile devices of PrEP core indicators and syndromic surveillance for acute HIV infection; system to monitor the PrEP cascade (number who tested HIV-negative, number eligible/offered PrEP, number who initiated PrEP, number adherent and retained) | [52] | Syndromic surveillance for COVID-19 symptoms and data collection of indicators related to COVID-19 response: testing uptake and results, contact-tracing outcomes, severity of illness, uptake of services, vaccine recipients, adverse events related to vaccines |
| Supply chain | Working with governments to enact policies and agreements that allow for continued manufacturing of commodities, and novel procurement and distribution platforms (electronic prescriptions, mail order, direct drug delivery) | N/A[b] | Leverage to include COVID-19 commodities such as vaccines |
| Community engagement | Engage community leaders in education of PrEP, including benefits; institute virtual peer-to-peer support groups; advocacy for PrEP to protect persons vulnerable to HIV acquisition | [14,20,22,23] | Education about COVID-19 prevention, treatment, and control, as well as advocacy for services needed by disenfranchised persons |

[a] ECHO: Extension for Community Healthcare Outcomes.

[b] N/A: not applicable.

# Discussion

## Principal Findings

COVID-19 mitigation measures such as physical distancing and lockdowns have created significant challenges for HIV and PrEP programming [8]. This systematic review is unique in that it provides a comprehensive overview of specific technology-based interventions as well as differentiated service delivery models that may be critical to program adaptation during COVID-19. Our findings demonstrate that interventions developed before COVID-19, dating back to 2013, for successful adaptation of PrEP programs for virtual service delivery for HIV testing, ART adherence, and PrEP exist and are currently in use. Innovations such as telemedicine; using the internet and smartphone apps for demand creation, support groups, and follow-up reminders; and multimonth dispensing with mobile pharmacies are evidence-based interventions designed to address distance to services and improve convenience. These innovations might also be particularly impactful in the context of COVID-19 [11-29]. Our review also identified examples of models for virtual service delivery that use technology to support PrEP users, such as PrEPTECH, IowaTelePrEP, and telehealth-led PrEP service delivery [41,42,45]. However, these models address some but not all aspects of PrEP implementation, such as commodity procurement and the ability to purchase medications, which is challenging when countries are locked down and companies cannot supply and distribute drugs.

To build upon the current literature and suggest a practical application for innovative technological adaptations, we used findings from the literature review to develop an example of a model of virtual PrEP delivery, which incorporates innovations identified in our literature search. We identified evidence-based interventions that could adapt the current PrEP service delivery platform to provide decentralized, virtual care. This model would allow for continued PrEP service delivery in the face of COVID-19 mitigation strategies but also may improve our ability to engage hard-to-reach populations who do not access care at facilities. The model is also aligned with approaches already described in some countries. For example, in Brazil, at the initial teleconsultation, individuals are assessed for PrEP by phone and undergo HIV rapid testing. Individuals receive a digital prescription to retrieve a 120-day PrEP supply plus two HIV self-test kits, because home delivery was deemed unaffordable. Subsequent follow-up teleconsultations are performed remotely by phone call, including instructions for the HIV self-test performance and the results are shared by digital photo. This approach was successful in maintaining PrEP services, including uptake, as part of the Implementation PrEP Study (ImPrEP) project [48]. In addition, community pharmacists can deliver drugs and manage minor ailments, which supports the use of task-shifting [49]. Our model can be implemented in countries with widespread access to the internet and smartphones. However, implementation could be challenging in areas where such technologies are limited or unreliable.

Globally, differentiated service delivery models to improve the reach of PrEP and HIV programs, to decongest facilities, and to limit exposure to SARS-CoV-2 are recommended [53]. Our model of service delivery could help to maintain PrEP services in resource-poor settings in all countries, including the United States and Canada, and might improve the program's ability to reach those most vulnerable by improving access to services and eliminating stigma associated with accessing facilities known to provide HIV services. Sexual and reproductive services could be leveraged to offer virtual HIV prevention services, particularly PrEP, as STI testing, condoms, and contraception should be offered with PrEP. Program evaluations are needed to understand the broader feasibility and impact of virtual service delivery models in low- and middle-income countries. To ensure that persons at substantial risk of HIV continue to benefit from PrEP, approaches to scale up virtual service delivery are underway in many countries [54]. HIV prevention services could also be leveraged for related prevention interventions such as STI testing, and to enhance the COVID-19 pandemic response.

Health care workers providing PrEP services can be trained virtually to deliver COVID-19 services, including education about mitigation measures and vaccination using online platforms [41,45]. The internet and smartphone apps can be used for service delivery such as intake assessments and appointment reminders or other public health communications such as contact-tracing programs alerting someone of exposure to SARS-CoV-2. COVID-19 testing can be offered through HIV testing platforms in the facility and community to create efficiencies. In addition, other prevention modalities for both HIV and COVID-19 could be delivered through the HIV prevention platform by leveraging the virtual service delivery of PrEP for COVID-19. For example, once COVID-19 vaccines [55] become widely available, PrEP service delivery could be leveraged for safe, widespread delivery by offering vaccination to clients who present for HIV testing.

These adaptations should be instituted with engagement of governments, stakeholders, and community leaders. Community engagement is fundamental to the success of syndemic control; community leaders can be influential and are key for disseminating factual information. Efforts should be made to accurately forecast needs, in terms of funding, personnel, commodities, and others, and to allocate resources such that resources are not exhausted and are adequately redistributed as needed. Systems should be agile and adopt new advances in HIV prevention rapidly. Although our review was motivated by concern regarding service interruptions related to COVID-19, programs should be developed both for mitigating current service interruptions and for increasing efficiencies and creating more resilience to future causes of service interruptions. A recent study of HIV service disruption in sub-Saharan Africa highlighted that the most important priority to avoid additional deaths due to HIV during the COVID-19 pandemic was to maintain the supply of antiretroviral drugs for people living with HIV [56]. Provision of other HIV prevention interventions to prevent an increase in HIV incidence was also deemed necessary [56]. Therefore, our model of virtual service delivery might be relevant for maintaining and achieving low levels of HIV incidence.

## Limitations

One important challenge that has not been addressed through our review and our model is the maintenance of supply chain and procurement mechanisms to ensure that HIV commodities such as drugs and tests remain available. National-level lockdowns have negatively impacted major pharmaceutical manufacturers, along with the global supply chain of drugs and medical commodities. Governments must ensure that HIV commodities procurement and delivery are maintained as essential services during pandemics that require lockdowns and quarantine for control. Governments should enact policies that allow for continued manufacturing of commodities and novel procurement and distribution platforms. Our literature review had other important limitations. We focused on HIV programs and may have missed relevant innovations used for other types of service delivery. We were not able to conduct meta-analyses for each PrEP intervention (Table 2) identified in our search given the small number of papers and the heterogeneity between studies, particularly of methodology. This limited our ability to conduct analyses related to syntheses of outcomes data. Lastly, as our search focused on service delivery, the review did not yield papers about policy needs related to virtual service delivery, which was outside the scope of our primary objectives.

## Conclusions

Although vaccines are critical to effectively controlling the COVID-19 pandemic, there are ongoing threats to COVID-19 control (and therefore to sustaining HIV prevention and care programs); most notably, the identification of variant strains with increased transmissibility and immune escape from current vaccines poses a significant threat to infection control [57]. COVID-19 control measures may need to continue to limit the spread of SARS-CoV-2 infection due to these variants in some countries [57]. The COVID-19 pandemic has catalyzed a new reality of virtual care [58]. Virtual health service delivery could improve accessibility and affordability of health care, and might improve health inequities, especially for people who are not proximate to care facilities, during COVID-19. However, this requires further investigation. There are also other relevant and newer technologies that have not yet been studied in this context. For example, machine learning can be used to identify individuals who might benefit from HIV testing, PrEP, and other risk reduction strategies [59]. Wearable devices with biosensing capabilities could be updated to improve adherence to daily medications; to provide location information for testing and pharmacies services and/or facilitate contact tracing; and to provide notifications to maintain social distancing [60]. Further investigation is warranted to assess the feasibility, acceptability, and effectiveness of these new technologies and understand their role in public health and medicine.

Innovations in virtual service provision of PrEP occurred before COVID-19 but have new relevance in the COVID-19 pandemic. The United Nations Program on HIV and AIDS (UNAIDS) 2020 target of 3 million on PrEP was not achieved; without innovations and evolution of standard models of delivery, reaching the 2025 target of 95% of those at risk using effective combination prevention options may be similarly beyond reach. Substantial gains in HIV care and the intended acceleration toward global HIV epidemic control may be lost. The innovations we describe might strengthen HIV prevention service delivery in the long run by engaging traditionally hard-to-reach or remote populations, reducing stigma, and by also creating a more accessible health care platform. These are platforms that can be leveraged both to mitigate the impacts of the COVID-19 pandemic on HIV services, and to support interventions for the COVID-19 response and facilitate pandemic control directly now and in the future.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
Literature review search strategy.
[DOCX File , 16 KB - publichealth_v8i6e37479_app1.docx ]

Multimedia Appendix 2
Risk of bias arising from the randomization process for the randomized control trial [19] using the Risk of Bias 2 tool.
[DOCX File , 20 KB - publichealth_v8i6e37479_app2.docx ]

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## Abbreviations

**ART:** antiretroviral therapy
**CDC:** Centers for Disease Control and Prevention
**ECHO:** Extension for Community Healthcare Outcomes
**EHE:** Ending the HIV Epidemic
**EPIC:** Enhancing PrEP in Community Settings
**ImPrEP:** Implementation PrEP Study
**mHealth:** mobile health
**PrEP:** pre-exposure prophylaxis
**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-analyses
**RCT:** randomized controlled trial
**STI:** sexually transmitted infection
**UNAIDS:** United Nations Program on HIV and AIDS

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Original Paper

# Characterizing Anchoring Bias in Vaccine Comparator Selection Due to Health Care Utilization With COVID-19 and Influenza: Observational Cohort Study

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## Abstract

**Background:** Observational data enables large-scale vaccine safety surveillance but requires careful evaluation of the potential sources of bias. One potential source of bias is the index date selection procedure for the unvaccinated cohort or unvaccinated comparison time ("anchoring").

**Objective:** Here, we evaluated the different index date selection procedures for 2 vaccinations: COVID-19 and influenza.

**Methods:** For each vaccine, we extracted patient baseline characteristics on the index date and up to 450 days prior and then compared them to the characteristics of the unvaccinated patients indexed on (1) an arbitrary date or (2) a date of a visit. Additionally, we compared vaccinated patients indexed on the date of vaccination and the same patients indexed on a prior date or visit.

**Results:** COVID-19 vaccination and influenza vaccination differ drastically from each other in terms of the populations vaccinated and their status on the day of vaccination. When compared to indexing on a visit in the unvaccinated population, influenza vaccination had markedly higher covariate proportions, and COVID-19 vaccination had lower proportions of most covariates on the index date. In contrast, COVID-19 vaccination had similar covariate proportions when compared to an arbitrary date. These effects attenuated, but were still present, with a longer lookback period. The effect of day 0 was present even when the patients served as their own controls.

**Conclusions:** Patient baseline characteristics are sensitive to the choice of the index date. In vaccine safety studies, unexposed index event should represent vaccination settings. Study designs previously used to assess influenza vaccination must be reassessed for COVID-19 to account for a potentially healthier population and lack of medical activity on the day of vaccination.

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**KEYWORDS**

COVID-19; vaccine; anchoring; comparator selection; time-at-risk; vaccination; bias; observational; utilization; flu; influenza; index; cohort

## Introduction

The world is faced with a deadly pandemic at a time of incredible technology such that new vaccines can be produced in a fraction of the previous development time and at a scale that can potentially vaccinate the entire human population. This brings new challenges in using observational data to evaluate vaccine safety, where the pressure to vaccinate quickly to prevent more deaths and viral variants reduces the time available to carry out studies [1]. This time pressure affects not just the collection of data for research but also the time it takes to develop and validate the evaluation methods. We therefore rely on the methods developed and validated in previous pandemics and seasonal infectious diseases, with influenza being an important example [2-4].

COVID-19 vaccination has been unlike any other in history. The target vaccination group has shifted from older adults and those with comorbidities in the early phases of vaccination to everyone including healthy, young people [5], with some nations already vaccinating the majority of their populations [6]. COVID-19 vaccines are delivered in a wide variety of settings, from pop-up centers unconnected to health care delivery to inpatient facilities for hospital discharge. Other vaccines such as those for influenza have a different delivery. They are often administered to specific vulnerable populations, such as pregnant women, patients at high risk of complications, or children, and are often given during health care visits [7-9].

The unique properties of COVID-19 vaccination may require adjusting study designs previously used for influenza vaccination, specifically the selection of a comparator cohort or an unvaccinated comparison time in cohort and self-controlled studies. Although, for the vaccinated group, the index date—vaccination—is clearly defined, the selection of the index date for the unexposed comparator group is more complex. Ideally, the index date in the unexposed group should be chosen based on the vaccination settings to reliably serve as a counterfactual. The selection procedure (which we have termed "anchoring") may itself influence the results of a study and induce bias in the analysis. For example, in studies of the background rates of adverse events, patients indexed on an arbitrary date were shown to have lower incidence of adverse events than the same patients indexed on a visit [10].

Here, we aimed to evaluate 2 alternative selection procedures for the index date in the unexposed group based on how vaccines are administered—coupled or decoupled to another health care encounter. We compared these approaches for 2 vaccinations, influenza and COVID-19, and investigated how anchoring influences the baseline patient characteristics of the unexposed group.

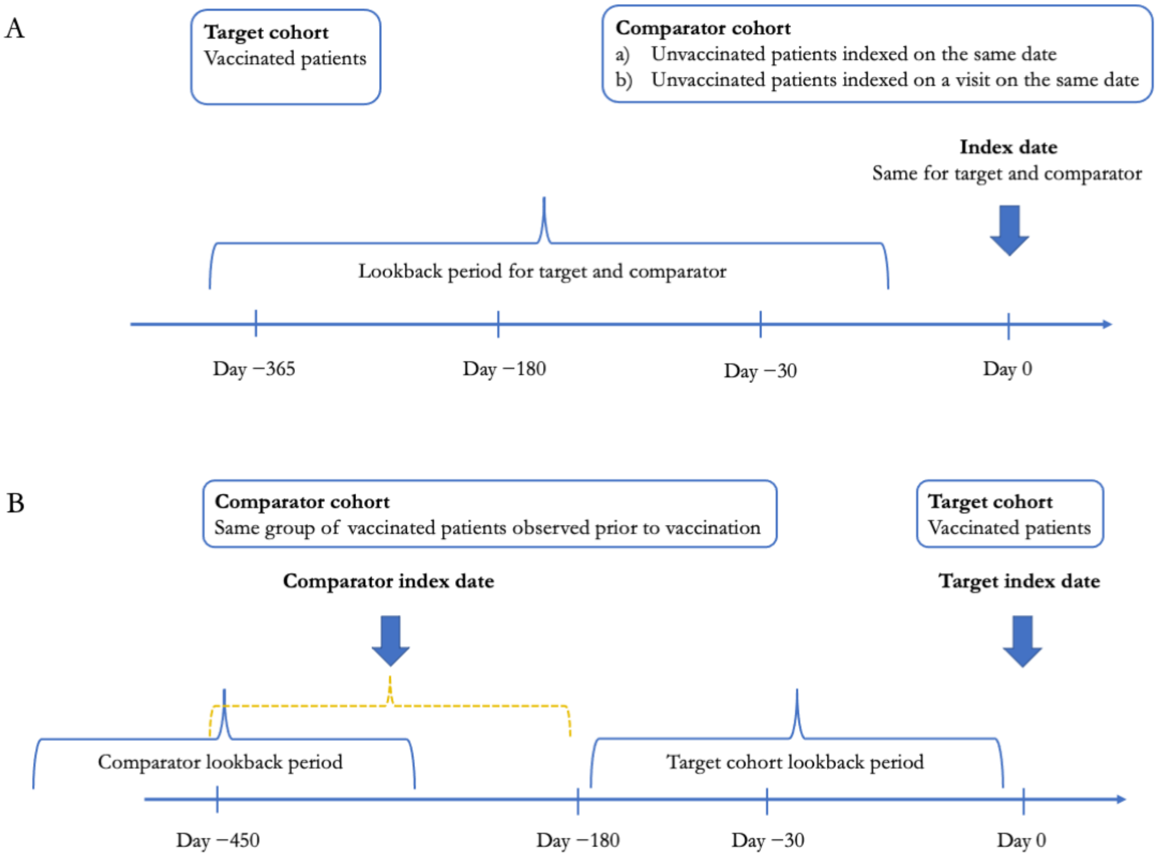
# Methods

## Data Collection and Analysis

We studied 2 types of vaccination: (1) influenza vaccine administered from 2017-2018 and (2) COVID-19 vaccine administered from 2020-2021 (the list of codes is presented in Table S1 in Multimedia Appendix 1). For each vaccine, we mimicked 2 study designs.

The first design (Figure 1A) corresponds to a cohort method, where the target group was vaccinated patients and the comparator group was unvaccinated patients. The index date for the target group was the date of vaccination; for the comparator, it was (1) a date selected from the unvaccinated patient's history (not necessarily with any medical event) such that it matched the index date of one of the target group participants or (2) a visit matched to the index date of one of the target group participants. Patients in each target and comparator pair were matched on age and gender.

**Figure 1.** Study design overview.



The second design (Figure 1B) corresponds to a self-controlled design (case-crossover design) [11], where the cases were the vaccinated patients indexed (or “anchored”) on the day of vaccination and the controls were the same patients indexed on an arbitrary date or a visit within 180-450 days prior to the vaccination date.

For each group, we extracted patient baseline characteristics (covariates) recorded within 5 time intervals: on the index date (day 0), on the day before the index date (day –1), from 30 to 1 days prior to the index date (short-term baseline covariates), from 180 to 31 days prior to the index date (medium-term baseline covariates), and from 450 to 181 days prior to the index date (long-term baseline covariates). Baseline covariates included all condition, procedure, measurement (laboratory tests and vital signs), and drug group codes available in the patients’ structured data within a specified time interval. For each covariate, we calculated covariate proportion, which is the proportion of patients with a covariate recorded in their electronic health record (EHR) within a given time interval along with its SD for binary variables or an average number with SD for continuous variables (such as the number of visits).

We then compared the covariates in each target-comparator pair and calculated the standardized difference of means. The covariates were said to be balanced if the standardized difference of means was less than 0.1 [12,13]. The standardized difference of means for each covariate was then plotted for each time interval and target-comparator pair.

We conducted the analysis on 2 EHR data sources: Columbia University Irving Medical Center health record data set (CUIMC) and Optum deidentified electronic health record data set (Optum EHR). Optum EHR’s data comprises medical record data from 87 million patients and includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, and procedures. The CUIMC EHR gathers data from the clinical data warehouse of the NewYork-Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY, based on its current and previous EHR systems, with data spanning over 30 years and including over 6 million patients. The data sources were selected based on the availability of both vaccines’ data and captured inpatient and ambulatory aspects of care. Both data sources were mapped to the Observational Medical Outcomes Partnership Common Data Model [14]. The Observational Medical Outcomes Partnership Common Data Model provides a homogeneous format for health care data and standardization of the underlying clinical coding systems that thus enables analysis code to be shared across participating data sets in the network.

All analysis was done in R statistical software (version 4; R Foundation for Statistical Computing). FeatureExtraction package (version 3.1; Observational Health Data Sciences and Informatics) was used to extract the baseline covariates.

### Ethics Approval

The protocol for this research was approved by the Columbia University Institutional Review Board (AAAO7805).

## Results

### Study Populations

The initial study population included 210,263 and 57,000 patients vaccinated with any COVID-19 vaccine from 2020-2021 in CUIMC and Optum EHR, respectively, and 60,142 and 4,991,051 patients vaccinated with an influenza vaccine from 2017-2018 in CUIMC and Optum EHR, respectively. The proportion of female patients was 62.7% (131,922/210,263) and 72.3% (41,204/57,000) for COVID-19 vaccinated patients and 61.4% (36,917/60,142) and 58.2% (2,906,757/4,991,051) for influenza vaccinated patients. The median (IQR) age was 57 (39-71) and 45 (34-56) years for COVID-19 vaccinated patients and 35 (12-63) and 50 (22-66) years for influenza vaccinated patients. We then matched each vaccinated population to the unvaccinated population on the date, age, and gender so that the distribution of age and gender between each target and comparator group was the same.

**Table 1.** The number of covariates with the standardized difference of means >0.1 for selected time intervals.

| Target-comparator pair | Index date (day 0), n/N (%) | | Long-term (from 450-181 days prior to the index date), n/N (%) | |
|---|---|---|---|---|
| | CUIMC[a] | Optum EHR[b] | CUIMC | Optum EHR |
| COVID-19–vaccinated patients compared to unvaccinated patients indexed on a date | 25/9073 (0.3) | 11/15,097 (<0.1) | 131/26,859 (0.5) | 56/51,075 (0.1) |
| COVID-19–vaccinated patients compared to unvaccinated patients indexed on a visit | 411/18,741 (2.2) | 110/21,739 (0.5) | 34/37,073 (<0.1) | 91/50,358 (0.2) |
| Influenza-vaccinated patients compared to unvaccinated patients indexed on a date | 469/12,684 (3.7) | 268/26,809 (1) | 881/25,782 (3.4) | 201/55,665 (0.4) |
| Influenza-vaccinated patients compared to unvaccinated patients indexed on a visit | 320/22,816 (1.4) | 94/32,931 (0.3) | 517/34,361 (1.5) | 114/56,387 (0.2) |

[a] CUIMC: Columbia University Irving Medical Center electronic health record data set.

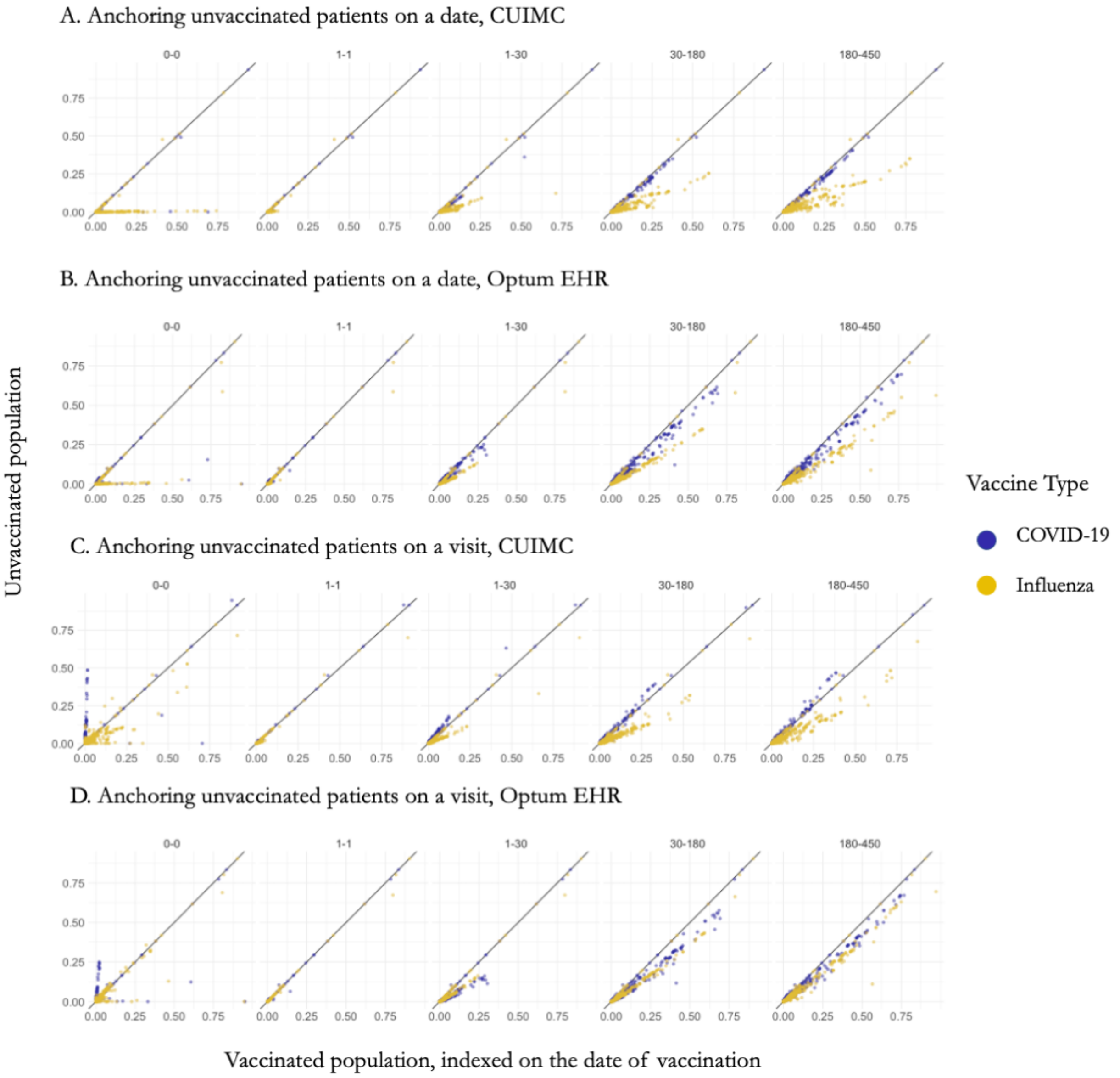
[b] Optum EHR: Optum electronic health record data set.

### Comparison of Vaccinated Patients and Unvaccinated Patients Indexed on a Date or a Visit

#### *Influenza-Vaccinated Population*

On the index date (day of vaccination=day 0), the influenza-vaccinated population had markedly higher proportion of most covariates than an arbitrary date in the comparison group (pinning most covariates against the x-axis in Figure 2, A and B, yellow). The largest difference in covariate proportions between the unvaccinated and vaccinated populations on day 0 was observed for inpatient and outpatient measurements such as blood count, metabolic panels, blood pressure, and basal metabolic index, including both the presence of measurements and proportion of patients with of abnormal results; this means that patients were far more likely to have measurements on the date of vaccination than on an arbitrary date. Moreover, the influenza-vaccinated population had higher covariate proportions even a year prior to the vaccination.

**Figure 2.** Baseline covariate proportion in vaccinated and unvaccinated populations on day 0, day –1, days –1 to –30, days –31 to –180, and days –181 to –450 in CUIMC and Optum EHR. Each dot represents a covariate. Blue: covariate proportion in COVID-19 vaccinated population versus unvaccinated population; yellow: in influenza vaccinated population versus unvaccinated population. CUIMC: Columbia University Medical Irving Center health record data set; Optum EHR: Optum electronic health record data set.



In contrast, comparison with the unvaccinated population indexed on a visit (Figure 2, C and D) showed a smaller difference between covariate proportions in CUIMC and almost no difference in Optum EHR, potentially indicating that a visit is a better counterfactual for a vaccination date than an arbitrary date.

Covariate proportions in vaccinated patients were closer to the proportions in the unvaccinated population indexed on a visit even with a longer lookback period (examples of covariates are provided in Multimedia Appendix 1).

### *COVID-19–Vaccinated Population*

As opposed to the influenza-vaccinated population, the difference in covariate proportion between the COVID-19–vaccinated and unvaccinated population indexed on an arbitrary date was moderate. We observed that COVID-19 vaccination was associated with a visit in 2.7% (5732/210,263) of patients (compared to 1.2% [2591/210,263] on an arbitrary date). In contrast, 55.8% (33,531/60,142) of the influenza-vaccinated population had a visit on the date of vaccination (compared to 0.6% [331/60,142] of unvaccinated population on an arbitrary date). The vaccinated population tended to have higher proportion of covariates prior to the index date (looking back a year prior).

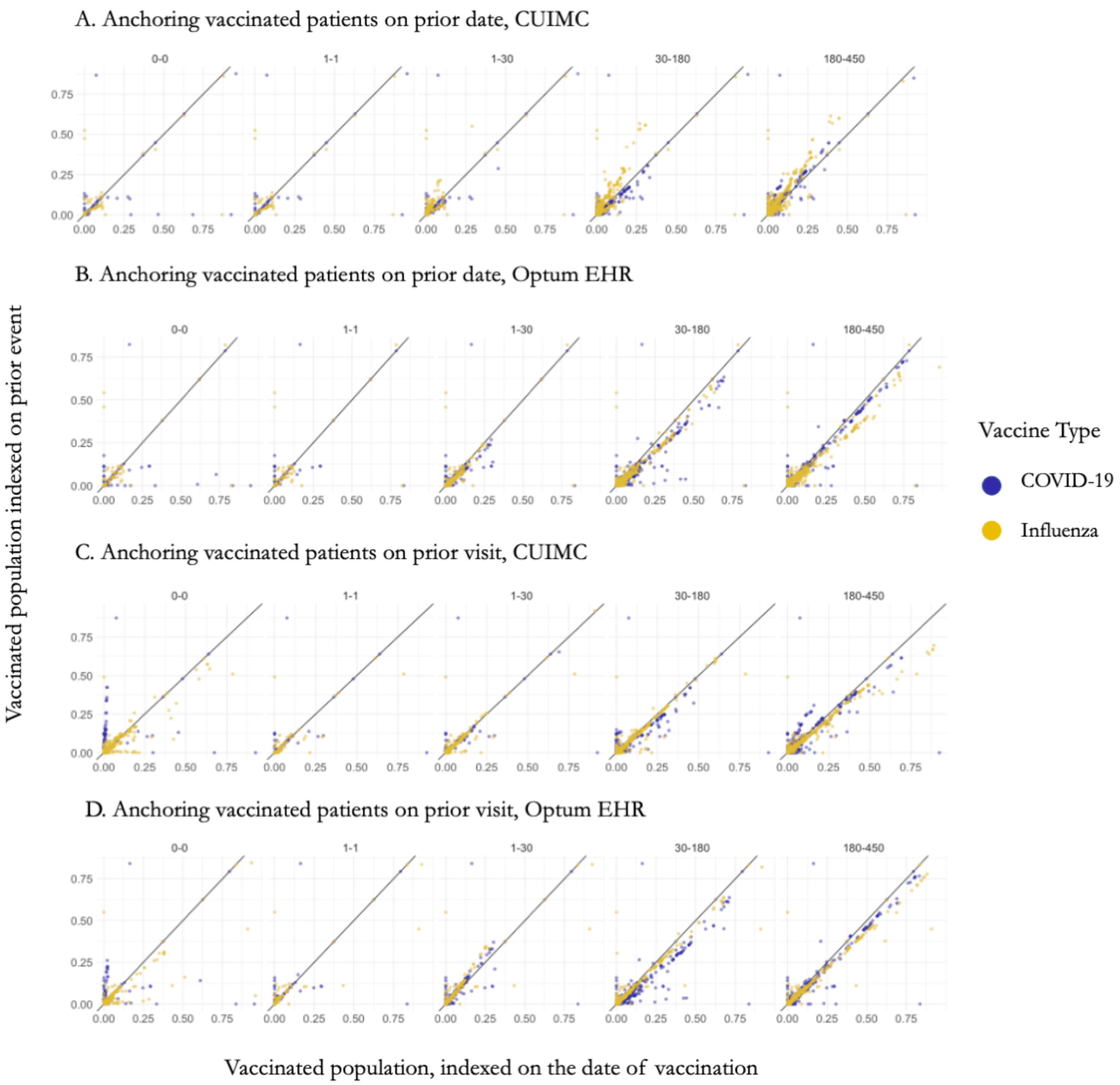
When compared to the unvaccinated population indexed on a visit, the COVID-19–vaccinated population had markedly lower proportion of most covariates. Those vaccinated with the COVID-19 vaccine had much lower rates of diagnoses of both chronic and acute diseases on the date of vaccination than a visit in the unvaccinated population. The list of conditions included common chronic conditions such as hypertension, depressive disorder, asthma, and diabetes mellitus along with acute conditions such as dyspnea, chest pain, and fever. This difference points out that an arbitrary date may be a better counterfactual for a vaccination date in COVID-19–vaccinated patients.

## Comparison of Vaccinated Patients Indexed on the Date of Vaccination and the Same Patients Indexed on a Prior Date or Visit

### *Influenza-Vaccinated Population*

Here, we compared vaccinated patients indexed on the vaccination date to the same patients indexed on a date or visit within a year prior, similar to the procedure in a self-controlled study. We observed that the date of influenza vaccination tended to have a higher proportion of covariates than an arbitrary date within a year prior (Figure 3, first column) and even higher than an arbitrary visit within a year prior. Patients indexed on the date of vaccination were more likely to have antecedent health care encounters, conditions, and laboratory tests within a year prior to the vaccination date than within a year prior to their previous visits (Figure 3, C and D). For comparison with an arbitrary date, we observed a mixed effect: in Optum EHR, vaccinated patients had more events preceding their vaccination, whereas in CUIMC they had fewer events. Nevertheless, in both data sources, the difference between covariate proportions was larger in magnitude when compared to an arbitrary date than when compared to an arbitrary visit.

**Figure 3.** Baseline covariate proportion in vaccinated population indexed on the date of vaccination compared to the same population indexed on a prior visit or date on day 0, day –1, days –1 to –30, days –31 to –180, and days –181 to –450 in CUIMC and Optum EHR. Each dot represents a covariate. Blue: covariate proportion in COVID-19 population; yellow: in influenza vaccinated population. CUIMC: Columbia University Irving Medical Center health record data set; Optum EHR: Optum electronic health record data set.



### *COVID-19–Vaccinated Population*

The COVID-19–vaccinated population showed a markedly lower proportion of covariates on the day of vaccination than a visit or an arbitrary date within a year prior to vaccination. The difference was attenuated with a longer lookback period; COVID-19–vaccinated patients had fewer health care events within a year prior to their vaccination than their previous history. We observed mixed effect when comparing to a date in the past; some covariates such as exposure to COVID-19, COVID-19 laboratory tests, vital signs, or acetaminophen were present in a higher proportion immediately before vaccination. Others such as glomerular filtration rate, thyrotropin measurement, urinalysis, or glomerulonephritis were observed in a lower proportion immediately before the vaccination.

# Discussion

## Principal Findings

We find that COVID-19 vaccination and influenza vaccination differ drastically from each other, with the proportion of most covariates much higher on the date of vaccination in the influenza group than the COVID-19 group. The results from looking back from 31 to 180 days and from 181 to 450 days before the vaccination (or index date) may be related to differences in the populations. The population vaccinated for influenza appears to have more comorbidities and past procedures and measurements than the average population, even after adjusting for age and gender, and the population vaccinated for COVID-19 appears to have a lower proportion of most medical covariates than the average population after adjusting for age and gender. This may be explained if influenza vaccination is targeted to sicker populations on average and if COVID-19 vaccination is targeted to the general public, which is healthier on average than those in our EHR data [7,9].

The drastic effects on day 0 (ie, the day of vaccination and its comparison) are likely related to the context in which the vaccination is given. If the comparison is an arbitrary date in the person's record, then influenza vaccination has markedly higher covariate proportions, reflecting the association of the vaccination with a health care encounter. Moreover, such a trend (not observed for the COVID-19 vaccine) was present even when comparing the date of influenza vaccination to prior patient visits.

The abovementioned trends for the COVID-19 vaccine were consistently observed in both data sources, and the differences between the data sources were mainly related to the coding practices. For example, in the CUIMC data, COVID-19 vaccination was not associated with a visit but rather with a patient encounter. On the contrary, COVID-19 vaccination in the Optum EHR was associated with the providers entering "Requires vaccination" and "Vaccine Administration" in the system along with the codes for the vaccines. For influenza vaccination, the observed patterns were also consistent when comparing the vaccinated population to the unvaccinated population. When looking at the vaccinated patients immediately before the vaccination compared to an arbitrary date in the past, the mixed effect observed can be attributable to the continuous surveillance of such patients in the CUIMC, which results in having higher health care utilization over an extended time period in the past.

The first implication of these results is that, when comparing vaccinated to unvaccinated patients or time, the anchoring event for the unvaccinated comparator must be selected carefully. Previous research acknowledged that comparing unexposed and exposed patients in the context of vaccine safety and effectiveness surveillance may lead to between-person confounding due to noncomparable groups [15]. For example, as noted before for influenza, vaccinated and unvaccinated patients differ in comorbidity prevalence [16]. Nevertheless, even in the same population, the choice of the index date or event influences both baseline covariates and the incidence rates of conditions following the index date. For COVID-19 vaccination, it appears that the comparison should not be purposely anchored on a health care visit unless it is a relevant vaccination subgroup (eg, those vaccinated at hospital discharge).

Adjusting for confounding will be extremely important, as it appears unlikely that a comparison can be chosen perfectly, although the comparisons between the same participants looking a year prior led to the best equivalency for both influenza and COVID-19 vaccinations. Moreover, the difference in patient characteristics requires a robust selection of covariates for a propensity score model or outcome model as opposed to the current exposed versus unexposed COVID-19 vaccine cohort studies, which only use a limited subset of covariates in their propensity score model [17].

Alternatively, this may argue for a self-controlled study design [18], which mitigates the difference in patient characteristics. However, this design is also sensitive to anchoring (which is what happens on day 0 and around it) and carries other challenges such as accounting for differences in COVID-19 risk over time. For example, we observed that when the time before vaccination is compared to the time before a visit in the past, the former time interval is characterized by higher prevalence of COVID-19 diagnosis and laboratory tests in both data sources, as the previous visits mainly had occurred in 2020 before the COVID-19 pandemic started.

This study has implications beyond using covariates for confounding adjustment. The day 0 results have direct implications for analyses of acute side effects such as anaphylaxis that include day 0 because the side effect often occurs immediately. Any study of such short-term effects must directly account for anchoring to the context in which the vaccination is given. Furthermore, studies that compare effectiveness or safety among vaccines must account for differences in populations and vaccination context. For example, single-dose vaccines may be given preferentially to sicker patients who are unable to return for a second dose, such as those being discharged from the hospital.

## Conclusions

Patient baseline covariates in the unexposed group or time are extremely sensitive to the choice of the index date (anchoring). COVID-19 vaccination and influenza vaccination differ drastically from each other in terms of the populations vaccinated and their status on the day of vaccination. Study designs previously used to assess influenza vaccination must be reassessed for COVID-19 to account for a potentially healthier population and lack of medical activity on the day of vaccination.

## Acknowledgments

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## Conflicts of Interest

GH and AO receive funding from the US National Institutes of Health and the US Food and Drug Administration. PBR and MJS are employees of Janssen Research and Development and shareholders in Johnson and Johnson. Funders had no role in the conceptualization, design, data collection, analysis, decision to publish, nor preparation of the manuscript.

Multimedia Appendix 1
Supplementary materials.
[DOC File , 1563 KB - publichealth_v8i6e33099_app1.doc ]

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## Abbreviations

**CUIMC:** Columbia University Irving Medical Center health record data set
**EHR:** electronic health record
**Optum EHR:** Optum electronic health record data set

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Original Paper

# Social Determinants in Self-Protective Behavior Related to COVID-19: Association Rule–Mining Study

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## Abstract

**Background:** Human behavior is crucial in health outcomes. Particularly, individual behavior is a determinant of the success of measures to overcome critical conditions, such as a pandemic. In addition to intrinsic public health challenges associated with COVID-19, in many countries, some individuals decided not to get vaccinated, streets were crowded, parties were happening, and businesses struggling to survive were partially open, despite lockdown or stay-at-home instructions. These behaviors contrast with the instructions for potential benefits associated with social distancing, use of masks, and vaccination to manage collective and individual risks.

**Objective:** Considering that human behavior is a result of individuals' social and economic conditions, we investigated the social and working characteristics associated with reports of appropriate protective behavior in Brazil.

**Methods:** We analyzed data from a large web survey of individuals reporting their behavior during the pandemic. We selected 3 common self-care measures: use of protective masks, distancing by at least 1 m when out of the house, and handwashing or use of alcohol, combined with assessment of the social context of respondents. We measured the frequency of the use of these self-protective measures. Using a frequent pattern–mining perspective, we generated association rules from a set of answers to questions that co-occur with at least a given frequency, identifying the pattern of characteristics of the groups divided according to protective behavior reports.

**Results:** The rationale was to identify a pool of working and social characteristics that might have better adhesion to behaviors and self-care measures, showing these are more socially determined than previously thought. We identified common patterns of socioeconomic and working determinants of compliance with protective self-care measures. Data mining showed that social determinants might be important to shape behavior in different stages of the pandemic.

**Conclusions:** Identification of context determinants might be helpful to identify unexpected facilitators and constraints to fully follow public policies. The context of diseases contributes to psychological and physical health outcomes, and context understanding might change the approach to a disease. Hidden social determinants might change protective behavior, and social determinants of protective behavior related to COVID-19 are related to work and economic conditions.

**Trial Registration:** Not applicable.

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**KEYWORDS**

social determinants; data mining; self-protective behavior; COVID-19; protection; behavior; sanitation; characteristic; Brazil; compliance; public health; policy; mask; risk

## Introduction

Collectively, individual behavior is a crucial determinant of the success of measures to overcome critical conditions, such as a pandemic. During 2020-2021, Brazil had more than 20 million confirmed cases of COVID-19 and about 600,000 COVID-19–related deaths [1]. SARS-CoV-2 circulated widely, and intensive care unit (ICU) beds available reduced quickly, causing an imminent risk of health system collapse in many Brazilian states. Due to high transmission rates and a sequence of new variants, populations were caught in a conflict between the need for social distancing and economic burden [1,2].

Social restrictions with early and mandatory quarantine were supposed to be effective and were extensively recommended to contain virus dissemination [3]. Despite lockdown, isolation, and self-care campaigns, there was conflicting behavior by some people occupying the streets due to partially open commercial activities, protests, and leisure activities. Data from mobile phones showed not more than 50% of isolation in any given moment, even in critical periods of high transmission, a lack of ICU beds, and extenuated health professional teams [4]. Commonly, there is no convergence between the severity of the pandemic and individual behavior. It is interesting to note that information does not always lead to better and rational decisions. For example, in the face of proximity to death, individuals can activate some psychological defenses, such as minimizing the threat of the virus and its impact on their life [5]. In addition, individual behavior to deal with prevention depends on many factors, such as trust in the government and its strategies [6] and perception of the leaders' style to solve moral dilemmas [7]. These perceptions affected the efficacy of public policies to prevent infection during the COVID-19 pandemic.

In developed countries, re-emerging new waves of apparently more transmissible variants, driven by refusal to vaccinate, increased the risk of emergence of new resistant strains [8]. The lack of compliance with containing measures during a pandemic is not new. In 1919, Major George A. Soper published a paper in *Science*, entitled “Lessons of the Pandemic,” regarding the Spanish flu pandemic [9]. He stated that 3 main factors stand in the way of prevention: First, public indifference, when people do not appreciate the risks they run due to a lack of comprehension of the disease; second, it does not lie in human nature for a person who has only a slight cold to shut up in rigid isolation as a means of protecting others on the bare chance that it may turn out to be a really dangerous infection; and third, the highly infectious nature of respiratory infections adds to the difficulty of their control, and the disease may be transmissible before the patient is aware that they are attacked. Despite all technological progress in the past 100 years, a health crisis still requires large-scale behavior modification, with a significant social and psychological burden on individuals and their families. It was estimated that up to 40% [10] of premature deaths were accountable to individual unhealthy lifestyle decisions and behaviors [11]. It is paramount to align individual human behavior with the recommendations by public health experts.

Social, economic, psychological, and physical environments promote different changes in population behavior across stages of life [12,13]. Some social determinants, such as socioeconomic status, might delineate the distribution of mental disorders in the population, with socially disadvantaged individuals suffering a greater impact [13]. For example, there is a 2.5 times greater risk of having depression or anxiety among youth with low socioeconomic status than among those with a higher socioeconomic status [12]. An economic disadvantage also brings conditions such as compromised immune systems, diabetes, heart disease, and chronic lung diseases, resulting in higher morbidity in individuals infected by SARS-CoV-2 [12]. Those at an economic disadvantage are more likely to be exposed to the virus, susceptible to its effects, and suffer negative outcomes.

In Italy, many factors were considered as predictors of well-being in self-reports: gender (men), age (older), socioeconomic status, occupational status (unemployed), higher coping efficacy and trust in institutions, and positive attitudes toward quarantine measures [14]. During the pandemic, working conditions might have increased the risk to both COVID-19 and the related psychological burden [15,16]. There is also evidence that having COVID-19 increased anxiety, affecting home relationship engagement and critical work, and resulted in more somatic symptoms [16]. The socioeconomic burden can affect behavior and make people less willing to adopt recommended safety measures [17]. Incentives to healthier attitudes might have potential benefits, minimizing the impacts of behavior over health or shaping them according to public policy [11]. A multilevel framework should be applied to improve strategies and hence reduce new cases, deaths, and the burden of the pandemic. Policy makers must understand the dynamics of social determinants, interplaying with individual beliefs and behaviors in order to identify putative targets and plan effective care and interventions to mitigate the effects of the pandemic.

The most common self-care and protection recommendations during the COVID-19 pandemic were the universal use of facial masks, frequent handwashing or use of alcohol, and distancing when staying out (at least 1 m from someone who doesn't live with you) [18]. The cumulative protective effect might buffer transmission rates and help to control the pandemic. Considering that individual perception and behavior might change the efficacy of public policies, and part of the population reported continuing regular prepandemic life activities, 2 questions were formulated: (1) What are the characteristics of people informing careful/self-protective behavior? (2) What are their living contexts? These questions aim to better understand how we can improve conditions and strategies toward self-care, not only for the current pandemic, but also to understand the gap between presumptive information about protective measures, health promotion campaigns, and the resulting individual and societal behavior.

# Methods

## Ethical Considerations

This study was approved by the National Commission of Ethics in Research (CONEP) on May 2, 2020 (CAAE #30823620.6.0000.5149) and complied with the Declaration of Helsinki (1989). All participants were informed that the survey would take about 25 minutes to be completed. The consent form was presented on the first page of the online form, and only participants who consented to participation were further enrolled.

## Recruitment and Participants

Participants needed to be 20 years of age or more, know how to read, and have access to the internet to enroll.

Two nonprobability samples from the general population were self-selected via a survey link promoted by the Associação Brasileira de Psiquiatria (ABP) targeting the whole country at two timepoints. Participants were also invited via posts on social media. Samples were compared in a repeated cross-sectional design. The sample from timepoint 1 (T1) was collected from May 9 to June 30, 2020. The sample from timepoint 2 (T2) was collected from November 10, 2020, to January 31, 2021. Overall, there were 10,162 participants. At T1, 7802 (69.9%) individuals gave consent to the research and filled the questionnaire, whereas 3062 (23.2%) individuals participated at T2. In addition, 702 (6.9%) individuals from both T1 and T2 identified by self-generated identification codes. Cases and deaths due to COVID-19 mostly increased in most parts of the country during the collection phase.

## Measures

### *E-survey Development and Pretesting*

The online survey was developed and collected through SurveyMonkey. Researchers and other collaborators tested the usability and technical functionality of the electronic questionnaire before sending it into the field. There were 61 questions displayed on 13 pages in a fixed order. No incentives were offered for survey participation. In this study, we used 4 variables from the "precautionary measures against COVID-19" question area as consequents and 11 from "sociodemographic variables" and 13 from the "work situation and economic perception" question areas as antecedents analyzed through association rule mining.

### *Sociodemographic Characteristics*

The online survey contained questions investigating the participants' gender, age, education, civil/relationship status, ethnicity, household size, residence country region, maternal education, household monthly income, and work type/situation. Regarding work type, we investigated the categories of businessperson, full-time employee, liberal profession, public/civil service, retiree/pensioner (investigated only at T2), self-employed, and unemployed. For economic classification, we used the Brazilian Economic Classification Criteria (CCEB) [19], which is a Brazilian instrument with questions about possession of durable goods and educational level of household heads. A subject score on the CCEB varies from 0 to 46, and it is classified in 1 of 6 classes with a distinct average monthly income: A (BRL 25,554.33 [US $5366.41], 2.5% of Brazilian population), B1 (BRL 11,279.14 [US $2368.62], 4.4%), B2 (BRL 5641.64 [US $1184.74], 16.5), C1 (BRL 3085.48 [US $647.95], 21.5% of Brazilian population), C2 (BRL 1748.59 [US $367.20], 26.8%), and DE (BRL 719.80 [US $151.16], 28.3%). At the time of writing, the exchange rate was BRL 1=US $0.21. In this study, we merged classes B1 and B2 into class B and classes C1 and C2 into class C.

### *Questions Related to the COVID-19 Outbreak*

Sentences related to the COVID-19 outbreak were presented in a yes/no checkbox. Participants were asked to select all options that applied to their experience in the past 14 days. We based most of the questionnaire on the same questions presented in the first study on psychological impacts of the COVID-19 pandemic in China by Wang et al [12], adding questions we found appropriate for the Brazilian context at the time (ie, April 2020). The structured questionnaire consisted of 54 sentences that covered several areas. Here, we focused on questions related to precautionary measures against COVID-19, work situation, and economic perception. The questionnaire's sentences are presented in Multimedia Appendix 1.

## Statistical Analysis: Theory/Calculation

Sociodemographic characteristics and responses on the COVID-19 questionnaire were described. Venn diagrams were used to visually describe the frequency of participants adopting at least 1 of the following preventive actions: (1) stay at least 1 m apart from people when out of the house; (2) sanitize hands with alcohol gel (70% ethyl alcohol) or wash hands for at least 20 seconds, whenever possible, when out of the house; and (3) only leave home when extremely necessary and wearing a face covering. We also depicted the frequency of participants who "kept going outdoors (leaving home) for work as usual." One diagram was made for each timepoint investigated.

## Association Rule Mining

Research questions were answered by formulating our problem as a frequent pattern–mining task [20]. A pattern is a set of question-answer pairs, where the possible answers that compose the pair are specific to each question. A pattern is frequent when a number of subjects present a given pattern in their responses and the number is above a threshold. These frequent patterns can be used to generate association rules. An association rule follows an if-then format and is used to express how often 2 or more answers to questions of interest are associated with each other in the database. For example, we may find an association rule that says that *if* a subject is of the female gender, *then* it is frequently associated with COVID-19-protective behaviors, such as "only leaves home when extremely necessary and wearing a face covering" and "stays at least 1 m apart from people when out of the house."

In short, association rules are generated from a set of answers to questions, also called items, that co-occur with a given frequency. Both the rule antecedent (the *if* part of the rule) and the rule consequent (the *then* part of the rule) may be formed by the answers to more than 1 question, but the set of answers that compose the rule has to occur together with the same frequency. The association between a set of answers to different questions is usually measured using 3 traditional metrics of interestingness: support, confidence, and lift.

Support shows how popular a set of question-answer pairs is, and is measured using the proportion of subjects who answered according to that set. For example, if we have responses from 100 subjects in the database and 70 (70%) of them only leave the house with a mask, the support of the answer "only leaves home when extremely necessary and wearing a face covering" is equal to 70/100 = 0.7. Confidence, in turn, measures how likely it is that a person gives a set of question-answers Y, given they gave a set of question-answers X, that is, the conditional probability of Y given X. Confidence is measured considering the frequency (support) of X and Y appearing together over the frequency (support) of X alone. One problem with confidence is that it may not capture the importance of the association, as it just accounts for the popularity of 1 question in the denominator.

The third popular metric, lift, solves this major drawback of confidence by quantifying to what extent the observed joint probability of X and Y deviates from the expected joint probability of them; in practice, it is the ratio between these 2 joint probabilities. A lift value of 1 means no correlation exists between X and Y, that is, the observed co-occurrence comes from the margins. A value greater than 1 means X and Y are positively correlated, and a value smaller than 1 means X and Y are negatively correlated. Replacing X and Y by the answers to questions from the pool, we were able to identify answers associated with both sociodemographic, COVID-19–related work situation, and economic perceptions, and adoption of human protection measures to prevent COVID-19 contamination and spread.

In this analysis, we used the Apriori algorithm [21] to determine the association rules. The support was a user-defined parameter. We used a minimum support of 5%, which establishes the minimum frequency of any question-answer pair to be considered relevant for the sake of an association rule, and a minimum confidence of 68%. For more details on frequent-pattern mining, please refer to Multimedia Appendix 1.

After the rules were generated a priori, we selected those that had in their consequent answers to questions related to measures individually taken to suppress COVID-19 transmission and contamination. We divided these rules into 2 groups: (1) those describing people who continued with their habits and lifestyle regardless of the pandemic and (2) those who were adopting at least 1 of the protection recommendations. The first group reported to continue going out normally regardless of the pandemic ("kept moving outdoors [leaving home] for work as usual"). The second group involved people who reported to take at least 1 of the following protective measures: (1) stay at least 1 m apart from people when out of the house; (2) sanitize hands with alcohol gel (70% ethyl alcohol) or wash hands for at least 20 seconds, whenever possible, when out of the house; or (3) only leave home when extremely necessary and wearing a face covering.

## Results

### Study Sample

The study sample was composed of individuals from the Brazilian adult population who have access to the internet and a computer. It was a population with predominance of women, Whites, married people, high education, from all Brazilian regions, and mostly middle class, living in a house with 3-5 people, at both timepoints. Tables 1-3 list the participants' sociodemographic characteristics, precautionary measures taken, and work situation and economic perceptions, respectively.

At T1, 131 (6%) individuals reported going out normally. At T2, 6 months later, 172 (31%) individuals reported going out normally. Despite the increase in people going out normally, most participants reported the use of protective measures against COVID-19.

**Table 1.** Sociodemographic characteristics during the COVID-19 pandemic at 2 cross-sectional timepoints.

| Characteristics | T1[a] (May-June 2020; N=7802), n (%) | T2[b,c] (November 2020-January 2021; N=3062), n (%) |
|---|---|---|
| **Gender** | | |
| Female | 5366 (68.8) | 2180 (71.2) |
| Male | 1148 (14.7) | 594 (19.4) |
| Missing | 1288 (16.5) | 288 (9.4) |
| **Age (years)** | | |
| 18-19 | 98 (1.3) | 70 (2.3) |
| 20-29 | 1188 (15.2) | 604 (19.7) |
| 30-39 | 1601 (20.5) | 735 (24.0) |
| 40-49 | 1464 (18.8) | 579 (18.9) |
| 50-59 | 1133 (14.5) | 429 (14.0) |
| 60-69 | 599 (7.7) | 211 (6.9) |
| 70-90 | 118 (1.5) | 41 (1.3) |
| Missing | 1601 (20.5) | 393 (12.9) |
| **Education** | | |
| No schooling | 21 (0.3) | 2 (0.1) |
| Doctorate degree (PhD) | 429 (5.5) | 156 (5.1) |
| Elementary school diploma/incomplete junior high school | 232 (3.0) | 78 (2.5) |
| Incomplete elementary school | 91 (1.2) | 18 (0.6) |
| High school diploma/incomplete higher education | 1871 (24.0) | 783 (25.6) |
| Master's degree | 638 (8.2) | 312 (10.2) |
| Higher education degree | 3079 (39.5) | 1427 (46.6) |
| Missing | 1441 (18.3) | 286 (9.3) |
| **Ethnicity** | | |
| Asian/Oriental | 108 (1.4) | 37 (1.2) |
| White | 3128 (40.1) | 1403 (45.8) |
| Indigenous | 20 (0.3) | 4 (0.1) |
| Brown | 1173 (15.0) | 551 (18.0) |
| Black | 244 (3.1) | 133 (4.3) |
| Missing | 3129 (40.1) | 934 (30.6) |
| **Marital status** | | |
| Married/cohabitation | 3206 (41.1) | 1226 (40.0) |
| Divorced | 801 (10.3) | 257 (8.4) |
| Single | 2204 (28.2) | 1237 (40.4) |
| Widowed | 33 (0.4) | 46 (1.5) |
| Missing | 1558 (20.0) | 296 (9.7) |
| **Work type** | | |
| Full-time employee | 1279 (16.4) | 580 (19.0) |
| Self-employed | 947 (12.1) | 285 (9.3) |
| Unemployed | 1431 (18.3) | 577 (18.8) |
| Liberal professional | 735 (9.4) | 326 (10.6) |
| Public/civil servant | 1871 (24.0) | 663 (21.7) |

| Characteristics | T1[a] (May-June 2020; N=7802), n (%) | T2[b,c] (November 2020-January 2021; N=3062), n (%) |
|---|---|---|
| Retiree/pensioner | N/A[d] | 202 (6.6) |
| Businessperson | N/A | 75 (2.4) |
| Missing | 1539 (19.8) | 354 (11.6) |
| **Economic class (BRL)** | | |
| A: BRL 25,554.33 (US $5366.41)[e] average household income | 889 (11.4) | 970 (31.7) |
| B: BRL 11,279.14 (US $2368.62) or BRL 5641.64 (US $1184.74) average household income | 2435 (31.2) | 485 (15.8) |
| C: BRL 3085.48 (US $647.95) or BRL 1748.59 (US $367.20) average household income | 1242 (15.9) | 1165 (38.1) |
| DE: BRL 719.80 (US $151.16) average household income | 125 (1.6) | 442 (14.4) |
| Missing | 3111 (39.9) | N/A |
| **Monthly household income (BRL)** | | |
| ≤500 (US $102.64) | 105 (2.6) | 11 (1.0) |
| 501-1000 (US $102.85-$205.28) | 235 (3.0) | 51 (1.7) |
| 1001-1500 (US $205.49-$307.92) | 349 (4.5) | 116 (3.8) |
| 1501-2000 (US $308.12-$410.56) | 368 (4.7) | 117 (3.8) |
| 2001-2500 (US $410.76-$513.20) | 267 (3.4) | 125 (4.1) |
| 2501-3000 (US $513.40-$615.84) | 382 (4.9) | 166 (5.4) |
| 3001-4000 (US $616.04-$821.12) | 417 (5.3) | 213 (7.0) |
| 4001-5000 (US $821.32-$1026.40) | 429 (5.5) | 250 (8.2) |
| 5001-10,000 (US $1026.60-$2052.80) | 970 (12.4) | 550 (18.0) |
| 10,001-25,000 (US $2053.00-$5131.99) | 765 (9.8) | 385 (12.6) |
| ≥25,001 (US $5132.20) | 269 (3.4) | 105 (3.4) |
| Missing | 3246 (40.5) | 962 (31.0) |
| **Household size** | | |
| 1 person | 470 (6.0) | 249 (8.1) |
| 2 people | 1286 (16.5) | 626 (20.4) |
| 3-5 people | 2557 (32.3) | 1189 (38.8) |
| 6 people or more | 172 (2.2) | 62 (2.0) |
| Missing | 3317 (42.5) | 936 (30.7) |
| **Maternal education** | | |
| No schooling/incomplete elementary school | 769 (9.9) | 331 (10.8) |
| Elementary school diploma/incomplete junior high school | 1085 (13.9) | 431 (14.1) |
| Junior high school diploma/incomplete high school | 541 (6.9) | 248 (8.1) |
| High school diploma/incomplete higher education | 1149 (14.7) | 571 (18.6) |
| Higher education degree | 1099 (14.1) | 541 (17.7) |
| Missing | 3159 (40.5) | 940 (30.7) |
| **Brazilian geographic region** | | |
| North | 273 (3.5) | 51 (1.7) |
| Northeast | 961 (12.3) | 230 (7.5) |
| Central-west | 362 (4.6) | 126 (4.1) |
| Southeast | 3624 (46.4) | 2058 (67.2) |

| Characteristics | T1[a] (May-June 2020; N=7802), n (%) | T2[b,c] (November 2020-January 2021; N=3062), n (%) |
|---|---|---|
| South | 1076 (13.8) | 313 (10.2) |
| Missing | 1506 (19.4) | 284 (9.3) |

[a] T1: timepoint 1.

[b] T2: timepoint 2.

[c] T1 and T2 were 6 months apart.

[d] N/A: not applicable.

[e] An exchange rate of BRL 1=US $0.21 was applied.

**Table 2.** Precautionary measures against COVID-19 in the past 14 days at 2 cross-sectional timepoints.

| Characteristics | T1[a] (May-June 2020; N=7802), n (%) | T2[b,c] (November 2020-January 2021; N=3062), n (%) |
|---|---|---|
| **Stays at least 1 m apart from people when out of the house** | | |
| No | 3277 (42) | 1134 (37) |
| Yes | 4525 (58) | 1928 (63) |
| **Sanitizes hands with alcohol gel (70% ethyl alcohol) or washes hands for at least 20 seconds, whenever possible, when out of the house** | | |
| No | 2939 (38) | 842 (27) |
| Yes | 4863 (62) | 2220 (73) |
| **Only leaves home when extremely necessary and wearing a face covering** | | |
| No | 2818 (36) | 1279 (42) |
| Yes | 4984 (64) | 1783 (58) |
| **Keeps moving outdoors (leaving home) for work as usual** | | |
| No | 7679 (98) | 2900 (95) |
| Yes | 123 (1.6) | 162 (5.3) |

[a] T1: timepoint 1.

[b] T2: timepoint 2.

[c] T1 and T2 were 6 months apart.

**Table 3.** COVID-19 pandemic work situation and economic perceptions at 2 cross-sectional timepoints.

| Characteristics | T1[a] (May-June 2020; N=7802) | T2[b,c] (November 2020-January 2021; N=3062) |
|---|---|---|
| **Feels more productive at work, n (%)** | | |
| No | 7126 (91.3) | 2709 (88.5) |
| Yes | 676 (8.7) | 353 (11.5) |
| **Feels less productive at work, n (%)** | | |
| No | 5616 (72.0) | 1980 (64.7) |
| Yes | 2186 (28.0) | 1082 (35.3) |
| **Already worked from home before COVID-19, n (%)** | | |
| No | 7423 (95.1) | 2871 (93.8) |
| Yes | 379 (4.9) | 191 (6.2) |
| **Working or studying from home (home-office), n (%)** | | |
| No | 5110 (65.9) | 1781 (58.2) |
| Yes | 2692 (34.5) | 1281 (41.8) |
| **Started using video calling apps/software often, n (%)** | | |
| No | 5144 (65.9) | 1606 (52.4) |
| Yes | 2658 (34.1) | 1456 (47.6) |
| **Working under reduced hours or taking turns with coworkers, n (%)** | | |
| No | 6999 (89.7) | 2819 (92.1) |
| Yes | 803 (10.3) | 243 (7.9) |
| **Waiting social distancing rules' suspension to go back to working or studying, n (%)** | | |
| No | 7213 (92.5) | 2963 (96.8) |
| Yes | 589 (7.5) | 99 (3.2) |
| **Need to leave home for work but is afraid of COVID-19, n (%)** | | |
| No | 6,981 (89) | 2,499 (82) |
| Yes | 821 (11) | 563 (18) |
| **Afraid of not being able to deal with present or yet-to-come financial difficulties, n (%)** | | |
| No | 5,663 (73) | 2,216 (72) |
| Yes | 2,139 (27) | 846 (28) |
| **Believes that economic struggles related to social distancing measures will be overcome soon (recovering will take 1 or 2 years after economic activity reopening/normalization), n (%)** | | |
| No | 5791 (74.2) | 2316 (75.6) |
| Yes | 2011 (25.8) | 746 (24.4) |
| **Believes that economic struggles related to social distancing measures will last longer (recovering will take at least 2 years or more after economic activity reopening/normalization), n (%)** | | |
| No | 4347 (55.7) | 1412 (46.1) |
| Yes | 3455 (44.3) | 1650 (53.9) |
| Average hours worked per day, mean (SD) | 6.63 (3.75) | 7.08 (3.65) |

[a] T1: timepoint 1.

[b] T2: timepoint 2.

[c] T1 and T2 were 6 months apart.

## Association Rule Mining

After filtering the association rules by their consequents to obtain people who reported following at least 1 of 4 selected behaviors, we obtained a set of 1694 rules for the data collected at T1 and 2490 rules for data collected at T2. Figure 1 shows Venn diagrams of the distribution of rule consequences and the number of people who were covered by the rules, considering different protective behaviors followed during the pandemic:

going out normally, frequent handwashing and use of alcohol, keeping distance when out of the house, and use of facial masks. The number of people who reported to continue going out normally represents less than 5% of the population, and hence, they did not appear in any rules, as the minimum support was set to 5%. However, we added this behavior to the diagram for completeness. Circles in a Venn diagram can overlap partially, overlap completely, or even be separate, letting one easily see the relationship between different groups of people with different sets of protective measures. From the diagram, only 45 (0.6%) and 56 (1.8%) individuals at T1 and T2, respectively, reported going out normally without taking any protective measures (frequent handwashing and use of alcohol, keeping distance when out of the house, and use of facial masks). Moreover, 9 (0.1%) and 4 (0.1%) individuals at T1 and T2, respectively, reported going out normally but taking all protective measures. Most individuals, 3711 (47.6%) at T1 and 1401 (45.8%) at T2, reported adopting all protective measures.

Figures 2 and 3 show the set of association rules generated from the data gathered in the first and second round of surveys, respectively, when considering people that took the 3 protective measures all together. The closed circle at the end of a sequence of answers indicates the end of a rule. From a total of 32,877 rules generated, considering all possible consequents, 11 (0.03%) included all the protective measures according to participants' answers in the first questionnaire (ie, the 3711, 47.6%, individuals in the intersection of the Venn diagram on the left in Figure 1) and 17 (0.03%) rules showed the same information for the 1401 (45.8%) participants of the second round in the shaded area representing all protective behaviors in the Venn diagram on the right in Figure 1. All rules in both figures had their confidence ranging from 0.681 to 0.736 and their lift in the (1.595,1.637) interval. These values indicated a high chance of 1 of the answers being associated with the next. Note that there were no patterns regarding the few people who were going out normally.

Reported fears included the economic struggle, fear of the disease, and fear of the potential to transmit it to their families.

**Figure 1.** A Brazilian profile (Venn diagrams) of adoption of human protection measures to prevent COVID-19 contamination and spread: frequency of people who (1) stay at least 1 m apart from people when out of the house; (2) sanitize hands with alcohol gel (70% ethyl alcohol) or wash hands for at least 20 seconds, whenever possible, when out of the house; (3) only leave home when extremely necessary and wearing a face covering; or (4) keep moving outdoors (leaving home) for work as usual. (A) COVID-19-preventive measures' profile at T1 (May-June 2020) (N=7802). (B) COVID-19-preventive profile at T2 (November 2020-January 2021) (N=3062). T1: timepoint 1; T2: timepoint 2.

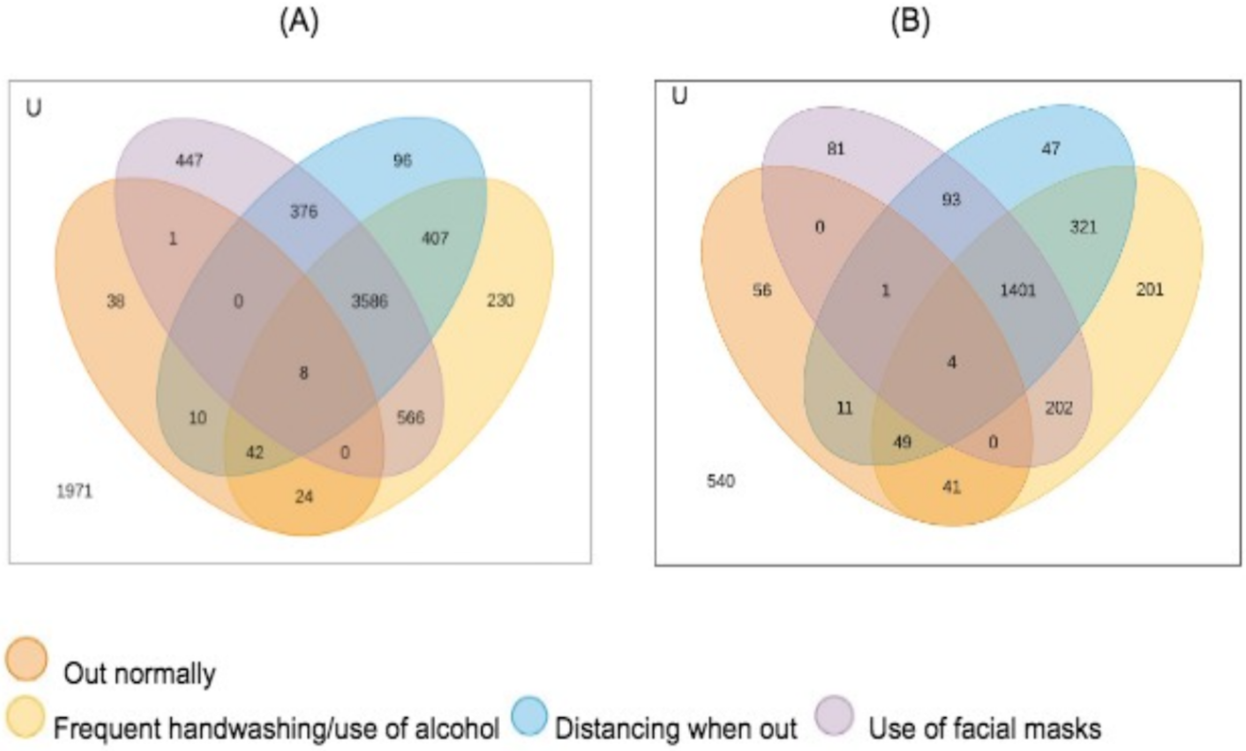


**Figure 2.** Rules generated considering the answers of people who took care of themselves in the first round of questionnaires.

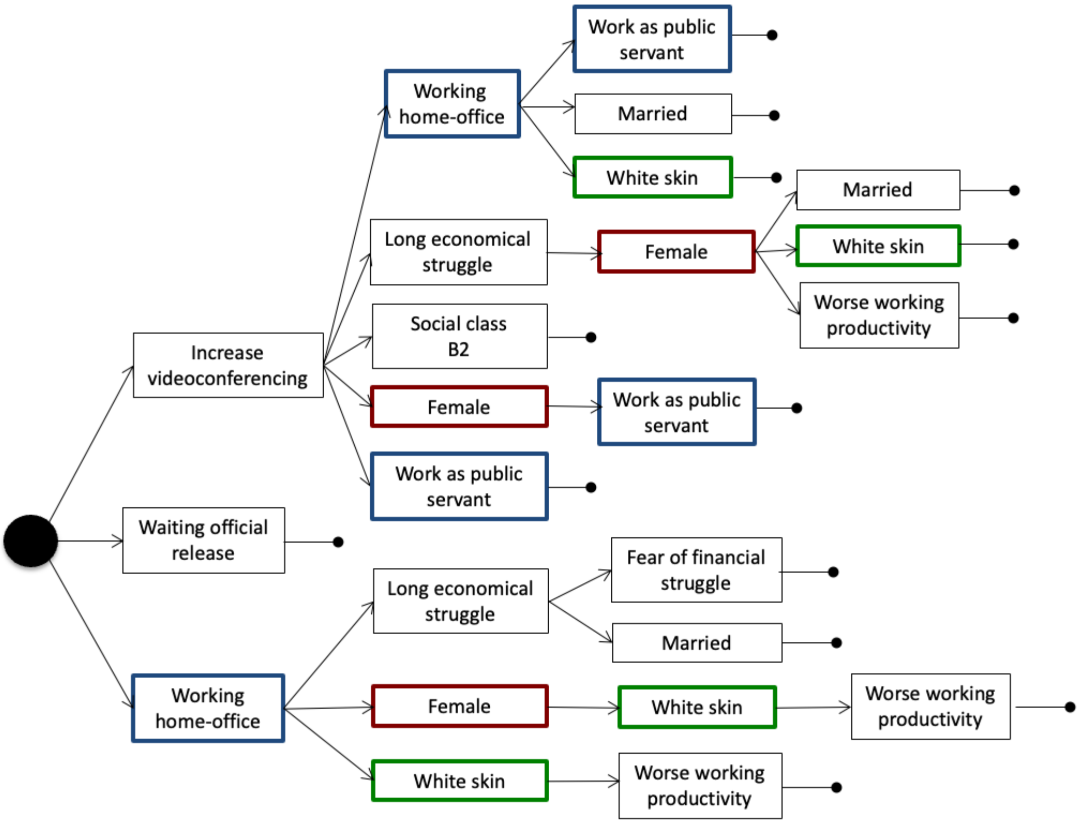
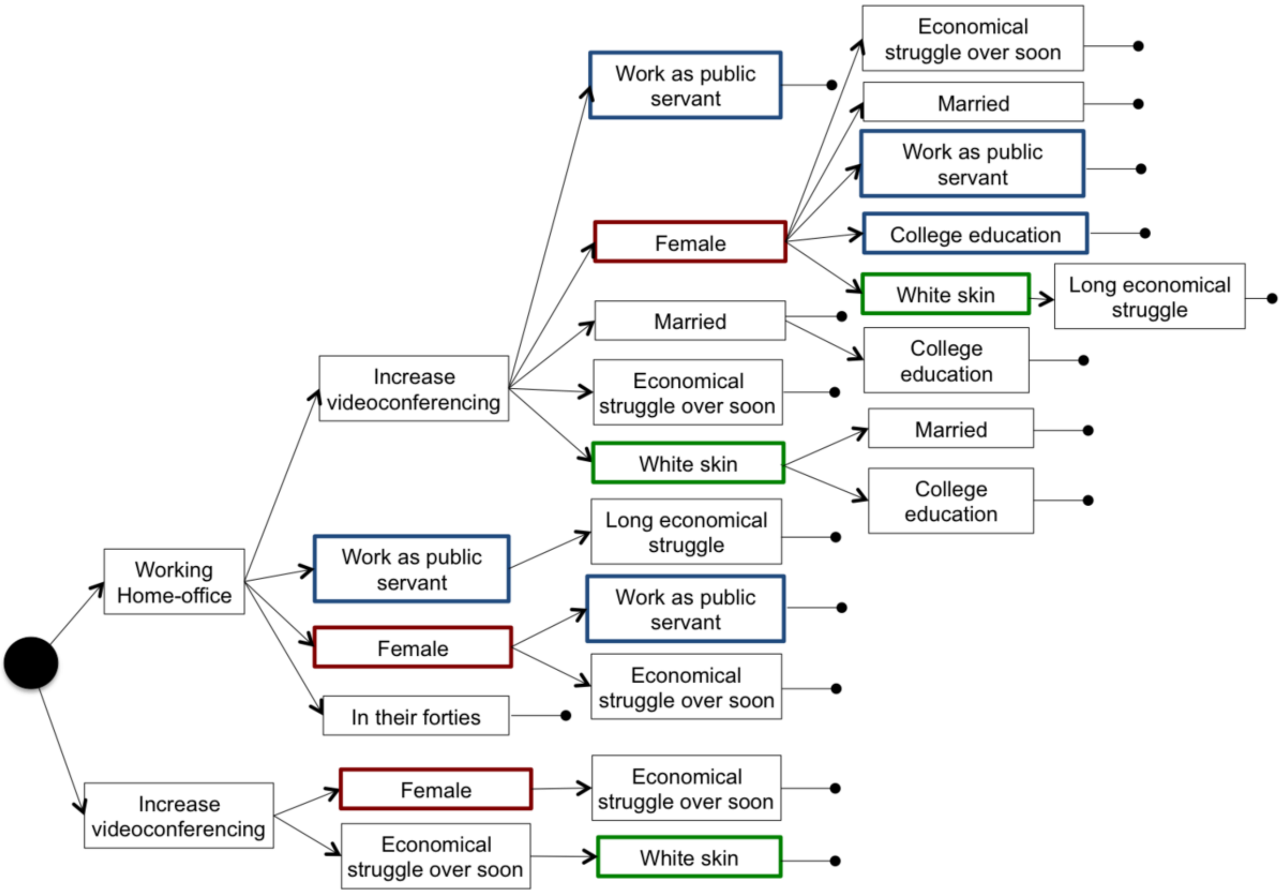


**Figure 3.** Rules generated considering the answers of people who took care of themselves in the second round of questionnaires.



## Discussion

### Principal Findings

To achieve the desired behavior for infection control (ie, extensive use of self-protective measures), increased use of videoconferencing and the possibility to work from home were present in all rules that explained better self-care behavior. The ability to change working conditions was combined with self-reports of being White, with a high educational profile and age around forties. A fear of economic struggle, in the short or the long term, composed many rules of preventive behavior. These findings might clarify hidden socioeconomic features associated with self-care measures. After 6 months, the rules were similar, and a feature related to work stability was evidenced: "being a public servant." Public servants in Brazil have tenure, and in many positions, they are allowed to perform their activities from home. These findings suggest that social distancing and self-care protection were implemented by those who were able to follow the stay-at-home policy, unveiling potential social disparities in health care.

The COVID-19 pandemic presented some particularities useful to help understanding the dissociation between the information given and the consequences of behavior. In Brazil, we observed a dissociation between the information given by health authorities and people's reactions in terms of individual and collective care [2]. It was not only a public health problem but also, on a large scale, an information crisis. In China, data from a 3-phase survey, collected during the first wave of COVID-19, showed low cooperation with prevention and control measures in the early stages, followed by a gradual increase as the pandemic progressed [22]. We aimed to understand the population's perception of the need for self-care and social distancing, considering the observed individual behavior and its consequences. We observed, in a large mental health online data set collected from May to June 2020, that a major part (75%) of the population reported being at home, believing in the potential severity of COVID-19, and trying to keep social distancing practices. Data was collected at 2 timepoints. In both, most of the assessed population did report using at least 2 self-care measures. Interestingly, the percentage of participants who followed the protective measures was almost the same in both periods, even with the significant increase in COVID-19 cases and deaths in Brazil. Most enrolled individuals reported not believing in information provided via the internet and conventional media (television and radio). However, they reported knowing how to protect themselves against COVID-19 and adopted self-care measures, showing that the information was reaching the target.

We did not focus only on short-term thinking about the current pandemic but also focused on social determinants of self-care behavior. Individuals with unfavorable economic, social, and environmental conditions have fewer buffers and suffer stronger consequences of cumulative stress [12]. In extreme situations, such as the pandemic, the presence of a social buffer can facilitate control and determine the individual risk for developing long-term mental health disorders. In a 2-month follow up of a Mexican population, financial and security situations did not change but increased the risk for distress [23]. So, social determinants might not only be important for compliance with preventive measures and minimize new cases but also be important to avoid long-term consequences of the pandemic. Behavioral changes can be influenced, for example, by economic rewards, boosting cooperation among people, and should be considered in designing more efficient public health policies.

Financial incentives to modify behavior are cost-effective and might induce quick responses [24]. Thus, using financial incentives or other extrinsic motivations might be a strategy for governments and private organizations to improve compliance with health measures in similar conditions [25]. Infrequent behaviors, such as those required in a pandemic or in a disaster, are good targets for financial incentives, but the use of extrinsic reward is also associated with lower self-motivation, and sustained behavior seems less impacted by the incentive [11]. It might be a cost-effective strategy, especially in middle- and low-income countries, where the response depends on what people have, rather than what they can have [11]. Although extrinsic motivators might be a game changer, there is a need to better understand the strategies to sustain wished behaviors. The Brazilian government initiated many strategies during the pandemic to minimize economic burden on small and midsize businesses and vulnerable individuals [2]. The impact of these aids needs to be better known to understand the impact of financial incentives on changing behavior; however, it has been a difficult population to reach using online strategies. For a while, with this data, we only observed the importance of work's stability and related features to follow self-protective care. Further studies on evaluation of interventions with extrinsic motivators are still necessary.

Information, misinformation, fake news, and disinformation coexist in social media [26], which generates confusion, making it harder to attribute credibility to information and to educate the population on necessary health policies. In this regard, one should consider Brazil's inequality [27]. With a Gini Index of 0.849, Brazil is the fifth country in the inequality rank. Wilkinson and Pickett [28] showed that trust levels are lower in countries and states where income differences are greater. Likewise, Frank [29] gathered data from the International Social Survey Program (ISSP), with 48,651 subjects from 33 countries, and participants indicated their level of agreement with the statement "There are only a few people I can completely trust." It was found that income inequality is correlated with country differences in trust ($r=-0.51$). Societies with low levels of trust may lack the ability to create the kind of social support and connections that promote health and successful aging [29]. Brazil specifically has remarkably low levels of social and interpersonal trust (5%)—in fact, 1 of the lowest in the world [30]. Since trust plays a key role in the creation of knowledge [31] and sustaining well-being outcomes, it is questionable whether the potential lack of trust among Brazilians also influences their trust in information disseminated by health organizations and had a significant impact on the spread of COVID-19 in the country.

Despite miscommunication and a lack of interpersonal trust, people reported awareness of self-protective measures [31].

Formal education affects a range of outcomes across life, such as adaptability to different standards, including switching to working from home, which was a common finding among those complying with protective measurements. It was a sample with a high educational profile, which certainly biased the responses and had an impact on the high adherence to self-care protection. In fact, people considered self-protected were those working from home and fearing the prospect of long-term impact and economic struggle.

In an unequal country, governmental financial aid to low-income families was essential to allow staying at home during the pandemic, as an act of solidarity emphasized by public health services as crucial for fighting COVID-19. Having people constantly present at work might potentially compromise contamination control. Thus, working from home seems to help mitigate the pandemic's impacts. Based on our data, governments should consider early and enough financial aid to promote adherence to health protective measures. In contrast, long and intermittent stay-at-home measures and a lack of mental health buffers might impair the well-being and health of children, adolescents, and adults. Working from home also had an impact on both mental and physical health [32]. Factors such as lack of communication with coworkers, distractions, children at home, and adjustment of working hours are factors that influence well-being related to home-office [32]. Considering the effect of working from home on mental health, it is possible that people decided to gradually return to the workplace regardless of known risks. Incentives to work from home must be coupled with the development of strategies to improve the well-being of those at home-office and their families. A long-term and multifactorial vision of the COVID-19 pandemic will be fundamental to evaluate and understand the ramifications of the social distancing strategies adopted worldwide.

## Limitations

Some constraints must be addressed. Besides having a representative sampling of the Brazilian population, we had underrepresentation in the lowest economic classes, which was particular for the data collection strategy based on online access. In our sampling, there was a clear bias of access to the internet and to the online survey. However, as the economic and social features prevail, it is reasonable to infer that the effects might be stronger in more vulnerable populations.

## Conclusion

Stable economic conditions and the possibility of working from home sound as an organizing social strategy to promote the use of self-care measures in a pandemic. The use of self-care protective measures is determined by social determinants that should be considered by policy makers.

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## Data Availability

De-identified participant data and a data dictionary will be made available under reasonable request to Prof. Malloy-Diniz.

## Authors' Contributions

GU, AML, and MARS were responsible for methodology, writing, analysis, and review; WM for methodology, writing, analysis, review, and supervision; AS and APdS for methodology, writing, analysis, review, and data curation; DdSC for conceptualization, data curation, review, and writing; LB, EAO, and AB for review; RG for writing and review; AGdS for funding acquisition, conceptualization, and review; LMD and DMM for methodology, writing, analysis, review, funding acquisition, conceptualization, and project administration; and GP for methodology, writing, analysis, review, investigation, visualization, and supervision.

## Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaires without copyright protection.

[XLSX File (Microsoft Excel File), 153 KB - publichealth_v8i6e34020_app1.xlsx ]

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## Abbreviations

**ICU:** intensive care unit
**T1:** timepoint 1
**T2:** timepoint 2

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Original Paper

# The Moderating Effect of Educational Background on the Efficacy of a Computer-Based Brief Intervention Addressing the Full Spectrum of Alcohol Use: Randomized Controlled Trial

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## Abstract

**Background:** The alcohol-attributable burden of disease is high among socially disadvantaged individuals. Interventional efforts intending to have a public health impact should also address the reduction of social inequalities due to alcohol.

**Objective:** The aim was to test the moderating role of educational background on the efficacy of a computer-based brief intervention addressing the full spectrum of alcohol use.

**Methods:** We recruited 1646 adults from the general population aged 18 to 64 years (920 women, 55.9%; mean age 31 years; 574 with less than 12 years of school education, 34.9%) who reported alcohol use in the past year. The participants were randomly assigned a brief alcohol intervention or to assessment only (participation rate, 66.9%, 1646/2463 eligible persons). Recruitment took place in a municipal registry office in one German city. All participants filled out a self-administered, tablet-based survey during the recruitment process and were assessed 3, 6, and 12 months later by study assistants via computer-assisted telephone interviews. The intervention consisted of 3 computer-generated and individualized feedback letters that were sent via mail at baseline, month 3, and month 6. The intervention was based on the transtheoretical model of behavior change and expert system software that generated the feedback letters automatically according to previously defined decision rules. The outcome was self-reported change in number of alcoholic drinks per week over 12 months. The moderator was school education according to highest general educational degree (less than 12 years of education vs 12 years or more). Covariates were sex, age, employment, smoking, and alcohol-related risk level.

**Results:** Latent growth modeling revealed that the intervention effect after 12 months was moderated by educational background (incidence rate ratio 1.38, 95% CI 1.08-1.76). Individuals with less than 12 years of school education increased their weekly alcohol use to a lesser extent when they received the intervention compared to assessment only (incidence rate ratio 1.30, 95% CI 1.05-1.62; Bayes factor 3.82). No difference was found between groups (incidence rate ratio 0.95, 95% CI 0.84-1.07; Bayes factor 0.30) among those with 12 or more years of school education.

**Conclusions:** The efficacy of an individualized brief alcohol intervention was moderated by the participants' educational background. Alcohol users with less than 12 years of school education benefited, whereas those with 12 or more years did not. People with lower levels of education might be more receptive to the behavior change mechanisms used by brief alcohol interventions. The intervention approach may support the reduction of health inequalities in the population at large if individuals with low or medium education can be reached.

**Trial Registration:** German Clinical Trials Register DRKS00014274; https://www.drks.de/DRKS00014274

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**KEYWORDS**

drinking; brief intervention; screening; school education; public health; prevention

## Introduction

Globally, alcohol use is one of the most important risk factors for impaired health [1]. The alcohol-attributable burden of disease has been found to be higher among those with low school education [2,3] or low socioeconomic status [4,5]. Furthermore, for a given amount of alcohol consumed, lower-educated groups have been found to experience disproportionately higher levels of alcohol-related harm, including alcohol-attributable mortality [6,7]. Although the underlying mechanisms of this relationship, commonly referred to as the alcohol harm paradox [8], are not yet fully understood [7,9], reducing social inequalities in alcohol-related harm can be regarded as a major public health concern [10].

Any interventional effort that intends to have a public health impact should address the reduction of social inequalities due to alcohol [11]. In the public health literature, the equity impact has proven to be a useful tool for operationalizing social gradients in intervention effects [12]. The equity impact of interventions can be positive if lower-educated groups are relatively more responsive to the intervention, neutral if the impact is the same for higher- and lower-educated groups, or negative if higher-educated groups are relatively more responsive to the intervention [12]. There is currently no convincing evidence on which types of population-based alcohol interventions, other than tax and price increases or availability restrictions, can reduce inequalities by educational background [13].

Brief alcohol interventions (BAIs) may be a tool to reduce alcohol consumption in populations with low levels of education. The umbrella term “BAI” includes interventions that aim at reducing alcohol-related harm by targeting people’s motivation to change their alcohol use [14]. BAIs have been proven efficacious in reducing alcohol use in primary care populations [15] and have the potential to produce effects in the population at large when disseminated as part of systematic screening [16,17]. Moreover, modern technologies enable the provision of computer-based BAIs to large numbers of recipients at low cost [18]. Although it is known that people with low education are less likely to take up an offered health behavior intervention [19,20], research on the moderating role of education in behavior change intervention effects is scarce [21]. Thus, the equity impact of BAIs warrants further study.

Promising but model-dependent findings from an individual patient data meta-analysis revealed that heavy drinkers with low education who received internet-based interventions had stronger reductions in alcohol consumption compared to more highly educated heavy drinkers [22]. Educational attainment has been found to moderate the strength of the relationship between health cognitions and health behavior [23]. Since health cognitions are a central target of the behavior change techniques in BAIs [24], the way people respond to BAIs might depend on their educational background.

Therefore, the aim of the present study was to shed light on the moderating role of educational background on the efficacy of a computer-based brief intervention addressing the full spectrum of alcohol use. The target group included all alcohol users, irrespective of their alcohol use severity. The rationale of the intervention was based on findings that alcohol consumption has linear dose-response relationships with cancer [25,26] and cardiovascular disease [27]. Thus, motivating a large group of people to maintain or reduce their alcohol use at low levels may produce beneficial public health effects. The intervention was evaluated in a randomized controlled trial using a general population sample [28]. An assessment-only control group was chosen as comparator because repeated assessments, which were necessary for the intervention, may already reduce alcohol consumption [29,30]. To be able to attribute potential effects to the intervention itself, research participation effects [31] had to be controlled for. Although there was no clear evidence for 12-month efficacy [32], intervention effects may vary by educational background.

## Methods

### Ethics Approval

The study was approved by the ethics committee of the University Medicine Greifswald, Germany (protocol number BB 147/15).

### Trial Description

This paper reports outcome data from the 2-armed, parallel-group randomized controlled trial “testing a proactive expert system intervention to prevent and to quit at-risk alcohol use” (PRINT). The study was prospectively registered at the German Clinical Trials Register (DRKS00014274; date of registration March 12, 2018). The corresponding study protocol [28], data on reach and retention [33], and primary outcome analyses [32] can be found elsewhere.

### Participants and Procedure

Between April and June 2018, trial participants were proactively recruited in the waiting area of the municipal registry office in Greifswald, Mecklenburg-West Pomerania, Germany. The registry office is the public authority in charge of registration, passports, and vehicle administration issues. During opening hours, study assistants approached all persons appearing in the waiting area. Those between the ages of 18 and 64 were invited to take part in a tablet-based, self-administered survey on health behaviors. Persons who were already approached during an earlier visit, were cognitively or physically incapable, had insufficient language or reading skills, or were employed at the conducting research institute were excluded.

The survey served as eligibility screening. Individuals who reported alcohol use in the past 12 months were invited to participate in the PRINT trial. Persons without a permanent address or telephone number were excluded. The study assistants informed the eligible individuals about the purpose, procedure, and data handling of the PRINT trial. All participants who gave their written informed consent were randomized to the intervention or assessment-only groups by the tablet computers, using simple randomization (with a 1:1 group allocation ratio) based on a random-number table and the individuals as units of randomization. The allocation sequence was concealed to the study assistants who carried out the recruitment.

The study assistants conducted computer-assisted telephone interviews after 3, 6, and 12 months. After 10 unsuccessful contact attempts, the participants received a questionnaire by email or postal mail, followed by up to 2 written reminders. Participants randomly assigned to the intervention group received computer-generated, individualized feedback letters by postal mail at baseline, month 3, and month 6. All participants received 2 vouchers worth €5 (US $5.34) each as compensation for their participation. One voucher was given out immediately after recruitment in the registry office and the other was sent via postal mail prior to the 12-month follow-up assessment. Participants remained blinded to their individual group assignment until they received the BAI or did not. The study assistants responsible for recruitment, telephone interviews, and management of participant data were blinded to the participants' group allocation.

## Intervention and Control Groups

The intervention consisted of up to 3 individualized feedback letters (at baseline, month 3, and month 6) based on the transtheoretical model of behavior change [34]. The intervention is described in more detail elsewhere [32]. The letters were generated automatically by expert system software [35], printed, and sent via postal mail. Feedback elements were chosen according to previously defined decision rules based on a participant's demographic and alcohol-related characteristics. The intervention was designed to address the full spectrum of alcohol use, from low-risk drinkers to participants with probable alcohol use disorder (AUD).

The feedback letters were tailored to the participants' current alcohol use risk level according to their scores on the Alcohol Use Disorders Identification Test (AUDIT) [36] and its consumption questions, AUDIT-Consumption (AUDIT-C) [37]. All feedback letters included information on recommendations for low-risk alcohol use, with the addendum that "low risk" does not equal "no risk," as well as written and graphical feedback on the amount of alcohol consumed in comparison to the individual norm group (ie, personalized normative feedback). Participants classified as at-risk drinkers received normative feedback on their motivational stage of change (precontemplation, contemplation, preparation, or action), decisional balance (perceived advantages and disadvantages of reducing alcohol use), self-efficacy, and processes of change [34]. Participants with AUD according to screening (AUDIT score ≥20) received slightly modified feedback that focused on the motivation to utilize professional treatment. Information on local alcohol treatment services was provided. Instead of the feedback given to the at-risk drinkers on the potential risk associated with their individual level of drinking, participants with probable AUD received feedback on symptoms they had already experienced according to the AUDIT. Feedback letters at months 3 and 6 included ipsative feedback delineating the individual development since baseline regarding actual behavior change and changes in motivational measures. The expert system used data gathered in the assessments to generate the feedback letters. Therefore, participating in the respective assessment was required to receive the intervention at that point in time.

