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Letter to the Editor

Allocation of scarce public health resources: ethical principles, COVID-19 vaccines, and the need for socially optimal dosing

Decision-making regarding scarce public health resource allocation is intrinsically ethical,[1] and so is directly relevant to the expected professional standards.[2] An ethical framework of four simple categories, each composed of two morally relevant principles, is generally considered to inform such decision-making.[3] The first is equality, which requires that all citizens be treated equally. This may be achieved through first-come, first-served access to resources (1a), or a lottery process, in which all individuals have an equal chance of selection (1b). The second is favoring the worst-off, which requires the prioritization of certain groups. This may be achieved by prioritizing those at the highest risk of poor outcomes (2a) or those who have lived the least life to date (2b). The third is utilitarianism, which requires maximizing aggregate benefits across a population. This may be achieved by maximizing the number of individual lives saved (3a), or by maximizing the number of life-years produced by considering prognoses across various groups (3b). The fourth is promoting and rewarding social usefulness. This may be achieved by a future-oriented recognition of instrumental value (4a) or past-oriented reciprocity of implemented behaviors (4b). While some are morally flawed (such as 1a), each of these principles is individually insufficient, meaning they must be combined into multiprinciple combinations to inform scarce resource allocation decision-making.

A pertinent example of such ethical decision-making is the ongoing allocation of COVID-19 vaccines. While presently less scarce in high-income societies, demand for these pharmaceuticals far exceeded supply in the initial stages of roll-out strategies and continues to do so in resource-poor settings. Examining a country's vaccination strategy reveals the ethical principles underlying its decision-making. For example, the United Kingdom[4] prioritized its highest risk groups (2a), including older, pregnant, and immunocompromized people. It also recognized the instrumental value of front-line healthcare workers (4a) by vaccinating professionals in patient-facing roles. Finally, it maximized aggregate benefits across its population by extending the interval between first and second doses, which served to increase the number of individual lives saved (3a) by administering first doses to more people sooner.

Using this ethical framework to examine the United Kingdom's vaccination strategy allows exploration of whether its moral acceptability may have been improved by the adoption of alternative multiprinciple combinations. For example, the use of a lottery (1b) would have reified equality and reduced discrimination against those not prioritized. By favoring younger people (2b), those who have lived the least amount of life would have been afforded the opportunity to live as long as existing elderly people. Finally, socially optimal vaccine dosing would have maximized aggregate benefits by increasing the total number of individual lives saved (3a).

While socially optimal vaccine dosing promises to maximize aggregate benefits across society, it is to date an unutilized strategy on the international stage.[5] Such strategies permit the administration of a less individually efficacious dose of a scarce resource to a larger number of people to increase its marginal efficacy within a specific population. For example, consider a 5000 μg supply of a scarce vaccine of which 50 μg and 25 μg doses are 95% and 75% effective at preventing death in the same at-risk population, respectively. In a population of 2000 people who would otherwise die, administering the 50 μg dose to 1000 people prevents 50 deaths but leaves 1000 individuals unprotected, thereby resulting in 1050 deaths, while administering the 25 μg dose to 2000 people prevents 1500 deaths, thereby resulting in 500 deaths. As such, 550 more deaths are prevented by administering the less individually efficacious dose to the entire population than administering the more individually efficacious dose to half of it. The marginal utility of the vaccine—the number of deaths averted per μg administered—has been increased, rendering this strategy more distributively just than its alternative.[6] While insufficient on an individual basis, this strategy is void of ethical flaws, rendering it a viable candidate for inclusion in multiprinciple combinations to underlie decision-making regarding scarce resource allocation.

Scarcity renders public health resource allocation an inherently ethical decision space. Using the above framework to examine a country's COVID-19 vaccination strategy provides opportunities to identify ethical principles that could be recruited to improve the moral acceptability of future decision-making regarding scarce public health resource allocation. For achieving this, socially optimal vaccine dosing should be made routinely available for all new vaccines. This necessitates exploration of a vaccine's dose-response relationship through randomized dose-finding clinical trials to reveal the socially optimal dose under conditions of scarcity. Such knowledge could deliver distributive justice by maximizing social benefits and mitigating inequalities.