The control group received assessment only; in other words, they answered the same tablet-based, self-administered baseline survey (Multimedia Appendix 1 and Multimedia Appendix 2) and computer-assisted telephone interviews at months 3, 6, and 12 as the intervention group.

## Measures

### Outcome

Change in the number of drinks per week from baseline to month 12 was the primary outcome. This measure was based on self-reported frequency (answering the question "How often did you have a drink containing alcohol in the past 30 days?") and quantity of alcohol use (answering the question "How many drinks did you have on a typical day when you were drinking?"). The definition of a standard alcoholic drink (0.25 L to 0.3 L beer, 0.1 L to 0.15 L wine or sparkling wine, or 4 cL spirits) was displayed on the tablet screen or read aloud by a study assistant during the interviews. To estimate the average number of drinks per week, frequency was multiplied by typical quantity, divided by 4.25 (ie, the average number of weeks in a month) and rounded down to the nearest integer.

### Moderator

Participants were asked to indicate their highest general educational degree at baseline. The response options were presented as an exhaustive list of possible school-leaving qualifications in Germany and equivalent foreign degrees, if applicable. The information provided was condensed into a categorical measure of educational background (low: 9 or less years of school education, medium: 10 to 11 years of school education, high: 12 or more years of school education). Due to the unequal distribution of educational background within the sample, the 2 former groups were combined to conduct the moderation analysis with sufficient statistical power. Thus, a binary indicator of educational background (less than 12 years vs 12 or more years of school education) was used. An additional moderation analysis with the 3-category indicator of educational background is reported as a sensitivity analysis in Multimedia Appendix 3.

### *Covariates*

Covariates were sex, age, employment status, smoking, and alcohol-related risk level. Participants were asked if they were female or male. Employment status encompassed full-time employment, part-time employment, being a student, unemployment, and other (being retired, a homemaker, or similar). Participants were asked to characterize their own smoking behavior (never, former, occasional, or daily smoking) and occasional and daily smokers were followed up with questions about typical frequency ("How many days per month do you smoke?") and quantity ("How many cigarettes or comparable tobacco products do you currently smoke on a day when you smoke?") of smoking. The average number of cigarettes consumed per day was derived as an indicator of smoking. Nonsmokers received a value of zero on that measure. Alcohol-related risk level (low-risk and at-risk) was measured via the AUDIT-C sum score, with sex-specific cut-off values (≥4 for women and ≥5 for men) indicating at-risk alcohol use [38].

## Sample Size Calculation

We hypothesized that there would be a 15% difference between the intervention group (8.5 drinks per week) and control group (10 drinks per week) at the 12-month follow-up. Calculations revealed that if the primary outcome followed a negative binomial distribution with a dispersion parameter of 1.0, 80% power, and 5% significance level, 659 participants per group would be required. With an expected dropout rate of 20%, a total sample size of N=1648 was planned.

## Statistical Analysis

Data were analyzed using latent growth curve modeling (LGM) in Mplus version 7. LGM is designed to analyze interindividual differences in intraindividual change over time. LGM is flexible in handling missing and nonnormally distributed data, as well as complex nonlinear growth trajectories [39]. Growth models were calculated with a full-information maximum likelihood estimator with robust standard errors using all available data (ie, including all baseline participants) assuming that data were missing at random. Thus, all analyses followed an intention-to-treat principle. Due to the positive skewness of the outcome, negative binomial models were calculated. Latent growth factors represented the change in number of alcoholic drinks per week. Rescaled likelihood ratio tests indicated that the model benefited from including higher-order functions (quadratic and cubic), allowing for nonlinear growth over time. Growth factor variances were estimated freely (except for the cubic growth factor). All models were adjusted by time-invariant covariates (sex, age, employment status, and smoking at baseline) and time-variant covariates (alcohol-related risk level at baseline and months 3, 6, and 12).

Study group, educational background, and their interaction were regressed on the growth factors to test if participants with less than 12 years versus 12 or more years of school education showed differential intervention effects. Differences between the intervention and control groups, as well as the interaction effect with educational background, were given as incidence rate ratios (IRRs) with the 95% CI. Additionally, the Bayes factor (BF) was calculated to estimate the sensitivity of the evidence for intervention effects after 12 months among the 2 subgroups [40]. Using the online Dienes calculator [41], the population value was assumed to follow a half-normal distribution for an expected intervention effect of 15%. BF values lower than 0.33 indicated evidence for lack of an effect, values above 3 evidence for the presence of an effect, and values in between indicated data insensitivity [42].

# Results

## Sample Characteristics

In total, 6645 registry office clients appeared in the waiting area during our recruitment period (Figure 1). Of 3969 clients meeting the inclusion criteria, 2947 (74.3%) completed the PRINT eligibility screening for alcohol use in the previous 12 months. Of 2462 eligible clients, 1646 (66.9%) consented to participate in the trial. Of those 1646 participants, 1406 (85.4%) and 1335 (81.1%) participated in the assessments after 3 and 6 months, respectively. For the 12-month follow-up assessment, 1314 of 1646 (79.8%) participants were reached. The sample (920 women of 1646 participants, 55.9%) had a mean age of 31.0 (SD 10.8) years. Regarding educational background, 574 of 1646 participants (34.9%) had less than 12 years of school education (Table 1).

**Figure 1.** Flow of participants through the trial.

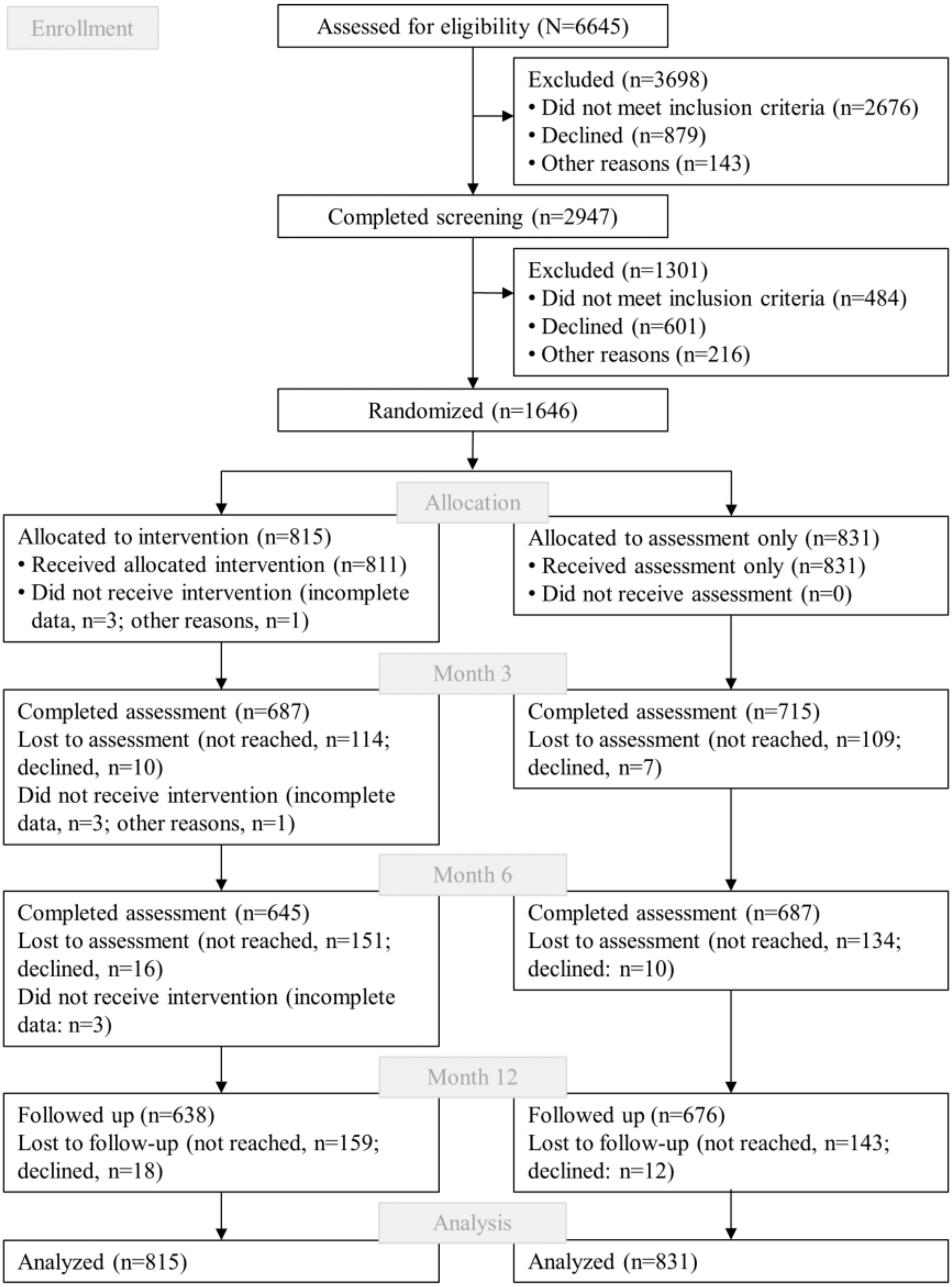

**Table 1.** Baseline study sample characteristics.

| Characteristics | Total sample, N=1646 | Less than 12 years of school education, n=574 | Twelve or more years of school education, n=1072 |
|---|---|---|---|
| Women, n (%) | 920 (55.9) | 300 (52.3) | 620 (57.8) |
| Age, mean (SD) years | 31.0 (10.8) | 35.0 (12) | 28.9 (9.5) |
| **School education, n (%)** | | | |
| ≤9 years | 101 (6.1) | 101 (17.6) | N/A[a] |
| 10 to 11 years | 473 (28.7) | 473 (82.4) | N/A |
| ≥12 years | 1072 (65.1) | N/A | 1072 (100) |
| **Employment status, n (%)** | | | |
| Employed full-time | 689 (41.9) | 333 (58) | 356 (33.2) |
| Employed part-time | 358 (21.7) | 97 (16.9) | 261 (24.4) |
| Student | 444 (27) | 34 (5.9) | 410 (38.2) |
| Unemployed | 53 (3.2) | 41 (7.1) | 12 (1.1) |
| Other | 102 (6.2) | 69 (12) | 33 (3.1) |
| Cigarettes per day, mean (SD) | 3.0 (6.2) | 6.0 (8.2) | 1.4 (4) |
| **Alcohol risk level, n (%)** | | | |
| Low-risk alcohol use | 1085 (65.9) | 423 (73.7) | 662 (61.8) |
| At-risk alcohol use | 561 (34.1) | 151 (26.3) | 410 (38.2) |
| Drinks per week, mean (SD) | 2.2 (3.9) | 1.8 (4.1) | 2.4 (3.9) |
| **Study group, n (%)** | | | |
| Intervention group | 815 (49.5) | 300 (52.3) | 515 (48) |
| Control group | 831 (50.5) | 274 (47.7) | 557 (52) |

[a] N/A: not applicable.

## Moderation Analysis

Participants with 12 or more years of school education who received the BAI increased their weekly alcohol use from 2.3 (SD 3.6) alcoholic standard drinks at baseline to 2.7 (SD 4.5) drinks at month 12 (Figure 2). BAI group participants with less than 12 years of school education reported 1.8 (SD 3.7) drinks at baseline and 1.9 (SD 3.6) drinks at month 12. Control group participants with 12 or more years of school education increased their weekly alcohol use from 2.4 (SD 4.1) drinks at baseline to 2.8 (SD 5.6) drinks at month 12. An increase was also observed in control group participants with less than 12 years of school education, who reported an average of 1.8 (SD 4.5) drinks at baseline and 2.3 (SD 4.1) drinks at month 12.

There was an intervention effect after 12 months in participants with less than 12 years of school education (IRR 1.30, 95% CI 1.05-1.62; BF [0, 0.14] 3.82), but not among participants with 12 or more years of school education (IRR 0.95, 95% CI 0.84-1.07; BF [0, 0.14] 0.30). Figure 3 illustrates the intervention effects as IRRs over time, with the shaded areas indicating 95% CI. Participants with less than 12 years of school education were significantly more likely to benefit from the intervention after 12 months compared to participants with 12 or more years of school education (IRR 1.38, 95% CI 1.08-1.76; *P*=.03) (Table 2). There was no significant interaction effect during the active intervention phase, either at month 3 (IRR 1.24, 95% CI 0.96-1.61; *P*=.44) or at month 6 (IRR 1.11, 95% CI 0.88-1.40; *P*=.17).

The results of an additional moderation analysis with a 3-category indicator of educational background (low: 9 or less years of school education, medium: 10 to 11 years of school education, high: 12 or more years of school education) can be found in Multimedia Appendix 3.

**Figure 2.** Observed change in number of drinks per week from baseline to month 12 in participants with less than 12 years and 12 or more years of school education. A: less than 12 years of school education; B: 12 or more years of school education; M: mean; BAI: brief alcohol intervention.

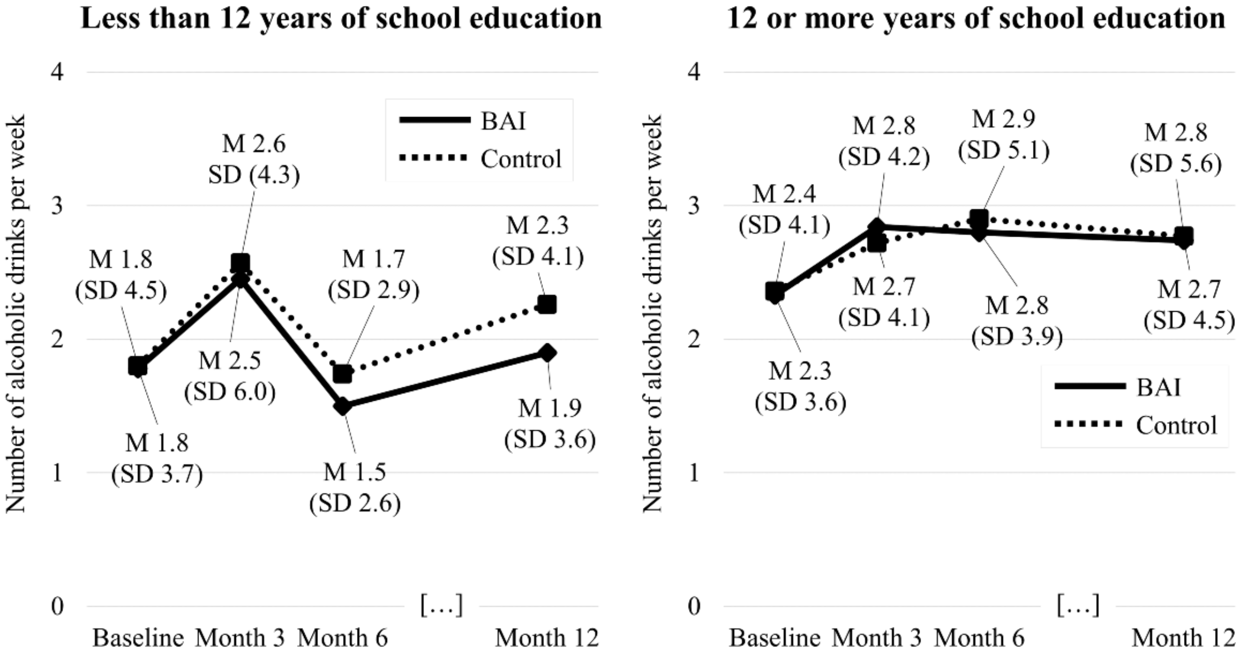

**Figure 3.** Intervention effect (compared to assessment only) for participants with less than 12 years and 12 or more years of school education. BAI: brief alcohol intervention; IRR: incidence rate ratio.

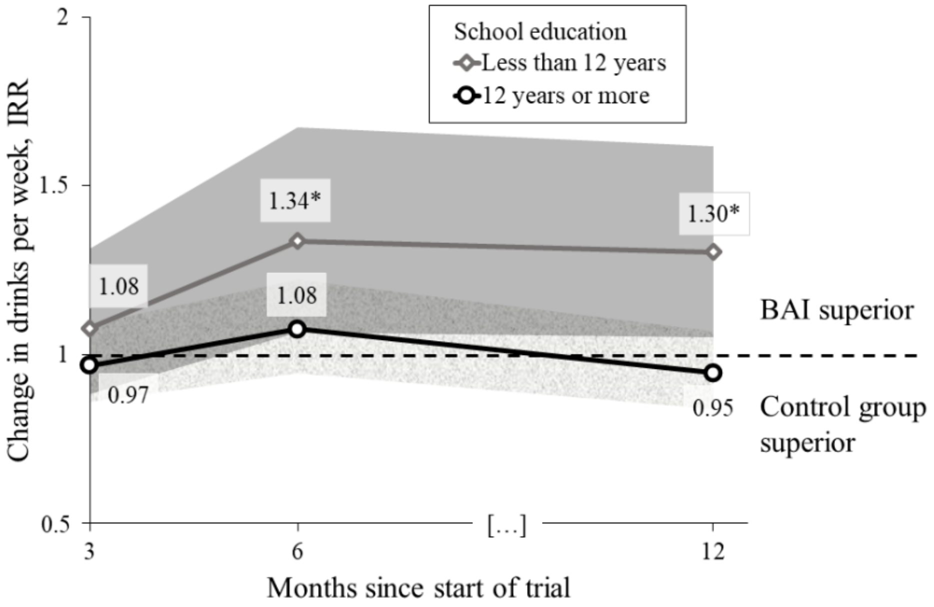

**Table 2.** Intervention effects over 12 months were moderated by educational background[a].

| Time points | Difference between intervention and control group, incidence rate ratio (95% CI) | | |
|---|---|---|---|
| | Less than 12 years of school education | Twelve or more years of school education | Interaction effect |
| **Active intervention phase** | | | |
| Month 3 | 1.08 (0.88-1.32) | 0.97 (0.86-1.09) | 1.11 (0.88-1.40) |
| Month 6 | 1.34 (1.07-1.68) | 1.08 (0.95-1.22) | 1.24 (0.96-1.61) |
| Follow-up (month 12) | 1.30 (1.05-1.62) | 0.95 (0.84-1.07) | 1.38 (1.08-1.76) |

[a] Latent growth model (N=1646) with higher-order growth factors for negative binomial distributed outcome data. The outcome was net change in number of alcoholic drinks per week. The model was adjusted for sex, age, employment status, smoking, and alcohol-related risk level. Incidence rate ratios with 95% CI are displayed.

# Discussion

## Principal Findings

The efficacy of a computer-based BAI addressing the full spectrum of alcohol use was moderated by educational background. After 12 months, alcohol users from the general population with lower school education benefited from the intervention, whereas those with higher school education did not. These findings allow the presumption that BAIs might be able to support the reduction of social inequalities due to alcohol. The present study showed that an individualized BAI based on expert system software was effective among study participants with lower school education.

## Comparison With Prior Work

To our knowledge, this is the first study to investigate the efficacy of a BAI in general population subgroups with different educational backgrounds. Previous studies focused mainly on other treatment moderators, such as sex, age, and consumption-related variables [43-46], but neglected school education as a potential moderator. Comparable evidence comes from a recent meta-analysis whose findings supported the notion that internet-based interventions may be particularly beneficial for heavy drinkers with a low educational background [22]. In contrast, a technology-based intervention targeting heavy drinking was found to be more effective for highly educated adolescents in Switzerland, compared to less-educated adolescents [47]. Notwithstanding these findings, the interaction of school education and BAI efficacy is not yet well understood [21]. This study contributes to the sparse literature by showing that a BAI based on expert system software is effective among alcohol users with low and medium education.

People with a lower educational background might be more receptive to the behavior change mechanisms included in BAIs. Underestimating one’s alcohol use relative to others (ie, normative misperception) has been found to be more pronounced among less-educated alcohol users [48]. If normative misperceptions precede and encourage alcohol use [49], correcting this fallacy by means of personalized normative feedback might reduce alcohol use over time [50], in particular among individuals who are more prone to believe that others drink more frequently and consume more alcohol than themselves. Personalized normative feedback was a central component of the intervention tested in this study [32]. Individuals with different educational backgrounds might have responded differently to this personalized normative feedback, possibly explaining the interaction between educational background and intervention efficacy. Feedback that compares alcohol use between an an individual and their peer group might have a stronger motivating effect to reduce drinking in people with less than 12 years of school education than in those with 12 or more years of school education. Moreover, less-educated individuals might have to justify their alcohol use more often and be denied autonomy over their alcohol use more often. The BAI was designed to incorporate the spirit of motivational interviewing [51] by being centered on the participants’ own point of view and valuing their motives and attitudes regarding their alcohol use. Feedback was provided in an appreciative manner, such as by pointing out the subjective advantages and disadvantages of the participants’ alcohol use. This experience of appreciation might have been more motivating for less-educated compared to higher-educated individuals.

The findings speak in favor of the view that population-based BAIs might have a positive equity impact. Addressing the alcohol harm paradox is a major public health issue [10]. BAIs might be a piece of the puzzle on the path to reducing social inequality due to alcohol if (a) they are disseminated with a systematic screening approach and (b) they reach a substantial part of the population with low school education. However, it is known that lower-educated individuals are less likely to take up an offered intervention [19,20], as was the case in the PRINT trial [33]. The percentage of participants who received the complete intervention, consisting of all 3 feedback letters, was higher among those with high (413/515, 80%) education than those with low or medium education (202/300, 67%). The latter were also more difficult to reach for the telephone interviews that were needed to deliver the intervention. Therefore, strategies need to be focused on how people with a lower educational background can be reached and retained for alcohol prevention. Settings may be chosen where less-educated individuals can be reached, such as job centers [52] or primary health care clinics [53], and are best combined with a proactive approach [54].

The intervention effect after 12 months was small in magnitude, possibly because the study was not restricted to at-risk alcohol users but targeted the full spectrum of alcohol use. Thus, the initial drinking level was lower than in previous BAI trials [15], resulting in a smaller margin for reduction in alcohol consumption. It must be acknowledged that it remains unclear if BAIs will diminish social inequalities in alcohol-attributable harm by addressing alcohol use per se. Consumption-related factors may not be sufficient to explain the alcohol harm paradox [55]. Rather, a more holistic view is needed, taking into account interactions with other health behaviors [8] and social risk factors such as deprivation [56].

## Limitations

This study has several strengths and limitations. The findings add to the sparse evidence on educational background as a moderator of BAI efficacy. High participation and retention rates in a general population sample ensured external validity. The intervention approach was novel, as it addressed the full spectrum of alcohol use, not only in at-risk drinkers. The limitations were 4-fold. First, selection bias was likely, since baseline factors such as alcohol-related risk level are associated with trial participation [33]. Second, all data were completely self-reported. Third, the main outcome was measured with a quantity-frequency approach that might have underestimated the true amount of alcohol consumed [57]. Fourth, this was a secondary data analysis. The PRINT trial was not designed or powered to scrutinize how the intervention worked in subgroups with different educational backgrounds. As lower-educated people were underrepresented in our sample, comparing more than 2 subgroups resulted in a loss of statistical power, wider confidence intervals, and data insensitivity for differential efficacy (additional moderation analysis is shown in Multimedia Appendix 3).

## Conclusions

The present study provided insight into the role of educational background in BAI efficacy in the general population. Future research might investigate the circumstances under which the expected positive equity impact of BAIs can be maximized. The intervention approach might be able to reduce health inequalities due to alcohol in the population at large if people with low or medium education can be reached.

## Acknowledgments

AS drafted the manuscript. AS and SB managed data collection, developed the research question, and performed the data analysis. SB designed the study and acquired funding. AS, JFA, CM, UJ, GB, and SB were involved in the interpretation of data and in critically revising the work for important intellectual content. All authors read and approved the final manuscript. The study was funded by the German Research Foundation (BA 5858/2–1, BA 5858/2–3), which had no influence on design, analysis, or interpretation of the data. This manuscript received Open Access Funding by the Publication Fund of Technische Universität Dresden. We thank all participants for their participation, the study assistants for data collection and management, and Christian Goeze for software programming.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
German questionnaire.
[PDF File (Adobe PDF File), 211 KB - publichealth_v8i6e33345_app1.pdf ]

Multimedia Appendix 2
English questionnaire.
[PDF File (Adobe PDF File), 209 KB - publichealth_v8i6e33345_app2.pdf ]

Multimedia Appendix 3
Additional moderation analysis.
[PDF File (Adobe PDF File), 151 KB - publichealth_v8i6e33345_app3.pdf ]

Multimedia Appendix 4
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 363 KB - publichealth_v8i6e33345_app4.pdf ]

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## Abbreviations

**AUD:** alcohol use disorder
**AUDIT:** Alcohol Use Disorders Identification Test
**AUDIT-C:** Alcohol Use Disorders Identification Test-Consumption
**BAI:** brief alcohol intervention
**IRR:** incidence rate ratio
**LGM:** latent growth curve modeling
**PRINT:** proactive expert system intervention to prevent and to quit at-risk alcohol use

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Original Paper

# User- and Message-Level Correlates of Endorsement and Engagement for HIV-Related Messages on Twitter: Cross-sectional Study

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## Abstract

**Background:** Youth and young adults continue to experience high rates of HIV and are also frequent users of social media. Social media platforms such as Twitter can bolster efforts to promote HIV prevention for these individuals, and while HIV-related messages exist on Twitter, little is known about the impact or reach of these messages for this population.

**Objective:** This study aims to address this gap in the literature by identifying user and message characteristics that are associated with tweet endorsement (favorited) and engagement (retweeted) among youth and young men (aged 13-24 years).

**Methods:** In a secondary analysis of data from a study of HIV-related messages posted by young men on Twitter, we used model selection techniques to examine user and tweet-level factors associated with tweet endorsement and engagement.

**Results:** Tweets from personal user accounts garnered greater endorsement and engagement than tweets from institutional users (aOR 3.27, 95% CI 2.75-3.89; *P*<.001). High follower count was associated with increased endorsement and engagement (aOR 1.05, 95% CI 1.04-1.06; *P*<.001); tweets that discussed STIs garnered lower endorsement and engagement (aOR 0.59, 95% CI 0.47-1.74; *P*<.001).

**Conclusions:** Findings suggest practitioners should partner with youth to design and disseminate HIV prevention messages on social media, incorporate content that resonates with youth audiences, and work to challenge stigma and foster social norms conducive to open conversation about sex, sexuality, and health.

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**KEYWORDS**

HIV prevention; social media; public health; young adults; LASSO; HIV; Twitter; digital health

## Introduction

Despite advances in prevention, the incidence of HIV among youth and young adults in the United States is a continued public health concern. From 2010-2016, adolescents and young adults experienced the highest rates of HIV infection relative to other age groups, with estimates suggesting that the number of individuals living with undiagnosed HIV infection is disproportionately greater within these populations [1]. By the end of 2016, an estimated 50,900 youth were living with HIV [2], yet nearly half (44%) were unaware of their HIV status [3]. These estimates are bolstered by findings that youth and young adults achieve low rates of HIV testing [4]. Moreover, youth and young adults are the least likely of any age group to be linked to HIV care once diagnosed [3] and face unique challenges related to accessing preventative health services [5]. The Ending the HIV Epidemic in the United States initiative highlights the need to expand HIV testing and strengthen linkage to treatment and prevention for populations highly impacted by HIV, including youth and young adults [6].

Social media platforms present unique opportunities for influencing health beliefs and behaviors among users. Such platforms are exceptionally popular among youth and young adult populations; more than 90% of young adults (aged 18-29 years) report having ever used at least one social media platform or messaging app, such as YouTube, Facebook, or Instagram [7], and in recent years, a third or more of teens and young adults reported Twitter use [8]. Young people use Twitter to both engage in conversation within established social networks and communicate with larger audiences [9]. In particular, there is evidence that young people use Twitter as a platform for discussing topics related to sex and health [10-12], creating opportunities for sharing resources and information.

There is substantial evidence that social media use among youth correlates with health outcomes; this research demonstrates both positive and negative health effects among media users [13]. Exposure to alcohol and smoking-related content on social media is correlated with greater self-reported use of alcohol and tobacco products [14,15], highlighting the negative repercussions of media use. However, research has also shown that exposure to sexual health messages on social media is associated with sexual risk reduction behaviors [16], nutrition behavior interventions using social media are linked to increased fruit and vegetable consumption [17], and use of social networking sites for sexual minority youth are associated with positive mental health outcomes.

Media discourse surrounding health topics can play an instrumental role in health-relevant beliefs and behaviors. The dissemination of health-relevant information, during routine exposure to mass media or through purposeful intervention, has been shown to influence health outcomes across a range of behaviors [18]. More specifically, these effects are evident in the domain of HIV/AIDS-related behavior, with evidence that exposure to HIV prevention campaigns through mass media leads to increases in HIV knowledge and greater use of condoms [19]. Social media can fill a similar role in the dissemination of health-related messages, and there is emerging evidence of the impact of social media on HIV-related outcomes [20,21]. Media effects are contingent on message exposure [22], without which audiences cannot receive and process message content. Theories of communication suggest that in addition to message content features, the characteristics of a message source (eg, sender) can influence the extent to which audiences attend to and engage with the message [22], a prerequisite for persuasion and ultimate behavior change [23,24]. Thus, message-consistent outcomes are linked with the extent to which individuals are exposed to a given message and the distinct features of the message source and content.

Previous research suggests that characteristics of message content on social media platforms are related to engagement with health-related messages, including HIV prevention messages [25-27]. This research has suggested that messages with practical information and supportive messages tend to garner greater engagement. The impact of messenger, or message source, on engagement with health messages has also been explored. One study found that messages originating from health-related organizations garnered greater engagement compared to messages from individuals, while messages from non–health-related organized garnered less engagement [25]. Another study found that while health experts were active in producing HIV-related content on Twitter, engagement with these messages was greatest when retweeted by a non–health expert celebrity [28]. Despite the growing interest in the role of social media in health messaging, little research has examined the characteristics of HIV-related social media messages as they relate to youth engagement with such media. To address this gap in the literature, this study aims to explore how user-level characteristics (eg, age, user type, friend count, and follower count) and tweet-level characteristics (eg, format, timing, geolocation, and content) are associated with tweet engagement with and endorsement of Twitter messages posted by adolescent and young adult men in the United States.

## Methods

### Data Description

This study is an expanded analysis of data collected as part of Virus 2 Viral, a study of Twitter message content among young men in the United States [20]. For the Virus 2 Viral study, researchers collected a random sample of tweets from the Twitter fire hose application programming interface (API) posted between January 1, 2016, and December 31, 2016. They filtered this sample to include only users of predicted male gender and predicted age 13 to 24 years (N=336,000 users) using established procedures [29]. For this study, we then expanded the original set of tweets by collecting full timelines (ie, the entire collection of tweets posted by a given user from 2009 to 2017) for those users identified in Virus 2 Viral. The subsequent procedures used to produce the final dataset mirror those described by Stevens et al [20], using this expanded set of tweets. We briefly describe these procedures below.

The initial corpus of tweets was then subset to include only those with HIV-relevant content. HIV-relevant content was identified using a keyword list of HIV-related terms (eg, terms related to HIV, AIDS, HIV testing, condoms, multiple sexual partners, sexually transmitted infections [STIs], sexual risk behavior, and preexposure prophylaxis [PrEP]), developed in partnership with youth researchers. This process generated a dataset of 24,388 tweets that had been posted between 2009 and 2017 and were grouped into 3 broad categories: HIV prevention-specific tweets (n=5057), general sex-related tweets (n=19,319), and risk behavior–promoting tweets (n=12). To retain tweets most relevant to HIV risk and prevention while reducing this data set to a more manageable size, we included the full sample of prevention-related tweets and risk behavior–promoting tweets and a random sample of general sex-related tweets (3091/19,319, 16.0%). This yielded a final data set of 8160 tweets from 1541 unique users that were then coded by a team of 4 research assistants (intraclass correlation coefficient at .80 or higher on all constructs) for message content and used for analysis. User type was determined based on a manual review of the user profile and recent postings of each user in the data set by a member of the research team and was recorded as either individual (eg, a personal account of an individual) or institutional (eg, public health agencies, social service organizations, or advocacy groups). User types that were ambiguous or could otherwise not be determined by the researcher were recorded as missing and were removed from the data set (n=150). The final analytic sample included 8010 tweets from 1499 unique users. A full description of the methods used for the parent study has been published elsewhere [20].

## Ethics Approval

The University of Pennsylvania institutional review board reviewed this study and designated it exempt because the study (protocol #827833) does not meet the definition of human subject research.

## Measure

### *Endorsement and Engagement*

Two different binary variables were used to measure the outcomes of tweet endorsement and engagement. A tweet was classified as endorsed if it received at least 1 favorite from another user (1=endorsement, 0=no endorsement) and as engaged if it was retweeted at least once (1=engagement, 0=no engagement).

### *User Characteristics*

Number of friends and followers were extracted for each user from the API. Predicted age was estimated using a previously validated machine learning algorithm that predicts user age from characteristics of that user's messages [29]. User type, determined by manual review of the user profile as described above, was recorded as either individual or institutional.

### *Tweet Characteristics*

Tweet language was extracted directly from the API and was coded as a binary variable (1=English, 0=other language). Time of tweet posting was collapsed into 3 categories: daytime for tweets posted between 9 AM and 5 PM EST, evening for tweets posted between 5 PM and midnight EST, and night for tweets posted between midnight and 9 AM EST. The geographic location from which a tweet was posted was measured using tweet-specific latitude/longitude coordinates when available and the self-reported location information in Twitter user profiles otherwise. Tweet locations were then collapsed into a variable to represent region, corresponding with the 4 US Census regions (Northeast, Midwest, South, and West). A tweet was identified as a reply if it was directed at another user using the "@user" syntax (1=reply, 0=not reply). Tweet length was calculated based on the number of characters in the tweet, including "@user" syntax, if present.

### *Tweet Content*

The content of a tweet was qualitatively coded by 4 research assistants and consisted of 19 nonexclusive binary variables corresponding to various aspects of the tweet's content. These categories are anti–risk-taking; condoms; HIV testing; HIV/AIDS; humor; lesbian, gay, bisexual, transgender, or queer; misinformation; modeling; multiple partners; norms; PrEP; pro–risk-taking; research, education, news; stigma; STIs; substance use; transactional sex; unprotected sex; and unrelated sexual content. Full details of the procedures used in the parent study for coding tweet content have been published elsewhere [20].

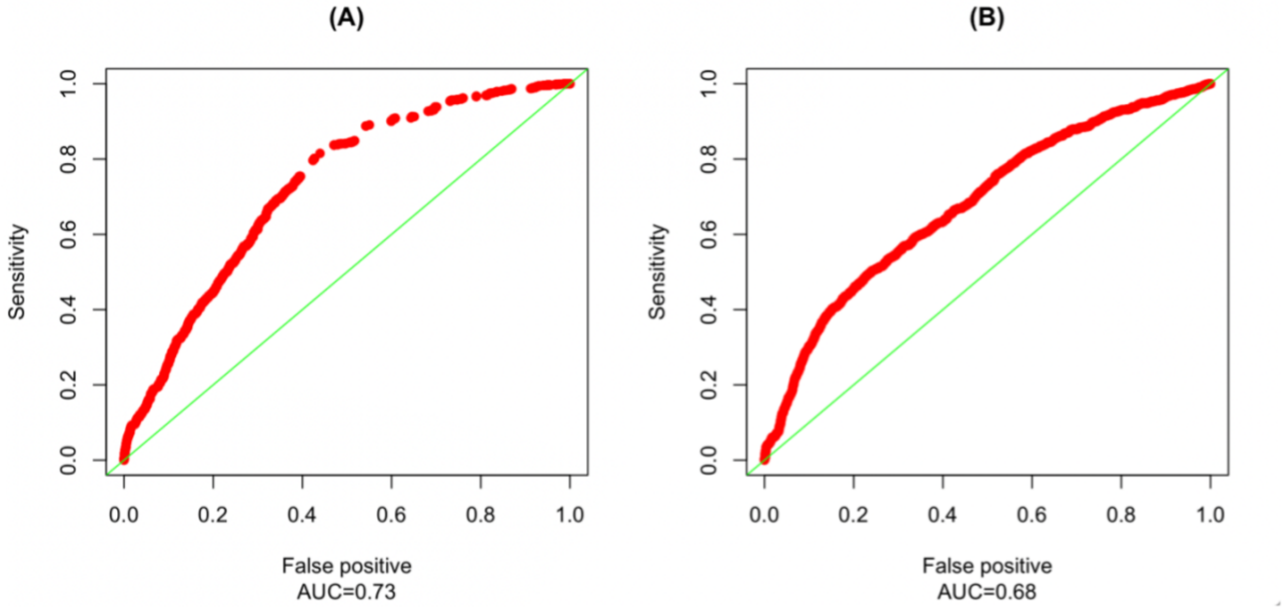
## Statistical Analysis

A series of logistic regression models were estimated to assess the influence of user-level and tweet-level characteristics on 2 discrete response variables: endorsement and engagement. We used least absolute shrinkage and selection operator (LASSO) as a model building technique. LASSO is a form of penalized regression that forces the regression coefficients of less important variables to zero, yielding models that have fewer variables and higher predictive accuracy [30].

As LASSO regression coefficients are biased and cannot be easily interpreted, we used an extension of this technique known as relaxed LASSO, which sequentially combines the LASSO method for initial model selection with multiple logistic regression for nonpenalized coefficient estimation [31]. Therefore, separate multiple logistic regression models were built for each outcome using the LASSO-selected variables. Final model selection was performed using a backward elimination procedure that only retained predictors statistically significant at the level of .05. From the final multiple logistic models, we estimated adjusted odds ratios (aORs) of predictors of interests while controlling for the effects of covariates. Statistical significance was assessed using *P* values from the Wald chi-square test. All analyses were conducted using the glmnet package [32] in R statistical software (R Foundation for Statistical Computing).

Finally, to evaluate the overall prediction accuracy of models, we plotted receiver operating curves (ROCs) and calculated the area under the curve (AUCs) [33]. The ROCs, presented in Figure 1, display the relationship between the false positive rate (the proportion of tweets incorrectly classified as endorsed or engaged) and true positive rate (the proportion of tweets correctly classified as endorsed or engaged; also known as sensitivity) of the classifier for all possible thresholds [34], with higher AUC values indicating better predictive power of the model. In other words, each point on the ROC curves indicates the false positive rate and true positive rate of the classifier at a given threshold. ROC curves and AUC are convenient tools to evaluate the performance (accuracy) of the classifier [34]. If the ROC curves were plotted close to the top left corner, this would indicate that the model was able to correctly classify endorsed or engaged tweets with any thresholds at a low false positive rate (AUC would be close to 1). Conversely, if the model could not accurately predict tweet endorsement or engagement (effectively generating random predictions), the ROC curve would be a diagonal line (ie, AUC=0.5).

**Figure 1.** Receiver operating curve and area under the curve for models predicting tweet endorsement (A) and engagement (B).



## Results

### User and Tweet Descriptive Statistics

Table 1 summarizes the descriptive statistics for user and tweet characteristics in the study sample. The mean predicted age of users was 18.72 (SD 3.08) years, with approximately half (4096/8010, 51.1%) identified as institutional users. Number of friends and number of followers were positively skewed. The median number of friends was 435 (IQR 273-800), compared with a mean of 822. The number of followers showed similar patterns, with a median of 591, IQR of 241 to 1179, and mean of 2005 followers. Although the mean number of followers was 2005, most tweets (6008/8010, 75.0%) came from users with fewer than 1179 followers. This difference was due to a small number of users with extremely high numbers of followers. Over half of all tweets (4411/8010, 55.1%) were posted during the daytime, while 26.8% (2146/8010) were posted in the evening and 18.1% (1453/8010) were posted at night. The average tweet length was 94 (SD 31.88) characters with a slight skewness toward longer messages. About 12.0% (959/8010) of tweets were categorized as replies to other users. With respect to tweet content, the most common message categories were HIV/AIDS (4438/8010, 55.4%); research, education, and news (3667/8010, 45.8%); unrelated sexual content (2314/8010, 28.9%); and anti–risk-taking (1208/8010, 15.1%); see Multimedia Appendix 1 for the frequency of each message category. Out of the tweets in the sample, 25.6% (2049/8010) were endorsed and 18.0% (1438/8010) garnered engagement.

**Table 1.** Descriptive statistics for user-level and message-level characteristics (n=8010).

| | Value |
|---|---|
| **Institution, n (%)** | |
| Yes | 4096 (51.14) |
| No | 3914 (48.86) |
| **Location of post, n (%)** | |
| Midwest | 663 (8.28) |
| Northeast | 2962 (36.98) |
| South | 2014 (25.14) |
| West | 2371 (29.60) |
| **Message language, n (%)** | |
| English | 7976 (99.58) |
| Not English | 34 (0.42) |
| **Reply, n (%)** | |
| Yes | 959 (11.97) |
| No | 7051 (88.03) |
| **Time of post, n (%)** | |
| Daytime (9 AM to 5 PM) | 4411 (55.07) |
| Evening (5 PM to midnight) | 2146 (26.79) |
| Night (midnight to 9 AM) | 1453 (18.14) |
| **Year of post, n (%)** | |
| 2009 | 30 (0.37) |
| 2010 | 6 (0.07) |
| 2011 | 62 (0.77) |
| 2012 | 62 (0.77) |
| 2013 | 158 (1.97) |
| 2014 | 346 (4.32) |
| 2015 | 1174 (14.66) |
| 2016 | 2472 (30.86) |
| 2017 | 3700 (46.19) |
| **Endorsement, n (%)** | |
| Yes | 2049 (25.58) |
| No | 5961 (74.42) |
| **Engagement, n (%)** | |
| Yes | 1438 (17.95) |
| No | 6572 (82.05) |
| Age[a] (years), median (IQR) | 18.72 (17.13-21.64) |
| Follower count, median (IQR) | 591 (241-1179) |
| Friend count, median (IQR) | 435 (273-800) |
| Message length, median (IQR) | 94 (71-121) |

[a] Age is a predicted age, computed based on tweet and user characteristics using machine learning algorithms developed by Sap et al [29].

## Factors Associated With Tweet Endorsement and Engagement

For each outcome of interest (tweet endorsement and tweet engagement), we estimated logistic regression models using LASSO-selected predictors and assessed overall model performance by plotting ROCs and measuring AUCs. We note that the initial model included all the variables (excluding the outcomes) listed in Table 1 and Multimedia Appendix 1 as predictors.

### *Endorsement*

The final model (score test $\chi^2_6$: 884.65) for the outcome of tweet endorsement was a 6-variable model, which included the following predictors: number of followers; region; year of tweet posted; user type; STI message content; and research, education, and news message content. As demonstrated in Figure 1, this model had an AUC of 0.73, suggesting acceptable performance [35].

As shown in Table 2, both user-level and tweet-level characteristics were significantly associated with tweet endorsement. With respect to user-level characteristics, the odds of a tweet being endorsed were 3.27 higher for tweets from personal user accounts compared with institutional users (aOR 3.27, 95% CI 2.75-3.89; *P*<.001), and each additional 100 followers that a user had was associated with a 0.53% increase in the odds that their tweet was endorsed (aOR 1.01, 95% CI 1.00-1.01; *P*<.001). User region was also significantly associated with endorsement. Regarding tweet-level characteristics, tweets discussing specific STIs had 41% lower odds of being endorsed, relative to tweets that did not discuss STIs (aOR 0.59, 95% CI 0.47-1.74; *P*<.001). Additionally, tweets that included discussion of research, education, or news related to HIV had 23% lower odds of being endorsed, compared with tweets that discussed HIV in a different context (aOR 0.77, 95% CI 0.65-0.92; *P*<.001). Year of posting was also significantly associated with endorsement.

**Table 2.** Summary of logistic regression analysis for variables predicting endorsement and engagement of Twitter users (n=8010).

| Predictor | Endorsement, aOR[a] (95% CI) | Engagement, aOR (95% CI) |
|---|---|---|
| **User level** | | |
| Age | —[b] | 0.92 (0.90-0.94) |
| Follower count (100 counts) | 1.01 (1.00-1.01) | 1.01 (1.00-1.01) |
| Personal user count | 3.27 (2.75-3.89) | 1.77 (1.52-2.05) |
| **Tweet level** | | |
| **Region[c]** | | |
| Northeast | 1.46 (1.31-1.99) | 1.69 (1.32-2.15) |
| South | 0.85 (0.82-1.25) | 1.16 (0.91-1.48) |
| West | 1.06 (0.71-1.08) | 0.68 (0.53-0.88) |
| **Time[d]** | | |
| Night | — | 1.08 (0.90-1.31) |
| Daytime | — | 1.36 (1.17-1.59) |
| Message length (10 words) | — | 1.04 (1.02-1.06) |
| Reply | — | 0.45 (0.36-0.57) |
| Year | 1.30 (1.23-1.38) | — |
| Message: norm | — | 1.62 (1.15-2.29) |
| Message: research, education, news | 0.77 (0.65-0.92) | — |
| Message: STI | 0.59 (0.47-0.74) | 0.61 (0.47-0.78) |

[a] aOR: adjusted odds ratio.

[b] Not applicable.

[c] Reference group: Midwest.

[d] Reference group: evening.

### *Engagement*

The final model (score test $\chi^2_9$: 404.89) for the outcome of tweet engagement included the following 9 predictors: predicted user age, number of followers, user type, tweet length, reply tweet (@user), time of post, region, norms message content, and STI message content. As demonstrated in Figure 1, the 9-variable model showed an AUC of 0.68, performing slightly below the acceptable threshold of 0.70 [35].

As shown in Table 2, both user-level and tweet-level characteristics were significantly associated with tweet engagement. For each additional year in the user's predicted age, the odds of a tweet garnering engagement decreased by 8% (aOR 0.92, 95% CI 0.90-0.94; *P*<.001). Additionally, tweets from personal user accounts (compared with institutional users) had 77% greater odds of garnering engagement (aOR 1.77, 95% CI 1.52-2.05; *P*<.001). Each additional 100 followers was associated with a 0.51% increase in the odds of a tweet garnering engagement (aOR 1.01, 95% CI 1.00-1.01; *P*<.001). Tweets that were replies (@user) were 55% less likely to garner engagement from other users (aOR 0.45, 95% CI 0.36-0.57; *P*<.001). User region was also significantly associated with engagement. Regarding tweet-level characteristics, tweets that discussed STIs had 39% lower odds of garnering engagement compared to tweets that did not discuss STIs (aOR 0.61, 95% CI 0.47-0.78; *P*<.001). Tweets that included discussion of social norms were 62% more likely to garner engagement compared with tweets that did not discuss social norms (aOR 1.62, 95% CI 1.15-2.29; *P*<.001). Tweet length and time of posting were also significantly associated with engagement.

## Discussion

### Principal Findings

This study was designed to assess the relationships between user-level and tweet-level characteristics and endorsement and engagement of tweets related to HIV risk and prevention posted by young men. Our analysis demonstrated that characteristics both of users and of the tweets themselves were associated with tweet endorsement and engagement. Given that fostering active interaction with media content around HIV prevention is a critical component of a public health social media strategy [36], these results have important implications for HIV prevention efforts.

We found that tweets from personal accounts were 3 times more likely to be endorsed, and 75% more likely to garner engagement, when compared with institutional users. This finding suggests that message source is an important factor in how HIV-related tweets are received and that HIV-relevant messages from institutional users may not resonate as strongly with youth. Previous research has shown that while institutional sources of online HIV information may be perceived as more credible, the experiences of peers may be more influential in shaping attitudes and self-efficacy to change behaviors [37]. Public health messaging efforts around HIV prevention should acknowledge these findings when considering how to use resources related to online communication; using institutional accounts to post messages to social media platforms may not result in meaningful engagement from youth. Thus, promoting peer-to-peer discussions of HIV-related topics through social media interventions may have greater potential to influence the attitudes and behaviors of youth [38]. However, it is important to note that although institutional tweets were not often retweeted or favorited, it is possible that they were still read by many users and the information was communicated as intended.

Results demonstrated that users with many followers were more likely to garner tweet endorsement and engagement relative to users with fewer followers; each additional 100 followers were associated with a 0.5% increase in the odds of both endorsement and engagement. This is not a surprising finding, given that having more followers increases one’s opportunity for tweet exposure, thereby increasing the likelihood that a given tweet is endorsed or elicits engagement. We did not find any association between users’ number of friends and endorsement or engagement, which suggests that having a robust following on Twitter may be more important than being highly connected to other users through friendship. Users with large followings may be celebrities or social media influencers, or simply perceived as such, and their position of influence could be leveraged to increase visibility of HIV prevention messages. However, considering the highly skewed distribution of followers in this data set, the relationship between the odds of endorsement or engagement and the follower count may not tell the whole story. Users may be more likely to engage with the messages from microinfluencers (eg, an influential user with fewer than 10,000 followers) than from celebrity influencers (eg, an influential user with more than 10,000 followers) due to feeling a closer sense of connection with these microinfluencers [39]; however, additional research on these relationships is warranted. These distinctions aside, influencers are well positioned to reach a large audience on Twitter and could be an important component of public health campaigns or other messaging efforts that use social media to engage with young people [40,41].

The findings from this study have implications for the implementation of popular opinion leader (POL) interventions. POL interventions aim to identify, enlist, and train key opinion leaders in a community to promote health behaviors and challenge risky social norms [42]. These leaders act as early adopters of behavior change and can serve as models and supports for peers who are considering making similar changes. Our results demonstrate that, in addition to such characteristics as the quality and originality of message content, users on social media with large numbers of followers may be positioned to garner significant engagement with their messages, thus making them good candidates as opinion leaders [43]. Future intervention development should seek ways to integrate the principles of POL into interventions related to HIV prevention through online social media.

Findings also demonstrated that the content of messages on Twitter was related to tweet endorsement and engagement. Tweets that mentioned STIs garnered decreased endorsement and decreased engagement, and tweets that were primarily focused on research, education, or news showed lower levels of endorsement. However, tweets that reflected social norms (an opinion about how oneself or others behave or should behave) garnered higher levels of engagement, suggesting that young people are eager to participate in conversations about the perceived behaviors of peers or evaluations of those behaviors. These results have important implications for efforts to develop health communication tools for HIV prevention. Stigma surrounding HIV and STIs may stifle conversations about sexual health, in light of evidence that young people tend to distance themselves from direct discussion of these issues in settings that are not sufficiently anonymous or confidential [44]. Furthermore, tweets that highlight research, education, or news about sexual health may not resonate with young people, leading to low rates of endorsement. Health communication around

HIV prevention must balance an acknowledgment of this stigma without further reinforcing it. Rather than avoid direct discussion of issues related to HIV prevention, public health educational efforts should embed these discussions in the larger context of sex and sexuality and connect these discussions to the social realities that young people live in (ie, acknowledging and/or challenging social norms).

Additional characteristics of messages were found to be associated with endorsement, engagement, or both. Users with greater predicted age showed lower odds of garnering engagement, which may reflect differences in platform use between adolescents and young adults. Variations in endorsement and engagement were seen by geographic region, with messages originating from the Northeast of the United States receiving the greatest levels of endorsement and engagement, mirroring the geographic distribution of Twitter activity that has been seen in previous studies [45]. Longer tweets received greater engagement, a finding that has been described in previous studies [28]. Previous studies have shown that engagement with messages on Twitter varies across the day and according to message content [46]. The variation in message engagement seen in our study, where engagement was highest for messages posted during the day and lowest during the evening, highlights the need to consider time of posting for public health messages. Replies garnered low engagement in our study, suggesting that dialogues between users about HIV do not stimulate engagement from young people. Finally messages posted during later years in the study received greater endorsement, likely reflecting a growth in the popularity of the platform over the study period.

Public health efforts to incorporate social media messaging into HIV prevention approaches will require novel strategies around message creation, delivery, and evaluation. The use of language and style that leverages the cultural elements of social media, such as incorporating memes and sharable elements into message content, may resonate more effectively with young people than appeals based solely on facts and knowledge [41]. Future research should aim to collect additional information about tweets, including qualitative codes related to themes beyond HIV prevention (eg, presence of a meme, celebrity reference), that may correlate more strongly with tweet engagement and endorsement. Furthermore, the use of POL techniques could help to overcome and challenge stigma around sexual health, allowing information about HIV prevention to be visible on social media platforms.

## Limitations

This study is subject to several notable limitations. First, our outcomes of tweet endorsement and engagement capture active interactions with social media content, not passive exposure to tweet content. Young people may be hesitant to endorse messages related to sex and sexual health because of stigma or embarrassment but may still be reading these messages anonymously [47]. However, data on tweet views are difficult to obtain, and research may be limited to measures of endorsement and engagement similar to ours. Second, there were several users who contributed a very large number of tweets (eg, one user accounted for 949 tweets) in this data set, raising concerns about the independence of observations. While capturing highly active and widely followed Twitter accounts is important to this line of work, future analyses should consider models that account for clustering of errors at the user level. Third, it is important to note that our models for tweet endorsement and tweet engagement showed only a modest capacity to discriminate between tweets that evinced the outcome and tweets that did not (acceptable discrimination for endorsement and slightly less than acceptable discrimination for engagement). While our study suggests that user and tweet-level characteristics have measurable associations with tweet endorsement and engagement, further work is needed to identify additional characteristics of users and tweets that might strengthen predictive modeling for endorsement and engagement with HIV-related messages on Twitter. Finally, it should also be noted that messages analyzed in this study were limited to Twitter messages geolocated to the United States. The patterns seen in our study may not be generalizable to social media messages on other platforms or in other countries.

## Conclusions

The widespread use of social media platforms among young people offers new opportunities for communication around HIV prevention. Conversations about sex and sexual health are widespread across these platforms, providing an opportunity for public health messaging to play a role in these conversations. Efforts to engage with young people on these sensitive and often stigmatized topics will require innovative strategies to foster meaningful connection with HIV prevention messages. Public health practitioners should partner with young people to design and disseminate these messages, incorporate content that resonates with youth audiences, and work to challenge stigma and foster social norms conducive to open and honest conversation about sex, sexuality, and health.

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## Authors' Contributions

All authors contributed to the study conception and design. Data collection and curation were performed by JO, SB, BS, and RS. Formal analysis was performed by JO. Funding acquisition and supervision/oversight was provided by RS. The first draft of the manuscript was written by JO, SB, ECK, and BS. All authors reviewed and edited previous versions of the manuscript and have read and approved the final manuscript.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
Qualitatively coded message frequency table (N=8010).
[DOCX File , 18 KB - publichealth_v8i6e32718_app1.docx ]

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## Abbreviations

**aOR:** adjusted odds ratio
**API:** application programming interface
**AUC:** area under the ROC curve
**LASSO:** least absolute shrinkage and selection operator
**POL:** popular opinion leader
**PrEP:** preexposure prophylaxis
**ROC:** receive operating curve
**STI:** sexually transmitted infection

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Original Paper

# Strengthening the Merci Mon Héros Campaign Through Adaptive Management: Application of Social Listening Methodology

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## Abstract

**Background:** Between 2014 and 2018, the penetration of smartphones in sub-Saharan Africa increased from 10% to 30%, enabling increased access to the internet, Facebook, Twitter, Pinterest, and YouTube. These platforms engage users in multidirectional communication and provide public health programs with the tools to inform and engage diverse audiences on a range of public health issues, as well as monitor opinions and behaviors on health topics.

**Objective:** This paper details the process used by the U.S. Agency for International Development–funded Breakthrough RESEARCH to apply social media monitoring and social listening techniques in Burkina Faso, Côte d'Ivoire, Niger, and Togo for the adaptive management of the Merci Mon Héros campaign. We documented how these approaches were applied and how the lessons learned can be used to support future public health communication campaigns.

**Methods:** The process involved 6 steps: (1) ensure there is a sufficient volume of topic-specific web-based conversation in the target countries; (2) develop measures to monitor the campaign's social media strategy; (3) identify search terms to assess campaign and related conversations; (4) quantitatively assess campaign audience demographics, campaign reach, and engagement through social media monitoring; (5) qualitatively assess audience attitudes, opinions, and behaviors and understand conversation context through social media listening; and (6) adapt campaign content and approach based on the analysis of social media data.

**Results:** We analyzed posts across social media platforms from November 2019 to October 2020 based on identified key search terms related to family planning, reproductive health, menstruation, sexual activity, and gender. Based on the quantitative and qualitative assessments in steps 4 and 5, there were several adaptive shifts in the campaign's content and approach, of which the following 3 shifts are highlighted. (1) Social media monitoring identified that the Facebook campaign fans were primarily male, which prompted the campaign to target calls to action to the male audience already following the campaign and shift marketing approaches to increase the proportion of female followers. (2) Shorter videos had a higher chance of being viewed in their entirety. In response to this, the campaign shortened video lengths and created screenshot teasers to promote videos. (3) The most negative sentiment related to the campaign videos was associated with beliefs against premarital sex. In response to this finding, the campaign included videos and Facebook Live sessions with religious leaders who promoted talking openly with young people to support intergenerational discussion about reproductive health.

**Conclusions:** Prior to launching health campaigns, programs should test the most relevant social media platforms and their limitations. Inherent biases to internet and social media access are important challenges, and ethical considerations around data privacy must continue to guide the advances in this technology's use for research. However, social listening and social media monitoring can be powerful monitoring and evaluation tools that can be used to aid the adaptive management of health campaigns that engage populations who have a digital presence.

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**KEYWORDS**

social media; health communication; young people; reproductive health

## Introduction

In 2020, there were an estimated 3.8 billion social media users worldwide and approximately 5.2 billion smartphone users [1]. Between 2014 and 2018, the penetration of smartphones in sub-Saharan Africa increased from 10% to 30%, enabling increased access to the internet [2]. Although internet penetration is lower in low- and middle-income countries (LMIC) than high-income countries, those in LMIC who have access to the internet through any devices are more likely to network using social media platforms [3]. Facebook, Twitter, Pinterest, and YouTube are the dominant social media platforms in most of francophone West Africa [4]. These platforms engage users in multidirectional communication and provide public health programs with the tools to inform and engage diverse audiences on a wide range of public health issues, as well as monitor opinions and behaviors on health topics [5,6]. Public health campaigns routinely include social media advertisements, create fan pages, and promote conversations on social media around campaign topics [7]. However, it is only in the last decade that evidence on the use of social media for health behavioral change campaigns has emerged in the literature for LMIC [8], with the focus primarily on reducing tobacco use [9], supporting patients undergoing HIV treatment [10], influencing sexual health behaviors [11], and influencing behaviors related to infectious diseases such as malaria [12]. Among the few studies focusing on adolescent sexual and reproductive health (SRH) behaviors, most address the acceptability of using social media to interact with young people and do not assess the extent to which social media campaigns have reached their intended audience and influenced health behaviors [13,14]. Studies using social listening techniques in LMIC have only recently emerged due to the relevance of these tools to monitor the COVID-19–related infodemic [15].

Adolescent pregnancy remains a major contributor to maternal and child mortality and intergenerational cycles of ill-health and poverty [16]. West and Central Africa have the highest annual adolescent birth rate in the world at 129 live births per 1000 young women aged 15-19 years, and the lowest use of modern contraception among all women at 16% [17,18]. Merci Mon Héros (MMH), or “Thank You My Hero” in French, is a multimedia campaign codeveloped and implemented by youth activists and the U.S. Agency for International Development (USAID)–funded West Africa Breakthrough ACTION (WABA) projects. WABA is a regional, USAID-funded initiative aiming to increase the coordination and effectiveness of social and behavioral change interventions in 4 priority countries: Burkina Faso, Côte d’Ivoire, Niger, and Togo. The MMH campaign is designed for youth and adults, with the aim of promoting an environment conducive to young people’s informed, voluntary family planning (FP) and reproductive health (RH) service access in francophone West Africa. The youth-led campaign videos (described in Table 1) and other content such as quizzes, concerts, and recorded conversations are disseminated via social media platforms, including Facebook, Instagram, Twitter, and YouTube, as well as through more traditional channels, such as television, radio, community activities, and others.

The USAID-funded Breakthrough RESEARCH project, in partnership with M&C Saatchi, collaborated with WABA to apply social listening and social media monitoring as part of a multimethod adaptive management and impact evaluation strategy of the MMH campaign. Social media monitoring refers to quantitatively tracking mentions and comments on social media regarding a specific topic, whereas social listening allows public health campaigns to better understand the context of web-based interactions by qualitatively tracking and analyzing conversation content [19].

This paper details the process of applying social media monitoring and social listening for the adaptive management of the MMH campaign in 4 countries: Burkina Faso, Côte d’Ivoire, Niger, and Togo. We documented how social media monitoring and social listening were applied to inform the MMH campaign and how the lessons learned can be used to support future public health campaigns.

**Table 1.** A sample of Merci Mon Héros campaign videos and Facebook Live events analyzed.

| Video | Primary message |
|---|---|
| Gracian | • Talk about sexuality with young people, without shame, from an early age so they can engage in healthy sexual and reproductive health behaviors |
| Camara | • Prepare young women for puberty and menarche with accurate information<br>• Talk to young people about sexual and reproductive health |
| Florence | • Young people need to know how to protect themselves<br>• Use a condom during sex to avoid the risk of sexually transmitted infections such as HIV |
| Mariette | • Girls need to be informed and educated about menstruation so they can prepare themselves psychologically and manage periods effectively |
| Serge | • Talk with youth about life goals and priorities so they can make reproductive health and family planning choices accordingly |
| Fanta | • Provide accurate information to young people about sexual and reproductive health and the onset of menstruation |
| Oury | • Inform youth about family planning options to avoid unintended pregnancy, and support rather than shame youth in the event of an unplanned pregnancy |
| Kouamé | • Encourage young people to visit a health provider to learn more about contraceptive methods and choosing one that is right for them |
| Sedjro | • Partner communication about family planning is important, and family planning decision-making should be shared |
| Mme Camara | • Contraceptive methods can help plan pregnancies<br>• Select or switch family planning methods as needed according to your current needs and priorities |
| Aichatou | • Parents should speak openly with young people about sexual and reproductive health, regardless of the parent’s or child’s sex or gender |
| Facebook Live events | • Female puberty<br>• Male puberty<br>• The menstrual cycle and calculating the fertile window |

# Methods

## Applying Social Listening to the MMH Campaign

The process of applying social media monitoring and social listening to the MMH campaign involved 6 steps: (1) ensure there is a sufficient volume of topic-specific web-based conversation in your target countries; (2) develop measures to monitor the campaign social media strategy; (3) identify search terms to assess campaign and related conversations; (4) quantitatively assess campaign audience demographics, campaign reach, and engagement through social media monitoring; (5) qualitatively assess audience attitudes, opinions, and behaviors and understand conversation context through social media listening; and (6) adapt campaign content and approach based on the analysis of social media data. Data requirements, procedures, considerations, and illustrative results are described under each step of the outlined process.

## Ethics Approval

This study obtained exempted status from the Population Council Institutional Review Board (EX2019011).

### Step 1: Ensure There Is a Sufficient Volume of Topic-Specific Web-Based Conversation in Your Target Countries

When starting any social listening exercise, it is necessary to first establish whether there is a sufficient volume of conversation to analyze. Typically, this is done by conducting a quick exploratory search of web-based content using a select group of keywords. This search string can be enhanced at a later point (see step 3)—at this point the purpose is simply to ensure that conversation does exist. There is no expected benchmark for the volume of posts, as this will vary substantially based on topic and review period. Broadening search terms if a limited volume of conversation is found may be useful for exploratory purposes. However, as the search string is honed and rules are defined, the sample of relevant posts will be reduced. If social listening is used to assess changes in web-based conversation before and after an intervention, nonexistent or limited content can still serve as a baseline measure.

### Step 2: Develop Measures to Monitor the Campaign Social Media Strategy

The MMH campaign was designed to create “surround sound” coverage through multiple channels and reach its 2 priority audiences—young people aged <24 years and adults aged ≥25 years who support and interact with them—in different ways. The goal of sharing content through social media channels was to leverage this space to normalize the habit of talking about youth SRH and contraception needs and empower young people to share their own stories and seek the information that would help them make informed, voluntary FP choices for their future. A team of young campaign designers from francophone Africa provided input into the channel selection. Facebook, Instagram, and YouTube were selected because they were considered the social media platforms most used by young people in the region. Throughout the campaign, Facebook was the most consistently used platform by MMH audiences, and as such, the web-based campaign strategy was largely developed with Facebook's format in mind (ie, short videos, quizzes, static images, frequency of posts, and livestreams). Twitter was included in the web-based strategy to reach relevant organizations and decision-makers. To contribute to MMH's "brand" on the internet and with an aim of being enveloped into existing web-based SRH conversations, the campaign created 2 hashtags—#MerciMonHéros and #BrisezLesTabous ("break taboos" in French)—and complementary topical (eg, hashtag #sexualité) and video-specific (eg, hashtag #Héros2Mariette) hashtags for each of the first 5 campaign videos.

We identified conversation volume as a key indicator to track changes over the time for topic-specific social media posts and comments related to FP, RH, and other relevant subtopics such as puberty and menstruation. Key indicators were also selected to help us track social media users' interaction with the campaign. Table 2 defines the 4 indicators identified at the start of the campaign to assess progress: conversation volume, reach, engagement, and views.

**Table 2.** Social media indicators.

| Indicator | Definition |
|---|---|
| Conversation volume | The number of social media posts pertaining to a specific topic (ie, menstruation, etc). |
| Reach | The number of screens that viewed the MMH[a] videos. |
| Engagement | The number of times people engaged with MMH posts through reactions, comments, shares, retweets, mentions, and likes. Engagement can occur through paid promotion or when social media users organically find the campaign content. |
| Views | The number of MMH video views of at least 30 seconds, where each video is at least 2 minutes long. |

[a]MMH: Merci Mon Héros.

### Step 3: Identify Search Terms to Assess Campaign and Related Conversations

To analyze social media content thematically, we defined search terms to identify social media conversations related to the campaign's topics of interest. The Breakthrough RESEARCH team developed a set of relevant keywords to capture conversations about behaviors supporting young people's conversations about and access to FP and RH services. The keywords included but were not limited to first sex, condoms, contraception, menstruation, and pregnancy, etc. These keywords were then shared with local youth stakeholders through Breakthrough ACTION to ensure we captured not only the correct usage in the local French language but also any known slang versions. These translated and context-specific search terms were entered into a Boolean search string—a type of search that allows users to combine or exclude keywords—designed to identify conversations across social media that were most relevant to the selected search terms. We used Crimson Hexagon's BrightView algorithm for text analysis software to analyze social media data [20]. The Crimson Hexagon software searched all public-facing social media for relevant conversations, including mentions from the Facebook campaign page, Twitter, social newsfeeds, blogs, forums, Reddit, Tumblr, and YouTube. Privacy limitations relating to Facebook and Instagram only allow a very limited number of posts to be included in the analysis beyond the Facebook campaign page. We collected social media content from October 2018 to October 2019 (baseline) and from November 2019 to January 2021 (initial campaign implementation period). Given that certain keywords generate a sizeable volume of irrelevant conversation, we used 2 techniques to minimize irrelevant conversation. By filtering our search and tying the keywords of interest to pronouns (eg, "I," "my," "his," and "her," etc), a substantial volume of irrelevant noise was cleaned from the results, ensuring the sample contained posts more suitable for qualitative analysis. In addition, we used machine learning technology to train the software to reduce irrelevant content by training our algorithm to classify a selection of social posts into key topic areas. Once a representative sample was completed by human classification, the machine learning algorithm then analyzed the remaining untrained posts and classified them accordingly based on the language and content detected in the posts.

### Step 4: Quantitatively Assess Campaign Audience Demographics, Campaign Reach, and Engagement Through Social Media Monitoring

We used social media monitoring techniques to quantify campaign engagement and track conversation volume during campaign implementation. Using demographic characteristics associated with user profiles, we further disaggregated campaign platform engagement by age, sex, and geographic location to understand the audience's demographic characteristics.

### Step 5: Qualitatively Assess Audience Attitudes, Opinions, and Behaviors and Understand Conversation Context Through Social Media Listening

We used Brandwatch, a social listening tool that enables analysts to investigate the data in various ways and at a granular level using topic wheels, word clouds, topic clustering, and bigram analysis. Data visualization options within the tool allow users to identify emerging themes. Some of the different techniques we used are outlined below:

- Topic wheel: This allows analysts to view the most frequently recurring keywords and phrases, which helps to easily identify how the main research themes relate to subthemes.
- Word clouds: Word clouds enable analysts to identify the most important and newly trending words, hashtags, emojis, and associated entities (people, places, and organizations) in the query.
- Topic clustering: Topic clustering displays topics and subtopics for segments of the overall data. The topics visualized in the output are selected based on how unique they are to the chosen segments. Clusters can be further filtered to identify positive or negative sentiment.
- Bigram analysis: A bigram analysis uses unstructured text data and measures how often words occur next to each other in text. This is a useful tool to identify emerging themes for further qualitative exploration.

Social listening findings validated the relevance of prioritized campaign topics (ie, the importance of encouraging honest dialogue about menstruation between parents and youth). We also quantified topic-specific conversation volumes for comparison at baseline (from October 2018 to October 2019) and endline (from November 2019 to January 2021) to assess if topic-specific conversation was increasing.

### Step 6: Adapt Campaign Content and Approach Based on the Analysis of Social Media Data

After using data visualization techniques to analyze the general social media conversation and campaign-specific engagement, we shared reports with WABA to inform evidence-based adaptations to the MMH campaign.

## Results

Figure 1 summarizes the conversation volume over the course of implementation and highlights when spikes in conversations related to campaign video themes occurred on social media. We found that 71% (20,611/29,030) of campaign followers were male social media users, with 60% (17,418/29,030) of the total users aged <24 years.

Table 3 shows the geographic distribution of campaign engagement by Facebook users, which, interestingly, does not mirror the levels of internet penetration. Among all Facebook users who engaged with the campaign content, most (32.28%, 937/2903) are from Ouagadougou, followed by Lomé (16.12%, 468/2903), Abidjan (14.16%, 411/2903), and Niamey (4.79%, 139/2903). Routine monitoring of Facebook page views indicated that although paid promotion of the campaign content garnered more campaign reach, organic viewers had better campaign video completion rates than paid promotion viewers (viewers who watched campaign videos to the end: 3.9%, 1031/26,435 vs 0.7%, 185/26,435, respectively).

The reports we shared with WABA provided extensive information related to trends in the conversation volume, campaign engagement, relevant hashtags, and extensive anonymized content data with direct quotes from user-generated content (see Table 4). Findings from the reports were used for program refinement throughout the initial MMH campaign period and beyond the social media monitoring time frames (beyond January 2021).

**Figure 1.** Merci Mon Héros conversation volume over the implementation period (from November 1, 2019, to October 20, 2020).

**Table 3.** Distribution of Facebook users who engaged with the Merci Mon Héros campaign content by city.

| City | Users (N=2903), n (%) |
|---|---|
| Ouagadougou | 937 (32.28) |
| Lomé | 467 (16.09) |
| Abidjan | 411 (14.16) |
| Conakry | 165 (5.68) |
| Niamey | 139 (4.79) |
| Libreville | 68 (2.34) |
| Bobo Dioulasso | 62 (2.14) |
| Bamako | 61 (2.1) |
| Cotonou | 59 (2.03) |
| Kinshasa | 44 (1.52) |

**Table 4.** Illustrative findings from the Merci Mon Héros social media monitoring and program adjustments.

| Social media monitoring finding | Program adjustment |
|---|---|
| Organic engagement yielded more engagement with the campaign than paid promotion alone. | • Maintained paid promotional posts to direct traffic to the site<br>• Looked into free ways to pull people in (Instagram and Facebook stories, Tweetups with multiple organizations, song and poetry contest, and increasing responses to individual social media posts)<br>• Researched other organizations and individuals with whom to collaborate |
| Facebook fans were primarily male. | • Shifted promotion campaigns toward young women<br>• Included increased calls for action targeting men, including messages around consent and talking to other men about reproductive health, etc. |
| Shorter videos increased view times. | • Shortened video duration<br>• Created video screenshot teasers to increase the likelihood a video would be watched |
| Menstruation topical content and Facebook Lives have some of the highest engagement levels. | • Decided to continue to include menstruation content and conduct at least 1 Facebook Live per month |
| The most negative sentiment tied to the campaign was associated with religious or cultural beliefs against premarital sex. | • Included videos and Facebook Lives with religious leaders who promoted talking openly with young people about reproductive health<br>• Developed content about how social support to young parents is more beneficial than rejecting young (single) parents |

## Discussion

The application of these 6 steps to inform the MMH campaign led to several challenges and lessons learned, reflecting the limitations of this methodology.

### Internet Users and Social Media Access

World Bank data indicate that internet penetration rates vary considerably in each of the 4 countries under review. Côte d'Ivoire's internet penetration was estimated at approximately 36% in 2019. This compares to approximately 16%, 12%, and 5% in Burkina Faso (2017), Togo (2017), and Niger (2018), respectively [21]. Further, social media would be accessed by just a subset of the web-based population, with urban, socioeconomic, and education skews [3]. However, given that social media was one of the media chosen for campaign implementation, potential biases posed by the methodology used for this study do not differ to those posed by the web-based campaign itself.

### Topic Volumes

Due to the highly nuanced nature of the conversation, topic volumes should not be viewed as complete or exhaustive. First, the search strings were created to minimize irrelevant conversation in the analysis. However, it is unlikely that a search string will ever be completely exhaustive due to the vast combination of words that could be used to discuss the topic, especially across multiple languages.

Second, some posts could feasibly sit across multiple topics, yet they are assigned to just one to analyze guideline volumetrics for the conversation. However, given the same principles and classifications are applied consistently across the analysis, we view the results as representative of the total conversation.

### Topic Sources

The analysis was designed to extract the mentions of public-facing social media platforms, including Twitter, YouTube comments, forums, blogs, Reddit, Pinterest, and Tumblr, etc. Notable exemptions from this list are Facebook, Instagram, and WhatsApp. Social listening tools such as Crimson Hexagon cannot track these sites due to their privacy policies. The only Facebook page that was included in this analysis is the Merci Mon Héros campaign page. Giving social listening analysts administrative access to campaign pages is crucial to be able to effectively conduct social media monitoring and social listening on Facebook.

## Machine Learning

Processes that involve machine learning should not be considered "standardized" given that the algorithms used for these analyses are constantly learning. As such, the machine becomes more accurate over time as it continues to understand the nuance within the topic material.

## Lessons Learned

There are many important differences between traditional research methodologies and social media monitoring and listening, yet each adds useful elements to the monitoring and evaluation of health campaigns. Population-based quantitative surveys allow researchers to develop findings that are generalizable and standardized and enable data disaggregation. Traditional qualitative research techniques allow for in-depth probing to explore and understand the themes of interest. In contrast, social listening techniques enable users to rapidly synthesize the universe of web-based chatter around selected topics. Demographic data for individual posts are not accessible, making data interpretation more challenging. Techniques for identifying sex, age, and socioeconomic status are evolving, mostly based on analyzing the keywords and account activity associated with individual profiles. As artificial intelligence becomes more sophisticated, social listening platforms will improve at detecting the demographic detail of users, and thus, this technology's use in research will continue to require careful ethical consideration.

Nonetheless, social media listening data can be quantified and tracked over time and used to retrospectively and prospectively analyze the data. Qualitative themes can be assessed, although these techniques do not allow for additional probing for clarification or the more nuanced understanding achieved by real-time traditional qualitative techniques. The following lessons were learned from the application of social media monitoring and social listening to the MMH campaign.

Future public health social media campaigns must:

- Understand who uses social media in the implementation countries and consider how the campaign's target audience and content align with the audiences that are active on social media platforms.
- Assess which social media platforms are most active and relevant in the country of interest and the privacy limitations associated with these platforms. Relatedly, if Facebook or Instagram are the key platforms for the target audiences in the country, it is crucial that social listening analysts have administrative access to campaign pages.
- Pilot multiple engagement strategies adapted to the social media channel (ie, Facebook and Instagram, etc.) to test, through social monitoring and listening, which strategies are associated with higher engagement in adolescent sexual health–related posts.
- Pair designated hashtags representing the goals of the campaign to facilitate the monitoring of conversations. The implementation of these hashtags should be consistent across social media channels.

## Conclusion

Social listening and social media monitoring are effective monitoring and evaluation support tools that can be used to aid adaptive management. With the rise in internet and social media penetration as well as the accelerated development of artificial intelligence to enhance rapid data extraction and analysis tools, these methodologies will become increasingly relevant for public health research and evaluation. Researchers should continue to look for tools that minimize or eliminate the need for in-person data collection to avoid disruptions to data collection such as those experienced at the onset of the COVID-19 pandemic. Inherent biases that exist around internet and social media access are important challenges that limit these methodologies. Additionally, ethical considerations around data privacy must continue to guide advances in this technology's use for research. However, for health communication campaigns that already engage populations who have a digital presence, social listening and social media monitoring can be powerful monitoring and evaluation tools.

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## Conflicts of Interest

None declared.

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## Abbreviations

**FP:** family planning
**LMIC:** low- and middle-income countries
**MMH:** Merci Mon Héros
**RH:** reproductive health
**SRH:** sexual and reproductive health
**USAID:** U.S. Agency for International Development
**WABA:** West Africa Breakthrough ACTION

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Original Paper

# The Distribution of HIV and AIDS Cases in Luzhou, China, From 2011 to 2020: Bayesian Spatiotemporal Analysis

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## Abstract

**Background:** The vastly increasing number of reported HIV and AIDS cases in Luzhou, China, in recent years, coupled with the city's unique geographical location at the intersection of 4 provinces, makes it particularly important to conduct a spatiotemporal analysis of HIV and AIDS cases.

**Objective:** The aim of this study is to understand the spatiotemporal distribution of HIV and the factors influencing this distribution in Luzhou, China, from 2011 to 2020.

**Methods:** Data on the incidence of HIV and AIDS in Luzhou from 2011 to 2020 were obtained from the AIDS Information Management System of the Luzhou Center for Disease Control and Prevention. ArcGIS was used to visualize the spatiotemporal distribution of HIV and AIDS cases. The Bayesian spatiotemporal model was used to investigate factors affecting the spatiotemporal distribution of HIV and AIDS, including the gross domestic product (GDP) per capita, urbanization rate, number of hospital beds, population density, and road mileage.

**Results:** The reported incidence of HIV and AIDS rose from 8.50 cases per 100,000 population in 2011 to 49.25 cases per 100,000 population in 2020—an increase of 578.87%. In the first 5 years, hotspots were concentrated in Jiangyang district, Longmatan district, and Luxian county. After 2016, Luzhou's high HIV incidence areas gradually shifted eastward, with Hejiang county having the highest average prevalence rate (41.68 cases per 100,000 population) from 2011 to 2020, being 2.28 times higher than that in Gulin county (18.30 cases per 100,000), where cold spots were concentrated. The risk for the incidence of HIV and AIDS was associated with the urbanization rate, population density, and GDP per capita. For every 1% increase in the urbanization rate, the relative risk (RR) increases by 1.3%, while an increase of 100 people per square kilometer would increase the RR by 8.7%; for every 1000 Yuan (US $148.12) increase in GDP per capita, the RR decreases by 1.5%.

**Conclusions:** In Luzhou, current HIV and AIDS prevention and control efforts must be focused on the location of each district or county government; we suggest the region balance urban development and HIV and AIDS prevention. Moreover, more attention should be paid to economically disadvantaged areas.

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**KEYWORDS**

HIV and AIDS; reported incidence; Bayesian model; spatio-temporal distribution

## Introduction

HIV and AIDS have been prevalent in China for more than 30 years. HIV and AIDS have become one of China's significant public health problems as it causes suffering to patients and seriously hinders healthy socioeconomic development [1]. Luzhou, located in southeastern Sichuan Province, is a central city in the combined region of Sichuan, Yunnan, Guizhou, and Chongqing, and is also an area in Sichuan Province, where the reported HIV epidemic is growing rapidly [2,3]. Despite considerable efforts by local governments, there remains much work required to fulfill the Political Declaration requirements on HIV and AIDS [4].

At present, domestic research on AIDS mainly focuses on epidemiology, prevention and control, clinical characteristics, etiology, and sociology [1]. By contrast, less research has been conducted on the process of its spatiotemporal spread. Nevertheless, some epidemiology studies have shown that the spread and distribution of HIV are closely related to geospatial factors [5]. Furthermore, although traditional regression models require variables of individuals to be independent of each other, these variables are likely to be correlated with each other owing to the influence of a familiar environment. Therefore, to identify deeper risk factors, researchers use Bayesian spatiotemporal models to be consistent with the correlation between individuals; to identify deeper risk factors, researchers use Bayesian spatiotemporal models that take into account spatial correlations. Yin et al [6] have used Bayesian spatiotemporal analysis to discover the impact of urbanization and residence on tuberculosis in other areas. Tian et al [7] have analyzed the impact of urbanization on the prevalence of scarlet fever. Card et al [8] reviewed the application of geographic information systems in HIV and emphasized the need for careful planning of resources concerning the geospatial movement and location of people living with HIV. Therefore, this study uses a Bayesian spatiotemporal model to analyze the impact of relevant data on the spatiotemporal distribution of HIV in Luzhou from 2011 to 2020 and provide a point of reference for the precise prevention and control of HIV in other prefecture-level cities in southwest China.

## Methods

### Ethics Approval

This study has been approved by the ethics committee of Southwest Medical University (KY2020225).

### Data Sources

The data on reported HIV and AIDS cases at district and township levels, in Luzhou, Sichuan province, from January 2011 to December 2020 were obtained from the AIDS Information Management System of the Luzhou Centre for Disease Control and Prevention; the date of registered onset and current address were collected for each case. Population data for each administrative district or township at year-end were collected from the Luzhou Bureau of Statistics, covering the years 2011 to 2020, obtained from the statistical yearbook [9] of the Luzhou Bureau of Statistics and relevant data provided by the Luzhou Health and Wellness Commission.

We downloaded the fundamental geographic data of municipal boundary with a scale of 1:400,000 from the National Geomatics of China, using ArcGIS (version 10.5; Environmental Systems Research Institute) to describe the spatial distribution of HIV and AIDS in Luzhou at the district and street levels. HIV and AIDS incidence rates were calculated at the city, district (county), and street (township) levels; a Bayesian spatiotemporal analysis was performed at the district and county levels, and spatial autocorrelation analysis was performed at the street and township levels.

### Analysis of Demographic Characteristics

We collected the following demographic information from the Luzhou Statistical Yearbook for use in the Bayesian spatiotemporal model and changed the units of some of the data to improve the final presentation: (1) population (the number of individuals who have lived in Luzhou for more than 6 months); (2) gross domestic product (GDP) per capita (the GDP divided by the population of the region), with 1000 Yuan (US $147.48) as the unit; (3) the urbanization rate (which is divided by the county's resident population); (4) disposable income per capita (the sum of the final consumption expenditures and savings available to residents; ie, the income available for discretionary use), using 1000 Yuan (US $147.48) as the unit; (5) total road mileage in the territory (the length of roads within the districts and counties of Luzhou); (6) the number of practicing (assistant) physicians and hospital beds (the number of physicians and beds per 1000 people within the area during the observation period); (7) and population density (the number of permanent residents divided by the total area of the district or county). The above data are based on the yearbook published in the current year.

### Spatial Autocorrelation Analysis

Spatial autocorrelation statistics have been commonly used to understand the spatial distribution and structure of diseases; they also allow for examining spatial dependence or autocorrelation in spatial data [10,11]. According to Waldo Tobler's first law of geography, "everything is related to everything else, but near things are more related than distant things"; therefore, neighboring counties' or townships' incidence rates of HIV should be more similar than those of nonneighboring counties or townships [12]. Spatial autocorrelation includes global spatial autocorrelation, which is used to estimate the overall degree of autocorrelation of spatial data, and local indicators of spatial association (LISA), which are used to assess the impact of individual locations on global statistics and determine the location and type of clusters. We performed all of the above analyses using GeoDa (version 1.10.0.8; Center for Spatial Data Science).

The Moran *I* is computed as follows [13]:

LISA are computed as follows [14]:

Where n is the number of districts, $x_i$ and $x_j$ are the values of the reported HIV and AIDS cases of districts $i$ and $j$, respectively. $x^{-}$ represents the average of all district-reported HIV and AIDS cases, and $w_{ij}$ is the spatial weight matrix corresponding to the district pair $i$ and $j$. In calculating the global autocorrelation, the Moran $I$, a negative correlation is indicated when $I<0$ and $P<.05$, and a positive correlation is indicated when $I>0$ and $P<.05$; the larger the value of $I$, the more obvious the spatial correlation.

### Bayesian Spatiotemporal Model Analysis

We studied the impact of the resident population, urbanization rate, disposable income per capita, GDP per capita, road mileage, number of physicians, and population density on the reported incidence of HIV using HIV case data and population data for each district from 2011 to 2020. In this study, it was assumed that the number of HIV cases in the $i$th ($i$=1,2,…,7) district in the $t$th ($t$=1,2,…,10) year followed a Poisson distribution, meaning $y_{it}$ ˜ Poisson($\lambda_{it}$) and $E(y_{it}) = \lambda_{it} = e_{it}\theta_{it}$.

$e_{it}$ denotes the expected number of HIV cases in year $t$ in district $I$; $\theta_{it}$ denotes the ratio of the number of actual cases to the expected number of cases in year $t$ in district $i$, which is the RR of disease incidence. We use the log function form of $\theta_{it}$ to build a Bayes model, computed as follows [15]. $\beta_0$ is the intercept, $x_i$ ($i$ =1,2, ..., 6) represents the urbanization rate, disposable income per capita, GDP per capita, road mileage, physicians, and density, respectively. $\beta_1$ to $\beta_6$ denote the regression coefficients of the corresponding variables.

$u_i$ is the spatial structure effect, reflecting spatial dependence, which is assumed to obey a conditional autoregressive process, with a Gaussian distribution, and the mean being the weighted average of neighboring regions $u_j$, $i \neq j$, computed as follows [16], where $\delta_i$ is the first-order neighborhood of region $i$, is the number of neighboring regions in region $i$, and $\sigma^2_e$ is the variance of the spatial effect. $v_t$ is the temporal structure effect for which the prior distribution is a first-order autoregressive AR(1), where the temporal effect $v_t$ at time $t$ is only related to the temporal effect $v_{t-1}$ at the previous time (ie, $v_t = \rho v_{t-1} + {}_t$).

The Bayesian spatiotemporal model analysis applies the CARBayesST and CARBayes packages in R (version 4.1.0; R Foundation for Statistical Computing) to estimate parameter values using Markov chain Monte Carlo simulations, resulting in mean values and 95% CIs for the posterior estimates of the parameters [17].

## Results

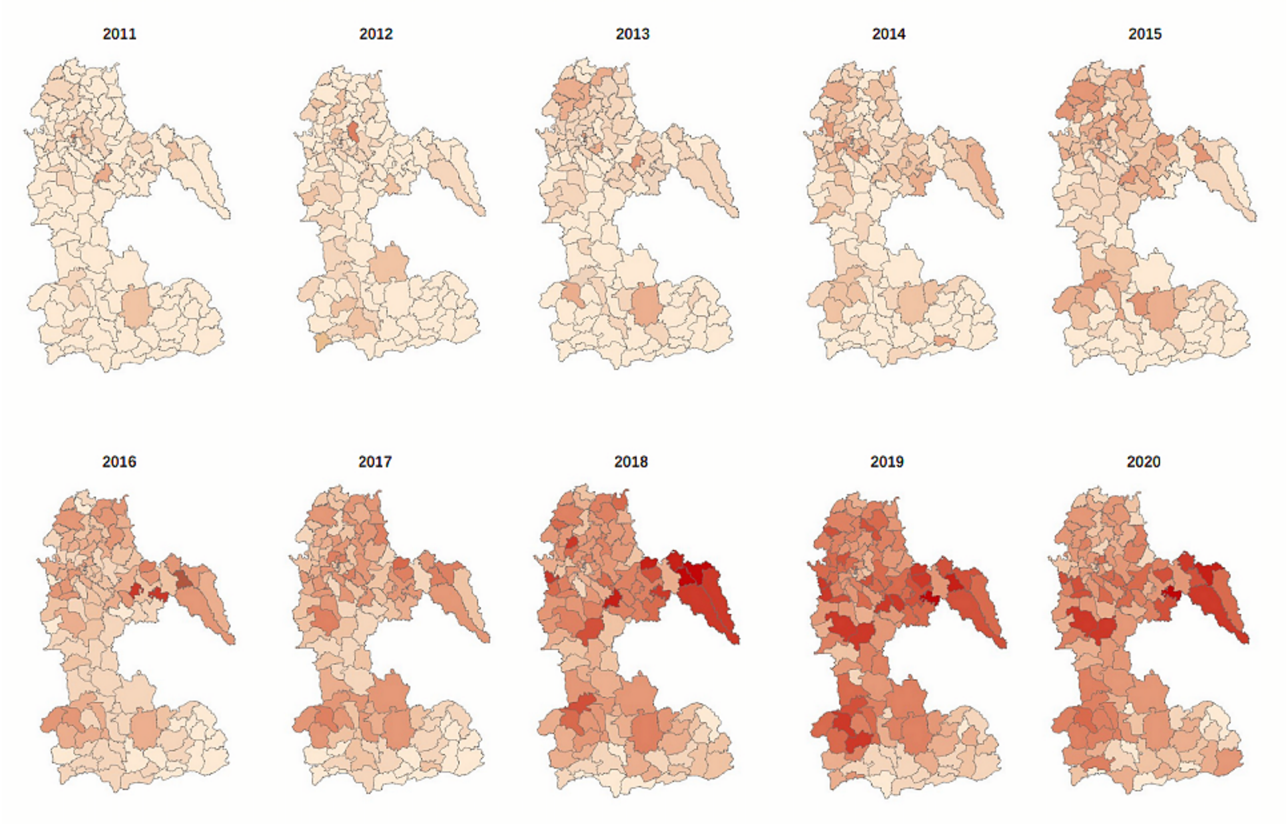
### Spatiotemporal Analysis of HIV and AIDS Incidence

A total of 13,111 HIV and AIDS cases were reported in Luzhou, Sichuan province, from 2011 to 2020. The reported incidence of HIV and AIDS rose from 8.50 cases per 100,000 population in 2011 to 49.25 cases per 100,000 in 2020, an increase of 578.87%. Table 1 shows that Hejiang county has the highest average incidence (41.68 cases per 100,000 populations) from 2011 to 2020, 2.28 times higher than that in Gulin county (18.30 cases per 100,000 population), which has the lowest average incidence rate. The highest cumulative number of cases occurred in Hejiang and Luxian counties, with 2904 and 2758 cases, respectively, during the last 10 years. In contrast, Gulin county has the lowest cumulative number of cases, only (1238/2904, 42.6%) of the cases in Hejiang county. The number of cases in each region showed an increasing trend year by year. The highest number of cases occurred in 2019, with 2850 new cases citywide, of which 688 cases were reported in Hejiang county. Figure 1 shows the change in HIV and AIDS in Luzhou from 2011-2020, where darker the color, more the HIV and AIDS cases.

**Table 1.** The number of HIV and AIDS cases and incidence rates by district and county in Luzhou from 2011 to 2020.

| Year | Cases per district, n/N (per 100,000) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Jiangyang | Naxi | Longmatan | Luxian | Hejiang | Xuyong | Gulin |
| 2011 | 59/585,000 (10.09) | 30/445,000 (6.74) | 72/352,000 (20.45) | 71/832,000 (8.53) | 59/707,000 (8.35) | 29/581,000 (4.99) | 38/706,000 (5.38) |
| 2012 | 69/586,000 (11.77) | 35/443,000 (7.90) | 62/358,000 (17.32) | 99/825,000 (12.00) | 66/706,000 (9.35) | 66/578,000 (11.42) | 46/701,000 (6.56) |
| 2013 | 95/595,000 (15.97) | 48/427,000 (11.24) | 69/360,000 (19.17) | 185/824,000 (22.45) | 94/697,000 (13.49) | 69/572,000 (12.06) | 79/692,000 (11.42) |
| 2014 | 135/606,000 (22.28) | 61/418,000 (14.59) | 88/369,000 (23.85) | 163/814,000 (20.02) | 126/695,000 (18.13) | 67/568,000 (11.80) | 80/685,000 (11.68) |
| 2015 | 136/526,000 (25.86) | 72/408,000 (17.65) | 115/384,000 (29.95) | 278/816,000 (34.07) | 154/699,600 (22.01) | 109/566,000 (19.26) | 93/678,000 (13.72) |
| 2016 | 168/654,000 (25.69) | 127/399,000 (31.83) | 116/407,000 (28.50) | 298/807,000 (36.93) | 262/696,000 (37.64) | 137/564,000 (24.29) | 103/672,000 (15.33) |
| 2017 | 235/681,000 (34.51) | 197/389,000 (50.64) | 145/426,000 (34.04) | 309/797,000 (38.77) | 276/695,000 (39.71) | 171/562,000 (30.43) | 139/664,000 (20.93) |
| 2018 | 257/707,000 (36.35) | 292/378,000 (77.25) | 199/444,000 (44.82) | 467/786,000 (59.41) | 646/692,000 (93.35) | 274/559,000 (49.02) | 230/660,000 (34.85) |
| 2019 | 394/737,000 (53.46) | 351/367,000 (95.64) | 216/464,000 (46.55) | 565/773,000 (73.09) | 688/691,000 (99.57) | 406/556,000 (73.02) | 230/656,000 (35.06) |
| 2020 | 361/762,000 (47.38) | 202/355,000 (56.90) | 184/480,000 (38.33) | 323/765,000 (42.22) | 533/689,000 (77.36) | 293/553,000 (52.98) | 200/652,000 (30.67) |
| Average | 1909/6,439,000 (29.65) | 1415/4,029,000 (35.12) | 1266/4,044,000 (31.31) | 2758/8,039,000 (34.31) | 2904/6,967,600 (41.68) | 1621/5,659,000 (28.64) | 1238/6,766,000 (18.30) |

**Figure 1.** Reported HIV and AIDS incidence rates by street/township in Luzhou from 2011 to 2020.



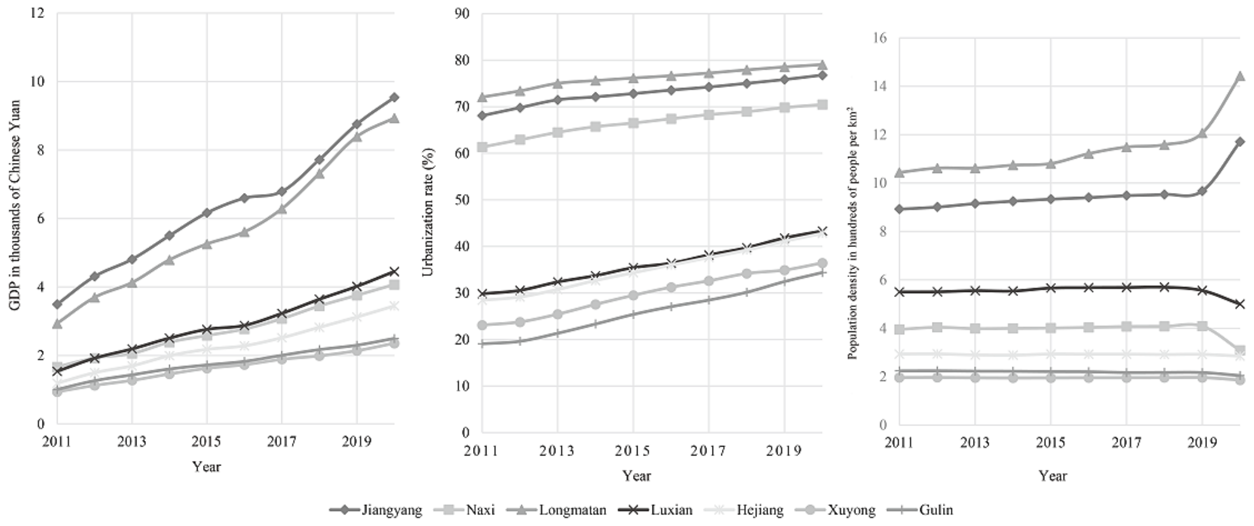
## Bayesian Analysis of HIV and AIDS Cases

We used a Bayesian spatiotemporal model to analyze factors such as urbanization rate, GDP per capita, road mileage, physicians, beds, and density, finding that urbanization rate and density increased the RR of having HIV, while GDP was a protective factor. For every 1% increase in the urbanization rate, the RR increases by 1.3%, while an increase of 100 people per square kilometer would increase the RR by 8.7%. Furthermore, for every 1000 Yuan (US $148.12) increase in GDP per capita, the RR value decreases by 1.5%. By contrast, the influence of the number of beds and road mileage on the risk of acquiring an HIV infection was not significant (Table 2). From 2011 to 2020, the GDP per capita of Luzhou City rose from 17,000 Yuan (US $2518.00) to 48,100 Yuan (US $7124.45), and the urbanization rate rose from 38.8% to 52%, while the population density remained at approximately 350 people per square kilometer, as shown in Figure 2.

**Table 2.** Bayesian model regression coefficient values.

| Variable | Median (95% CI) | A posteriori estimated relative risk values (95% CI) |
|---|---|---|
| Gross domestic product per capita | –0.016 (–0.0296 to –0.0048) | 0.985 (0.973 to 0.999) |
| Urbanization rate | 0.014 (0.004 to 0.027) | 1.013 (1.000 to 1.027) |
| Density | 0.092 (0.033 to 0.159) | 1.087 (1.020 to 1.164) |
| Road mileage | 0.002 (0.000 to 0.005) | 1.002 (1.000 to 1.004) |
| Number of beds | 0.018 (–0.035 to 0.069) | 1.019 (0.967 to 1.074) |

**Figure 2.** Trends in gross domestic product (GDP) per capita, population density, and urbanization rate by district and county.



## Spatial Autocorrelation Analysis of HIV and AIDS Incidence

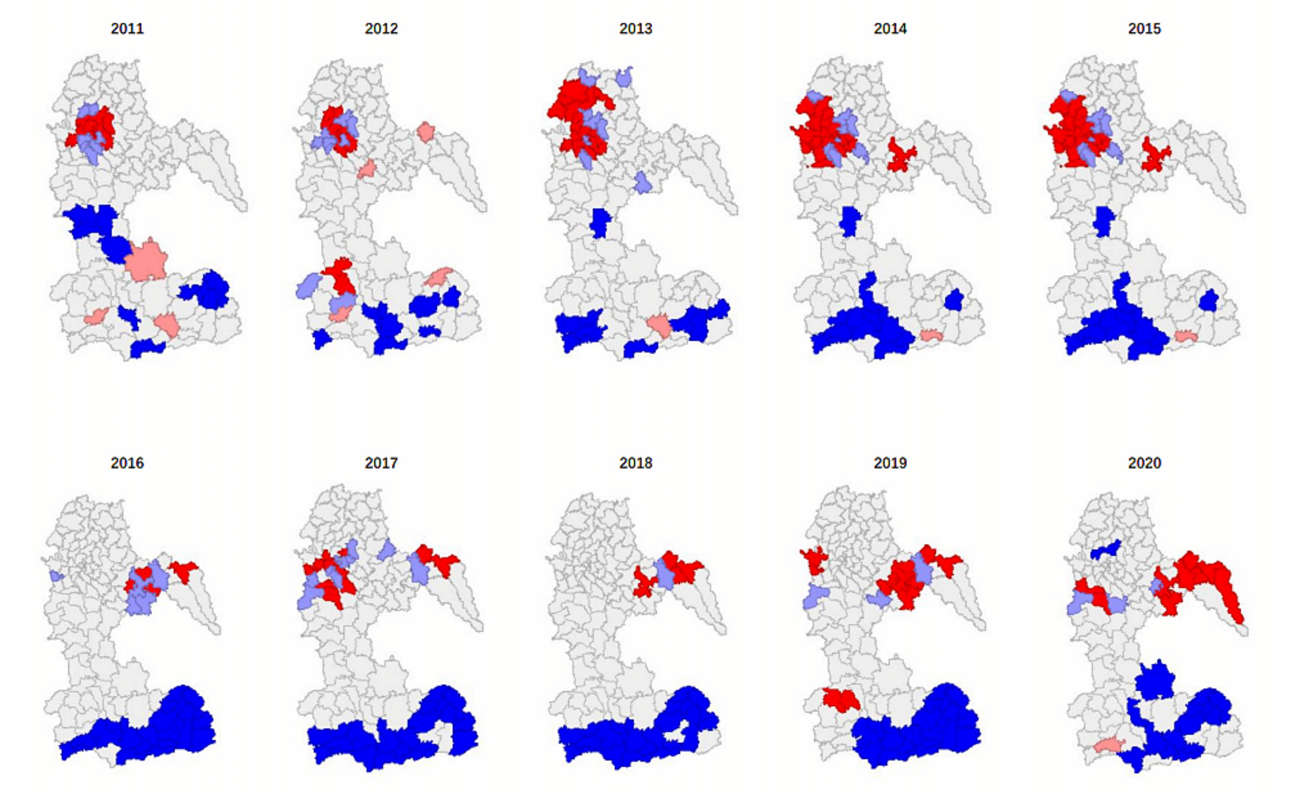
The HIV and AIDS incidence in Luzhou at the township (street) level from 2011 to 2020 is shown in Multimedia Appendix 1. The highest incidence occurred in Danlin Township, Anfu Street, Fuji Township, Hetou Township, and Ganyu Township. Table 3 shows the results of the spatial autocorrelation analysis on HIV and AIDS incidence over the last decade, with Moran *I* values ranging from 0.174 to 0.483 (*P*<.05 for each Moran *I* value). This analysis indicates a high positive spatial autocorrelation of HIV and AIDS incidence at the street (township) level.

Figure 3 illustrates the distribution of LISA values across Luzhou City. It shows the high-high (HH) incidence clusters in Taian township, Anfu township, and Lianhuachi township from 2011 to 2015. Since 2016, HH incidence clusters have moved toward the southeast, including some streets in Hejiang county. Most townships in Naxi county, Longmatan district, and Luxian county have transitioned to being without obvious spatial clustering after 2015. This analysis also showed that clusters of “cold spots” in core low-low areas were located in most townships in Gulin county. A map of the districts and counties of Luzhou is provided in Multimedia Appendix 2 to facilitate clarification of the administrative divisions of Luzhou.

**Table 3.** The results of the spatial autocorrelation test on HIV and AIDS incidence in China from 2011 to 2020.

| Year | Moran *I* | *E(I)* | *Z* value | *P* value |
|---|---|---|---|---|
| 2011 | 0.211 | –0.0082 | 4.1506 | .003 |
| 2012 | 0.174 | –0.0082 | 3.3516 | .005 |
| 2013 | 0.246 | –0.0082 | 4.3966 | .001 |
| 2014 | 0.308 | –0.0082 | 5.5326 | .001 |
| 2015 | 0.317 | –0.0082 | 5.8649 | .001 |
| 2016 | 0.336 | –0.0082 | 6.0172 | .001 |
| 2017 | 0.421 | –0.0082 | 7.3177 | .001 |
| 2018 | 0.483 | –0.0082 | 8.3788 | .001 |
| 2019 | 0.444 | –0.0082 | 7.9508 | .001 |
| 2020 | 0.411 | –0.0082 | 7.0059 | .001 |

**Figure 3.** Local indicators of spatial association cluster map of HIV and AIDS incidence in Luzhou from 2011 to 2020.



## Discussion

This study analyzed the spatial and temporal distribution of HIV and AIDS incidence in Luzhou based on the number of HIV and AIDS cases and demographic data from 2011 to 2020 using Markov chain Monte Carlo methods and Bayesian spatiotemporal models. The Bayesian spatiotemporal model integrated the temporal information, spatial information, parameter uncertainty (prior distribution) embedded, and correlated factors associated spatiotemporally, which resolved the estimation bias caused by the spatial structure and made the estimates more stable and reliable [16]. We found that for every 1% increase in the urbanization rate, the RR value increases by 1.3%, while an increase of 100 people per square kilometer would increase the RR by 8.7%. In contrast, for every 1000 Yuan (US $148.42) increase in GDP per capita, the RR value decreases by 1.5%. Thus, density and urbanization rate may be essential factors in the rise in HIV and AIDS incidence in Luzhou, while GDP per capita slows its rise.

Previous studies based on Bayesian spatiotemporal models had shown that urbanization is positively associated with the prevalence of infectious diseases such as scarlet fever and tuberculosis [6,7]; it has also been shown that population density is associated with hemorrhagic fever in renal syndrome [18]. This study also found that increased urbanization and population density increased the RR of having HIV or AIDS. The urbanization rate increased by 4.88%, and population density increased by 6 persons per square kilometer (varying by county) from 2011 to 2020, suggesting that this may be one of the underlying reasons for the increase in reported HIV and AIDS incidence in Luzhou. By contrast, GDP per capita emerged as a protective factor against the incidence of HIV and AIDS. Consistent with previous studies, the regions with the worst AIDS epidemics globally were often less economically developed regions; sub-Saharan Africa, where 40% of the population lives below the poverty line of US $1.40 per day, had the highest incidence of AIDS globally [19].

Further analysis of our data for the past 10 years for the 7 counties of Luzhou showed that Longmatan district and Jiangyang district had the highest urbanization rates with the minor differences and the highest and fastest-growing GDP per capita; this area is also the economic, cultural, medical, and educational center of Luzhou with relatively complete infrastructure. However, its population density far exceeds that of other counties, increasing the RR. Combining the 3 factors, the reported HIV and AIDS incidence in the region is at a medium level. Therefore, it is suggested that the region balance urban development and HIV and AIDS prevention, increase publicity on high-risk behavior, raise awareness of self-protection methods, and increase investment in HIV and AIDS prevention and treatment.

The highest HIV and AIDS incidence was in Hejiang County, which increased to 91.74% in 2018 (compared to only 39% in 2017). This increase had implications for the predictions of the Bayesian spatiotemporal model. The GDP per capita, urbanization rate, and population density had minor variations around 2018, so we believe that the emergence of this phenomenon was related to Luzhou’s policies [20,21]. The policies increased screening for HIV and AIDS, and more cases are being detected as a result. This allowed some HIV and AIDS cases in patients who had been infected for a long time but were not aware of it to be detected earlier. Early detection is an integral part of HIV and AIDS prevention and treatment [22,23], which can reduce the risk of transmission, ensure the efficiency of antiviral treatment, and increase the lifespan of individuals with HIV or AIDS, suggesting the need for early screening.

By contrast, Gulin, which had the lowest average HIV and AIDS incidence rate, has always shown a low incidence overall as it has not been the worst affected area, has been relatively stable in all factors, and is far from economic and cultural centers. However, in recent years, the population density in Gulin Township has increased, and the number of cases and incidence rates have continued to increase. With the increasing openness of sexual attitudes and the frequent occurrence of nonmarital commercial sex, Gulin Town will become a priority area for HIV and AIDS prevention and treatment in Luzhou.

To further verify the previously mentioned influencing factors, we conducted a spatial clustering analysis of HIV and AIDS in Luzhou at the street or township scale. We found that HIV and AIDS incidence hotspots were concentrated near the streets where each district and county government is located (Anfu Street, Hongxing Street, Fuji township, Hejiang township, Xuyong township, and Gulin township). As economic and social progress continues [24,25], and urbanization rates increase (especially near each district and county government), the population is becoming more and more concentrated and densely populated. From 2011 to 2015, these areas, centered on Nancheng Street in Jiangyang district, Hongxing Street in Longmatan district, and Fuji Township in Luxian, have the highest incidence of HIV and AIDS. In the case of the townships of Lushan county, for example, the GDP per capita has increased from 15,300 Yuan (US $2266.57) per person in 2011 to 44,500 Yuan (US $6592.30) per person in 2020, almost 3 times what it was 10 years ago, an increase that has meant the townships of Lushan county are no longer the hotspots they once were, providing evidence to suggest that economic growth is a protective factor against HIV and AIDS [26,27].

After 2016, Luzhou’s high HIV and AIDS incidence area gradually shifted eastward, mainly concentrating in Xiantan, Nantan, Bailu, and Ganyu townships in Hejiang county. The area has a low level of economic development and insufficient human resources for health compared to other areas. The GDP per capita in the area is lower than the average in Luzhou, and the low level of economic development may be one of the reasons for the high prevalence of AIDS in the township [28,29]; the cold spots in Luzhou from 2011 to 2020 were mainly concentrated in Xuyong county and southern Gulin county. The results of the small-scale hotspot analysis also verified the influence of urbanization, population density, and GDP per capita on the spatial and temporal distribution of HIV and AIDS in Luzhou.

There are still some limitations in this study. First, population data are all from the Luzhou City Statistical Yearbook and are collected at the county level only; population data at the street and township levels are estimated using data from the sixth census in 2010 [30], and the incidence rates were not accurate for each year. Second, the indicators included in this paper are all macrocontrol statistics, but the causes affecting the incidence of AIDS are complex and varied, and it may not be possible to cover all the influencing factors. Lastly, the incidence of AIDS is reported late [31], and it is expected that the delay or lag between the number of reported HIV and AIDS infections and the exact number of HIV and AIDS infections will result in a difference in RR. Therefore, further studies are needed to collect more detailed data and conduct more in-depth studies.

In conclusion, from 2011 to 2020, the incidence and number of HIV and AIDS cases in all districts and counties of Luzhou have increased significantly, and the work of prevention and treatment still faces many challenges [32]. This study suggests that increasing urbanization rates and population density may be important reasons for the rise in reported HIV and AIDS incidence in Luzhou, while the growth in GDP per capita plays a protective role. This study has important implications for the precise prevention and control of HIV and AIDS in other prefecture-level cities in southwest China.

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## Authors' Contributions

SF, NR, and YL participated in the study conception and design, literature search, and statistical analysis. NR, YL, RW, WZ, TX, and HC participated in gathering data, tabulating the tables, and generating the graphs. NR drafted and wrote the report. SF, AL, and RC participated in language polishing and provided comments on the manuscript. All the authors participated in interpreting data and study findings, and critically reviewing and substantively revising the manuscript. All authors have approved the final version of the manuscript to be published. All authors agreed to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Conflicts of Interest

None declared.

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Multimedia Appendix 1
Heat map of reported HIV incidence rates by street/township in Luzhou, China, from 2011 to 2020.
[PNG File , 973 KB - publichealth_v8i6e37491_app1.png ]

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Multimedia Appendix 2
The district and county level map of Luzhou, China.
[PNG File , 28 KB - publichealth_v8i6e37491_app2.png ]

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## Abbreviations

**GDP:** gross domestic product
**RR:** relative risk

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Original Paper

# Correlates of Engagement Within an Online HIV Prevention Intervention for Single Young Men Who Have Sex With Men: Randomized Controlled Trial

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## Abstract

**Background:** Digital HIV interventions (DHI) have been efficacious in reducing sexual risk behaviors among sexual minority populations, yet challenges in promoting and sustaining users' engagement in DHI persist. Understanding the correlates of DHI engagement and their impact on HIV-related outcomes remains a priority. This study used data from a DHI (myDEx) designed to promote HIV prevention behaviors among single young men who have sex with men (YMSM; ages 18-24 years) seeking partners online.

**Objective:** The goal of this study is to conduct a secondary analysis of the myDex project data to examine whether YMSM's online behaviors (eg, online partner-seeking behaviors and motivations) are linked to participants' engagement (ie, the number of log-ins and the number of sessions viewed).

**Methods:** We recruited 180 YMSM who were randomized into either myDEx arm or attention-control arm using a stratified 2:1 block randomization. In the myDEx arm, we had 120 YMSM who had access to the 6-session intervention content over a 3-month period. We used Poisson regressions to assess the association between YMSM's baseline characteristics on their DHI engagement. We then examined the association between the participants' engagement and their self-reported changes in HIV-related outcomes at the 3-month follow-up.

**Results:** The mean number of log-ins was 5.44 (range 2-14), and the number of sessions viewed was 6.93 (range 0-22) across the 3-month trial period. In multivariable models, the number of log-ins was positively associated with high education attainment (estimated Poisson regression coefficient [β]=.22; *P*=.045). The number of sessions viewed was associated with several baseline characteristics, including the greater number of sessions viewed among non-Hispanic YMSM (β=.27; *P*=.002), higher education attainment (β=.22; *P*=.003), higher perceived usefulness of online dating for hookups (β=.13; *P*=.002) and perceived loneliness (β=.06; *P*=.004), as well as lower experienced online discrimination (β=–.01; *P*=.007) and limerence (β=–.02; *P*=.004). The number of sessions viewed was negatively associated with changes in internalized homophobia (β=–.06; *P*<.001) and with changes in perceived usefulness of online dating for hookups (β=–.20; *P*<.001). There were no significant associations between the number of log-ins and changes in the participants' behaviors at the 90-day follow-up.

**Conclusions:** DHI engagement is linked to participants' sociodemographic and online behaviors. Given the importance of intervention engagement in the intervention's effectiveness, DHIs with personalized intervention components that consider the individuals' differences could increase the overall engagement and efficacy of DHIs.

**Trial Registration:** ClinicalTrials.gov NCT02842060; https://clinicaltrials.gov/ct2/show/NCT02842060.

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**KEYWORDS**

paradata; mobile health; mHealth; digital health intervention; risk reduction; HIV prevention; public health; digital health; sexual health; sexual risks

## Introduction

HIV infections among young men who have sex with men (YMSM) between 13 and 29 years of age are of particular concern in the United States [1]. HIV prevention digital health interventions (DHI) provide opportunities to reach YMSM and offer HIV-related prevention information given their appeal and broad reach [2]. High technology use among youth makes DHIs feasible, enables easier and faster spread of information, offers a greater number of opportunities for real-time behavior change cues and nudges, and provides greater access to social support and engagement, particularly for individuals who might experience stigma in their real-world environments [3-5]. By design, DHIs are appealing because they can be delivered remotely, allow for self-guided learning, and encourage asynchronous interaction with others. As a result, evaluating the effectiveness of DHIs requires a different set of considerations, as compared to face-to-face interventions that are delivered by a facilitator in a specific time and place. Researchers have recently noted how these engagement considerations remain the crucial factor in evaluating the true intervention effects of DHIs [5].

DHIs have been linked to changes in cognitive and behavioral risk factors, increases in the adoption of HIV prevention behaviors, and the development of supportive relationships online [6,7]. While the strengths of DHIs are noteworthy, a recent review [8] of 16 DHI studies on HIV prevention and treatment (8 studies encouraged HIV testing, 7 studies targeted condom use, 3 studies promoted preexposure prophylaxis initiation and adherence, and 3 studies encouraged antiretroviral therapy adherence) among gay, bisexual, and other men who have sex with men (MSM) published between 2012 and 2019 found that 33% of the interventions that intended to promote HIV testing and 43% of those that intended to increase condom use were not statistically effective [8]. The absence of observed effects in these interventions may be related to participants' engagement with the interventions. In a recent review, Hightow-Weidman and Bauermeister [9] documented how participants' engagement with DHI content was associated with key HIV prevention outcomes across 4 distinct HIV interventions designed for YMSM. They found that intervention exposure and dosage, between-arm and within-arm, strengthened the observed intervention effects.

Limited engagement can impact an intervention's effect on behavior change; however, it is imperative that researchers examine participants' engagement with DHI to enhance the precision in calculating the efficacy of their interventions and ultimately maximize the effectiveness and efficiency of their interventions. For example, researchers found that engagement moderated the efficacy of healthMpowerment.org (HMP), a theory-based phone-optimized DHI for young Black MSM. Participants who met the recommended engagement time with the intervention (ie, 60 minutes or more during the 3-month intervention period) showed greater reduction in the number of condomless anal intercourse (CAI) episodes compared to those who did not comply with the recommended engagement time [7]. Moreover, the total time spent on HMP was correlated with overall site satisfaction during usability assessment [10], and participants who engaged with the intervention components where those who could share experiences and receive social support (eg, Forum, Getting Real, and Ask Dr.W), and the content of the intervention exhibited reduced levels of stigma [11]. Therefore, without engagement metrics, it is hard to know whether a DHI was delivered to participants, achieving the intervention "dose" required for optimal behavior change, as these applications offer an array of different activities and features without dictating a standardized sequence of activities, amount of exposure or frequency, and duration of interactivity.

Researchers have promoted the use of *paradata* metrics for measuring engagement with DHIs [9,12]. *Paradata* can be defined as automatically generated process data that capture participants' actions within an application [13-15], and can be transformed to characterize the amount, frequency, duration, and depth of engagement across and within DHIs [9]. Thus, *paradata* metrics are crucial to understanding how differential engagement might impact behavior change and help inform what constitutes meaningful engagement [16]. To date, limited attention has been paid to whether participants' characteristics may serve as correlates of DHI engagement. Several recent studies have noted that participants' sociodemographic characteristics may be associated with DHI engagement [17,18]. Beyond examining sociodemographic differences in DHI engagement, few studies have examined whether other psychosocial factors are related to DHI engagement. Understanding the antecedents to DHI engagement may help researchers and practitioners alike to create implementation strategies that improve engagement and, in turn, maximize its potential effects.

In order to characterize users' engagement, this study examines how the interplay of internet use patterns and partner-seeking characteristics influence engagement in DHIs. Therefore, the goal of this study is to conduct a secondary analysis of the myDex project data to examine whether YMSM's online behaviors (eg, online partner-seeking behaviors and motivations) are linked to participants' engagement with the DHI. To advance this goal, our study had 3 objectives. First, we examined whether YMSM's internet-using patterns, relationship characteristics, psychological facilitators and barriers, and sexual behaviors predicts their DHI engagement. Second, we explored whether participants' engagement during the 90-day intervention impacted psychobehavioral changes in internet use patterns, relationship characteristics, psychological facilitators and barriers, and sexual behaviors from baseline to the 90-day follow-up. Third, we evaluated whether there are different correlates between frequency of engagement (number of log-ins) and amount of engagement (number of sessions viewed).

## Methods

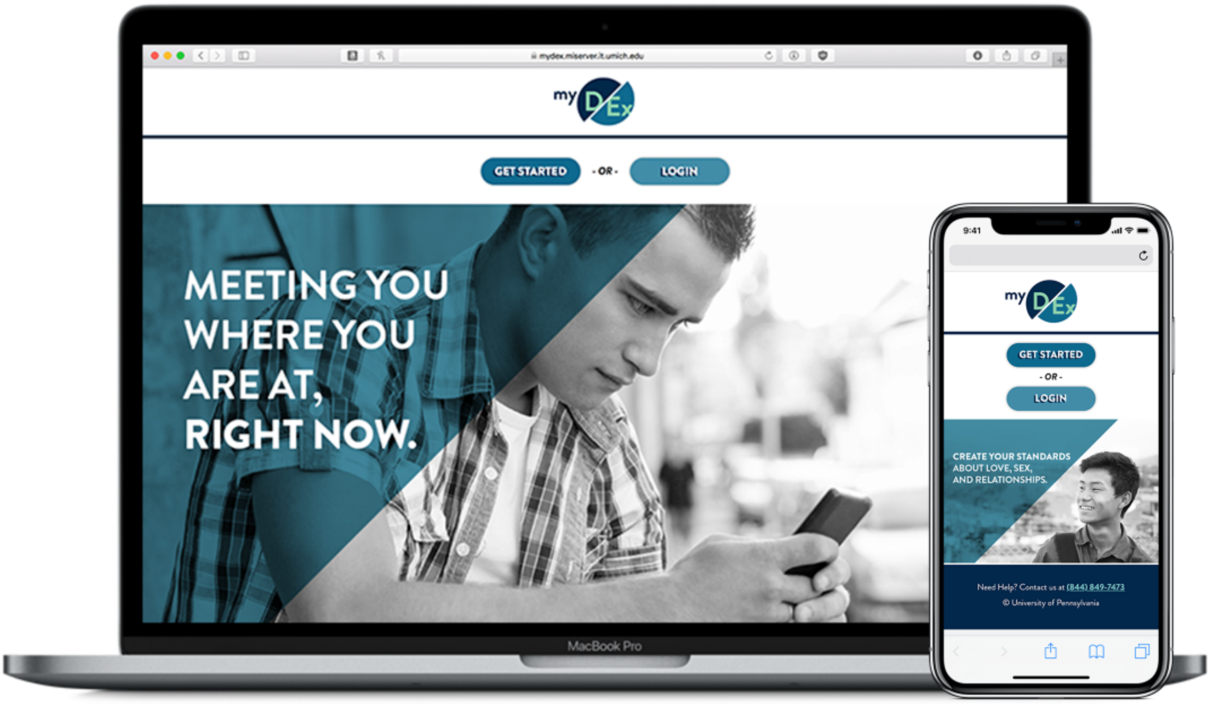
### Ethics Approval

The research and ethics presented in this study have been reviewed and approved by the University of Michigan Institutional Review Board (HUM00091627). The University of Pennsylvania ceded regulatory oversight to the University of Michigan (University of Pennsylvania IRB #824885). The study is also registered on ClinicalTrials.gov (NCT02842060).

### Study Procedure

Data from this study come for the myDEx web application, a DHI trial delivering dating and partner-seeking behavior content for single YMSM presumed to be HIV-negative and who engage in CAI with sexual partners met online (Figure 1). A detailed protocol for myDEx has been outlined elsewhere [19]. The participants were recruited across the United States through advertisements on online social media and sexual networking platforms. Social network advertisements were targeted to men who fit the study's age criterion and who lived in the United States.

**Figure 1.** Screenshot of myDEx intervention.



To participate, participants had to self-report the following: (1) male sex at birth and male gender identity; (2) age of 18 to 24 years; (3) HIV-negative or HIV-unaware serostatus; (4) single relationship status; (5) prior use of online dating applications; and (6) report CAI with at least one male partner in the prior 6 months. Upon completion of an online informed consent form, eligible participants completed a 30-minute web-based baseline questionnaire ascertaining their sexual and online behaviors, mental health, and demographic information.

A sample of 180 single YMSM (aged 18-24 years; 50% [n=90] racial or ethnic minorities) were recruited between November 2016 and January 2017 and randomized to either the intervention arm (myDEx) or the attention-control arm using a stratified 2:1 block randomization design.

The participants were given access to myDEx for 90 days. The intervention (myDEx) was divided into 6 sessions, each addressing distinct cognitive and affective content areas (Table 1). Within each session, intervention content was organized into the following three levels: (1) core messages, (2) in-depth discussion of topics linked to the core message, and (3) an interactive activity linked to the information presented. Within each session, the participants had access to brief activities and videos designed to build their HIV risk reduction skills and promote self-reflection about their sexual health and partner-seeking behaviors. We designed the sessions to keep users engaged for at least 10 minutes. The participants were required to complete the first session before being able to access the other 5 sessions and interactive activities [19]. The participants could view the sessions multiple times. However, we did not have a priori threshold for the number of sessions viewed and log-ins, nor did we set an expectation for users to use the intervention over a number of sessions or log-ins. This study analyzed (1) the effect of baseline characteristics on engagement in the myDEx intervention over 90 days and (2) the associations between engagement in the myDEx intervention as well as changes in the participants' characteristics during 90 days among 120 single YMSM in the myDEx intervention arm.

**Table 1.** Content of 6 sessions in myDEx.

| Session | Content |
|---|---|
| Session 1: "Sexuality & Relationships" | The importance of feeling comfortable talking about sexuality, desires within relationships, and health |
| Session 2: "Desires & Behaviors" | Different relationship types (eg, romantic relationships, friends with benefits, and hookups) and sexual decision-making |
| Session 3: "What Makes Good Sex" | Comprehensive sex education: same-sex behaviors, including the importance of sex positivity, varying sexual practices, and sexual consent |
| Session 4: "Sexual Well-being" | HIV and STI[a] risks reduction when engaging in anal sex: (1) what lubricants and condoms are best suited for anal intercourse; (2) facts about HIV and STI transmission; and (3) the importance of status disclosure prior to sex. |
| Session 5: "Getting The Sex You Want" | Strategies to improve sexual communication with partners before, during, and after sex |
| Session 6: "Your Body, Your Health" | Summarizes key messages from prior modules; offers nearby HIV/STI testing resources and PrEP[b] locations. |

[a] STI: sexually transmitted infection.

[b] PrEP: preexposure prophylaxis.

## Measures

This study analyzed the myDEx intervention arm (n=120) *paradata* over 90 days, participant characteristics at baseline, and participant characteristics at the 90-day follow-up. Participants characteristics were examined for associations with intervention engagement.

### *Participant Paradata*

Over the 90-day trial period, the participants' actions in myDex were collected as *paradata*. *Paradata* can be transformed to characterize the amount, frequency, duration, and depth of engagement with a web-based intervention [9]. Amount refers to a quantity of something in number, size, or value. Frequency is the number of occurrences of a repeating event over a particular time. Duration is the time during which something continues. Depth represents the usage of different intervention components. In this study, we employed two types of *paradata* metrics, which are (1) the frequency of engagement (number of log-ins) and (2) the amount of engagement (number of sessions viewed). We measured the frequency of intervention use by counting the number of log-ins during the intervention period and the amount by counting the number of sessions viewed per log-in.

### *Demographic Characteristics*

We asked the participants to report their age and ethnicity. In addition, the participants were asked to report their highest level of education (some high school, graduated high school, technical school, associate degree, some college, college, some graduate school, or graduate degree). Then, education was dichotomized as "less than associate degree" or "associate degree, college graduate, or more than college."

### *Internet Use Patterns*

#### Frequency and Usefulness of Online Dating

The participants were asked about frequency and usefulness of online dating to find a date, and the same set of questions were asked regarding finding a hookup in the past 30 days. The frequency of engaging in online dating had the following six response options: (1) "Never," (2) "Once a month or less," (3) "2-3 times a month," (4) "About once a week," (5) "2-6 times a week," and (6) "About once a day." The usefulness of using online dating employed a 4-point Likert-type scale from "Not at all" to "Very much."

#### Online Discrimination

We used an 8-item adapted version of the Everyday Discrimination Scale [20] to measure experienced discrimination when looking for partners online (α=.81). The example items were as follows: "People act as if they think you are not smart" and "You are treated with less courtesy than other people are." The response had 6 response options ranging from "Never" to "Almost every day." We created a continuous score by summing 8 items (range 0-40), with higher scores indicating higher experienced discriminations when looking for a partner online.

### *Psychological Facilitators and Barriers*

#### Internalized Homophobia

We used a 7-item, revised Reactions to Homosexuality Scale [21] to measure internalized homophobia. The scale includes statements such as "Even if I could change my sexual orientation, I wouldn't" and "I feel comfortable being a homosexual man." Scoring is reversed for 1 item, which is positive affect statements. The scale employed a 5-point Likert scale with response options from Strongly Disagree to Strongly Agree. Then, total score was computed by creating sum score (range 5-35) with higher scores indicating higher internalized homophobia (α=.72).

#### Loneliness

We used the 3-Item UCLA Loneliness Scale to measure overall social isolation [22]. The items were as follows: (1) "How often do you feel that you lack companionship?" (2) "How often do you feel left out?" and (3) "How often do you feel isolated from others?" The response categories were coded 1=hardly ever, 2=some of the time, and 3=often. We used the sum scores of these 3 items, with higher scores indicating greater social isolation (range 3-9; α=.84).

#### Mental Health

We used the Center for Epidemiologic Studies Depression Scale with 10 items to measure mental health status in the past week [23]. The scale includes 3 items on depressed affect, 5 items on somatic symptoms, and 2 on positive affect. The scale employed a 4-point Likert scale ranging from “rarely or none of the time” to “all of the time.” Scoring is reversed for 2 items (“I felt hopeful about the future” and “I was happy”), which are positive affect statements. Total scores can range from 0 to 30 (α=.83), with higher scores indicating greater severity of symptoms.

#### Self-esteem

Rosenberg et al [24] developed a scale with 10 items (eg, “On the whole, I am satisfied with myself”) with responses rated on a 4-point Likert-type scale (“strongly agree” to “strongly disagree”) to estimate individuals’ self-esteem. Scoring was reversed for negatively worded items. A higher score indicates greater self-esteem (range 0-30; α=.90).

### *Relationship Characteristics*

#### Ideal Relationship Characteristics (Intimacy, Commitment, and Passion)

We used the Triadic Love Scale to assess YMSM’s perceived relationship characteristics [25]. The participants responded to the importance of quality in their ideal romantic relationship with their partner. The original scale with 20-item employs a 4-point Likert-type scale with response options ranging from “Not at all important” to “Very important.” Three subscales were derived from the following scales: intimacy (eg, “To feel close to your partner”; 9 items; α=.90); commitment (eg, “To feel a sense of responsibility towards your relationship”; 5 items; α=.75); and passion (eg, “To explore your sexuality with your partner”; 6 items; α=.82). In this study, we computed a mean score for each subscale (range 1-4), where higher scores indicate greater ideation on that component.

#### Limerence

We adapted a limerence scale to measure the intense feelings of dependence, insecurity, and doubt about a relationship and experiences with intrusive and intense thoughts about partners [26]. We asked the participants 8 items using a 5-point scale ranging from 1 (“Strongly disagree”) to 5 (“Strongly agree”). The scale includes statements such as “I think about how being in a relationship would solve my problems,” “I have sex to feel loved,” and “I obsess about a specific person even though it may not work out.” We computed a score summing 8 items ranging from 8 to 40, where higher scores indicate greater limerence (α=.84).

### *Sexual Risk Behaviors*

#### Decisional Balance to Condom Use

We used the Decisional Balance Scale to examine the participants’ decisional balance to use or forego condoms with partners [27]. The participants were asked 7 paired statements. For each item, the participants rated their preference for sex without condoms, followed by the same question asking about preference for sex with condoms. The items included “Sex [with/without] condoms is very intimate to me” and “Sex [with/without] condoms makes me feel close to my partner.” Each item was measured using a 4-point scale ranging from “Strongly disagree” to “Strongly agree.” A net difference for decisional balance items was created by summing the net difference between condomless sex and condom use scores across the items, resulting in 7 net scores ranging from –3 to +3. Finally, we created the total decisional balance to use condoms scores by computing a mean score of these 7 items. Positive scores indicate greater endorsement of sex without condoms, while scores close to zero indicate a decisional balance between sex with and without condoms (α=.89).

#### Self-efficacy to Use Condoms

We used an 8-item scale to measure how hard or easy it is to use condoms with a date (α=.82), respectively, and the same set of questions was used for a hookup (α=.77). The example items were as follows: “To have condoms with you in case you have sex?” and “To discuss having safer sex with a hookup partner online?” The self-efficacy to use condoms scale employed a 4-point Likert-type scale from “Very easy to do” to “Very hard to do” (range 8-32). The total self-efficacy to use condoms was computed by summing the scores of these 8 items. Higher scores indicate hardship in using condoms when thinking about a date or a hookup.

#### The Number of Sex Partners and Anal Intercourse

We used an adapted version of the Sexual Practices Assessment Schedule [28,29] to quantify the number of male partners in the prior 30 days. First, the participants indicated the total number of male sexual partners with whom they had sex (oral or anal). Then, they were asked to report the number of male sexual partners with whom they had receptive and insertive anal sex. Lastly, the participants were asked to indicate the number of partners with whom they did not use condoms. We created a continuous variable to measure the number of sex partners and the number of engagements in receptive or insertive anal intercourse. We excluded outliers for the number of sex partners and anal intercourse.

### Statistical Analysis

Descriptive statistics were used to summarize the study participants’ characteristics including internet use patterns, relationship characteristics, psychological facilitators and barriers, and sexual behaviors. Differences in the participants’ characteristics between baseline and 90-day follow-up were compared using McNemar tests and paired *t* tests. Then, we used Poisson regressions with robust variance to assess the effect of the participants’ baseline characteristics on 2 engagement outcomes (ie, the number of sessions viewed and the number of log-ins) and the associations between changes in the participants’ characteristics and engagement within the myDEx intervention for 90 days. Multivariable models were fitted based on significant variables in bivariable models ($P<.05$). All analyses were conducted in SAS 9.4 (SAS Institute Inc) [30].

## Results

### Description of the Study Participants

We summarized the participants’ characteristics in Multimedia Appendix 1. Among 120 participants, the mean age was 21.67 (SD 1.81) years. Most participants were identified as White (n=89, 74.2%), followed by Black (n=18, 15.0%), Other (n=12, 10.0%), and Asian (n=10, 8.3%). One-third of the participants (n=35, 29%) were Latino, and most participants (n=98, 81.67%)

received education of some associate degree or higher. A majority of participants (n=91, 75.8%) used the internet for 1 to 6 hours per day. Almost half of the participants used online dating at least once a week to find a date (n=59, 49.2%), while a majority of participants used online dating less than 2-3 times a month to find a hookup (n=100, 83.2%). However, the participants considered online dating a useful tool to find a hookup (n=55, 45.8%) rather than a date (n=36, 30%). They also experienced moderate levels of discrimination in online settings. In addition, they showed a propensity toward seeking out novel or risky sexual stimulation (mean 20.5, SD 7.8) and had moderate ideation on intimate (mean 3.8, SD 0.3), passionate (mean 3.6, SD 0.4) and committed (mean 3.7, SD 0.4) relationships. Additionally, they reported the intense feelings of dependence, insecurity, and doubt about a relationship as well as experiences with intrusive and intense thoughts about partners (mean 22.9, SD 6.6).

We summarized engagement in the myDEx intervention over 90 days with the frequency of engagement (number of log-ins) and the amount of engagement (number of sessions viewed). On average, the participants logged into the myDEx intervention 5.44 times (range 2-14) and viewed sessions 6.93 times (range 0-22) during the 90 days of intervention.

## Baseline Characteristics and myDEx Engagement

### *The Number of Log-ins*

In bivariable models (Multimedia Appendix 2), the participants were more likely to log into myDEx during the 90 days of intervention if they had higher educational attainment (estimated Poisson regression coefficients [β]=.23; *P*=.04) and reported higher frequency of online dating to find a hookup (β=.07; *P*=.03), higher perceived usefulness of online dating for a hookup (β=.09; *P*=.01), greater loneliness (β=.05; *P*=.02), and higher number of sex partners (β=.04; *P*=.003).

In a multivariable model, higher education attainment (β=.22; *P*=.045) and loneliness (β=.04; *P*=.07) remained associated with the number of log-ins during the intervention.

### *The Number of Sessions Viewed*

Similar to the number of log-in models, in bivariable models, the participants who identified as Hispanic (β=–.25; *P*=.002) and reported higher discrimination experiences in an online setting (β=–.01; *P*=.02) and limerence (β=–.01; *P*=.02) at baseline viewed fewer sessions. However, the participants viewed more sessions after the 90-day intervention if they had higher educational attainment (β=.25; *P*=.002), reported higher frequency of online dating use to find a hookup (β=.06; *P*=.02), perceived greater usefulness of online dating to find a hookup (β=.14; *P*<.001), experienced greater loneliness (β=.05; *P*=.01), and had a greater number of sex partners (β=.04; *P*=.001) at baseline.

In a multivariable model, the number of sessions viewed was associated with non-Hispanic ethnicity (β=–.27; *P*=.002), higher educational attainment (β=.22; *P*=.003), perceived usefulness of online dating for hookups (β=.13; *P*=.002), loneliness (β=.06; *P*=.004), experienced online discrimination (β=–.01; *P*=.007), and limerence (β=–.02; *P*=.004).

## Changes in the Participants' Behaviors Based on myDEx Engagement

At the 90-day follow-up, the participants' frequency of online dating to find a date or a hookup decreased significantly (Multimedia Appendix 1). At baseline, 12.5% (n=15) of the participants had not used online dating to find a date in the past month, but at the 90-day follow-up, 33.7% (n=32) of the participants had not used online dating to find a date in the past month (*P*=.004). Similarly, 20% (n=24) of the participants never used the internet to find a hookup at baseline, but this percentage increased to 46.3% (n=44) at the 90-day follow-up (*P*=.007). In addition, their experienced discrimination in an online setting decreased significantly from baseline to the 90-day follow-up (baseline mean 17.0; and 90-day follow-up mean 3.25; *P*<.001). The participants also showed improvements in their decisional balance of having sex with and without condoms (baseline mean –0.42; and 90-day follow-up mean –0.26; *P*=.03) and reported fewer sex partners in the past month (baseline mean 2.39; and 90-day follow-up mean 1.15; *P*<.001). We examined whether these changes over time were correlated with YMSM's engagement with the DHI.

### *The Number of Log-ins*

There were no significant associations in bivariate or multivariable models between the number of log-ins and changes in the participants' behaviors at the 90-day follow-up (Multimedia Appendix 3).

### *The Number of Sessions Viewed*

In bivariate models, the number of sessions viewed was negatively associated with the perceived usefulness of online dating for hookups (β=–.21; *P*<.001) and internalized homophobia (β=–.03; *P*=.008). However, the number of sessions viewed were positively associated with increased ideation of an intimate romantic relationship (β=–.29; *P*=.04) and increased number of insertive anal intercourse events (β=.08; *P*=.02).

In the multivariable model, the number of sessions viewed was negatively associated with internalized homophobia (β=–.06; *P*<.001) and with changes in perceived usefulness of online dating for hookups (β=–.20; *P*<.001). No other statistically significant associations were observed.

# Discussion

## Principal Results

DHIs have great potential for HIV prevention, but there is divergence in their effectiveness in the existing literature [8]. The discrepancy in DHI effectiveness may be attributable to variations in the participants' engagement. Therefore, researchers have recently noted how engagement considerations are a crucial factor in evaluating the true intervention effects of DHIs [12,31,32]. In this study, we elucidated whether DHI engagement as defined by 2 *paradata* indicators (ie, frequency of log-ins and number of sessions viewed) are associated with participants' characteristics and the intervention's effect on several HIV-related behavior at the 90-day follow-up.

The participants who engaged in the myDEx intervention logged in at least 2 times, with a maximum of 14 times, in the 90-day intervention period. Moreover, the participants viewed an average of 7 sessions. However, there were 8/120 (6.7%) participants who never viewed any of the sessions, including the initial mandatory session. Varied engagement was driven by differences in the participants' sociodemographic characteristics and online behaviors. Similar to the study by Bonett et al [17], we found that both frequency and amount of engagement were greater among YMSM with higher educational attainment. We also noted lower amounts of engagement among Latino participants. DHIs have the potential to reduce HIV inequities among underserved communities, including racial and ethnic minority communities and populations with fewer socioeconomic resources [33]; however, our findings suggest that these inequities may not be resolved if the same populations are less likely to engage with DHIs. Efforts to address the digital divide by addressing health literacy [34], cultural competency [35], and high-quality access to technologies that facilitate DHI engagement are warranted. We recommend that future intervention studies examine the extent to which increasing health literacy and cultural factors as well as addressing online access barriers (eg, reducing entry barriers) may be warranted [36-38] to increase engagement among underserved populations that could benefit from DHIs.

Engagement was also linked to YMSM's online partner-seeking behaviors at baseline. Engagement was greater among YMSM who perceived online dating applications as a useful hookup tool and who self-reported interpersonal difficulties both online and offline (eg, greater loneliness and social isolation, greater discrimination in online settings, and reported overzealous romantic ideation or limerence). Taken together, these findings suggest the need to acknowledge and address the role that psychological factors may play in YMSM's DHI engagement. Given the correlation between psychological factors and HIV risk behaviors [39,40], researchers should explore how to address these psychological factors as part of the DHI implementation strategy to reduce the presence or severity of these HIV risk correlates while also creating opportunities to address other HIV risk factors in YMSM's lives. For example, participants who self-report social isolation or online discrimination at baseline may benefit from access or nudges to intervention components focused on social support earlier on in the intervention, whereas those reporting limerence may benefit from intervention content and activities related to affect regulation earlier in the intervention.

The participants who viewed a greater number of sessions showed significant decreases in experienced discrimination in an online setting and internalized homophobia over time. Given the complexity of cognitive decision-making in health behavior [41], we do not know whether participants who had negative experiences in an online setting engaged with the intervention more than others to enhance their resilience, which could increase their ability to bounce back from those negative experiences and resolve internalized homophobia. For instance, it is plausible that participants who experienced discrimination in an online setting and had high levels of internalized homophobia viewed more sessions in an effort to enhance their resilience [42]. To examine whether these changes would improve DHI engagement, we encourage researchers to leverage innovations in research designs in future efforts. For instance, to detangle these complex behavior-change processes during a DHI, researchers may need to monitor the participants' engagement and changes in their psychosocial behaviors in real time to understand these complex processes and respond by providing adequate intervention strategies. Just-in-time adaptive intervention designs [43] may facilitate these efforts given their ability to automatically detect changes in participants' behaviors in real time and to deliver intervention components most relevant to the participants' ongoing needs [36,44]. Just-in-time adaptive interventions have been used for various health behaviors, including addiction, mental health, and healthy diet [45]. Future intervention research examining whether optimized designs can increase DHI engagement is warranted.

The examination of various *paradata* metrics facilitates the understanding of accurate and meaningful engagement and outcome in DHIs. In this study, the amount of engagement (ie, sessions viewed) was significantly associated with internet use patterns, psychological facilitators and barriers, and partner-seeking correlates. However, the frequency of engagement (ie, the number of log-ins) was not associated with any of these factors. There is a tendency to assume the number of log-ins as the only *paradata* metric, but the results of this study highlight that the amount of intervention content participants consumed is a more meaningful measure to capture their behavior change. While traditional face-to-face interventions can control participants' engagement through an intervention facilitator, DHIs offer no similar function to guarantee full use after the participants log in. However, we cannot conclude that the quality of engagement is better than the quantity of engagement. It is possible that meaningful correlates with the number of log-ins were not examined in this study, and meaningful *paradata* metrics could vary by study. Therefore, a rigorous measurement of *paradata* metrics to describe meaningful engagement in DHIs is needed. Future research investigating an array of *paradata* metrics to explain true engagement is warranted.

### Limitations

There are several limitations in this study. First, we selected 2 standardized metrics of engagement to understand frequency and amount as engagement domains, yet we recognize that other domains (eg, depth and duration) and metrics (eg, time spent in each component and use over time) may also be important to examine [9]. It may be worthwhile to consider how the proportion of engagement was linked to active learning (eg, interactive activities) compared to passive learning (eg, reading content) in future research. Unfortunately, we did not collect depth of engagement in our study. Future intervention studies examining how different engagement domains (in-depth engagement) may be related to DHI engagement are warranted. Second, we did not have a priori threshold to define optimal engagement for the number of sessions viewed and log-ins. In the absence of thresholds that may be used across studies, we will use the engagement data collected during this pilot trial to inform thresholds for a subsequent, large-scale clinical trial of the myDEx intervention. It also remains unclear whether comparable rates of engagement would be observed outside of a clinical trial. Therefore, future research examining how participants engage in myDEx, both within and outside of a clinical setting, is needed to characterize its potential as an intervention that may be used beyond a 3-month period. Third, we could not establish causal relationships between engagement and changes in characteristics. This study hypothesized that increased engagement led to changes in psychosocial and behavioral characteristics, but this can be interpreted in the opposite direction, such that changes in behavior lead to more engagement. Future research examining how changes in participants' DHI engagement over time are related to the changes in hypothesized intervention mechanisms and key outcomes is warranted.

## Conclusions

*Paradata* analyses are a vital component of DHI evaluation. Determining intervention efficacy has proven challenging due to the absence of a consensus on what constitutes effective or meaningful engagement [16]. This study highlighted internet use patterns, psychological facilitators and barriers, and partner-seeking correlates associated with intervention engagement. Therefore, DHIs with personalized intervention components that consider the individuals' differences could increase the overall engagement and efficacy of the intervention. Moreover, research identifying which components are popular in an intervention, which components work best for whom, and which intervention duration would derive the optimum result is warranted to increase the participants' engagement.

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## Conflicts of Interest

None declared.

Multimedia Appendix 1
Comparing descriptive statistics at baseline and 90-day follow-up.
[DOCX File , 20 KB - publichealth_v8i6e33867_app1.docx ]

Multimedia Appendix 2
Associations between baseline characteristics and myDEx engagement.
[DOCX File , 18 KB - publichealth_v8i6e33867_app2.docx ]

Multimedia Appendix 3
Changes in the participants' behaviors based on myDEx engagement.
[DOCX File , 17 KB - publichealth_v8i6e33867_app3.docx ]

Multimedia Appendix 4
CONSORT-eHEALTH Checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1224 KB - publichealth_v8i6e33867_app4.pdf ]

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## Abbreviations

**CAI:** condomless anal intercourse
**DHI:** digital health intervention
**HMP:** healthMpowerment.org
**MSM:** men who have sex with men
**YMSM:** young men who have sex with men

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Original Paper

# Effect of Switching Antiretroviral Treatment Regimen in Patients With Drug-Resistant HIV-1 Infection: Retrospective Observational Cohort Study

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## Abstract

**Background:** Evidence on the efficacy of antiretroviral therapy (ART) regimen switches on the mortality of patients with HIV drug resistance (HIVDR) is limited.

**Objective:** We aim to provide policy guidance for ART regimen selection and evaluate the effectiveness of ART regime switches for people living with HIV and HIV-1 drug resistance.

**Methods:** This retrospective observational cohort study included 179 people living with HIV and HIV-1 drug resistance from 2011 to 2020. The time that participants switched treatment regimens either to protease inhibitor (PI)–based ART regimens (PIs) or nonnucleoside reverse transcriptase inhibitor (NNRTI)–based ART regimens (NNRTIs) was taken as an observation starting point and followed up every 12 months. The parametric g-formula was used to estimate the 5-year risk of mortality under the situations of (1) natural course, (2) immediate switch to NNRTIs, (3) immediate switch to PIs, and (4) if CD4(+) T cells<200 switched to PIs.

**Results:** The follow-up time of the 179 patients ranged from 30 to 119 months. The median follow-up time was 90 months. During a follow-up of 15,606 person-months, 27 individuals died in the cohort. The estimated 5-year risk of mortality under natural course, immediate switch to NNRTIs, immediate switch to PIs, and if CD4(+), and switch to PIs if T cells<200 were 11.62% (95% CI 7.82-17.11), 31.88% (95% CI 20.79-44.94), 2.87% (95% CI 0.32-7.07), and 5.30% (95% CI 2.07-10.21), respectively. The risk ratios (RRs) of immediate switch to NNRTIs, immediate switch to PIs, and switch to PIs if CD4(+) T cells<200, compared with natural course mortality rate, were 2.74 (95% CI 2.01-3.47), 0.25 (95% CI: 0.04-0.54), and 0.46 (95% CI 0.22-0.71), respectively. The risk differences were 20.26% (95% CI 10.96-28.61), –8.76% (95% CI –13.34 to –5.09) and –6.32% (95% CI –9.75 to –3.11), respectively.

**Conclusions:** Our study found that a PI-based ART regimen was beneficial for reducing mortality in people living with HIV and HIV-1 drug resistance. More effort should be given to find HIV-1 drug resistance earlier to ensure a timely adjustment to PI-based ART, thereby maximizing the benefit of early switch treatment for people living with HIV and HIV-1 drug resistance.

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**KEYWORDS**

HIV; antiretroviral therapy; drug resistance; protease inhibitors; parametric g-formula

# Introduction

The widespread use of antiretroviral therapy (ART) has effectively prolonged the life span of people living with HIV and has reduced the risk of HIV transmission [1]. However, many challenges have emerged with the promotion and use of ART [2,3]. HIV drug resistance (HIVDR) is a critical cause of virological failure in people living with HIV. It compromises the therapeutic effects for individuals and endangers the population [4]. Between 2016 and 2030, a pretreatment HIVDR level of over 10% (mean 15%), 16% of AIDS deaths, 9% of new infections, and 8% of ART program costs in sub-Saharan Africa will be attributable to HIVDR [5]. In limited-income countries, ART failure based on nonnucleoside reverse transcriptase inhibitors (NNRTIs) occurs in 10%-30% of people living with HIV per year [6-8].

A protease inhibitor (PI)–based ART regimen includes 2 nucleoside reverse transcriptase inhibitor (NRTI) drugs (zidovudine/tenofovir and lamivudine, TDF/AZT and 3TC), and 1 of the PI drugs (lopinavir and ritonavir; LPV/r) [9]. Boosted PI options are currently recommended as part of second-line regimens due to their safety and efficacy, as proven by systematic reviews and meta-analyses [10,11]. Patients with HIVDR on NNRTIs should, in principle, switch to PIs as soon as possible, as a delay in switching treatment regimens has led to increased mortality [12-16]. However, it is still common to delay the switch [17,18]. Several observational studies have investigated the estimated effect of the delayed switch to PIs on mortality. Tsegaye et al [15] found that the risk of death was 4.8 times higher for people with HIV who did not switch to PIs than those who did switch. Gsponer et al [16] showed a drastic reduction in mortality for patients who switched to PIs compared to those who did not based on an immunological criterion of failing and the benefit of switching early. Petersen et al [19] estimated that among HIV-infected patients with confirmed virologic failure on NNRTIs, remaining on NNRTIs led to an increase in mortality relative to switching to PIs.

In China, only a few studies have compared the differences in immunological outcomes and drug resistance between PIs and NNRTIs among people living with HIV [20,21], more so for people living with HIV who developed resistance to NNRTIs, as not all of them could immediately switch to PIs and instead switched to other NNRTIs due to limited health resources. However, no studies have compared the mortality difference between switching to other NNRTIs and switching to PIs in China. Since information on the effect of ART regimen switches on the mortality of patients with HIV is limited, research is warranted to accurately judge ART regimen switches and guide the regimen selection for optimal treatment.

To fill these research gaps, we conducted a 9-year retrospective cohort study to compare the impact of switches to other NNRTIs and switches to PIs on mortality in Sichuan, where the largest population of people with HIV resides in China [22]. The parametric g-formula adjusted the time-varying confounders affected by previous treatments [23]. We chose the parametric g-formula since traditional multivariate regression techniques may yield biased treatment effect estimates in our context. In contrast, the parametric g-formula can appropriately adjust for measured time-varying confounders. This research aims to guide policies on ART regimen selection and evaluate the effectiveness of ART regimen switches in people living with HIV and HIV-1 drug resistance.

# Methods

## Study Design and Participants

A retrospective observational cohort study was conducted based on the National Free Antiretroviral Treatment Program database of Sichuan. This confidential, nonpublic database is managed by the Chinese Center for Disease Control and Prevention. Each province, municipality, and autonomous region has access to data within its jurisdiction.

Participants of this study were selected from the database according to the following inclusion criteria: people living with HIV who (1) were under NNRTIs based ART regimens for 12 months in Sichuan during 2011-2014; (2) failed those NNRTI-based ART regimens with viral load ≥1000 copies/ml; (3) were tested for HIV-1 genotype resistance and confirmed to have HIV-1 drug resistance; and (4) received at least 1 test of CD4(+) T cells and viral load during the follow-up period. The exclusion criteria included people living with HIV (1) without immunological outcomes after switching ART regimen during the follow-up period; and (2) who did not have the demographic information (eg, gender, age, and ART) in the baseline database. A total of 2037 people living with HIV tested for HIV-1 genotype resistance, and 197 were confirmed to have HIV-1 drug resistance. Of these 197 people with HIV, 18 were excluded without detecting CD4(+) T cells and viral load during the follow-up period. Finally, 179 people with HIV were included in the final analysis.

In 2011, the first person living with HIV entered the cohort, and the last one entered in 2014. The starting point of observation was defined as when the person with HIV switched treatment regimens, and each person living with HIV was followed up from the entry date to the date of death or the end of this study (December 2020). A total of 179 participants met the inclusion criteria and were included in this study. They were followed up approximately every 12 months for documentation of their CD4(+) T cell count, viral load, and drug resistance. We estimated and compared the mortality risks of 3 simulated ART regimen switch scenarios with the real-world scenario (natural course), including (1) immediate switch to NNRTIs, (2) immediate switch to PIs, and (3) switch to PIs if CD4(+) T cells<200

## Ethics Approval

The Ethical Committee of Sichuan Center for Disease Control and Prevention approved this study (No. SCCDCIRB2021-025). This study was conducted in accordance with the Declaration of Helsinki.

## Data Collection

The NNRTI and PI regimens were carried out following the approved guidelines [24]. NNRTI regimens consisted of tenofovir/zidovudine (TDF/AZT) + lamivudine (3TC) +

efavirenz/ nevirapine (EFV/NVP). PI regimens included tenofovir/zidovudine (TDF/AZT) + lamivudine (3TC) + lopinavir and ritonavir (LPV/r).

The CD4(+) T cell count and viral load were collected at the starting point every 12 months of follow-up to evaluate the immunological reconstruction effect. ART regimens and survival status were also included in the follow-up. To deal with missing CD4(+) T cell count during the followed-up period, we used the expectation-maximization-bootstrap algorithm for multiple imputations [25]. The imputation model included all baseline and follow-up variables (including lagged and lead versions). The algorithm accounted for the nonlinear and longitudinal structure of the data.

### Covariates

All baseline characteristics were taken as covariates—demographic and HIV-related characteristics and immunological outcomes. Demographic characteristics included age, gender, and education level. HIV-related characteristics included transmission patterns, history of sexually transmitted diseases, and history of tuberculosis treatment.

### Laboratory Tests

All participants provided blood specimens to measure CD4(+) T cell count at the starting point and during follow-up after switching treatment regimens, measured using flow cytometry (FACSC Calibur, BD). Real-time molecular beacon detection was applied to detect the viral load of HIV (NucliSens EasyQ Analyzer). Reverse transcription-polymerase chain reaction (RT-PCR) was used to amplify a 1300-bp fragment of the HIV pol gene for drug resistance mutation analysis and viral subtype determination. Successfully amplified sequences were analyzed for HIVDR using the Stanford University HIV Drug Resistance Database. All experimental protocols followed the manufacturer's instructions. People living with HIV with low or higher drug resistance to one or more drugs were considered as having HIVDR [26-28].

### Statistical Analysis

Adjustment is usually used for confounders in regression models (eg, the Cox proportional hazards model), which is equivalent to estimating the hazard ratios of a specific stratum and then averaging the information-weighted hazard ratios. When some of these confounding factors are also causal intermediates, the effects of exposure are adjusted [29]. However, the first step in g-formula is to obtain the weighted averages of the stratum-specific hazards and then combine the averaged (standardized) hazards into a summary hazard ratio. The potential bias arising from time-varying covariates that can be both confounders and causal intermediates is a drawback of using regression models [30,31], which can be overcome by using the g-formula [32]. This study considers that patients' treatment regimens differed by their CD4(+) T cell count and viral load, which were also influenced by their previous treatment regimens and other baseline covariates. The outcomes (death) were influenced by time-varying treatment regimens and time-varying covariates (eg, CD4(+) T cell count and viral load level), and baseline characteristics (Multimedia Appendix 1). Our estimates had to adjust the time-varying confounders CD4(+) T cell count and viral load level and confounders measured at baseline. Since standard statistical methods cannot appropriately adjust for time-varying confounders affected by previous ART treatment [23], we applied the parametric g-formula to obtain adjusted estimates (eg, mortality risk) for each treatment strategy under the assumptions of conditional exchangeability, positivity, no residual confounding, no measurement error, and no model misspecification [32,33].

Specifically, the procedure of the parametric g-formula had 3 steps. First, we fit separate logistic regression models for the treatment and viral load and linear regression models for CD4(+) T cell count. All regression models included time-varying covariates (treatment, viral load level, and CD4(+) T cell count) and baseline variables (age, gender, education level, marital status, patterns of transmission, history of sexually transmitted diseases, and history of tuberculosis treatment). The assumed relationships between all variables are depicted in Multimedia Appendix 1. Second, a pseudo sample more prominent than the overall sample size, set as 10,000 in this study, was generated by Monte Carlo simulation based on the distribution of the postbaseline outcomes and time-varying covariates separately under each ART regimen switch scenario. Third, a bootstrap sampling method was used to repeat the aforementioned process 500 times to obtain the 95% CIs [34].

The RRs and risk differences (RDs) and their 95% CIs were estimated to compare the mortality risk between the natural course and 3 hypothetical ART switch strategies. To explore the validity of our parametric assumptions, we compared the observed (nonparametric estimates) means of the outcome and time-varying covariates with those predicted by our models (parametric g-formula estimates) (Multimedia Appendix 2). All statistical analyses were performed using R 4.0.3 (R Foundation for Statistical Computing).

### Sensitivity Analyses

A total of 4 sensitivity analyses were performed in this study to ensure the stability of the results. First, we excluded people older than 60 years at baseline since they may have a higher risk of death. Second, CRF01_AE was the primary subtype of people living with HIV in Sichuan; thus, we restricted to the subset of participants with the CRF01_AE subtype to estimate the mortality risk. Third, we fit linear regression models for the viral load as a continuous variable to estimate the results. Fourth, we reexamined the hazard ratios using a time-dependent Cox proportional risk model.

## Results

### Baseline Characteristics of the Participants

A total of 179 participants (79 immediately switched to the PIs, 35 immediately switched to the NNRTIs, and 65 switched to other NNRTIs and then to PIs) were included in our study. The initial conditions of people living with HIV among the 3 switched ART groups were comparable except for the age, CD4(+) T cell counts, and viral load (Multimedia Appendix 3). Of the 179 participants, 138 (77.1%) were male, 90 (50.3%) were married, and 91 (50.8%) were younger than 40 years at baseline (Table 1). Heterosexual transmission was the dominant transmission route (72.6%). About 24.6% of the participants achieved higher than a senior high school level education. Of the participants, 19 (10.6%) had other sexually transmitted diseases (STDs), 18 (6.9%) had tuberculosis, and 110 (61.5%) had CRF_01AE HIV-1 subtype (Table 1). Additionally, 145 participants (81%) had CD4(+) T cell counts<200, and 114 (63.7%) had viral load ≥10,000 copies/ml (Table 1).

**Table 1.** Baseline characteristics of the study participants.

| Baseline characteristics | Overall mean (SD) | Median (IQR) follow-up, month | Mortality (per 1000 person-months) |
|---|---|---|---|
| Overall | 179 (100) | 90 (80-101.5) | 1.73 |
| **Age (years)** | | | |
| ≤40 | 91 (50.8) | 93 (85.5-103) | 1.22 |
| >40 | 88 (49.2) | 87.5 (74.75-99.5) | 2.30 |
| **Gender** | | | |
| Male | 138 (77.1) | 92 (80.25-102) | 1.66 |
| Female | 41 (22.9) | 88 (76-99) | 1.95 |
| **Education level** | | | |
| No formal education | 9 (5.0) | 93 (87-105) | 2.39 |
| Primary or junior high school | 126 (70.4) | 91 (77.75-102.75) | 1.92 |
| Senior high school or more | 44 (24.6) | 90 (81.75-98) | 1.04 |
| **Marital status** | | | |
| Married | 90 (50.3) | 89 (79-95) | 1.75 |
| Unmarried/widowed/divorced/separated | 89 (49.7) | 93 (81.75-104.75) | 1.71 |
| **Pattern of transmission** | | | |
| Heterosexual | 130 (72.6) | 90.5 (80-102.75) | 1.76 |
| Homosexual | 36 (20.1) | 90 (81.75-98) | 1.29 |
| Other | 13 (7.3) | 89 (80-98) | 2.67 |
| **Had other STDs**[a] | | | |
| Yes | 19 (10.6) | 92 (82.5-94) | 2.56 |
| No | 119 (66.5) | 90 (80-101) | 1.93 |
| Unknown | 41 (22.9) | 91 (76-103) | 0.81 |
| **Had been treated for tuberculosis** | | | |
| Yes | 18 (10.1) | 92.5 (86.25-103) | 0 |
| No | 161 (89.9) | 90 (79-101) | 1.94 |
| **Baseline CD4(+) T (cells/ μ L)** | | | |
| <200 | 145 (81.0) | 90 (77-101) | 1.92 |
| ≥200 | 34 (19.0) | 92 (82.25-104.5) | 0.96 |
| **Baseline viral load copies/Ml** | | | |
| <10000 | 65 (36.3) | 93 (87-103) | 1.53 |
| ≥10000 | 114 (63.7) | 88.5 (77.5-98.75) | 1.85 |
| **HIV subtype** | | | |
| CRF01_AE | 110 (61.5) | 90.5 (80.25-101.75) | 1.56 |
| CRF07_BC | 50 (27.9) | 89 (75.25-94) | 2.37 |
| Others | 19 (10.6) | 98.0 (84.5-104.5) | 1.15 |

[a] STD: sexually transmitted disease.

## Follow-up and Mortality

The follow-up time of 179 patients ranged from 30 to 119 months, and the median follow-up time was 90 months. During a follow-up of 15,606 person-months, 27 individuals from the cohort died. The overall mortality was 1.73 per 1000 person-months (Table 1). The observed mortality rates were higher in individuals with lower CD4(+) T cell count and older age at baseline (Table 1).

## Estimated Risk of Mortality

The estimated 5-year risk of mortality under natural course was 11.62% (95% CI 7.82-17.11). The estimated 5-year risk of mortality of the 3 ART regimen switch scenarios of an immediate switch to NNRTIs, immediate switch to PIs, and switch to PIs if CD4(+) T cells <200 was 31.88% (95% CI 20.79-44.94), 2.87% (95% CI 0.32-7.07), and 5.30% (95% CI 2.07-10.21), respectively (Table 2). The mortality risk for the 4 treatment regimens scenarios increased over time, with the fastest mortality rate for immediate switch to NNRTIs scenario and the slowest rate for immediate switch to PIs scenario (Figure 1).

Using the parametric g-formula, the RRs of immediate switch to NNRTIs, immediate switch to PIs, and switch to PIs if CD4(+) T cells<200, compared with natural course mortality rate, were 2.74 (95% CI 2.01-3.47), 0.25 (95% CI 0.04-0.54), and 0.46 (95% CI: 0.22-0.71), respectively, and the RDs were 20.26% (95% CI 10.96-28.61), −8.76% (95% CI −13.34 to −5.09), and −6.32% (95% CI −9.75 to −3.11), respectively. The effect of the sensitivity analyses estimates of the 5-year risk of mortality, RRs, and RDs of the 3 ART regimen switch scenarios were robust (Multimedia Appendix 4, Figures 2-4). The Cox proportional risk model results showed the hazard ratio (HR) of mortality among people living with HIV with an immediate switch to PIs (HR=0.11, 95% CI 0.03-0.39), and the switch to other NNRTIs and then to PIs (HR=0.08, 95% CI 0.02-0.33) was lower than those with the immediate switch to NNRTIs (Multimedia Appendix 5).

**Table 2.** Estimated risks of mortality under 4 antiretroviral therapy (ART) switched strategies for individuals tested for HIV-1 genotype resistance from ART in Sichuan from 2011 to 2020[a].

| Switched treatment regimens | 5-year risk of mortality (95% CI) | RR[b], (95% CI) | RD[c], % (95% CI) |
|---|---|---|---|
| Natural course | 11.62 (7.82-17.11) | 1 (Ref[d]) | 0 (Ref[d]) |
| Immediate switch to NNRTIs[e] | 31.88 (20.79-44.94) | 2.74 (2.01-3.47) | 20.26 (10.96- 28.61) |
| Immediate switch to PIs[f] | 2.87 (0.32-7.07) | 0.25 (0.04-0.54) | −8.76 (−13.34 to −5.09) |
| If CD4(+) T cells<200 switched to PIs. | 5.30 (2.07-10.21) | 0.46 (0.22-0.71) | −6.32 (−9.75 to −3.11) |

[a] Estimates based on the parametric g-formula adjusted for measured time-varying confounders (CD4(+) T cells count, viral load, and treatment) and baseline characteristics (age, gender, education level, marital status, pattern of transmission, history of sexually transmitted diseases, and history of tuberculosis treatment). Natural course means that the ART regimen is observed without simulated intervention. Natural course mortality was subtracted from estimated mortality for each group.

[b] RR: risk ratio.

[c] RD: risk difference.

[d] Ref: reference object.

[e] NNRTIs: nonnucleoside reverse transcriptase inhibitor–based ART.

[f] PIs: protease inhibitor–based ART.

**Figure 1.** Mean of the mortality outcome for individuals who were tested for HIV-1 genotype resistance from antiretroviral therapy (ART) in Sichuan, China, simulated via the parametric g-formula. NNRTIs: nonnucleoside reverse transcriptase inhibitor–based antiretroviral therapy; PIs: protease inhibitor–based ART.

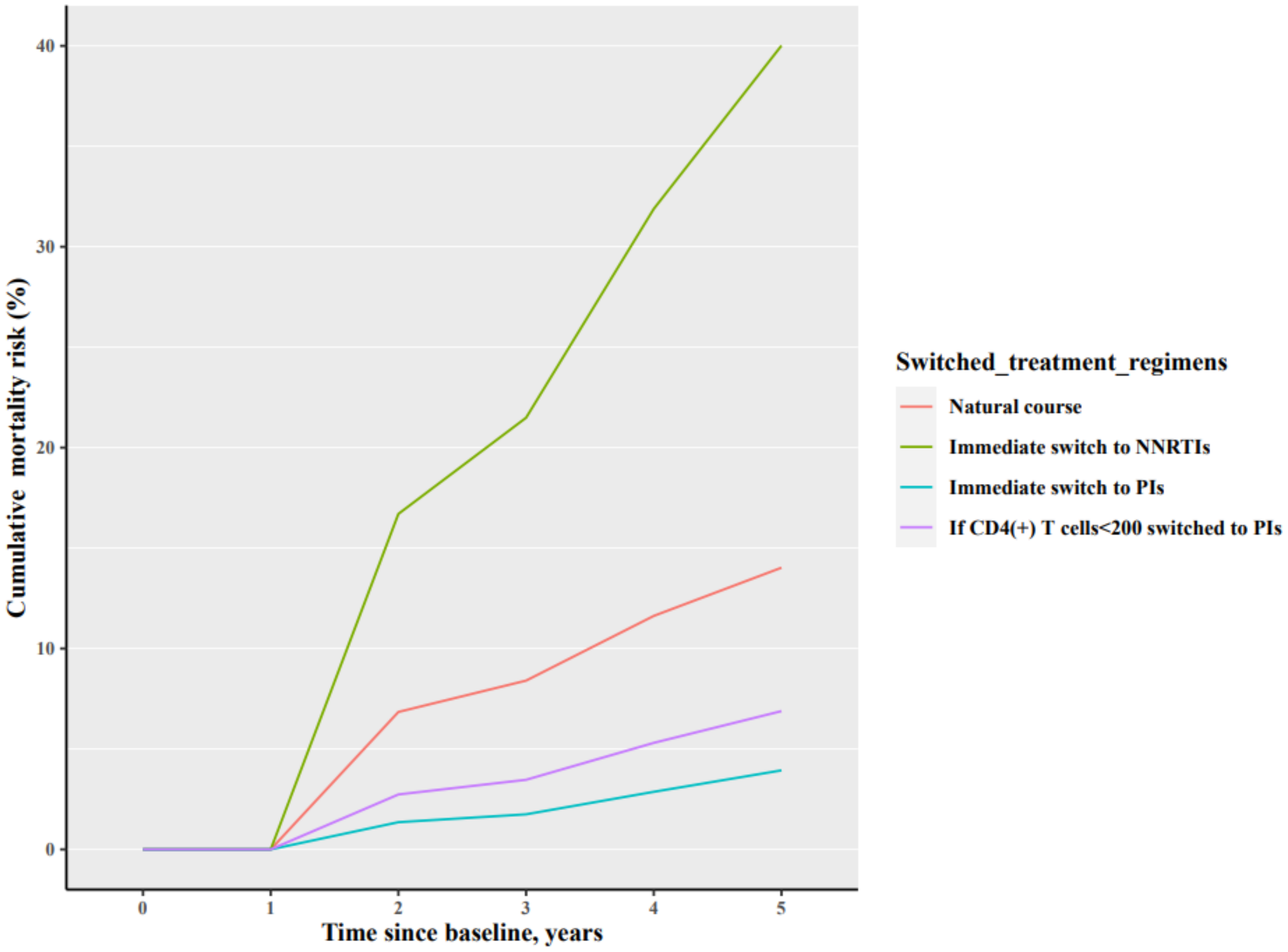


**Figure 2.** Five-year risk of mortality under 4 analyses. 1: primary analyses (viral load as a binary variable); 2: individuals lower than 60 years at baseline; 3: individuals with a CRF01_AE subtype; 4: viral load as a continuous variable. NNRTIs: nonnucleoside reverse transcriptase inhibitor–based antiretroviral therapy (ART); PIs: protease inhibitor–based ART.

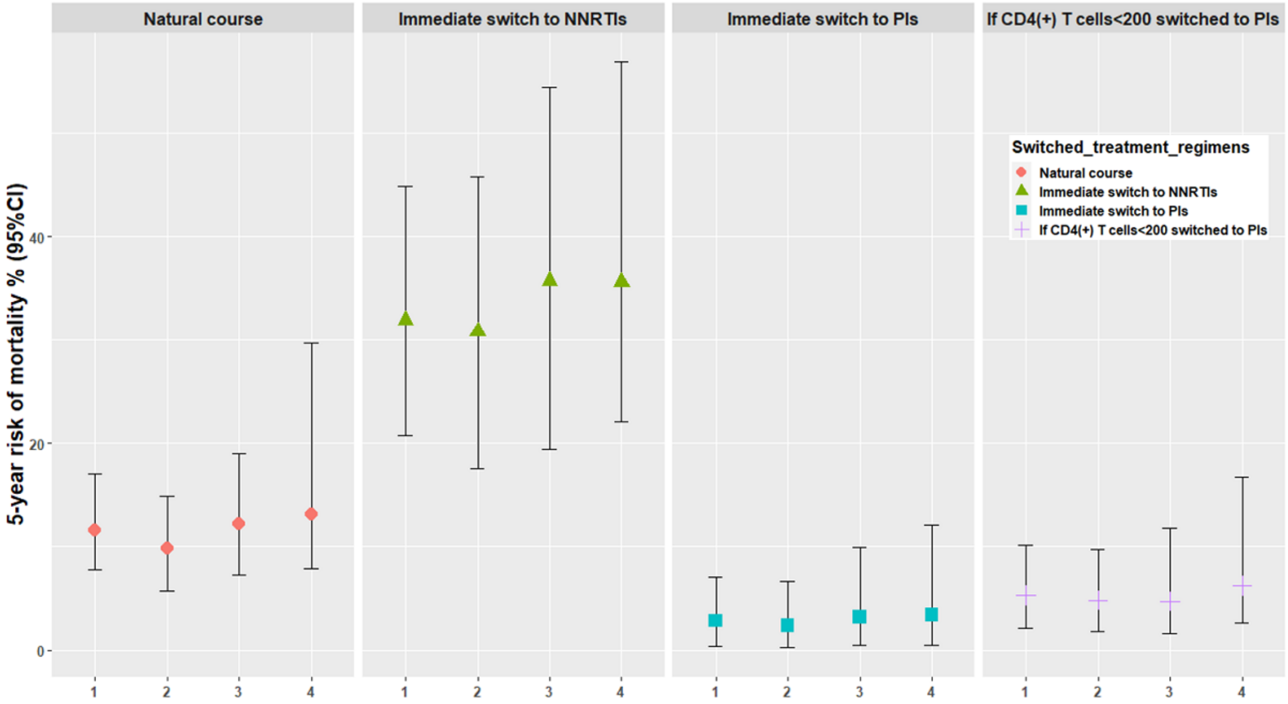


**Figure 3.** Risk ratio of mortality under 4 analyses. 1: primary analyses (viral load as a binary variable); 2: individuals lower than 60 years old at baseline; 3: individuals with a CRF01_AE subtype; 4: viral load as a continuous variable. NNRTIs: nonnucleoside reverse transcriptase inhibitor–based antiretroviral therapy (ART); PIs: protease inhibitor–based ART; RR: risk ratio.

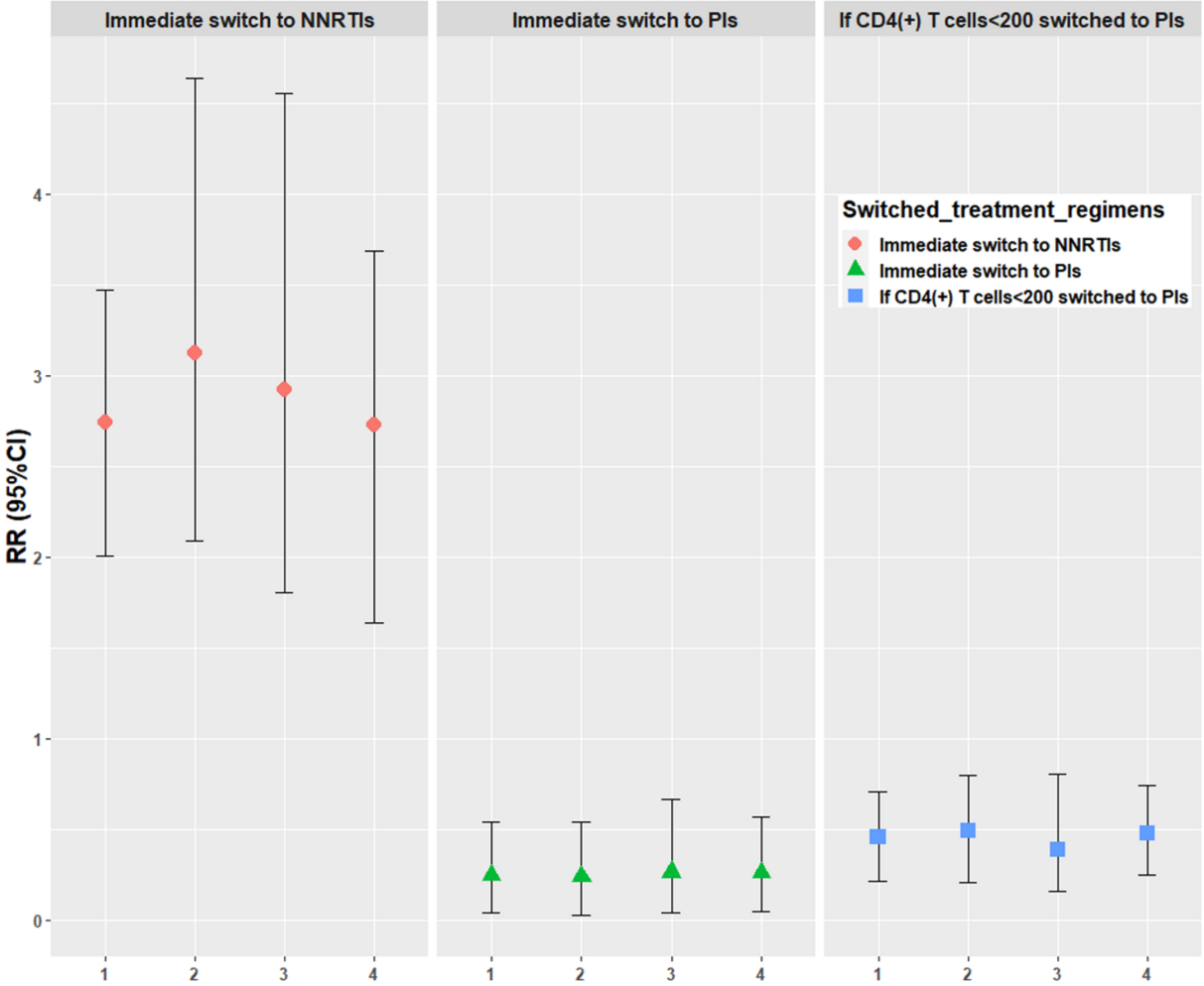
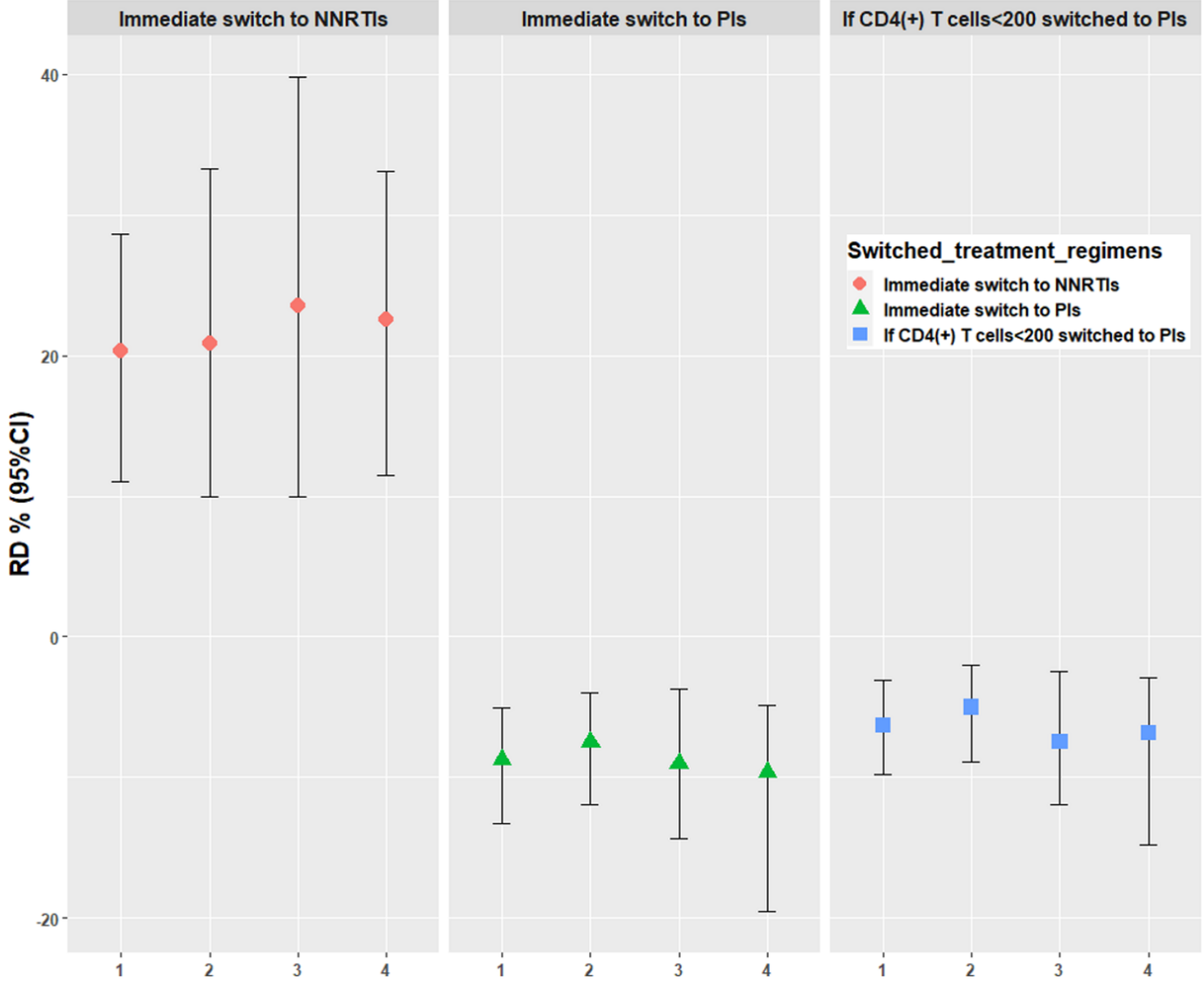


**Figure 4.** Risk difference of mortality under 4 analyses. 1: primary analyses (viral load as a binary variable), 2: individuals lower than 60 years old at baseline; 3: individuals with a CRF01_AE subtype; 4: viral load as a continuous variable. NNRTIs: nonnucleoside reverse transcriptase inhibitor–based antiretroviral therapy (ART); PIs: protease inhibitor–based ART; RD: risk difference.



## Discussion

### Principal Findings

This retrospective cohort study compared the mortality risk of ART switch regimens among people living with HIV with resistance to NNRTIs using the parametric g-formula method. It provided real-world evidence on the efficacy of PIs and NNRTIs switches. Our results indicate that switching to NNRTIs resulted in a higher mortality rate during the 9- year follow-up period. The 2 scenarios showing a switch to PIs were associated with lower mortality rates. This finding suggests that an immediate switch to PIs after confirmation of drug resistance can help reduce the mortality of people living with HIV and HIV-1 drug resistance.

The 5-year risk of mortality was 8.76% lower for an immediate switch to PIs and 6.32% lower when switched to PIs if CD4(+) T cells<200 compared to the natural course group, which means that in a hypothetical cohort of 100 patients with drug resistance, PIs would prevent about 6-8 deaths over 5 years. On the contrary, the 5-year risk of mortality was 20.26% higher for an immediate switch to NNRTIs when comparing the natural course scenario, meaning that NNRTIs would have an increase of 20 deaths over 5 years.

People living with HIV who switched to PIs had a lower mortality risk. Possible reasons for this might be that PIs could cross the resistance gene barrier and act on the resistant strains to inhibit virus replication [35] or that our participants might have had cross-resistance to NNRTIs and NRTI drugs [36]. If only NNRTIs drugs in the original ART regime were replaced (eg, switching NVP to EFV) or the drug type of NRTIs was replaced (eg, switching AZT to TDF), the immunological outcomes did not change due to the cross-resistance. There was a higher mortality risk if participants continued NNRTI-based ART.

A few studies reported that the resistance rates of NNRTIs and NRTIs were 80%-92% and 95%-100% after the failure of the NNRTI-based ART regimen, respectively [37,38]. With the therapy time prolonged, the resistance mutations of the reverse transcriptase inhibitor would accumulate, leading to severer cross-resistance. If the participants still switched to the NNRTIs, cross-resistance of the strains resulted in no significant improvement in follow-up therapy. Although LPV/r in China is free, the first condition for switching to PIs regimen is NNRTI resistance due to the limited resources of LPV/r in most provinces [20,39,40]. Therefore, it is important to monitor and detect drug-resistant patients to NNRTIs in a timely manner and switch to PIs to successfully inhibit the replication of NRTI- and NNRTI-mutant viruses. This monitoring will improve the virological and immunological effects, consequentially reducing mortality. Additionally, switching to PIs if CD4(+) T cells <200 is also effective for reducing the mortality risk if switching immediately without assessing cell count is impossible in some resource-limited areas.

## Strengths and Limitations

Our study has 2 strengths. First, we simulated interventions to evaluate the risk, risk difference, and risk ratio of mortality by contrasting estimates from idealized study settings with those from more realistic settings. Compared with standard statistical calculations, the parametric g-formula can be more easily used to evaluate the causal effect of complex interventions [41]. In particular, dynamic treatments [42] and joint interventions considering multiple factors can be explored naturally with this method. Second, to our knowledge, this is the first study to compare the mortality difference between switching to other NNRTIs and switching to PIs among people living with HIV with NNRTIs resistance, avoiding the ethical issues of randomized clinical trials.

Nonetheless, several limitations should be considered. First, as in all nonrandomized studies, our approach provided consistent (unbiased) estimates of the cumulative incidence of mortality under several assumptions: all variables (eg, CD4(+) T cell count, viral load, treatment, and death) were measured without error; patients' ART treatment at different CD4(+) T cell counts are exchangeable within levels of measured covariates, in that there are no unmeasured confounding variables [30]. However, we did not collect ART adherence information, which may influence the decision to switch ART regimens in patience with resistance to NNRTIs and may have biased our estimates. Second, the parametric g-formula requires that all models be correctly specified. This condition cannot be guaranteed, but it seems plausible because our models resulted in simulated data sets with means of the outcome and time-varying covariates similar to those in the original data (Multimedia Appendix 2). Third, although we collected the data of all patients who received HIV-1 genotype resistance, were confirmed to have HIV-1 drug resistance, and could be followed up, only 179 participants were included in our research. The small sample size may have led to low test efficiency. Moreover, many patients may not have receive HIV-1 genotype resistance between 2011 and 2014 since the drug resistance monitoring was only conducted in about 20% of people living with HIV, which may induce potential selection bias and influence the extrapolation of our results.

## Conclusion

Our study found that the PI regimen helped improve the survival time of people living with HIV and HIV-1 drug resistance. More efforts should be conducted to detect HIV-1 drug resistance earlier to ensure timely regimen switches, thereby maximizing the benefit of early switch ART regimens for people living with HIV and HIV-1 drug resistance and reducing their mortality.