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Original Research

Assessing humoral immune response after two doses of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthcare workers

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ABSTRACT

Objectives: During COVID-19 pandemic, the absence of immunity in the population left them susceptible to infection with SARS-CoV-2; healthcare workers (HCWs) being in the highest risk group. This study intends to assess and follow up the humoral immunity in HCWs vaccinated with an inactive virus vaccine (CoronaVac).

Study design: This is a prospective observational study.

Methods: A total of 1072 HCWs were investigated for the presence of immunoglobulin G antibodies to the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2 after vaccination. Blood samples were obtained after 28 days of the first dose, 21 days of the second dose, and 3 months after the second dose. Detection of antispike antibodies was performed by the chemiluminescent microparticle immunoassay method (SARS-CoV-2 IgG II Quant, Abbott, Ireland). The results greater than or equal to the cutoff value of 50.0 AU/mL were reported as positive.

Results: Four weeks after the first dose of vaccine, antispike antibodies were detected in 834/1072 (77.8%) of HCWs. Seropositivity was higher among females (84.6%) than males (70.6% $p < 0.001$) and was found to be highest in both women and men between the ages of 18–34 years. Antispike antibodies were detected in 1008 of 1012 (99.6%) after 21 days of the second dose and in 803 of 836 (96.1%) after 3 months of the second dose.

Conclusions: CoronaVac was found to be highly immunogenic after two consecutive doses performed 28 days apart to HCWs; however, the immunogenicity declined significantly ($p < 0.001$) after 3 months following the second dose of vaccine.

Introduction

Since the COVID-19 outbreak began, researchers around the world have been trying to develop vaccines against 'Severe Acute Respiratory Syndrome Coronavirus 2' (SARS-CoV-2), with more than 200 vaccines being currently in preclinical or clinical development.[1] Efforts toward the development of a vaccine have led to several candidate vaccines, including inactivated vaccines, live virus vaccines, recombinant protein vaccines, vectored vaccines, and DNA or RNA vaccines.[2–5]

CoronaVac is a chemically inactivated whole virus vaccine for COVID-19 developed by Chinese biopharmaceutical company Sinovac Biotech (Beijing, China) and is created from African green monkey kidney cells (Vero cells) that have been inoculated with SARS-CoV-2 CN02 strain. It has shown good immunogenicity in mice, rats, and non-human primates with vaccine-induced neutralizing antibodies, which could neutralize 10 representative strains of SARS-CoV-2.[6]

CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2, which supported the approval of emergency use of CoronaVac in China in July 2020.[7] It is being used in vaccination campaigns by certain countries in Asia, South and North America, and Europe also. As of March 2021, 70 million doses of CoronaVac had been administered worldwide. CoronaVac elicited anti–receptor-binding domain (RBD) antibodies and neutralizing antibodies in 97.4% of individuals receiving the vaccine at 0 and 28 days.[8]

Within the scope of combating COVID-19 pandemic, Turkish Ministry of Health had given emergency use approval for the use of CoronaVac and vaccination in Turkey started with priority groups, primary healthcare workers (HCWs) on January 14, 2021. On June 1, 2021, WHO validated CoronaVac for emergency use, giving

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countries, funders, procuring agencies, and communities the assurance that it meets international standards for safety, efficacy, and manufacturing.

Vaccination has been shown to provide potent protection from COVID-19; however, there are concerns that waning immunity and viral variation may lead to a loss of protection over time.[9] Elucidation of the kinetics and duration of the humoral response induced by active immunization is important for interpreting results from serological surveys and for the management of COVID-19. To determine the humoral immune response induced by CoronaVac against SARS-CoV-2 after two consecutive doses and to guess the need for the administration of a third or booster dose, we planned to detect antispike antibodies in HCWs after the first and second doses, as well as after 3 months following the second dose of vaccine.