## Acknowledgments

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## Authors' Contributions

SY, DY and QW took conceived the study idea, wrote the protocol, developed the methodologies, conducted analyses, and drafted and wrote the manuscript. SY, QW, YL, and CF made critical revisions to the manuscript. SY contributed to the write up of the study protocol and revised the paper. DY, H Yang, H Yu and SL collected, cleaned, and analyzed the data. All authors have read and approved the manuscript.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
Directed acyclic graph.
[DOCX File , 24 KB - publichealth_v8i6e33429_app1.docx ]

Multimedia Appendix 2
Mean of the mortality outcome and time-varying variables in persons living with HIV and HIV-1 drug resistance.
[DOCX File , 98 KB - publichealth_v8i6e33429_app2.docx ]

Multimedia Appendix 3
Basic characteristics of the population with 2 antiretroviral therapy (ART) regimens at the observed starting point.

[DOCX File , 17 KB - publichealth_v8i6e33429_app3.docx ]

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Multimedia Appendix 4
Estimated risks of mortality under 4 antiretroviral therapy (ART) switched strategies for 3 sensitivity analyses.
[DOCX File , 15 KB - publichealth_v8i6e33429_app4.docx ]

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Multimedia Appendix 5
Hazard ratios (HRs) and 95% CIs for association between mortality and antiretroviral therapy (ART) switched strategies according to Cox proportional hazards model.
[DOCX File , 14 KB - publichealth_v8i6e33429_app5.docx ]

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## Abbreviations

**ART:** antiretroviral therapy
**AZT:** zidovudine
**EFV:** efavirenz
**FPV/r:** fosamprenavir/ritonavir
**HIVDR:** HIV drug resistance
**HR:** hazard ratio
**ISLE:** International Institute of Spatial Lifecourse Epidemiology
**LPV/r:** lopinavir/ritonavir
**NNRTI:** nonnucleoside reverse transcriptase inhibitor
**NRTI:** nucleoside reverse transcriptase inhibitor
**NVP:** nevirapine
**NFV:** nelfinavir
**PI:** protease inhibitor
**RR:** risk ratio
**RD:** risk difference
**TDF:** tenofovir
**TPV/r:** tipranavir/ritonavir
**3TC:** lamivudine

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Original Paper

# Enablers and Barriers to HIV Services for Gay and Bisexual Men in the COVID-19 Era: Fusing Data Sets from Two Global Online Surveys Via File Concatenation With Adjusted Weights

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## Abstract

**Background:** Gay and bisexual men are 26 times more likely to acquire HIV than other adult men and represent nearly 1 in 4 new HIV infections worldwide. There is concern that the COVID-19 pandemic may be complicating efforts to prevent new HIV infections, reduce AIDS-related deaths, and expand access to HIV services. The impact of the COVID-19 pandemic on gay and bisexual men’s ability to access services is not fully understood.

**Objective:** The aim of this study was to understand access to HIV services at the start of the COVID-19 pandemic.

**Methods:** Our study used data collected from two independent global online surveys conducted with convenience samples of gay and bisexual men. Both data sets had common demographic measurements; however, only the COVID-19 Disparities Survey (n=13,562) collected the outcomes of interest (HIV services access at the height of the first COVID-19 wave) and only the Global Men’s Health and Rights Survey 4 (GMHR-4; n=6188) gathered pre-COVID-19 pandemic exposures/covariates of interest (social/structural enablers of and barriers to HIV services access). We used data fusion methods to combine these data sets utilizing overlapping demographic variables and assessed relationships between exposures and outcomes. We hypothesized that engagement with the gay community and comfort with one’s health care provider would be positively associated with HIV services access and negatively associated with poorer mental health and economic instability as the COVID-19 outbreaks took hold. Conversely, we hypothesized that sexual stigma and experiences of discrimination by a health care provider would be negatively associated with HIV services access and positively associated with poorer mental health and economic instability.

**Results:** With 19,643 observations after combining data sets, our study confirmed hypothesized associations between enablers of and barriers to HIV prevention, care, and treatment. For example, community engagement was positively associated with access to an HIV provider (regression coefficient=0.81, 95% CI 0.75 to 0.86; *P*<.001), while sexual stigma was negatively associated with access to HIV treatment (coefficient=–1.39, 95% CI –1.42 to –1.36; *P*<.001).

**Conclusions:** HIV services access for gay and bisexual men remained obstructed and perhaps became worse during the first wave of the COVID-19 pandemic. Community-led research that utilizes novel methodological approaches can be helpful in times of crisis to inform urgently needed tailored responses that can be delivered in real time. More research is needed to understand the full impact COVID-19 is having on gay and bisexual men worldwide.

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**KEYWORDS**

COVID-19; HIV services; gay and bisexual men; sexual health

## Introduction

Gay men and other men who have sex with men (MSM; hereafter referred to as gay and bisexual men) [1] are 26 times more likely to acquire HIV than other adult men, and in 2019 represented nearly 1 in 4 new HIV infections worldwide [2,3]. While biological and social factors converge to elevate the risk for HIV acquisition and transmission [4], structural barriers such as sexual stigma, discrimination, and criminalization of sex between men impede access to and utilization of HIV testing, prevention, and treatment services [5,6]. Conversely, factors such as community engagement and having supportive health care providers enable service access and utilization for gay and bisexual men [7].

The world remains off track in meeting global HIV targets, especially for socially marginalized and criminalized groups. For example, surveys from 114 nationally representative data sets in 38 African countries with nearly 1.5 million sexually active adults aged 15-49 years conducted from 2003 to 2018 were examined to estimate trends in annual HIV testing and condom use during the last occurrence of highest-risk sex. These data were used to calculate the probability of reaching key Joint United Nations Programme on HIV/AIDS (UNAIDS) targets. Investigators observed limited progress and little chance of reaching global targets [8]. There is now concern that the COVID-19 pandemic may further complicate efforts to bend the HIV incidence curve; reduce AIDS-related deaths; and expand prevention, care, and treatment coverage [2]. Recent research suggests that COVID-19 is exacerbating challenges gay and bisexual men face in their attempts to access HIV and other sexual health services. A recent study found deleterious economic and mental health consequences of COVID-19 and public health responses among a global sample of gay and bisexual men [9]. The same study also found significant interruptions to HIV testing, prevention, treatment, and care services. The role of COVID-19–related social and structural factors in gay and bisexual men's access to HIV-related services is less understood.

More evidence is needed for providing early and potentially critical programmatic and policy-related interventions in the era of COVID-19. This study utilized a statistical matching method that combined data sets (ie, data fusion) from two separate global online cross-sectional surveys to enable drawing inferences about the impact of the COVID-19 pandemic on gay and bisexual men's ability to access services. Neither data set could address the question individually, as one had only outcomes and demographics and the other only exposures and demographics. Data fusion allowed us to relate outcomes to exposures across the data sets. Specifically, this approach allowed us to explore social and structural enablers of and barriers to HIV service access among gay and bisexual men worldwide during the early days of the COVID-19 pandemic. We hypothesized that engagement with the gay community and comfort with one's health care provider would be positively associated with HIV services access and negatively associated with poorer mental health and economic instability despite the challenges brought about by COVID-19 outbreaks. Conversely, we hypothesized that sexual stigma and experiences of discrimination by a health care provider would be negatively associated with HIV services access and positively associated with poorer mental health and economic instability.

Our hypotheses are informed by social ecological theory, which suggests that various factors at structural, community, interpersonal, and individual levels facilitate or impede access to resources such as HIV and other health services. Social ecological theory is useful for identifying high-impact leverage points in the successful implementation of health-promoting interventions and for strategic alignment of policy and services across a continuum of population health needs [10,11].

## Methods

### Study Design

Our study used data collected from two independent surveys conducted with gay and bisexual men. The first, Global Men's Health and Rights Survey 4 (GMHR-4), was designed to explore correlates to HIV services access and utilization. GMHR-4 was launched on September 4, 2019, and closed on March 31, 2020 [12,13]. Slightly over 1% of participants took the survey after February 2020. Earlier versions of the survey are described elsewhere in greater detail [5,14]. GMHR-4 data were collected from a nonprobability internet sample of gay and bisexual men, recruited via organizational outreach, email listservs, gay dating apps, and websites. Participants were invited to complete a 20- to 30-minute online survey. Eligible participants who consented to take the survey needed to identify as male (cisgender or transgender); have had sex with another man in the last 6 months; be 18 years or older; and able to complete the online survey in Arabic, Chinese, English, French, Indonesian, Portuguese, Russian, Spanish, Swahili, or Vietnamese. No geographical restrictions were applied.

The second survey, COVID-19 Disparities Survey, was administered by Hornet between April 16, 2020, through May 4, 2020 [9]. Hornet is a free, smartphone-based gay social networking app with over 25 million users worldwide. Its users are predominantly gay and bisexual men. The COVID-19 Disparities Survey was a brief, 10- to 15-minute questionnaire, which sought to explore the impacts of COVID-19 on economic status, mental health, and HIV services access among Hornet users. Eligible participants were Hornet users, 18 years or older.

### Ethics Approval

Ethical approval for the use of GMHR-4 data was obtained from the Western Institutional Review Board, which determined that GMHR-4 was exempt under 45 CFR 46.104(d)(2) (#1-1174358-1). Study procedures for the COVID-19 Disparities Survey were reviewed by the Johns Hopkins School of Public Health Institutional Review Board, which designated the protocol as exempt under Category 4.

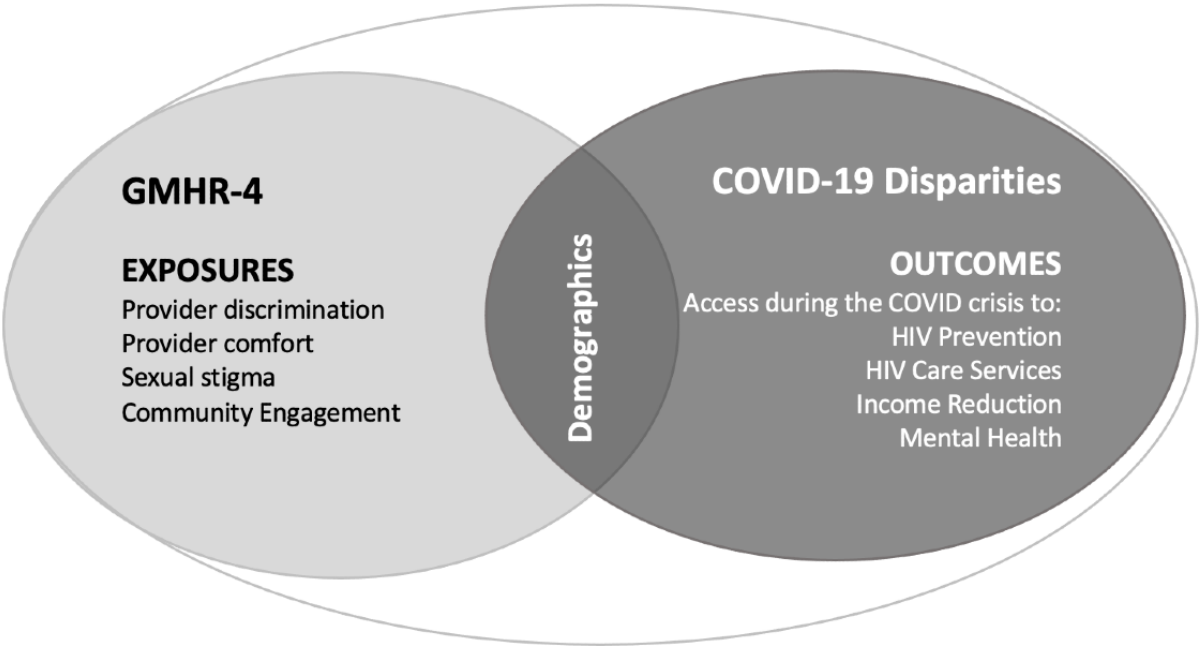
## Measures

Both surveys included *demographic questions* (eg, age, country of residence, sexual orientation, gender identity, relationship status, racial/ethnic minority status, ability to meet one’s basic financial needs, health care coverage, and HIV status). GMHR-4 included questions responded to on 5-point Likert scales, which asked about: (1) *engagement with the gay community,* assessed on a 10-item scale (Cronbach α=.72), including “During the past 6 months, how often have you participated in gay/bisexual/MSM with social groups?” with a response scale ranging from 1=never to 5=more than 12 times*;* (2) *comfort with one’s health care provider,* assessed on a 3-item scale (Cronbach α=.85), including “In your country, how comfortable do you feel discussing your sexual health concerns with your health care provider?” where 1=very uncomfortable and 5=very comfortable; (3) experiences of *sexual stigma* (ie, homophobia) using a 7-item scale (Cronbach α=.82), including “In your country, how many people believe that male homosexuals are disgusting?”, where 1=none, 2=a few, 3=some, 4=most, 5=all; and (4) *provider discrimination*, a 6-item scale (Cronbach α=.87), including “In the last 6 months, has a health care provider refused to treat you because you are gay/bisexual/MSM?” where responses ranged from 1=no-never to 5=yes more than 5 times.

The COVID-19 Disparities Survey asked participants about the impact COVID-19 was having on their economic situation; mental health; and ability to access HIV testing, prevention, care, and treatment services. *Economic impact* was assessed using the question: “How much are you expecting your income to reduce because of the COVID-19 crisis?” The economic impact question used a categorical response scale from 0% to 100%, ordered in 10-point increments. *Mental health* was assessed using validated items from the Patient Health Questionnaire-4 (PHQ-4), which is used to screen for depression and anxiety; scores ≥3 indicate psychological distress [15].

HIV services impact measures asked whether participants experienced changes in *access to condoms, HIV onsite HIV testing,* and *pre-exposure prophylaxis* (PrEP), such as “Do you feel you have access to HIV prevention strategies during the COVID-19 crisis, i.e., condoms, PrEP, onsite HIV testing?” The 5-point Likert scale response options ranged from “definitely yes” to “definitely no.” For participants living with HIV, the survey asked about *access to HIV providers*, such as “Since the beginning of the COVID-19 crisis, have you been able to see your HIV provider if you needed to?”, with the following response options: “Yes, in person”; “Yes, via telemedicine”; “No, because of reduced hours”; “No, because it is closed”; “Not applicable.” In addition, the survey assessed *treatment access* by asking, “Do special measures related to COVID-19 impact your ability to access or refill your HIV medicine?” Response options included: “I cannot access or refill my HIV medicine”; “I can access or refill my HIV medicine, but access is burdensome or complicated”; and “Not applicable.” Measures used for the data fusion analysis (described below) are depicted in Figure 1.

**Figure 1.** Venn diagram of Global Men’s Health and Rights Survey 4 (GMHR-4) and COVID-19 Disparities survey measures used for data fusion analysis. Demographic measures that overlap between the two studies' samples include: age, country of residence, sexual orientation, gender identity, relationship status, racial/ethnic minority status, ability to meet one’s basic financial needs, health care coverage, and HIV status.



## Statistical Analysis

Because we were examining data from two different surveys with only partial variable overlap (demographics in both data sets, exposures in one data set, and outcomes in the other data set), and we were interested in associations between nonoverlapping variables across these questionnaires, we utilized statistical matching (ie, data fusion) methods to combine the data sets [16,17] in STATA v15 (College Station, TX) with the community-contributed *smpc* and *smmatch* programs [18]. The data fusion method works as follows: data set A (which contains variables Y and X) and data set B (which contains variables X and Z) are concatenated and weighted. Y is regressed on X and Z is regressed on X, and a prespecified partial correlation $\rho_{Y,Z|X}$ (discussed below) is used to calculate joint regression coefficients and predict Y and Z values in the concatenated data set. Each individual missing Z (ie, from data set A) is matched to the closest new predicted Z in data set B. After matching, the observed value of the match is imputed as the missing value. A similar process is used for individuals missing Y (ie, from dataset B) [19]. In practice, a range of 5 partial correlation values has been shown to work well and reduce bias [17], and results can then be combined utilizing existing equations and frameworks from multiple imputation (but we note that the method is different than the usual multiple imputation). All predictors and outcomes are treated as continuous variables.

To make an initial informed estimate of the partial correlations between the outcomes from the COVID-19 Disparities Survey data set and the GMHR-4 predictors in the imputation prediction regression models, we calculated the partial correlations between each of the GMHR-4 predictors with the measure that we believed was the closest proxy to each of the outcomes in the COVID-19 data set, while accounting for the jointly observed demographic characteristics (income, education, relationship status, urbanicity [urban vs rural], racial/ethnic minority status, health insurance, and region [Global North vs Global South]). For example, we calculated the partial correlation between the exposure, community engagement, and access to HIV testing in the GMHR-4 data set, while accounting for the jointly observed demographic variables. We then used this partial correlation value in the prediction model for community engagement and the outcome of access to HIV testing during COVID-19 in the COVID-19 Disparities Survey data set. That is, we assumed that the partial correlation between community engagement and access to HIV testing in GMHR-4 was a reasonable approximation for the partial correlation between community engagement in GMHR-4 and access to HIV testing during COVID-19 in the COVID-19 Disparities Survey data set. The range of partial correlations used in the fusion procedure included this initial informed estimate, ±5%, and ±10%.

For each partial correlation value and resulting fused data set, we then performed linear regressions between the imputed outcomes and exposures [17]. In these models, outcomes included access (during the COVID-19 crisis) to onsite HIV testing, condoms, PrEP, HIV care, HIV treatment, and mental health services; exposures (covariates of interest) included sexual stigma, provider discrimination, provider comfort, and engagement in the gay community. The models also adjusted for income, education, relationship status, urbanicity (urban vs rural), racial/ethnic minority status, health insurance, and region (Global North vs Global South). In sensitivity analyses, we limited the covariates in the regression models to the demographic characteristics above, exclusive of urbanicity and region.

## Results

### Sample Characteristics/Matched Variables

A total of 19,643 observations from gay and bisexual men were included in this study after combining outcomes from the GMHR-4 (n=6189) with exposures from the COVID-19 Disparities Survey (n=13,454) through overlapping demographics via data fusion (see Figure 1). Among the total sample, 44.00% (8643/19,643) of participants were under the age of 30 years and 57.00% (11,197/19,643) indicated an inability to financially meet their basic needs. Participants had a high level of education, with 54.00% (10,607/19,643) having completed college. Global northerners (participants from Europe, Canada, the United States, Australia, and New Zealand) and southerners (participants from Africa, Asia, the Caribbean, Latin America, the Middle East, and Pacific Islands) were nearly equally represented in the combined data set. Higher proportions of GMHR-4 study participants reported an HIV-positive status, were from the Global South, and had completed a college education when compared with study respondents from the COVID-19 Disparities Survey. Participant demographics are more fully summarized in Table 1.

**Table 1.** Participant demographic characteristics jointly observed across both data sets.

| Characteristics | Total[a] (N=19,643), n (%) | GMHR-4[b] (n=6189), n (%) | COVID-19 Disparities (n=13,454), n (%) |
|---|---|---|---|
| **Age (years)** | | | |
| <20 | 1287 (6.55) | 537 (8.68) | 750 (5.57) |
| 20-29 | 7234 (36.83) | 2687 (43.42) | 4547 (33.80) |
| 30-49 | 9240 (47.04) | 2528 (40.85) | 6712 (49.89) |
| 50+ | 1878 (9.56) | 433 (7.00) | 1445 (10.74) |
| **Economic status** | | | |
| Not able to meet needs well | 11,275 (57.40) | 3982 (64.34) | 7293 (54.21) |
| Able to meet needs well | 8368 (42.60) | 2207 (35.66) | 6161 (45.79) |
| **Education** | | | |
| Did not complete college | 9031 (45.98) | 1553 (25.09) | 7478 (55.58) |
| Completed college | 10,612 (54.02) | 4636 (74.91) | 5976 (44.42) |
| **Relationship status** | | | |
| In a relationship | 5725 (29.15) | 1673 (27.03) | 4052 (30.12) |
| Not in a relationship | 13,918 (70.85) | 4516 (72.97) | 9402 (69.88) |
| **Location of residence** | | | |
| Not in a city/urban area | 4070 (20.72) | 831 (13.43) | 3239 (24.07) |
| Resides in a city/urban area | 15,573 (79.28) | 5358 (86.57) | 10,215 (75.93) |
| **Racial and ethnic background** | | | |
| Not a racial or ethnic minority | 16,117 (82.05) | 4733 (76.47) | 11,384 (84.61) |
| Racial or ethnic minority | 3526 (17.95) | 1456 (23.53) | 2070 (15.39) |
| **Health insurance** | | | |
| No | 5398 (27.48) | 1908 (30.82) | 3490 (25.94) |
| Yes | 14,245 (72.52) | 4281 (69.17) | 9964 (74.06) |
| **Region** | | | |
| Global South | 9671 (49.23) | 5563 (89.89) | 4108 (30.53) |
| Global North | 9741 (49.59) | 598 (9.66) | 9143 (67.96) |
| **HIV status** | | | |
| Not living with HIV | 17,194 (87.53) | 5173 (83.58) | 12,021 (89.35) |
| Living with HIV | 2449 (12.47) | 1016 (16.42) | 1433 (10.65) |

[a] Values may not necessarily add to column totals due to missing responses from participants.

[b] GMHR-4: Global Men’s Health and Rights Survey 4.

## Partial Correlations

Partial correlations between each GMHR-4 predictor with the measure that we believed represented the closest proxy to each of the outcomes in the COVID-19 data set were calculated and are presented in Table 2. Partial correlations were estimated while adjusting for jointly observed demographic characteristics, including age, country of residence, sexual orientation, gender identity, relationship status, racial/ethnic minority status, ability to meet one’s basic financial needs, health care coverage, and HIV status.

**Table 2.** Partial correlations between Global Men's Health and Rights Survey 4 (GMHR-4) predictor and GMHR-4 proxy measures for COVID-19 outcome variables[a].

| Predictors | HIV testing | Condoms | PrEP[b] | Access to HIV provider | Access to ART[c] refills | Low income | Poor mental health |
|---|---|---|---|---|---|---|---|
| Community engagement | 0.08 | 0.05 | 0.13 | 0.11 | 0.11 | 0.02 | –0.06 |
| Comfort with provider | 0.21 | 0.19 | 0.25 | 0.26 | 0.26 | –0.17 | –0.15 |
| Sexual stigma | –0.15 | –0.19 | –0.21 | –0.21 | –0.18 | 0.17 | 0.15 |
| Provider discrimination | –0.07 | –0.08 | –0.06 | –0.05 | –0.04 | 0.09 | 0.10 |

[a] Values calculated for partial correlations were used as anchors for the range of partial correlations used in smpc and smmatch, with the range set at ±5% and ±10% of values.

[b] PrEP: pre-exposure prophylaxis.

[c] ART: antiretroviral therapy.

## Enablers and Barriers to HIV Services

Although sexual stigma was commonly reported by study participants (mean 3.53, SD 0.61), discrimination from one's health care provider was low (mean 1.14, SD 0.39). Comfort with one's provider was also frequently reported (mean 2.98, SD 1.25). Our study found poor community engagement, as evidenced by a low mean score (mean 1.32, SD 0.43).

## Access to HIV Prevention

Study participants reported relatively high access to HIV testing (mean 3.7, SD 0.43) and condoms (mean 4.6, SD 0.9), but suboptimal access to PrEP (mean 3.2, SD 1.4). Our study confirmed hypothesized associations between enablers of and barriers to HIV prevention. Community engagement and comfort with one's health care provider were positively associated with access to HIV testing, condoms, and PrEP. Conversely, sexual stigma and experiences of provider discrimination were negatively associated with access to the same set of prevention services. Associations were statistically significant (*P*<.005). Coefficients and confidence intervals are shown in Table 3.

**Table 3.** Associations between hypothesized predictors and access to HIV prevention[a].

| Predictors | HIV onsite testing access | | | Condom access | | | PrEP[b] access | | |
|---|---|---|---|---|---|---|---|---|---|
| | Coef[c] | 95% CI | *P* value | Coef | 95% CI | *P* value | Coef | 95% CI | *P* value |
| Community engagement | 1.16 | 1.14 to 1.18 | <.001 | 0.95 | 0.92 to 0.99 | <.001 | 1.23 | 1.16 to 1.30 | <.001 |
| Comfort with provider | 0.78 | 0.77 to 0.79 | <.001 | 0.69 | 0.68 to 0.70 | <.001 | 0.90 | 0.89 to 0.91 | <.001 |
| Sexual stigma | –0.86 | –0.87 to-0.84 | <.001 | –1.05 | –1.08 to –1.02 | <.001 | –1.05 | –1.07 to –1.03 | <.001 |
| Provider discrimination | –0.96 | –1.01 to –0.92 | <.001 | –0.81 | –0.84 to –0.77 | <.001 | –1.17 | –1.19 to –1.14 | <.001 |

[a] Regression models also adjusted for income, education, relationship status, urbanicity (urban vs rural), racial/ethnic minority status, health insurance, and region (Global North vs Global South) as covariates. In sensitivity analyses omitting urbanicity and region, results were similar with respect to magnitude and level of significance of estimates.

[b] PrEP: pre-exposure prophylaxis.

[c] Coeff: regression coefficient.

## Access to HIV Care and Treatment

Our study found access to HIV care (mean 2.4, SD 0.8) and HIV treatment (mean 2.1, SD 1.2) to be low. Enablers of and barriers to HIV care and treatment were significantly associated in the predicted directions. For example, community engagement was positively associated with access to an HIV provider and sexual stigma was negatively associated with access to HIV treatment. A detailed summary of associations is presented in Table 4.

**Table 4.** Associations between hypothesized predictors and access to HIV care and treatment[a].

| Predictors | HIV provider access | | | Access to ART[b] refills | | |
|---|---|---|---|---|---|---|
| | Coef[c] | 95% CI | *P* value | Coef | 95% CI | *P* value |
| Community engagement | 0.81 | 0.75 to 0.86 | <.001 | 1.23 | 1.19 to 1.27 | <.001 |
| Comfort with provider | 0.54 | 0.53 to 0.55 | <.001 | 0.79 | 0.78 to 0.80 | <.001 |
| Sexual stigma | –0.87 | –0.95 to –0.78 | <.001 | –1.08 | –1.11 to –1.05 | <.001 |
| Provider discrimination | –0.77 | –0.81 to –0.73 | <.001 | –1.13 | –1.17 to –1.09 | <.001 |

[a] Regression models also adjusted for income, education, relationship status, urbanicity (urban vs rural), racial/ethnic minority status, health insurance, and region (Global North vs Global South) as covariates. In sensitivity analyses omitting urbanicity and region, results were similar with respect to magnitude and level of significance of estimates.

[b] ART: antiretroviral therapy.

[c] Coef: regression coefficient.

## Mental Health

The mean PHQ-4 score was 4.7, indicative of prevalent depression and anxiety among respondents who were included in this study. Community engagement and comfort with one’s health care provider were each negatively associated with poorer mental health. However, poorer mental health outcomes were significantly associated with experiences of sexual stigma and provider discrimination (see Table 5).

**Table 5.** Associations between hypothesized predictors and poorer mental health[a].

| Predictors | Poorer mental health (PHQ-4[b]) | | |
|---|---|---|---|
| | Coef[c] | 95% CI | *P* value |
| Community engagement | –3.03 | –3.19 to –2.87 | <.001 |
| Comfort with provider | –2.19 | –2.23 to –2.15 | <.001 |
| Sexual stigma | 2.48 | 2.42 to 2.54 | <.001 |
| Provider discrimination | 3.15 | 2.94 to 3.35 | <.001 |

[a] Regression models also adjusted for income, education, relationship status, urbanicity (urban vs rural), racial/ethnic minority status, health insurance, and region (Global North vs Global South) as covariates. In sensitivity analyses omitting urbanicity and region, results were similar with respect to magnitude and level of significance of estimates.

[b] PHQ-4: Patient Health Questionnaire-4.

[c] Coef: regression coefficient.

## Economic Impact

Although the mean score for the question assessing anticipated income reduction was low (2.4), the SD (3.6) suggests broad variability in participant responses. As displayed in Table 6, regression analyses confirmed hypothesized associations between predictor and outcome variables of interest, with one important exception: community engagement was positively associated with anticipated income reduction.

**Table 6.** Associations between hypothesized predictors and economic instability[a].

| Predictors | Anticipated income reduction during COVID-19 | | |
|---|---|---|---|
| | Coef[b] | 95% CI | *P* value |
| Community engagement | 0.84 | 0.74 to 0.93 | <.001 |
| Comfort with provider | –0.65 | –0.65 to –0.64 | <.001 |
| Sexual stigma | 0.74 | 0.73 to 0.75 | <.001 |
| Provider discrimination | 0.89 | 0.85 to 0.92 | <.001 |

[a] Regression models also adjusted for income, education, relationship status, urbanicity (urban vs rural), racial/ethnic minority status, health insurance, and region (Global North vs Global South) as covariates. In sensitivity analyses omitting urbanicity and region, results were similar with respect to magnitude and level of significance of estimates.

[b] Coef: regression coefficient.

## Discussion

### Principal Findings

To our knowledge, this is the first community-led, HIV-related research study to systematically combine data sets via data fusion from two separate online surveys of gay and bisexual men. The strategy enabled us to compare variables that would otherwise not be comparable. Specifically, we could combine outcomes from one data set with exposures from the other data set with a fusion process through the overlap [18]. This approach allowed us to confirm hypothesized associations between sexual stigma, provider discrimination, community engagement, and comfort with one’s health care provider, each experienced prior to the global onset of the COVID-19 pandemic, with access to HIV services, income reduction, and mental health impact at the height of the pandemic’s first surge.

Our study suggests that experiences of sexual stigma and provider discrimination continue to be common and likely persist through the COVID-19 pandemic. In addition, despite low overall levels of engagement with the gay community, when reported, community engagement may be moderating the deleterious effects of sexual stigma and provider discrimination on mental health and economic security. This may be because communities are sources of information, safety, support, and affinity [20-24]. Although community engagement was positively associated with anticipated reductions in income, this finding makes sense if study participants are actively engaging community-based or -led organizations for support. Study findings confirm prior research showing the enabling effects of community engagement and comfort with one’s health care provider on access to HIV prevention, testing, treatment, and care services for gay and bisexual men [25]. Moreover, HIV and other health services are more likely to be perceived as accessible and to be utilized if they are delivered by peers [26-28].

All exposures or predictors were assessed using scales contained in GMHR-4, based on data collected in the weeks and months prior to the pandemic. All outcomes were measured using items from the COVID-19 Disparities Survey. Although we cannot directly infer causal relationships between predictor and outcome variables, measures utilized asked COVID-19 Disparities Survey participants to consider COVID-19 in their responses, allowing us the unique opportunity to infer associations beyond the time parameters prescribed by GMHR-4. Our findings point to actionable factors that both enable and inhibit access to HIV services for gay and bisexual men in the COVID-19 era.

### Strengths and Limitations

There are some study limitations that are important to mention. First, both the GMHR-4 and COVID-19 Disparities Survey utilized online convenience samples, recruited through networks of advocates, service providers, and online dating apps. The study is therefore subject to selection bias for gay and bisexual men who are connected through networks and for whom internet-based technologies are more easily available. Study participants may thus have greater access to information and motivation to respond to surveys. Based on the sociodemographic characteristics of the sample, participants may likely have been gay and bisexual men who were less affected by the negative consequences of the COVID-19 pandemic. Consequently, findings reported here may reflect an underestimation of the true magnitude of COVID-19’s impact. In addition, the COVID-19 Disparities Survey was conducted at different stages of the epidemic’s spread and the magnitude of national responses likely varied from country to country. Convenience sampling also violates the assumption of the data fusion method that the two data sets were drawn as simple random samples from the same population [16], which may also bias our results. In addition, we note that our two data sets had more pronounced differences from each other in education and region. However, the matching procedure itself used to impute values is based on matching to similar covariate values. Moreover, results depended on our specification and assumptions used in the partial correlation for imputation. Nevertheless, we used estimates in our partial correlation calculation that we expected to be close and further combined over a range of partial correlation values [17]. Additional research is needed to determine the accuracy of our assumptions in the partial correlations we calculated. Like other observational studies, there may be other unmeasured confounders (eg, mental health, socioeconomic status) that may be associated with our exposures of interest and access to HIV services. Finally, the results relied on data that are cross-sectional in nature, which precludes our ability to examine temporal changes in predictors and outcomes measured. Further research, including qualitative studies, are needed to fully explore: (1) unequal access to HIV services, including their causes; (2) factors that enable access to both services and health; and (3) the impact COVID-19 is having on gay and bisexual men worldwide.

Despite these limitations, our study underscores the continued need to better understand and address impediments to service access among gay and bisexual men, especially in the context of the COVID-19 pandemic. Key strengths of this study include the range of domains used that can be harnessed for future research related to the HIV and COVID-19 pandemics and their impact on vulnerable populations. These include individual financial security, mental and sexual health, access to services, and program utilization. Moreover, the data sets used include samples from countries hardest hit by COVID-19, including Brazil, France, Mexico, and Russia.

Studies highlighting factors thought to enable access to HIV services are rare among gay and bisexual men [29]. Further, barriers to HIV services unique to international samples of gay and bisexual men are only sporadically studied [5,6,30,31], and are not universally and specifically addressed in national HIV responses [32]. Understanding the enablers of and barriers to HIV services access is critically important to getting the world back on track to achieving zero new infections, zero AIDS deaths, and zero discrimination [33]. Having a full and nuanced grasp of service enablers and barriers is especially important now, as we witness the impact of a second, unrelated global pandemic. This is because pre-existing vulnerabilities may become exacerbated during times of crisis, moderated to the extent that enabling factors are consistently and strategically buttressed with funding and technical support [34].

## Conclusions

Community-led research employing novel methodological approaches are paramount during times of crisis. The use of approaches such as data fusion to combine data sets can help to quickly clarify salient enabling factors rapidly and cost-efficiently, as well as expose the economic, mental health, and service impacts of sexual stigma and provider discrimination. Such information can potentially lead to tailored responses delivered in real time, which can be critically important during public health emergencies such as that represented by the COVID-19 pandemic. Community-led, methodologically creative, and cost-efficient approaches should be encouraged and funded, especially during such times.

Our study specifically highlights the importance of reinforcing enablers such as community engagement and comfort with one's health care provider, while addressing stigma and discrimination as critically and equally central to ensuring equitable HIV services access among gay and bisexual men worldwide. Although not new, the findings reported here suggest that addressing factors that enable and deter access to HIV services may be especially important in buffering against the mental health and economic impacts of new and unrelated pandemics. Moreover, our study raises the question of whether the COVID-19 pandemic has resulted in worsening HIV services access among gay and bisexual men, a question that remains open and ready for further research. Future research is needed, including prospective studies of gay and bisexual men that more deeply examine the associations between exposures and outcomes of interest within the same sample. Future studies should also examine the concerns of gay and bisexual men more comprehensively, beyond those related to HIV, in a world transfixed and transformed by COVID-19.

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## Conflicts of Interest

None declared.

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## Abbreviations

**GMHR-4:** Global Men’s Health and Rights Survey-4
**MSM:** men who have sex with men
**PHQ-4:** Patient Health Questionnaire-4
**PrEP:** pre-exposure prophylaxis
**UNAIDS:** Joint United Nations Programme on HIV/AIDS

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Original Paper

# Estimating COVID-19 Hospitalizations in the United States With Surveillance Data Using a Bayesian Hierarchical Model: Modeling Study

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## Abstract

**Background:** In the United States, COVID-19 is a nationally notifiable disease, meaning cases and hospitalizations are reported by states to the Centers for Disease Control and Prevention (CDC). Identifying and reporting every case from every facility in the United States may not be feasible in the long term. Creating sustainable methods for estimating the burden of COVID-19 from established sentinel surveillance systems is becoming more important.

**Objective:** We aimed to provide a method leveraging surveillance data to create a long-term solution to estimate monthly rates of hospitalizations for COVID-19.

**Methods:** We estimated monthly hospitalization rates for COVID-19 from May 2020 through April 2021 for the 50 states using surveillance data from the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) and a Bayesian hierarchical model for extrapolation. Hospitalization rates were calculated from patients hospitalized with a lab-confirmed SARS-CoV-2 test during or within 14 days before admission. We created a model for 6 age groups (0-17, 18-49, 50-64, 65-74, 75-84, and ≥85 years) separately. We identified covariates from multiple data sources that varied by age, state, and month and performed covariate selection for each age group based on 2 methods, Least Absolute Shrinkage and Selection Operator (LASSO) and spike and slab selection methods. We validated our method by checking the sensitivity of model estimates to covariate selection and model extrapolation as well as comparing our results to external data.

**Results:** We estimated 3,583,100 (90% credible interval [CrI] 3,250,500-3,945,400) hospitalizations for a cumulative incidence of 1093.9 (992.4-1204.6) hospitalizations per 100,000 population with COVID-19 in the United States from May 2020 through April 2021. Cumulative incidence varied from 359 to 1856 per 100,000 between states. The age group with the highest cumulative incidence was those aged ≥85 years (5575.6; 90% CrI 5066.4-6133.7). The monthly hospitalization rate was highest in December (183.7; 90% CrI 154.3-217.4). Our monthly estimates by state showed variations in magnitudes of peak rates, number of peaks, and timing of peaks between states.

**Conclusions:** Our novel approach to estimate hospitalizations for COVID-19 has potential to provide sustainable estimates for monitoring COVID-19 burden as well as a flexible framework leveraging surveillance data.

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**KEYWORDS**

COVID-19; SARS-CoV-2; hospitalization; Bayesian; COVID-NET; extrapolation; hospital; estimation; prediction; United States; surveillance; data; model; modeling; hierarchical; rate; novel; framework; monitoring

## Introduction

Monitoring disease burden and severity is a critical component of public health research, communication, and response. The current COVID-19 pandemic, which is caused by SARS-CoV-2, has been ongoing since early 2020 and presents novel challenges and barriers to monitoring due to the unique transmission, nature of the virus, and variety of symptom presentations. In the United States, COVID-19 cases, hospitalizations, and deaths are captured through the National Notifiable Disease Surveillance System (NNDSS) and death certificates reported to the National Vital Statistics System (NVSS) [1-3]. However, the hospitalization status of cases reported by states through the NNDSS is often incomplete and thus might inaccurately represent the burden of COVID-19 hospitalization in the United States. In addition, since July 15, 2020, hospitalizations known or suspected to be related to COVID-19 have been reported daily through the Department of Health and Human Services (HHS) Protect, known as the unified hospital time-series data [4]. This data collection is a burden on facilities that is likely unsustainable in the long term.

Current research and methods for estimating hospitalizations of COVID-19 are limited. In mid-2020, the Centers for Disease Control and Prevention (CDC) developed a multiplier method for estimating SARS-CoV-2 infections and hospitalizations for COVID-19 based on state- and territory-reported line-level case data [5]. To date, these COVID-19 burden estimates from this case-based multiplier model are calculated and published on the CDC’s website [6]. Other papers have leveraged seroprevalence surveys to estimate SARS-CoV-2 infections and hospitalizations for COVID-19 [7,8]. These methods rely on data systems such as case reporting or wide-scale, special seroprevalence surveys that were initiated during the pandemic but might not exist in the future, as the pandemic winds down. Case count data and consistent, representative seroprevalence data may eventually be discontinued due to the pandemic slowing down and resources and attention going elsewhere, leaving a need for longer-term systems that can be sustained.

Since March 2020, the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) has collected data on laboratory-confirmed SARS-CoV-2–positive patients from a network of hospitals in 14 US states [9]. Although this sentinel surveillance system does not cover the entire United States, it is expected to continue monitoring rates of COVID-19 hospitalization even after the pandemic ends. The COVID-NET system was built off of the similar long-standing Influenza Hospitalization Surveillance Network (FluSurv-NET), which has been monitoring population-based rates of influenza hospitalization for almost 20 years [10]. Although the network does not currently make any further determination about the relationship between a positive SARS-CoV-2 test and the reason for hospitalization for each identified patient, this system and data are the best source available for the long-term surveillance of COVID-19 hospitalizations.

We created a method to utilize COVID-NET data to provide national and state-specific estimates of hospitalization to provide a long-term, sustainable framework to generate estimates of COVID-19 disease burden in the United States. The aim of this study was to estimate monthly COVID-19 hospitalization rates, defined as hospitalized patients with positive tests for SARS-CoV-2 infections, for all 50 states from May 2020 through April 2021. We adapted a Bayesian hierarchical model to estimate and extrapolate hospitalization rates, accounting for uncertainty and variability between states and across time.

## Methods

### COVID-NET Surveillance Hospitalization Data and Adjustments

We used COVID-19 hospitalization data from COVID-NET. The network identifies hospitalized patients with a positive SARS-CoV-2 test, including molecular assay and antigen detection, during hospitalization or within 14 days prior to hospitalization [9]. Hospitalization rates are calculated by the number of residents in a catchment area, defined as the area or population around the reporting hospital that the hospital potentially services, of the COVID-NET sites who are hospitalized with a confirmed, positive SARS-CoV-2 test divided by the total population within that defined catchment area. The network is made up of over 250 acute care hospitals representing 99 counties in 14 states: California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah. Overall, the network covers about 10% of the United States population. For this analysis, case data were aggregated by month of hospitalization, state reporting, and the following 6 age groups: 0-17 years, 18-49 years, 50-64 years, 65-74 years, 75-84 years, and ≥85 years. Age groups were chosen based on available data age groupings as well as interest in breaking apart older age groups, which have been impacted more by severe COVID-19.

Recognizing that all hospital patients are unlikely to be tested for SARS-CoV-2 and, therefore, some true cases are not classified as COVID-19 patients, COVID-19 hospitalization rates are adjusted by weighting them for SARS-CoV-2 testing practices (ie, the probability of being tested for SARS-CoV-2 during their hospitalization). In addition, testing practices changed over the course of the pandemic. The probability of being tested was calculated from the IBM Watson Health Explorys electronic health record database (IBM Corporation), which includes more than 39 health system partners across the country. All states participating in COVID-NET, except Connecticut, used the same testing probabilities calculated from IBM Watson data, which were aggregated testing practices of all partners stratified by month and age group. The testing probabilities for these 13 states ranged from 0.28 to 0.67. Connecticut provided site-specific testing practice data through COVID-NET, which ranged from 0.32 to 1.00. Rates were also adjusted to account for the SARS-CoV-2 assay sensitivity because, depending on the sensitivity of the assay, some patients could have false-negative test results (ie, would not be identified as a COVID-19 hospitalization). The assay sensitivity was assumed to be 0.885, which is the midpoint for the range found in a systemic review [11]. The adjusted hospitalization counts were used to calculate rates using COVID-NET catchment populations for each site. Due to the range in hospitalizations by age groups over time, 6 models were run, 1 for each age group:

where $s$=1, ..., $S$ for each COVID-NET state and $m$=1, ..., $M$ for each month.

## Covariate Data and Selection

To extrapolate COVID-19 hospitalization rates from COVID-NET sites to states not included in the COVID-NET network, we incorporated model covariates based on state, month, and age-specific demographic and epidemiological data. We used different data measures to account for differences between states with COVID-NET sites and those states without COVID-NET sites from multiple sources (Table 1). Including covariates in the model helps to quantify differences between age groups, months, and states and allows for the model to account for these differences when estimating how many COVID-19 hospitalizations have occurred. We considered both time-varying and time-invariant state-level covariates that captured other COVID-19 disease trends, population demographics, and population health indicators. For the time-varying covariates, we considered the percent of SARS-CoV-2 positive tests from commercial and public health laboratories, percent of all-cause deaths that were coded as COVID-19 deaths from the National Center for Health Statistics and NVSS, and the following hospital capacity variables: percent patients with COVID-19 out of all inpatients and percent intensive care unit (ICU) beds occupied out of all ICU beds [12-16]. We incorporated a 1-week lag to the percent positive COVID-19 tests to account for time between symptom onset and hospitalization and a 1-week lead to the percent of COVID-19 deaths out of all deaths to account for time between hospitalization and death. For the time-invariant covariates, we considered the percent Native American and percent Black American and the population prevalence of the following conditions or diseases from the Behavioral Risk Factor Surveillance System (BRFSS): obesity, heart disease, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, and asthma [17,18]. Underlying medical and chronic conditions were found to be highly prevalent in hospitalized patients with COVID-19 and were therefore included as possible covariates [18]. Time- and age-varying data for population prevalence of underlying medical and chronic conditions were not available. Table 1 summarizes all of the variables that were considered as covariates. We used covariate selection methods to determine which of the possible covariates to include in the model. For the <18-year-old age group, only asthma was included as a possible covariate from the chronic conditions or diseases because of a lack of evidence that the prevalence of other chronic conditions or diseases affected COVID-19 hospitalization in that age group [19].

**Table 1.** Variables considered to be covariates in our Bayesian model to extrapolate COVID-19 hospitalizations for all 50 US states with stratification and source.

| Variables | Stratified by | Source |
|---|---|---|
| Laboratory surveillance: SARS-CoV-2 % positive using rt-PCR[a] tests | Month, state, age | Commercial lab and public health lab data |
| Vital records death: % of all-cause deaths that were coded as COVID-19 deaths | Month, state, age | National Center for Health Statistics National Vital Surveillance System |
| Hospital capacity: % COVID patients out of all inpatients, % ICU[b] occupied out of all ICU beds | Month, state | HHS[c] Protect/National Center for Health Statistics |
| Race/ethnicity: % American Indian, % Black, % racial minority[d] | State, age | National Center for Health Statistics/National Vital Statistics System |
| Chronic conditions/diseases: % obesity, % heart disease, % COPD[e], % Diabetes, % CKD[f], % asthma | State | CDC[g] MMWR[h] Stacks/Behavioral Risk Factor Surveillance System |

[a] rt-PCR: reverse transcription–polymerase chain reaction.

[b] ICU: intensive care unit

[c] HHS: Department of Health and Human Services.

[d] Racial minority was defined as non-White and non-Hispanic.

[e] COPD: chronic obstructive pulmonary disease.

[f] CKD: chronic kidney disease.

[g] CDC: Centers for Disease Control and Prevention.

[h] MMWR: Morbidity and Mortality Weekly Report.

Extreme values were detected for time-varying covariates and subsequently transformed using Winsorization (ie, minimized the influence of outliers by replacing them by the maximum or minimum values at a threshold of distribution percentiles) [20]. We used the adjusted COVID-NET hospitalization rates as the outcome to select covariates separately for each age group.

Covariate selection methods assist with avoiding collinearity and ensuring that the most relevant and impactful covariates are included. Our method for covariate selection utilized Least Absolute Shrinkage and Selection Operator (LASSO) and spike and slab [21,22]. Covariates were included in the final model for the specific age group if they were selected by LASSO and then the model incorporated spike and slab selection. The LASSO chooses a subset of predictors by introducing an upper bound for the sum of squares and minimizing the errors present in the model. Spike and slab is a Bayesian approach in which we assigned priors to the regression coefficients to be zero or nonzero, which is where the name comes from. From that, the posterior distributions show a biseparation effect in the model coefficients—those that peak at zero and those significantly different from zero. Assumption for nonzero was high in the model due to LASSO selection being done first.

## Bayesian Hierarchical Model and Extrapolation

We implemented a Bayesian hierarchical model for extrapolation adapted from a model to estimate global influenza burden rates [23]. Parameter estimation and inference were conducted under a fully Bayesian framework to better quantify uncertainties in predicted hospitalization rates, including those that are extrapolated to states without COVID-NET data.

We let $A_{sm}$ denote the estimated, adjusted COVID-19 hospitalization count from the COVID-NET states during months from the pandemic, starting in May 2020, where $s=1,\ldots,S$, and $S=14$ states in COVID-NET, $m=1,\ldots,M$, and $M=12$ for each month included in the model (ie the observed data adjusted in section COVID-NET Surveillance Hospitalization Data and Adjustments). Because the observed hospitalization estimate is a count, we can view them as deriving from a Poisson probability [24]. This is used to account for the random variation from the observed data. Those estimated, adjusted COVID-19 hospitalization counts, along with the COVID-NET catchment populations and the selected covariates, were used as inputs into the following Bayesian hierarchical model:

Level 1: $A_{sm} \sim Pois(\theta_{sm} * Population_s/100{,}000)$

where $A_{sm}$ = Adjusted COVIDNET $\text{Count}_{\text{sm}}$ (the estimated hospitalization count for state and month from COVID-NET data), $Population_s$ is the catchment population for state $s$, and $\theta_{sm}$ is the unobserved true hospitalization rate.

Level 2: $\theta_{sm} \sim logN(\mu + \gamma_1 X_{1,sm} + \ldots + \gamma_k X_{k,sm}, \sigma^2)$

where $X$ is the value of covariate $i$ in state $s$ at time $m$, $k=1,\ldots,K$, $K$ = the number of selected covariates, and covariates are with mean 0 and variance 1.

Level 3: $\gamma_k \sim N(0, 1000000^{(1-gk)} * 0.001)$

$g_k \sim Bern(0.9)$

Priors: $\mu \sim N(0, 10^{-6})$

$\sigma^2 \sim Unif(0, 1000)$

where $k=1,\ldots,K$ and $K$ = the number of selected covariates.

Inference was carried out utilizing Markov chain Monte Carlo (MCMC) simulations with 20,000 iterations. The model outputs included samples from the posterior distribution of COVID-19–associated hospitalizations for each state and month. Using these samples, we calculated the median and 90% credible intervals (CrIs) for hospitalization counts, rounded to the hundreds due to MCMC errors, and used the state population by age group to calculate final hospitalization rates. To calculate overall age, age by month, age by state, and state by month hospitalizations and rates, we first summed the posterior samples. Since the median of sums does not equal the sum of medians, this led to slightly different total hospitalizations depending on which grouping was used to sum. For consistency, we calculated total hospitalizations from overall age medians, total monthly hospitalizations from age by month, and total state hospitalizations by age by state. We chose 20,000 iterations after starting with 2000 iterations and slowly increasing to obtain stable estimates that also minimized simulation error.

## Validation and Comparison

We conducted sensitivity analyses to assess the effect of covariate selection and input data on the model. Multiple combinations of covariates were examined for each age group to assess how robust the hospitalization estimates were to covariate selection. To validate and test the sensitivity of the model, first, we compared how the model estimated hospitalizations for each COVID-NET state with the observed hospitalization rate from COVID-NET. In another sensitivity analysis, we dropped data from each COVID-NET state, one by one, and then compared the observed hospitalization rates to the extrapolated rates for each dropped state. Finally, we also compared our COVID-19 hospitalization estimates against other public estimates and databases, including COVID-19 hospitalization rates reported through Healthdata.gov (The Unified Hospital Timeseries data), the COVID Tracking project, and from the CDC’s case-based multiplier model [5,6,25-28]. The Unified Hospital Timeseries data and COVID Tracking project are publicly available data sets providing state-aggregated data for COVID-19 hospitalizations over time. According to Healthdata.gov, the Unified Hospital Timeseries data had reliable counts of new hospitalizations with COVID-19 starting in the fall of 2020 when over 95% reporting from all hospitals reported by the HHS. The Unified Hospital Timeseries data are from reports at the facility level and do not account for nonresponse or missingness. The COVID Tracking Project compiled data taken directly from the websites of state or territory public health authorities but stopped and switched to reporting the Unified Hospital Timeseries on March 7, 2021. The CDC’s case-based multiplier model estimates hospitalization in 2-month increments and by HHS regions, not by state. Our model output was aggregated appropriately for comparisons.

## Ethical Statement

This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and determined to be consistent with nonhuman participant research activity (#0900f3eb81da6749). Informed consent was waived, as data were deidentified and aggregated.

## Results

The covariates selected for each age group varied (Multimedia Appendix 1). The SARS-CoV-2 percent positive, the percentage of inpatients with COVID-19 out of all inpatients, and the percentage of hospitalizations that were ICU admissions were selected for each of the age groups. The 18- to 49-year-old age group had the most covariates selected, and the <18-year-old age group had the fewest covariates selected.

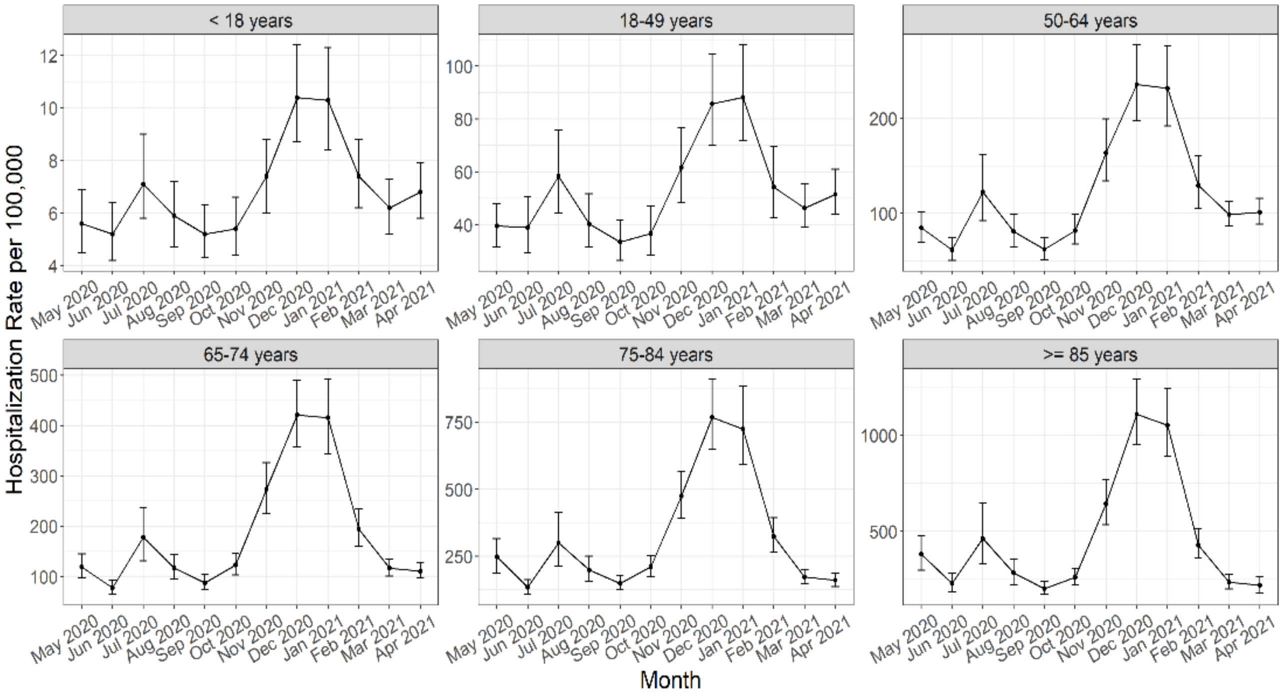
From May 2020 through April 2021 in the United States, we estimated there were 3,583,100 (90% CrI 3,250,500-3,945,400) hospitalizations representing a rate of 1093.9 (90% CrI 992.4-1204.6) hospitalizations per 100,000 population with COVID-19. The estimated rates varied by age group, state, and month. The highest rates of hospitalization were among those aged ≥85 years, with a rate of 5575.6 per 100,000 population (90% CrI 5066.4-6133.7), and the lowest hospitalization rate was for those <18 years of age, with a rate of 83.9 per 100,000 population (90% CrI 76.8-91.4). Table 2 summarizes the final estimated counts and rates of hospitalizations by age group from May 2020 through April 2021.

Hospitalization rates for all age groups peaked in either December 2020 or January 2021. Figure 1 shows the epidemiologic curves of hospitalizations over time by age group. During the study period, we observed the largest peak in hospitalization rates in December 2020 (183.7/100,000), followed by January 2021 (180.1/100,000). A second, smaller peak in COVID-19 hospitalizations was observed for all age groups in July 2020 (90.6/100,000). The lowest rate of hospitalization was observed across age groups in September 2020 (46.9/100,000). Following the peak in COVID-19 hospitalization rates during the winter months, COVID-19 hospitalizations declined until the month of April 2021 (Figure 1).

**Table 2.** Cumulative COVID-19 hospitalization count (median) and rate per 100,000 population and accompanying 90% credible intervals (CrIs) for each age group and overall from May 2020 through April 2021 for 50 US states from our Bayesian model output.

| Age group | Hospitalization count | 90% CrIs | Hospitalization rate per 100,000 | 90% CrI |
|---|---|---|---|---|
| <18 years | 61,200 | 56,000-66,600 | 83.9 | 76.8-91.4 |
| 18-49 years | 892,700 | 805,700-992,100 | 647.7 | 584.6-719.8 |
| 50-64 years | 927,900 | 846,900-1,016,100 | 1477.1 | 1348.2-1617.6 |
| 65-74 years | 709,800 | 645,200-776,500 | 2258.0 | 2052.5-2470.3 |
| 75-84 years | 623,900 | 562,600-689,700 | 3912.7 | 3528.7-4325.7 |
| ≥85 years | 367,600 | 334,000-404,400 | 5575.6 | 5066.4-6133.7 |
| Total | 3,583,100 | 3,250,500-3,945,400 | 1093.9 | 992.4-1204.6 |

**Figure 1.** COVID-19 hospitalization rates per 100,000 population and 90% credible intervals by age group over time from May 2020 through April 2021 for 50 US states from our Bayesian model output. The Y-axis limits are adjusted to the unique range for each age group (ie, they are not set to the same scale).



At a state level, cumulative hospitalization rates from May 2020 through April 2020 ranged from 359.3 (90% CrI 241.5-476.6) hospitalizations per 100,000 people in Vermont to 1855.6 (90% CrI 1184.3-2640.1) hospitalizations per 100,000 people in Nebraska. Figure 2 shows the overall cumulative hospitalization rate per 100,000 people from May 2020 to April 2021 for all states with a heat map (Figure 2A) and by bar graph (Figure 2B) to show the range of hospitalization burden across the country. COVID-NET states are well distributed throughout the highest to lowest rates by state.

Considering state-specific hospitalization rates over time, not all states had the same peaks or magnitudes of peaks. Figure 3 shows the epidemiological curves across the study period for the top 10 states with the highest upper 90% credible interval for cumulative hospitalization rates from May 2020 through April 2021. From these example states, we were able to observe differences in the time trends between states regarding the timing and number of peaks. States including Texas, Nevada, Alabama, Arizona, and Tennessee have 2 peaks; however, they differed by timing and magnitude of the peaks. In contrast, Nebraska, Kansas, Virginia, Missouri, and Oklahoma experienced only 1 major peak, which also differed by timing and magnitude. Hospitalization rates per 100,000 population from the final output model over time are provided in Figure 3.

To assess the sensitivity of the selected covariates, we ran the model using multiple combinations of the covariates, including those selected by the LASSO method alone and those by the spike and slab method alone. Hospitalization estimates did not vary greatly overall or by age depending on covariate combinations and were almost 100% consistent between LASSO alone, spike and slab alone, and when both were used, which are the covariates used in the final model for each age group. To validate the final model, we compared the observed COVID-NET hospitalization rates to the final model's estimated hospitalization rates. The rates are higher from the final model. However, the trends over time and by age group follow the observed, input rates (Multimedia Appendix 2). The supplementary images are a plot of each COVID-NET state comparing observed (input), estimated (final model), and extrapolated monthly hospitalization rate in the leave-one-state-out analysis, showing rates over time and by age group. Model median results for other states were mostly consistent whether the specific COVID-NET state was dropped or not. Almost all of the COVID-NET states' extrapolated estimates (ie, when dropped) had a 90% CrI that included the observed (input) estimate and estimated (final model) rate. The older age groups were more consistent and had more overlap between estimates than the younger age groups in the leave-one-state-out analysis. Finally, we compared our output with other hospitalization estimates and data for the final step of our sensitivity analysis. We compared our results with the Unified Hospital Timeseries data and data published on The COVID Tracking Project [25,26]. Figure 4 shows a comparison of hospitalization rate from each source over time. We also compared our results to the current published numbers from the CDC's case-based multiplier model (Multimedia Appendix 3) [5,6,27].

**Figure 2.** Cumulative COVID-19 hospitalization rate per 100,000 population by state from May 2020 through April 2021 in the United States from our Bayesian model output: (A) heat map of the United States of cumulative hospitalization rate per 100,000 population from May 2020 through April 2021 and (B) bar chart of cumulative hospitalization rate per 100,000 population from May 2020 through April 2021, with 90% credible intervals and states from COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) in blue.

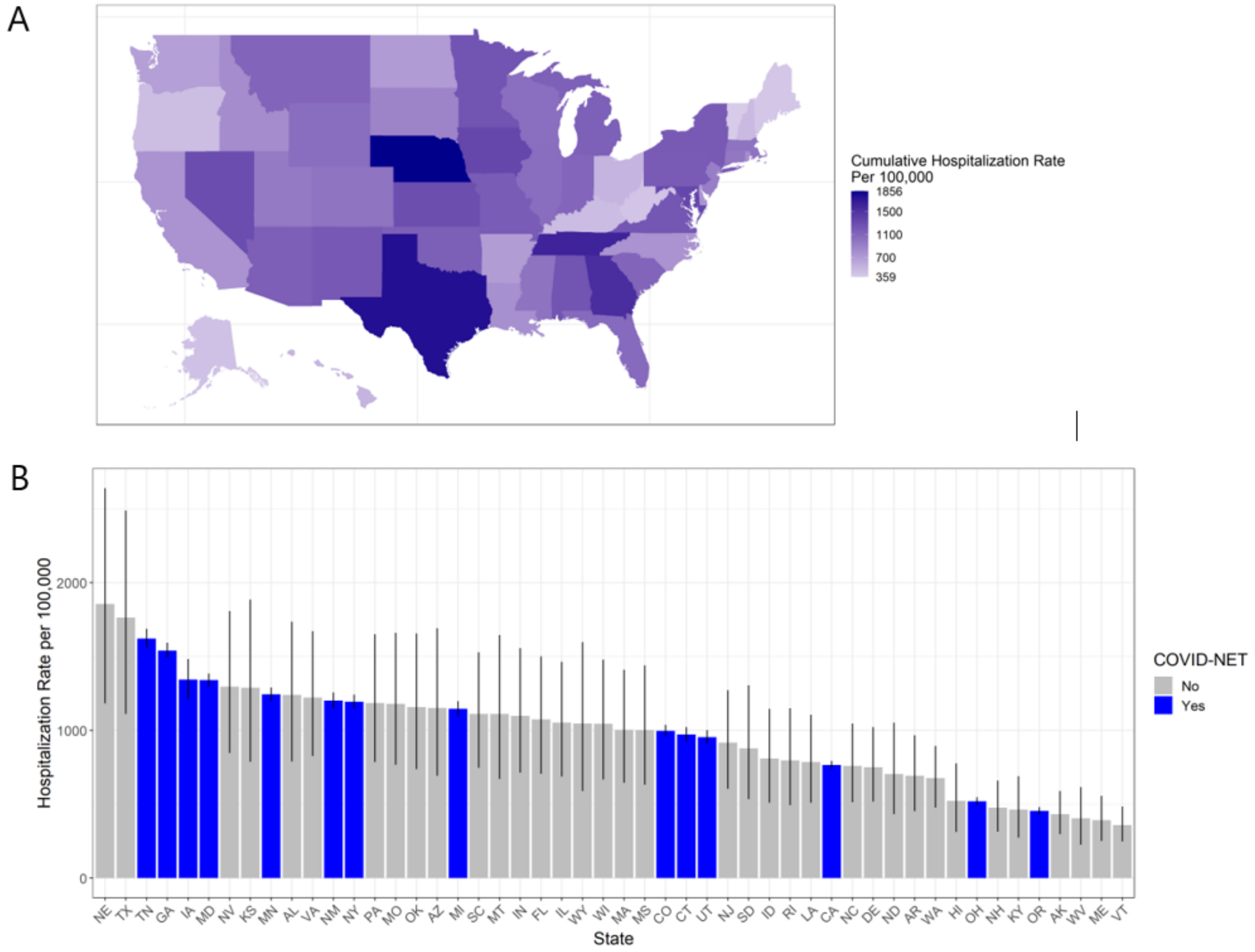


**Figure 3.** COVID-19 hospitalization rates per 100,000 population over time for the top 10 US states with the highest upper 90% credible interval for cumulative COVID-19 hospitalization rates from May 2020 through April 2021 from the Bayesian model output: (A) Nebraska, (B) Texas, (C) Kansas, (D) Nevada, (E) Alabama, (F) Arizona, (G) Tennessee, (H) Virginia, (I) Missouri, and (J) Oklahoma.

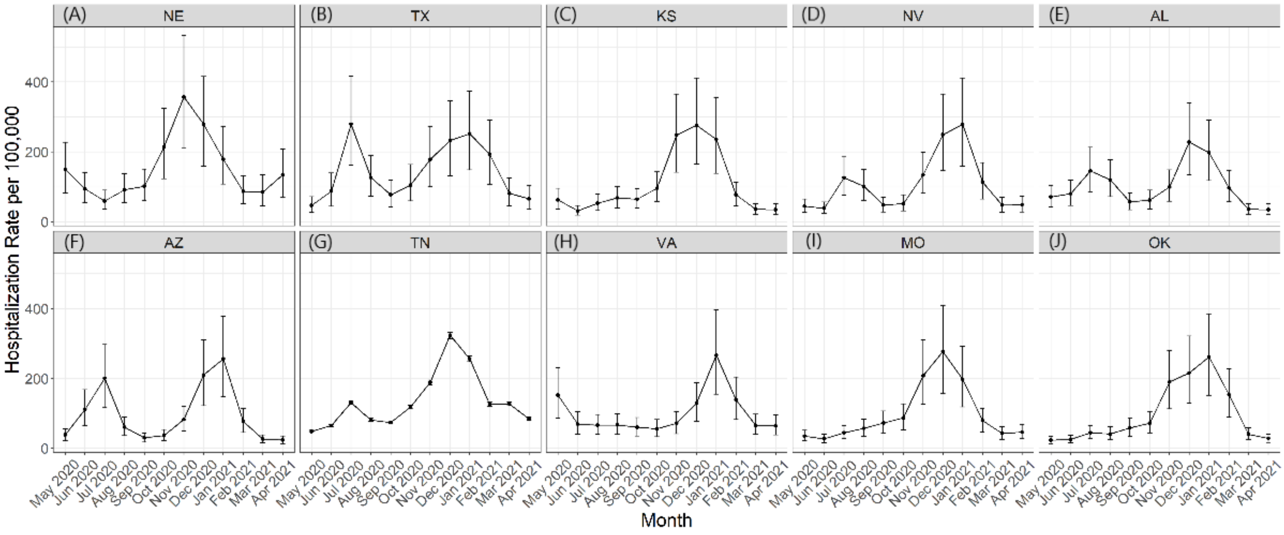
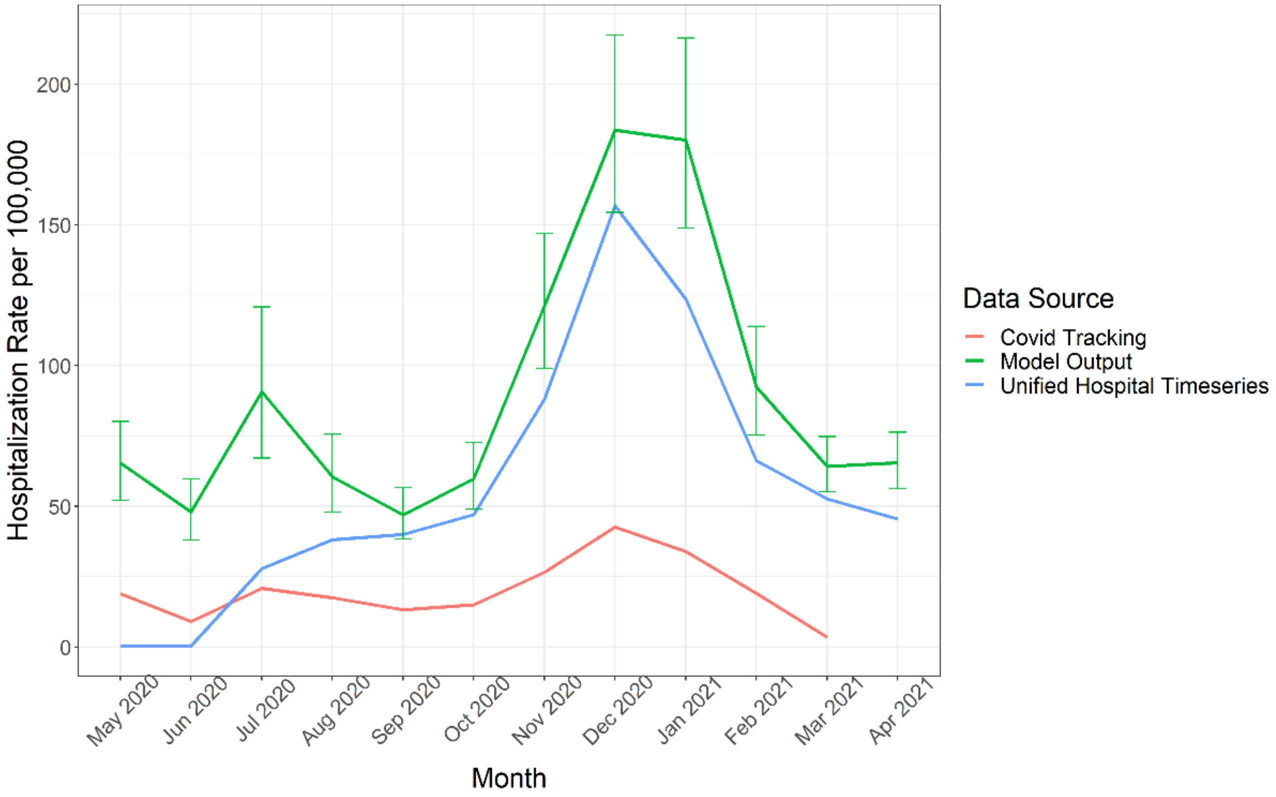


**Figure 4.** Comparison of COVID-19 hospitalization rates per 100,000 population over time from May 2020 through April 2021 in the United States from our Bayesian model output with 90% credible intervals, the Unified Hospital Timeseries data, and data from The COVID Tracking Project.



## Discussion

Overall, our method estimated that 3,583,100 hospitalizations occurred in the United States from May 2020 through April 2021, with estimated rates varying by age group, state, and month. These estimates demonstrate the large burden of COVID-19 hospitalizations in the United States and provide visibility on variations in disease burden by age group, state, and time. As expected, the most severe burden of COVID-19 hospitalizations occurred among older age groups, specifically among people aged ≥65 years old. The largest peak in hospitalizations occurred in December 2020 and January 2021, aligning with the largest peak in reported case rates [28].

Our approach to estimating the burden of COVID-19 hospitalization using long-term surveillance data has several benefits. First, we designed our model to build on an existing system that was initially started to track hospitalizations for influenza and has expanded to capture other respiratory viruses including COVID-19. COVID-NET was built on a long-standing surveillance infrastructure that has been conducting surveillance for respiratory infections, including influenza and respiratory syncytial virus, for many years and is expected to continue monitoring COVID-19 hospitalization rates into the future [29]. Our model calculated estimates of state-level hospitalization rates by month and age group, rather than assuming the 14 COVID-NET sentinel sites are representative of the United States. Each US state has experienced the pandemic differently, and our models allow us to capture the variations in the number and magnitude of peaks and state-specific trends in hospitalization rates. Further, using covariates to extrapolate data from the COVID-NET sites to the rest of the United States provides useful information to understand state-level differences in hospitalization. The covariates add information to the input hospitalization rates to then create a better story for the states to which it extrapolates. This model helps preserve notable differences in the epidemiology of COVID-19 between states.

When we compared our model against the published Unified Hospital Timeseries and the COVID-Tracking Project, our COVID-19 hospitalization estimates were higher but showed the same trends and included the Unified Hospital Timeseries' rates in our 90% CrIs for a few months (Figure 4). We also compared our model to the case-based multiplier model. The CDC developed the case-based multiplier model using nationally notifiable COVID-19 case report data and assumptions for underdetection of confirmed cases, which is still being used to produce published burden estimates [5,6]. Our Bayesian model offers an alternative method of estimation by leveraging sentinel surveillance data if or when case report data become unreliable or unavailable. When we compared our model's output to the case-based multiplier model during time periods that overlapped, we found that our model generated more conservative estimates of hospitalization. Our model's output was lower than the estimates from the case-based multiplier model (Multimedia Appendix 3). From June 2020 to March 2021, our model estimated a cumulative incidence of 904.3 per 100,000 population whereas the case-based multiplier estimated 1345.3 per 100,000 population. When comparing estimates by age group, months, and HHS regions, specific differences are highlighted. Our model had much lower estimates of hospitalization rates per 100,000 for the 0- to 17-year-old age group (210.7 for the case-based multiplier model and 67.4 for ours) and ≥65-year-old age group (4401.7 for the case-based multiplier model and 2800.8 for ours), while the other age groups were only slightly lower (Multimedia Appendix 3). In addition, our February through March estimate and HHS regions 2 and 9 were much lower. However, our model had higher estimates for a few HHS regions compared with the case-based multiplier estimates. Our method has several advantages over the case-based multiplier method. First, the case report data used were often incomplete for hospitalization status and relied on the imputation of hospitalization status. In our method, the input hospitalization data were from a surveillance system that actively identified laboratory-confirmed COVID-19 hospitalizations. This may account for the differences observed in the hospitalization estimates between the models. Imputation could lead to more hospitalizations than those counted from the surveillance system. For example, if those not missing in case data have a bias toward being hospitalized, then those with missing hospitalization status in the case data would also have a bias toward being hospitalized when imputed. A second difference between the methods was that the case-based multiplier method adjusted reported cases for factors that influenced case detection, including health care–seeking behaviors and testing practices at the HHS region level. Therefore, they adjusted and estimated at the HHS region level rather than the state level like our method. Estimating at the regional versus the state level may also explain differences in estimates.

The case-based multiplier model relies on COVID-19 being a nationally notifiable disease and continued case reporting by states and jurisdictions, which may not continue long term. In contrast, our method relies on routine sentinel surveillance data and allows for extrapolation to places without data. Both the case report data and seroprevalence data used by Angulo et al [7] as the basis for their national COVID-19 disease burden estimates were data sources created to inform the pandemic response, but it is unclear how long these data will continue to be collected.

Although we utilized this method for estimating state-level hospitalization rates for COVID-19 in the United States from May 2020 through April 2021, our method can be adapted for different outcomes or measures of interest both domestically and in international settings. The main components needed are reliable surveillance data in enough areas to have diversity in disease occurrence and covariates that help explain the variation between all areas of extrapolation. There are surveillance systems set up that do not have complete coverage. For example, this approach was adapted from an analysis using a Bayesian Hierarchical model to extrapolate influenza yearly rates by country [23]. This method provides an opportunity to leverage surveillance data and inform more accurate estimates of disease burden. Efforts to further expand the method to other levels of disease severity including infection, illness, or death are ongoing.

Our method also has some limitations. First and foremost, we are estimating hospitalizations with positive tests for SARS-CoV-2 infections, as the contributing surveillance data do not currently attribute whether patients were hospitalized due to complications caused by the infection. Even for hospitalizations that are incidental, like an elective surgery, the hospital still has to deal with cohorting and infection control for that person, which adds burden on the hospital. Second, since our goal was to use routine surveillance data, our time frame for estimates began in May 2020 in states where we believe the surveillance systems were established and providing stable data after being set up in the early months of the pandemic. Therefore, we cannot estimate cumulative hospitalizations since the start of the pandemic. Third, we assume that COVID-NET captures all patients who were tested for COVID-19 and had a positive result. Although we adjusted for testing practices (ie, those not tested), we could be underestimating hospitalizations if this assumption is not true and confirmed positives are not being reported. Fourth, we assumed that testing practices did not differ by states, except in Connecticut where testing practice data for COVID-NET sites were available. This assumption could result in either an over- or underestimation of hospitalizations. In addition, we assumed testing sensitivity for COVID-19 in COVID-NET was 0.885, which can lead to an over- or underestimation of hospitalizations depending on true sensitivity. We also did not adjust for false positives because the reported specificity for tests in COVID-NET is extremely high [11]. However, this could also lead to an overestimation of hospitalizations. Fifth, our method assumes that the COVID-NET sites are representative of the entire state. In some states, such as Maryland, COVID-NET includes all counties; in other states, such as Iowa, it includes only 1 county. Although the model accounted for uncertainty and variability between states, we are still limited by representativeness within a state between the COVID-NET site and the truth of the entire state. As a result, our model may be under- or overestimating hospitalizations at the state level for COVID-NET states depending on how well the particular catchment area reflects COVID-19 activity in the state. Sixth, our method assumes that COVID-NET states capture enough diversity across the nation to extrapolate data to all states, which may not be true. Although the 14 states from COVID-NET vary in many ways, we cannot be sure that they cover the variation in COVID-19 hospitalizations, including variations in things that may impact hospitalizations like mitigation strategies and vaccination rates. For example, we could not extrapolate to Washington DC or New York City appropriately due to the extreme variation between a state and a purely metropolitan city. Seventh, although the covariates are meant to inform the extrapolation, the covariates are limited by the quality, completeness, and availability of the data. There could be vital information around COVID-19 hospitalization rates that are missing, such as other chronic conditions, underlying risk factors in the population, mitigation measures, and vaccination rates. Although our model has time-varying covariates that describe the COVID-19 impact in each state, including percent positive, percent COVID-19 deaths, and hospital capacity covariates, vaccination rates were not included so we may be under- or overestimating age groups and states based on potential unaccounted variation from the correlation to vaccination rates. Another limitation is the wide CrIs. Median estimates from the model’s output distributions of hospitalizations seem to be reasonable through our sensitivity, validation, and comparison analysis, but the 90% CrIs are wide for some of the states where extrapolation was carried out. This limits the precision of true hospitalizations and inference of medians presented. Finally, since we ran a different model for each age group, we are limited in the interpretation of hospitalization estimates by month and state since combining models' outputs may underestimate variability and does not capture correlations between age groups. Although we calculated hospitalizations by month and state, combined variance is unknown, so CrIs may be wider than reported.

In conclusion, we estimated that about 4 million COVID-19 hospitalizations occurred in the United States from May 2020 through April 2021. As COVID-19 continues to circulate and cause illness, it will be important to develop a sustainable method to continue to estimate the disease burden of COVID-19 that can account for regional variation in timing and incidence of disease activity as well as changes in detection and reporting of COVID-19 and that utilizes ongoing surveillance data. With an unknown future of COVID-19, burden estimates will continue to be needed. Having a burden estimation method that uses a sentinel surveillance system ensures we will have the ability to create burden estimates despite changes in case data reporting. Knowing disease burden helps us understand vaccine-averted burden, post–COVID-19 conditions, and more important public health research. Our method leverages routine surveillance data that are expected to continue after the pandemic and a Bayesian hierarchical modeling approach as a novel way to continue estimating COVID-19 hospitalizations. The model offers an approach that will be useful not only to COVID-19 hospitalization estimations but also to other levels of the disease burden pyramid, including SARS-CoV-2 infections and COVID-19 deaths.

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## Authors' Contributions

AC, ADI, HHC, NNP, MG, MS, and CR were involved in the study conceptualization. AC, ADI, NNP, MG, MW, and CR analyzed the primary and input data. AC and HHC coded the model, and AC was responsible for running all model analyses. AC, ADI, NNP, MG, MS, FPH, MW, and CR validated the data used in the analysis. AC and CR led the initial drafting of the manuscript. All authors contributed ideas for analysis and manuscript edits and subsequent drafts. All authors had access to the underlying data, have seen and approved the final manuscript, and were responsible for the decision to submit.

## Conflicts of Interest

None declared.

Multimedia Appendix 1

Covariates selected for each Bayesian model for extrapolation of COVID-19 hospitalizations for all 50 US states by age group out of all covariates. For the 0-17 years age group, only asthma was included as a possible covariate from the chronic conditions/diseases. CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, inpat: inpatients.

[DOCX File , 18 KB - publichealth_v8i6e34296_app1.docx ]

Multimedia Appendix 2

Comparison of COVID-19 hospitalization rates per 100,000 population and 90% credible intervals (error bars) from our Bayesian model by age group for each US state in COVID-NET showing observed rate (COVID-NET input rate), estimated rate (final model), and extrapolated rate (dropped). Y-axis limits adjust to the unique minimum and maximum rate for each age group.

[DOCX File , 2181 KB - publichealth_v8i6e34296_app2.docx ]

Multimedia Appendix 3

Comparison of COVID-19 hospitalization estimates between our Bayesian model and case-based multiplier model by age group, months, and HHS regions, including distribution of hospitalization for each group from June 2020 through March 2021.

[DOCX File , 21 KB - publichealth_v8i6e34296_app3.docx ]

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## Abbreviations

**BRFSS:** Behavioral Risk Factor Surveillance System
**CDC:** Centers for Disease Control and Prevention
**COPD:** chronic obstructive pulmonary disease
**COVID-NET:** COVID-19-Associated Hospitalization Surveillance Network
**CrI:** credible interval
**FluSurv-NET:** Influenza Hospitalization Surveillance Network
**HHS:** Department of Health and Human Services
**ICU:** intensive care unit
**LASSO:** Least Absolute Shrinkage and Selection Operator
**MCMC:** Markov chain Monte Carlo
**NNDSS:** National Notifiable Disease Surveillance System
**NVSS:** National Vital Statistics System

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Original Paper

# COVID-19 Surveillance in the Biobank at the Colorado Center for Personalized Medicine: Observational Study

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## Abstract

**Background:** Characterizing the experience and impact of the COVID-19 pandemic among various populations remains challenging due to the limitations inherent in common data sources, such as electronic health records (EHRs) or cross-sectional surveys.

**Objective:** This study aims to describe testing behaviors, symptoms, impact, vaccination status, and case ascertainment during the COVID-19 pandemic using integrated data sources.

**Methods:** In summer 2020 and 2021, we surveyed participants enrolled in the Biobank at the Colorado Center for Personalized Medicine (CCPM; N=180,599) about their experience with COVID-19. The prevalence of testing, symptoms, and impacts of COVID-19 on employment, family life, and physical and mental health were calculated overall and by demographic categories. Survey respondents who reported receiving a positive COVID-19 test result were considered a “confirmed case” of COVID-19. Using EHRs, we compared COVID-19 case ascertainment and characteristics in EHRs versus the survey. Positive cases were identified in EHRs using the International Statistical Classification of Diseases, 10th revision (ICD-10) diagnosis codes, health care encounter types, and encounter primary diagnoses.

**Results:** Of the 25,063 (13.9%) survey respondents, 10,661 (42.5%) had been tested for COVID-19, and of those, 1366 (12.8%) tested positive. Nearly half of those tested had symptoms or had been exposed to someone who was infected. Young adults (18-29 years) and Hispanics were more likely to have positive tests compared to older adults and persons of other racial/ethnic groups. Mental health (n=13,688, 54.6%) and family life (n=12,233, 48.8%) were most negatively affected by the pandemic and more so among younger groups and women; negative impacts on employment were more commonly reported among Black respondents. Of the 10,249 individuals who responded to vaccination questions from version 2 of the survey (summer 2021), 9770 (95.3%) had received the vaccine. After integration with EHR data up to the time of the survey completion, 1006 (4%) of the survey respondents had a discordant COVID-19 case status between EHRs and the survey. Using all longitudinal EHR and survey data, we identified 11,472 (6.4%) COVID-19-positive cases among Biobank participants. In comparison to COVID-19 cases identified through the survey, EHR-identified cases were younger and more likely to be Hispanic.

**Conclusions:** We found that the COVID-19 pandemic has had far-reaching and varying effects among our Biobank participants. Integrated data assets, such as the Biobank at the CCPM, are key resources for population health monitoring in response to public health emergencies, such as the COVID-19 pandemic.

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**KEYWORDS**

COVID-19; surveillance; pandemic; biobank; EHR; public health; integrated data; population health; health monitoring; electronic health record; eHealth; health record; emergency response; vaccination status; vaccination; testing; symptom; disease impact

## Introduction

The COVID-19 global pandemic has caused a significant burden on the health and well-being of our families and communities. It has changed the way we work, socialize, and go about our daily lives. To date, over 888,000 Americans have died from COVID-19, and more than 49 million have been infected with the virus, many of whom have been hospitalized or suffered from a range of symptoms lasting from days to years [1]. Further, the burden of this disease, with respect to infection rates, hospitalizations, deaths, and impacts on physical and mental health, is not evenly distributed throughout the population. Understanding the nature and magnitude of this disease has been challenging due to the evolving nature of this virus, changing recommendations from public health around testing and self-quarantine, and our own health behaviors to avoid exposure.

As we strive to understand this novel virus in terms of risk and outcomes, it is important to assess the impact of COVID-19 among various populations, including those who may experience serious versus mild effects from infection, those who experience symptoms but do not undergo testing, and those who never contract the disease. This broad inquiry requires multiple data sources. Electronic health records (EHRs) are useful for capturing information about persons who seek medical care or become hospitalized due to COVID-19, and thus may reflect more severe cases [2-4]. However, due to incomplete and unstructured data collection in EHRs, self-reported population surveys can provide information about persons with more mild disease who may opt not to seek medical care and those never infected [5]. Combining data sources from EHRs and surveys can mitigate limitations and biases inherent in each as well as optimize capture of the COVID-19 experience in a broader population.

We sought to characterize the experience and impact of the COVID-19 virus among a large and diverse group of persons enrolled in the Biobank at the Colorado Center for Personalized Medicine (CCPM), a collaborative initiative supported by UCHealth and the University of Colorado Anschutz Medical Campus. Specifically, we assessed the prevalence of testing and positive test results, the type and frequency of symptoms, health care utilization, severity of disease, and the impacts of the pandemic on mental and physical health, and employment. Uniquely, for this analysis, we were able to combine clinical data from EHRs with self-reported information collected via an online survey that was offered to all Biobank participants.

We present here results from our analysis of self-reported survey data and clinical data recorded in EHRs for Biobank participants. By combining these unique data sources, we were able to capture more COVID-19-positive cases and assess population differences in symptoms, health care utilization, severity (hospitalization), and personal impact. We also highlight the value of biobanks such as ours in facilitating rapid and comprehensive inquiries about emerging public health threats such as COVID-19.

## Methods

### Study Population

Enrollment in the CCPM Biobank is open to all UCHealth patients who are 18 years of age or older and able to provide consent for themselves through My Health Connection, the mobile EHR patient portal for UCHealth. Enrolled participants consent to use of their clinical data from EHRs and to being recontacted about new research opportunities and to complete surveys. To date, the Biobank has enrolled over 200,000 adult participants from among the 2.5 million UCHealth patients across Colorado. Biobank participants are representative of the whole UCHealth population with respect to age, gender, race/ethnicity, and comorbidity status (Multimedia Appendix 1). For this study, all living Biobank participants with a valid email address were invited to complete an online survey about their experience with the COVID-19 pandemic. Participants were identified by a unique ID generated by Health Data Compass (HDC), the system-wide data warehouse for UCHealth. For this analysis, HDC linked survey responses to participants' clinical data in EHRs using this unique ID, removed personal identifiers, and deposited the data into a datamart that was accessible to the authors.

### Survey Development and Administration

We developed our survey based on an instrument developed by the International Common Disease Alliance (ICDA) [6] early in the pandemic. Our survey included questions about testing for COVID-19, test results, symptoms related to COVID-19 infection, health care utilization following a positive test or symptoms, underlying health conditions, the impact of COVID-19 on health and well-being, potential household exposure to COVID-19, and current smoking behaviors (Multimedia Appendix 2). Given the novelty of the COVID-19 pandemic, no validated questionnaires were available at the time of our survey development and administration.

We created the survey in REDCap [7], a Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant database and research management platform, and created unique survey links for each Biobank participant. Personal invitations to complete the survey were sent by email to all participants beginning in June 2020, with a follow-up reminder to nonresponders within 2 weeks. We repeated the process in October 2020 for all participants newly enrolled between June and October 2020. We revised the survey in March 2021 to include additional questions on vaccine uptake, adverse reactions to the vaccine, and long-term symptoms postinfection (Multimedia Appendix 3). The revised survey was sent to all participants who had not responded to the initial survey and newly enrolled participants through May 2021. In total, survey invites were sent to 180,599 individual participants over the course of 15 months.

### COVID-19 Case and Severity Definitions: Survey and EHRs

A summary of available data and definitions from the EHR and survey is provided in Multimedia Appendix 4. Survey respondents who reported receiving a positive COVID-19 test result were considered a "confirmed case" of COVID-19. Self-reported cases also reported whether the respondent tested positive for COVID-19, saw a doctor in person or through telehealth, visited the emergency room (ER), were hospitalized overnight, stayed home/isolated, or did nothing different. We looked at severity in terms of either hospitalization due to COVID-19 or death after COVID-19. Respondents who reported having 1 or more overnight stays in the hospital were considered to be "hospitalized."

Positive cases were identified in EHRs using *International Statistical Classification of Diseases, 10th revision* (ICD-10) diagnosis codes, health care encounter types, and encounter primary diagnoses. Participants who received an ICD-10 diagnosis code of U07.1 or at least 1 of 11 COVID-19-specific encounter primary diagnoses (Multimedia Appendix 5) were considered an "EHR-confirmed case." Participants who were hospitalized in a UCHealth hospital overnight during the 3 days before or up to 21 days after their COVID-19 diagnosis date and who had at least 1 of 64 COVID-19-related encounter primary diagnoses (Multimedia Appendix 6) were considered to be "EHR hospitalized." To compare positive cases identified from EHRs and the survey, we examined the number of hospitalized cases that were discordant between these data sources.

All-cause mortality data stored in the HDC clinical data warehouse include the cause of death as certified by a physician or coroner/medical examiner, related ICD-10 cause of death codes generated by Centers for Disease Control and prevention (CDC), and age at death. These data are obtained through routine linkage of UCHealth patients with the vital statistics/death certificates provided by the Department of Vital Statistics at the Colorado Department of Public Health and the Environment (CDPHE). Accounting for the ~3-month lag time to register certificates, map ICD-10 cause of death codes, and update the clinical databases, the ascertainment of mortality among UCHealth patients for this analysis is nearly 95% complete.

### Other Definitions

Age and race/ethnicity were determined from EHRs. Race and ethnic indicators were extracted as encoded in EHRs and categorized into 4 racial-ethnic groups to preserve >10 individuals in each group in all analyses, including non-Hispanic White, non-Hispanic Black, any Hispanic, and other.

### Statistical Analysis

We generated descriptive statistics to characterize our study population and responses to survey questions using R version 4.0.5 (R Core Team) [8]. We also stratified respondents with respect to COVID-19 infection status based on reported test status and symptomology. We compared COVID-19-positive individuals who were identified via the survey and via EHRs by demographics and severity (overnight hospitalization and death). We investigated case status and hospitalization misclassification in both the survey and EHRs by comparing those who were discordant in the survey and EHRs. We calculated differences between groups using chi-square and $t$ test statistics for categorical and continuous measures, respectively. As expected, due to the large sample size in the study, most comparisons were statistically significant at a 2-sided $\alpha$ of <.05. Therefore, we focused results and interpretation on effect sizes and the corresponding SE of the estimate.

### Ethical Considerations

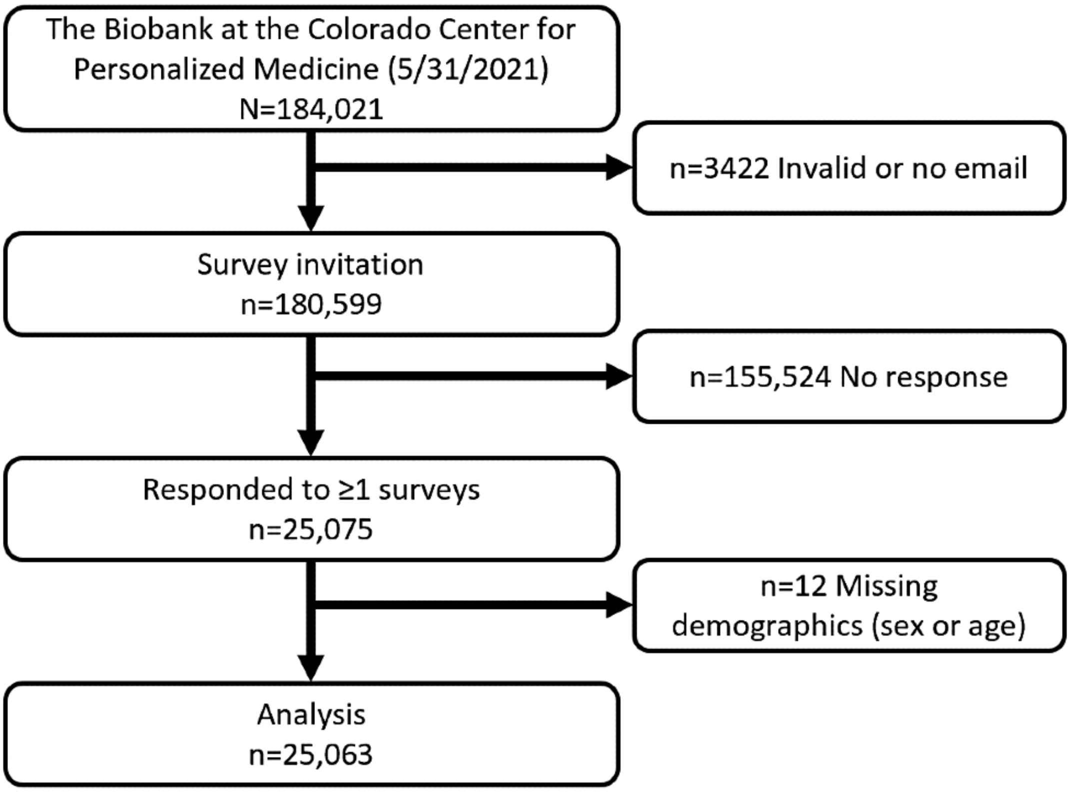
The Colorado Multiple Institutional Review Board (COMIRB) approved all CCPM Biobank study protocols (COMIRB #15-0461), and this research was performed in accordance with relevant guidelines/regulations.

## Results

### Survey Response

Of 180,599 Biobank participants with valid email addresses, 25,063 (13.9% response rate) completed at least 1 survey and had complete demographic information (Figure 1). Compared to nonrespondents (Multimedia Appendix 7), respondents were older (mean age 55.0 years vs 48.6 years, $P<.001$) and enriched for a higher proportion of females (n=15,695, 62.6%, vs n=91,707, 59.0%, $P<.001$) and individuals of non-Hispanic White race/ethnicity (n=21,917, 87.4%, vs n=119,848, 77.1%, $P<.001$).

**Figure 1.** The CCPM Biobank COVID-19 survey population. CCPM: Colorado Center for Personalized Medicine.



## COVID-19 Testing

Among all survey respondents, 10,661 (42.5%) reported being tested for COVID-19. The most common reasons for testing were having symptoms (n=3148, 29.5%), exposure to someone who tested positive for COVID-19 (n=1975, 18.5%), doctor recommendation (n=1565, 14.7%), requirement of the employer (n=950, 8.9%), and recent international travel (n=362, 3.4%). An additional 4352 (40.8%) of individuals tested reported other reasons for testing that included having surgery or other medical procedure, planned travel, a desire or need to be around large groups or family members, and work site offerings for testing.

Of those tested, 1366 (12.8%) tested positive for COVID-19 (Table 1) and were considered confirmed cases. The distributions of age, sex, race/ethnicity, college education, number of symptoms, number of preexisting comorbidities, overall health status, and exposure to a household member who tested positive for COVID-19 were different across the 3 groups of those who tested positive, tested negative, and were not tested (all *P*<.001). Young adults (aged 18-29 years) were overrepresented among the tested-positive group, representing 146 (10.7%) of those who tested positive compared to 619 (6.7%) of those who tested negative and 738 (5.1%) of those who were not tested (*P* for trend <.001). Similarly, individuals of Hispanic race/ethnicity were overrepresented in the tested-positive group at 125 (9.2%) compared to 528 (5.7%) of those who tested negative and 619 (4.3%) of those who were not tested. Individuals who tested positive were also more likely to report symptoms, household exposure to COVID-19, and poor health status (Table 1; all *P*<.001).

**Table 1.** COVID-19 testing in the Biobank among survey respondents.

| Characteristics | Total respondents (N=25,063) | Tested (N=10,661) | | | Not tested (N=14,402) | | *P* value[a] |
|---|---|---|---|---|---|---|---|
| | | Tested positive (N=1366) | Tested negative (N=9295) | *P* value[b] | Respondents | *P* value[c] | |
| Age (years), mean (SD) | 55.0 (15.8) | 48.9 (14.6) | 53.7 (15.6) | <.001 | 56.5 (15.8) | <.001 | <.001 |
| **Age (years), n (%)** | | | | <.001 | N/A[d] | <.001 | <.001 |
| 18-29 | 1503 (6.0) | 146 (10.7) | 619 (6.7) | N/A | 738 (5.1) | N/A | N/A |
| 30-64 | 15,049 (60.0) | 1000 (73.2) | 5890 (63.4) | N/A | 8159 (56.7) | N/A | N/A |
| 65+ | 8511 (34.0) | 220 (16.1) | 2786 (30.0) | N/A | 5505 (38.2) | N/A | N/A |
| **Sex, n (%)** | | | | .09 | N/A | <.001 | <.001 |
| Female | 15,695 (62.6) | 902 (66.0) | 5915 (63.6) | N/A | 8878 (61.6) | N/A | N/A |
| Male | 9368 (37.4) | 464 (34.0) | 3380 (36.4) | N/A | 5524 (38.4) | N/A | N/A |
| **Race/ethnicity, n (%)** | | | | <.001 | N/A | <.001 | <.001 |
| Non-Hispanic White | 21,916 (87.4) | 1117 (81.8) | 8072 (86.8) | N/A | 12,727 (88.4) | N/A | N/A |
| Non-Hispanic Black | 308 (1.2) | 24.0 (1.8) | 133 (1.4) | N/A | 151 (1.0) | N/A | N/A |
| Hispanic | 1272 (5.1) | 125 (9.2) | 528 (5.7) | N/A | 619 (4.3) | N/A | N/A |
| Other | 1567 (6.3) | 100 (7.3) | 562 (6.0) | N/A | 905 (6.3) | N/A | N/A |
| **Bachelor’s degree, n (%)** | | | | <.001 | | .13 | <.001 |
| Yes | 19407 (77.4) | 973 (71.2) | 7219 (77.7) | N/A | 11,215 (77.9) | N/A | N/A |
| No | 5482 (21.9) | 381 (27.9) | 2008 (21.6) | N/A | 3093 (21.5) | N/A | N/A |
| Unknown | 174 (0.7) | 12.0 (0.9) | 68.0 (0.7) | N/A | 94.0 (0.7) | N/A | N/A |
| Number of acute symptoms, mean (SD) | 0.261 (1.05) | 2.09 (2.61) | 0.393 (1.15) | <.001 | 0.00222 (0.0897) | <.001 | <.001 |
| Number of comorbidities, mean (SD) | 1.51 (1.38) | 1.46 (1.46) | 1.59 (1.44) | .004 | 1.46 (1.32) | <.001 | <.001 |
| **Health status, n (%)** | | | | <.001 | N/A | <.001 | <.001 |
| Excellent | 5664 (22.6) | 235 (17.2) | 1993 (21.4) | N/A | 3436 (23.9) | N/A | N/A |
| Very good | 10,532 (42.0) | 444 (32.5) | 3784 (40.7) | N/A | 6304 (43.8) | N/A | N/A |
| Good | 6558 (26.2) | 440 (32.2) | 2527 (27.2) | N/A | 3591 (24.9) | N/A | N/A |
| Fair | 1859 (7.4) | 196 (14.3) | 793 (8.5) | N/A | 870 (6.0) | N/A | N/A |
| Poor | 323 (1.3) | 45.0 (3.3) | 151 (1.6) | N/A | 127 (0.9) | N/A | N/A |
| Unknown | 127 (0.5) | 6.00 (0.4) | 47.0 (0.5) | N/A | 74.0 (0.5) | N/A | N/A |
| **Questionnaire version, n (%)** | | | | <.001 | N/A | <.001 | <.001 |
| 1-Summer-fall 2020 | 14,814 (59.1) | 410 (30.0) | 3718 (40.0) | N/A | 10,686 (74.2) | N/A | N/A |
| 2-Summer-fall 2021 | 10,249 (40.9) | 956 (70.0) | 5577 (60.0) | N/A | 3716 (25.8) | N/A | N/A |
| **EHR[e] COVID-19 case, n (%)** | | | | <.001 | N/A | <.001 | <.001 |
| Yes | 717 (2.9) | 519 (38.0) | 125 (1.3) | N/A | 73.0 (0.5) | N/A | N/A |
| No | 24,346 (97.1) | 847 (62.0) | 9170 (98.7) | N/A | 14,329 (99.5) | N/A | N/A |
| **Household member tested positive, n (%)** | | | | <.001 | N/A | <.001 | <.001 |
| No | 19,472 (77.7) | 482 (35.3) | 7268 (78.2) | N/A | 11,722 (81.4) | N/A | N/A |
| Yes | 1519 (6.1) | 691 (50.6) | 517 (5.6) | N/A | 311 (2.2) | N/A | N/A |
| Unknown | 4072 (16.2) | 193 (14.1) | 1510 (16.2) | N/A | 2369 (16.4) | N/A | N/A |
| **Genetic data, n (%)** | | | | .17 | N/A | <.001 | <.001 |
| No | 20,182 (80.5) | 1157 (84.7) | 7732 (83.2) | N/A | 11,293 (78.4) | N/A | N/A |

| Characteristics | Total respondents (N=25,063) | Tested (N=10,661) | | | Not tested (N=14,402) | | P value[a] |
|---|---|---|---|---|---|---|---|
| | | Tested positive (N=1366) | Tested negative (N=9295) | P value[b] | Respondents | P value[c] | |
| Yes | 4881 (19.5) | 209 (15.3) | 1563 (16.8) | N/A | 3109 (21.6) | N/A | N/A |

[a] From chi-square or ANOVA, comparing tested positive versus tested negative versus not tested.

[b] From chi-square or ANOVA, comparing tested positive versus tested negative.

[c] From chi-square or ANOVA, comparing tested versus not tested.

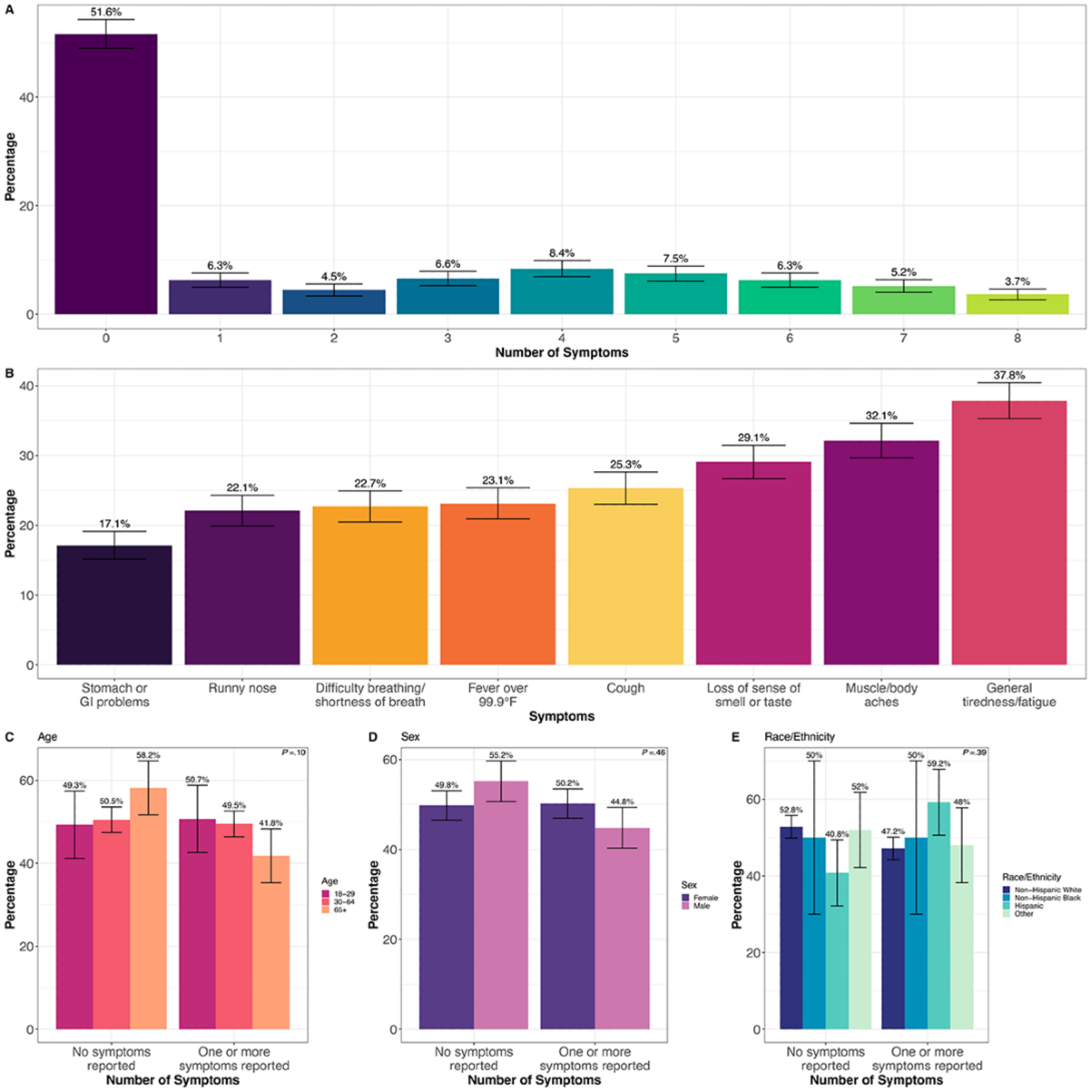
[d] N/A: not applicable.

[e] EHR: electronic health record.

## COVID-19 Case Symptomology

Of the 1366 COVID-19-positive individuals identified from the survey, 1154 (84.4%) individuals had at least 1 of the following COVID-19-related symptoms since February 2020: cough, fever over 99.9°F, general tiredness/fatigue, muscle/body aches, runny nose, difficulty breathing/shortness of breath, loss of sense of smell or taste, and stomach or gastrointestinal (GI) problems (Figure 2). However, only 661 (48.4%) reported at least 1 symptom 14 days before or after a positive COVID-19 test. The number of symptoms individuals reported was relatively even from 1 to 8 symptoms, ranging from 50 (3.7%) individuals reporting all 8 symptoms and 115 (8.4%) reporting 4 symptoms (Figure 2A). General tiredness/fatigue and muscle/body aches were the most commonly reported symptoms within 14 days of a positive COVID-19 test, at 517 (37.8%) and 439 (32.1%) individuals, respectively (Figure 2B). The next most common symptom was loss of sense of smell or taste, with 397 (29.1%) individuals reporting within 14 days of a positive COVID-19 test (Figure 2B). However, an additional 283 (20.7%) individuals reported this symptom outside the 28-day window. A quarter of the individuals (n=346, 25.3%) reported a cough within 14 days of a positive COVID-19 test, and 310 (22.7%) and 302 (22.1%) reported difficulty breathing/shortness of breath and a runny nose, respectively (Figure 2B). Only 234 (17.1%) of individuals reported stomach or GI problems (Figure 2B). The remainder (n=705, 51.6%) reported no symptoms within 14 days before or after their COVID-19 positive test. There were no significant differences in asymptomatic cases compared to symptomatic cases (having at least 1 symptom) when comparing by age, sex, or race/ethnicity (Figure 2C-E).

**Figure 2.** Symptomology among COVID-19 cases. Each symptom was reported 14 days before or 14 days after a positive COVID-19 test. (A) Number of symptoms reported among COVID-19 cases. (B) Percentage of COVID-19-positive cases that reported each symptom. Comparing asymptomatic cases with symptomatic cases (at least 1 symptom) by (C) age, (D) sex, and (E) race/ethnicity. *P* value from the Pearson chi-square test for different distributions across demographic groups. Error bars indicate the 95% CI for the percentage point estimate. GI: gastrointestinal.

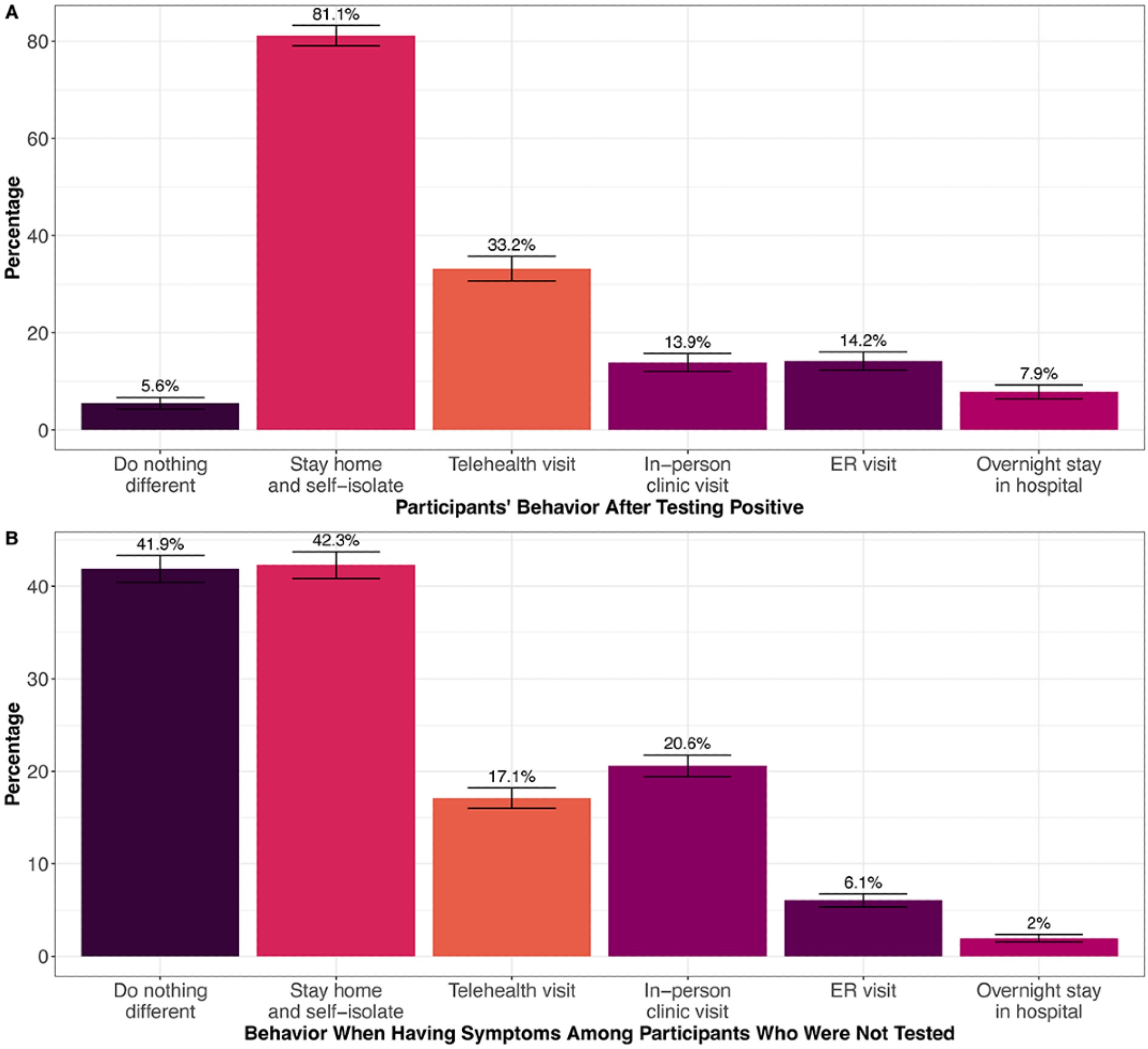


## Health Behaviors and Impact on the Health Care System

To assess health behaviors among COVID-19 cases and the potential impact on the health care system, we asked these individuals what they did as a result of testing positive (Figure 3A). Of the 1366 respondents with positive tests, 1108 (81.1%) stayed home and self-isolated, and 76 (5.6%) did not report any changes in behavior (Figure 3A). Of those who did not change behavior, 63 (82.9%) did not have any symptoms reported 14 days before or after their COVID-19 test. Of the 1366 individuals who tested positive, 625 (45.8%) sought out at least 1 form of medical care: 190 (13.9%) saw a doctor at an in-person visit, 454 (33.2%) saw a doctor via telehealth, 194 (14.2%) went to the ER, and 108 (7.9%) had an overnight stay in a hospital (Figure 3A). A subset of 229 (16.7%) individuals reported being tested at a UCHealth facility versus 213 (15.6%) outside UCHealth, with no response from 924 (67.6%) respondents. Of the 229 (16.7%) respondents who said they tested positive at a UCHealth facility, only 137 (59.8%) were identified as a “case” within EHRs. There was a high rate of missingness for the question on who performed the test (n=924, 67.6%), so there may be confusion by participants about who supplied the COVID-19 test.

Among respondents who were not tested but reported having at least 1 COVID-related symptom, 1901 (41.9%) said they did nothing different, whereas 1920 (42.3%) stayed home and self-isolated (Figure 3B). A third (n=1515, 30.4%) sought out at least 1 form of medical care, 934 (20.6%) had an in-person clinic visit, 77 (17.1%) had a telehealth clinic visit, 275 (6.1%) went to the ER, and 90 (2.0%) had an overnight stay in the hospital (Figure 3B).

**Figure 3.** The impact of COVID-19 on the health care system. (A) Participants' behavior after testing positive for COVID-19 and (B) participants' behavior when having symptoms, among those with at least 1 symptom who did not get tested for COVID-19. Error bars indicate the 95% CI for the percentage point estimate. ER: emergency room.

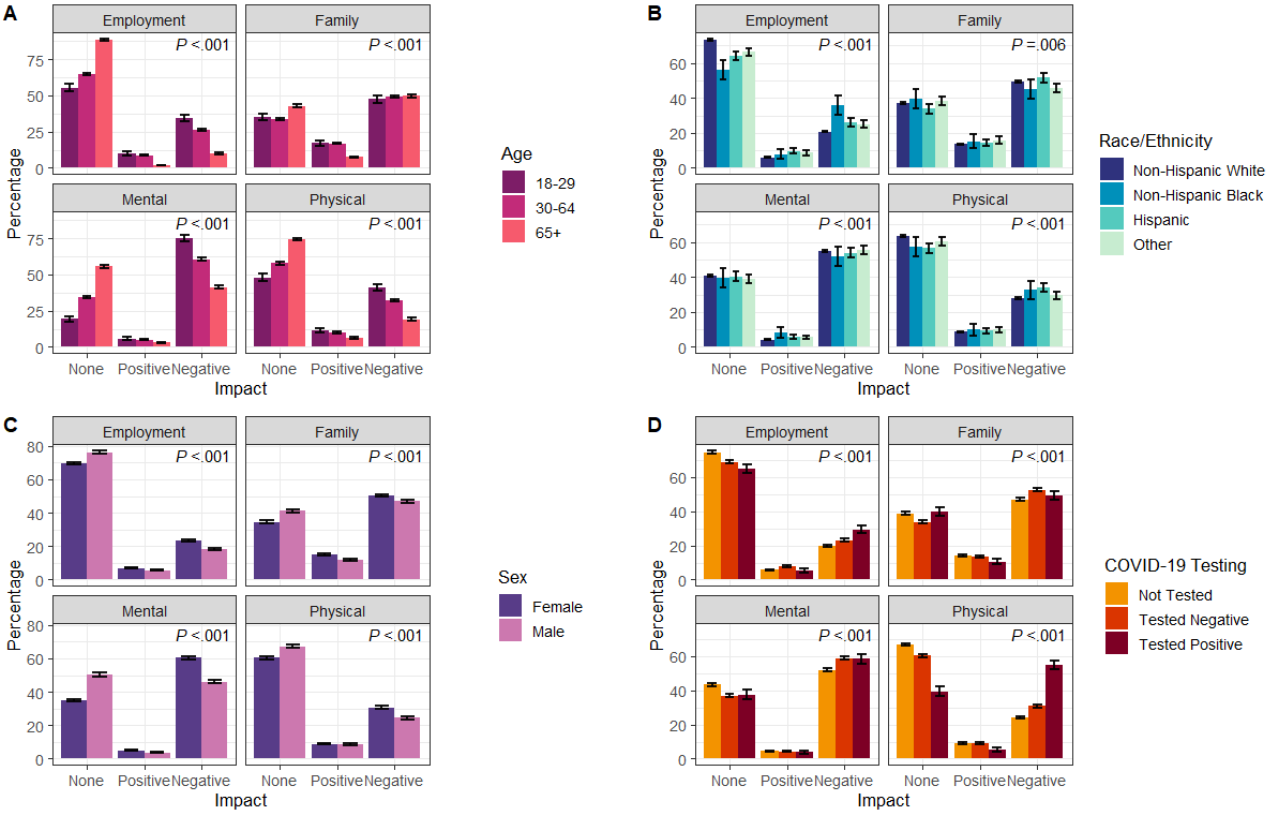


## Impact of the COVID-19 Pandemic

The impact of the COVID-19 pandemic on employment, family life, mental health, or physical health was largely negative, with 18,861 (75.3%) of respondents reporting a negative impact from the COVID-19 pandemic in at least 1 of these domains compared to 5856 (23.4%) of respondents reporting a positive impact in at least 1 domain (*P*<.001). Mental health and family life were most negatively affected by the pandemic, at 13,688 (54.6%) and 12,233 (48.8%) of respondents reporting a negative impact, respectively. The negative impact in the other 2 domains was lower at 7059 (28.2%) for physical health and 5320 (21.2%) for employment (*P*<.001).

The impact of the COVID-19 pandemic was not equal across groups by age, race/ethnicity, sex, and COVID-19 testing status (maximum *P*=.006; Figure 4). A higher proportion of young adults reported a negative mental health impact (1123/1499, 74.9%, 95% CI 72.7%-77.1%) than adults aged 30-64 years (9092/14,975, 60.7%, 95% CI 59.6%-61.5%) and older adults (65+ years; 3473/8445, 41.1%, 95% CI 40.1%-42.2%). A similar linear trend across age groups was seen for the negative impact of the pandemic on employment and physical health (Figure 4A). Using self-reported race/ethnicity as captured in EHRs, a higher proportion of non-Hispanic Black respondents reported a negative impact on their employment (108/302, 35.8%, 95% CI 30.4%-41.2%) compared to other race/ethnic groups (non-Hispanic White: 4498/21,628, 20.8%; Hispanic: 328/1257, 26.1%; other: 386/1550, 24.9%; Figure 4B). Women reported a greater negative impact of COVID-19 compared to men across all domains: employment (3625/15,470 [23.4%] versus 1695/9267 [18.3%]), family life (7865/15,579 [50.5%] versus 4368/9298 [47.0%]), mental health (9407/15,609 [60.3%] versus 4281/9310 [46.0%]), and physical health (4796/15,600 [30.7%] versus 2263/9293 [24.4%]) (Figure 4C, all *P*<.001). Respondents who tested positive for COVID-19 reported a higher negative impact on their physical health (744/1353, 55.0%, 95% CI 52.3%-57.6%) than those who tested negative (2854/9234, 30.9%, 95% CI 30.0%-31.9%) and those who did not report a COVID-19 test (3461/14,306, 24.2%, 95% CI 23.5%-24.9%, Figure 4D).

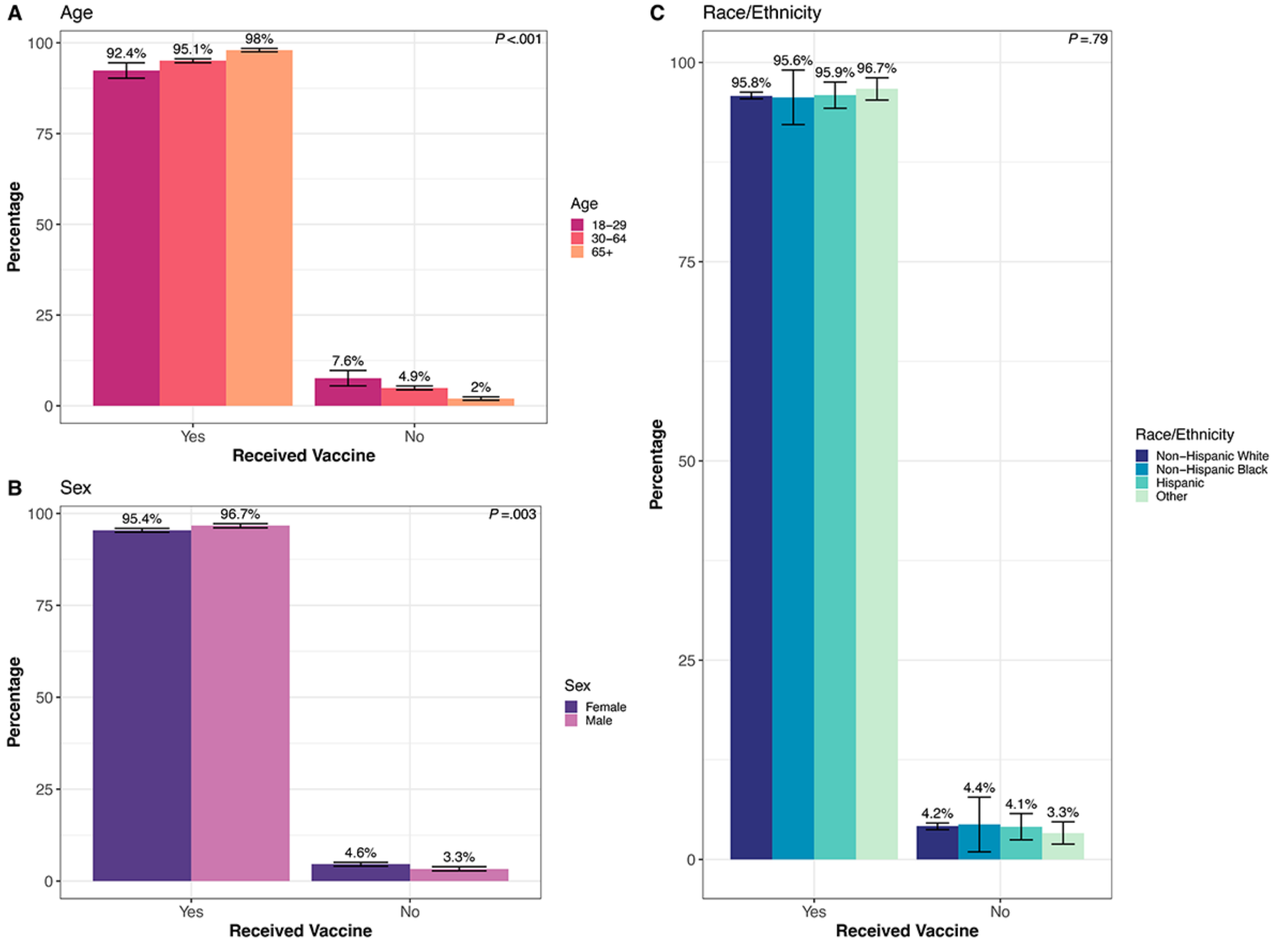
**Figure 4.** The impact of COVID-19 on employment, family life, and mental and physical health by (A) age, (B) race/ethnicity, (C) sex, and (D) COVID-19 test status. *P* value from the Pearson chi-square test for different distributions across impact and demographic groups. Error bars indicate the 95% CI for the percentage point estimate.



## COVID-19 Vaccination

In our second round of the survey (administered in spring/summer 2021), we added questions about COVID-19 vaccination. Of the 10,249 (40.9%) of the total overall survey population (N=25,063) who responded to the second survey, 9770 (95.3%) received the vaccine. Younger people were less likely to have received a vaccine: 46 (7.6%) of those aged 18-29 years did *not* receive a vaccine compared to 303 (4.9%) of those aged 30-64 years and 69 (2.0%) of those aged 65+ years (*P*<.001, Figure 5A). Women were slightly less likely to receive a vaccine (n=289, 4.6%, of women vs n=129, 3.3%, of men, *P*=.003, Figure 5B). The vaccination rate was similar across race/ethnicity categories, with 368 (4.2%) non-Hispanic Whites, <10 (4.4%) non-Hispanic Blacks, 23 (4.1%) Hispanics, and 21 (3.3%) in the other race category not receiving vaccines (*P*=.79, Figure 5C). The median income of the home 3-digit zip code was lower for unvaccinated participants: US $67,800 in the unvaccinated compared to US $71,500 in the vaccinated group (*P*<.001). The median percentage of the population that received a bachelor's degree by 3-digit zip code was lower for unvaccinated (37.7%) compared to vaccinated (47.3%) participants (*P*<.001).

**Figure 5.** Vaccine uptake by (A) age, (B) sex, and (C) race/ethnicity. *P* value from the Pearson chi-square test for different distributions across impact and demographic groups. Error bars indicate the 95% CI for the percentage point estimate.



## Demographics of COVID-19 Cases Captured by EHRs vs the Survey

We identified 11,472 (6.4%) COVID-19 positive cases from among 180,599 eligible Biobank participants: 1366 (11.9%) from the survey and 10,639 (92.7%) from EHRs; 533 (4.6%) cases were identified in both sources (Figure 6).

In comparing COVID-19 cases from EHRs to those in the survey (Figure 7), we found that cases identified in EHRs were younger, with 17.2% of individuals in the 18-29 age group compared to 10.7% in the survey group (*P*<.001, Figure 7A). A higher percentage of cases identified in EHRs were Hispanic compared to survey cases (14.7% vs 9.2%, respectively, *P*<.001, Figure 7B). EHR cases also had a slightly lower proportion of women (61.9%) compared to the survey group (66.0%; *P*=.003, Figure 7C). The median income for the 3-digit zip code was the same, US $69,900 in both groups. The median percentage of the population that received a bachelor's degree by 3-digit zip code was slightly lower in the EHR (41.3%) group compared to the survey (45.7%) group (*P*<.001).

**Figure 6.** COVID-19-positive CCPM Biobank participants identified through the UCHealth EHRs and the survey. CCPM: Colorado Center for Personalized Medicine; EHR: electronic health record.

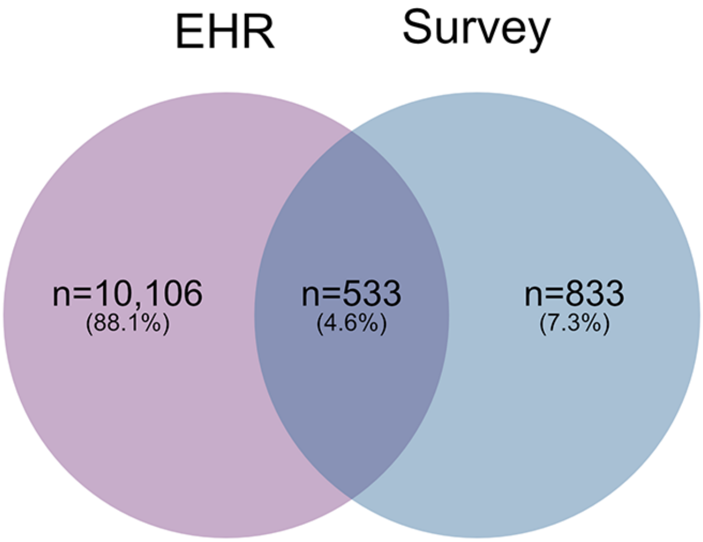
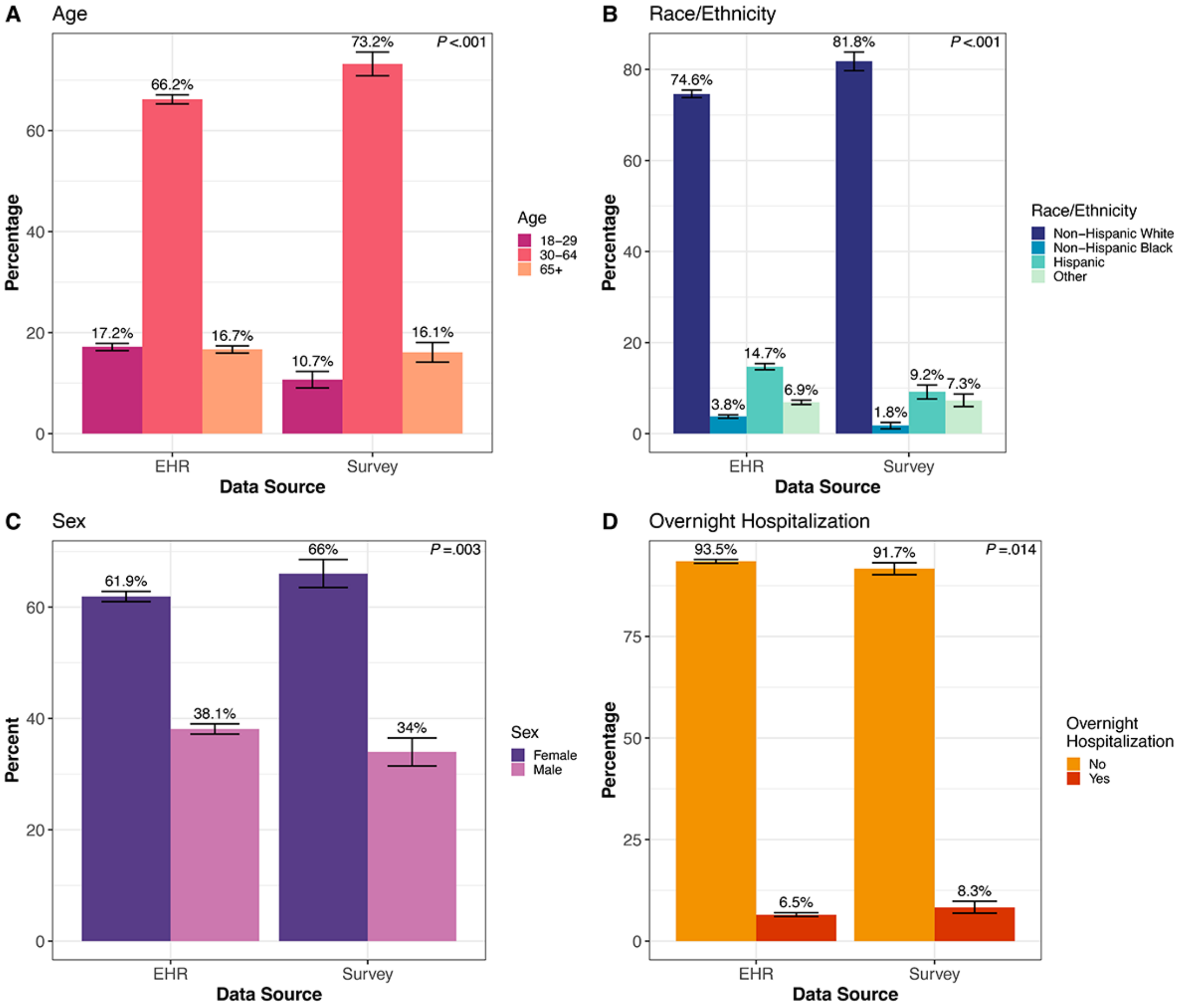


**Figure 7.** Comparison of COVID-19 cases captured in the EHRs and the survey by (A) age, (B) race/ethnicity, (C) sex, and (D) COVID-19-related overnight hospitalization. *P* value from the Pearson chi-square test for different distributions across impact and demographic groups. Error bars indicate the 95% CI for the percentage point estimate. EHR: electronic health record.



### COVID-19 Case Severity in EHRs and the Survey

A higher percentage of COVID-19-positive cases identified from the survey were hospitalized overnight (8.3%) compared to the EHR (6.5%) group (*P*=.01, Figure 7D). Using all-cause mortality data obtained from CDPHE vital statistics, 130 (2.3%) individuals in the EHR group died, leading to a death rate of 1.2%. In addition, 4 (0.29%) people in the survey group died, with a death rate of 0.2%.

The EHR is a longitudinal data source; therefore, we can capture COVID-19 cases on a continuing basis, whereas the survey reflects a point in time and can only identify individuals who had COVID-19 before they took the survey. Of 907 COVID-19 cases identified in EHRs who completed the survey but did not report a positive COVID-19 diagnosis in the survey, 379 (41.8%) reported receiving a negative COVID-19 test result and 528 (58.2%) had not taken a COVID-19 test and were presumed to be negative. The majority of these individuals (n=732, 80.7%) completed the survey before they were diagnosed with COVID-19 in EHRs.

### COVID-19 Case and Hospitalization Discordance Between EHRs and the Survey

To quantify discordance of the COVID-19 case status between EHRs and the survey, we looked across our entire set of survey respondents (N=25,063). We only counted a participant as "EHR COVID-19 positive" if the diagnosis made was prior to taking the survey, not COVID-19 cases that happened after the survey was taken. Although neither the survey nor EHRs are a gold standard for case classification, we can look at the discordance between them to identify the potential for misclassification. Overall, there were a total of 1006 (4%) respondents discordant for COVID-19 case status. Of the 25,063 individuals who took the survey, 173 (0.7%) were identified as COVID-19 positive in EHRs but negative or not tested in the survey, leading to a discordance rate of 0.7% (Table 2). In addition, 833 (3.3%) individuals were identified as COVID-19 positive in the survey but negative in EHRs, leading to a discordance rate of 3.3%.

To quantify discordance of the hospitalization status in both EHRs and in the survey, we restricted it to individuals who responded to the survey and were COVID-19 positive in either EHRs or the survey (n=2273). EHR hospitalizations were only considered if they were prior to taking the survey. There were 6 (0.3%) individuals who were positive for hospitalization in EHRs but negative in the survey, a discordance rate of 0.3% (Table 3). There were 59 (2.6%) individuals who were positive for hospitalization in the survey who were negative in EHRs, a discordance rate of 2.6%.

**Table 2.** Case status misclassification between the survey and EHRs[a] (N=25,063).

| COVID-19 status | Survey COVID-19 positive, n (%) | Survey COVID-19 other (negative or not tested), n (%) | Total, n (%) |
|---|---|---|---|
| EHR COVID-19 positive | 533 (2.1) | 173 (0.7) | 706 (2.8) |
| EHR COVID-19 other (negative or not tested) | 833 (3.3) | 23,524 (93.9) | 24,357 (97.2) |
| Total | 1366 (5.5) | 23,697 (94.4) | 25,063 (100) |

[a] EHR: electronic health record.

**Table 3.** Hospitalization misclassification between the survey and EHRs[a] (N=2273).

| Hospitalization | Survey hospitalization positive, n (%) | Survey hospitalization negative, n (%) | Total, n (%) |
|---|---|---|---|
| EHR hospitalization positive | 49 (2.2) | 6 (0.3) | 55 (2.4) |
| EHR hospitalization negative | 59 (2.6) | 2159 (95) | 2218 (97.6) |
| Total | 108 (4.8) | 2165 (95.2) | 2273 (100) |

[a] EHR: electronic health record.

## Discussion

### Principal Findings

We found that the COVID-19 pandemic has had far-reaching and varying effects among our Biobank participants. Of the 25,063 survey respondents, 10,661 (42.5%) were tested for the virus, 1366 (12.8%) of those tested were positive, and among positive cases, 1154 (84.5%) reported having 1 or more COVID-related symptoms since February 2020 and 625 (45.8%) sought medical care following their diagnosis. The vast majority of all survey respondents (n=18,861, 75%) reported a negative impact from the COVID-19 pandemic—most commonly around mental health and family life. Differences between data captured in EHRs versus those captured in the survey reveal the benefit of using both sources in combination. For example, mild cases with subclinical manifestations of infection that did not result in seeking care may be missing from EHRs but captured in a survey.

### Strengths and Limitations

EHRs are a longitudinal data source that collect clinical information on all patients diagnosed with or treated for COVID-19 within the UCHealth system irrespective of proclivity to participate in research or respond to surveys. As such, EHRs captured COVID-19 cases from Biobank participants that the survey did not. However, a key strength of this study was our ability to leverage an existing, living resource in the CCPM Biobank and survey engine to assess the health and well-being of our participants in ways that are not highlighted by EHRs. Because Biobank participants consent to recontact, we have an opportunity to follow up with subpopulations within our cohort to collect additional information and monitor outcomes such as reinfection and vaccine uptake. Although our overall response to the survey was sizeable, we acknowledge that the composition of the underlying patient population at UCHealth who enrolled in the Biobank and differential responses to the survey may have introduced some bias—results may not generalize outside of the CCPM Biobank and UCHealth population. However, our ability to incorporate EHR data allowed us to build a research population of Biobank participants that is more representative of the entire patient population.

There are benefits and limitations to COVID-19 case ascertainment using either a survey or EHRs. Because both methods of ascertainment draw from the CCPM Biobank, they are both limited to individuals who have sought treatment at a UCHealth facility and enrolled in the CCPM Biobank. Furthermore, the survey is a convenience sample of individuals who responded to an email asking them to participate. The EHR will capture any health care encounter at a UCHealth facility, but it is an open system, and it will not capture all health care encounters for all every Biobank participant. The ascertainment bias in both methods can be a challenge for future analytical studies. We hope that by describing the demographics and case severity in both these methods of collection, future analytical studies will better be able to adjust for these biases.

## Comparison With Prior Work

Our overall case positivity rate of 13% is comparable to those reported by other EHR-based retrospective studies conducted in 2020 and 2021 [9,10]. However, our finding of higher positivity rates (20%) among our younger participants (aged 18-39 years) and Hispanics (19%) has not been reported previously and may reflect differences in reasons for testing in these groups (eg, due to having symptoms or recent exposure vs other reasons). Though not surprising that a large proportion of respondents reported having symptoms, given the breadth of symptoms reported (eg, runny nose, fever, body aches), it is notable that 3026 (34.4%) of those with symptoms did not undergo testing nor seek medical care. It is likely that a percentage of this group had COVID-19 and would not be counted as such via public health surveillance efforts, which could lead to substantial underestimates of the true infection rate in the general population.

We found that females more often reported negative impacts than males in all domains—employment, family life, and mental and physical health. This disproportionate negative impact on females is consistent with prior public health emergencies [11], including the 2016 Zika and 2014 Ebola outbreaks [12]. Among US women, this has been described in several areas, including the health care workforce, reproductive health, drug development, gender-based violence, and mental health [13]. It is both notable and concerning that nearly 1123 (75%) of younger adults (aged 18-29 years) reported negative impacts on their mental health, which was higher than for any other group. The younger end of this range captures members of Generation Z, who are more likely to report poor mental health compared to prior generations [14,15]. However, they are also more likely to receive mental health therapy or treatment [14] and, therefore, may accept interventions to address the negative mental health consequences of the COVID-19 pandemic. Further, we found that negative impacts on employment were more commonly reported among Black participants. These findings highlight the breadth of negative impacts of this pandemic in our community and reveal the disproportionate impact experienced by certain subgroups that should be targeted in future intervention efforts.

Our study population had a much higher vaccination rate compared to Colorado overall and the general US population. Over 95% of our survey participants are fully vaccinated compared to 76% of adults throughout Colorado [16]. Vaccination directly reduces the likelihood of infection and severity of disease, but it also has an indirect effect on society via reduced viral transmission and herd immunity. Because of this impact on others, getting vaccinated is considered a prosocial behavior [17-19]. Being a participant in a biobank has also been positively associated with prosocial behavior, as the individuals who participate in biobanks tend to be motivated by furthering research for the greater good [20,21]. Since our study population only includes those who elected to be in the Biobank and additionally those who responded to the survey, these are likely individuals with high levels of prosocial behaviors, which likely explains the high vaccination rate.

COVID-19 has variable clinical presentations ranging from asymptomatic infections to severe symptoms that require hospitalization. We expected that COVID-19 patients identified in EHRs would be more likely to have severe COVID-19 and less likely to have asymptomatic infections than those captured by the survey [22,23]. However, we found that there was a slightly higher percentage of COVID-19 hospitalizations among survey cases compared to EHR cases. This unexpected result may be explained, in part, by the fact that individuals who were hospitalized with COVID-19 may be highly motivated to contribute to COVID-19 research by taking the survey. This likely includes individuals who went to non-UCHealth hospitals, which would not have been identified in EHRs. With respect to participant demographics, it is notable that a higher percentage of younger (18-29 years) and Hispanic/Latino COVID-19-positive cases were identified via EHRs versus the survey. This may, in part, be explained by lower survey response rates in these groups. Hispanic/Latino individuals may have been less likely to take the survey because of language barriers (the survey was only in English), limited internet access, or other structural barriers [24]. Lower participation among Hispanic individuals is consistent with observations in other outreach efforts [25] and is a limitation of the convenience survey design. Additionally, the Hispanic population in Colorado, as in many other states, had a higher incidence of COVID-19 infections, hospitalizations, and death [4,26-29], which may explain why they are more likely to be identified through EHRs.

## Conclusion

The combination of EHR and survey data provides a powerful opportunity to monitor and describe the ongoing effects of the

COVID-19 pandemic in our communities. As the pandemic continues, there is a critical need for optimal COVID-19 case ascertainment in order to capture both mild and severe cases and monitor specific long-term outcomes, such as postacute sequelae of SARS-CoV-2 infection (PASC) or downstream breakthrough infections postvaccination. In an open health system, as is common in the United States, the development of a combined resource such as ours (with EHR and survey data) represents long-term potential for additional recruitment and follow-up as a critical complement to large-scale informatics-focused investigations, such as the National COVID Cohort Collaborative [30]. As the pandemic continues, we anticipate that resources such as the CCPM Biobank and other biobanks will continue to be a key resource for ongoing data collection relevant to population health monitoring during the era of COVID-19 and other emerging public health issues.

## Acknowledgments

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## Conflicts of Interest

None declared.

Multimedia Appendix 1
Characteristics of participants in the Biobank at the Colorado Center for Personalized Medicine Compared to the UC Health System.
[DOCX File , 18 KB - publichealth_v8i6e37327_app1.docx ]

Multimedia Appendix 2
COVID-19 survey instrument administered in 2020.
[DOCX File , 2173 KB - publichealth_v8i6e37327_app2.docx ]

Multimedia Appendix 3
COVID-19 Survey Instrument Administered in 2021.
[DOCX File , 3457 KB - publichealth_v8i6e37327_app3.docx ]

Multimedia Appendix 4
Data availability from the EHR and the survey.
[DOCX File , 101 KB - publichealth_v8i6e37327_app4.docx ]

Multimedia Appendix 5
COVID-19 specific encounter primary diagnoses used in addition to U07.1 to identify “EHR-confirmed case” from UC Health EHR data.
[DOCX File , 13 KB - publichealth_v8i6e37327_app5.docx ]

Multimedia Appendix 6
Specific encounter primary diagnoses used in conjunction with hospitalization, timing of hospitalization, and COVID-19 case definitions to identify “EHR-hospitalization” from UC Health EHR data.
[DOCX File , 15 KB - publichealth_v8i6e37327_app6.docx ]

Multimedia Appendix 7
Characteristics of Biobank participants by COVID-19 survey response.
[DOCX File , 17 KB - publichealth_v8i6e37327_app7.docx ]

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## Abbreviations

**CCPM:** Colorado Center for Personalized Medicine
**CDPHE:** Colorado Department of Public Health and the Environment
**EHR:** electronic health record
**ER:** emergency room
**GI:** gastrointestinal
**HDC:** Health Data Compass
**ICD-10:** International Statistical Classification of Diseases, 10th revision

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Original Paper

# Changes in Temporal Properties of Notifiable Infectious Disease Epidemics in China During the COVID-19 Pandemic: Population-Based Surveillance Study

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## *Abstract*

**Background:** COVID-19 was first reported in 2019, and the Chinese government immediately carried out stringent and effective control measures in response to the epidemic.

**Objective:** Nonpharmaceutical interventions (NPIs) may have impacted incidences of other infectious diseases as well. Potential explanations underlying this reduction, however, are not clear. Hence, in this study, we aim to study the influence of the COVID-19 prevention policies on other infectious diseases (mainly class B infectious diseases) in China.

**Methods:** Time series data sets between 2017 and 2021 for 23 notifiable infectious diseases were extracted from public data sets from the National Health Commission of the People’s Republic of China. Several indices (peak and trough amplitudes, infection selectivity, preferred time to outbreak, oscillatory strength) of each infectious disease were calculated before and after the COVID-19 outbreak.

**Results:** We found that the prevention and control policies for COVID-19 had a strong, significant reduction effect on outbreaks of other infectious diseases. A clear event-related trough (ERT) was observed after the outbreak of COVID-19 under the strict control policies, and its decreasing amplitude is related to the infection selectivity and preferred outbreak time of the disease before COVID-19. We also calculated the oscillatory strength before and after the COVID-19 outbreak and found that it was significantly stronger before the COVID-19 outbreak and does not correlate with the trough amplitude.

**Conclusions:** Our results directly demonstrate that prevention policies for COVID-19 have immediate additional benefits for controlling most class B infectious diseases, and several factors (infection selectivity, preferred outbreak time) may have contributed to the reduction in outbreaks. This study may guide the implementation of nonpharmaceutical interventions to control a wider range of infectious diseases.

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**KEYWORDS**

class B infectious disease; COVID-19; event-related trough; infection selectivity; oscillation; public health interventions; pandemic; surveillance; health policy; epidemiology; prevention policy; public health; risk prevention

## *Introduction*

Atypical pneumonia caused by a new coronavirus was first reported in December 2019 [1-4] and was subsequently termed “COVID-19” by the World Health Organization (WHO) on February 12, 2020. Later, human-to-human transmission of COVID-19 was confirmed, resulting in a pandemic outbreak worldwide [5-13]. After the outbreak, the Chinese government took immediate action to implement strict public health policies [14], such as lockdown, quarantine measures, and social distancing. Domestic and international travel was restricted, mass gatherings were reduced, and public entertainment venues and schools were closed. The government also asked people to be more vigilant and take personal precautions, such as sanitizing hands and wearing surgical masks. Under these policies, the number of COVID-19 infections in China sharply decreased, and this situation has lasted until recently [15-17]. In addition to the COVID-19 outbreak, other fatal infectious diseases have also had outbreaks [18], which may have been overlooked. In China, the national infectious disease surveillance system has been recording outbreaks of other diseases [19]. Infectious diseases are divided into notifiable classes A, B, and C. In this classification, class B notifiable diseases have the potential to cause severe epidemic outbreaks, such as hepatitis B virus (HBV) [20], scarlet fever [21], measles [22], and rabies [23-25]. Notably, COVID-19 is classified as a class B disease.

During the COVID-19 pandemic, local and international governments relied on nonpharmaceutical measures until vaccines were available. Unlike vaccines or medicine, which are restricted by supply and logistics [26], nonpharmaceutical interventions (NPIs) could have a broader impact on multiple infectious diseases. Take the influenza virus as an example. Human beings have little immunity to it, which allows it to spread rapidly from one person to another. In the absence of effective vaccines to immunize people, NPIs are one of the best strategies to control pandemics. Several studies have found that policies to prevent COVID-19 and other NPIs could reduce the number of infections of influenza [17,27-29], tuberculosis [30,31], and some other diseases [32,33] to a large degree, while the characteristics of an epidemic are not only limited to the static number of the infected cases but also limited to the temporal dynamics of the epidemic. The temporal features of an infectious epidemic after NPIs is not precisely defined, although common sense suggests that the number of cases may decrease. The question whether under a consistent and rigorous prevention policy, this decrease would rebound or only fall to 0 arises. New analysis indicators are required to define it clearly. There are some characteristics of temporal dynamics, such as the tuning curve of the infectious disease in a year [34-37] and the spectrogram of the epidemic [38-42] analyzed by the Fourier method. The tuning curve of monthly infected cases illustrates the essential profile of each disease outbreak and gives a direct picture of the monthly situation, but it lacks quantitative features (eg, infection selectivity and preferred outbreak time) that were highly summarized from the tuning curve and lack of further analysis. Although these temporal indices have been mentioned in previous studies, it remains unclear how they changed with strict NPIs during the COVID-19 outbreak and to what extent they contributed to the reduction in infectious cases under the NPIs.

In the light of this, in this study, we investigated the impact of NPIs on other class B infectious diseases. We extracted the time series data for 23 class B notifiable infectious diseases between 2017 to 2021 from public data sets of the National Health Commission of the People’s Republic of China [43]. During the COVID-19 pandemic, the strict NPIs in China have always been existing, which can be described by the stringency index taken from the Oxford COVID-19 Government Response Tracker [44]. We expected to find a significant trough of most class B infectious diseases after the outbreak and subsequent interventions for COVID-19, which we defined as the event-related trough (ERT). The ERT can be used to investigate the fluctuations in several infections that are time-locked to an event without intervention. We then explored how infection selectivity and the preferred month of the outbreak of the infectious diseases may affect the ERT. Finally, we calculated the oscillatory strength of each infectious disease and compared the power before and after the COVID-19 outbreak.

## Methods

### Data and Sources

Time series data available for the monthly reported and confirmed cases of 23 class B notifiable infectious diseases in China's mainland, from April 2017 to September 2021, were obtained from the National Health Commission of the People's Republic of China. The data set is open to the public around the world and is reported by the Chinese Centre for Disease Control and Prevention (CDC) each month. These 23 diseases are HIV/AIDS, hepatitis (including hepatitis A virus, HAV; HBV; hepatitis C virus, HCV; and hepatitis E virus, HEV), measles, hemorrhagic fever, dengue and severe dengue, rabies, Japanese encephalitis, anthrax, *Shigella* spp. or *Entamoeba histolytica*, tuberculosis, typhoid and paratyphoid fever, pertussis, neonatal tetanus, scarlet fever, brucellosis, gonorrhea, *Treponema pallidum*, leptospirosis, schistosomiasis, and malaria. The data sampling rate was 1 time point per month (12 time points per year) from the monthly report of the National Health Commission of the People's Republic of China. We used 2 criteria to select these diseases. First, the maximum number of infectious cases each month in recent years should be larger than 10. Second, the time points should be continuously publicly reported within the years of interest. We were mainly interested in how other class B infectious diseases might be influenced by policies related to COVID-19, considering that COVID-19 is also classified as class B. We did not include class A diseases due to their low incidences. Class C diseases, such as the flu, were not included, because they are less fatal and controllable and would not have the same impact as class B diseases.

Indicators of government response in China were taken from the Oxford COVID-19 Government Response Tracker [44]. In this work, we use the stringency index (all closure indicators, such as lockdown policies and travel bans, and health system policies that record public information campaigns and contact tracing), which records the strictness of lockdown-style policies. The index scores the level of government responses between 0 and 100. The higher the score is, the stricter the government interventions were (Multimedia Appendix 1).

### Ethical Considerations

For this study, we used public data from the National Health Commission of the People's Republic of China. Our study did not involve any intervention on human participants. This study was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University, China.

### Trough and Peak Amplitude Before and After the COVID-19 Outbreak

We defined a new concept named the ERT, which originates from the event-related potential (ERP) in neuroscience [45]. The ERT describes the direct impact of specific events on reducing the number of infectious diseases. This event could be a pharmaceutical or nonpharmaceutical intervention to prevent the spread of infectious disease. In this study, the specific event is the strong prevention and control policies implemented at the outbreak of the COVID-19 epidemic, which are an NPI. The ERT is the lowest increase of an outbreak in the period of 6 months after the outbreak of COVID-19. The trough amplitude before COVID-19 is the lowest value of the infection in the 3-year period before COVID-19 (Equation 1). The peak amplitude (Equation 2) before and after the COVID-19 outbreak is the highest value of the infection before and after COVID-19. We also calculated the trough ratio index as the ratio of troughs before and after the outbreak of COVID-19 (Equation 3).

Trough amplitude = arg min(infected cases after outbreak of the epidemic) (1)

Peak amplitude = arg max(infected cases after outbreak of the epidemic) (2)

Trough ratio index = arg min(infected cases before outbreak of the epidemic)/arg min(infected cases after outbreak of the epidemic) (3)

### Tuning Curves for Monthly Infected Cases Before and After the COVID-19 Outbreak

The tuning curve of the monthly infected cases illustrates the essential profile of the outbreak of each disease in China, which gives a direct picture of the situation each month based on the historical data. We assumed that all infectious diseases included in this study have a similar trend each year for the years of observation (Multimedia Appendix 2), similar to previous studies [18]. Thus, we took the monthly average number of infected cases and computed them into a tuning curve (Equation 4). Each infectious disease in this study has a tuning curve before and after the COVID-19 outbreak, and the oscillatory pattern within a year is clear.

$$\text{Tuning curve}_{\text{month}} = \text{sum}(\text{infected cases}_{\text{month}})/N, \quad (4)$$

where N is the number of years.

### Preferred Month and Selectivity of the Epidemic Outbreak Before and After COVID-19

Two indices of the disease were defined: preferred month and infection selectivity (Equation 5), which are important indicators of the infectious property of the epidemics caused by a disease in a year. The preferred month index is defined as the month in a year that has the most cases of infections. The infection selectivity index is defined as (1 – ratio of the minimum and the maximum number of infected cases in a year). If the selectivity index is closer to 1, it means outbreaks only occur in specific months. If the selectivity index is closer to 0, it means that outbreaks occur throughout the year.

Selectivity index = 1 – [min(mean infected cases in a year)/max(mean infected cases in a year)] (5)

### Power Spectrum Analysis

The oscillatory property of an infectious disease is an important indicator of the regular fluctuations and recurrence of epidemics. To better quantify these fluctuations, we used spectrum analysis. Similar methods have been used in classic and modern studies in the field of infectious diseases [38-42] and some other biological research [46,47]. Spectrum analysis is a technique for decomposing complex signals into simpler signals based on

Fourier transform (Equation 6). Many biological signals can be expressed as the sum of various simple signals of different frequencies and produce information about a signal at different frequencies (eg, amplitude, power, intensity, phase).

The power spectral density (PSD; Equation 7) for each infectious disease before and after the outbreak of COVID-19 was computed using the multitaper method with the Chronux toolbox [48], an open source, data analysis toolbox [49]. Power spectra of the time series data (infected cases of each disease) were calculated in 2 time periods (2017-2020 and 2020-2021).

where $W_T(t)$ is 1 within the arbitrary period and 0 elsewhere, and T is centered about some arbitrary time $t=t_0$.

### Correlation Analysis

We performed Pearson correlation to measure the relationship of several indices (ERT, selectivity, oscillatory strength, and mean infected number) before and after the COVID-19 outbreak. Pearson correlation was also performed in the correlation analysis between trough ratio and selectivity, between the change in power and change in infected numbers, and between the change in power and change in trough amplitude. Spearman correlation was performed to measure the relationship between the trough amplitude and the peak amplitude before and after the COVID-19 outbreak. The significance (*P* value) of the correlation was corrected with Bonferroni correction.

### Statistical Analysis

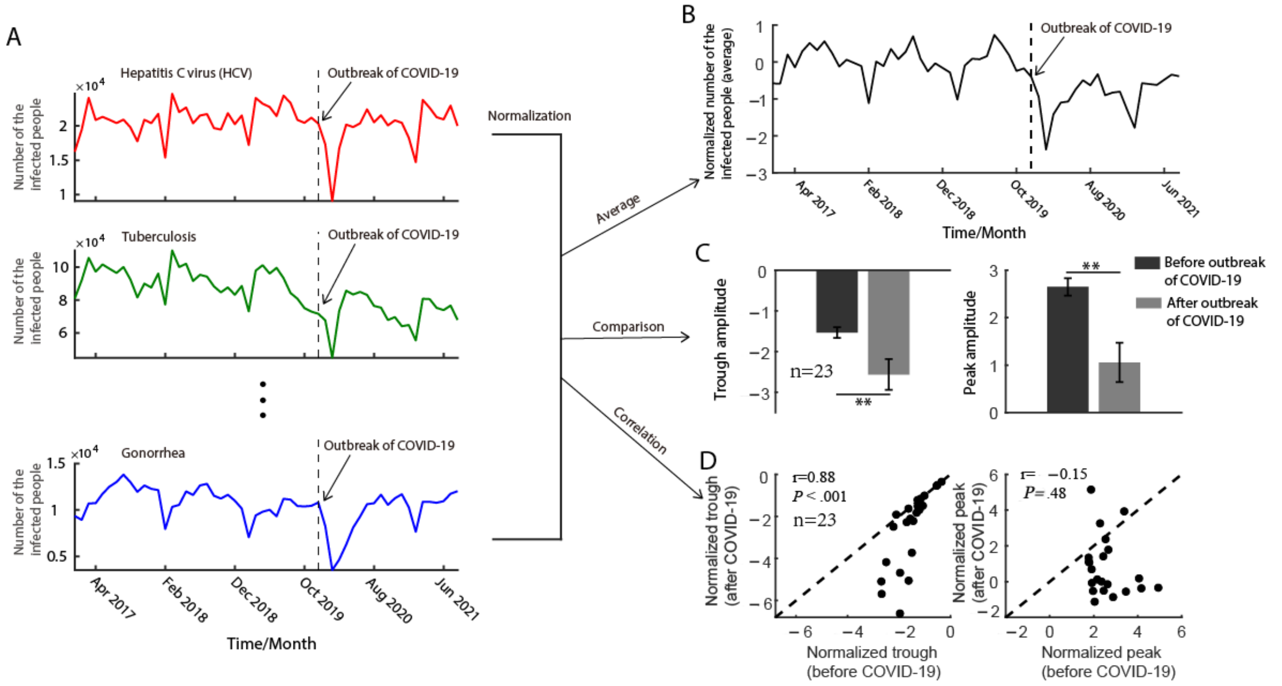
We performed an independent-sample *t* test to compare the difference between several indices (trough amplitude, peak amplitude) before and after the COVID-19 outbreak and test the difference in the trough ratio between diseases with a different preferred time of outbreak. The pairwise *t* test was performed to compare the oscillatory power and the average infected number before and after the COVID-19 outbreak.

## Results

### Monthly Data

This study analyzed monthly data from April 2017 to September 2021 of confirmed cases of 23 class B notifiable infectious diseases in China's mainland. After the COVID-19 outbreak, most class B infectious diseases had an obvious sudden trough, which we defined as the ERT (see Figure 1A for 3 typical examples). The stringency index of China showed that during the COVID-19 pandemic, the strict NPIs in China have always been existing (Multimedia Appendix 1), which allows us to analyze the long-term effect after the COVID-19 outbreak.

**Figure 1.** Infectious disease before and after the COVID-19 outbreak (A) Monthly infected cases from 2017 to 2021 of three examples (HCV, Tuberculosis, and Gonorrhea). The curve after the vertical dotted line shows specifically the infected cases after the COVID-19 outbreak. (B) The normalized mean number of infected cases before and after the COVID-19 outbreak. (C) Trough amplitude (left) and peak amplitude (right) before and after the COVID-19 outbreak (** is for *P*<.01). (D) The relationship between the normalized trough (left) and peak (right) before and after the COVID-19 outbreak.



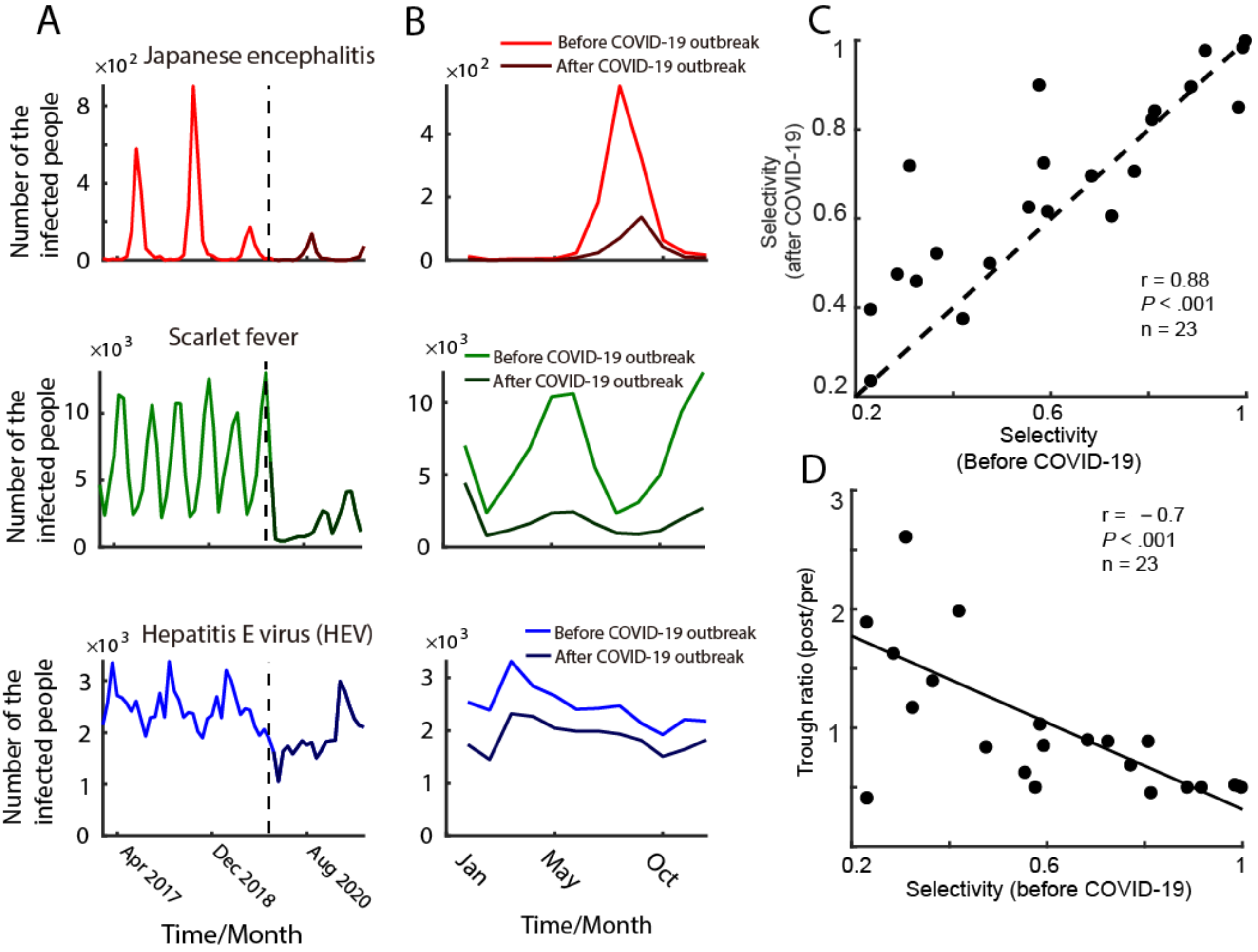
### Significant Event-Related Trough Occurred After the Strict Control Policy for the COVID-19 Outbreak in China

We showed several examples of diseases that had an obvious ERT after the COVID-19 outbreak (HCV, tuberculosis, and gonorrhea); see Figure 1A, and see Multimedia Appendix 3 for all diseases. To compare the time series of all diseases on a notionally common scale, we normalized the time series of the number of infected people by subtracting the mean number of infections before COVID-19 and dividing it by its SD. Hence, the mean number of infections before COVID-19 was 0 for all the diseases (Figure 1B). The pattern shows an obvious and sudden decrease in confirmed cases after the COVID-19 outbreak (see Figure 1B). To investigate whether the peak and trough amplitudes may change due to the outbreak, we compared the differences between peak and trough amplitudes before and after the event (policy in response to COVID-19). Results showed that the amplitude of both peak (*P*<.01) and trough (*P*<.01) significantly decreased, which indicated that the outbreak strongly moderated the oscillation amplitude (see Figure 1C). We then calculated the correlation between the normalized trough before and after the outbreak event, and we found that the trough after the outbreak was significantly correlated (r=0.88, *P*<.001) to the trough before but the peak was not correlated (r=–0.15, *P*=.48; see Figure 1D).

## Infection Selectivity and Preferred Outbreak Time Strongly Related to the Trough Ratio Before and After the COVID-19 Outbreak

The ERT might be affected by the basic properties (infection selectivity and preferred outbreak time) of infectious disease outbreaks. To further clarify potential factors that would cause an ERT, we determined the property of oscillations for infectious diseases in a year by defining 2 indicators: infection selectivity and preferred outbreak time of the infectious disease. We selected 3 infectious diseases that have different selectivity as examples (Figure 2A,B; see Multimedia Appendix 4 for all diseases). The infection selectivity index is defined as (1 – ratio of the minimum and the maximum number of infected cases in a year). If the selectivity index is closer to 1, then the shape of the tuning curve is sharper (eg, Japanese encephalitis), and vice versa (eg, HEV). The preferred month index is defined as the month in a year that has the most cases of infections. Results showed that there was a significant increase in infection selectivity after the outbreak of COVID-19, and infection selectivity before and after the outbreak was positively correlated (with Bonferroni correction; Figure 2C). When we compared the selectivity before the outbreak and the trough ratio, we found that the stronger the infection selectivity, the smaller the trough ratio (Figure 2D). We also conducted a partial correlation analysis between infection selectivity and trough ratio, controlling for the preferred time of outbreak, which was significant (r=–0.58, *P*=.004). The association between infection selectivity and trough ratio confounded by seasons was, however, weak.

**Figure 2.** Relationship between selectivity and trough ratio before and after the COVID-19 outbreak (A) Monthly infected cases from 2017 to 2021 of three examples (Japanese encephalitis, Scarlet fever, and HEV). The curve after the vertical dotted line shows specifically the infected cases after the COVID-19 outbreak. (B) The number of infected cases every month in a year calculated before (light-colored curve) and after the COVID-19 outbreak (dark-colored curve) corresponding to the time-series data of plot A. (C) The scatter plot of the selectivity before and after the COVID-19 outbreak. (D) The relationship between the selectivity (before) and trough ratio (post/pre).

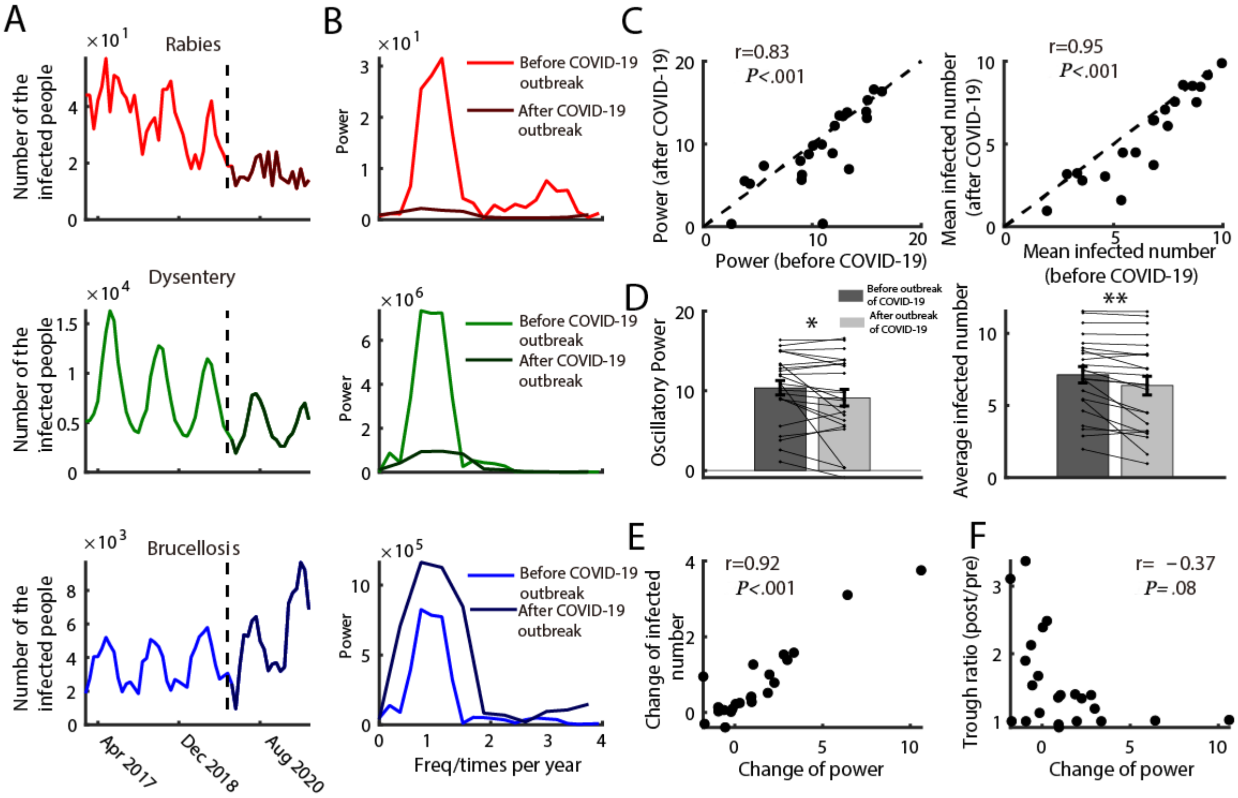


### Relationship Between an Infection and Its Oscillatory Power Before and After the COVID-19 Outbreak

We quantified the oscillatory strength of outbreaks using power spectrum analysis (Figures 3A and 3B; see Multimedia Appendix 5 for all diseases). We then explored the relationship between infected cases and their corresponding strength of oscillatory power before and after the COVID-19 outbreak. Results indicated that the oscillatory strength (r=0.83, *P*<.001) and mean infected cases (r=0.95, *P*<.001) before the COVID-19 outbreak were significantly positively correlated to the indices after the COVID-19 outbreak (Figure 3C), showing that the stronger the oscillatory power was before the outbreak, the stronger it was after the outbreak. The same was true for mean infected cases.

To determine the differences between oscillatory power before and after the COVID-19 outbreak and between mean infected cases before and after the COVID-19 outbreak, we also split the data and compared the indices before and after the event. Consistent with our hypothesis, results showed both decreases in oscillatory power and mean infected cases after the COVID-19 outbreak (Figure 3D). We further examined the relationship between the change in power between the change in infected numbers and trough amplitude. Results showed that the change in power and the change in infected numbers was significantly correlated (r=0.92, *P*<.001). The more the change in oscillatory power, the more changes in the number of confirmed cases (Figure 3E). However, the change in power was not related to the change in trough amplitude (r=–0.37, *P*=.08 with Bonferroni correction; Figure 3F). In sum, the COVID-19 outbreak reduced the outbreaks of class B notifiable infectious diseases, as indicated by oscillatory power and mean infected cases.

**Figure 3.** Relationship between the infection and its oscillatory power before and after COVID outbreak (A) Infected cases from 2017 to 2021 of three examples (Rabies, Dysentery, and Brucellosis). The curve after the vertical dotted line represents specifically the infected cases after the COVID-19 outbreak. (B) The power spectrum calculated before (light-colored curve) and after the COVID-19 outbreak (dark-colored curve) corresponding to the time-series data of plot A. (C) The scatter plot of the power (left) and mean infected number (right) before and after the COVID-19 outbreak. (D) The histogram of the oscillatory power (left) and averaged infected cases (right) before and after the COVID-19 outbreak. (E) The scatter plot of the change of power and change of infected number. (F) The scatter plot of the change of power and change of trough amplitude.

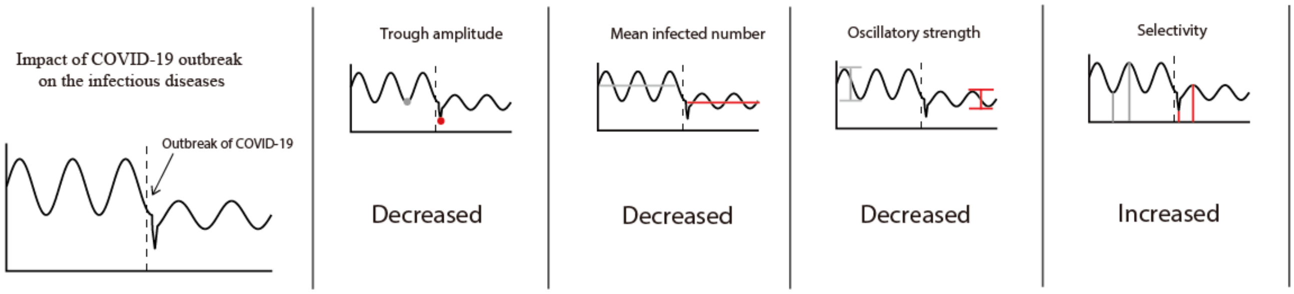


## Discussion

### Principal Findings

In this study, we defined several novel concepts and robust metrics (ERT, selectivity of infection, preferred time to outbreak, oscillatory strength of the infectious disease) to quantify and capture the temporal characteristics of infectious disease outbreaks and event-related fluctuations in China. Our results showed that a clear ERT occurred for most class B infectious diseases after the COVID-19 outbreak under the strict public health policy. We further found that the ERT was related to the nature of diseases, such as their infection selectivity and preferred outbreak time. However, their oscillatory strength was somehow unrelated. We also compared these indices of the infectious diseases before and after the outbreak of COVID-19. The impact of the COVID-19 outbreak influenced the infectious diseases by reducing the trough amplitude, mean infected cases, and oscillatory strength but increasing infectious selectivity (see Figure 4).

**Figure 4.** A summary of the main finding. As illustrated in the four plots, the impact of the COVID-outbreak influenced the infectious diseases in four aspects: decreased the trough amplitude, the mean infected cases, and the oscillatory strength, but increased the seasonal selectivity.



## Comparison With Prior Work

To the best of our knowledge, this is the first study to systematically investigate the influence of the COVID-19 outbreak on the temporal characteristics of other class B infectious diseases in China, including both respiratory infectious diseases and other types, such as those transmitted through sex, body fluids, the digestive tract, contact, and mosquitos. The key contribution of this study is that several new concepts were purported, such as the ERT, selectivity of infectious diseases, the preferred outbreak time, and the power strength of infectious oscillation. Some previous studies have investigated basic properties of a few infectious diseases in China [18,22-25,50-52] and countries worldwide [39,40,53-55], and NPIs to mitigate COVID-19 could have affected the transmission dynamics of influenza and other respiratory diseases [17,27-29,56,57]. However, previous research did not quantify the reduction using a specific temporal index. We first defined the ERT in the field of infectious diseases to capture the immediate influence of the strong interventions related to the public health events, such as the prevention policy on disease outbreaks. The ERT could measure the temporal feature when studying the effect of some specific interventions in the future, which increases 1 dimension (temporal dynamics) compared with a simple reduction number.

Another novel finding of this study is that we also built up a connection between the ERT and some other important indicators (selective property and oscillatory property), which were neglected in prior works. In this study, we found that the ERT is related to the selectivity (Figure 2D) of an infectious disease, which gives a new understanding of how an epidemic could be more easily controlled (when a disease has high selectivity). In the future, infectious selectivity would play a more important role than before, especially when combined with the tuning curve of a disease. It would depict new pictures of the basic property of each disease and give more practical guidance on the prevention and control of epidemics. The oscillatory properties of infectious diseases were also analyzed in some previous studies [18,22-25,38-40,53-55,58-60], which could be driven by both natural [11,61,62] and human [63-68] factors. However, prior studies did not investigate the influence of COVID-19 measures or other NPIs to control epidemics on the oscillatory strength of infectious diseases systematically. Our results indicate that the oscillatory strength significantly decreased after the COVID-19 outbreak, which was accompanied by a decrease in the mean infections. This finding supports the conceptual hybrid model [18]. We also found that the oscillatory strength before the COVID-19 outbreak did not correlate to the change in trough, which further suggests that the ERT is not related to some seasonal factors but more to the measurement of the COVID-19 outbreak. The oscillatory phenomenon of population-based epidemics would be the new impetus for the study of public health. In the future, this index could be connected to more natural and human factors, which would contribute to constructing a more generic stimulated model to explain history and predict the future situation.

## Limitations

One limitation of our study is that the data we used are from the entire mainland China but are not specific to different provinces or cities, which may lack spatial resolution. Another limitation of our study is that the results were based on a macroscopic rather than a microscopic view of most class B infectious diseases. Further studies are needed to clarify the deeper underlying mechanisms of the COVID-19 pandemic. With these findings, we could better provide the government with recommendations on the optimal timing to intervene before achieving herd immunity, thereby helping to design fit-for-purpose policies.

## Conclusion

In sum, the study developed a new and potentially universal approach to revealing the dynamics of infectious diseases. The transmissibility and severity of infectious diseases fluctuate regularly. The introduction of the concept of the ERT in infectious diseases can better capture the immediate influence of interventions related to previous public health events. Our results confirmed that early commencement of strong public health interventions has additional benefits on other infectious diseases.

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## Authors' Contributions

CH, ML, and XZ conceived and designed the study. CH, ML, NH, YZ, JJ, and ZL contributed to the literature search. CH, JL, JT, SL, YZ, XZ, XW, and YL contributed to data collection. CH, YC, MG, XF, JQ, and MG contributed to data analysis and interpretation of results. All authors contributed to writing the paper.

## Conflicts of Interest

The coauthors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Multimedia Appendix 1
Stringency index in China after January 2020 (data from the Oxford COVID-19 Government Response Tracker).
[PNG File , 48 KB - publichealth_v8i6e35343_app1.png ]

Multimedia Appendix 2
Annual average of all infected cases diseases. HIV: Human Immunodeficiency Virus; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus.
[PNG File , 448 KB - publichealth_v8i6e35343_app2.png ]

Multimedia Appendix 3
Monthly cases of infection for all diseases. HIV: Human Immunodeficiency Virus; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus.
[PNG File , 369 KB - publichealth_v8i6e35343_app3.png ]

Multimedia Appendix 4
Annual average of all infected cases of diseases before (gray) and after (black) the COVID-19 outbreak. HIV: Human Immunodeficiency Virus; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus.
[PNG File , 383 KB - publichealth_v8i6e35343_app4.png ]

Multimedia Appendix 5
Power spectrum of all infected cases before (gray) and after (black) the COVID-19 outbreak. HIV: Human Immunodeficiency Virus; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus.
[PNG File , 378 KB - publichealth_v8i6e35343_app5.png ]

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## Abbreviations

**ERT:** event-related trough
**HBV:** hepatitis B virus
**HCV:** hepatitis C virus
**HEV:** hepatitis E virus
**NPI:** nonpharmaceutical intervention

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Original Paper

# Vaccination Intention and Behavior of the General Public in China: Cross-sectional Survey and Moderated Mediation Model Analysis

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## Abstract

**Background:** Promoting vaccination and eliminating vaccine hesitancy are key measures for controlling vaccine-preventable diseases.

**Objective:** We aimed to understand the beliefs surrounding and drivers of vaccination behavior, and their relationships with and influence on vaccination intention and practices.

**Methods:** We conducted a web-based survey in 31 provinces in mainland China from May 24, 2021 to June 15, 2021, with questions pertaining to vaccination in 5 dimensions: attitude, subjective norms, perceived behavioral control, intention, and behavior. We performed hierarchical regression analysis and structural equation modeling based on the theory of planned behavior—in which, the variables attitude, subjective norms, and intention each affect the variable intention; the variable intention mediates the relationships of attitude and subjective norms with behavior, and the variable perceived behavioral control moderates the strength of this mediation—to test the validity of the theoretical framework.

**Results:** A total of 9924 participants, aged 18 to 59 years, were included in this study. Vaccination intention mediated the relationships of attitude and subjective norms with vaccination behavior. The indirect effect of attitude on vaccination behavior was 0.164 and that of subjective norms was 0.255, and the difference was statistically significant ($P$<.001). The moderated mediation analysis further indicated that perceived behavioral control would affect the mediation when used as moderator, and the interaction terms for attitude (β=–0.052, $P$<.001) and subjective norms (β=–0.028, $P$=.006) with perceived behavioral control were significant.

**Conclusions:** Subjective norms have stronger positive influences on vaccination practices than attitudes. Perceived behavioral control, as a moderator, has a substitution relationship with attitudes and subjective norms and weakens their positive effects on vaccination behavior.

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**KEYWORDS**

vaccine; theory of planned behavior; attitude; subjective norms; perceived behavior control; moderator; mediation

## Introduction

Vaccines play a crucial role in protection against infectious diseases. Vaccination is an important component of both family and public health. However, confusion and misunderstanding still surround vaccines, even though they protect against a wide variety of organisms that cause disease, such as influenza, cervical cancer, hepatitis B, COVID-19, pneumonia, and rabies. A recent study [1] by the COVID-19 reaction team at Imperial College London, found that high vaccine hesitancy rates can significantly prolong the time required for nondrug interventions to maintain and decrease the mortality associated with COVID-19. Therefore, exploring the mechanisms behind vaccination behavior to reduce vaccine hesitancy and improve vaccination rates has become a key research topic. Research on vaccine acceptance suggests that individual decisions about vaccination behavior are much more complex and may involve emotional, cultural, social, spiritual, or political factors, as well as cognitive factors [2,3]. It has been demonstrated that theory-based behavioral interventions are more effective [4-9]. However, rather than building on the premise of theoretical models to test hypotheses, most studies [10-12] that have collected data to conduct exploratory studies of knowledge, attitudes, and beliefs or have focused on demographic factors related to vaccination practices.

Currently, the theory of planned behavior, which is one of the most commonly used psychological theories to explain health behavior, is considered to be the most suitable for explaining vaccination behavior [5,13-15], and has been used effectively as a theoretical framework for designing health behavior interventions [16,17]. Another framework—the health belief model—is also widely used in behavioral health fields; however, studies [18-20] have shown that the health belief model is more suited to description rather than explanation of health behavior and has weak predictive validity. Although Webb et al [21] found that theory of planned behavior–based interventions were more effective than those based on other theories, existing studies on theory of planned behavior have not been in-depth—a systematic review [22] demonstrated that most researchers did not address adaptive feedback, merely focused on intention as the outcome, and ignored mediating effects between intentions and behaviors. Yet, the purpose of the theory of planned behavior was to account for perceived behavioral control, which, as a representative of actual behavioral control, should have an impact on the overall model [23].

The beliefs and behavioral drivers of vaccination need to be studied to be able to develop better targeted intervention strategies. We aimed to confirm the theoretical validity and ability of the theory of planned behavior to explain vaccination practices.

## Methods

### Ethics Approval

The Wuxi Center for Disease Control and Prevention Ethics Committee approved this study (2020No10).

### Participants and Procedure

From May 24 to June 15, 2021, we conducted surveys in 31 provinces in mainland China using web-based questionnaires. We used convenience sampling. The link to the questionnaire was created through *Wen Juan Xing*, which is a platform dedicated to the creation and dissemination of questionnaires, and forwarded by the WeChat platform of the Jiangsu Provincial Center for Disease Control and Prevention. Written information was provided as a statement that could be read, which assured participants that the study was conducted on a voluntary basis and for research purposes only. All surveys were conducted in Chinese. (The surveys were translated into English by 2 researchers only for the purpose of this paper.) Questionnaires answered by people under 18 years and over 60 years were not analyzed. To prevent repeated submission of questionnaires, WeChat real name verification was required when using the link to fill out the questionnaire, and an IP address could only be used to submit a questionnaire once. Questionnaires completed in less than 60 seconds were automatically discarded. Questionnaires with selections at the same level of the Likert scale were also considered invalid.

The questionnaire (Multimedia Appendix 1) was used to collect demographic information (age, gender, ethnicity, usual place of residence, education level, annual household income, and whether respondents worked in the health care industry, residential status), chronic disease history, and information on self-assessment of health status.

### Theoretical Background

The theory of planned behavior is widely used to study intentions and behaviors. In this model, intentions are considered the most direct predictor of behaviors and are weighted based on attitudes, which is the degree to which behaviors are positively or negatively evaluated, and subjective norms, which is the pressure society places on implementing or not implementing behaviors. The effects of attitudes and subjective norms are mediated by perceived behavioral control, which is people's perceptions of their ability to perform a given behavior. When perceived behavioral control is accurate, it acts as a proxy for actual behavioral control, that is, the extent to which a person has the ability, resources, and other conditions required to perform the behavior.

In this study, the variable *attitude* represented people's positive or negative perceptions of the vaccine. The variable *subjective norms* referred to the expectations of family, friends, and physicians. The variable *perceived behavioral control* represented people's beliefs about barriers to vaccination (such as the time, cost, and side effects caused by vaccination). Each item was assessed using a 5-point Likert scale (Table 1).