Methods

Study setting

HCWs of both genders, aged ≥18 years, who agreed to participate in this prospective study and those who underwent two-dose (28-day interval) SARS-CoV-2 vaccination with CoronaVac between January 14, 2021, and February 21, 2021, were included. The study, approved by the Ministry of Health Scientific Research Platform, was run at the microbiology laboratory of Sanko Hospital, which is a tertiary-care teaching university hospital located in Gaziantep, Turkey. Ethics approval was obtained from Institutional Clinical Research Ethics Committee (Approval number: 2021/02/01). All participants signed the voluntary informed consent form ensuring they undergo screening evaluation and completed a questionnaire consisting of 17 questions designed to obtain information about demographic and clinical data including former exposure to COVID-19. HCWs who refused vaccination or were not able to finish sample collection were excluded.

Vaccination protocol

The vaccine used in this study was manufactured by Sinovac Biotech (Beijing, China) from inactivated CN02 strain of SARS-CoV-2 created from Vero cells and contained 3 μg/0.5 mL (equivalent to 600 SU per dose) and aluminum hydroxide as adjuvant. Vaccination of HCWs was performed in hospital with the schedule of two consecutive doses of 600 SU (0.5 mL) administered 28 days apart to deltoid.

Sample collection

Sequential blood samples were collected from HCWs to determine the levels of antispike IgG antibodies: first, 28 days after the initial dose (between February 11 and 17, 2021); second, after 21 days following the second dose (between March 4 and 10, 2021); and finally, 3 months after the second dose of vaccination (between May 17 and 23, 2021). Participants underwent blood sampling with standard venipuncture at the hospital. Transfer of the samples and serum separation was done at the laboratory within 2 h of collection.

Analysis of samples and interpretation of results

Immunoglobulin G (IgG) antibodies to the RBD of the S1 subunit of the spike protein of SARS-CoV-2 were quantitatively determined from the serum samples. The analysis was performed by the chemiluminescent microparticle immunoassay method using SARS-CoV-2 IgG II Quant kit (Abbott, Ireland) according to the manufacturer's instructions. Detection was carried on with Architect *i*2000SR instrument (Abbott, IL). Test results greater than or equal to the cutoff value stated in assay's package insert (50.0 AU/mL) were reported as reactive and interpreted as positive for SARS-CoV-2 antispike IgG antibodies. The results below the cutoff value are reported as non-reactive and interpreted as negative.

Statistical analysis

As descriptive statistics, median and minimum to maximum values for continuous variables and frequency and percentage values for qualitative variables were given. In group comparisons, chi-square test was used. When expected values were less than five Fisher's exact test was used. In all evaluations, $p < 0.05$ was considered statistically significant.

Results

Of 1290 HCWs occupied at the research hospital, 1079 were vaccinated with CoronaVac, and 211 refused any vaccination throughout the study period. All vaccinated HCWs were approached for the present study; seven of them did not want to participate in the study, 1072 volunteers gave written informed consent and completed the two-dose vaccination program. HCWs who refused or were unable to give blood sample after the second dose and/or after 3 months of the second dose were excluded from the study.

The median age of the participants was 33.2 years (95% confidence interval [CI], 0.67: 32.6–33.9 years). The cohort had a slightly greater representation from female individuals, with 51.5% female and 48.5% male. The age distribution of this cohort was as follows: 18–34 years old, 642 (59.9%); 35–59 years old, 406 (37.8%); and 60 years and older, 24 (2.2%; Table 1).

HCWs consisted of academicians who were not actively dealing with patients (4.7%); doctors actively examining patients (7%); 4th, 5th, and 6th grade medical faculty students doing internship in several wards at the hospital (14.1%); other health care assistants, such as nurses, dieticians, physiotherapists, pharmacists, emergency medical technicians, radiology technicians, anesthesia technicians, and laboratory technicians (29.8%); and assistant staff, such as caregivers, patient counselors, security, transportation, cleaning staff (33.1%), and administrative staff (11.3%) working at Sanko University hospital. Occupational roles and COVID-19 history of HCWs including those working in units serving COVID-19 patients in the last 12 months are provided in Table 2.

After 28 days of the first dose of CoronaVac, antispike IgG antibodies were detectable in 834 of 1072 (77.8%; 95% CI, 0.025: 75.44%–80.4%) HCWs. Seropositivity was higher among females (467/552; 84.6%) than males (367/520; 70.6% $p < 0.001$) and was found to be highest in both women and men between the ages of 18–34 years (88.9% and 79.5%, respectively). Among HCWs aged between 35 and 59 years, antispike IgG antibodies in females and males were 75.3% and 64.2%, respectively, and among those ≥60 years, 37.5% in both genders. There was statistically significant

Table 1
Demographic characteristics of healthcare workers.

Age (yrs)	No. (%) of HCWs			Margin of error (95% CI)
	Female	Male	Total	
18–34	398 (72)	244 (47)	642 (59.9)	0.276 (25.3–25.8)
35–59	146 (26)	260 (50)	406 (37.8)	0.581 (42.5–43.7)
≥60	8 (2)	16 (3)	24 (2.2)	1.783 (63.1–66.7)
Total	**552 (51.5)**	**520 (48.5)**	**1072 (100)**	

Table 2
Occupational roles and COVID-19 history of HCWs including those working in units serving COVID-19 patients.

Occupational role	No. (%) of HCWs	PCR-confirmed COVID-19 cases, n (%)
Occupation of HCWs		
Academic member	50 (4.7)	6 (12)
Doctor of medicine	74 (7)	23 (31)
Medicine student	152 (14.1)	15 (9.8)
Health care assistant	319 (29.8)	95 (29.7)
Assistant staff	355 (33.1)	100 (28.1)
Administrative staff	122 (11.3)	38 (31.1)
Total	**1072 (100)**	**277 (25.8)**
Occupation of HCWs in units serving COVID-19 patients		
Emergency	139 (65.2)	34 (24.4)
COVID-19 service	37 (17.4)	15 (40.5)
Intensive care unit	24 (11.3)	10 (41.6)
Radiology-CT unit	10 (4.7)	4 (40)
COVID-19 laboratory	3 (1.4)	0 (0)
Total	**213 (100)**	**63 (29.6)**

difference between all age groups in terms of antibody positivity ($p < 0.05$ for all). Assessment of SARS-CoV-2 antispike IgG in HCWs on day 28 after the first dose of CoronaVac is given in Supplementary Table 3.

Of 1072 HCWs, 277 (25.8%) informed that they had been previously tested PCR positive for SARS-CoV-2 on a combined nasal and oropharyngeal swab. Forty-nine (4.6%) of HCWs reported that they were not sure if they had COVID-19 before vaccination, although none had a prior PCR-confirmed diagnosis of COVID-19. The proportion of HCWs infected with SARS-CoV-2 by age group and gender and their antispike IgG results are given in Supplementary Table 3.

Of 1072 HCWs, 225 (21%) informed that they had at least one chronic disease; hypertension was the most common reported clinical complaint (59.6%). Only a minority of the participants (2.2%) reported receiving immunosuppressive therapy in the last 12 months. Clinical information of HCWs is given in Table 3.

Participants were required to record any adverse reactions within 28 days after the first dose, such as the injection site adverse events (e.g. pain, redness, and swelling), headache, or systemic adverse events (e.g. fatigue/weakness, fever/chills, muscle/joint pain, and vomiting/diarrhea). Adverse events to CoronaVac were observed in 385 (35.9%) of 1072 HCWs. Headache was the most common adverse effect reported by 280 (26.1%) participants. No vaccine-related serious adverse event was noted. Detailed information on adverse events is demonstrated in Table 4.

Table 3
Clinical characteristics of HCWs.