**Table 1.** Translation of the questionnaire.

| Dimension and questions | Scale |
|---|---|
| **Attitude** | 1 (strongly disagree) to 5 (strongly agree) |
| Q1. I think that vaccination is safe. | |
| Q2. I think that vaccination is effective. | |
| Q3. I think that vaccination is beneficial. | |
| Q4. I think that vaccination is important. | |
| **Subjective norms** | 1 (strongly disagree) to 5 (strongly agree) |
| Q5. Did my family, doctors, and close friends think I should be vaccinated? | |
| Q6. Will I do what they think I should do? | |
| Q7. Can vaccination can protect close relatives from relevant vaccine-preventable diseases? | |
| **Perceived behavior control** | 1 (strongly disagree) to 5 (strongly agree) |
| Q8. The possibility of still being infected after vaccination would discourage me from getting vaccinated. | |
| Q9. The exorbitant cost of vaccinating would stop me from getting vaccinated. | |
| Q10. Vaccination causes a decline in autoimmunity. | |
| Q11. Concerns about side effects of the vaccine stop me from getting vaccinated. | |
| Q12. Difficulty in obtaining an appointment for vaccination would prevent me from getting vaccinated. | |
| **Intention** | 1 (completely impossible) to 5 (completely possible) |
| Q13. The possibility of considering getting vaccinated. | |
| Q14. The possibility of trying to get vaccinated. | |
| Q15. The possibility of actually getting vaccinated. | |
| **Behavior** | 1 (completely impossible) to 5 (completely possible) |
| Q16. How likely are you to go for a COVID-19 vaccine? | |
| Q17. What is the possibility of getting an influenza shot this year? | |
| Q18. What is the level of hesitation about vaccinating? | |

## Hypotheses

### *Hypothesis 1*

*Attitude* will have a positive association with vaccination *behavior*.

### *Hypothesis 2*

*Subjective norms* will have a positive association with vaccination *behavior*.

### *Hypothesis 3*

Vaccination *intention* will have a positive association with vaccination *behavior*.

### *Hypothesis 4*

Vaccination *intention* will mediate the relationships of *attitude* (hypothesis 4a) and *subjective norms* (hypothesis 4b) with vaccination *behavior*.

### *Hypothesis 5*

*Perceived behavior control* will moderate the strength of the mediated relationships of *attitude* (hypothesis 5a) and *subjective norms* (hypothesis 5b) with vaccination *behavior* via vaccination *intention*.

## Model Testing

Before structural equation modeling, confirmatory factor analysis was conducted to assess the reliability and validity of the constructs. Reliability was assessed by calculating the squared multiple correlation [24] and composite reliability [25]. We also examined parameter estimates and their associated *t* values, factor loadings, and the average variance extracted [26]. We established discriminant validity by calculating the square root of the average variance extracted for each latent variable. The error variances and modification indices of items were estimated.

### Model Fitting

The goodness-of-fit index (GFI), adjusted GFI, comparative fit index (CFI), and the root mean square error of approximation (RMSEA) were used to evaluate the model fit [27]. For GFI, CFI, and adjusted GFI, values closer to 1 are better, and values greater than 0.95 indicate relatively good fit; RMSEA values less than 0.06 indicate relatively good fit [27,28].

### Statistical Analysis

We used bootstrapping (5000 trials) to test mediator effects [29]. Hierarchical moderator regression was used to test moderation effects, and all variables were standardized to avoid multicollinearity [30]. The control variables were entered in the block 1 (gender, education level, health care occupation, annual household income, main living condition, self-evaluation of health, chronic diseases, past behavior), followed by the standardized value of the main effect (*attitude*, *subjective norms*, and *perceived behavioral control*) in block 2, and finally, the interactions and moderators (*subjective norms * perceived behavioral control*, *attitude * perceived behavioral control*) in block 3.

AMOS software (version 23; IBM Corp) was used to estimate the structural equation coefficients between latent variables in the model. Hierarchical moderator regression analysis was performed using SPSS software (version 23; IBM Corp). Statistical significance was set at *P*<.05.

## Results

### Participant Information

A total of 9924 participants (male: 5407/9924, 54.5%; female: 4517/9924, 45.5%) were included in this study (Table 2). Most respondents had a college degree or higher (7589/9924, 76.4%), and did not work in health care–related industries (7007/9924, 70.6%).

In this study, the proportion showing vaccine hesitancy (respondents who selected not sure, hesitant, and very hesitant for Q18) was estimated to be about 26.6% (2640/9924). Of the total sample, 77% (7643/9924) reported that they had received COVID-19 vaccinations, and 29.4% (2922/9924) had received the influenza vaccinations in the previous year. Of the women, 22% (992/4517) had received human papillomavirus (HPV) vaccinations. Of the total sample, of the majority believed that they would choose to receive COVID-19 (8614/9924, 86.8%) and influenza (3315/9924, 33.4%), vaccinations this year.

**Table 2.** Participant information.

| Characteristic | Respondents (n=9924), n (%) |
|---|---|
| **Age group (years)** | |
| 18-24 | 2362 (23.8) |
| 25-34 | 3963 (39.9) |
| 35-44 | 2334 (23.5) |
| 45-54 | 1125 (11.3) |
| 55-59 | 140 (1.4) |
| **Gender** | |
| Male | 5407 (54.5) |
| Female | 4517 (45.5) |
| **Educational level** | |
| High school graduate or below | 2335 (23.5) |
| College or equivalent | 6822 (68.7) |
| Master’s diploma or above | 767 (7.7) |
| **Health care occupation** | |
| Yes | 2917 (29.4) |
| No | 7007 (70.6) |
| **Annual household income (US $)** | |
| <16,000 | 4285 (43.2) |
| 16,000-32,000 | 4259 (42.9) |
| 32,000-80,000 | 1112 (11.2) |
| >80,000 | 268 (2.7) |
| **Main living condition** | |
| Living with others | 9145 (92.2) |
| Alone | 779 (7.8) |
| **Self-evaluation of health** | |
| Very bad | 359 (3.6) |
| Bad | 242 (2.4) |
| General | 3168 (31.9) |
| Well | 3816 (38.5) |
| Very well | 2339 (23.6) |
| **Chronic diseases** | |
| Yes | 1275 (12.8) |
| No | 8649 (87.2) |
| **Influenza vaccination history (last year)** | |
| Yes | 2922 (29.4) |
| No | 7002 (70.6) |
| **COVID-19 vaccination history** | |
| Yes | 7643 (77.0) |
| No | 2281 (23.0) |
| **HPV[a] vaccination history (n=4517)** | |
| Yes | 992 (22.0) |
| No | 3525 (78.0) |

[a]HPV: human papillomavirus.

## Measurement Model and Fitting

The 18 items were found to be reliable and valid based on each item’s estimated error variance and modification index (Table S1 and Table S2 in Multimedia Appendix 2). Composite reliability values were greater than 0.6 and average variance extracted values were greater than 0.5, except those for the dimension *behavior* (Table 3).

The square roots of average variance extracted of the dimensions *attitude*, *subjective norms*, *intention*, and *perceived behavioral control* exceeded the related correlations (Table 4), indicating discriminant validity in the structures in this study [25]. The overall model achieved a good fit (GFI 0.991; CFI 0.992; adjusted GFI 0.987; RMSEA 0.029); therefore, the measurements and structural model were acceptable.

**Table 3.** Item reliability.

| Dimension | Parameter significance estimation | | | | Factor loading | Squared multiple correlation | Composite reliability | Average variance extracted |
|---|---|---|---|---|---|---|---|---|
| | Unstandardized estimate | SE | *t* value | *P* value | Standardized estimate | | | |
| **Attitude** | | | | | | | 0.902 | 0.698 |
| Q1 | 1.000 | | | | 0.831 | 0.691 | | |
| Q2 | 1.020 | 0.011 | 96.496 | <.001 | 0.837 | 0.701 | | |
| Q3 | 0.968 | 0.010 | 96.319 | <.001 | 0.836 | 0.699 | | |
| Q4 | 0.988 | 0.010 | 96.319 | <.001 | 0.836 | 0.699 | | |
| **Subjective norms** | | | | | | | 0.759 | 0.514 |
| Q5 | 1.000 | | | | 0.628 | 0.394 | | |
| Q6 | 1.104 | 0.022 | 50.029 | <.001 | 0.750 | 0.563 | | |
| Q7 | 1.135 | 0.023 | 49.800 | <.001 | 0.765 | 0.585 | | |
| **Perceived behavioral control** | | | | | | | 0.910 | 0.671 |
| Q8 | 1.000 | | | | 0.814 | 0.663 | | |
| Q9 | 0.976 | 0.012 | 84.038 | <.001 | 0.761 | 0.579 | | |
| Q10 | 1.008 | 0.010 | 99.196 | <.001 | 0.860 | 0.740 | | |
| Q11 | 1.017 | 0.011 | 94.843 | <.001 | 0.832 | 0.692 | | |
| Q12 | 0.996 | 0.011 | 93.580 | <.001 | 0.824 | 0.679 | | |
| **Intention** | | | | | | | 0.863 | 0.678 |
| Q13 | 1.000 | | | | 0.811 | 0.658 | | |
| Q14 | 1.028 | 0.012 | 84.088 | <.001 | 0.837 | 0.701 | | |
| Q15 | 0.979 | 0.012 | 83.315 | <.001 | 0.821 | 0.674 | | |
| **Behavior** | | | | | | | 0.549 | 0.300 |
| Q16 | 1.000 | | | | 0.434 | 0.188 | | |
| Q17 | 2.062 | 0.083 | 24.826 | <.001 | 0.453 | 0.205 | | |
| Q18 | 3.069 | 0.156 | 19.664 | <.001 | 0.712 | 0.507 | | |

**Table 4.** Construct validity.

| Dimension | Average variance extracted | Dimension, correlation | | | | |
|---|---|---|---|---|---|---|
| | | Perceived behavioral control | Behavior | Intention | Subjective norms | Attitude |
| Perceived behavioral control | 0.671 | 0.819 | —[a] | — | — | — |
| Behavior | 0.300 | 0.618 | 0.548 | — | — | — |
| Intention | 0.678 | 0.419 | 0.671 | 0.823 | — | — |
| Subjective norms | 0.514 | 0.406 | 0.601 | 0.683 | 0.717 | — |
| Attitude | 0.698 | 0.486 | 0.639 | 0.587 | 0.551 | 0.835 |

[a] Repeated correlation coefficients are omitted. The first occurrence value in each column of dimension is the square root of the average variance extracted for each latent variable.

## Hierarchical Moderator Regression Analysis

Annual household income, education, gender, health care occupation, chronic diseases, health self-assessment, and past vaccination behavior affected vaccination behavior ($\Delta R^2$=0.121, *P*<.001); however, whether participants lived alone or not did not significantly affect vaccination behavior as a control variable (*P*=.08) (Table S3 in Multimedia Appendix 2). In block 3, the *attitude* * *perceived behavioral control* and *subjective norms* * *perceived behavioral control* terms significantly changed the model compared with block 2 ($\Delta R^2$=0.003, *P*<.001).

In block 3, *perceived behavioral control* was positively and significantly correlated with vaccination behavior (β= 0.274, *P*<.001); however, *attitude* * *perceived behavioral control* (β=–0.052, *P*<.001) and *subjective norms* * *perceived behavioral control* (β=–0.028, *P*=.006) had reverse inhibitory effects on vaccination *behavior*. This not only indicates that *perceived behavioral control* moderates the impact of *attitude* on *behavior* and that of *subjective norms* on *behavior*, supporting hypotheses 5a and 5b, it also shows that there is a substitution relationship between *attitude*, *subjective norms*, and *perceived behavioral control* in their influence on vaccination *behavior*. Overall, *perceived behavioral control* weakens the positive effects of *attitude* and *subjective norms* on vaccination *behavior*, and when *perceived behavioral control* is low, the promotion effects of *attitude* and *subjective norms* on *behavior* are more pronounced, but with increases in *perceived behavioral control*, the positive effects of *attitude* and *subjective norms* on *behavior* gradually decrease. Specifically, the slope describing effect of *attitude* on *behavior* will decrease by 0.050 SD and that of *subjective norms* on *behavior* will decrease by 0.021 SD when *perceived behavioral control* increases by 1 SD (Table 5; Table S3 in Multimedia Appendix 2).

**Table 5.** Model information in hierarchical moderator regression analysis.

| Model | $\triangle R^2$ | *F* value | *P* value |
|---|---|---|---|
| Block 1 | 0.121 | 151.760 | <.001 |
| Block 2 | 0.233 | 1192.784 | <.001 |
| Block 3 | 0.003 | 23.348 | <.001 |

## Structural Equation Model of Vaccination Behavior

Both *attitude* (direct effect: β=0.493, *P*<.001) and *subjective norms* (direct effect: β=0.244, *P*<.001) showed significant positive associations with *behavior*. Hence, hypotheses 1 and 2 were confirmed. *Intention* also positively and significantly affected vaccination *behavior* (direct effect: β=0.462, *P*<.001); therefore, hypothesis 3 was confirmed. In addition, bootstrapping indicated that *intention* was present as a positive and significant mediator between *attitude* and vaccination *behavior* (indirect effect: β=0.159, *P*<.001). Similarly, the mediating effect between *subjective norms* and vaccination *behavior* was positive and significant (indirect effect β=0.258, *P*<.001); therefore, hypotheses 4a and 4b were confirmed (Table 6). Furthermore, the difference between the indirect effect of *attitude* on *behavior* and that of *subjective norms* on *behavior* was statistically significant (difference=–0.091, *P*<.001), which indicated that *subjective norms* had a greater influence on vaccination *behavior* than *attitude*.

**Table 6.** Direct, indirect, and total effects.

| Effects | Unstandardized point estimate | SE | Bootstrapping |  | Bootstrapping, bias-corrected |  | *P* value |
|---|---|---|---|---|---|---|---|
|  |  |  | 95% CI lower | 95% CI upper | 95% CI lower | 95% CI upper |  |
| **Direct** |  |  |  |  |  |  |  |
| Attitude---Intention | 0.344 | 0.021 | 0.303 | 0.384 | 0.303 | 0.384 | <.001 |
| Subjective norms---Intention | 0.558 | 0.025 | 0.510 | 0.609 | 0.510 | 0.609 | <.001 |
| Intention---Behavior | 0.462 | 0.030 | 0.404 | 0.522 | 0.403 | 0.521 | <.001 |
| Attitude---Behavior | 0.493 | 0.029 | 0.437 | 0.550 | 0.437 | 0.551 | <.001 |
| Subjective norms---Behavior | 0.244 | 0.032 | 0.182 | 0.307 | 0.182 | 0.307 | <.001 |
| **Indirect** |  |  |  |  |  |  |  |
| Attitude---Behavior | 0.159 | 0.014 | 0.132 | 0.187 | 0.132 | 0.188 | <.001 |
| Subjective norms---Behavior | 0.258 | 0.019 | 0.222 | 0.298 | 0.222 | 0.299 | <.001 |
| **Total** |  |  |  |  |  |  |  |
| Attitude---Behavior | 0.652 | 0.030 | 0.594 | 0.710 | 0.594 | 0.710 | <.001 |
| Subjective norms---Behavior | 0.501 | 0.030 | 0.443 | 0.562 | 0.443 | 0.562 | <.001 |

# *Discussion*

## Principal Results

Our findings support the hypothesis that intentions mediate vaccination behavior, attitudes, and subjective norms and addresses concern about the mediating process of intention in the theory of planned behavior [31], while also justifying initial theoretical claims that distal attitudes and subjective norms can influence behavior, through proximal intention mediators [32]. In particular, *perceived behavioral control* was found to be a moderator that influences the mediating processes *attitude→intention→behavior* and *subjective norms→intention→behavior*.

## Comparison With Prior Work

A large meta-analysis [15] of applications of theory of planned behavior showed that subjective norms were weak predictors of intention and behavior. Recent studies [33,34] that have used the theory of planned behavior empirically for health behavior have suggested that subjective norms are not the most critical predictor. In contrast, some argued that subjective norms are strong predictors [35,36]. Our findings are similar to those in [35,36], and the indirect effects in our study further show that subjective norms have greater impacts on behavior than attitudes. This indicates that decisions about health issues are more likely to be influenced by social surroundings. Debate about whether subjective norms have a strong or weak influence on behavior might due to differences in the types of behaviors that have been targeted. In contrast to high-frequency health behaviors, such as exercise, smoking cessation, when making decisions about vaccination, people expect to be counseled by someone close to them (eg, family members and close friends [37]), or someone they trust (eg, a physician [38]). Additionally, socially desirable responses likely contributed to our finding that attitudes have less explanatory power for behavior. Socially desirable responses are defined as the tendency to give a positive self-description, which is relatively common for potentially sensitive problems. Korn [39] suggested that vaccination is a prosocial behavior and demonstrated that it is part of the social contract by showing that there is significant intergroup bias in vaccinated and unvaccinated cohorts. Therefore, it is reasonable that participants glorified attitudes toward the vaccine and responded positively to the investigation, rather than providing their true thoughts.

Our findings also show that high *perceived behavioral control* weakens the effect between *attitude*, *subjective norms*, and vaccination *behavior*, using *intention* as a mediator. Additionally, *perceived behavioral control* has an alternative relationship with *attitude* and *subjective norms*, when present as a moderator in the model. These findings extend those in existing literature on perceived behavioral control. However, perceived behavioral control was considered to be a positive predictor of intentions in many existing studies [40-42]. Our findings (block 2 in the hierarchical regression analysis) also confirm this view. It is important to consider that if a given behavior is seen as positive and implementable, people tend to engage in that behavior. However, the gap between intentions and behavior exists precisely because intention is not sufficient to ensure that a person converts ideas into actual behavior, due to the limitations of actual capabilities. Thus, we find that the mechanisms by which *perceived behavioral control* affect *intention* and *behavior* are different. In other words, the influence of *perceived behavioral control* on *intention* is as positive as *attitude* and *subjective norms*. However, when using *perceived behavioral control* to predict behavior, it should be thought of as actual behavior control [23]. Therefore, it is more appropriate to use *perceived behavioral control* as a moderating variable to influence the mediating effect of *intention* on *behavior*.

## Practical Applications

The moderated mediation model provides evidence for the practical application of theory of planned behavior in vaccination behavior. Future interventions for people who are unwilling to be vaccinated or subjectively postpone vaccination should not only focus on changing their negative attitudes toward the vaccine but should also pay attention to the ideas of their families and close friends about vaccination and intervention. This will facilitate positive intentions to get vaccinated. In a study [43] that explored factory workers' vaccination behavior using the theory of planned behavior, it was also shown that a positive attitude and the support of health care workers, relatives, and friends can contribute to individuals getting vaccinated, and in another study [44], it was found that trusted individuals had a unique influence on young women in encouraging them to get their HPV vaccination. In addition, health authorities may need to take measures such as communicating risk or giving rewards for vaccinations to improve influenza and HPV vaccine uptake.

## Limitations

This study was conducted in the form of a web-based survey; thus, convenience sampling might have caused selection bias. Additionally, we used a cross-sectional survey; thus, information on respondents' vaccine-related behavior at the time of the survey was used in behavior dimension. For this reason, the values of composite reliability and average variance extracted for the *behavior* dimension were below the ideal value. However, the overall model fit was ideal, with GFI, adjusted GFI, and CFI >0.9 and RMSEA <0.06.

Data from 1 month after the survey showed that the actual COVID-19 vaccination rate (having completed at least one shot), in China was 74% [45], approximating the self-reported behavioral data in this study (8614/9924, 86.8%). Although the self-reported data of this study are credible, cautious interpretation of the sample's representativeness of vaccination behavior is needed.

The *behavior* dimension was measured with 3 items—self-reported COVID-19 vaccination behavior and influenza vaccination behavior, as well as overall vaccine hesitancy. This is because according to the schedule of immunization in China [46], there are 5 main vaccines for adults 18 to 59 years of age—COVID-19, influenza, HPV, hepatitis B, and rabies. Yearly influenza and the recent COVID-19 vaccine were the used to examine vaccination behavior because the administration of the other 3 types are limited—hepatitis B vaccinations are valid for a long period, rabies vaccinations are for emergency use after possible exposure, and HPV vaccinations are mainly target the female population in China.

## Conclusions

Our findings showed that subjective norms have a stronger influence than attitudes on this particular vaccination practice. Moreover, perceived behavioral control not only is a positive facilitator of intention but also has an alternative relationship with attitudes and subjective norms. As a moderator, perceived behavioral control conversely weakens the positive effects of attitudes and subjective norms on vaccination behaviors. When perceived behavioral control is low, the positive influence of attitudes and subjective norms are evident. However, when perceived behavioral control is high, the positive effects of attitudes and subjective norms gradually decrease. In particular, as a moderator, perceived behavioral control has more predictive power for vaccination behavior.

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HJ, LY, and SZ designed the study. QW, LY, GY, and TC conducted the literature review and designed the questionnaire. GY, LJ, SZ, and NS assisted with the web-based investigation. LY, QW, and SX analyzed the data. HJ, QW, GY, and LZ interpreted the results. All authors critically revised the manuscript for important intellectual content. This work was supported by the Wuxi City Technology Development Fund (grant N20191007); the Postgraduate Research and Practice Innovation Program of Jiangsu Province (grant KYCX21_0160); and the Public Health Research Center of Jiangnan University (grant JUPH201845). The funders and sponsors did not participate in the work.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[PDF File (Adobe PDF File), 759 KB - publichealth_v8i6e34666_app1.pdf ]

Multimedia Appendix 2
Supplementary material.
[PDF File (Adobe PDF File), 578 KB - publichealth_v8i6e34666_app2.pdf ]

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## Abbreviations

**CFI:** comparative fit index
**GFI:** goodness-of-fit index
**HPV:** human papillomavirus
**RMSEA:** root mean square error of approximation

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Original Paper

# Overlapping Delta and Omicron Outbreaks During the COVID-19 Pandemic: Dynamic Panel Data Estimates

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## Abstract

**Background:** The Omicron variant of SARS-CoV-2 is more transmissible than prior variants of concern (VOCs). It has caused the largest outbreaks in the pandemic, with increases in mortality and hospitalizations. Early data on the spread of Omicron were captured in countries with relatively low case counts, so it was unclear how the arrival of Omicron would impact the trajectory of the pandemic in countries already experiencing high levels of community transmission of Delta.

**Objective:** The objective of this study is to quantify and explain the impact of Omicron on pandemic trajectories and how they differ between countries that were or were not in a Delta outbreak at the time Omicron occurred.

**Methods:** We used SARS-CoV-2 surveillance and genetic sequence data to classify countries into 2 groups: those that were in a Delta outbreak (defined by at least 10 novel daily transmissions per 100,000 population) when Omicron was first sequenced in the country and those that were not. We used trend analysis, survival curves, and dynamic panel regression models to compare outbreaks in the 2 groups over the period from November 1, 2021, to February 11, 2022. We summarized the outbreaks in terms of their peak rate of SARS-CoV-2 infections and the duration of time the outbreaks took to reach the peak rate.

**Results:** Countries that were already in an outbreak with predominantly Delta lineages when Omicron arrived took longer to reach their peak rate and saw greater than a twofold increase (2.04) in the average apex of the Omicron outbreak compared to countries that were not yet in an outbreak.

**Conclusions:** These results suggest that high community transmission of Delta at the time of the first detection of Omicron was not protective, but rather preluded larger outbreaks in those countries. Outbreak status may reflect a generally susceptible population, due to overlapping factors, including climate, policy, and individual behavior. In the absence of strong mitigation measures, arrival of a new, more transmissible variant in these countries is therefore more likely to lead to larger outbreaks. Alternately, countries with enhanced surveillance programs and incentives may be more likely to both exist in an outbreak status and detect more cases during an outbreak, resulting in a spurious relationship. Either way, these data argue against herd immunity mitigating future outbreaks with variants that have undergone significant antigenic shifts.

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**KEYWORDS**

Omicron variant of concern; Delta; COVID-19; SARS-CoV-2; B.1.1.529; outbreak; Arellano-Bond estimator; dynamic panel data; stringency index; surveillance; disease transmission metrics

## *Introduction*

### Background

Omicron, or B.1.1.529, the latest SARS-CoV-2 variant of concern (VOC), was first sequenced in Botswana in early November 2021 [1]. South Africa reported Omicron to the World Health Organization (WHO) on November 24, 2021, and the WHO designated it as a VOC on November 26, 2021 [2,3]. Early reports of Omicron from South Africa alarmed infectious disease scientists due to both its rapid spread in the population and the high degree of molecular divergence in the spike protein [4,5]. Omicron spread quickly through South Africa’s population despite serological evidence of prior SARS-CoV-2 infections or vaccinations in 60%-80% of its population [6]. Omicron was better able to evade natural and vaccine-induced immunity compared to previous variants [7,8]. Ultimately, it was found to be less severe in terms of infection and symptoms than other VOCs [9], especially for those persons who received 2 messenger RNA (mRNA) vaccines and a booster [10]. However, estimated vaccine effectiveness in terms of transmissions was still lower against Omicron compared to Delta [11]. Full mRNA vaccinations plus booster caused a 70% reduction in deaths and hospitalizations compared to no vaccine [12-14]. With higher transmissibility, case counts began setting daily records [15] and health systems were overwhelmed as the Omicron VOC spread SARS-CoV-2 [2,16].

Omicron shifted the course of the pandemic because of its increased transmissibility and its relatively enhanced ability to evade immunity from vaccination or prior infection [17,18]. Early research demonstrated that the Omicron VOC gave fewer days of warning leading up to an outbreak compared to Delta, Alpha, Beta, and the original reference strain (D614) [19]. By early 2022, it was evident that Omicron was setting 2-year record highs in the number of daily new transmissions, displacing Delta as the most transmissible VOC [19]. Moreover, Omicron infections had a significant growth advantage over Delta, with a doubling period of new cases of 1.5-3 days [20,21]. The magnitude of the outbreak, as measured by its apex, was 1.5 to 2-fold higher than prior outbreaks [19].

Early observations in sub-Saharan Africa showed a consistent trend where Omicron cases quickly accelerated, and then quickly decelerated after peaking with only a slight tail [19]. However, these countries had relatively low cases counts prior to the arrival of Omicron. As Omicron spread to countries already experiencing high community transmission of Delta, it was unclear whether the trajectory of the outbreak would be altered. On the one hand, policy mitigation efforts put in place to combat ongoing outbreaks, combined with a higher frequency of natural immunity in the population, could reduce the magnitude of a subsequent outbreak [22]. On the other hand, a preexisting outbreak may signal underlying factors (stringency of mitigation measures, weather, etc) that are favorable to larger outbreaks with more transmissible variants [23-25]. In this study, we compared the trajectories/trends in the Omicron outbreak between countries that had low levels of community transmission of Delta and those that were already in a Delta-driven outbreak [19].

### Objective

The objective of this study is to quantify and explain the impact of Omicron on pandemic trajectories and how they differ between countries that were or were not in a SARS-CoV-2 outbreak with Delta at the time Omicron arrived.

## *Methods*

### Data Collection

We used SARS-CoV-2 surveillance data to identify the duration and apex of outbreaks [26] and GISAID (Global Initiative on Sharing Avian Influenza Data) to identify VOCs [27]. We modeled the data using trend analysis [28-37], survival curves [38,39], and dynamic panel regression [40,41]. We conducted the analysis in R version 4.1.1 (R Foundation for Statistical Computing) with the *plm* (version 2.4-1), *survival* (version 3.2-13), and *survminer* (version 0.4.9) packages [42-45]. The sample period covered November 1, 2021, to February 11, 2022.

To estimate the date Omicron first appeared in a country, we used publicly available data on sequenced SARS-CoV-2 variants from GISAID [27]. We used Nextclade nomenclature [46] to collect clade designations from sequences and Pangolin nomenclature for lineage designations of SARS-CoV-2 [47,48]. We also contrasted prevalence data with data compiled from outbreak.info [49]. We classified countries into 2 groups: (1) outbreak countries that exceeded a threshold of 10 novel daily SARS-CoV-2 transmissions per 100,000 population at the onset date of Omicron, defined by the first instance of an Omicron clade in GISAID, and (2) nonoutbreak countries below this transmission threshold at the first instance of an Omicron clade. The outbreak threshold follows the convention adopted by the US Centers for Disease Control and Prevention (CDC).

To maximize comparability across outbreaks, we restricted the sample to dates between November 1, 2021, and February 11, 2022. Within this period, surveillance sequencing in all countries consisted predominantly of Delta and Omicron variants, with all other variants comprising less than 0.03% of total sequences.

We excluded island countries with populations below a half million people because their outbreaks follow distinct trajectories [40]. Sequencing data are not available for every country [27], so our sample was restricted to 80 countries. Of them, 42 (52.5%) were already in an outbreak at the onset of Omicron, and 38 (47.5%) were not.

### Statistical Analysis

We estimated Kaplan-Meier survival curves for the outbreak and nonoutbreak groups to compare the length of time a country takes to reach its apex speed after the onset of Omicron [39]. We consider any country whose apex speed occurred on the final date of the sample to be censored. We also provided a trend comparison for several neighbor countries, at least 1 of whom was in the outbreak group and 1 of whom was not.

We used linear trend analysis to compare apex speed across the outbreak and nonoutbreak groups. To control for differences in population vaccination rates, prior infection rates, time since the onset of Omicron, and any time-invariant, country-specific heterogeneity, we estimated a dynamic panel regression model with the Arellano-Bond method [40,41]. We modeled the daily rate of novel transmissions as a function of 1-day and 1-week lagged transmissions, cumulative infection and vaccination rates, a binary weekend indicator, the number of days since the onset of Omicron, the number of days since a Delta outbreak began, a binary indicator for whether the date is after the earliest sequenced Omicron variant isolated in the country, and an interaction between the latter and an indicator for whether the country was in the outbreak group. The interaction term provides a test for whether Omicron generated larger increases in speed for the outbreak countries versus the nonoutbreak countries.

We tested the possibility of a weather-driven spurious effect that resulted in different outbreak trajectories with an extension of the survival analysis. We compared Kaplan-Meier survival curves for outbreaks in countries in the Northern and Southern Hemispheres. To address the possibility of SARS-CoV-2 policy response as a confounder, we calculated the average stringency index for each country over the sample period [50]. We conducted a Welch *t* test to compare the average index score in countries in the outbreak versus nonoutbreak groups.

## Results

### Omicron and Outbreak Trajectory

Figure 1 is a map of SARS-CoV-2 outbreaks on December 15, 2022. At this point in time, we can see countries already in a Delta outbreak, countries in an Omicron outbreak in the South of sub-Saharan Africa, and countries with exponential growth due to the introduction of Omicron to the genetic pool. Countries in blue are not in an outbreak. Countries in orange are not in an outbreak but are experiencing alarming growth across 7 consecutive days that will likely go into an outbreak if left unabated. Countries in red in North America, Europe, Central Asia, and some of East Asia and the Pacific are already in an outbreak, primarily driven by Delta.

Table 1 presents both speed (or the number of daily new SARS-CoV-2 transmissions per 100,000 population) at the onset of Omicron and peak speed for all countries in the sample. The countries experiencing high levels of community transmission of Delta at the time of Omicron's arrival ("already in outbreak") averaged a speed of 52.6 at the onset of Omicron, while the countries experiencing low levels of transmission at the onset of Omicron ("not in outbreak") averaged a speed of 3.2. The respective average peak speeds were 308.7 and 128.6. Thus, even after controlling for the initial differences in speed, the countries already in an outbreak saw greater than a twofold increase (2.04=[308.7 – 52.6]/[128.6 – 3.2]) in the average apex of an outbreak.

**Figure 1.** Map of Delta and Omicron outbreaks. Note that countries in red were in an outbreak on December 15, 2022, as defined by a daily rate of at least 10 novel SARS-CoV-2 transmissions per 100,000 population. Countries in orange were not in an outbreak but displayed 7 consecutive days of an increase in the rate of novel SARS-CoV-2 transmissions per 100,000 population.

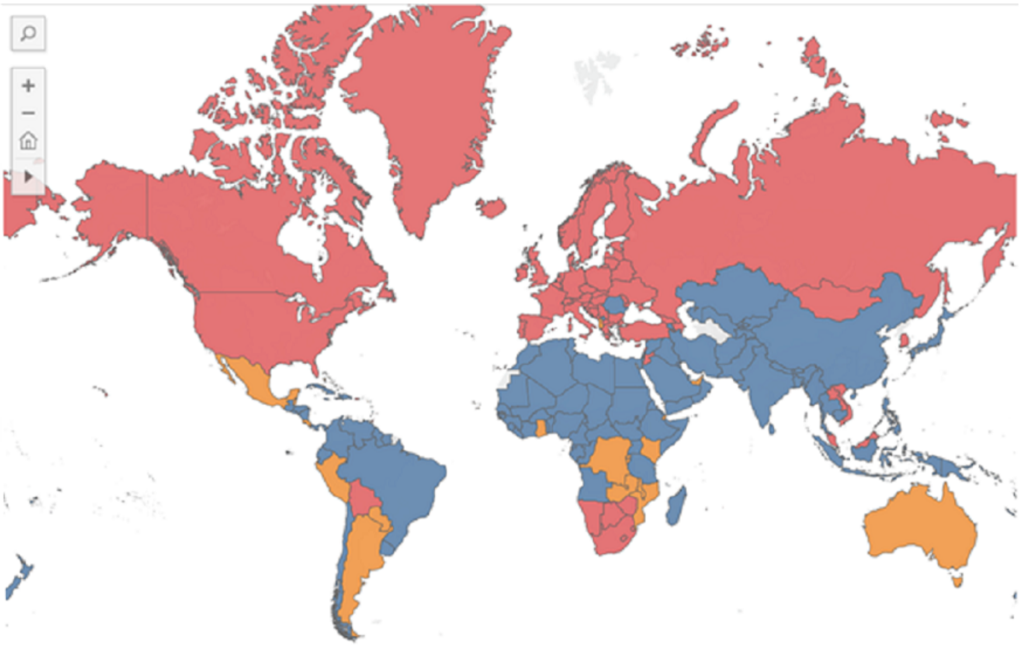


**Table 1.** Outbreak status when index Omicron case sequenced.

| Country | Speed at Omicron | Peak speed | Average speed | Average peak speed |
|---|---|---|---|---|
| **Already in outbreak** | | | 52.6 | 308.7 |
| Austria | 154.5 | 374.8 | N/A[a] | N/A |
| Belgium | 119.3 | 449.9 | N/A | N/A |
| Bosnia and Herzegovina | 13.1 | 73.9 | N/A | N/A |
| Botswana | 39 | 63.9 | N/A | N/A |
| Bulgaria | 18.7 | 128.7 | N/A | N/A |
| Chile | 12.4 | 186.2 | N/A | N/A |
| Croatia | 108.4 | 217 | N/A | N/A |
| Czech Republic | 85.2 | 355.5 | N/A | N/A |
| Denmark | 67.1 | 807.5 | N/A | N/A |
| Estonia | 38.4 | 520.9 | N/A | N/A |
| Finland | 19.8 | 152.3 | N/A | N/A |
| France | 13.5 | 562.3 | N/A | N/A |
| Georgia | 83.2 | 543.7 | N/A | N/A |
| Germany | 58.7 | 231.4 | N/A | N/A |
| Greece | 61.6 | 347.6 | N/A | N/A |
| Ireland | 90.3 | 481 | N/A | N/A |
| Italy | 15.8 | 300.7 | N/A | N/A |
| Jordan | 47.9 | 192.9 | N/A | N/A |
| Lebanon | 22 | 121 | N/A | N/A |
| Liechtenstein | 141.3 | 380.7 | N/A | N/A |
| Lithuania | 64.5 | 402.5 | N/A | N/A |
| Luxembourg | 61.6 | 369.9 | N/A | N/A |
| Malaysia | 17.9 | 44.7 | N/A | N/A |
| Malta | 19.7 | 258.8 | N/A | N/A |
| Montenegro | 38.1 | 393.6 | N/A | N/A |
| Netherlands | 78.1 | 707.1 | N/A | N/A |
| North Macedonia | 12.8 | 84.6 | N/A | N/A |
| Norway | 45.3 | 376.5 | N/A | N/A |
| Poland | 61.7 | 129.7 | N/A | N/A |
| Portugal | 18.6 | 546.8 | N/A | N/A |
| Russia | 22.4 | 124.2 | N/A | N/A |
| Serbia | 17 | 220.8 | N/A | N/A |
| Singapore | 20.4 | 178.7 | N/A | N/A |
| Slovakia | 200.4 | 413.9 | N/A | N/A |
| Slovenia | 106 | 730.3 | N/A | N/A |
| Spain | 14.4 | 308 | N/A | N/A |
| Switzerland | 53.1 | 419.1 | N/A | N/A |
| Turkey | 27.7 | 122.6 | N/A | N/A |
| Ukraine | 16.8 | 85.5 | N/A | N/A |
| United Kingdom | 60.1 | 291.7 | N/A | N/A |
| United States | 22.8 | 245.4 | N/A | N/A |

| Country | Speed at Omicron | Peak speed | Average speed | Average peak speed |
|---|---|---|---|---|
| Vietnam | 18.8 | 20.8 | N/A | N/A |
| **Not in outbreak** | | | 3.2 | 128.6 |
| Argentina | 4.2 | 252.3 | N/A | N/A |
| Armenia | 2.5 | 114.7 | N/A | N/A |
| Australia | 5.5 | 428.3 | N/A | N/A |
| Azerbaijan | 5.1 | 69.5 | N/A | N/A |
| Brazil | 4.9 | 89 | N/A | N/A |
| Brunei | 2.5 | 116.4 | N/A | N/A |
| Canada | 6.4 | 126 | N/A | N/A |
| Colombia | 4.2 | 60.1 | N/A | N/A |
| Costa Rica | 1.7 | 144.1 | N/A | N/A |
| Ecuador | 3.3 | 52.1 | N/A | N/A |
| Guatemala | 1.2 | 19.4 | N/A | N/A |
| India | 0.8 | 22.6 | N/A | N/A |
| Indonesia | 0.1 | 13.7 | N/A | N/A |
| Iran | 2.8 | 42 | N/A | N/A |
| Iraq | 0.8 | 18.1 | N/A | N/A |
| Israel | 5.3 | 1177.3 | N/A | N/A |
| Japan | 0.1 | 74.2 | N/A | N/A |
| Kazakhstan | 2.6 | 74 | N/A | N/A |
| Kuwait | 0.6 | 147 | N/A | N/A |
| Mexico | 1.7 | 38.3 | N/A | N/A |
| Moldova | 7.4 | 110.7 | N/A | N/A |
| Morocco | 0.4 | 20.2 | N/A | N/A |
| Nepal | 1 | 29.3 | N/A | N/A |
| Oman | 0.2 | 44 | N/A | N/A |
| Panama | 5.7 | 247.9 | N/A | N/A |
| Peru | 4.2 | 152.7 | N/A | N/A |
| Philippines | 0.5 | 31.9 | N/A | N/A |
| Qatar | 4.9 | 142.4 | N/A | N/A |
| Romania | 8.2 | 156.1 | N/A | N/A |
| Saudi Arabia | 0.1 | 16.1 | N/A | N/A |
| South Africa | 0.6 | 39.5 | N/A | N/A |
| South Korea | 6.4 | 90.1 | N/A | N/A |
| Suriname | 4.9 | 169.1 | N/A | N/A |
| Sweden | 8.9 | 405.2 | N/A | N/A |
| Thailand | 9.2 | 18.7 | N/A | N/A |
| Tunisia | 1.3 | 79.8 | N/A | N/A |
| Zambia | 0.06 | 21.1 | N/A | N/A |
| Zimbabwe | 0.2 | 32.4 | N/A | N/A |

[a] N/A: not applicable.

Figure 2 plots Kaplan-Meier survival curves for the 2 groups of countries [39]. An “event” was defined as the peak speed of the outbreak. We chose peak speed over the end of an outbreak because a substantial majority of sample countries remained in outbreak at the time of this writing. The survival curves present the probability a country will have reached its peak (y axis) for any given number of days since the onset of Omicron (x axis).

A key advantage of the Kaplan-Meier survival curve is its accommodation of countries that may not have hit their peak speed yet [38]. We considered any country whose peak speed occurs on the most recent day of available data "censored," which means we only know it took at least as long as the observation period for the country to reach its peak. The Kaplan-Meier method includes these countries in its survival curve estimates until they are censored, at which point they exit the sample. The vertical hash marks in Figure 2 denote these exit points.

From Figure 2, countries already in an outbreak clearly take longer to reach their eventual peak than countries not initially in an outbreak. A log-rank test rejects the null hypothesis of equality between the 2 survival curves at the .10 significance level but not at the .05 level (*P*=.09) [51].

The survival analysis answers the question of how long the Omicron outbreak takes to peak in countries that were or were not in an outbreak at the time of Omicron's arrival. However, the survival curves provide no information on the relative magnitudes of the peaks. To that end, Figure 3 presents a scatter plot of the difference between the eventual peak speed and the Omicron onset speed (y axis) as a function of the onset speed (x axis). The linear best fit line, in dashed gray, shows a positive association between the onset speed and the additional speed accrued after the onset of Omicron. The estimated slope coefficient is 1.62, which is statistically significant at the .01 level with a *P* value of .002.

Figure 3 plots the difference between onset and peak speed on the y axis because peak speed alone is mechanically a function of onset speed. The onset speed cannot exceed peak speed. If an outbreak immediately contracted upon the arrival of Omicron, then peak speed is simply equal to onset speed. Figure 3 therefore shows that countries that had high onset speeds at first isolation of Omicron tended to have higher peak speeds after the onset of Omicron. Higher initial speeds are correlated with higher growth after Omicron.

Figures 2 and 3 show that the Omicron-driven outbreaks took longer to build to relatively higher peak speeds in countries already experiencing outbreaks of Delta. Neither figure controls for potentially important confounders, such as population size and vaccination rates. Furthermore, neither figure controls for the length of time since the onset of Omicron. Some outbreaks may have yet to reach their apex.

To control for these confounders, Table 2 presents the results of a dynamic panel regression [41]. The model was adapted from an empirically validated system to provide novel SARS-CoV-2 surveillance metrics [35,52,53]. The dependent variable is the rate of novel SARS-CoV-2 transmissions, which is a function of transmissions on the previous day and in the past week. Unsurprisingly, these *1-day_lag* and *7-day_lag* variables are positive and statistically significant predictors of current transmissions. The coefficient estimate for *1-day_lag* is 0.1, which means, after controlling for the other covariates, every 10 SARS-CoV-2 transmissions today predict 1 transmission tomorrow. The coefficient estimate for *7-day_lag* is 0.7, which means every 1 transmission this week predicts just under 1 transmission next week.

**Figure 2.** Time from arrival of Omicron until peak of outbreak. Note: Countries are considered censored if their peak speed occurred on the final day of the sample period. The cross hashes in the figure denote these censor points.

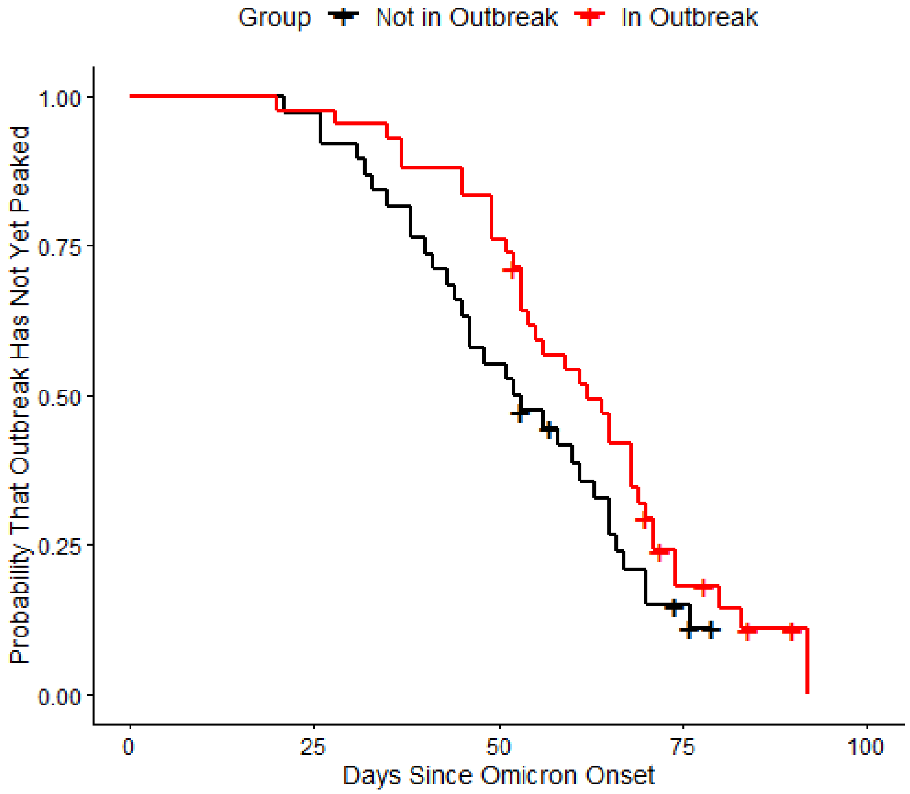


**Figure 3.** Peak of outbreak as a function of speed at Omicron arrival. Note: Not depicted, but included in the trend line calculation, is the outlier country of Israel, which reached a peak speed of 1177.3 daily novel transmissions per 100,000 population, up from a speed of 5.3 when Omicron was first sequenced in the country. The peak speed in Israel was approximately 4.5 SDs above the mean for all countries.

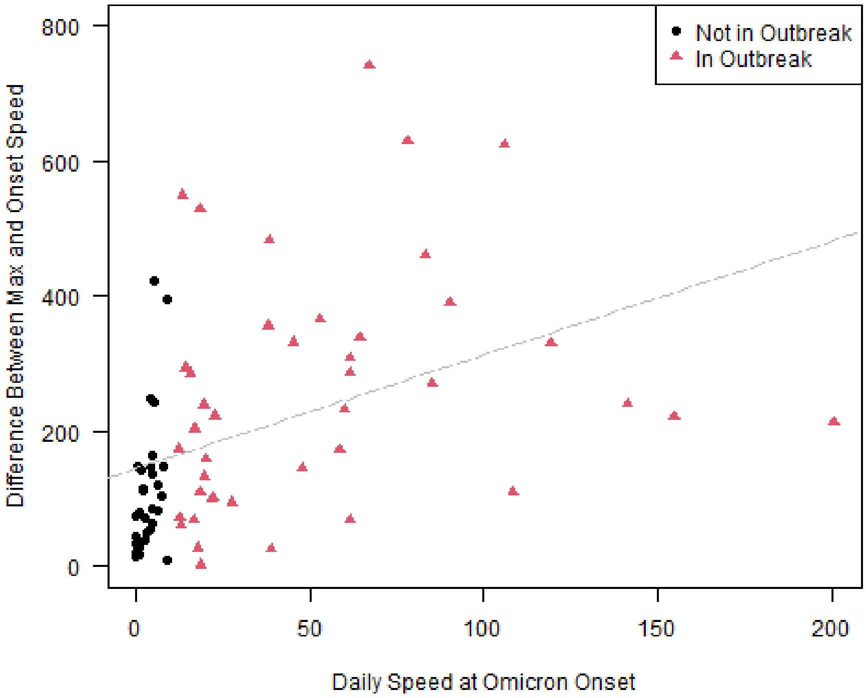


**Table 2.** Arellano-Bond dynamic panel data estimatesa.

| Variable | Coefficient (SE) | *P* value |
|---|---|---|
| *1-day_lag* | 0.1 (0.03) | <.001 |
| *7-day_lag* | 0.7 (0.15) | <.001 |
| *after_omi* | –62.9 (35.1) | .07 |
| *aft_omi·in_brk* | 84.1 (40.2) | .04 |
| *days_since_omi* | 0.8 (0.4) | .05 |
| *days_since_del_outbrk* | 0.4 (0.2) | .06 |
| *weekend* | –13.5 (4.7) | .004 |
| *total_cases_rate* | –1.1e-03 (2.2e-03) | .61 |
| *total_vacc_rate* | 1.3e-04 (9.4e-05) | .17 |

[a] Balanced panel: n=80, *t*=98 – 99, N=7868; Sargan test: $\chi^2_{(842)}$=80 (*P*>.99); autocorrelation test 1: normal=–1.94 (*P*=.05); autocorrelation test 2: normal=–3.20 (*P*=.01).

The *after_omi* and *aft_omi·in_brk* variables provide a test for whether daily speeds during the Omicron outbreak were higher in those countries already experiencing a Delta outbreak. The former variable is an indicator set to 1 for any date after the onset of Omicron, and the latter is an interaction between *after_omi* and *in_brk*, an indicator set to 1 if a country was in a Delta outbreak at the onset of Omicron. The coefficient estimate for *aft_omi·in_brk* is 84.1 and significant at the .05 level. For the interpretation, those countries that were in a Delta outbreak saw daily speeds increase by an average of 21.2 (=84.1 – 62.9) novel transmissions per 100,000 population after the onset of Omicron.

The negative coefficient of –62.9 on the *after_omi* predictor might seem counterintuitive, but 2 factors explain the sign. First, the model controls for *days_since_omi*, which is the number of days since the onset of Omicron and the end of the sample period. The expected daily speed rises by 0.8 novel transmissions per 100,000 population for each day since the onset of Omicron, and this result is significant at the .05 level. Thus, as time passes, *days_since_omi* will eventually outweigh *after_omi*. The second factor is the tail end of Delta outbreaks. The negative effect of *after_omi* only applies to countries that were not in an outbreak at the onset of Omicron. Those countries tended to have recently exited a Delta outbreak, and *after_omi* partly captures the deceleration in speed before Omicron outbreaks gathered momentum. For the countries that were already in an outbreak at the onset of Omicron, the *days_since_del_outbrk* variable controls for how long ago the Delta outbreak began. The coefficient of 0.4 means those countries saw an average additional 0.4 transmissions per

100,000 population for each day after the Delta outbreak began. The variable is significant at the .10 level but not the .05 level.

The model also controls for weekend dates. The coefficient on the indicator variable for weekend dates, *weekend*, is negative and statistically significant at the .01 level. This result is expected because many countries fail to report complete data over weekends.

Lastly, *total_cases_rate* and *total_vacc_rate*, respectively, contain cumulative prior infections and vaccinations, as measured in rates per 100,000 population. The coefficient on *total_cases_rate* is not statistically significant at the .10 level, which is expected because prior infections offer little protection against Omicron [54]. The coefficient on *total_vacc_rate* is also not significant at the .10 level, which is expected from the considerable vaccine escape of Omicron [55]. The positive sign on the coefficient is explained by the differential vaccination rates across countries. The worst Omicron outbreaks have tended to occur in countries with higher vaccination rates. In the sample, countries already in an outbreak at the onset of Omicron had an average vaccination rate over 40% higher than the rate for countries not in an outbreak.

On a more subtle point, the technical feat of the Arellano-Bond dynamic panel is its ability to control for time-invariant, country-specific factors [41]. Examples include public health policies, demographics, population density, culture, and history. The dynamic panel estimates automatically control for these factors to the extent they remain stable over the sample period. Thus, even after controlling for vaccinations, time since the onset of Omicron, time a country had been in a Delta outbreak (if one existed at the onset of Omicron), and time-invariant, country-specific factors, the Omicron outbreak in countries with high community transmission of Delta reached larger peaks than in countries with low transmission of Delta.

## Country Comparisons

To further examine the difference between Omicron-and-Delta outbreaks and Omicron outbreaks, we compared the outbreak trajectory of several neighbor countries, at least 1 of which was in a Delta outbreak at the onset of Omicron and 1 of which was not.

Figure 4 plots the rate of novel SARS-CoV-2 transmissions per 100,000 population for Canada and the United States over the sample period. The vertical gray lines indicate the date Omicron was first sequenced in each country (dashed for Canada, solid for the United States). The horizontal gray line depicts the CDC outbreak threshold for reference. A country is in a state of outbreak when its speed exceeds 10 cases per day per 100,000 population. At the onset of Omicron, Canada was not in an outbreak but the United States was.

When Omicron was first sequenced in Canada, the country had a speed of 6.4, while the speed for the United States was 22.8 at the onset date. The subsequent peak speeds for the countries were 126 and 245.4, respectively. The United States took longer to reach its peak from the date Omicron arrived, and its peak was nearly twice as high as Canada's.

Figure 5 plots the sequencing results of SARS-CoV-2 samples from Canada and the United States from May 2021 until February 2022. Over this period, the Delta and Omicron VOCs were the primary contributors to outbreaks in both countries. The United States sequenced 10 times as many SARS-CoV-2 samples as Canada, but both countries follow roughly similar trends.

**Figure 4.** Outbreaks in Canada and the United States. Note: The vertical lines indicate the date Omicron was first sequenced in each country. The solid and dashed lines correspond to those of each country in the legend.

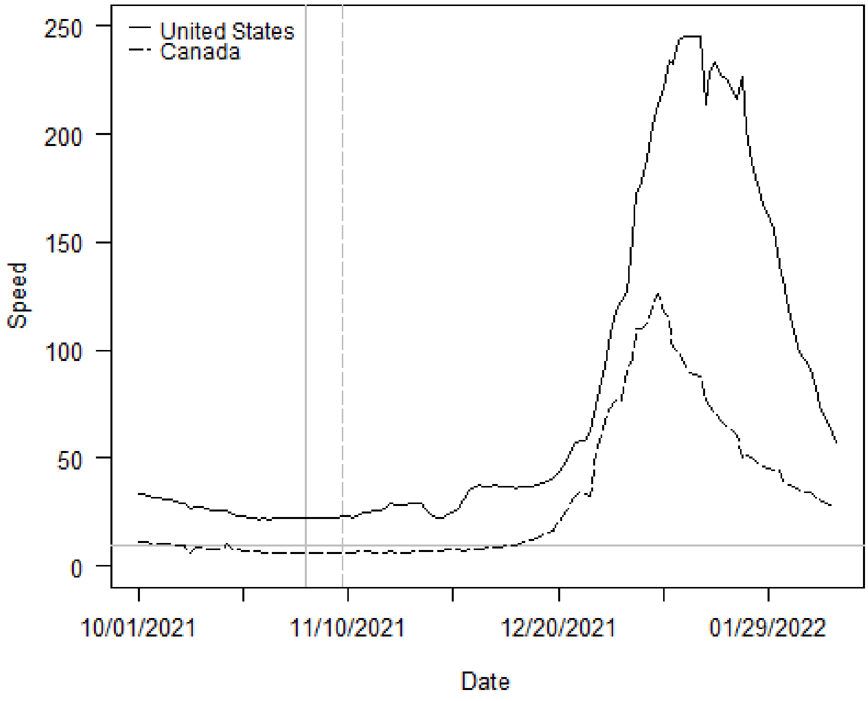
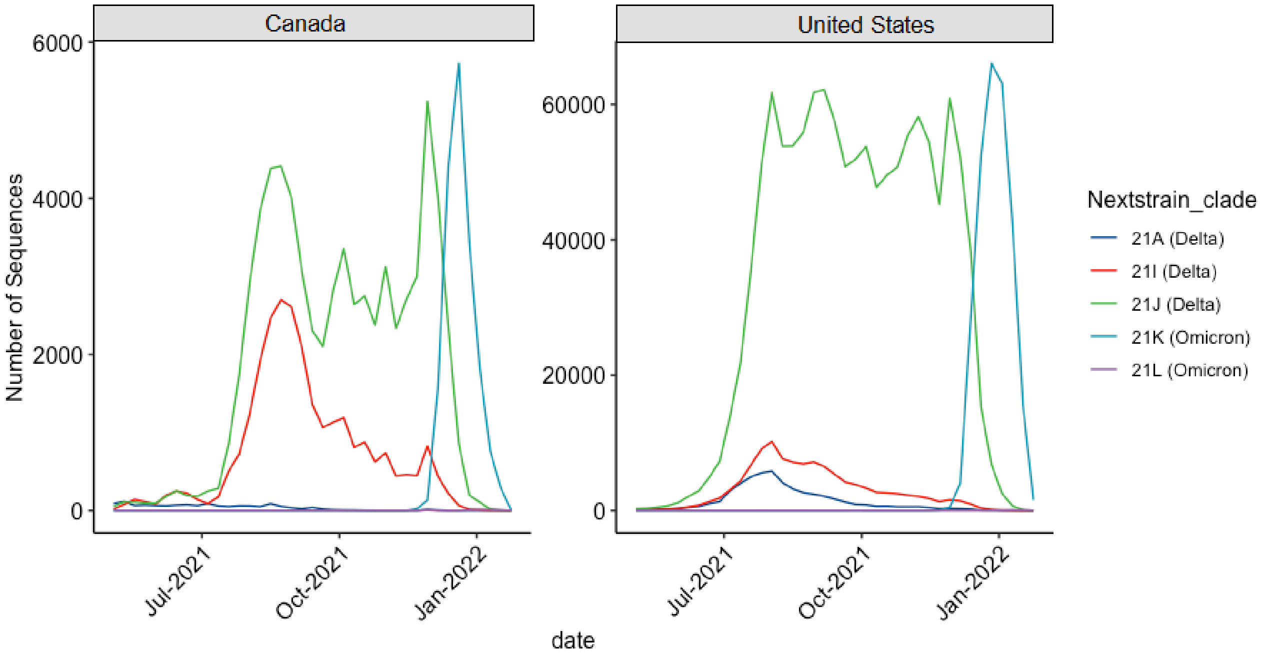


**Figure 5.** The evolution of Delta and Omicron VOCs in Canada and the United States. Note: The y axis denotes the total number of sequences for each VOC on a given date. VOCs other than Delta and Omicron were too infrequent to depict on the plot. VOC: variant of concern.



In the late summer and early fall of 2021, predominantly Delta clades were identified as part of the viral pool of SARS-CoV-2 cases in both Canada and the United States. Canada had a minor Delta outbreak, where the daily number of Delta cases slightly surpassed 10 per 100,000 population between September 15, 2021, and October 7, 2021. Canada was well below the threshold of an outbreak when Omicron was first sequenced. In contrast, the United States went into an outbreak largely driven by the Delta variant on July 19, 2021, and remained in an outbreak through the Omicron peak. Canada later went into an outbreak, largely driven by Omicron, in December, but the magnitude was roughly half that of the US outbreak. Although both countries are now only reporting sporadic new Delta cases, Delta overlapped with Omicron for the majority of the Omicron outbreak that began in December 2021. Canada cleared its Delta outbreak before the United States and before the advent of Omicron.

Figure 6 provides a similar illustration for Armenia, Azerbaijan, and Georgia. Neither Armenia nor Azerbaijan was in a state of outbreak when Omicron was first sequenced in the countries, but Georgia was. The subsequent peak in Georgia was 543.7, far larger than the peaks of 114.7 and 69.5, respectively, in Armenia and Azerbaijan. Although the outbreak in Azerbaijan continues to grow, the recent decrease in acceleration indicates the country is near its apex.

Figure 7 provides a similar plot for Kazakhstan and Russia. Kazakhstan was not in an outbreak at the onset of Omicron, but neighbor Russia was. The peak in Russia was 124.2, and the peak in Kazakhstan was 74.0. Russia continues to see an escalation in new transmissions, but the recent decrease in acceleration indicates the country is near its apex.

Taken together, Figures 4-7 support the broader findings in Figures 2 and 3 that countries already in an outbreak at the time of Omicron’s arrival had longer durations and reached higher peaks in cases compared to countries where community transmission of Delta was already low. However, this pattern does not always hold. Israel is the most extreme exception. Despite not beginning in an outbreak, the country reached a peak speed of 1177.3 novel transmissions per 100,000 population, as shown in Figure 8. Still, these specific country illustrations provide a context and guidance for a discussion of why outbreaks in countries already in a Delta outbreak at the onset of Omicron had different trajectories than outbreaks in countries with low initially community transmission.

**Figure 6.** Outbreaks in Armenia, Azerbaijan, and Georgia. Note: The vertical lines indicate the date Omicron was first sequenced in each country. The solid and dashed lines correspond to those of each country in the legend.

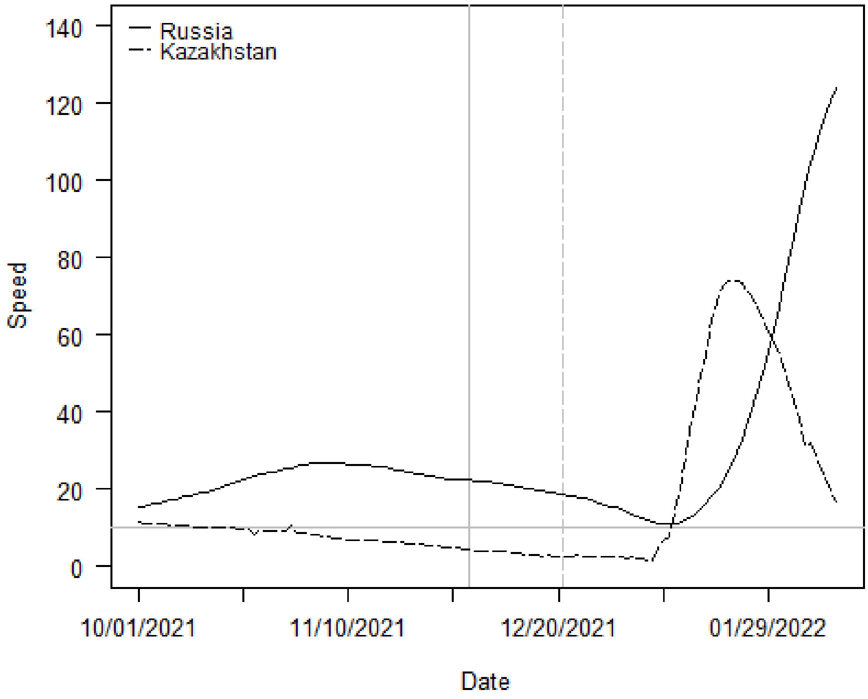


**Figure 7.** Outbreaks in Kazakhstan and Russia. Note: The vertical lines indicate the date Omicron was first sequenced in each country. The solid and dashed lines correspond to those of each country in the legend.

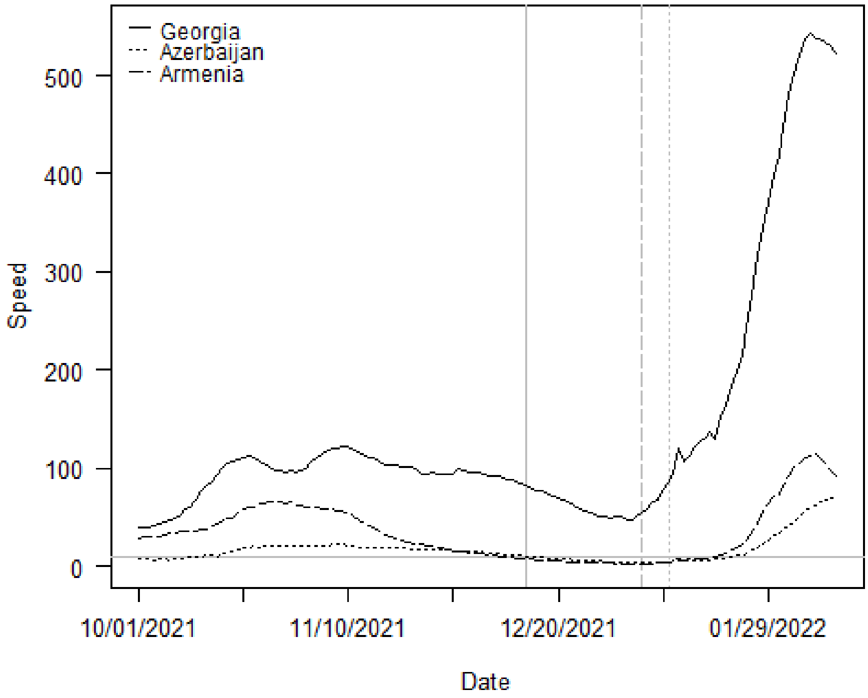
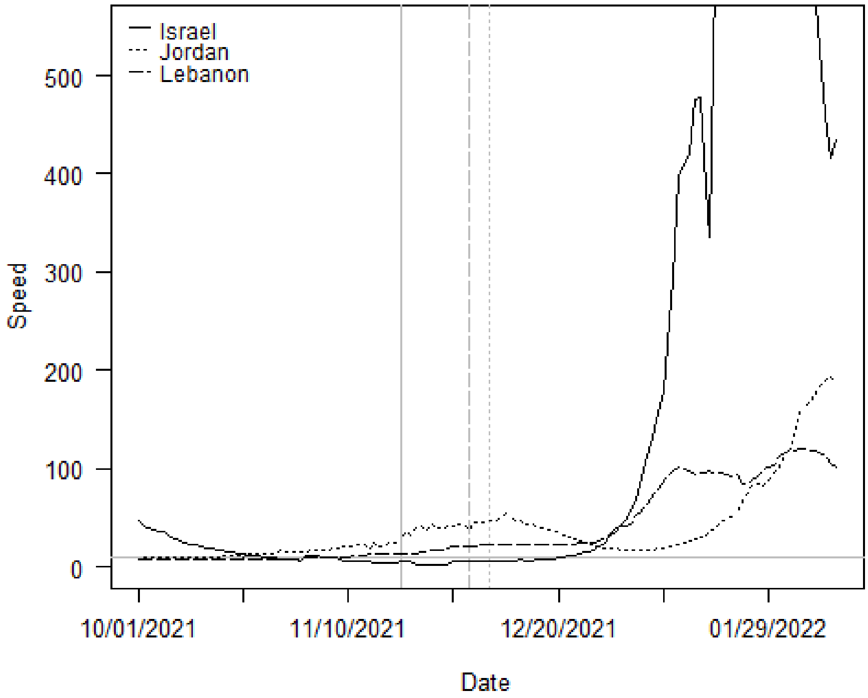


**Figure 8.** Outbreaks in Israel, Jordan, and Lebanon. Note: The vertical lines indicate the date Omicron was first sequenced in each country. The solid, dashed, and dotted lines correspond to those of each country in the legend.



## Discussion

### Principal Findings

In this study, we measured the trajectory of the pandemic for every country, beginning on the first day that Omicron was sequenced, and we compared the magnitude and speed of the subsequent outbreak in countries that had high versus low levels of preexisting Delta transmission. These countries were determined to be in an outbreak or not in an outbreak at the time of their first reported Omicron sequence based on a threshold of 10 daily new SARS-CoV-2 transmissions per 100,000 population.

Our analysis of epidemiological curve trajectories for countries not in an outbreak at the time of Omicron's arrival, such as sub-Saharan African countries and India, showed these outbreaks escalate, peak, and de-escalate rapidly, ending the outbreak with a small tail [19]. In contrast, Omicron outbreaks in countries already experiencing a Delta outbreak take relatively longer to peak and attenuate. This observation holds regardless of whether the Delta outbreak peaked before Omicron was introduced or whether the Delta outbreak was still trending upward. For example, Canada had peaked before Omicron was sequenced, while the United States peaked afterward. The apex of the Omicron-driven peak was over twofold higher in countries already in a Delta-driven outbreak. The former countries reached an average apex of 308.7 daily new cases per 100,000 population, while the latter countries reached an average apex of 128.6 (see Table 1). Even after controlling for the daily speed of the pandemic when Omicron was first identified in a particular country, we find that the magnitude of Omicron outbreaks in countries not already in an outbreak is slightly less than half the magnitude of Omicron outbreaks in countries with high levels of Delta transmission.

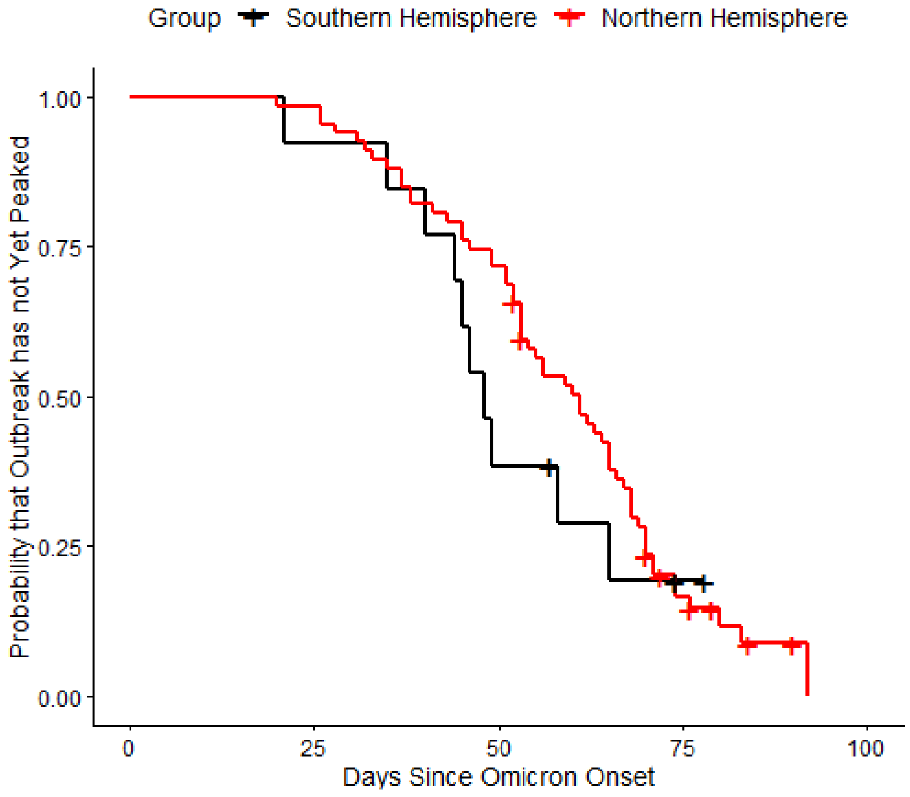
Prior to the emergence of Omicron, the Delta VOC made up over 97% of cases worldwide, with several countries experiencing Delta-driven outbreaks at the time of Omicron's emergence in November 2021. Omicron subsequently led to outbreaks and outcompeted Delta in every country where genomic surveillance data are available, now accounting for over 97% of cases worldwide [56]. Although it was initially thought that high levels of Delta transmission in some countries could blunt the impact of Omicron, our data strongly suggest that outbreaks reached higher peak speeds and magnitudes in countries already experiencing Delta outbreaks.

The propensity of countries already in a Delta-driven outbreak to have more intense Omicron-driven outbreaks could be explained by at least 4 overlapping (and not mutually exclusive) factors: (1) policy, (2) climate, (3) epidemiologic trends, and (4) public health infrastructure.

First, a preexisting Delta outbreak may have signaled ineffective policies that underlay epidemiological trends, which took longer to build, peak, and attenuate during the Omicron outbreak. For example, countries already in a Delta outbreak already may have had less stringent public health measures that could have resulted in the significantly higher speeds and larger peaks upon the arrival of Omicron. To explore the possibility, we calculated the average stringency index for each country over the sample period [50]. The daily index takes a value between 0 and 100, with higher scores indicating stricter national or subnational SARS-CoV-2 policy responses. The index was unavailable for Armenia, Montenegro, and North Macedonia, which left 77 (96.3%) countries for comparison. The average score for countries in a preexisting Delta outbreak was 49.4 compared to an average of 48.2 for countries not in an outbreak at the time of Omicron's arrival. A Welch *t* test failed to reject the null hypothesis of equal means across the 2 groups ($P$=.68). Because the number of countries in each group was greater than 30, the test passes the conventional guideline for approximate convergence in the central limit theorem [57]. If a *P* value provides a roughly graded measure of strength against the null hypothesis, the value suggests that other hypotheses may be more compatible with the data [58,59]. The Pearson correlation coefficient between the average score and a binary variable for the country group was also low, at –.04, with a 95% CI of –0.26 to 0.19. The Pearson coefficient is a measure of linear dependence between variables, which makes it the appropriate choice for an examination of policy intervention as a confounder in the linear dynamic panel regressions [60,61]. To summarize, policy differences seem to have limited explanatory power for the different trajectories of the Omicron outbreaks in these countries. Notwithstanding, although the enacted policies might not differ, the willingness of each country's population to adhere to these policies might, with "COVID fatigue" resulting in relaxed implementation.

A second explanation could be climate or socioeconomic conditions. Most countries that were still in a Delta outbreak reside in the Northern Hemisphere, and Omicron arrived over the winter months. If weather can affect the spread of SARS-CoV-2, then countries in colder regions might tend to have larger outbreaks of any variant [23-25]. Indeed, large outbreaks were observed in these countries during the winter of 2020-2021 prior to the emergence of the Delta or Omicron VOC, suggesting a seasonal trend independent of variant. Figure 9 provides survival curves analogous to those in Figure 2 but for countries that lie entirely in the Northern Hemisphere and those that do not. The curves cross at several points, which means sometimes outbreaks in the Northern Hemisphere take longer to reach their peak (from the onset date of Omicron), and sometimes outbreaks in the Southern Hemisphere do. The *P* value from a log-rank test is also higher than it was for the comparison between outbreak and nonoutbreak countries (*P*=.40 vs .09). Still, a portion of the Northern Hemisphere survival curve lies beyond the Southern Hemisphere curve, which suggests weather may partly explain why countries already in an outbreak were more adversely impacted by the arrival of Omicron. There is some visual evidence in Figure 9 that outbreaks in the Northern Hemisphere lasted longer. The Arellano-Bond method, however, controls for time-invariant, country-specific factors [41]. Climate is one such factor to the extent it remains constant for each country in the sample. In the regression estimates, temperature confounders would have to be caused by variable weather conditions over the sample period.

**Figure 9.** Time from arrival of Omicron until peak of outbreak by hemisphere. Note: Countries are included in the Northern Hemisphere group if their geographical area lies entirely in the Northern Hemisphere. All other countries are included in the Southern Hemisphere group.



A third possible explanation is that the enhanced ability of Omicron to infect vaccinated individuals resulted in overlapping outbreaks with Delta in slightly different populations, increasing overall case counts. Rather than an Omicron-driven outbreak, a better description would be a Delta outbreak *and* an Omicron outbreak, at least until Delta was outcompeted. Omicron does have a higher potential for immune escape compared to prior VOCs [8,62-66]. Natural infection from SARS-CoV-2 generated a strong protection against reinfection with Alpha [67,68], Beta [67], and Delta [69], but this protection was somewhat diminished, though still robust, against Omicron [70,71]. People infected with prior VOCs remain at risk for contracting the Omicron variant [70]. Furthermore, the vaccines developed to prevent contracting SARS-CoV-2 are somewhat less effective at protection against contracting the Omicron variant [72,73]. However, although Omicron has some advantage in causing breakthrough or reinfections, it is also highly transmissible in individuals with no prior immunity, just like the Delta VOC. Therefore, it is unlikely that the 2 variants existed in independent populations and caused overlapping outbreaks. The 2 VOCs were more likely in direct competition. Omicron's fitness advantage allowed it to quickly outcompete Delta, which is reflected in the genomic surveillance data (eg, Figure 5).

A fourth potential explanation is that the public health infrastructure in the outbreak countries better enabled them to (1) track cases in real time, (2) accurately determine the earliest date of Omicron arrival, and (3) track major surges in cases. First, given the outbreak threshold of 10 daily SARS-CoV-2 transmissions per 100,000 population, a country with better case tracking would be more likely to be in an outbreak state. Second, higher sampling for genomic surveillance is likely to result in an earlier detection of Omicron relative to the eventual peak. Third, a country with better testing infrastructure can process more tests in the context of a case surge, while other countries might be prematurely capped by capacity. Taken together, these 3 factors could explain the observed results in outbreak versus nonoutbreak countries.

Regardless of the reason for higher peaks and speeds of the Omicron outbreak in countries with preexisting Delta outbreaks, it is clear that high levels of community transmission of Delta did not substantially decrease population-level susceptibility to Omicron. First, countries in Delta outbreaks at the time of Omicron emergence still had case counts well below what would be required to elicit herd immunity. Second, even if vaccine-based immunity or natural immunity were long-lasting enough to reach herd immunity against a particular variant, an antigenic shift of SARS-CoV-2 will likely continue to drive immune evasion, as has been well documented for other RNA viruses. That being said, although Omicron resulted in many breakthrough infections and reinfections, a vast majority of these resulted in only mild disease. Thus, although case counts in many countries reached record peaks, an increasingly protected population from severe disease will likely result in a transition from a pandemic virus to an endemic virus.

## Limitations

Sequencing data are unavailable for many countries, which were not included in this study. However, enough countries remained (N=80) to statistically examine why Omicron outbreaks in countries already experiencing a Delta outbreak were significantly larger in magnitude and duration than Omicron-only outbreaks.

We also know that sequencing the index case of Omicron in each country may not capture the earliest date Omicron first arrived or a sustained transmission that led to the eventual outbreak of cases [74]. This assignment provides a proxy for when the Omicron outbreaks began. As long as the inaccuracies in the date of assignment from sequencing data are random and small, they should not cause significant bias in the dynamic panel estimates. For most countries, reassignment of the Omicron onset date causes negligible changes in the estimates. We acknowledge that the CDC classification threshold for an outbreak is somewhat arbitrary. Small deviations from the CDC threshold rate of 10 daily SARS-CoV-2 transmissions per 100,000 population would neither reclassify most countries in the sample nor cause a significant change in estimates. Larger deviations naturally would. To address this point, we also included Figure 3 to show a broader association between the initial rate of daily SARS-CoV-2 transmissions and later peak rates, which is independent of the outbreak classification threshold.

Because we are writing this study in as close to real time as possible, the Kaplan-Meier survival curves may contain some inaccuracies. Specifically, if the peak speed occurred before the last date of the sample period, an outbreak might reverse its de-escalation in the future and reach a new, higher peak speed.

The second-order autocorrelation test for the dynamic panel estimates rejected the null hypothesis of zero autocorrelation in the unobservable error component. Although rejection in the first-order autocorrelation test is a common feature of the Arellano-Bond first-difference operation, rejection in the second-order test indicates a possible bias in coefficient estimates caused by autocorrelation in the error component [75].

Lastly, although we addressed several possible confounders, the Arellano-Bond method controls for time-invariant, country-specific variables [41]. Unobserved variations in human behavior over the sample period, for example, might remain as a source of omitted variable bias. Furthermore, the analysis of climate through hemisphere distinction is unable to capture all the nuances of local weather conditions. Temperature, wind, and humidity can all affect the spread of SARS-CoV-2 [24,25,76-78]. Likewise, the analysis of local risk factors and management capacity through the stringency index is unable to capture all the nuances of local risk and interventions [79-81].

## Comparison With Prior Work

This study builds on prior work of the Omicron VOC by Lundberg et al [19]. The original study was the first to compare singular Omicron outbreaks to previous outbreaks driven by the original SARS-CoV-2 variant, Beta, Alpha, and Delta in sub-Saharan Africa. This study compares the Omicron outbreaks in countries with high versus low community transmission of the Delta VOC at the time of Omicron's arrival.

## Conclusion

Although it may be years before we fully understand the interplay between different SARS-CoV-2 variants, these data are likely to inform trends among groups of countries that could help predict the trajectories of future variants, given differences in preexisting case counts. Although Omicron has been emphasized as a less harmful variant, it has caused annual records of morbidity and mortality due to enhanced transmissibility and rapid spread. High community spread of Delta prior to the arrival of Omicron in some countries did not interfere with the spread of Omicron but rather portended a larger outbreak upon the arrival of the more transmissible variant.

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## Conflicts of Interest

None declared.

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## Abbreviations

**CDC:** Centers for Disease Control and Prevention
**GISAID:** Global Initiative on Sharing Avian Influenza Data
**mRNA:** messenger RNA
**VOC:** variant of concern
**WHO:** World Health Organization

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Original Paper

# Enhancing COVID-19 Epidemic Forecasting Accuracy by Combining Real-time and Historical Data From Multiple Internet-Based Sources: Analysis of Social Media Data, Online News Articles, and Search Queries

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## Abstract

**Background:** The SARS-COV-2 virus and its variants pose extraordinary challenges for public health worldwide. Timely and accurate forecasting of the COVID-19 epidemic is key to sustaining interventions and policies and efficient resource allocation. Internet-based data sources have shown great potential to supplement traditional infectious disease surveillance, and the combination of different Internet-based data sources has shown greater power to enhance epidemic forecasting accuracy than using a single Internet-based data source. However, existing methods incorporating multiple Internet-based data sources only used real-time data from these sources as exogenous inputs but did not take all the historical data into account. Moreover, the predictive power of different Internet-based data sources in providing early warning for COVID-19 outbreaks has not been fully explored.

**Objective:** The main aim of our study is to explore whether combining real-time and historical data from multiple Internet-based sources could improve the COVID-19 forecasting accuracy over the existing baseline models. A secondary aim is to explore the COVID-19 forecasting timeliness based on different Internet-based data sources.

**Methods:** We first used core terms and symptom-related keyword-based methods to extract COVID-19–related Internet-based data from December 21, 2019, to February 29, 2020. The Internet-based data we explored included 90,493,912 online news articles, 37,401,900 microblogs, and all the Baidu search query data during that period. We then proposed an autoregressive model with exogenous inputs, incorporating real-time and historical data from multiple Internet-based sources. Our proposed model was compared with baseline models, and all the models were tested during the first wave of COVID-19 epidemics in Hubei province and the rest of mainland China separately. We also used lagged Pearson correlations for COVID-19 forecasting timeliness analysis.

**Results:** Our proposed model achieved the highest accuracy in all 5 accuracy measures, compared with all the baseline models of both Hubei province and the rest of mainland China. In mainland China, except for Hubei, the COVID-19 epidemic forecasting accuracy differences between our proposed model (model i) and all the other baseline models were statistically significant (model 1, $t_{198}$=–8.722, $P$<.001; model 2, $t_{198}$=–5.000, $P$<.001, model 3, $t_{198}$=–1.882, $P$=.06; model 4, $t_{198}$=–4.644, $P$<.001; model 5,

$t_{198}$=–4.488, *P*<.001). In Hubei province, our proposed model's forecasting accuracy improved significantly compared with the baseline model using historical new confirmed COVID-19 case counts only (model 1, $t_{198}$=–1.732, *P*=.09). Our results also showed that Internet-based sources could provide a 2- to 6-day earlier warning for COVID-19 outbreaks.

**Conclusions:** Our approach incorporating real-time and historical data from multiple Internet-based sources could improve forecasting accuracy for epidemics of COVID-19 and its variants, which may help improve public health agencies' interventions and resource allocation in mitigating and controlling new waves of COVID-19 or other relevant epidemics.

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**KEYWORDS**

SARS-CoV-2; COVID 19; epidemic forecasting; disease surveillance; infectious disease epidemiology; social medial; online news; search query; autoregression model

## *Introduction*

COVID-19 poses extraordinary challenges for public health systems worldwide. As of November 26, 2021, COVID-19 had affected 222 countries and territories [1] and caused 259,502,031 confirmed cases, including 5,183,003 deaths worldwide [2]. Moreover, variants of the COVID-19 virus led to further challenges for public health. After the highly contagious Alpha variant swept across Europe and the United States in early 2021, the Delta variant replaced Alpha and became the dominant COVID variant worldwide [3]. The Delta variant is around 60% more transmissible than the Alpha variant, is moderately resistant to vaccines [4], and caused a new wave of the COVID-19 epidemic in Europe in late 2021 [5,6]. Omicron, an even more worrying variant, was reported from South Africa on November 24, 2021; it is said to out-compete the Delta variant and has been identified in Botswana, Belgium, Hong Kong, and Israel [7,8]. More timely and accurate forecasting of the incidence of COVID-19 and its variants is key to improving the efficiency of resource allocation and timeliness of intervention policy implementation [9-11].

Internet-based data sources, such as social media data (like microblogs), online news article data, and search query data, accumulate huge amounts of data all the time and have been proven to be an effective supplement to traditional infectious disease surveillance systems [12,13]. The underlying mechanism is that, before experiencing serious symptoms and going to a sentinel hospital, patients with symptoms may search for disease-related information on search engines like Google [14], complain about disease-related symptoms on social media like microblogs [15], or even share disease-related personal experiences on personal news articles platforms like instant articles [16]. This gives Internet-based data the ability to provide early warning for disease outbreaks [17,18] or provide supplemental information to enhance epidemic forecasting accuracy [14,16]. For instance, Wilson and Brownstein [19] retrieved official public health emergency–related online articles to support the early warning of Listeria outbreaks. Yang et al [14] proposed an autoregression model with Google search query data (AGRO) to improve the forecasting accuracy for influenza epidemics [14]. McGough et al [20] produced an improved estimation for the Zika virus in Latin America with a 1-week lead time. They used a multivariable linear regression model, combining real-time search query data, social media data (Twitter), outbreak news report counts, and historical officially reported case counts [20]. Internet-based data contain a large volume of unstructured text data [21] accompanied by noise caused by linguistic errors or misinformation [22]. To deal with Internet-based data, researchers have adopted a combination of methods, which include, but are not limited to, natural language processing, classification or clustering algorithms based on machine learning, and time-series models [12,23,24].

As COVID-19 has been and continues to be the most consequential infectious disease worldwide in this century, many researchers have used various Internet-based data sources to supplement COVID-19 surveillance [4,10,25]. Like previous research on other infectious diseases, COVID-19 forecasting research based on Internet-based data focuses mainly on 2 aspects: improving forecasting accuracy and improving forecasting timeliness. To improve COVID-19 forecasting accuracy, Shen et al [26] used the Granger causality test and showed that adding COVID-19 symptom–related microblogs could help enhance the COVID-19 predictive power. Liu et al [11] adopted a multivariable model and showed that adding real-time search query data and news article data into the traditional COVID-19 forecasting model could lead to more accurate forecasting results. The combination of different Internet-based data sources has shown greater power to enhance the forecasting accuracy of infectious diseases (including COVID-19) than using a single Internet-based data source [20]. However, existing methods incorporating more than one Internet-based data source used only real-time data from these sources as exogenous inputs but did not use historical data from all possible sources.

As for improving COVID-19 forecasting timeliness, Yuan et al [10] examined the lagged correlation between COVID-19 symptoms and core term–related search queries and daily new COVID-19 cases in the United States. They found that COVID-19–related search queries could provide a 12- to 14-day earlier warning for COVID-19 epidemics [10]. Similarly, Li et al [27] [26]proved that the Baidu search index and Weibo (social media platform similar to Twitter) index could both provide warning for COVID-19 outbreaks in China 8 days to 12 days earlier. However, the power of different Internet-based data sources to improve COVID-19 epidemic forecasting timeliness has not been fully explored [16]. The length of early warning time that Internet-based data could provide is not consistent across studies, varying from 0 [28] to 21 days [29]. Moreover, even though unofficial online news articles have shown great potential in supplementing COVID-19 surveillance [16,30,31], few studies have explored using unofficial online news articles to improve COVID-19 forecasting timeliness.

Our study explored whether combining real-time and historical data from multiple Internet-based sources could improve COVID-19 forecasting accuracy over the existing baseline models. We also compared COVID-19 forecasting timelines based on different Internet-based data sources.

## Methods

### Data Collection and Processing

We focused on the first wave of the COVID-19 epidemic in mainland China and compiled data on daily new confirmed COVID-19 case counts, online news articles, microblogs, and search queries from various sources. Following a previous study [26], we collected data from mainland China, with separate analyses for Hubei province and the remaining provinces. The official laboratory-confirmed case counts in mainland China, except Hubei province, can be retrieved since January 19, 2020 [21], while the official laboratory-confirmed case counts in Hubei province can be retrieved since January 10, 2020 [11]. The max time lags we explored were 20 days, following the example from previous studies [10,26]. Thus, we traced the Internet-based sources to December 21, 2019. We chose the end of our study period as February 29, 2020, when the primary wave of the COVID-19 epidemic in China had passed and the new confirmed case number decreased to single figures [21].

Daily new confirmed COVID-19 case counts were collected from the Chinese Center for Disease Control and Prevention (China CDC) website [32], which started collecting data on January 16, 2020. Earlier counts in Hubei province between January 10, 2020, and January 16, 2020, were compiled based on reports from the Health Commission of Hubei Province [33]. We then collected online news article data and microblog data from Sina Network Opinion Surveillance System (SNOSS) [34], a commercially available web-based platform that collects various Internet-based data in mainland China. Search query data were collected from the Baidu Index website [35]. We were the first to identify online news articles about COVID-19 and COVID-19–related microblogs using an approach based on COVID-19 core terms and symptom-related keywords. We also used COVID-19–related symptoms and core terms to extract COVID-19–related search queries, following a previous study [36]. Detailed Internet-based data extraction and filtering methods are described in Multimedia Appendix 1.

### Statistical Analysis

We first described the Internet-based data we retrieved and the COVID-19–related data we extracted. We then summarized all the COVID-19 forecasting-related data in 1 figure, including the fraction of online news articles and microblogs, search query counts, and lab-confirmed new case counts in mainland China, except Hubei, and Hubei province. All the data were normalized into an interval of 0 to 100 for better comparison. The figures aimed to show the Internet-based data sources' potential to provide warnings for COVID-19 epidemics.

We also conducted lagged Pearson correlation analyses to evaluate the strength of relationships between different Internet-based data sources and daily new confirmed COVID-19 case counts. The max time lag explored was 20 days [26]. Because outliers can have a large influence on the Pearson correlation [37], we replaced the outlier data in Hubei on February 12, 2020, with the average of the 2 nearest neighbors [38]. A high correlation threshold of 0.7 was used, based on previous research [27].

### Model Formulation

Following previous infectious disease surveillance research [14,15,39], including COVID-19 forecasting research [11,26], we proposed an autoregressive model with exogenous inputs [40,41]. We used the proportion of daily new confirmed COVID-19 case counts as a dependent variable. For the proportions of daily new confirmed case counts bounded between 0 and 1, we used logit transformation on the variable to turn it into unbounded scores [14,39,42]. The proportion was calculated by dividing the number of new confirmed COVID-19 case counts over the related population, which was based on the latest Chinese national population census [43]. We then proposed our model by adding log-transformed COVID-19–related Internet-based data as exogenous inputs, including the fraction of online news article, microblogs, and search query counts. Let $p_t$ be the new confirmed COVID-19 case proportion. For days when $p_t = 0$, we added a small positive number, λ, in the logit transformation. λ was calculated by dividing the square of the first quantile by the third quantile of all the proportions [44]. Let $y_t = logit(p_{t+}\lambda)$ be the logit-transformed new confirmed COVID-19 case proportion at day t. Let $x_t$ be the log-transformed fraction of COVID-19–related online news articles at day t, $z_t$ be the log-transformed fraction of COVID-19–related microblogs at day t, and $s_t$ be the log-transformed COVID-19–related search volume at day t. We chose "fever" to represent search queries, for it showed the highest correlations with new confirmed COVID-19 counts.

We proposed our autoregressive model with exogenous inputs, denoted as

Incorporating the real-time and historical data from online news articles, microblogs, and search query volume:

Where $a_i$ quantifies the contribution from the historical new confirmed COVID-19 case counts, $b_j$ quantifies the contribution from the historical fraction of COVID-19–related online news articles, $c_h$ quantifies the contribution from the historical fraction of COVID-19–related online news articles, $d_k$ quantifies the contribution from the historical COVID-19–related search queries, $M$ is a binary variable that equals 1 when data are in Hubei and equals 0 when data are outside Hubei, $f$ is a constant term, and $_t$ is a vector of independent random disturbance. $I_t$ is a time-varying binary variable that equals 1 on February 12, 2020, when Hubei adopted the fifth edition of the diagnostic criteria. $I_t$ controls for the exogenous shock of case counts on that day [26]. $lag_{NC}$, $lag_{News}$, $lag_{Mblog}$, and $lag_{Query}$ ranged from 1 to 20 and were the optimal values that led to the highest forecasting accuracy (lowest root-mean-square error [RMSE]) for related baseline models described in the next paragraph using a single Internet-based data source (see Table S1 in Multimedia Appendix 2 for detailed lag selections).