Clinical characteristic	HCWs, n (%)	Antispike IgG	
		Positive, n (%)	Negative, n (%)
Chronic disease in HCWs			
No	847 (79)	675 (79.7)	172 (20.3)
Yes	225[21]	140 (62.2)	85 (37.8)
Hypertension	134 (59.6)	92	42
Asthma	20 (8.9)	18	2
Diabetes mellitus	17 (7.6)	10	7
Rheumatologic disease	9[4]	6	3
Heart failure	4 (1.8)	3	1
Hyperlipidemia	2 (0.9)	0	2
Malignancy	1 (0.4)	1	0
Hepatitis B	1 (0.4)	1	0
Other	37 (16.4)	9	28
Immunosuppressive treatment			
No	1049 (97.8)	817 (77.9)	232 (22.1)
Yes	23 (2.2)	17 (73.9)	6 (26.1)

Table 4
Adverse events seen in HCWs within 28 days following 1st dose of CoronaVac.

Adverse events	HCWs, n (%)
No	687 (64.1)
Yes	385 (35.9)
Headache	280 (26.1)
Injection site pain	61 (5.7)
Fatigue/weakness	78 (7.3)
Fever/chills	34 (3.2)
Muscle/joint pain	61 (5.7)
Vomiting/diarrhea	15 (1.4)
Other	24 (2.2)

Although all HCWs completed their allocated two-dose vaccination schedule, serum samples were obtained from 1012 of 1072 participants after 21 days following the second dose, 521 (51.5%) were female, and 491 (48.5%) were male. Sixty HCWs refused or were unable to give blood sample after the second dose of vaccine. After the second dose, antispike IgG antibodies were detected in 1008 of 1012 (99.6%) HCWs. There were only four of 1012 (0.39%) who were seronegative after the second dose of vaccine; none had a PCR-confirmed diagnosis of COVID-19 before. Assessment of SARS-CoV-2 antispike IgG in HCWs on day 21 after the second dose of CoronaVac is shown in Supplementary Table 6.

Three months after the second dose of vaccine, 836 HCWs gave blood samples for antibody detection. Antispike IgG antibodies were detectable in 803 of 836 (96.1%). It was observed that the percentage of antibody positivity declined with time, and the percentage of negative HCWs ($n = 33$) increased with age. The difference between positive antibody rates obtained 3 weeks and 3 months after the second dose (99.6% and 96.1%, respectively) was statistically significant ($p < 0.001$). Assessment of SARS-CoV-2 antispike IgG in HCWs 3 months after the second dose of CoronaVac is shown in Supplementary Table 7. Comparison of the quantitative values (AU/mL) of SARS-CoV-2 antispike IgG values depending on age and time is demonstrated in Fig. 1.

Discussion

Reports indicate that there are more than 200 SARS-CoV-2 vaccine candidates either in development, in initial preclinical stages, or have entered human clinical trials.[1] Here, we demonstrate the results of a prospective longitudinal study of HCWs to assess the antispike IgG positivity after two consecutive doses of an inactivated virus vaccine, CoronaVac.

Generally, measurement of the seroprevalence of antibodies, especially neutralizing antibodies, against SARS-CoV-2 from population-based epidemiological surveys is informative for the assessment of the proportion of the population who have at some point been infected with the virus and provides insight into the design of vaccination programs.[10,11]

The reference standard method for detection of neutralizing antibodies, which may be used as a correlate of protective immunity, remains plaque reduction neutralization tests. However, these tests are not routinely performed in clinical laboratories, as they require biosafety level 3 containment facilities, are laborious, and are not amenable to automation.[12] The presence of neutralizing antibodies has been correlated to antibody reactivity to viral structural proteins, such as RBD, S, and N using in vitro immunoassays.[13,14] Although data are still limited, there is mounting evidence that antibodies detected by commercial serologic assays correlate with in vitro neutralizing capacity.[15] The sensitivity and specificity of immunoassays were reported to be excellent for detection of the antispike humoral response to SARS-CoV-2 infection with a sensitivity between 84% and 87.1%, specificity between