We considered 5 baseline models, including (1) AR($lag_{NC}$): autoregression model based on historical new confirmed COVID-19 case counts only [16,26], (2) AR($lag_{NC}$)+News($lag_{News}$): autoregression model adding the fraction of COVID-19–related online news articles as an exogenous input [16], (3) AR($lag_{NC}$)+Mblog($lag_{Mblog}$): autoregression model adding the fraction of microblogs as an exogenous input [26], (4) AR($lag_{NC}$)+Query($lag_{Query}$): autoregression model adding search volume as an exogenous input [36], and (5) AR($lag_{NC}$)+News(1)+Mblog(1)+Query(1): multivariable linear model adding the fraction of real-time online news articles, the fraction of microblogs, and search query volume into historical official COVID-19 report data [11,20] (see Multimedia Appendix 3 for detailed model formulations).

Retrospective estimations of the daily proportion of confirmed COVID-19 counts were produced through the proposed model and baseline models. The estimation period was from January 19, 2020, to February 29, 2020, for mainland China, except for Hubei. For Hubei province, even though the official laboratory-confirmed COVID-19 cases can be retrieved since January 10, 2020, there was a severe lack of laboratory testing capacity at the beginning of this unexpected epidemic. Specifically, there were thousands of COVID-19–suspected cases that could not be confirmed due to the lack of testing capacity before January 27, 2020, and the daily test capacity in Hubei had to be extended 10 times on January 27, 2020 to address this issue [45]. The officially reported daily new confirmed COVID-19 case counts before January 27, 2020 reflected the testing capacity rather than the evolution of the epidemic. Thus, we tested the proposed model and other baseline models from January 27, 2020, to February 29, 2020, in Hubei.

We used the variance inflation factor (VIF) to measure multicollinearity in the independent variables. A VIF over 4 indicates a moderate level of multicollinearity, and a VIF exceeding 10 shows severe multicollinearity [46]. A repeated k-fold cross-validation [47,48] was adopted to evaluate the proposed model and baseline models. In this study, we split the data into 10 folds and repeated the cross-validation procedure 10 times [47]. We adopted the 5 most commonly used accuracy measures to compare the models' forecasting results with the actual daily new confirmed COVID-19 case counts. The accuracy measures included the RMSE, mean absolute error (MAE), mean absolute percentage error (MAPE), correlation with forecasting target, and correlation of increment with forecasting target (the formulas for the accuracy indexes are presented in Multimedia Appendix 4) [14,49]. We conducted the analyses with the R version 4.0.2 statistical software package caret [50] version 6.0-86 and DAAG [51] version 1.24.

## Results

### Internet-Based Data Statistics

Overall, we extracted 608,335 (out of 75,431,068) and 123,955 (out of 15,062,844) COVID-19–related online news articles for mainland China, except Hubei, and Hubei province separately, respectively. Unofficial online news articles accounted for about 92.8% (83,966,946/90,493,912) of all the news articles traced. We also identified 476,932 (out of 32,475,162) and 191,296 (out of 4,926,738) COVID-19–related microblogs posted in mainland China, except Hubei, and Hubei province, respectively. For the COVID-19–related search queries, we retrieved 24,165,139 queries in mainland China, except Hubei, and 988,402 related queries in Hubei province. The daily new confirmed COVID-19 case counts, the fraction of COVID-19–related online news articles, the fraction of COVID-19–related microblogs, and COVID-19–related search query counts are displayed in Figures 1 and 2.

Figure 1 shows that the first peak of daily confirmed COVID-19 case counts was reached on January 30, 2020, in provinces except Hubei. Compared with the official COVID-19 case counts, the peak in COVID-19–related online news articles was 2 days earlier (January 28, 2020), the peak in microblogs was 3 days earlier (January 27, 2020), and the peaks in search queries were 4 days to 7 days earlier (from January 23, 2020, to January 26, 2020).

Figure 2 shows that the highest peak of daily new confirmed COVID-19 case counts was reached on February 4, 2020, in Hubei province. Compared with the peak of official COVID-19 case counts, the peak in COVID-19–related online news articles was 12 days earlier (January 23, 2020), peak in microblogs was 13 days earlier (January 22, 2020), and peaks in search queries were 10 days to 12 days earlier (from January 23, 2020, to January 25, 2020). An outlier of incidence was found on February 12, 2020, when the new confirmed COVID-19 case counts increased dramatically as Hubei province started implementing the fifth edition of the COVID-19 diagnostic criteria. The new diagnostic criteria introduced more flexible diagnostic standards and turned many previously suspected cases into confirmed cases. This outlier could impact the forecasting accuracy and has been dealt with carefully in the model formulation and data analysis.

Lagged Pearson correlation analyses between different Internet-based data sources and daily new confirmed COVID-19 case counts were also conducted to illustrate the predictive power. The highest correlations for different sources with different time lags are summarized in Table 1 (see Tables S2 and S3 in Multimedia Appendix 2 for more details).

Table 1 shows that, in mainland China except Hubei, the highest correlation for online news articles was 0.619 with 2 days' time lag, the highest correlation for microblogs was 0.613 with 2 days' time lag, and the highest correlations for search queries ranged from 0.831 to 0.949 with time lags of 3 days to 6 days. In Hubei province, the highest correlation for online news articles was 0.667 with 14 days' time lag, the highest correlation for microblogs was 0.632 with 7 days' time lag, and the highest correlations for search queries ranged from 0.750 to 0.826 with time lags of 10 days to 12 days. Although the highest correlations for online news articles and microblogs were below the high correlation threshold (0.7), these correlations were all above 0.6, which was relatively high.

**Figure 1.** Daily time series of new confirmed COVID-19 case counts (NC), the fraction of COVID-19 related microblogs (Mblog), the fraction of COVID-19–related online news articles (News), and numbers of COVID-19–related search queries with the keyword “fever,” “dry cough,” “chest distress,” “pneumonia,” or “coronavirus” in mainland China, except Hubei province, from December 21, 2019 to February 29, 2020.

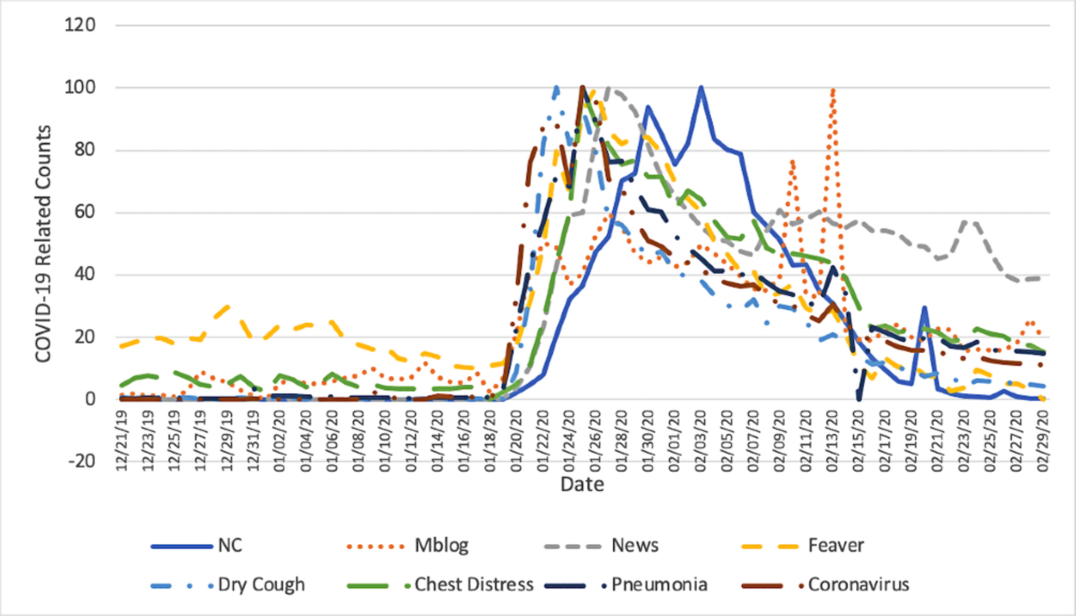


**Figure 2.** Daily time series of new confirmed COVID-19 case counts (NC), the fraction of COVID-19 related microblogs (Mblog), the fraction of COVID-19–related online news articles (News), and numbers of COVID-19–related search queries with the keyword “fever,” “dry cough,” “chest distress,” “pneumonia,” or “coronavirus” in Hubei province from December 21, 2019 to February 29, 2020.

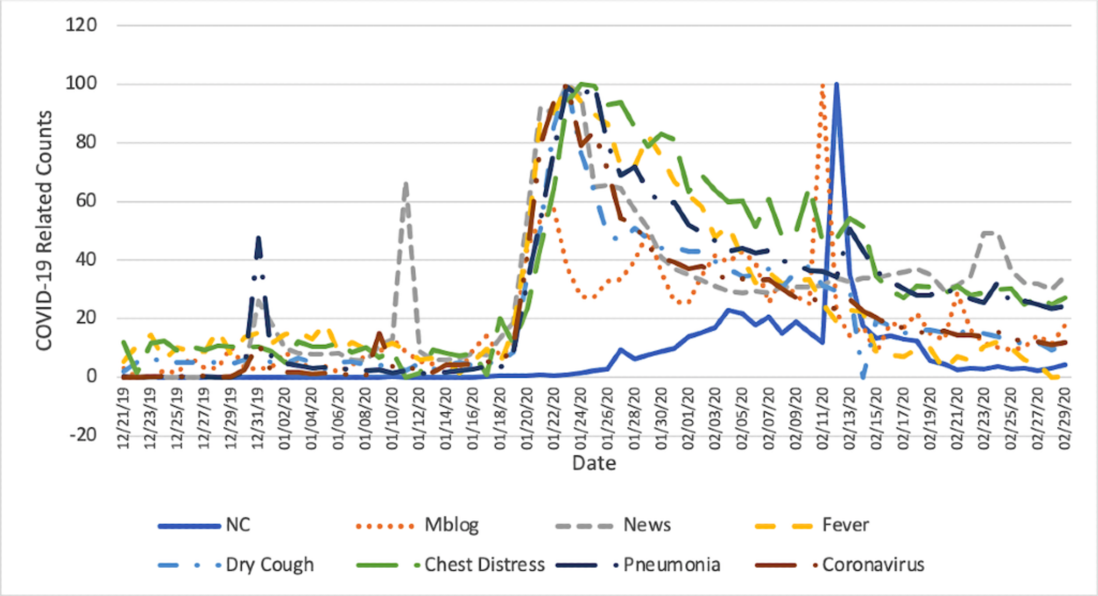


**Table 1.** Strongest correlation coefficients, *P* values, and related time lag between new confirmed COVID-19 case counts and the fraction of COVID-19–related microblogs, fraction of COVID-19–related online news articles, and numbers of COVID-19–related search queries between December 21, 2019, and February 29, 2020.

| Source | Outside Hubei | | | Hubei | | |
|---|---|---|---|---|---|---|
| | Highest correlation | *P* value | Days earlier | Highest correlation | *P* value | Days earlier |
| News articles | 0.619 | <.001 | 2 | 0.667 | <.001 | 14 |
| Microblogs | 0.613 | <.001 | 2 | 0.632 | <.001 | 7 |
| Search for "fever" | 0.949 | <.001 | 4 | 0.826 | <.001 | 12 |
| Search for "dry cough" | 0.831 | <.001 | 6 | 0.775 | <.001 | 12 |
| Search for "chest distress" | 0.867 | <.001 | 3 | 0.806 | <.001 | 10 |
| Search for "pneumonia" | 0.854 | <.001 | 5 | 0.750 | <.001 | 11 |
| Search for "coronavirus" | 0.831 | <.001 | 6 | 0.765 | <.001 | 12 |

## Model Evaluation

The forecasting results for our proposed model and baseline models are presented in Tables 2 and 3. Optimal lags of different data sources, which result in the lowest RMSE for related baseline models incorporating a single Internet-based data source, are shown (see Table S1 in Multimedia Appendix 2 for the optimal lag selection). The last 2 columns show the paired *t* test results comparing our proposed model with the baseline models.

**Table 2.** COVID-19 epidemic forecasting model comparison for mainland China, except Hubei, between January 19, 2020, and February 29, 2020.

| Model (lag) | Model number | RMSE[a] | MAE[b] | MAPE[c] | Correlation | Incremental correlation | $t_{198}$ | *P* value |
|---|---|---|---|---|---|---|---|---|
| AR(7)+News(1)+ Mblog(10)+Query(1) | model i | 87.461 | 47.780 | 0.154 | 0.960 | 0.435 | N/A[d] | N/A |
| AR(7) | model 1 | 152.182 | 97.852 | 0.579 | 0.852 | 0.006 | –8.722 | <.001 |
| AR(7)+News(1) | model 2 | 117.223 | 68.158 | 0.374 | 0.911 | 0.066 | –5.000 | <.001 |
| AR(7)+Mblog(10) | model 3 | 93.754 | 51.375 | 0.185 | 0.948 | 0.403 | –1.882 | .06 |
| AR(7)+Query(1) | model 4 | 138.724 | 85.024 | 0.421 | 0.905 | 0.168 | –4.644 | <.001 |
| AR(7)+News(1)+ Mblog(1)+Query(1) | model 5 | 90.494 | 53.332 | 0.306 | 0.954 | 0.167 | –4.488 | <.001 |

[a] RMSE: root-mean-square error.

[b] MAE: mean absolute error.

[c] MAPE: mean absolute percentage error.

[d] N/A: not applicable.

**Table 3.** COVID-19 epidemic forecasting model comparison for Hubei province, China, between January 27, 2020, and February 29, 2020.

| Model (lag) (model no.) | Model number | RMSE[a] | MAE[b] | MAPE[c] | Correlation | Incremental correlation | $t_{198}$ | *P* value |
|---|---|---|---|---|---|---|---|---|
| AR(1)+News(3)+ Mblog(1)+Query(3) | model i | 325.216 | 225.620 | 0.168 | 0.990 | 0.984 | N/A[d] | N/A |
| AR(1) | model 1 | 658.238 | 403.665 | 0.267 | 0.963 | 0.958 | –1.732 | .09 |
| AR(1)+News(2) | model 2 | 488.974 | 325.731 | 0.226 | 0.978 | 0.976 | –1.196 | .24 |
| AR(1)+Mblog(1) | model 3 | 431.457 | 311.196 | 0.228 | 0.983 | 0.977 | –0.252 | .80 |
| AR(1)+Query(3) | model 4 | 437.368 | 286.900 | 0.201 | 0.983 | 0.976 | –0.364 | .72 |
| AR(1)+News(1)+ Mblog(1)+Query(1) | model 5 | 360.725 | 272.602 | 0.206 | 0.988 | 0.981 | –0.965 | .34 |

[a] RMSE: root-mean-square error.

[b] MAE: mean absolute error.

[c] MAPE: mean absolute percentage error.

[d] N/A: not applicable.

The results from the 5 accuracy measures were interpreted. The results in Tables 2 and 3 show that our proposed model (model i) achieved the highest accuracy in all 5 accuracy measures, compared with all the baseline models in both Hubei province and the rest of mainland China. Plots depicting forecasting results and estimation errors for the proposed model and baseline models are also shown in Figures 3 and 4.

We then assessed the statistical significance of the forecasting accuracy improvement between different models based on paired *t* tests on the models' RMSEs. For mainland China, except Hubei, Table 2 and Figure 3 show that our proposed model (model i) could significantly improve the forecasting accuracy, compared with all the other baseline models (model 1, $t_{198}$=–8.722, *P*<.001; model 2, $t_{198}$=–5.000, *P*<.001; model 3, $t_{198}$=–1.882, *P*=.06; model 4, $t_{198}$=–4.644, *P*<.001; model 5, $t_{198}$=–4.488, *P*<.001). For Hubei province, Table 3 and Figure 4 show our proposed model's (model i) forecasting accuracy improved significantly (at a significance level of .10) compared with the forecasting model using historical new confirmed COVID-19 case counts only (model 1, $t_{198}$=–1.732, *P*=.09) and no significant differences compared with other baseline models (model 2, $t_{198}$=–1.196, *P*=.24; model 3, $t_{198}$=–0.252, *P*=.80; model 4, $t_{198}$=–0.364, *P*=.72; model 5, $t_{198}$=–0.965, *P*=.34). The forecasting accuracy differences between other baseline models using Internet-based data sources and model 1 are not significant (model 2, $t_{198}$=–0.900, *P*=.37; model 3, $t_{198}$=–1.630, *P*=.11; model 4, $t_{198}$=–1.324, *P*=.19; model 5, $t_{198}$=–0.786, *P*=.43).

We also evaluated the practical significance of the forecasting models from the perspective of MAPE. For provinces outside Hubei of mainland China in Table 2, our proposed model showed significant accuracy improvement. Specifically, our proposed forecasting model's unexplained error percentage was 15.4%, while the unexplained error percentages for the other models were as follows: forecasting model based on historical new confirmed COVID-19 case counts only (model 1), 57.9%; model incorporating COVID-19–related online news articles (model 2), 37.4%; model incorporating COVID-19–related microblogs (model 3), 18.5%; model incorporating COVID-19–related search queries (model 4), 42.1%; model combining real-time Internet-based sources into historical new COVID-19 case counts (model 5), 30.6%. Meanwhile, for Hubei province in Table 3, the improvement in accuracy with our proposed model was also nearly significant. The unexplained error percentage for our proposed model was 16.8%, while the unexplained error percentages for the other models were as follows: model 1, 26.7%; model 2, 22.6%; model 3, 22.8%; model 4, 20.1%; model 5, 20.6%.

The collinearity diagnostics revealed that real-time social media data, online news articles, and search queries are independent of each other in supplementing COVID-19 surveillance. More detailed results and discussions are presented in Multimedia Appendix 5.

**Figure 3.** (A) Forecasting results for mainland China, except Hubei, between January 19, 2020 and February 29, 2020, during which the daily estimations of our proposed model and baseline models were compared against the daily new confirmed COVID-19 case counts (NC), and (B) the estimation error, defined as the estimated value minus the daily new confirmed COVID-19 case counts.

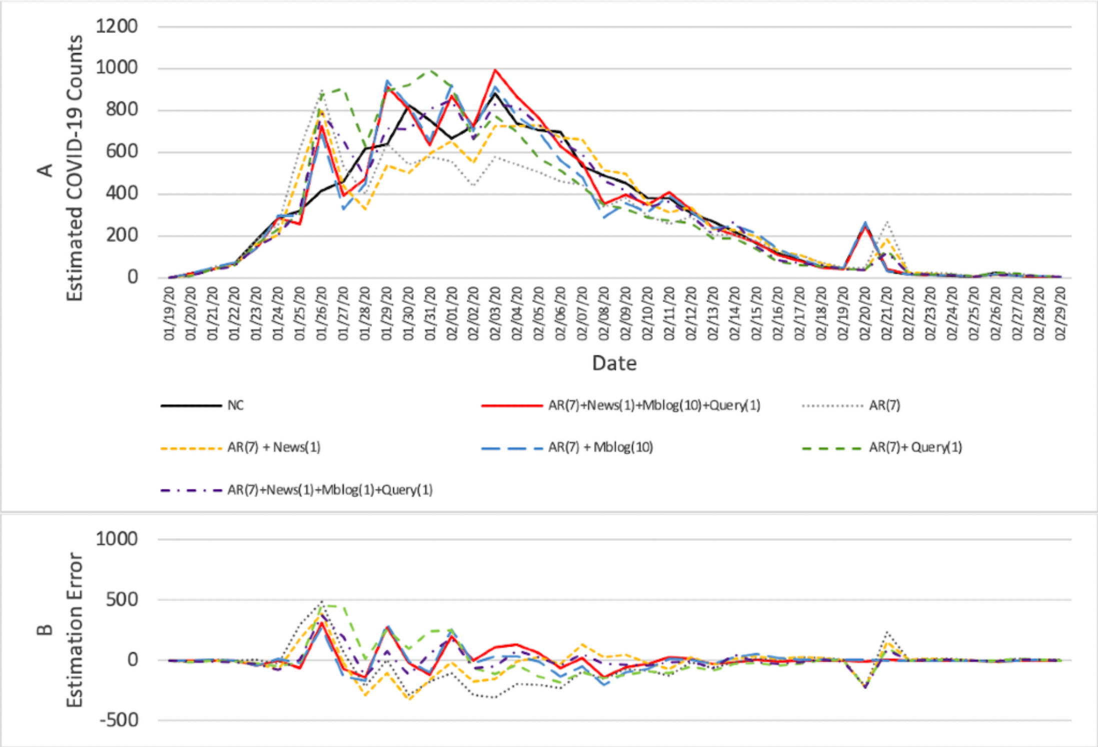
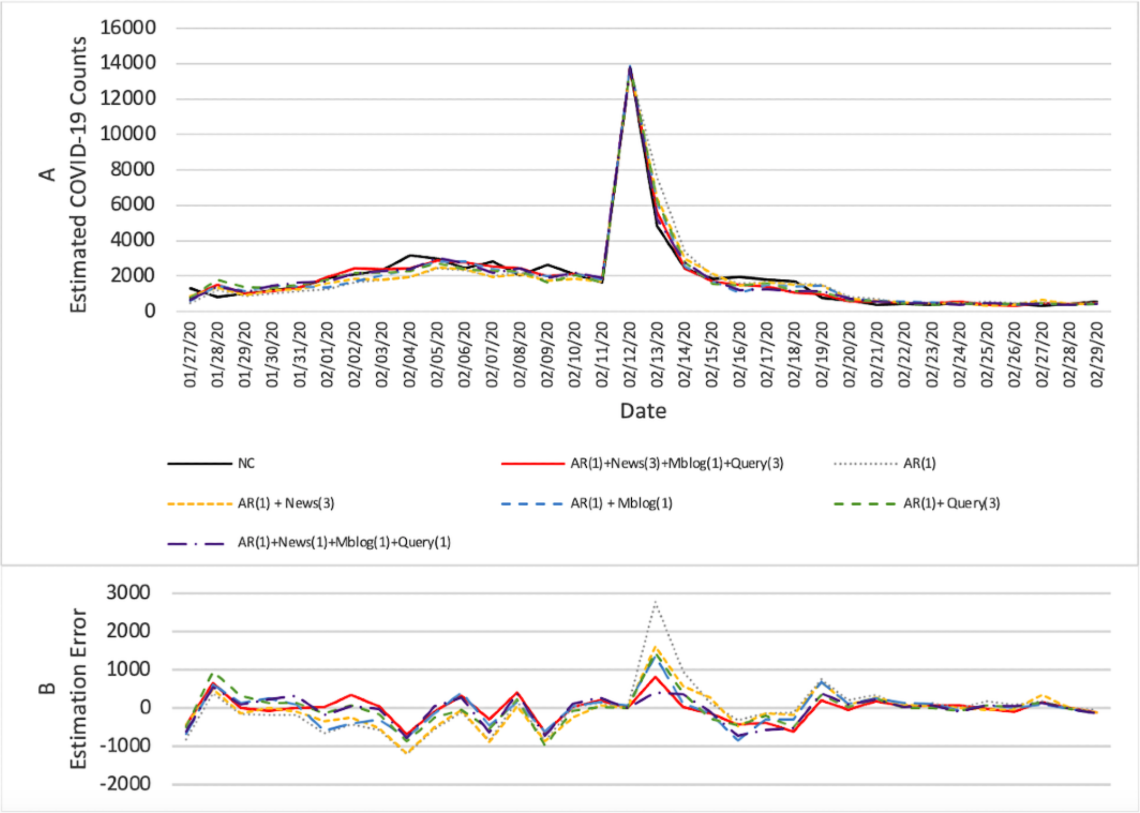


**Figure 4.** (A) Forecasting results for Hubei province between January 27, 2020 and February 29, 2020, during which the daily estimations of our proposed model and baseline models were compared against the daily new confirmed COVID-19 case counts (NC), and (B) the estimation error, defined as the estimated value minus the daily new confirmed COVID-19 case counts.



## Discussion

### Principal Findings

The SARS-COV-2 virus and its variants pose extraordinary challenges for public health systems worldwide. More accurate forecasting of COVID-19 epidemics is key to improving the efficiency of resource allocation and the implementation of intervention policies [11,26]. Our proposed model innovatively incorporates both real-time and historical data from multiple Internet-based sources for COVID-19 epidemic forecasting. Tested during the first wave of the COVID-19 epidemic in mainland China, except Hubei, our proposed model showed statistically significant improved forecasting accuracy compared with the other baseline models. Tested in Hubei province, our proposed model outperformed all the baseline models in all 5 accuracy indexes, revealed significant practical influence, and showed statistically significant improved forecasting accuracy compared with baseline model 1 using the lab-confirmed case count only. Other baseline models incorporating different Internet-based data sources did not show significant differences compared with baseline model 1. This may be because people knew little of the disease at first and all talked online about the novel coronavirus pneumonia in Wuhan, Hubei, which could lead to disturbances in the Internet-based data sources [52]. In this condition, a single Internet-based data source or real-time data only may not be able to improve the COVID-19 forecasting accuracy, and our proposed model shows the ability to mitigate the disturbance and enhance COVID-19 surveillance by combining real-time and historical data from multiple Internet-based data sources.

This study also explored COVID-19 forecasting timeliness using different Internet-based data sources. Unlike previous studies that mainly focused on official online news articles, our study also took into account unofficial online news articles, which accounted for about 92.5% of all online news articles. The results show that COVID-19–related online news articles could provide a warning for the COVID-19 epidemic in mainland China, except Hubai, about 2 days earlier and in Hubai about 12 days to 14 days earlier. A similar early warning ability was also shown for microblogs and search queries. We found significant differences in the lag in an early warning for mainland China, except Hubei, and Hubei province, which may be caused by 2 reasons. First, Hubei experienced an extreme shortage of testing capacity in the beginning [26], which could have delayed the peak of lab-confirmed new case counts. Second, at the beginning of the first COVID-19 epidemic, people were curious about this unknown disease and tended to search or post related information even when they did not have associated symptoms [52]. This could advance the corresponding peak in Internet-based sources. As of the time of this writing, people were familiar with COVID-19–related information, and Internet-based sources, including online news articles, are supposed to provide a 2- to 6-day early warning for COVID-19 outbreaks.

Our study innovatively proposes core terms and symptom-related keyword-based approaches to extract COVID-19–related Internet-based data sources. The keyword-based approaches allow us to constantly and conveniently update the core terms and symptoms to keep up with the mutation of the COVID-19 virus. For example, people infected with the Delta variant are more likely to have a “runny nose,” “headache,” or “sore throat” and less likely to experience “loss of smell” [53]. Researchers then could focus more on the core term of “Delta variant” and the symptoms of “runny nose,” “headache,” and “sore throat” in online public data–based COVID-19 surveillance for this new round of epidemic in Europe [6]. We thus argue that our proposed model could help governments better prepare and respond to a new wave of COVID-19 and its variants.

Another interesting finding of our study is that the peak of daily new confirmed case counts in Hubei was reached on February 4, 2020, while the peak in the rest of mainland China was reached on January 30, 2020 (5 days earlier than Hubei Province). This finding was contrary to our common sense, for Hubei was the epicenter of the initial outbreak, and the rest of mainland China was influenced by this epidemic later. One possible reason for the delay of the COVID-19 epidemic peak in Hubei was the extreme shortage of medical resources at the beginning of the epidemic, including testing ability and hospital beds [26,45]. Many suspected cases could not be tested until the testing ability was extended 10 times on January 27 [45]. And until 15 mobile cabin hospitals were built in early February 2020, many confirmed cases with no or mild symptoms had to be quarantined at home rather than stay in the hospital, which increased the risk of COVID-19 transmission [54]. Different from Hubei, the rest of mainland China experienced a much smaller number of COVID-19 cases and had much more adequate medical resources [26], which made it possible to test and quarantine all the COVID-19 suspected cases in time. Thus, even though the rest of mainland China was influenced by the COVID-19 epidemic later than Hubei province, it is possible that the rest of mainland China could control the disease and reach the peak of daily new confirmed case counts earlier than Hubei. Future research could explore the factors contributing to the delay or advance of the epidemic peaks.

Overall, the results show that incorporating both real-time and historical data from multiple Internet-based sources into the COVID-19 forecasting model could significantly improve the forecasting accuracy, compared with other baseline models. Internet-based data sources, including online news articles, microblogs, and search queries, could provide early warning for COVID-19 outbreaks. These findings have broad public health implications. Internet-based data are timely, low-cost, and rich in information, making them critical in the surveillance of COVID-19 outbreaks. This application is even more important in rural areas, where the health infrastructure does not allow for widespread screening. COVID-19 surveillance using Internet-based data could provide much-needed information to help the government trace the outbreak and more effectively allocate resources, including testing capacity, oxygen cylinders, and hospital beds. Internet-based platforms allow users to capture detailed real-time snapshots of COVID-19–related events that happen to them or near them. As the COVID-19 virus continues to mutate, Internet-based sources with richer information have the potential to identify novel COVID-19 variants through deeper information analysis.

## Limitations

There are several limitations and potential future directions of this study that we would like to mention. First, our study only used retrospective data from mainland China and did not test the proposed model in countries that are currently experiencing an epidemic of COVID-19 and its variants. This is mainly because of data accessibility. We could not find available databases or online platforms that allowed us to access a large volume of real-time and historical microblogs and unofficial online news articles in other countries. We encourage future work to use the proposed method in different countries to test its generalizability and robustness.

Second, our study did not incorporate machine learning methods in the data filtering process. In this study, we explored the full database of Internet-based sources in mainland China from the SNOSS and Baidu Search Index, where the raw data are not available for downloading and further analysis. Future research could apply advanced machine learning methods to the raw data of various Internet-based sources to achieve more accurate epidemic-related data extraction and deeper information analyses. For example, future research can use the support vector machine to help extract COVID-19–related online data [55] or use a topic modeling algorithm to generate major themes about the COVID-19 epidemic [56]. Deeper content analyses could help identify real-time characteristics of the COVID-19 epidemic, which may act as early warning signals for new emerging COVID-19 variants or other epidemics.

Finally, our study mainly used symptom- and core term–related keywords to extract COVID-19–related Internet-based data, which has been proven to provide the most accurate predictions compared with other types of keywords [9,15]. Our underlying assumption is that, before getting severe symptoms and going to a sentinel hospital, patients with mild symptoms would likely search for or post COVID-19–related symptoms or core terms online. Our Internet-based method could identify patients with COVID-19 symptoms but lose sight of patients in the incubation period with no symptoms, which meant our method could only provide warning 2 days to 6 days earlier for the epidemic outbreaks. As our study’s major aim was to improve the COVID-19 forecasting accuracy, we did not explore new methods to improve the forecasting timeliness of Internet-based data in our study. We call for future studies to explore novel Internet-based sources, like traffic data and weather [21,57], to help improve the forecasting timeliness for COVID-19 epidemics.

## Conclusions

COVID-19 and its variants have been and continue to be a major public health threat worldwide. COVID-19 core term– and symptom-related Internet-based data could provide invaluable warning signals to the public and supplement existing COVID-19 surveillance systems. This study showed that our proposed COVID-19 forecasting method, incorporating both real-time and historical data from multiple Internet-based sources, could significantly improve the forecasting accuracy compared with other baseline models. Our results also show that Internet-based sources, including online news articles, could provide a warning 2 days to 6 days earlier for COVID-19 outbreaks.

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## Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed descriptions of the Internet-based data extraction and filtering methods.
[DOCX File , 28 KB - publichealth_v8i6e35266_app1.docx ]

Multimedia Appendix 2
Supplementary tables.
[DOCX File , 37 KB - publichealth_v8i6e35266_app2.docx ]

Multimedia Appendix 3
Descriptions and formulations of baseline models.
[DOCX File , 19 KB - publichealth_v8i6e35266_app3.docx ]

Multimedia Appendix 4
Accuracy indexes.
[DOCX File , 13 KB - publichealth_v8i6e35266_app4.docx ]

Multimedia Appendix 5
Collinearity diagnostics.
[DOCX File , 23 KB - publichealth_v8i6e35266_app5.docx ]

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## Abbreviations

**CDC:** Center for Disease Control and Prevention
**MAE:** mean absolute error
**MAPE:** mean absolute percentage error
**RMSE:** root-mean-squared error
**SNOSS:** Sina Network Opinion Surveillance System
**VIF:** variance inflation factor

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Original Paper

# Attitudes Toward the Global Allocation of Chinese COVID-19 Vaccines: Cross-sectional Online Survey of Adults Living in China

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## Abstract

**Background:** COVID-19 vaccines are in short supply worldwide. China was among the first countries to pledge supplies of the COVID-19 vaccine as a global public product, and to date, the country has provided more than 600 million vaccines to more than 200 countries and regions with low COVID-19 vaccination rates. Understanding the public's attitude in China toward the global distribution of COVID-19 vaccines could inform global and national decisions, policies, and debates.

**Objective:** The aim of this study was to determine the attitudes of adults living in China regarding the global allocation of COVID-19 vaccines developed in China and how these attitudes vary across provinces and by sociodemographic characteristics.

**Methods:** We conducted a cross-sectional online survey among adults registered with the survey company KuRunData. The survey asked participants 31 questions about their attitudes regarding the global allocation of COVID-19 vaccines developed in China. We disaggregated responses by province and sociodemographic characteristics. All analyses used survey sampling weights.

**Results:** A total of 10,000 participants completed the questionnaire. Participants generally favored providing COVID-19 vaccines to foreign countries before fulfilling domestic needs (75.6%, 95% CI 74.6%-76.5%). Women (3778/4921, 76.8%; odds ratio 1.18, 95% CI 1.07-1.32; *P*=.002) and those living in rural areas (3123/4065, 76.8%; odds ratio 1.13, 95% CI 1.01-1.27; *P*=.03) were especially likely to hold this opinion. Most respondents preferred providing financial support through international platforms rather than directly offering support to individual countries (72.1%, 95% CI 71%-73.1%), while for vaccine products they preferred direct provision to relevant countries instead of via a delivery platform such as COVAX (77.3%, 95% CI 76.3%-78.2%).

**Conclusions:** Among our survey sample, we found that adults are generally supportive of the international distribution of COVID-19 vaccines, which may encourage policy makers to support and implement the distribution of COVID-19 vaccines developed in China worldwide. Conducting similar surveys in other countries could help align policy makers' actions on COVID-19 vaccine distribution with the preferences of their constituencies.

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**KEYWORDS**

COVID-19 vaccines; China; global allocation; public attitudes; cross-sectional; survey; vaccines; COVID-19; pandemic; public health; health policy; epidemiology

## *Introduction*

Vaccination is a promising approach to achieving global control of COVID-19. It is estimated that over 14 million future deaths could be prevented if COVID-19 vaccines could be delivered sufficiently [1-3]. As of December 31, 2021, over 70% of people in high-income countries are fully vaccinated against COVID-19; while in low-income countries, that number is only 4% [4]. Inequitable allocation of vaccines may lead to avoidable death, social dissatisfaction, and adverse mental health consequences [5,6].

Expanding vaccine coverage to low-income countries is difficult due to insufficient COVID-19 vaccine production and supply; at present, only 22 countries have the capacity to produce COVID-19 vaccines [7]. For most countries, the available vaccines that they can acquire depend on international assistance provided by procurement or purchasing from foreign vaccine companies, bilateral aid between countries, or multilateral aid via institutions (eg, COVAX, a global risk-sharing mechanism for pooled procurement and equitable distribution of COVID-19 vaccines coled by the World Health Organization [WHO], The Global Alliance for Vaccines and Immunizations [GAVI], and the Coalition for Epidemic Preparedness Innovations, with GAVI responsible for vaccine delivery).

Understanding population-level attitudes toward the global allocation of vaccines is important for several reasons. First, international organizations such as the WHO, which coordinates and allocates COVID-19 vaccines at the global level, need to ensure fair allocation and delivery of vaccines with minimal conflicts and dissatisfactions [8-10]. Knowing the public's attitudes toward the global delivery of vaccines can inform policy making and can support global policy makers to effectively mobilize international communities through their widespread support. Second, public attitudes can have a substantial impact on a country's national foreign aid policies [11]. National governments may avoid formulating foreign policies that contradict public opinions for political reasons. Third, identifying population groups with high and low support for global COVID-19 vaccine allocation is crucial for developing targeted education and communication campaigns to enhance the recognition and support for a more equitable distribution of vaccines worldwide.

We are not aware of studies exploring public attitudes toward the global allocation of locally produced COVID-19 vaccines (ie, the allocation of COVID-19 vaccines from a domestic population to a global community). Existing research on public attitudes has focused exclusively on domestic allocation of COVID-19 vaccines (ie, priority setting among population groups locally). That literature highlights the public's broad support for vaccinating medical staff first [12-16]. Within China [12], the United States [13], and Italy [14], further research suggests public support for vaccination among older adults, although a study drawing upon Belgian perspectives found support instead for those who are chronically ill, hold essential professions, or who are most likely to spread the virus [15].

Chinese COVID-19 vaccines manufactured by Sinopharm and Sinovac were listed for emergency use by the WHO in 2021 (on May 7 [17] and June 1 [18], respectively). The WHO Strategic Advisory Group of Experts has thoroughly assessed the data on quality, safety, and efficacy of the vaccine, and has recommended its use for people 18 years and older [19,20]. The immunogenicity and safety of the Chinese recombinant COVID-19 vaccine (adenovirus type 5 vector) codeveloped by CanSinoBIO and the Beijing Institute of Biotechnology have been confirmed through randomized controlled trials [21,22]. The Chinese government was among the first to pledge COVID-19 vaccines as a global public good [23]. As of October 17, 2021, China has provided more than 1.5 billion doses to more than 100 countries and international organizations as donations or as a purchased export [24]. At the same time, China is under intense pressure to meet a sizable domestic demand. To achieve an 80% vaccination rate by the end of 2021, an average of 230 million doses is required each month [25-27].

This study explores the Chinese public's attitudes toward global COVID-19 vaccine allocation. In doing so, we provide evidence to policy makers in China for formulating future strategies of global COVID-19 vaccine distribution. Furthermore, work such as this can guide similar public surveys in other COVID-19 vaccine-producing countries.

# Methods

## Sampling Process

The survey was implemented by KuRunData, an online private survey platform that maintains a database of potential survey participants and delivers surveys. KuRunData recruits members through its own platform [28] and partnerships with other websites, and by encouraging registered members to recruit new members through the popular mobile app WeChat Mini. KuRunData verifies that members have access to mobile phones and the internet, and are capable of navigating online surveys. For this study, we used KuRunData to sample approximately the same number of participants in each of China's provincial-level administrative units, with the total sample size goal being 10,000 adults. Potential participants were unable to access the questionnaire once this sample size goal was reached. Within each province, KuRunData aimed to sample a proportion of participants that was reflective of the demographic composition of the province's population (as per the 2020 China Statistical Yearbook [29]) by sex and urban-rural residence. Adults in the survey pool were invited to participate in the survey by KuRunData's own platform on a first-come-first-served basis. They were informed that they would receive between ¥2 and ¥5 (equivalent to US $0.30-$0.80) for completing the questionnaire, according to their membership level. Before filling in the questionnaire, participants had to provide their informed written consent with signature confirmation. The informed consent page described the project's background and purpose, the possible risks, the payment after completing the questionnaire, and the confidentiality of information and records. To be able to access the questionnaire, participants must have opened and scrolled through the informed consent description for at least 15 seconds and self-declared understanding the purpose and risks of the study before signing. The survey was administered between February 19 and March 28, 2021.

## Questionnaire

The questionnaire included 31 questions, partitioned into the following sections: informed consent and introduction, attitudes toward delivery and distribution of COVID-19 vaccines, and sociodemographic characteristics. The questionnaire was written in standard simplified Chinese and is shown in Multimedia Appendix 1. Participants had to answer a question to reach the next question.

## Data Quality Checks

First, we made sure that the KuRunData platform verified the time taken to complete the questionnaire to ensure that participants read questions before answering. Specifically, survey samples were deleted if the participant took less than 240 seconds or more than 900 seconds to complete the questionnaire. Second, questions included strings that tested for whether there was conflict in the respondents' logic, for example, if the age selected by the respondent is too small to match the situation of marriage, education, and occupation selected by the respondent in any possible way. A total of 243 samples were deleted because of these reasons.

## Data Analysis

All analyses used sampling weights to account for the complex survey design. The sampling weights were the inverse of the probability of selecting participants given the following variables: sex, rural versus urban residence, and province. These probabilities were calculated using population counts from the 2020 China Statistical Yearbook within each province. In the second part of the questionnaire (on attitudes toward delivery and distribution of COVID-19 vaccines), questions with multiple options were combined as binary variables. For each question, we computed the percentage of participants who selected certain options to summarize the survey findings. For binomial proportions, we constructed 2-sided 95% CIs using the Wilson score interval. To examine how attitudes varied by participants' characteristics, we regressed the binary response onto age (10-year age groups); sex; household income; educational attainment; rural versus urban residence; vocation; and whether a participant had a family member, friend, or acquaintance who they knew had been infected with COVID-19. All regressions were logistic regressions and included only one of these variables plus a binary indicator for each province (province-level fixed effects). We also performed multivariable regression to demonstrate the results with all these variables included in Multimedia Appendix 2, Table A2. In a separate analysis, we used ordinal probit regression as a robustness check and treated the response to Q4 and Q9 as ordinal variables, which takes on the values 1 to 4 for Q4 and 1 to 5 for Q9. For Q4, those with a rank of 1 have the highest willingness to provide COVID-19 vaccines to foreign countries, while those with a rank of 4 have the lowest. For Q9, those with a rank of 1 have the highest price, while those with a rank of 5 have the lowest. The related results are listed in Multimedia Appendix 2, Table A3.

## Ethics

The study was approved by the Research Ethics Commission of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (001-2021), and the Research Ethics Commission of Zhejiang University (003-2020).

# Results

## Sample Characteristics

A total of 10,000 participants were invited to take the survey. All respondents completed the whole survey. Selected participants' sociodemographic characteristics are shown in Table 1, and the full table is listed in Multimedia Appendix 2, Table A1. A total of 4921 females and 5079 males completed the questionnaire. In the survey sample, 9% (900) of the participants were aged 18 or 19 years, the majority (n=7250, 72.5%) were aged 20-59 years, and 18.5% (n=1850) were 60 years or older. Only one-tenth (n=1063, 10.6%) of participants had never been to school or only been to elementary school. About one-third (n=3512, 35.1%) of participants had received high school or technical secondary school education, and one-third (n=3371, 33.7%) had completed an undergraduate degree. Most the of participants (n=9444, 94.4%) were of *Han* ethnicity. A majority of participants (n=5935, 59.4%) lived in urban areas. About 1.7% (n=171) of participants worked as a health care provider, including nurses (n=35, 0.4%), physicians (n=46, 0.5%), community health workers (n=51, 0.5%), pharmacists (n=13, 0.1%), and “other” health care providers (n=26, 0.3%).

**Table 1.** Sociodemographic characteristics of the survey participants.

| Characteristic | Survey participants | | Population of China[a] (%) |
|---|---|---|---|
| | Proportion (weighted %)[b] | Participants, n (%) | |
| **Sex** | | | |
| Female | 48.9 | 4921 (49.2) | 48.9 |
| **Age group (years)** | | | |
| <20 | 10.1 | 900 (9.0) | 21.9 |
| 20-29 | 17.2 | 1645 (16.5) | 13.1 |
| 30-39 | 17.4 | 1895 (19.0) | 15.7 |
| 40-49 | 20.3 | 1890 (18.9) | 15.8 |
| 50-59 | 17.7 | 1820 (18.2) | 15.3 |
| ≥60 | 17.3 | 1850 (18.5) | 18.1 |
| **Rural-urban residency** | | | |
| Urban | 61.1 | 5935 (59.4) | 60.6 |
| **Works as a health care provider** | | | |
| No | 98.3 | 9829 (98.3) | 99.1 |
| Nurse | 0.4 | 35 (0.4) | 0.3 |
| Physician | 0.5 | 46 (0.5) | 0.3 |
| Community health worker | 0.4 | 51 (0.5) | <0.1 |
| Pharmacist | 0.1 | 13 (0.1) | <0.1 |
| Other health care provider | 0.3 | 26 (0.3) | 0.2 |

[a] As per the 2020 China Statistical Yearbook.

[b] Weighted using survey sampling weights.

## Attitude Toward Global Allocation of Chinese COVID-19 Vaccines

As shown in Table 2, about three-quarters of participants (75.6%, 95% CI 74.6%-76.5%) agreed to provide COVID-19 vaccines to foreign countries before fulfilling all domestic needs. Most participants (64.4%, 95% CI 63.3%-65.4%) preferred providing COVID-19 vaccines as a more appropriate way to aid foreign countries compared with offering financial support or sending medical teams. In terms of financial support, participants preferred providing assistance through international platforms (72.1%, 95% CI 71%-73.1%) rather than directly offering assistance to the foreign countries. If COVID-19 vaccines were provided to foreign countries, countries that have diplomatic relations with China were considered as the priority by 56.6% (95% CI 55.5%-57.7%) of participants. Considering the way to deliver vaccines to foreign countries, 77.3% (95% CI 76.3%-78.2%) of participants preferred to provide vaccine products (finished vaccine products or transferring vaccine technology) directly to relevant countries instead of providing vaccines via a delivery platform like COVAX. Less than one-quarter of participants (22.7%, 95% CI 21.8%-23.7%) agreed to provide COVID-19 vaccines to foreign countries at the same or even lower than the cost, and over one half (56.5%, 95% CI 55.4%-57.6%) kept the view that the Chinese government should bear a larger proportion of the cost.

**Table 2.** Summary of survey findings.

| Survey question, combined response, and original response | Proportion, % (95% CI) |
|---|---|
| **In your opinion, if there is a shortage of Chinese COVID-19 vaccines, how should the domestic and international demand first be met?** | |
| **Provide to foreign countries before satisfying all domestic needs** | |
| The vaccination needs of global (both domestic and abroad) high-risk and high-danger groups should be met first before other needs are taken into consideration. | 19.9 (19.0-20.8) |
| The vaccination needs of domestic high-risk and high-danger groups should be met first before the vaccination needs abroad are supported. | 55.7 (54.6-56.8) |
| **Satisfy the vaccination needs of all Chinese people before providing to others** | |
| The vaccination needs of all domestic groups should be met first before the vaccination needs abroad are supported. | 22.7 (21.8-23.6) |
| Only the domestic vaccination needs should be met, and the remaining vaccines should be taken as national strategic reserves without supporting the vaccination needs abroad. | 1.8 (1.5-2.1) |
| **In response to the COVID-19 global pandemic, what do you think China should first consider in providing assistance to relevant countries?** | |
| **To provide COVID-19 vaccines developed by Chinese scientific research institutions and enterprises** | |
| Providing COVID-19 vaccines | 64.3 (63.3-65.4) |
| **To provide financial support, medical teams, or others** | |
| Providing financial aid | 13.5 (12.8-14.3) |
| Send medical teams | 18.6 (17.7-19.5) |
| Others, please specify | 1.0 (0.8-1.3) |
| None of the above | 2.5 (2.2-2.9) |
| **If COVID-19 vaccines that are developed by Chinese research institutions and companies are to support foreign countries, which countries do you think should be most supported?** | |
| **Friendly countries that have diplomatic relations with China** | |
| Countries with friendly diplomatic relations | 56.7 (55.4-57.7) |
| **Low-income countries, countries in need, or countries suggested by the WHO[a] to support** | |
| Lowest-income countries | 6.0 (5.5-6.6) |
| Any countries in need | 21.0 (20.1-21.9) |
| Countries recommended to be supported by the WHO | 16.4 (15.6-17.2) |
| **In response to the COVID-19 global pandemic, what do you think China should first consider if it were to provide financial aid to other countries?** | |
| **To provide financial support directly to foreign countries** | |
| Donate the funds to the designated country, and the government of the recipient country will arrange its own pandemic prevention efforts | 27.9 (26.9-29.0) |
| **To provide financial support via authoritative international organizations or specialized organizations** | |
| Donate the funds to international organizations (eg, the WHO) for comprehensive arrangement and coordination of the response to the pandemic | 42.6 (41.5-43.8) |
| Donate the funds to specialized vaccine organizations (eg, the GAVI[b] Alliance) to purchase COVID-19 vaccines for less-developed countries | 29.4 (28.4-30.5) |
| **What plan do you think China should prioritize if it were to provide the Chinese COVID-19 vaccines to other countries?** | |
| **To provide finished vaccine products directly to foreign countries, or to transfer vaccine technology to relevant countries to allow local production** | |
| Plan A: Directly providing vaccine products to relevant countries | 61.2 (60.1-62.3) |
| Plan B: Provide vaccine technology transfer to relevant countries and have their local enterprises produce the vaccines | 16.1 (15.3-16.9) |
| **To provide vaccines via the delivery platform of authoritative international organizations** | |
| Plan C: Leverage the vaccine delivery platforms of international professional organizations | 22.7 (21.8-23.7) |

| Survey question, combined response, and original response | Proportion, % (95% CI) |
|---|---|
| **In your opinion, at what price should the COVID-19 vaccines developed by the Chinese scientific institutions and enterprises be provided to foreign countries?** | |
| **At market price or a small profit** | |
| Market price | 39.9 (38.8-41.0) |
| A price with meager profits | 37.4 (36.3-38.5) |
| **At or even lower than cost price** | |
| Cost price | 18.0 (17.1-18.9) |
| A price with meager loss | 1.4 (1.2-1.7) |
| Free of charge | 3.3 (2.9-3.8) |
| **If the Chinese COVID-19 vaccines are priced below cost, who should bear the price loss when the vaccines are foreigners who are receiving foreign aid?** | |
| **The government should bear a larger proportion of the loss than the enterprise.** | |
| All borne by the enterprises | 3.1 (2.8-3.5) |
| Most borne by the enterprises and partially borne by the Chinese government | 19.2 (18.3-20.1) |
| Equally borne by the enterprises and the Chinese government | 21.2 (20.3-22.1) |
| **The enterprise should bear a larger proportion of the loss than the government.** | |
| Most borne by the Chinese government and partially borne by the enterprises | 36.9 (35.8-38.0) |
| All borne by the Chinese government | 19.7 (18.8-20.6) |

[a] WHO: World Health Organization.

[b] GAVI: Global Alliance for Vaccines and Immunizations.

### Variation in Attitude Toward International Delivery of COVID-19 Vaccines by Sociodemographic Characteristics

Regarding the willingness to provide COVID-19 vaccines to foreign countries, participants who were female and living in a rural area tended to agree that COVID-19 vaccines can be provided to foreign countries before fulfilling all domestic needs (Table 3). Females were 1.18 (95% CI 1.07-1.32) times more likely than males to agree to provide COVID-19 vaccines to foreign countries. The probability that urban residents agreed was 0.89 (95% CI 0.79-0.99) that of rural residents. Multivariate regression and ordered logistic regression results showed the same results (see Multimedia Appendix 2, Tables A2 and A3).

In terms of COVID-19 vaccine pricing, urban residents and higher annual household income groups were more inclined to believe that COVID-19 vaccines should be provided abroad at market price, instead of at a lower price or free of charge (Table 3). The probability that urban residents agreed to provide COVID-19 vaccines abroad at a low price or free of charge was 0.88 (95% CI 0.78-0.98) that of rural residents. The probability that people whose annual household income was ¥90,000-¥119,999 (US $14,229-$18,972) agreed to provide COVID-19 vaccines abroad at a low price or free of charge was 0.62 (95% CI 0.49-0.80) that of the <¥ 30,000 (US $4743) income group. In multivariate regression, rural-urban residency was not significant, which might be explained by the collinearity between annual household income and rural-urban residency (see Multimedia Appendix 2, Table A2). The ordered logistic regression result showed the same results (see Multimedia Appendix 2, Table A3).

**Table 3.** Variation in attitude toward international delivery of COVID-19 vaccines by sociodemographic characteristics.[a]

| Characteristic | Supporting COVID-19 vaccine provision to foreign countries before fulfilling all domestic needs[b] | | | Supporting COVID-19 vaccines as low-priced or free global public goods[c] | | |
|---|---|---|---|---|---|---|
| | Participants, n (%) | OR[d] (95% CI) | *P* value | Participants, n (%) | OR (95% CI) | *P* value |
| **Sex** | | | | | | |
| Male (n=5079) | 3779 (74.4) | 1 (ref) | N/A[e] | 1110 (21.9) | 1 (ref) | N/A |
| Female (n=4921) | 3778 (76.8) | 1.18 (1.07-1.32) | .002 | 1147 (23.3) | 1.10 (0.98-1.22) | .10 |
| **Age group (years)** | | | | | | |
| 18-19 (n=900) | 724 (80.4) | 1 (ref) | N/A | 227 (25.2) | 1 (ref) | N/A |
| 20-29 (n=1645) | 1299 (79.0) | 0.84 (0.67-1.05) | .13 | 371 (22.6) | 0.87 (0.70-1.08) | .21 |
| 30-39 (n=1895) | 1400 (73.9) | 0.67 (0.54-0.84) | <.001 | 441 (23.3) | 0.88 (0.71-1.09) | .24 |
| 40-49 (n=1890) | 1400 (74.1) | 0.69 (0.55-0.85) | .001 | 437 (23.1) | 0.89 (0.73-1.10) | .29 |
| 50-59 (n=1820) | 1375 (75.5) | 0.72 (0.58-0.90) | .004 | 383 (21.0) | 0.75 (0.61-0.93) | .009 |
| >60 (n=1850) | 1359 (73.5) | 0.64 (0.52-0.80) | <.001 | 398 (21.5) | 0.80 (0.65-0.99) | .04 |
| **Annual household income (¥)** | | | | | | |
| <30,000 (n=572) | 419 (73.3) | 1 (ref) | N/A | 173 (30.2) | 1 (ref) | N/A |
| 30,000-59,999 (n=1307) | 1013 (77.5) | 1.25 (0.97-1.61) | .09 | 306 (23.4) | 0.72 (0.56-0.93) | .01 |
| 60,000-89,999 (n=1929) | 1458 (75.6) | 1.18 (0.93-1.51) | .18 | 459 (23.8) | 0.72 (0.57-0.92) | .008 |
| 90,000-119,999 (n=1726) | 1311 (76.0) | 1.25 (0.98-1.60) | .07 | 386 (22.4) | 0.62 (0.49-0.80) | <.001 |
| 120,000-149,999 (n=1726) | 1317 (76.3) | 1.25 (0.97-1.60) | .08 | 385 (22.3) | 0.64 (0.50-0.82) | <.001 |
| 150,000-199,999 (n=1882) | 1407 (74.8) | 1.17 (0.91-1.49) | .22 | 364 (19.3) | 0.56 (0.44-0.72) | <.001 |
| ≥200,000 (n=858) | 632 (73.7) | 1.08 (0.82-1.43) | .58 | 184 (21.4) | 0.56 (0.42-0.75) | <.001 |
| **Education** | | | | | | |
| Never been to school (n=526) | 398 (75.7) | 1 (ref) | N/A | 123 (23.4) | 1 (ref) | N/A |
| Elementary school (n=537) | 391 (72.8) | 0.79 (0.57-1.10) | .16 | 119 (22.2) | 1.10 (0.78-1.54) | .59 |
| Middle school (n=1753) | 1318 (75.2) | 0.97 (0.74-1.27) | .83 | 384 (21.9) | 1.04 (0.79-1.37) | .77 |
| High school/technical secondary school (n=3512) | 2679 (76.3) | 1.02 (0.79-1.32) | .87 | 831 (23.7) | 1.14 (0.88-1.47) | .32 |
| College/undergraduate (n=3371) | 2534 (75.2) | 1.00 (0.78-1.29) | .99 | 731 (21.7) | 0.96 (0.74-1.24) | .76 |
| Graduate and above (n=301) | 237 (78.7) | 1.20 (0.80-1.81) | .37 | 69 (22.9) | 1.03 (0.69-1.53) | .89 |
| **Rural-urban residency** | | | | | | |
| Rural (n=4065) | 3123 (76.8) | 1 (ref) | N/A | 970 (23.9) | 1 (ref) | N/A |
| Urban (n=5935) | 4434 (74.7) | 0.89 (0.79-0.99) | .03 | 1287 (21.7) | 0.88 (0.78-0.98) | .02 |
| **Works as a health care provider** | | | | | | |
| No (n=9829) | 7418 (75.5) | 1 (ref) | N/A | 2212 (22.5) | 1 (ref) | N/A |
| Nurse (n=35) | 30 (85.7) | 2.44 (0.89-6.66) | .08 | 12 (34.3) | 1.72 (0.79-3.73) | .17 |
| Physician (n=46) | 38 (82.6) | 1.00 (0.43-2.36) | .99 | 10 (21.7) | 1.09 (0.49-2.43) | .83 |
| Community health worker (n=51) | 40 (78.4) | 1.06 (0.49-2.26) | .89 | 13 (25.5) | 1.28 (0.63-2.61) | .49 |
| Pharmacist (n=13) | 10 (76.9) | 1.13 (0.30-4.30) | .86 | 4 (30.8) | 1.25 (0.34-4.56) | .74 |
| Other health care provider (n=26) | 21 (80.8) | 1.40 (0.51-3.88) | .51 | 6 (23.1) | 0.79 (0.30-2.12) | .64 |
| **Knows someone with a confirmed SARS-CoV-2 infection** | | | | | | |
| No (n=9972) | 7537 (75.6) | 1 (ref) | N/A | 2253 (22.6) | 1 (ref) | N/A |
| Self (n=3) | 2 (66.7) | 1.22 (0.11-14.11) | .87 | 0 (0.0) | 0.00 (0.00-0.00) | <.001 |
| Family member (n=3) | 2 (66.7) | 0.48 (0.04-5.57) | .56 | 0 (0.0) | 0.00 (0.00-0.00) | <.001 |

| Characteristic | Supporting COVID-19 vaccine provision to foreign countries before fulfilling all domestic needs[b] | | | Supporting COVID-19 vaccines as low-priced or free global public goods[c] | | |
|---|---|---|---|---|---|---|
| | Participants, n (%) | OR[d] (95% CI) | *P* value | Participants, n (%) | OR (95% CI) | *P* value |
| Friend (n=8) | 6 (75.0) | 1.00 (0.19-5.23) | >.99 | 3 (37.5) | 1.85 (0.39-8.73) | .44 |
| Neighbor (n=3) | 2 (66.7) | 1.03 (0.08-13.07) | .98 | 0 (0.0) | 0.00 (0.00-0.00) | <.001 |
| Coworker (n=3) | 1 (33.3) | 0.05 (0.00-0.56) | .02 | 1 (33.3) | 3.16 (0.29-34.90) | .35 |
| Others (n=8) | 7 (87.5) | 8.43 (1.03-69.13) | .047 | 0 (0.0) | 0.00 (0.00-0.00) | <.001 |

[a] All regressions included only one of the variables (sex; age group; income; education; rural-urban residency; vocation; whether or not a participant has a family member, friend, or acquaintance who they know to have been infected with SARS-CoV-2) shown in the table and a binary indicator for each province (province-level fixed effects).

[b] "Satisfy the vaccination needs of all Chinese people before providing to others" is the reference response.

[c] "At market price or a small profit" is the reference response.

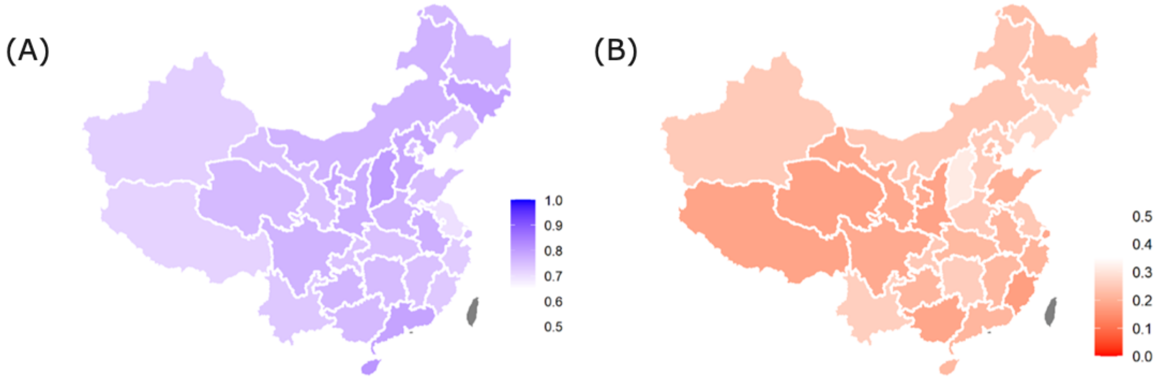
[d] OR: odds ratio.

[e] N/A: not applicable.

### Geographical Differences in People's Attitude Toward International Delivery of COVID-19 Vaccines

There was a moderate degree of geographical variation in peoples' attitudes toward international delivery of COVID-19 vaccines. The percentage of the population that supported provision of COVID-19 vaccines to foreign countries before fulfilling all domestic needs ranged from 69.7% (95% CI 64.8%-74.3%) in Jiangsu Province to 81% (95% CI 76.2%-85.1%) in Hainan Province (Figure 1a), and the percentage of the population that favored provision of COVID-19 vaccines at a low-price or as a free global public good ranged from 17.3% (95% CI 13.4%-22.1%) in Fujian Province to 31.2% (95% CI 26.2%-36.7%) in Shanxi Province (Figure 1b). As for Hubei Province, which was first exposed to serious COVID-19 prevalence in early 2020, the proportion of the above two questions were 74.4% (95% CI 69.1%-79%) and 22% (95% CI 17.7%-27%), respectively, and were among the middle of the geographical difference. There was a low degree of regional variation in people's attitudes toward other questions on international delivery of COVID-19 vaccines, as detailed in Multimedia Appendix 2, Figure A1.

**Figure 1.** The proportion of the population by province (A) supporting COVID-19 vaccine provision to foreign countries before fulfilling all domestic needs and (B) supporting COVID-19 vaccines as low-priced or free global public goods.



## Discussion

This study investigated population-level attitudes toward the global allocation of Chinese COVID-19 vaccines based on a large-scale online survey. Our study has four main findings. First, in general, the Chinese public strongly supports the provision of domestic vaccines as international assistance—even if herd immunity has not been achieved domestically. Second, participants had mixed preferences regarding multilateral and bilateral international assistance. In terms of financial support, most people preferred donation to international organizations such as the WHO rather than directly to specific countries; regarding COVID-19 vaccines on the other hand, most participants preferred direct bilateral provision of vaccines to relevant countries. Third, female participants and those living in a rural area tended to state a higher willingness to provide Chinese COVID-19 vaccines abroad. This may be because rural areas are vast, and participants from rural areas face a lower risk of COVID-19 than urban areas, but further research is necessary to determine a rationale. Fourth, participants with a high household income had a lower willingness to provide Chinese COVID-19 vaccines to foreign countries at low prices or free of charge compared to lower-income individuals.

Several factors may explain Chinese adults' support for international vaccine assistance. First, China has thus far contained the epidemic through a series of nonpharmaceutical interventions such as prompt physical distancing [30,31]; an effective test, trace, and isolate system [32]; the adoption of facility-based isolation, widely used in Asia, but not in Western countries [33-36]; and clear communication and education

[37,38]. As such, existing research has highlighted how Chinese residents often do not view themselves as “desperately needing” vaccination [39]. Second, the Chinese public receive messages from domestic key opinion leaders [40,41] as well as news from the national media and the WHO [42] that the virus causing COVID-19 will not disappear in the short term and is likely to circulate worldwide [43,44], and that the only way to end the global pandemic is through global collaboration to jointly contain the epidemic in all countries. Third, China has committed at the 2020 World Health Assembly to make Chinese vaccines a global public good and to ensure that they are provided to low- and middle-income countries at an affordable price [45]. This announcement that was widely reported via domestic channels [46-48] may have affected the attitudes of the Chinese public.

Participants in this study preferred providing funding via global institutions such as the WHO instead of direct bilateral economic aid during the pandemic, but in terms of COVID-19 vaccines, they preferred direct support to foreign countries. Scholars have used principal-agent theory to explain people’s preference toward multilateral or bilateral foreign aid and found that people often prefer multilateral foreign aid because they think it is a way to share responsibilities mutually with partner countries through the platform of international organizations. On the other hand, people often prefer bilateral aid because they think their country can have more control over the aid [11]. However, previous studies did not distinguish people’s attitudes on different aid categories such as direct economic aid or products. Based on these findings, we suggest that the Chinese public may recognize the benefit of providing financial support to the WHO because international health assistance requires collective action. However, the Chinese public may regard providing vaccines as a specific task, such that the advantage of delegation does not appear to outweigh the cost of foregoing the opportunity of choosing recipient countries.

Although people from different countries may have divergent views, the evidence from China suggests public support for international vaccine assistance. This finding has important policy implications for current global vaccine delivery and allocation work that could be particularly relevant for global policy makers within the WHO and in countries with considerable capability to produce vaccines. Although some policy approaches reflect a desire to complete domestic vaccination first before considering international assistance and exports [49], the evidence from China implies that the public may have different views—preferring instead to address international demand regardless of whether domestic herd immunity has been reached. Scientists and academics in other countries or anybody who is neutral in this matter could conduct national surveys to explore the public’s view. If the public supports the international assistance or export of COVID-19 vaccines, politicians may feel encouraged to stop stockpiling vaccines.

In addition, this research provides evidence for global policy makers such as the WHO to encourage and call on more countries to provide vaccine assistance in the name of public support. To date, the WHO and other global leaders working within COVAX have called on governments and the private sector to facilitate the global distribution and contribution of COVID-19 vaccines in an equitable way [50,51], but they have not yet appealed to the public. This research suggests that a majority of the Chinese public support international assistance with COVID-19 vaccination and that the public sees merit in financial support to the WHO during the pandemic. Regular global surveys on such preferences among the public of different nations could inform global leaders when making decisions about financial or in-kind support.

While a strength of this study is its nationwide coverage and relatively large sample size of 10,000 participants, it also has several important limitations. First, the survey was restricted to China, and thus, our findings may not be transferable to other countries or regions. Second, our sample of participants is unlikely to be representative of the general population in China because individuals had to be registered with KuRunData to be eligible for this study and were invited to participate on a first-come-first-served basis. Third, social desirability bias could have influenced participants to answer in ways that they thought they should, rather than how they truly felt.

In conclusion, participants in this online survey were generally supportive of the national government’s provision of domestically produced vaccines to other countries. However, preferences varied somewhat between population subgroups. Our findings could be useful for global and national policy makers as they seek to facilitate an equitable global allocation of COVID-19 vaccines.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire text in English and Chinese.
[DOCX File , 63 KB - publichealth_v8i6e33484_app1.docx ]

Multimedia Appendix 2
Supplementary material.
[DOCX File , 7920 KB - publichealth_v8i6e33484_app2.docx ]

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## Abbreviations

**GAVI:** Global Alliance for Vaccines and Immunizations
**WHO:** World Health Organization

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Original Paper

# Testing the Efficacy of Attitudinal Inoculation Videos to Enhance COVID-19 Vaccine Acceptance: Quasi-Experimental Intervention Trial

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## Abstract

**Background:** Over the course of the COVID-19 pandemic, a variety of COVID-19-related misinformation has spread and been amplified online. The spread of misinformation can influence COVID-19 beliefs and protective actions, including vaccine hesitancy. Belief in vaccine misinformation is associated with lower vaccination rates and higher vaccine resistance. Attitudinal inoculation is a preventative approach to combating misinformation and disinformation, which leverages the power of narrative, rhetoric, values, and emotion.

**Objective:** This study seeks to test inoculation messages in the form of short video messages to promote resistance against persuasion by COVID-19 vaccine misinformation.

**Methods:** We designed a series of 30-second inoculation videos and conducted a quasi-experimental study to test the use of attitudinal inoculation in a population of individuals who were unvaccinated (N=1991). The 3 intervention videos were distinguished by their script design, with intervention video 1 focusing on narrative/rhetorical ("Narrative") presentation of information, intervention video 2 focusing on delivering a fact-based information ("Fact"), and intervention video 3 using a hybrid design ("Hybrid"). Analysis of covariance (ANCOVA) models were used to compare the main effect of the intervention on the 3 outcome variables: ability to recognize misinformation tactics ("Recognize"), willingness to share misinformation ("Share"), and willingness to take the COVID-19 vaccine ("Willingness").

**Results:** There were significant effects across all 3 outcome variables comparing inoculation intervention groups to controls. For the Recognize outcome, the ability to recognize rhetorical strategies, there was a significant intervention group effect (P<.001). For the Share outcome, support for sharing the mis- and disinformation, the intervention group main effect was statistically significant (P=.02). For the Willingness outcome, there was a significant intervention group effect; intervention groups were more willing to get the COVID-19 vaccine compared to controls (P=.01).

**Conclusions:** Across all intervention groups, inoculated individuals showed greater resistance to misinformation than their noninoculated counterparts. Relative to those who were not inoculated, inoculated participants showed significantly greater ability to recognize and identify rhetorical strategies used in misinformation, were less likely to share false information, and had greater willingness to get the COVID-19 vaccine. Attitudinal inoculation delivered through short video messages should be tested in public health messaging campaigns to counter mis- and disinformation.

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**KEYWORDS**

attitudinal inoculation; intervention; COVID-19 vaccine; vaccine hesitancy; COVID-19; vaccine; vaccination; public health; health intervention; misinformation; infodemiology; vaccine misinformation

## Introduction

The study of misinformation and disinformation and how to counter them is not new. There are centuries-old examples of the challenges in rebutting misleading or manipulative information [1-3]. However, although false and manipulative media are not new, “the digital age has changed how such messages are created, circulated, and interpreted, as well as their potential effects” [4]. As features of the COVID-19 media ecosystem, misinformation and disinformation are functionally similar, in that both either contradict or distort the current scientific and public health consensus as to the nature of the virus and appropriate steps to combat it [5,6]. However, the 2 terms refer to separate phenomena insofar as concerns motive. “Misinformation” is unintentionally inaccurate, while “disinformation,” is intentionally inaccurate and meant to mislead [7]. In the context of public health, the term “infodemic” was coined to refer to “an overflow of information of varying quality that surges across digital and physical environments during an acute public health event” [8]. Infodemiology, as a field of study and intervention, dates back to 1996 [9,10]. Eysenbach defines infodemiology as the “science of distribution and determinants of information in an electronic medium, specifically the Internet, or in a population, with the ultimate aim to inform public health and public policy” [9]. As Eysenbach describes it, infodemiology rests on the premise that public health and patterns of communication are correlated, and perhaps even causally connected.

Since the pandemic’s beginning, a variety of COVID-19-related misinformation and disinformation has spread and been amplified online [11]. The content and spread of misinformation can influence COVID-19 beliefs and protective actions [12,13]. Despite the availability of the COVID-19 vaccine in the United States, hesitancy among the general population remains a challenge. In their review of 39 nationally representative polls taken in the first half of 2021, Steelfisher et al [14] found that nearly 30% of the population remains hesitant to get the COVID-19 vaccine. Belief in vaccine misinformation is associated with lower vaccination rates and higher vaccine resistance [15]. The spread of misinformation and disinformation online can increase COVID-19 vaccine hesitancy [16]. Studies conducted at varying time points in 2020 have found that reliance on social media is associated with higher levels of holding both conspiracy beliefs and higher levels of vaccine hesitancy [17-20].

Studies of how to address the current infodemic are nascent. The inaugural World Health Organization (WHO) Infodemiology Conference of 2021 called for more research on interventions to address the infodemic [11]. Countering misinformation is a critical piece of infodemic management because misinformation impacts protective actions and vaccine hesitancy. Infodemiology research has shown that quality health information can be elusive to the public, especially in evolving situations, such as a pandemic [21]. One common approach used by public health risk communicators focuses on “facts.” However, as Eysenbach [21] points out, in times of evolving science, factual information can be hard to determine, and initial reports and decisions are made based on the best information available at any given time. Currently, the most common approach to countering misinformation is to engage in fact checking. Research evaluating the utility of online fact checking suggests that even under less uncertain conditions, it remains an uneven but relatively effective counterstrategy to disinformation [22-26]. However, fact checking carries with it 2 challenges: asymmetry and volume. Feelings of social ostracism are shown to decrease receptivity to counter disinformation fact checking [27]. Media consumers with less overall political knowledge are likewise less receptive, as are political conservatives more generally [28]. Meanwhile, the sheer volume with which bad actors are increasingly equipped to “flood the zone” with mis- and disinformation [29] can exhaust most audience’s ability to sift good information from bad, apart from more formal, time-and-resource-intensive fact-checking projects. Human moderators cannot match the speed and volume of false information and, furthermore, require an ever-changing range of subject expertise that content moderators cannot reasonably be expected to acquire [30,31]. Studies into the relative efficacy of logic-based versus emotionally based public health communication have suggested that the use of narrative [32-34], appeals to values [35,36], and rhetoric of personal, lived experience [37-39] yield better persuasive outcomes than more abstract, fact-based, or logical counterparts. Per Maertens et al [40], this might relate to the “broad spectrum” of potential viewpoints that such approaches address. That is, fact checking’s narrower focus on specific *content* addresses fewer points of persuasive vulnerability than a broader focus on *form* offered by rhetoric, narrative, and values.

Attitudinal inoculation (or, simply, “inoculation”) is a preventative approach to combating misinformation and disinformation that leverages the power of narrative, rhetoric, values, and emotion. Inoculation theory promises that people can become resistant to persuasion if they perceive a threat from an attempt to change their beliefs or attitudes and if they receive information to refute this attempt [41]. It originates in the midcentury work of William McGuire [41-43]. It uses the biological metaphor of viral inoculation to propose that “[t]hrough exposing individuals to messages containing a weakened argument against an attitude they hold, it is possible to ‘inoculate’ the individuals against future attacks on the attitude” [44]. Inoculation consists of exposing someone to a persuasive message that contains weakened arguments against an established attitude, which develops resistance against stronger persuasive attacks in the future [41].

Inoculation is preemptive, addressing audiences holding “healthy (ie, preferred) positions,” or agnostic and undecided [45]. It scales against the “flooded zone” of information, allowing individuals to bypass entire categories of misleading, manipulative, or simply distracting information. Inoculation is suited to address the needs of low-information audiences, ideologically polarized and conspiratorial groups, and groups that are traditionally difficult audiences to reach with corrections [46]. Inoculation may partially overcome the post hoc correction challenges of asymmetry and volume, while accounting for variations in the efficacy of fact-based versus narrative/rhetoric-based approaches.

Studies have supported the effectiveness of attitudinal inoculation as a tool for strengthening resistance to persuasion on public health topics, such as underage alcohol consumption, adolescent smoking initiation, deceptive nutrition-related food claims, unprotected sex, and child vaccine safety claims [47,48]. Additionally, attitudinal inoculation has been shown as an effective strategy for counterradicalization. In a foundational study, inoculation conferred resistance to persuasion by far-right and far-left extremist propaganda by reducing the credibility of the extremist groups that produced the propaganda and increasing reactance (the combination of anger and counterarguing) against the propaganda itself. By reducing source credibility and increasing reactance, inoculation ultimately reduced participant intentions to support the group that produced the propaganda [49].

The potential for attitudinal inoculation to combat COVID-19 vaccine misinformation was proposed by van der Linden et al [50]. Although attitudinal inoculation enjoys a rich body of literature, and infodemiology likewise can claim extensive source material, the specific application of both approaches to the crisis of the COVID-19 pandemic is scant at best. This study is among the first to answer the call made by van der Linden et al [50]. It not only sought to test the effectiveness of attitudinal inoculation against COVID-19 misinformation and disinformation but also attempted to address questions relating to persuasive communication, which bear direct relevance to the matter of public health communication in the pandemic. As described before, the relative efficacy of fact versus narrative or rhetoric in persuasive messaging has been studied across many dimensions of public health. Our study testing the use of video-based attitudinal inoculation to inoculate viewers against misinformation on COVID-19 vaccine injury is the first of its kind to compare the effectiveness of using facts versus narrative-rhetoric approaches to attitudinal inoculation messages relating to COVID-19 vaccine misinformation and disinformation. The goal of our research was to build upon the work of Braddock, van der Linden, and other inoculation theorists by using inoculation messages in the form of short video messages to promote resistance against persuasion by COVID-19 vaccine misinformation.

## *Methods*

### Identification of Antivax Narratives

This study was built upon our formative evaluation work that identified common rhetorical strategies and COVID-19 vaccine misinformation narratives and used formative surveys to explore their prevalence and validate select survey items that were used in this study [20,51,52]. The narratives were identified by analyzing 6 months of content from 10 online channels of antivaccine or COVID-19 denialist propaganda. These took the form of Twitter accounts, amateur videos, documentaries, Facebook groups, blogs, and Instagram pages. From these media sources, we created a list of 22 key narrative tropes and 16 rhetorical strategies, which represented the discursive foundation of the antivaccine and COVID-19 denialist media data collected, and created a codebook [53]. Narratives ranged from general claims that the COVID-19 vaccine could cause physical injury to the theory it was a bioweapon promoted by intelligence agencies for shadowy and perhaps even supernatural purposes. Some rhetorics framed their arguments along the lines of bodily autonomy by co-opting the language of women’s reproductive rights, while others relied on audio-visual cues, such as nauseating colors and low-frequency sounds, to cue unease in their audience.

### Development of Inoculation Messages

Based on the identification of the antivax narratives, we selected a prominent metanarrative related to vaccine injury that was used to develop 3 different inoculation messages: (1) a fact-based video, focused on countering false statistics about the science and safety of vaccines; (2) a narrative and rhetoric-focused video, which “prebunked” (ie, practice of countering potential misinformation by warning people against it before it is disseminated) common antivaccine misinformation strategies; and (3) a hybrid video that tested a combination of factual rebuttal with narrative/rhetorical prebunking. These 3 approaches were selected in order to deepen understanding of the relative efficacy of fact-based and narrative/rhetoric-based persuasion. As discussed before, the relative efficacy of each approach has been addressed across a variety of fields, from extremist deradicalization to public health.

### Development of Inoculation Videos

We designed a series of 30-second inoculation videos and conducted a quasi-experimental study to test the use of attitudinal inoculation in a population of individuals who were unvaccinated. We developed 3 inoculation videos. Each 30-second video contained a “microdose,” a weakened example of manipulation, which has been shown not to cause harm in a controlled research setting. The microdoses, while weakened, constitute an “active threat” that let people generate cognitive “antibodies” [40,54,55]. The differences between the 3 inoculation videos are shown in Table 1.

**Table 1.** Description of video types.

| Video types | Purpose | Example of video script |
|---|---|---|
| Narrative and rhetoric inoculation | Inoculate viewers against vaccine misinformation strategies, such as manipulation, scapegoating, or conspiratorial reasoning. | • "Sometimes, people trying to change your mind this way will show pictures of needles, crying babies, or extreme close-ups of viruses. Sometimes, they'll make videos with sounds that are scientifically proven to provoke a feeling of unease in humans. Strange, but true!" |
| Factual rebuttal inoculation | Counter false information about science and safety about vaccines. | • "Sometimes, these people talk about 'vaccine injury'. Actual injuries related to vaccines are extremely rare. Only two out of every one million people who received vaccine results even claimed to have been injured. Of those claims, about a third turned out not to be actual injuries related to vaccines." |
| Hybrid | Combine fact-based information and inoculation against misinformation strategies. | • "Sometimes, these people talk about 'vaccine injury'. Actual injuries related to vaccines are so rare, you are nearly twice as likely to be struck by lightning."<br>• "Actual injuries related to vaccines are extremely rare. You are 769 times more likely to die from COVID than to experience any vaccine injury."<br>• "Sometimes, people trying to change your mind this way will show pictures of needles, crying babies, or extreme close-ups of viruses. Sometimes, they'll make videos with sounds that are scientifically proven to provoke a feeling of unease in humans. Strange, but true!" |

## Study Hypothesis

Based upon our prior research on the relationship between knowledge, attitude, and behavior, we posited 3 hypotheses:

- Hypothesis 1: Relative to noninoculated participants, inoculated participants will demonstrate a greater ability to identify rhetorical strategies typically used in mis- and disinformation videos.
- Hypothesis 2: Relative to noninoculated participants, inoculated participants will be less likely to report engaging in behaviors that support the spread of COVID-19 mis- and disinformation videos.
- Hypothesis 3: Relative to noninoculated participants, inoculated participants will report greater intention to get vaccinated against COVID-19.

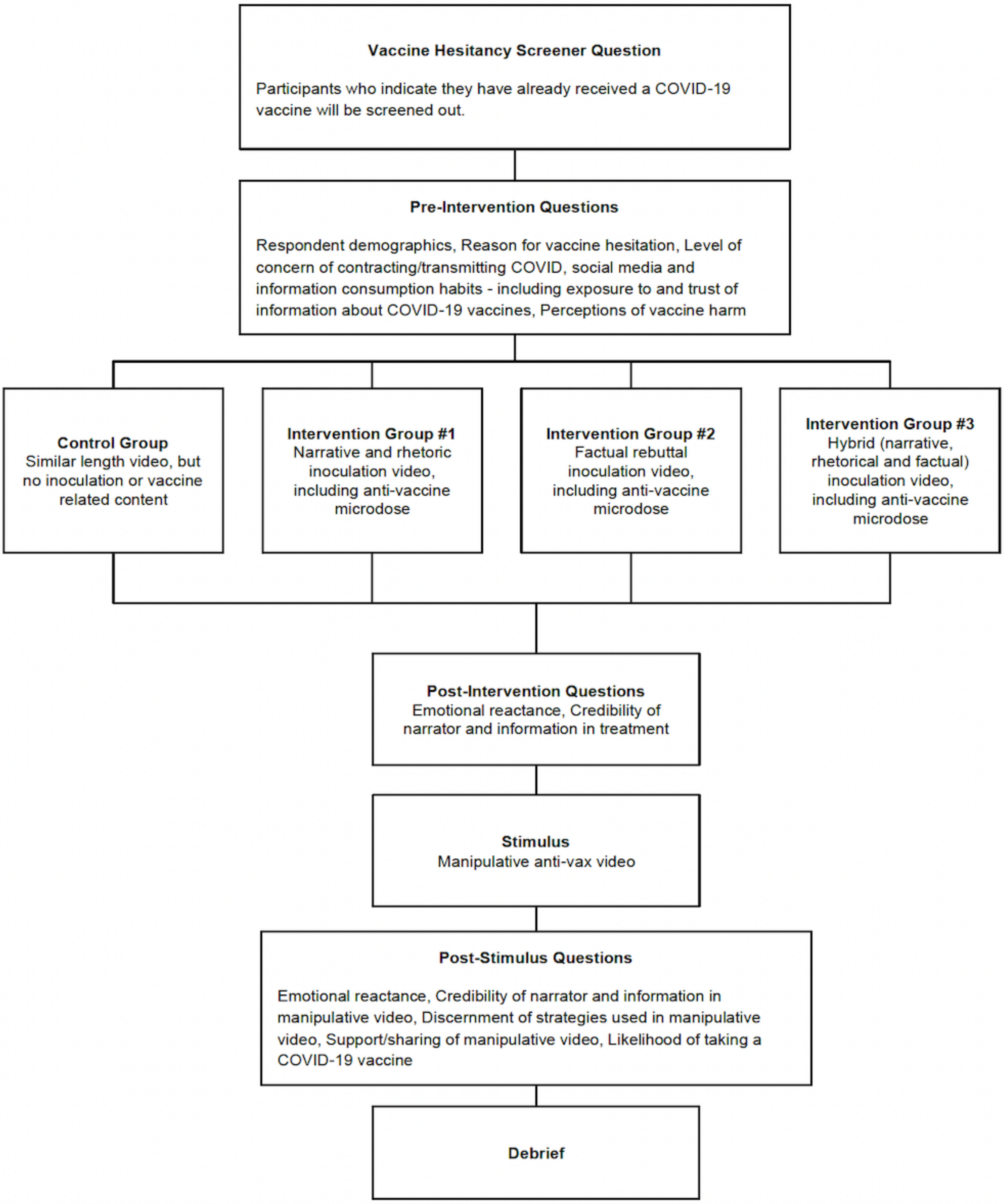
## Study Design

We conducted a quasi-experimental study with a pre-post intervention questionnaire and control group using an organic sampling survey method between June 3 and 5, 2021 [56]. Using this method, 4 separate surveys were conducted for each of the video exposure interventions, and as such, randomization was not possible. We conducted our surveys through the Pollfish (an online survey company) survey platform. Participants were eligible to participate if they indicated they had *not* received a COVID-19 vaccine, were over the age of 18 years, and lived in the United States. In total, 500 US adults were recruited into each study arm by Pollfish via mobile technology. Respondents were recruited into 1 of 4 study arms, 1 for each type of inoculation message, plus a control group that received a video unrelated to inoculation or vaccines using the design outlined Figure 1.

All participants first answered questions about their demographics, social media and information consumption, exposure to and trust of information about COVID-19 vaccines, and perceptions of vaccine harm. Then, participants in the 3 treatment groups were "inoculated" by showing them a 30-second scripted video that highlights narrative or rhetorical tactics used in vaccine misinformation (intervention group 1, "Narrative," n=500), contains factual rebuttal of vaccine misinformation (intervention group 2, "Fact," n=500), or a hybrid of both (intervention group 3, "Hybrid," n=500). The control group (n=500) watched a neutral video that described how to make a paper airplane. Participants were then asked a series of questions on their perceptions of the video.

After watching the inoculation video, participants were shown a video stimulus that utilizes the manipulation techniques participants were alerted to in the inoculation video. The same stimulus video was displayed to participants in the control group and all treatment groups. Participants were then asked the same series of questions on their perceptions of the video. The same questions were asked following the intervention/control video and the stimulus video in order to avoid alerting the respondent as to the type of video being assessed.

**Figure 1.** Study design.



## Ethical Considerations

The study protocol was approved by the American University Institutional Review Board (IRB-2022-295).

## Variables of Interest

We had 3 hypotheses of interest. Each hypothesis corresponded to a different dependent variable below. The first hypothesis was related to the ability to identify misinformation, the second was related to willingness to share information, and the third was related to willingness to get vaccinated. The measures described below were designed to correspond to these 3 research questions, though the survey also included other items related to emotional reactance to the content.

### *Dependent Variables (Question Number - Variable Name)*

We selected 3 particular outcomes of interest:

- The ability to recognize rhetorical strategies in a video containing misinformation about the COVID-19 vaccine, such as unusual colors, scary music, and vague language (Q25 - Recognize)
- Willingness to share the video containing misinformation about the COVID-19 vaccine (Q24 - Share)
- Willingness to get vaccinated (Q26 - Willingness)

### *Independent Variables*

We had the following independent variables:

- Demographic variables: gender (male, female), age (continuous), race (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, other), income (continuous), education (less than high school, high school/General Educational Development (GED), some college, bachelor's degree, postgraduate degree, other)
- General vaccine attitude covariates: "Most vaccines do not cause immediate injuries or side effects," "Most vaccines do not lead to long-term side effects," "Vaccines cause more harm than benefit," "Taking a vaccine is likely to give me a disease," "Vaccination can protect me from getting a disease," "Vaccines cause autism," and "Vaccines are designed as a form of government control," which was tested and then analyzed as a factor that controlled for vaccine attitudes (see analysis plan)

## Statistical Analyses

The analyses included 3 steps: first, to conduct descriptive statistics of baseline sample characteristics; second, to analyze multi-item scale development; and third, to test the effect of the 3 interventions in comparison to controls on the endpoints collected after the second video. All final models were adjusted for demographics (age, gender, race, education, and income); baseline value, if available; and mean scores calculated about general attitudes toward vaccines.

### *Descriptive Statistics of Baseline Sample Characteristics*

Baseline characteristics of the sample, including age, gender, race, income, education, and attitudinal variables, were described using means and SDs for continuous variables and counts and percentages for categorical variables. Descriptive statistics were calculated for the entire sample and by intervention group.

### *Multi-Item Scale Development*

Principal component analysis (PCA) was used to test the dimensionality of multi-item scales, which included the scales for prior general vaccine attitudes and the 3 primary study outcomes, namely Recognize, Share, and Willingness. We planned to retain components associated with eigenvalues greater than 1 as long as factor loadings and internal consistency within components, as measured by Cronbach α, were acceptable (>.7). When more than 1 component was retained, the varimax rotation was applied to the model to aid in the interpretation of the factor loadings. For retained components, scores were created as the mean of their items.

### *Statistical Analysis of Effects of Interventions on Outcomes*

Analysis of covariance (ANCOVA) models were used to compare the main effect of the intervention on the 3 outcome variables. The model for each outcome included the main effect of the intervention adjusted for age, gender, race, education, income, and the scores for prior general attitudes toward vaccines that was formed in the second step of our analysis. For the Share scale, the model also included the baseline Share score from after the first video. For the 3 outcomes, we were interested in testing the null hypothesis of no difference between intervention groups using a 2-tailed statistical test. To control the type 1 error rate resulting from multiple endpoints, we used the Holm method. For outcomes with a significant intervention group *F* test, we tested paired differences between the intervention groups and the control group and controlled for multiple comparisons using the Dunnett test. The power of the statistical test for an ANOVA with 3 intervention groups and 1 control group where the Dunnett test is used to compare each treatment mean with the control mean, one would require 477 subjects in each group in order to achieve 81% power to detect a mean difference of 0.33 between at least 1 pair of intervention and control groups, assuming an SD of 1.8 within each group and a family-wise type 1 error rate of .017, which corresponds to the first rejection level of the Holm method for this study.

# Results

## Sample Characteristics

This analysis included 1991 subjects. Although 500 (25.1%) subjects were enrolled in each intervention group, not all subjects completed the survey questionnaire, leaving an analysis population of 495 (24.9%) participants in the control group and 480 (24.1%) in the narrative-rhetorical, 489 (24.6%) in the factual, and 489 (24.6%) in the hybrid video intervention groups. Overall, the study population had a mean age of 40.7 (SD 11.8) years, and 968 (50%) were female, 1439 (74%) were non-Hispanic White, 1173 (60%) had a bachelor's degree or higher education, and 773 (40%) reported an income of US $100,000 or more. A summary of baseline characteristics for the entire sample and by intervention group is given in Table 2.

**Table 2.** Baseline characteristics.

| Characteristic | All groups (N=1953) | Controls (N=495) | Narrative (N=495) | Fact (N=489) | Hybrid (N=489) | *P* value[a] |
|---|---|---|---|---|---|---|
| Age (in years), mean (SD) | 40.8 (11.8) | 41.0 (11.7) | 36.6 (11.6) | 41.6 (11.4) | 43.6 (11.4) | <.001 |
| Female gender, n (%) | 968 (50) | 248 (50) | 234 (49) | 243 (50) | 243 (50) | .98 |
| **Race, n (%)** | | | | | | .03 |
| Non-Hispanic White | 1439 (74) | 380 (77) | 347 (72) | 356 (73) | 356 (73) | N/A[b] |
| Non-Hispanic Black | 206 (11) | 29 (6) | 59 (12) | 59 (12) | 59 (12) | N/A |
| Hispanic/Latino | 98 (5) | 35 (7) | 21 (4) | 21 (4) | 21 (4) | N/A |
| Non-Hispanic Asian | 73 (4) | 13 (3) | 20 (4) | 20 (4) | 20 (4) | N/A |
| Other | 137 (7) | 38 (8) | 33 (7) | 33 (7) | 33 (7) | N/A |
| **Income (US $), n (%)** | | | | | | .02 |
| <25,000 | 238 (12) | 76 (15) | 54 (11) | 54 (11) | 54 (11) | N/A |
| 25,000-49,999 | 245 (12) | 75 (15) | 56 (11) | 57 (12) | 57 (11) | N/A |
| 50,000-74,999 | 273 (14) | 48 (10) | 75 (15) | 75 (15) | 75 (15) | N/A |
| 75,000-99,999 | 310 (16) | 74 (15) | 78 (16) | 79 (16) | 79 (16) | N/A |
| 100,000-124,999 | 170 (9) | 42 (8) | 42 (9) | 43 (9) | 43 (9) | N/A |
| 125,000-149,999 | 200 (10) | 51 (10) | 47 (10) | 51 (10) | 51 (10) | N/A |
| ≥150,000 | 403 (21) | 83 (17) | 106 (22) | 107 (22) | 107 (22) | N/A |
| Prefer not to say | 114 (6) | 46 (9) | 22 (5) | 23 (5) | 23 (5) | N/A |
| **Education, n (%)** | | | | | | <.001 |
| Less than high school | 164 (8) | 17 (3) | 49 (10) | 49 (10) | 49 (10) | N/A |
| High school/GED[c] | 290 (15) | 103 (21) | 61 (13) | 63 (13) | 63 (13) | N/A |
| Some college | 254 (13) | 104 (21) | 50 (10) | 50 (10) | 50 (10) | N/A |
| Bachelor’s degree | 405 (21) | 105 (21) | 100 (21) | 100 (20) | 100 (20) | N/A |
| Postgraduate degree | 768 (39) | 166 (34) | 196 (41) | 203 (42) | 203 (42) | N/A |
| Other | 72 (4) | 0 (0) | 24 (5) | 24 (5) | 24 (5) | N/A |

[a] Test of significant intervention group effect using ANOVA model for Age and Pearson chi-square test for categorical variables.

[b] N/A: not applicable.

[c] GED: General Educational Development.

## Results of Statistical Analysis of Scales

PCA of the 7 items measuring prior attitudes toward vaccines retained 2 factors that accounted for 65% of the variance in the data. All items had a high factor loading on 1 of the 2 factors, with loading in the range of 0.71-0.83, while also having small factor loadings of less than 0.2 on the other factor (Table 3). Items loading most heavily on the first component asked the level of agreement to the statements “Most vaccines do not cause immediate injuries or side effects,” “Most vaccines do not lead to long-term side effects,” and “Vaccination can protect me from getting a disease,” while the remaining items that asked “Vaccines cause more harm than benefit,” “Taking a vaccine is likely to give me a disease,” “Vaccines cause autism,” and “Vaccines are designed as a form of government control” loaded highly onto the second component. Cronbach α for the 3 items loading on the first component was .70, while the 4 items loading on the second component had a Cronbach α of .83, indicating good internal consistency within each set of items. Because these 7 items formed 2 distinct constructs with good reliability, we created 2 scores for general attitudes toward vaccines by taking a subject’s mean response to the questions that loaded highly onto each factor.

For the 3 questions measuring the Recognize outcome, PCA showed the items to be unidimensional, with a single factor accounting for 72% of the variance. Factor loadings were all greater than 0.84, and Cronbach α was .81. PCA of the 5 items measuring the Share outcome also retained a single factor that accounted for 70% of the variance in the data. Factor loadings were high (0.70-0.89), and Cronbach α was .89.

**Table 3.** PCA[a] factor structure.

| Construct items | Factor 1 loading | Factor 2 loading |
|---|---|---|
| **General attitudes toward vaccines** | | |
| Most vaccines do not cause immediate injuries or side effects. | 0.79 | 0.13 |
| Most vaccines do not lead to long-term side effects. | 0.69 | 0.11 |
| Vaccines cause more harm than benefit. | 0.09 | 0.74 |
| Taking a vaccine is likely to give me a disease. | 0.09 | 0.75 |
| Vaccination can protect me from getting a disease. | 0.49 | 0.10 |
| Vaccines cause autism. | 0.19 | 0.75 |
| Vaccines are designed as a form of government control. | 0.14 | 0.66 |
| **Recognize** | | |
| Scary music | 0.78 | N/A[b] |
| Weird colors | 0.78 | N/A |
| Vague language (words that are unclear or not specific) | 0.73 | N/A |
| **Sharing** | | |
| How likely are you to share this second video with people in your social media network? | 0.83 | N/A |
| How likely are your friends to share this second video on their social media networks? | 0.81 | N/A |
| If you could, how likely would you be to support the producer of this second video by following them (receiving future posts from them) on social media? | 0.88 | N/A |
| If you could, how likely would you be to financially support the producer of this second video? | 0.82 | N/A |
| How likely are you to check the facts on the second video you just watched? | 0.60 | N/A |

[a] PCA: principal component analysis.

[b] N/A: not applicable.

## Effect of Interventions on Outcomes of Interest

### *Hypothesis 1. The Ability to Recognize Rhetorical Strategies in a Video Containing Misinformation About the COVID-19 Vaccine (Recognize)*

For the Recognize score, the ability to recognize rhetorical strategies, there was a significant intervention group effect ($F_{(3,1929)}$=8.5, $P<.001$); see Table 4. Since this was the smallest of the intervention group effect $P$ values among the 3 study endpoints, the Holm method rejected the null hypothesis of the no-intervention-group effect when $P<.05/3=.02$, which was achieved. The least squares (LS) means (SE) of the Recognize scale for controls and the 3 video intervention groups were 3.67 (0.09), 3.98 (0.09), 4.10 (0.09), and 4.14 (0.09), respectively. The LS mean differences between intervention groups (Narrative, Fact, and Hybrid) and controls were 0.31 ($P$=.01), 0.43 ($P<.001$), and 0.47 ($P<0.001$), respectively, with all $P$ values being significant after adjusting for multiple comparison using the Dunnett test. These tests indicated that each intervention group had a statistically significant greater awareness of the tactics used to gain attention in the second video compared to controls.

**Table 4.** ANCOVA[a] models' estimated intervention effects, mean scores, and differences.

| Intervention LS[b] means and SEs | | | Differences from control intervention | |
|---|---|---|---|---|
| Outcome by intervention | $F$ statistic $P$ value[c] | LS mean (SE)[c] | LS mean (SE) | Adjusted $P$ value[d] |
| **Recognition of rhetorical strategies ("Recognize")** | | | | |
| Intervention effect | <.001 | N/A[e] | N/A | N/A |
| Control | N/A | 3.67 (0.09) | N/A | N/A |
| Narrative | N/A | 3.98 (0.09) | 0.31 (0.11) | .01 |
| Fact | N/A | 4.10 (0.09) | 0.43 (0.10) | <.001 |
| Hybrid | N/A | 4.14 (0.09) | 0.47 (0.10) | <.001 |
| **Willingness to share misinformation content ("Share")** | | | | |
| Intervention effect | .017 | N/A | N/A | N/A |
| Control | N/A | 4.11 (0.08) | N/A | N/A |
| Narrative | N/A | 3.90 (0.07) | –0.21(0.09) | .03 |
| Fact | N/A | 3.90 (0.07) | –0.22 (0.09) | .022 |
| Hybrid | N/A | 3.89 (0.07) | –0.22 (0.09) | .019 |
| **Willingness to get vaccinated ("Willingness")** | | | | |
| Intervention effect | .006 | N/A | N/A | N/A |
| Control | N/A | 2.77 (0.09) | N/A | N/A |
| Narrative | N/A | 3.05 (0.09) | 0.28 (0.10) | .012 |
| Fact | N/A | 3.05 (0.09) | 0.28 (0.10) | .011 |
| Hybrid | N/A | 3.05 (0.09) | 0.28 (0.10) | .01 |

[a] ANCOVA: analysis of covariance.

[b] LS: least squares.

[c] $F$ statistic, LS mean, and SE were obtained from an ANCOVA model for each outcome, with the intervention group as the main effect and adjusting for age, gender, race, education, income, and scores from 2 scales of general attitudes toward vaccines.

[d] $P$ value adjusted for multiple comparisons between controls and intervention groups using the Dunnett test after finding a significant main effect for intervention.

[e] N/A: not applicable.

### *Hypothesis 2. Support for Sharing the Video Containing Misinformation About the COVID-19 Vaccine (Sharing)*

For the Share scale, support for sharing the mis- and disinformation, the intervention group main effect was statistically significant ($F_{(3,1928)}$=3.4, $P$=.02) using the Holm $P$ value threshold of .05. For the control and intervention groups (Narrative, Fact, and Hybrid), the LS means (SE) were 4.11 (0.08), 3.90 (0.07), 3.90 (0.07), and 3.89 (0.07), respectively. The LS means for the difference between the control group and the 3 intervention groups were 0.21 ($P$=.03), 0.22 ($P$=.022), and 0.22 ($P$=.019) lower than that for the control group, respectively, indicating lower support for sharing/supporting the second video in each intervention group compared to controls.

### *Hypothesis 3. Willingness to Get vaccinated (Willingness)*

The intervention group effect for the Willingness scale, willingness to get the vaccine, had the second smallest $P$ value ($F_{(3,1929)}$=4.1, $P$=.01) among the 3 study endpoints, which was significant at the Holm method adjusted cut-off of 0.05/2=.03. The LS means (SE) for the willingness scale for the control and 3 intervention groups were 2.77 (0.09), 3.05 (0.09), 3.05 (0.09), and 3.05 (0.09), respectively. The difference between the control groups and the 3 intervention groups (Narrative, Fact, and Hybrid) were 0.28 ($P$=.012), 0.28 ($P$=.011), and 0.28 ($P$=.01) points higher than that for the controls, respectively, indicating that subjects in the intervention groups were more willing to get the COVID-19 vaccine compared to controls.

## Discussion

### Principal Findings

The purpose of this study was to identify the effect of attitudinal inoculation videos on the ability to identify misinformation, willingness to share misinformation, and willingness to vaccinate. We found there was a significant effect of having been exposed to an inoculation video compared to a control video across each outcome of interest. Our results support our initial hypotheses that inoculation messaging can increase the ability to identify misinformation, decrease willingness to share misinformation, and increase willingness to vaccinate.

Our study explored not only whether there is an effect of inoculating participants but also whether inoculating against a narrative/rhetorical strategy or against factual misinformation is more effective. We also tested a hybrid video that combined fact-based and narrative/rhetorical strategies within the inoculation message. Past studies into the relative efficacy of narrative/rhetoric compared to fact-based appeals have suggested that narrative approaches are more likely to be persuasive to viewers [32-34,37-39,55]. However, we did not find significant differences across the 3 active intervention groups, suggesting that the content of the intervention video (narrative/rhetoric, fact based, or hybrid) does not impact the effect of the intervention. This may be attributable to the nuanced differences in the scripts used, which might have been difficult to distinguish in such a short time frame. Additionally, because there was only 1 video for each video script strategy, it is not possible to say whether there may be differences in other videos that used these same strategies. It is even possible that the cinematographic and casting choices behind each video (ie, the production and the medical workers who narrated them) themselves made indirect narrative and rhetorical appeals to viewers. These appeals include, for example, clean sets, approachable body language, hopeful music, and other emotionally engaging features of the videos. This, in turn, might have produced a “flattening” effect, rendering the appeals of the videos more uniform.

The intervention videos were designed to protect people against being misled by flawed argumentation used in common online mis- and disinformation, such as conspiracy theories [57,58]. In practice, this means that watching a video with an inoculation message and a weakened microdose of manipulation techniques allows viewers to discern more readily subsequent misinformation that makes use of similar flawed argumentation techniques. In this study, we were able to achieve this in videos that were only 30 seconds in duration. This is critical because 30 seconds is consistent with short attention spans for online video consumption on social media and the length of many ads online, enabling such a video to be shown in ad slots. Prior inoculation studies have tested longer-form videos or text [49,51,58]. These findings for the effects of 30-second videos have implications for the ability to disseminate inoculation messages in social media ad slots.

Furthermore, online platforms are a viable place to disseminate these interventions to affect perceptions and behavior, because information on vaccine injury is viewed and spread on social media and exposure to online misinformation is associated with lower vaccination intentions [17,59,60]. Social media platforms that may hesitate at the prospect of hosting inoculation videos containing a microdose of misinformation might be reassured that in the proper context of an inoculation message, these microdoses are vital to the overall discrediting of misinformation and disinformation.

## Limitations

This study has limitations. First, the study sample was not representative of the general population but rather was more highly educated, mobile app users. Testing the effects of the intervention with a broader audience and determining whether there are differential effects among particular subsamples of the population will add to the understanding of the effect of these types of videos. Second, as described before, further investigation is needed to explore whether there may be meaningful differences in narrative versus fact versus hybrid models that could not be detected in this study due to the study design; however, in general, our results suggest that fact-based rhetorical strategies can be as effective as a narrative-rhetoric or hybrid approach.

## Conclusion

As an infodemic management strategy, approaches that go beyond fact checking, and do not simply focus on countering 1 piece of content, may be valuable. We found that attitudinal inoculation in video-based messages may be an intervention strategy that can be used in designing public health messaging campaigns to counter mis- and disinformation. Online dissemination of these videos could be a viable strategy to increase vaccine uptake and can be tried more broadly. Videos that use attitudinal inoculation to combat COVID-19 vaccine misinformation should be tested with a broader audience beyond the United States and on social media platforms, such as YouTube and TikTok. More research is needed to understand how videos with attitudinal inoculation perform when individuals are in a typical information consumption environment and faced with competing demands for attention.

## Conflicts of Interest

None declared.

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## Abbreviations

**ANCOVA:** analysis of covariance
**GED:** General Educational Development
**LS:** least squares
**PCA:** principal component analysis

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Original Paper

# Reasons for COVID-19 Vaccine Hesitancy Among Chinese People Living With HIV/AIDS: Structural Equation Modeling Analysis

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## Abstract

**Background:** Many countries and organizations recommended people living with HIV/AIDS (PLWHA) receive the COVID-19 vaccine. However, vaccine hesitancy still exists and becomes a barrier for promoting COVID-19 vaccination among PLWHA.

**Objective:** This study aims to investigate factors that contributed to COVID-19 vaccine hesitancy among PLWHA.

**Methods:** The study used a multicenter cross-sectional design and an online survey mode. We recruited PLWHA aged 18-65 years from 5 metropolitan cities in China between January 2021 and February 2021. Participants completed an online survey through Golden Data, a widely used encrypted web-based survey platform. Multiple linear regression models were used to assess the background characteristics in relation to COVID-19 vaccine hesitancy, and structural equation modeling was performed to assess the relationships among perceived benefits, perceived risks, self-efficacy, subjective norms, and COVID-19 vaccine hesitancy.

**Results:** Among 1735 participants, 41.61% (722/1735) reported COVID-19 vaccine hesitancy. Older age, no other vaccinations in the past 3 years, and having chronic disease history were positively associated with COVID-19 vaccine hesitancy. Structural equation modeling revealed a direct relationship of perceived benefits, perceived risks, and subjective norms with self-efficacy and vaccine hesitancy and an indirect relationship of perceived benefits, perceived risks, and subjective norms with vaccine hesitancy. Moreover, self-efficacy toward COVID-19 vaccination was low. PLWHA had concerns of HIV disclosure during COVID-19 vaccination. Family member support could have an impact on COVID-19 vaccination decision-making.

**Conclusions:** COVID-19 vaccine hesitancy was high among PLWHA in China. To reduce COVID-19 vaccine hesitancy, programs and strategies should be adopted to eliminate the concerns for COVID-19 vaccination, disseminate accurate information on the safety and efficacy of the COVID-19 vaccine, encourage family member support for COVID-19 vaccination, and improve PLWHA's trust of medical professionals.

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**KEYWORDS**

COVID-19 vaccine; vaccine hesitancy; PLWHA; structural equation modeling

## Introduction

The COVID-19 pandemic has become a global health challenge and poses a serious health threat [1]. Compared with the HIV-negative population, people living with HIV/AIDS (PLWHA) with a weakened immune condition or with comorbidities have an increased risk of having poorer outcomes from COVID-19 [2]. Moreover, PLWHA who are immunocompromised are more likely to have a more severe illness and a longer disease course from COVID-19 [3-5]. Some longitudinal studies have reported that PLWHA have higher COVID-19 mortality than the HIV-negative population [6-8]. Therefore, it is critical for PLWHA to receive vaccines to prevent COVID-19. Many countries and organizations recommended PLWHA to receive a COVID-19 vaccine [9-14]. The Joint United Nations Programme on HIV/AIDS has declared that the COVID-19 vaccines authorized by regulators can significantly reduce the risks of severe COVID-19 illness and death and are safe for most people, including PLWHA [11]. The UK Department of Health and US Centers for Disease Control and Prevention released guidance that recommended PLWHA, regardless of CD4 count, should be vaccinated against COVID-19 [12,13]. In March 2021, China launched an updated COVID-19 guideline that also recommended PLWHA receive COVID-19 vaccines [14].

Although the evidence on the side effects and protective efficacy of COVID-19 vaccination in PLWHA is insufficient, some studies have shown that COVID-19 vaccine hesitancy is higher among PLWHA than HIV-negative people [15,16]. For example, a study in British Columbia, Canada, showed that 65.2% of PLWHA reported intending to receive a COVID-19 vaccine recommended and available to them, which was lower than HIV-negative people (79.6%). That is to say, COVID-19 vaccine hesitancy is higher among PLWHA than HIV-negative people [15]. In a cross-sectional study conducted in Beijing, China, the rate of COVID-19 vaccine hesitancy of the PLWHA population was 27.5%, which was higher than HIV-negative people (17.75%) [16]. Hence, vaccine hesitancy exists and becomes a barrier for promoting COVID-19 vaccination among PLWHA. Vaccine hesitancy was defined by the World Health Organization as the delay in acceptance or refusal of vaccination despite the availability of vaccination services [17]. Vaccine hesitancy was listed as one of the top 10 global health threats in 2019 [18]. It is urgently needed to eliminate COVID-19 vaccine hesitancy and improve the coverage rate for PLWHA who might encounter more barriers and have more concerns about COVID-19 vaccination. A recent study reported that vaccine hesitancy was influenced by various factors, such as perceived benefits and risks of a vaccine, perceived safety of a vaccine, confidence in a vaccine, attitudes toward a vaccine, and an individual's demand [17,19-21]. Perceived vaccine safety was reported as an essential factor that can lead to a vaccination decision [22]. In other words, people who perceive a vaccine as unsafe are more likely to refuse or delay vaccination (vaccine hesitancy) [23]. Perceived risks of a vaccine could also result in vaccine hesitancy [24]. Moreover, a recent French study that investigated COVID-19 vaccine hesitancy in PLWHA indicated a high hesitancy rate of 28.7%, and PLWHA had concerns about serious side effects of COVID-19 vaccination [25]. Another study that investigated vaccine hesitancy among African American PLWHA demonstrated that people trusted some COVID-19 vaccination sources, such as social service and health care providers, more than others [26].

Although previous studies determined some factors that were associated with PLWHA's vaccine hesitancy, complex relationships among multiple factors might exist but remain unassessed. A structural equation modeling (SEM) approach that provides a flexible framework to analyze multiple variables and takes into consideration relationships among variables could provide a more compelling explanation of COVID-19 vaccine hesitancy. However, there is a lack of research investigating the factors correlated with PLWHA's vaccine hesitancy through SEM. Therefore, we designed a survey that investigated factors associated with COVID-19 vaccine hesitancy among PLWHA using SEM. Some factors that were reported in the literature were assessed and included in the model, such as perceived benefits, perceived risks, self-efficacy, and subjective norms. The findings of the study aimed to provide valuable evidence for a deep understanding of COVID-19 vaccine hesitancy, therefore contribute to policy making and programming efforts with the goals of addressing vaccine hesitancy and promoting COVID-19 vaccination among PLWHA.

## Methods

### Study Design

The study used a multicenter cross-sectional design and an online survey mode. Recruitment was conducted in 5 large cities from 4 regions of China between January 2021 and February 2021. These cities included 2 in the North (Tianjin and Beijing), 1 in the Northeast (Hohhot), 1 in the East (Nanjing), and 1 in the South (Nanning). To achieve the study objectives, we have set up the following criteria for cities to be qualified and included in this study: (1) must have community-based organizations (CBOs) providing services to PLWHA; (2) each city has a minimum of 3000 reported PLWHA; (3) COVID-19 vaccination was first scaled up in these sites; and (4) there is an adequate supply of vaccines in these sites.

We used 2 methods to calculate the sample size.

The first one was based on the estimation of the rate of COVID-19 vaccine hesitancy among the PLWHA population based on the clustering sample method. According to a cross-sectional study conducted in Beijing, China, the rate of COVID-19 vaccine hesitancy of the PLWHA population was 27.5% [16]. We first estimated the sample size using the following sample size formula from a simple randomized sampling method. The $\alpha$ is the significance level; if $\alpha$ was 0.05, $Z_{1-\alpha/2}$ could be assumed to be 1.96. $\delta$ is the allowable error, and was considered to be 0.05. The p, or the estimated COVID hesitancy rate in the PLWHA population, was considered to be 27.5%. Then, we used the design effect (deff) to further calculate the sample size based on a clustering sampling method. The deff was defined as the ratio of the variance, taking into account the clustering sample design and the variance of a simple random sample design with the same number of observations, deff was considered to be 2 based on previous studies [27-29]. Eventually, a sample size of 613 was initially generated based on a clustering sample study design. A minimum sample size of 852 was acquired after taking into consideration the no response rate of participants (20%) and the portion of unacceptable responses (10%). The sample size formula was expressed as:

For the second sample size calculation, Nunnally [30] believed that the minimum sample size should be at least 10 times the analyzed variables to conduct a SEM analysis. There are 23 variables in this study without considering background characteristics, so a sample size of 230 was initially needed. A minimum sample size of 320 was acquired after taking into consideration the no response rate of participants (20%) and the portion of unacceptable responses (10%).

Last, we used 852 as the minimum sample size of this study.

## Participants

Eligible participants were individuals aged 18-65 years who had been diagnosed with HIV or AIDS and were living in 1 of the 5 cities. Exclusion criteria included (1) being illiterate and unable to complete the online questionnaire and (2) PLWHA who had been vaccinated against COVID-19.

## Recruitment and Data Collection

We recruited participants mainly through CBOs, which provide services mainly to PLWHA and have been cooperating closely with HIV clinical service providers in the 5 study sites. In China, HIV outreach services to PLWHA have been transferred from government agencies to CBOs [31]. At present, CBOs are the primary providers of these routine tasks. In addition, a large portion of PLWHAs is followed up by CBOs. The questionnaire survey was carried out using Golden Data, a commonly used, encrypted, web-based survey platform. Each participant took about 13-15 minutes to complete this survey. An electronic coupon with a value of 20 Chinese yuan (US $3.10) was sent to the participant upon completion. The database we used was protected by a password and could only be accessed by designated research team members. More detailed information about recruitment and data collection can be found in Multimedia Appendix 1.

## Instrumentation

A panel consisting of public health researchers, psychologists, clinicians, CBO staff, and participant representatives was assembled to develop the questionnaire for the study. Ten participant representatives responded to the online survey and provided feedback for improvement. The panel revised and finalized the questionnaire based on the pilot responses and the feedback. The 10 participants were not included in the final analyses of the study.

The questionnaire included the following sections: (1) background characteristics (eg, including sociodemographic characteristics, presence of chronic conditions, history of other vaccination in the past 3 years, HIV disease information), (2) vaccine hesitancy, (3) perceived risks, (4) self-efficacy, (5) perceived benefits, and (6) subjective norms. Constructs (2) to (6) were assessed using a 5-point Likert scale. Latent variables that may have direct or indirect relationships with COVID-19 vaccine hesitancy were also measured according to the hypotheses.

In this study, vaccination hesitancy was defined as the proportion of respondents who reported “definitely not” or “probably not” or “unsure” to undergo the COVID-19 vaccination program based on a recent peer-reviewed study by Fisher et al [32].

## Study Hypotheses

Based on the literature, we proposed the following study hypotheses:

- Hypothesis 1: Perceived benefit is negatively associated with COVID-19 vaccine hesitancy (the higher the perceived benefits, the lower the degree of COVID-19 vaccine hesitancy).
- Hypothesis 2: Perceived risk is positively associated with COVID-19 vaccine hesitancy (the higher the perceived risks, the higher the degree of COVID-19 vaccine hesitancy).
- Hypothesis 3: Subjective norms are negatively associated with COVID-19 vaccine hesitancy (the higher the subjective norms, the lower the degree of COVID-19 vaccine hesitancy).
- Hypothesis 4: Self-efficacy is negatively associated with COVID-19 vaccine hesitancy (the higher the self-efficacy, the lower the degree of COVID-19 vaccine hesitancy).

- Hypothesis 5: Self-efficacy is positively associated with perceived benefits (the higher the self-efficacy, the higher the degree of perceived benefits).
- Hypothesis 6: Self-efficacy is negatively associated with perceived risks (the higher the self-efficacy, the lower the degree of perceived risks).
- Hypothesis 7: Self-efficacy is positively associated with subjective norms (the higher the self-efficacy, the higher the degree of subjective norms).

### Statistical Analysis

Descriptive statistics were performed to summarize the background characteristics associated with and frequencies of COVID-19 vaccine hesitancy. The total average scores and dimensional average scores for vaccine hesitancy, perceived benefits, perceived risks, self-efficacy, and subjective norms were generated. A 1-way ANOVA test was used to identify the factors predicting COVID-19 vaccine hesitancy. SPSS software (version 24.0; IBM Corporation) was used to perform all data analyses. The significance level was set at a 2-tailed *P* value of <.05.

### Model Analysis

First, means and standard deviations were generated to describe the basic information; skewness and kurtosis were computed to describe the distribution of the data. Furthermore, we used Amos 24.0 to construct the SEM and used the nonparametric percentile bootstrap method of bias correction to test the indirect relationships.

### Ethics Approval

The institutional review boards of the Changzhi Medical College (RT2021003) approved this study. Respondents were informed that their participation was voluntary, and consent was implied by completion of the questionnaire.

## Results

### Background Characteristics

A total of 1883 PLWHA completed the online survey from the 5 metropolitan cities. We excluded 148 participants who had been vaccinated for COVID-19. A total of 1735 participants were included in this study. The majority of the participants were 18-39 years old (1285/1735, 74.06%) and identified themselves as male (1638/1735, 94.41%; Table 1). In terms of relationship status, education, and employment status, 67.44% (1170/1735) of participants were currently single, 62.25% (1080/1735) had received a college education or higher, and 69.91% (1213/1735) had a full-time job. Only 77.22% (1339/1735) of the participants had basic health insurance. Moreover, 17.35% (301/1735) of the participants received their HIV diagnosis within 1 year prior, 97.58% (1693/1735) of the participants were on antiretroviral therapy (ART), 70.55% (1224/1735) reported they had an undetectable viral load, and 46.86% (813/1735) reported their CD4 T cell counts were above 500 cells/μL.

**Table 1.** Background characteristics of participants (n=1735).

| Sociodemographic characteristics and chronic disease and HIV-related indicators | Results, n (%) |
|---|---|
| **Age group (years)** | |
| 18-29 | 523 (30.14) |
| 30-39 | 762 (43.92) |
| 40-49 | 325 (18.73) |
| ≥50 | 125 (7.20) |
| **Gender at birth** | |
| Male | 1638 (94.41) |
| Female | 97 (5.59) |
| **Gender identity** | |
| Male | 1420 (81.84) |
| Female | 164 (9.45) |
| Transgender | 146 (8.41) |
| Others | 5 (0.29) |
| **Relationship status** | |
| Currently single | 1170 (67.44) |
| Cohabited/married with a same-sex partner | 236 (13.60) |
| Cohabited/married with an opposite-sex partner | 329 (18.96) |
| **Highest education level attained** | |
| Junior high or below | 277 (15.97) |
| Senior high or equivalent | 378 (21.79) |
| College and above | 1080 (62.25) |
| **Employment status** | |
| Full-time | 1213 (69.91) |
| Part-time/unemployed/retired/students/others | 522 (30.09) |
| **Monthly personal income (Chinese yuan/US $)** | |
| No fixed income | 204 (11.76) |
| <1000/154 | 94 (5.42) |
| 1000-2999/154-462 | 230 (13.26) |
| 3000-4999/462-770 | 501 (28.88) |
| 5000-6999/770-1078 | 338 (19.48) |
| 7000-9999/1078-1540) | 174 (10.03) |
| ≥10,000/1540) | 194 (11.18) |
| **Type of health insurance** | |
| No | 197 (11.35) |
| Basic health insurance only | 1339 (77.18) |
| Commercial health insurance only | 35 (2.02) |
| Both basic and commercial health insurance | 157 (9.05) |
| Others | 7 (0.40) |
| **Study site** | |
| Beijing | 495 (28.53) |
| Tianjin | 320 (18.44) |
| Nanjing | 313 (18.04) |

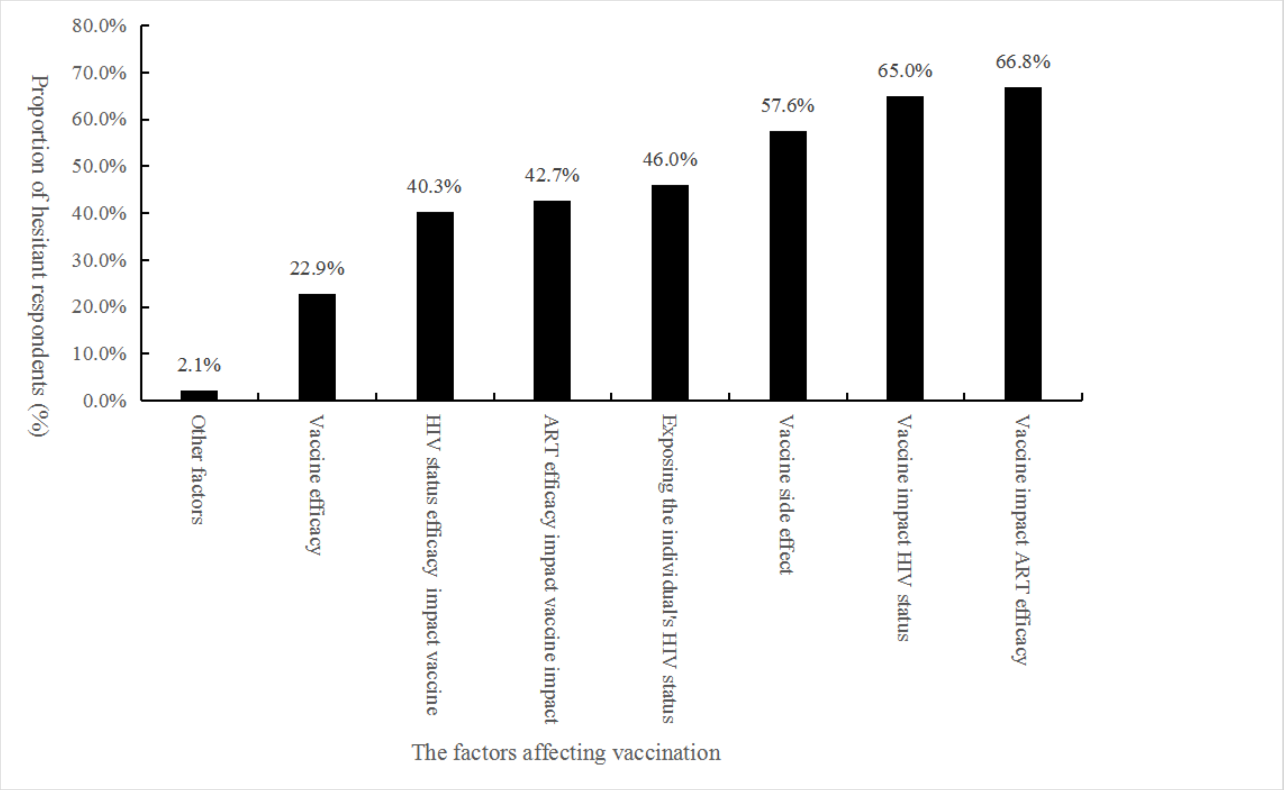
| Sociodemographic characteristics and chronic disease and HIV-related indicators | Results, n (%) |
|---|---|
| Hohhot | 315 (18.16) |
| Nanning | 292 (16.83) |
| **Current tobacco use** | |
| No | 1253 (72.22) |
| Yes | 482 (27.78) |
| **Current alcohol use** | |
| No | 1395 (80.40) |
| Yes | 340 (19.60) |
| **Self-reported BMI (kg/m$^2$)** | |
| <18.5 | 155 (8.93) |
| 18.5-23.9 | 1128 (65.01) |
| 24.0-27.9 | 364 (20.98) |
| ≥28 | 88 (5.07) |
| **Presence of chronic disease conditions (not including HIV)** | |
| No | 1157 (66.69) |
| Yes | 578 (33.31) |
| **Medication use for treating chronic diseases (not including HIV)** | |
| No | 1639 (94.47) |
| Yes | 96 (5.53) |
| **History of other vaccinations in the past 3 years** | |
| No | 1324 (76.31) |
| Yes | 411 (23.69) |
| **Time since HIV diagnosis (years)** | |
| ≤1 | 301 (17.35) |
| 2-5 | 806 (46.46) |
| >5 | 628 (36.20) |
| **On antiretroviral therapy** | |
| No | 42 (2.42) |
| Yes | 1693 (97.58) |
| **HIV viral load in the most recent episode of testing (copies/mL)** | |
| Undetectable (<50) | 1224 (70.55) |
| Detectable (≥50) | 197 (11.35) |
| Not sure | 314 (18.10) |
| **CD4+ T cell count in the most recent episode of testing, cells/mm$^3$** | |
| >500 | 813 (46.86) |
| 350-499 | 354 (20.40) |
| 200-349 | 177 (10.20) |
| <200 | 59 (3.40) |
| Unknown | 332 (19.14) |

## Attitudes Toward COVID-19 Vaccines

Regarding the responses to the statement “the likelihood of receiving free COVID-19 vaccination in the future,” 58.4% (1013/1735) of the participants responded that they would accept. Only 2.2% (38/1735) of the participants responded that they would definitely not get vaccinated, 6.7% (116/1735) of the participants said they would probably not get vaccinated, and 32.7% (568/1735) of the participants said they were unsure. In total, 41.6% (722/1735) of participants had vaccine hesitancy (Table S1 in Multimedia Appendix 2).

Among the 722 participants who hesitated to be vaccinated, when they were asked about factors affecting their vaccine willingness, a majority (482/722, 66.8%) of participants demonstrated concerns about a possible influence on ART, and 65% (469/722) had concerns about a possible influence on HIV disease status, that is the HIV disease would progress abnormally, including a rebound of viral load, or a decrease of absolute CD4+ T cell counts after COVID-19 vaccination. Moreover, 57.6% (416/722) of participants had concerns about the possible side effects of the COVID-19 vaccine. Nearly one-half of the participants (332/722, 46%) demonstrated fear of HIV disclosure. Many participants (308/722, 42.7%) had concerns that ART might affect the effectiveness of the vaccine, 40.3% (291/722) of participants worried that their HIV status might affect the effectiveness of the vaccine, and 22.9% (165/722) had concerns about the vaccine effectiveness alone. A small number of participants (15/722, 2.1%) reported other factors that were associated with their vaccine hesitancy (Figure 1).

**Figure 1.** Self-reported reasons of COVID-19 vaccine hesitancy in people living with HIV/AIDS (PLWHA; n=722). ART: antiretroviral therapy.



## Vaccine Hesitancy and Background Characteristics

A 1-way ANOVA was used to assess differences in COVID-19 vaccine hesitancy scores among participants with different demographic characteristics. Compared with the group aged 18-29 years old, participants over 29 years old were more hesitant to get the COVID-19 vaccine (*P*=.009; Table S2 in Multimedia Appendix 2). Participants who had chronic diseases or a chronic disease history were more hesitant than those who did not have (PLWHA without chronic diseases: 2.62 vs PLWHA with chronic diseases or history: 2.42; *P*<.001). PLWHA who did not have other vaccinations in the past 3 years were more hesitant than the ones who did (eg, without other vaccinations: 2.35 vs with other vaccinations: 2.21; *P*=.01).

The significant variables in the univariate analyses were included in the multiple linear regression model. Multiple linear regression analyses identified that the tolerance of independent variables was greater than 0.1, and the variance expansion factor ranged from 1.01 to 1.40. All were less than 10, which indicated there was no multicollinearity and the results of the linear regression model were reliable.

The results of the multivariate linear regression analyses showed that, in general, older age (except for the group aged 40-49 years) was positively associated with COVID-19 vaccine hesitancy. Having received another vaccination in the past 3 years was negatively correlated with COVID-19 vaccine hesitancy (β=–0.07, *P*=.01; Table 2). Having chronic diseases or a chronic disease history was positively correlated with COVID-19 vaccine hesitancy (β=2.77, *P*=.01).

**Table 2.** Multivariate analyses of vaccine hesitancy by background characteristics.

| Characteristics | Unstandardized coefficient | | Standardized coefficient (β) | *t* value (df) | *P* value | Collinearity statistics | |
|---|---|---|---|---|---|---|---|
| | B | SE | | | | Tolerance | VIF[a] |
| Intercept | 2.22 | 0.04 | N/A[b] | 50.23 | <.001 | N/A | N/A |
| **Age (years)** | | | | | | | |
| 18-29 | Ref[c] | Ref | Ref | Ref (3) | Ref | Ref | Ref |
| 30-39 | 0.12 | 0.05 | 0.06 | 2.23 (1) | .03 | 0.71 | 1.40 |
| 40-49 | 0.10 | 0.07 | 0.04 | 1.47 (1) | .14 | 0.73 | 1.37 |
| ≥50 | 0.23 | 0.10 | 0.06 | 2.35 (1) | .02 | 0.83 | 1.20 |
| Presence of chronic disease conditions | 0.14 | 0.05 | 0.07 | 2.77 (1) | .01 | 0.93 | 1.07 |
| History of other vaccinations in the past 3 years | –0.15 | 0.05 | –0.07 | –2.86 (1) | <.001 | 1.00 | 1.01 |

[a] VIF: variance inflation factor.

[b] N/A: not applicable.

[c] Ref: reference.

## Correlation Matrix

The results showed a negative correlation between perceived benefits and vaccine hesitancy and a positive correlation between perceived risks and vaccine hesitancy (both *P*<.001; Table S3 in Multimedia Appendix 2). Self-efficacy and subjective norms were negatively correlated with vaccine hesitancy (both *P*<.001).

## Measurement Scores

Generally, when the absolute value of the skewness coefficient of an observation variable is <3 and the absolute value of the kurtosis coefficient is <8, the data can be regarded as having a normal distribution. According to the kurtosis results (from –1.29 to 1.45) and skewness (from –1.23 to 0.72), the study data were normally distributed.

The mean self-efficacy score was the lowest of all indicators; in other words, participants' confidence of COVID-19 vaccination was generally low. The mean perceived risk was the highest. In addition, the concern about HIV disclosure showed the highest mean score among all perceived risks. Moreover, PLWHA would accept the suggestions of family members on COVID-19 vaccination. However, recommendations from a HIV-positive peer and medical professionals had less influence on the acceptance of a COVID-19 vaccine (Table S4 in Multimedia Appendix 2).

## Results of Confirmatory Factor Analysis and SEM

This study hypothesized that perceived risks, perceived benefits, self-efficacy, and subjective norms were associated with COVID-19 vaccine hesitancy; therefore, these 4 factors were included in the SEM to explore their direct or indirect relationships with vaccine hesitancy.

### *Confirmatory Factor Analysis*

Confirmatory factor analysis was used to confirm that each latent factor was being measured appropriately. We used the root mean square error of approximation, normed fit index (NFI), incremental fit index (IFI), Tucker-Lewis index (TLI), and comparative fit index (CFI) to assess whether the model was fit appropriately. The values of NFI, IFI, TLI, and CFI were 0.93, 0.94, 0.93, and 0.94, respectively (all >0.90). The results showed that the hypothesized model had an adequate fit (Table S5 in Multimedia Appendix 2).

Table 3 showed that the factor loadings for the items were between 0.52 and 0.92 (above 0.5), and the Cronbach α values were between 0.85 and 0.92. It indicated that this online survey had good reliability. The average variance extracted (AVE) and the construct reliability were above 0.5 and 0.7, respectively, which indicated that the convergent validity and internal consistency of this survey were good. According to the discriminant validity analysis, all square roots of AVE were higher than the correlation values, which indicated a good evaluation (Table 4).

**Table 3.** Results of reliability and convergent validity analyses.

| Constructs and items | Measures | Estimate | *P* value | Cronbach α | AVE[a] | CR[b] |
|---|---|---|---|---|---|---|
| **Perceived benefits** | | | | 0.86 | 0.53 | 0.87 |
| PB1 | COVID-19 vaccination is effective in improving immune function. | 0.65 | <.001 | | | |
| PB2 | COVID-19 vaccination is effective in reducing your risk of SARS-CoV-2 infection. | 0.75 | <.001 | | | |
| PB3 | COVID-19 vaccination is effective in reducing mortality caused by COVID-19. | 0.86 | <.001 | | | |
| PB4 | COVID-19 vaccination is effective in reducing the severity of COVID-19. | 0.81 | <.001 | | | |
| PB5 | COVID-19 vaccination is effective in reducing the risk of spreading. | 0.70 | <.001 | | | |
| PB6 | Getting COVID-19 vaccination can make you feel relieved. | 0.52 | <.001 | | | |
| **Perceived risks** | | | | 0.90 | 0.58 | 0.91 |
| PR1 | COVID-19 vaccination has severe side effects. | 0.81 | <.001 | | | |
| PR2 | COVID-19 vaccination uptake has a significant negative influence on the effectiveness of ART[c]. | 0.76 | <.001 | | | |
| PR3 | COVID-19 vaccination uptake can reduce immunity. | 0.70 | <.001 | | | |
| PR4 | You have concerns about the risk of exposing your PLWHA[d] identity when taking up the COVID-19 vaccine. | 0.69 | <.001 | | | |
| PR5 | COVID-19 vaccination uptake can bring trouble/psychological pressure. | 0.84 | <.001 | | | |
| PR6 | COVID-19 vaccination uptake may not produce protective antibodies due to HIV infection. | 0.80 | <.001 | | | |
| PR7 | The side effects of COVID-19 vaccination are severer for PLWHA than those without HIV infection. | 0.70 | <.001 | | | |
| **Self-efficacy** | | | | 0.92 | 0.70 | 0.92 |
| SFE1 | You will take up the COVID-19 vaccine even if it interrupts your daily routine. | 0.79 | <.001 | | | |
| SFE2 | You will get the COVID-19 vaccine even when you do not feel well. | 0.81 | <.001 | | | |
| SFE3 | You will get the COVID-19 vaccine even if the side effects would affect your daily activities. | 0.92 | <.001 | | | |
| SFE4 | You will get the COVID-19 vaccine even if HIV infection would reduce its effectiveness. | 0.84 | <.001 | | | |
| SFE5 | You will get the COVID-19 vaccine even if it reduces the effectiveness of ART. | 0.82 | <.001 | | | |
| **Subjective norms** | | | | 0.85 | 0.60 | 0.86 |
| SN1 | Your family members will support you to get the COVID-19 vaccine. | 0.88 | <.001 | | | |
| SN2 | Your HIV-infected friends will support you to get the COVID-19 vaccine. | 0.84 | <.001 | | | |
| SN3 | Medical professionals will support you to get the COVID-19 vaccine. | 0.74 | <.001 | | | |

| Constructs and items | Measures | Estimate | *P* value | Cronbach α | AVE[a] | CR[b] |
|---|---|---|---|---|---|---|
| SN4 | CBO[e] workers will support you to get the COVID-19 vaccine. | 0.62 | <.001 | | | |

[a] AVE: average variance extracted.

[b] CR: construct reliability.

[c] ART: antiretroviral therapy.

[d] PLWHA: person living with HIV/AIDS.

[e] CBO: community-based organization.

**Table 4.** Display discriminant validity analysis.

| Constructs | Perceived benefits | Perceived risks | Self-efficacy | Subjective norms |
|---|---|---|---|---|
| Perceived benefits | 0.53 | 0.32 | 0.34 | 0.19 |
| Perceived risks | 0.32 | 0.58 | –0.16 | –0.19 |
| Self-efficacy | 0.34 | –0.16 | 0.70 | 0.41 |
| Subjective norms | 0.19 | –0.19 | 0.41 | 0.60 |
| The square root of AVE[a] | 0.72 | 0.76 | 0.84 | 0.78 |

[a] AVE: average variance extracted.

### Structural Equation Modeling

Table 5 shows that the results supported hypothesis 1 (H1) to hypothesis 7 (H7). In other words, respondents who had higher perceived benefits, lower perceived risks, higher self-efficacy, and more support from social networks were more willing to receive the COVID-19 vaccine or were less hesitant to be vaccinated against COVID-19. Perceived benefits, perceived risks, and subjective norms yielded significant direct effects on self-efficacy (β=0.35; β=–0.25; β=0.30, respectively; all *P*<.001). The relationship between perceived benefits and vaccine hesitancy was partially mediated by self-efficacy (β=0.03, *P*<.001). The relationship between perceived risks and vaccine hesitancy also was partially mediated by self-efficacy (β=0.08, *P*<.001). Similarly, the relationship between subjective norms and vaccine hesitancy was partially mediated by self-efficacy (β=–0.29, *P*<.001). Furthermore, there were direct relationships between perceived benefits, perceived risks, and subjective norms and COVID-19 vaccine hesitancy (β=–0.15; β=–0.08; β=–0.29; β=–0.20, respectively; all *P*<.001). SEM results are visualized in Figure 2.

**Table 5.** Estimation results of the COVID-19 vaccine hesitancy model.

| Hypothesis | Unstandardized path coefficient | Standardized path coefficient | SE | CR[a] | *P* value | Support |
|---|---|---|---|---|---|---|
| H1:PB[b]-VH[c] | –0.17 | –0.15 | 0.03 | –5.33 | <.001 | Yes |
| H2:PR[d]-VH | 0.07 | 0.08 | 0.02 | 2.96 | <.001 | Yes |
| H3:SN[e]-VH | –0.44 | –0.29 | 0.04 | –11.00 | .003 | Yes |
| H4:SFE[f]-VH | –0.17 | –0.20 | 0.02 | –7.37 | <.001 | Yes |
| H5:PB-SFE | 0.49 | 0.35 | 0.00 | 12.20 | <.001 | Yes |
| H6:PR-SFE | –0.24 | –0.22 | 0.03 | –8.21 | <.001 | Yes |
| H7:SN-SFE | 0.56 | 0.30 | 0.05 | 11.72 | <.001 | Yes |

[a] CR: critical ratio.

[b] PB: perceived benefits.

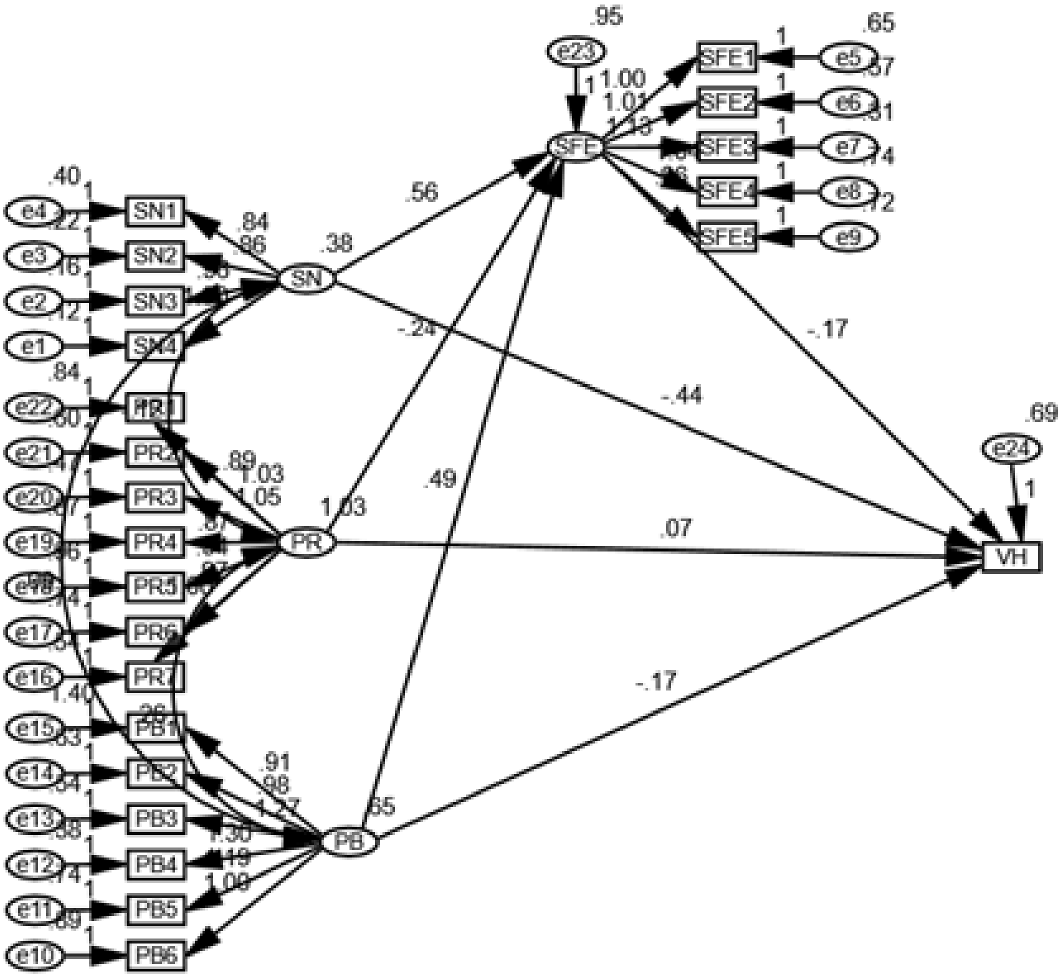
[c] VH: vaccine hesitancy.

[d] PR: perceived risk.

[e] SN: subjective norms.

[f] SFE: self-efficacy.

**Figure 2.** Structural equation modeling results on relationships of perceived benefits (PB), perceived risks (PR), subjective norms (SN), self-efficacy (SFE), and COVID-19 vaccine hesitancy (VH).



## Discussion

### Principal Findings

This study utilized SEM to investigate relationships among perceived benefits, perceived risks, self-efficacy, subjective norms, and COVID-19 vaccine hesitancy. The study found a high COVID-19 vaccine hesitancy rate among PLWHA in China. Factors associated with vaccine hesitancy were age, a history of chronic diseases, and other vaccinations in the past 3 years. In addition, confidence in COVID-19 vaccination showed the lowest mean of all measured indicators, while perceived risks had the highest mean score. People were highly concerned about possible HIV disclosure during the COVID-19 vaccination. The findings of this study provided valuable information on designing a COVID-19 vaccination campaign addressing possible barriers and improving COVID-19 acceptance among PLWHA.

In this study, 41.61% (722/1735) of participants reported COVID-19 vaccine hesitancy. The rate was higher than the result of 16.4% generated by a previous nationwide online survey in China [33]. Although the updated Chinese guideline included PLWHA for COVID-19 vaccination, PLWHA might have a higher vaccine hesitancy rate than the general population because of concerns about HIV disclosure, interactions with ART and HIV disease, side effects, and others. Moreover, the vaccine hesitancy rate was higher than that of PLWHA in other nations and regions. Various factors might contribute to the difference, such as sociocultural factors, national policy and guidance, and types of vaccines.

This study found that vaccine hesitancy was associated with age, and the relationship showed an inverted U-shaped curve. Except for the group aged 40-49 years, older participants showed higher vaccine hesitancy than the younger group. This finding was consistent with a recent French study [34]. Moreover, we found other vaccinations in the past 3 years and a history of chronic diseases were significant predictors of COVID-19 vaccine hesitancy. PLWHA who did not have other vaccinations in the past 3 years and had a history of chronic diseases were more hesitant be vaccinated against COVID-19. The findings could help promote COVID-19 vaccination among PLWHA. More detailed guidelines on COVID-19 vaccination for people with chronic diseases could be widely disseminated to the public and health care providers. PLWHA and HIV doctors must work on managing chronic diseases and eliminating concerns on COVID-19 vaccination.

We found perceived benefits, perceived risks, and subjective norms yielded significant direct effects on self-efficacy and COVID-19 vaccine hesitancy. The relationships between perceived benefits, perceived risks, subjective norms, and vaccine hesitancy were partially mediated by self-efficacy. The SEM results showed that the higher the perceived benefits, the higher the self-efficacy and the lower the degree of hesitation. Therefore, in order to reduce vaccine hesitation in PLWHA, an education campaign could be developed to provide evidence of the safety and effectiveness of the vaccine, highlighting the latest COVID-19 vaccination guidelines for PLWHA, and informing about the benefits of COVID-19 vaccination from both population and individual perspectives. Previous studies also have highlighted that the safety and efficacy of the COVID-19 vaccine were associated with individuals' vaccine hesitancy [35,36].

Perceived risks included participants' perceptions on vaccine safety and the fear of HIV disclosure. The SEM results showed that the higher the perceived risks, the lower the self-efficacy and the higher the degree of hesitation. Moreover, the fear of HIV disclosure during COVID-19 vaccination was a major concern. HIV stigma exists, and people might hesitate to disclose their HIV status when they receive a COVID-19 vaccine. Unintentional HIV disclosure and related stigma might aggravate their psychological burden [8,37,38]. Some strategies could be proposed to address COVID-19 vaccine hesitancy; for example, HIV clinics could collaborate with COVID-19 vaccination sites to provide COVID-19 vaccines to PLWHA. Health care providers at COVID-19 vaccination sites could underline and inform people about a protocol while protecting individuals' information and privacy.

Subjective norms included the support of family members, HIV-infected friends, medical professionals, and CBO workers. The SEM analysis results showed that, with a higher score for subjective norms, the higher the self-efficacy and the lower the degree of hesitation. PLWHA would prefer to accept suggestions regarding COVID-19 vaccination from the support of their family members. On the other hand, the support of an HIV-positive person and medical professionals showed less influence on PLWHA's decision making. It showed that PLWHA need the strength of their families. COVID-19 vaccination programs based on PLWHA families could be implemented to improve self-efficacy and reduce vaccine hesitancy in PLWHA through family support and mobilization. Although professional medical providers were one of the most trusted groups that could influence vaccine decision making [39], PLWHA could distrust medical staff because of HIV-related stigma and other reasons [40].

This study had limitations. First, this was a cross-sectional study, so no causality was established. Second, this survey was conducted in PLWHA from 5 large Chinese cities; therefore, the results may not be generalizable to PLWHA in China as COVID-19 vaccine availability, COVID-19 vaccine education, and regional policies and programs might be different among cities and regions. Third, because most of the reported PLWHAs in the 5 selected cities were male, the participants were also majority male. This may influence medical hesitancy, as women are more likely to access medical care. Fourth, because policies and guidelines related to the COVID-19 vaccine have been changing frequently, people's attitudes about COVID-19 vaccination may vary. Therefore, the findings were sensitive to some factors, such as political and vaccine-related circumstances. Fifth, most measurements in this study were self-constructed and adopted from existing measurements in the general population. The internal validity of these scales was acceptable. However, external validation data were unavailable. Finally, this study did not use random sampling based on the sampling framework, which cannot represent the current situation regarding the vaccination willingness of the entire PLWHA population in China. The extrapolation of the research results needs to be cautious.

## Conclusions

COVID-19 vaccine hesitancy was high among PLWHA in China. To reduce vaccine hesitation and increase vaccine coverage in PLWHA, social sectors, health facilities, and local communities must work on joint efforts and collaborations to implement strategies and programs that increase COVID-19 vaccination efficacy and eliminate barriers.

## Acknowledgments

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## Authors' Contributions

RC, YY, and JX conceptualized the study and wrote, reviewed, and edited the manuscript. RC, XH, XZ, SL, and YY designed the methodology. JY, XH, MY, GF, GL, QY, and QZ curated the data. RC, JY, and YY performed the formal analysis. JY, XH, MY, GF, and GL performed project administration. XH and JY obtained the resources. QZ, SL,YY, and JX supervised the study. YY and RC contributed equally as first authors. JY, XZ, SL and JX contributed equally as corresponding authors. All authors have read and approved the final manuscript as submitted.

## Conflicts of Interest

None declared.

Multimedia Appendix 1
The process of specific recruitment and data collection.
[DOCX File , 13 KB - publichealth_v8i6e33995_app1.docx ]

Multimedia Appendix 2
Supplementary tables.
[DOCX File , 34 KB - publichealth_v8i6e33995_app2.docx ]

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## Abbreviations

**ART:** antiretroviral therapy
**AVE:** average variance extracted
**CBO:** community-based organization
**CFI:** comparative fit index
**deff:** design effect
**IFI:** incremental fit index
**NFI:** normed fit index
**PLWHA:** people living with HIV/AIDS
**SEM:** structural equation modeling
**TLI:** Tucker-Lewis index

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Original Paper

# Mobile Phone Ownership and Use Among Women Screening for Cervical Cancer in a Community-Based Setting in Western Kenya: Observational Study

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## Abstract

**Background:** Mobile phone ownership among women of reproductive age in western Kenya is not well described, and our understanding of its link with care-seeking behaviors is nascent. Understanding access to and use of mobile phones among this population as well as willingness to participate in mobile health interventions are important in improving and more effectively implementing mobile health strategies.

**Objective:** This study aims to describe patterns of mobile phone ownership and use among women attending cervical cancer screening and to identify key considerations for the use of SMS text message–guided linkage to treatment strategies and other programmatic implications for cervical cancer screening in Kenya.

**Methods:** This analysis was nested within a cluster randomized trial evaluating various strategies for human papillomavirus (HPV)–based cervical cancer screening and prevention in a rural area in western Kenya between February and November 2018. A total of 3299 women were surveyed at the time of screening and treatment. Questionnaires included items detailing demographics, health history, prior care-seeking behaviors, and patterns of mobile phone ownership and use. We used bivariate and multivariable log-binomial regression to analyze associations between independent variables and treatment uptake among women testing positive for high-risk HPV.

**Results:** Rates of mobile phone ownership (2351/3299, 71.26%) and reported daily use (2441/3299, 73.99%) were high among women. Most women (1953/3277, 59.59%) were comfortable receiving their screening results via SMS text messages, although the most commonly *preferred* method of notification was via phone calls. Higher levels of education (risk ratio 1.23, 95% CI 1.02-1.50), missing work to attend screening (risk ratio 1.29, 95% CI 1.10-1.52), and previous cervical cancer screening (risk ratio 1.27, 95% CI 1.05-1.55) were significantly associated with a higher risk of attending treatment after testing high-risk HPV–positive, although the rates of overall treatment uptake remained low (278/551, 50.5%) among this population. Those who shared a mobile phone with their partner or spouse were less likely to attend treatment than those who owned a phone (adjusted risk ratio 0.69, 95% CI 0.46-1.05). Treatment uptake did not vary significantly according to the type of notification method, which were SMS text message, phone call, or home visit.

**Conclusions:** Although the rates of mobile phone ownership and use among women in western Kenya are high, we found that individual preferences for communication of messages about HPV results and treatment varied and that treatment rates were low across the entire cohort, with no difference by modality (SMS text message, phone call, or home visit). Therefore, although text-based results performed as well as phone calls and home visits, our findings highlight the need for more work to tailor communication about HPV results and support women as they navigate the follow-up process.

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**KEYWORDS**

cell phone; mobile health; mHealth; cervical cancer screening; Kenya; human papillomavirus; HPV testing

# Introduction

## Background

Cervical cancer disproportionately affects women in low- and middle-income countries (LMICs). It is the fourth most common cancer worldwide [1], with nearly 90% of cervical cancer–related deaths occurring in LMICs [1-3]. The vast majority of these deaths are preventable, as advances in screening methodologies, including cytology-based testing, have helped to decrease cervical cancer mortality in high-income countries [4,5]. Although the World Health Organization has recommended simplified and lower-cost screening strategies for LMICs, many countries such as Kenya still face a range of challenges in implementing and scaling cervical cancer prevention programs. These challenges include low numbers of trained health care providers, lack of physical and financial resources, complicated screening logistics, low community awareness of disease risk and screening opportunities, and personal health beliefs [6,7]. According to Kenya's 2014 Demographic and Health Surveys (DHS), only 14% of women surveyed had ever been screened for cervical cancer; however, the country experiences the highest cervical cancer incidence rate within the East African region (33.8 per 100,000 women) and one of the highest in the world [1,8]. Thus, new and innovative approaches are required to overcome the current shortcomings in screening and linkage to treatment.

Human papillomavirus (HPV)–based screening, recently endorsed by the World Health Organization for use in screen-and-treat strategies in LMICs [9], can be collected via self-sampling, facilitating the decentralization of care from health facilities into community settings. In addition, HPV-based screening can be offered by nonphysician clinicians. This could increase the availability and acceptance of testing among women in low-resource settings. However, to be effective, HPV-based screening programs must be accompanied by effective counseling and education and electronic tracking systems for laboratory results and patient follow-up. One strategy to bridge these system-, provider-, and patient-level gaps is through the use of mobile phone technology. Mobile phone–based health (mobile health [mHealth]) interventions appear to be promising solutions to many of the infrastructure- and access-related challenges faced by LMICs and nonurban communities [10,11]. Many approaches to using telecommunications technology, including the collection of client data, medication adherence notifications, service reminders, and knowledge sharing campaigns, have been implemented in a variety of settings [12-15].

The efficacy of mHealth interventions relies, in part, on the level of access to and ownership of mobile phones among target populations. Improvements in cell phone network capability, decreasing costs of mobile phone ownership, and urbanization have led to growing mobile phone ownership throughout sub-Saharan Africa [16,17]. In recent decades, there has been a significant increase in mobile phone access in Kenya, with mobile subscription rates increasing from 0.02 to 86.1 per 100 people between 1997 and 2017 [16,18,19]. However, disparities in cell phone ownership and access by gender, residence type (urban or rural), educational attainment, and wealth remain [20]. Women constitute more than half of those currently unreached by the mobile phone market, and those who are poorer and less educated tend to be even less connected [21,22]. An analysis of mobile phone access from Kenya's 2014 DHS revealed that 86.7% of women reported having a mobile phone in their household but did not provide insight into personal ownership, which is important to consider if potentially sensitive information is to be shared during an mHealth intervention [23]. Mobile phone ownership among women of reproductive age in western Kenya is not well described, and our understanding of its link with care-seeking behaviors is nascent. Understanding access to and use of mobile phones among this population as well as willingness to participate in mHealth interventions is important in improving and more effectively implementing mHealth strategies.

A recent cluster randomized trial in rural western Kenya showed that HPV testing via self-collection within community health campaigns (CHCs) was an acceptable and well-attended strategy for cervical cancer screening. However, the study found that treatment uptake among HPV-positive women was <50% [24]. Consequently, we used an enhanced strategy to link women to treatment, which used SMS text messages to provide women with screening results, educational content, and treatment reminders.

## Study Objectives

The objectives of this study were (1) to describe patterns of mobile phone ownership and use among women attending cervical cancer screening, (2) to identify key considerations for the use of SMS text message–guided linkage to treatment strategies and other programmatic implications for cervical cancer screening in Kenya, and (3) to determine whether mobile phone ownership or the method of results notification are independent predictors of treatment uptake among women who tested positive for HPV.

# Methods

## Study Setting and Sample

This analysis was nested within a cluster randomized trial evaluating various strategies for HPV-based cervical cancer screening and prevention in a rural area of western Kenya [24]. The cluster randomized trial enrolled women eligible for screening based on the Kenya Ministry of Health guidelines (aged 25-65 years with an intact uterus and cervix). High-risk human papillomavirus (hrHPV)–based screening was offered free of charge via self-sampling to women in health facilities or CHCs. To address levels of treatment uptake of <50%, the study staff engaged key stakeholders to develop an *enhanced linkage-to-treatment* strategy. The strategy included decentralized treatment sites with increased frequency and educational content via mobile phone messaging for women who had been screened for HPV. This study analyzed mobile phone ownership data and treatment uptake from the trial after the implementation of the enhanced strategy, which was identical across arms.

### Study Design

A total of 6 CHCs were conducted in Migori County, Kenya, between February and November 2018. Each CHC lasted 2 weeks and took place at different sites around the community with a predetermined schedule that was promoted during community mobilization. After self-collection and laboratory processing, the study staff notified women of their results via their preferred notification method: phone calls, SMS text messages, or home visits. Those who tested positive for hrHPV were referred to a treatment site deemed most accessible based on their community, where cryotherapy was available 5 days per week at no charge to the participants.

Data for this analysis originated from questionnaires administered at the time of screening and treatment (Multimedia Appendices 1 and 2). After informed consent was obtained, trained study staff verbally delivered the questionnaires and recorded participant responses electronically with tablets using OpenDataKit. The questionnaires included items detailing demographics, health history, prior care-seeking behaviors, and patterns of mobile phone ownership and use. Methods for data privacy and storage as well as specimen collection and storage have been described elsewhere [24].

### Quantitative Analysis

Women who attended one of the CHCs during the study period, consented to participate, completed the prescreening questionnaire, and were screened were included in this analysis. Basic descriptive statistics were used to characterize the study population. These included frequencies and percentages of demographic factors. In addition, we analyzed factors related to the implementation of SMS text messaging in screening and treatment strategies and their association with mobile phone ownership, compared using the chi-square test of independence. We considered women who reported personal ownership of their most frequently used mobile phone as mobile phone owners and those who did not report personal ownership but did report the use of a mobile phone as mobile phone sharers. Women who reported never having used a mobile phone were considered as nonusers. We carried out bivariate log-binomial regression to analyze associations between independent variables, including mobile phone ownership and chosen method of result notification, and the main outcome variable, attendance at treatment after having screened positive for hrHPV. We dichotomized treatment attendance, defined as attending a designated treatment facility within 3 months (not self-reported), as *no*=0 (did not attend treatment) and *yes*=1 (attended or attempted treatment). This distinction was made regardless of whether participants actually received treatment, as some were deemed ineligible for treatment because of pregnancy at the time of presentation, menses, or suspicion of cervical cancer. To control for potential confounding factors, age and all variables associated with the outcome (significant at the $P<.10$ level) in the bivariate analysis were included in the multivariable log-binomial regression analyses. We reported adjusted risk ratios and 95% CI resulting from multivariable log-binomial regression analysis and considered statistical significance at the 5% significance level (two-sided $P<.05$) for all tests. All aforementioned analyses were performed using STATA/SE 17 software (Stata Corporation).

### Ethics Approval

We obtained ethics approval for this study from the ethics review unit of the Kenya Medical Research Institute (protocol #2918) and the institutional review board of Duke University (protocol #Pro00077442). The parent cluster randomized trial was registered at ClinicalTrials.gov (NCT02124252). All participants provided written consent at the time of screening. The participants provided verbal affirmation during all follow-up visits.

## Results

Overall, 3299 women attended and were screened for HPV at one of the study CHCs. The average age was 38.2 (SD 11.3) years, with 60.02% (1980/3299) of the women aged between 25 and 39 years (Table 1). A large majority of the participants (2779/3299, 84.24%) reported having a primary school education or less, and very few participants (102/3299, 3.09%) had completed a collegiate degree. Nearly all women (3212/3299, 97.36%) who were screened were either married or widowed, and most (2364/2521, 93.77%) of those who reported having a partner lived with that person. The majority of women (1893/3299, 57.38%) worked outside of the home, and overall, women had an average of 4.9 (SD 2.9) children. Few women (497/3299, 15.06%) had previously been screened for cervical cancer, whereas almost all women (3185/3299, 96.54%) had previously been tested for HIV, and 24.29% (773/3182) of women self-reported that they were living with HIV. Although nearly all women (3252/3299, 98.58%) reported being sexually active, less than half of them (1328/3299, 40.25%) reported using modern family planning methods. The overall hrHPV positivity rate during CHCs was 16.70% (551/3299; Table 1).

**Table 1.** Demographic characteristics of the study population by mobile phone ownership in a prospective study of mobile phone ownership in Migori, Kenya, between February and November 2018.

| Characteristic | Total (N=3299) | Owners (n=2351) | Sharers (n=394) | Nonusers (n=554) |
|---|---|---|---|---|
| Age (years), mean (SD) | 38.2 (11.3) | 38.0 (10.9) | 35.4 (10.9) | 40.5 (12.6) |
| **Age (years; n=3295), n (%)** | | | | |
| 25-29 | 955 (29) | 647 (27.5) | 162 (41.1) | 146 (26.5) |
| 30-39 | 1025 (31.1) | 765 (32.6) | 112 (28.4) | 148 (26.8) |
| 40-49 | 686 (20.8) | 520 (22.1) | 67 (17.0) | 99 (17.9) |
| 50-59 | 453 (13.8) | 312 (13.3) | 39 (9.9) | 102 (18.5) |
| 60-65 | 176 (5.3) | 105 (4.5) | 14 (3.6) | 57 (10.3) |
| **Relationship status, n (%)** | | | | |
| Single | 37 (1.1) | 27 (1.1) | 5 (1.3) | 5 (0.9) |
| Single with partner | 11 (0.3) | 9 (0.4) | 1 (0.2) | 1 (0.2) |
| Married | 2510 (76.1) | 1779 (75.7) | 348 (88.3) | 383 (69.1) |
| Widowed | 702 (21.3) | 502 (21.3) | 39 (9.9) | 161 (29.1) |
| Separated or divorced | 39 (1.2) | 34 (1.5) | 1 (0.3) | 4 (0.7) |
| **Live with partner (n=2521), n (%)** | | | | |
| Yes | 2364 (93.8) | 1655 (92.6) | 341 (97.7) | 368 (95.8) |
| No | 157 (6.2) | 133 (7.4) | 8 (2.3) | 16 (4.2) |
| **Education level, n (%)** | | | | |
| Primary school or less | 2779 (84.2) | 1900 (80.8) | 346 (87.8) | 533 (96.2) |
| Some secondary school | 520 (15.8) | 451 (19.2) | 48 (12.2) | 21 (3.8) |
| **Work outside of home, n (%)** | | | | |
| Yes | 1893 (57.4) | 1442 (61.3) | 194 (49.2) | 257 (46.4) |
| No | 1406 (42.6) | 909 (38.7) | 200 (50.8) | 297 (53.6) |
| Number of children, mean (SD) | 4.9 (2.9) | 4.8 (2.8) | 4.8 (3.1) | 5.4 (3.1) |
| **Previous cervical cancer screening, n (%)** | | | | |
| Yes | 497 (15.1) | 413 (17.6) | 41 (10.4) | 43 (7.8) |
| No | 2799 (84.8) | 1937 (82.4) | 353 (89.6) | 509 (91.9) |
| Unsure | 3 (0.1) | 1 (0) | 0 (0) | 2 (0.3) |
| **Previous testing for HIV, n (%)** | | | | |
| Yes | 3185 (96.5) | 2288 (97.3) | 379 (96.2) | 518 (93.5) |
| No | 102 (3.1) | 57 (2.4) | 14 (3.6) | 31 (5.6) |
| Unsure | 12 (0.4) | 6 (0.3) | 1 (0.2) | 5 (0.9) |
| **HIV status (n=3182)[a], n (%)** | | | | |
| Positive | 773 (24.3) | 587 (25.7) | 63 (16.6) | 123 (23.7) |
| Negative | 2390 (75) | 1688 (73.8) | 313 (82.6) | 389 (75.1) |
| Unsure | 19 (0.6) | 10 (0.4) | 3 (0.8) | 6 (1.2) |
| **Currently using family planning or contraception, n (%)** | | | | |
| Yes | 1328 (40.3) | 996 (42.4) | 165 (41.9) | 167 (30.1) |
| No | 1921 (58.2) | 1323 (56.3) | 221 (56.1) | 377 (68.1) |
| Unsure | 3 (0.1) | 2 (0.1) | 0 (0) | 1 (0.2) |
| Not sexually active | 47 (1.4) | 30 (1.3) | 8 (2) | 9 (1.6) |
| **Human papillomavirus result, n (%)** | | | | |

| Characteristic | Total (N=3299) | Owners (n=2351) | Sharers (n=394) | Nonusers (n=554) |
|---|---|---|---|---|
| Positive | 551 (16.7) | 393 (16.7) | 66 (16.8) | 92 (16.6) |
| Negative | 2748 (83.3) | 1958 (83.3) | 328 (83.2) | 462 (83.4) |

[a] A total of 3 participants refused to answer.

Among the 83.21% (2745/3299) of participants who reported having ever used a mobile phone, 85.64% (2351/2745) reported owning a mobile phone, and 14.31% (394/2745) reported sharing a mobile phone with their partner, child, family members, friends, neighbors, or other individuals. Compared with those who shared or did not use a mobile phone, mobile phone owners tended to be more highly educated, more commonly did not live with their partner, worked outside of the home at a greater proportion, and had fewer children. In addition, these women demonstrated greater health seeking behavior, as they had previously screened for HPV, tested for HIV, and used modern family planning methods at a higher proportion than mobile phone sharers and nonusers. Proportions of previous cervical cancer screening, HIV testing, and contraceptive use were the lowest among women who had never used a mobile phone. Self-reported HIV-positive status was more common among those who owned a mobile phone as compared with those who did not. No appreciable difference in hrHPV positivity was observed according to mobile phone ownership (Table 1).

Nearly three-quarters of women who shared their mobile phones did so with a spouse or partner, whereas few shared with children, other family members, friends, and neighbors. Although most women who reported having used a mobile phone said they used the device 7 days a week, a greater proportion of mobile phone owners used their device daily when compared with sharers (Table 2). Frequent technical issues were reported by both owners and sharers. A total of 56.81% (1559/2744) of women reported encountering challenges with use on a weekly basis, whereas just over approximately 13% (350/2744) reported daily issues. Approximately 15% (412/2744) of the participants stated that they never faced challenges using their device. Nearly two-thirds of women felt comfortable reading and receiving SMS text messages, whereas a quarter said they were unable to do so. Similarly, the majority of women were comfortable writing and sending SMS text messages. As expected, comfort with SMS text messages was not commonly reported by nonusers.

Most women (1953/3277, 59.60%) said that they would be comfortable receiving hrHPV test results via SMS text message, with 20.48% (671/3277) being very comfortable and 39.12% (1282/3277) being comfortable. Mobile phone owners and sharers dominated this majority, as only approximately 14% of nonusers reported comfort with SMS text message for notification of results (Table 3). However, when given the choice between different notification types, only 1 out of 4 women (25.98%) said that they would *prefer* to receive their results by SMS text message if negative, with 22.52% (743/3299) of women preferring SMS text message if their HPV result was positive. Of the 3.46% (114/3299) of participants whose preference for SMS text message changed based on possible HPV results, the overwhelming majority preferred a phone call for their results, whereas very few indicated a preference for home visits if their HPV result was positive. SMS text message was the only notification method that showed such variation based on potential screening outcome (Table 3). Preference for home visit result notification remained the same regardless of the hypothetical HPV result, whereas the proportion of women preferring a phone call decreased slightly if the result was positive. Regardless of mobile phone ownership, most women willing to receive results via SMS text message preferred notifications in Dholuo or English.

Overall, half of the surveyed women *preferred* to receive a phone call for results, either positive or negative, with the second most common method being home visits if positive and SMS if negative. However, notification method preferences varied significantly by mobile phone ownership. Nearly all women who reported personal ownership of a mobile phone preferred a phone-based method for notification of results (2100/2351, 89.32% if hrHPV-positive, and 2171/2351, 92.34% if hrHPV-negative). A lower proportion of mobile phone sharers preferred a phone-based notification (243/394, 61.7% if hrHPV-positive, and 251/394, 63.7% if hrHPV-negative). Unsurprisingly, very few nonusers preferred a phone-based notification (68/554, 12.3% if hrHPV-positive, and 71/554, 12.8% if hrHPV-negative; $P<.001$ if negative or positive).

In bivariable analysis, at least a secondary education, having missed work to attend screening, and previous cervical cancer screening resulted in a significantly higher risk of treatment uptake (crude risk ratio 1.23, 95% CI 1.02-1.50; crude risk ratio 1.29, 95% CI 1.10-1.52; and crude risk ratio 1.27, 95% CI 1.05-1.55, respectively; Table 4). In addition, the unadjusted risk of treatment uptake among women who shared a mobile phone with their spouse or partner was significantly lower than that among those who owned their own phone (crude risk ratio 0.65, 95% CI 0.43-0.97; Table 5). The unadjusted risk of treatment uptake was highest among those who received an SMS text message for result notification, although not significantly higher than phone calls or home visits in the bivariable analysis (Table 6). Number of children, working outside of the home, use of modern family planning methods, being told to attend screening by a family member, and frequency of mobile phone use were not significantly associated with treatment uptake, and therefore, they were not considered in multivariable analysis (Table 4). In multivariable analysis, the risk of treatment uptake for women who shared a mobile phone with their spouse or partner was lower than that for those who owned a mobile phone (adjusted risk ratio 0.69, 95% CI 0.46-1.05); however, the difference was not statistically significant. There was no appreciable difference in the risk of treatment uptake between mobile phone owners and nonusers (Table 5). In addition, when accounting for at least a secondary education, having missed work to attend screening, previous cervical cancer screening, and mobile phone ownership, the risk of treatment uptake did not vary significantly by notification type.

**Table 2.** Patterns of mobile phone ownership and use among women attending community-based cervical cancer screening in a prospective study in Migori, Kenya, between February and November 2018.

| Technology use characteristics | Total (N=3299), n (%) | Owners (n=2351), n (%) | Sharers (n=394), n (%) |
|---|---|---|---|
| **Owner of commonly used mobile phone (n=2745)** | | | |
| My own | 2351 (85.6) | 2351 (100) | N/A[a] |
| Spouse or partner | 288 (10.5) | N/A | 288 (73.1) |
| Child | 34 (1.2) | N/A | 34 (8.6) |
| Other family | 30 (1.1) | N/A | 30 (7.6) |
| Others | 42 (1.5) | N/A | 42 (10.7) |
| **Frequency of mobile phone use among users (n=2745)** | | | |
| <7 days a week | 304 (11.1) | 138 (5.9) | 166 (42.1) |
| 7 days a week | 2441 (88.9) | 2213 (94.1) | 228 (57.9) |
| **Frequency of technical issues (n=2744)[b]** | | | |
| Never | 393 (14.3) | 346 (14.7) | 47 (11.9) |
| At least once per month | 313 (11.4) | 274 (11.6) | 39 (9.9) |
| At least once per week | 1559 (56.8) | 1379 (58.7) | 180 (45.7) |
| At least once per day | 350 (12.8) | 305 (13.0) | 45 (11.4) |
| Unsure | 115 (4.2) | 35 (1.5) | 80 (20.3) |
| Other | 15 (0.5) | 11 (0.5) | 3 (0.8) |
| **Comfort reading and receiving SMS text message** | | | |
| Not able | 814 (24.7) | 384 (16.3) | 87 (22.1) |
| Very uncomfortable | 68 (2.1) | 39 (1.7) | 7 (1.8) |
| Uncomfortable | 295 (8.9) | 149 (6.3) | 45 (11.4) |
| Comfortable | 1453 (44.0) | 1197 (50.9) | 190 (48.2) |
| Very comfortable | 650 (19.7) | 580 (24.7) | 57 (14.5) |
| Unsure | 19 (0.6) | 2 (0.1) | 8 (2.0) |
| **Comfort writing and sending SMS text message (N=3298)[b]** | | | |
| Not able | 912 (27.6) | 465 (19.8) | 95 (24.1) |
| Very uncomfortable | 68 (2.1) | 39 (1.7) | 6 (1.5) |
| Uncomfortable | 372 (11.3) | 215 (9.2) | 54 (13.7) |
| Comfortable | 1275 (38.7) | 1046 (44.5) | 176 (44.7) |
| Very comfortable | 644 (19.5) | 576 (24.5) | 55 (14.0) |
| Unsure | 27 (0.8) | 10 (0.4) | 7 (1.8) |

[a] N/A: not applicable.

[b] One participant refused to answer.

**Table 3.** Considerations for programmatic implementation and an SMS text message–guided linkage to treatment strategy based on a study of mobile phone ownership in Migori, Kenya, between February and November 2018.

| Programmatic considerations | Total (N=3299), n (%) | Owners (n=2351), n (%) | Sharers (n=394), n (%) | Nonusers (n=554), n (%) |
|---|---|---|---|---|
| **Comfort receiving screening results via SMS text message (n=3277)**[a] | | | | |
| Very uncomfortable | 327 (10) | 153 (6.5) | 25 (6.3) | 149 (27.9) |
| Uncomfortable | 892 (27.2) | 508 (21.6) | 133 (33.8) | 251 (47) |
| Comfortable | 1282 (39.1) | 1058 (45) | 165 (41.2) | 59 (11) |
| Very comfortable | 671 (20.5) | 604 (25.7) | 55 (14) | 12 (2.2) |
| Unsure | 105 (3.2) | 27 (1.2) | 15 (3.8) | 63 (11.8) |
| **Preferred notification method if HPV[b]-negative[c]** | | | | |
| SMS text message | 857 (26) | 777 (33) | 61 (15.5) | 19 (3.4) |
| Phone call | 1636 (49.6) | 1394 (59.3) | 190 (48.2) | 52 (9.4) |
| Home visit | 806 (24.4) | 180 (7.7) | 143 (36.3) | 483 (87.2) |
| **Preferred notification method if HPV-positive[c]** | | | | |
| SMS text message | 743 (22.5) | 666 (28.3) | 59 (15) | 18 (3.2) |
| Phone call | 1668 (50.6) | 1434 (61) | 184 (46.7) | 50 (9) |
| Home visit | 888 (26.9) | 251 (10.7) | 151 (38.3) | 486 (87.7) |
| **Preferred language of SMS notification (n=897)** | | | | |
| English | 184 (20.5) | 174 (21.5) | 7 (10.4) | 3 (15) |
| Kiswahili | 164 (18.3) | 142 (17.5) | 20 (29.9) | 2 (10) |
| Dholuo | 549 (61.2) | 494 (61) | 40 (59.7) | 15 (75) |

[a] A total of 22 participants refused to answer (20 of which were nonusers).

[b] HPV: human papillomavirus.

[c] Participants were asked about notification preferences at the time of screening, before knowing their HPV status. These are intended to convey women’s preferences in the event of a positive or negative result. This is not a comparison of method preference based on actual screening results.

**Table 4.** Factors associated with treatment uptake in bivariate analysis among women in a prospective study in Migori, Kenya, between February and November 2018 (n=551).

| Characteristic | Treatment uptake | No treatment uptake | Crude risk ratio (95% CI) |
|---|---|---|---|
| Age (years), mean (SD) | 36.4 (10.6) | 35.5 (10.6) | 1.00 (1.00-1.01) |
| **Education level, n (%)** | | | |
| Primary school or less | 224 (48.6) | 237 (51.4) | —[a] |
| Some secondary school | 54 (60) | 36 (40) | 1.23 (1.02-1.50) |
| Number of children, mean (SD) | 4.5 (2.8) | 4.1 (2.7) | 1.02 (1.00-1.05) |
| **Work outside of home, n (%)** | | | |
| No | 110 (46.6) | 126 (53.4) | — |
| Yes | 168 (53.3) | 147 (46.7) | 1.14 (0.96-1.36) |
| **Missed work to attend screening, n (%)** | | | |
| No | 165 (45.8) | 195 (54.2) | — |
| Yes | 113 (59.2) | 78 (40.8) | 1.29 (1.10-1.52) |
| **Told by family to attend screening, n (%)** | | | |
| No | 96 (46.2) | 112 (53.8) | — |
| Yes | 182 (53.1) | 161 (46.9) | 1.15 (0.96-1.37) |
| **Previous cervical cancer screening, n (%)** | | | |
| No | 228 (48.5) | 242 (51.5) | — |
| Yes | 50 (61.7) | 31 (38.3) | 1.27 (1.05-1.55) |
| **Currently using family planning or contraception, n (%)** | | | |
| No | 151 (49.5) | 154 (50.5) | — |
| Yes | 124 (52.5) | 112 (47.5) | 1.06 (0.90-1.25) |
| Not sexually active | 2 (22.2) | 7 (77.8) | 0.45 (0.13-1.53) |
| **Frequency of mobile phone use, n (%)** | | | |
| <7 days a week | 18 (38.3) | 29 (61.7) | — |
| 7 days a week | 212 (51.5) | 200 (48.5) | 1.34 (0.92-1.95) |

[a] Reference category.

**Table 5.** Effect of mobile phone ownership on treatment uptake among women in Migori, Kenya, between February and November 2018 (n=551).

| Mobile phone ownership | Treatment uptake, n (%) | No treatment uptake, n (%) | Crude risk ratio (95% CI) | Adjusted risk ratio[a] (95% CI) |
|---|---|---|---|---|
| Owners | 207 (52.7) | 186 (47.3) | —[b] | — |
| **Sharers** | | | | |
| Spouse or partner | 16 (34) | 31 (66) | 0.65 (0.43-0.97) | 0.69 (0.46-1.05) |
| Other[c] | 7 (36.8) | 12 (63.2) | 0.70 (0.39-1.27) | 0.69 (0.38-1.25) |
| Nonusers | 48 (52.2) | 44 (47.8) | 0.99 (0.80-1.23) | 1.06 (0.84-1.32) |

[a] Adjusted for having missed work to attend screening, prior cervical cancer screening, age, and education.

[b] Reference category.

[c] Includes children, other family, friends, neighbors, and others.

**Table 6.** Effect of notification type on treatment uptake among women in Migori, Kenya, between February and November 2018 (n=551).

| Notification type | Treatment uptake, n (%) | No treatment uptake, n (%) | Crude risk ratio (95% CI) | Adjusted risk ratio[a] (95% CI) |
|---|---|---|---|---|
| SMS text message | 72 (56.3) | 56 (43.7) | —[b] | — |
| Phone call | 135 (48.7) | 142 (51.3) | 0.87 (0.71-1.05) | 0.92 (0.76-1.12) |
| Home visit | 71 (48.6) | 75 (51.4) | 0.86 (0.69-1.08) | 0.89 (0.67-1.19) |

[a] Adjusted for having missed work to attend screening, prior cervical cancer screening, age, education, and mobile phone ownership (owner, sharer, and nonuser).

[b] Reference category.

## Discussion

### Principal Findings

This study examined patterns of mobile phone ownership and use among women screening for cervical cancer in western Kenya. Mobile phone ownership rates and reported daily use were high, with more than three-quarters of women having ever used a mobile phone and ≥7 in 10 women owning their own phone. Most women were comfortable receiving their screening results via SMS text messages, although the most commonly *preferred* method of notification was via phone calls. Those who shared a mobile phone with their spouse or partner were less likely to attend treatment than those who owned a phone; however, overall, the method by which women received their screening results did not significantly impact their treatment uptake.

Understanding mobile phone ownership and comfort with use are essential for planning mHealth interventions. We observed rates of mobile phone ownership and use consistent with similar studies of women of reproductive age in sub-Saharan Africa, namely, Ethiopia, Burkina Faso, and Nigeria, which reported rates between 46% and 77% [25-27]. Although a recent study from northern Kenya reported mobile phone access at 99% among a small sample of women (n=104), our results seem more aligned with an analysis of mobile phone access conducted by Lee et al [23], who analyzed Kenya's 2014 DHS mobile phone data in relation to contraceptive knowledge and use [28]. This nationally representative survey of 31,059 women reported mobile phone access of 87%, which is consistent with our data [23]. However, women surveyed for the DHS were asked about household-level access rather than personal-level ownership [23]. Such a distinction and related differences in women's access are important to consider, especially given the sensitive nature of information that may be shared regarding HPV test results, treatment plans, and posttreatment instructions around sexual activity. Women who share a mobile phone with a partner or child may be less willing to engage in such interventions because of fear of unwanted disclosure or breach of privacy.

Many studies have identified links between mobile phone access and care-seeking behaviors [23,26,27,29]. Although the results of this study did not show a relationship between mobile phone ownership and treatment uptake, our data highlight many important considerations for the use of mHealth interventions. First, the ability to read, write, send, and receive SMS text messages among one's target population is important to consider when designing text-based mHealth interventions. If populations have high levels of comfort with such tasks, as demonstrated by this survey, additional avenues of communication may be available between clients and providers. In addition to the unidirectional transmission of information, such as treatment or medication reminders, two-way communication is made possible, which could increase communication between client and provider and potentially reduce unnecessary visits to health facilities, freeing up time and space for health care workers. Such channels of communication can be maintained by live health workers or by automated chatbots and other algorithms. Given the high reported comfort with screening results via SMS text message, as well as comfort with reading, writing, sending, and receiving SMS text messages, such strategies appear feasible within western Kenya. Second, although mHealth has shown promise in bridging logistical gaps in similar situations, programs must ensure alternative means of communication or contact between health facilities and target populations to provide adequate and equitable access to women with varying levels of mobile connectivity or mobile phone access. In their work in Burkina Faso, Greenleaf et al [26] refer to such variance in access as "selective ownership" and argue that this can create an "ownership bias" in mHealth intervention uptake, making it difficult to reach populations most as risk. Such pitfalls can decrease intervention efficacy and alienate women who do not own or have access to a mobile phone, which based on our data, would exclude women with lower levels of educational attainment and poorer health seeking behaviors, putting them at risk for worse health outcomes. "Pre-intervention assessment," as suggested by Jennings et al [27] conducting research in Nigeria, could illuminate such issues and allow health officials to preempt and address problems of equity for women in the intervention setting.

In addition to the aforementioned mHealth intervention considerations, this study illustrated the need for further research on a variety of topics related to the implementation of mHealth for cervical cancer screening. More information is needed to understand the lack of preference for text notification and why preferences change depending on the hrHPV status. The decrease in preference for SMS text message result notification if a participant was to screen hrHPV-positive compared with hrHPV-negative is likely a result of a desire for increased privacy, which could be related to cultural factors such as stigma. However, our data do not allow us to draw concrete conclusions on this, as we did not ask about factors that influenced preference, or lack thereof. Further studies should be conducted to survey women of reproductive age to help better understand these barriers and facilitators of SMS text message use and privacy as well as strategies for messaging at the time of screening, which would make SMS text messages more appealing. Second, frequent challenges and technical difficulties when using mobile phones were reported among the study population. These challenges could limit the feasibility and efficacy of an SMS text message–based system, as testing results and treatment reminders may be missed or not received owing to technical issues. Further examination of the nature of technical challenges and how they might impact the receipt of SMS text messages from program implementors is needed to further tailor this campaign. Third, regardless of the differences in treatment access by mobile phone ownership, the overall uptake remained low, even after the implementation of the enhanced linkage to the treatment strategy. Although this low level of treatment uptake (50.5%) improves upon treatment rates observed before implementation of the enhanced linkage strategy (between 31% and 39% uptake), the consistently low levels highlight the need for further exploration of opportunities for multipronged approaches to increasing uptake and access to care [24]. Identifying and bridging gaps in the cervical cancer prevention cascade is necessary to address the inequitable and preventable deaths caused by this disease. Finally, given the potential health benefits and increases in autonomy, there is a need to support increases in access to mobile phones and mobile phone networks for women of reproductive age [22].

## Limitations

Although we achieved a large sample size among the target population of women in rural Kenya, the study had a number of limitations. First, although treatment uptake was measured at the time of presentation to the clinic, the self-reported nature of our survey data limited our ability to make strong claims about the observed patterns of mobile phone ownership and use and how they impacted uptake. In addition, social desirability bias could have led to measurement errors, with women not accurately reporting health behaviors or mobile phone use given societal expectations. In addition, as services confirming receipt or review of SMS text messages would have imparted costs to the participants, we did not collect this information and were not able to report on how this may have affected treatment uptake. Although socioeconomic status was relatively homogenous among our study population, there was no strong operationalization of socioeconomic status within the survey. Therefore, it is difficult to conclude whether the observed associations are because of mobile phone ownership or a more upstream effect of economic status. Finally, our data may lack generalizability as we only considered women who attended a CHC, which is a self-selective action and could be affected by many factors. If such factors systematically inhibit a significant portion of women from these locations, the results of this study would be biased and not generalizable to the target population as a whole. A random, community-based, representative survey is warranted to evaluate the validity and generalizability of the findings of this study.

## Conclusions

This study examined the rates of mobile phone ownership, access, and the patterns of daily use among women of reproductive age in western Kenya. In addition, we highlighted many key considerations for the implementation of mHealth interventions in resource-limited settings, specifically those using SMS text messaging. Although rates of mobile phone ownership and use among women in western Kenya are high, we found that individual preferences for communication of messages about HPV results and treatment varied, and treatment rates were low across the entire cohort, with no difference by modality (SMS text message, phone call, or home visit). Further work is needed to tailor communication about HPV results and to support women as they navigate the follow-up process.

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## Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire administered at screening.
[DOC File , 453 KB - publichealth_v8i6e28885_app1.doc ]

Multimedia Appendix 2
Questionnaire administered at treatment.
[DOCX File , 159 KB - publichealth_v8i6e28885_app2.docx ]

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## Abbreviations

**CHC:** community health campaign
**DHS:** Demographic and Health Surveys
**HPV:** human papillomavirus
**hrHPV:** high-risk human papillomavirus
**LMIC:** low- and middle-income country
**mHealth:** mobile health

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