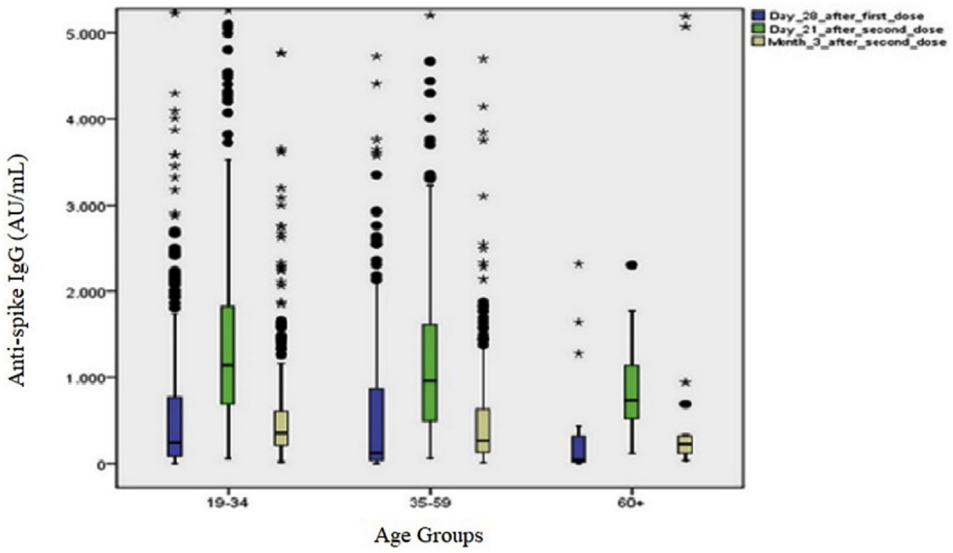

Fig. 1. Comparison of the quantitative values (AU/mL) of SARS-CoV-2 antispike IgG values depending on age and time (• and * in the graph indicate outlier values).

98.9% and 100% and were analogous to the antispike antibody assays used during immunogenicity assessments in vaccine clinical trials.[16,17]

Antibodies to spike RBD can inhibit binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptor, generating a strong viral neutralizing response. A wide range of COVID-19 vaccines in development use strategies that generate antibody response to the spike protein and the RBD domain of the S1 subunit.[18–21] Chemiluminescent anti-SARS-CoV-2 serologic assays, as used in this study, have been reported to exhibit high sensitivity (97.8%), as summarized in a systematic review and meta-analysis.[22]

In this study, we used the Abbott SARS-CoV-2 IgG II Quant kit, which is designed to detect IgG antibodies, including neutralizing antibodies, to the RBD of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma. Serum samples obtained from HCWs after the first and second doses of vaccination with CoronaVac showed 77.8% and 99.6% seroconversion, respectively. If we extract HCWs who have had a PCR-confirmed COVID-19 (n = 277) or who were not sure to be infected with COVID-19 (n = 49) before participating in the study, seropositivity after the first dose remains 70.5% (526/746). Antibody positivity rate was 71.4% (37/49) in HCWs who were not sure whether they had COVID-19 or not.

In messenger RNA (mRNA) vaccine trial studies, antispike seroconversion was observed 100% by day 15 following vaccination with mRNA-1273 and by day 21 following vaccination with BNT162b2.[23,24] According to our results, CoronaVac reached the seroconversion rate of mRNA vaccines after the second dose (i.e. 99.6%), and we found that two doses of this vaccine were highly immunogenic in healthy adults aged 18–59 years.

People aged >60 years have an increasing risk of severe illness and death from COVID-19, especially those with underlying chronic conditions. The response to vaccines is usually reduced in older adults due to immune senescence. Zhiwei et al.[25] reported in their phase 1/2 clinical trial that CoronaVac was well tolerated and immunogenic in healthy adults aged ≥60 years, and neutralizing antibody responses to live SARS-CoV-2 was not reduced in that population. Our findings showed that antispike antibody response in HCWs aged ≥60 years (n = 24) after the first dose was relatively low (37.5%); however, immunogenicity reached a level close to that in the 18–59 years age group after the second dose (95.6%).

Our study has some limitations; we did not check the seroprevalence of SARS-CoV-2 antispike antibodies in HCWs before vaccination; therefore, we could not give data for seroconversion. We mostly reported immune response for healthy adults aged between 18 and 59 years of age and included only a small number of individuals from more susceptible groups in our study population (e.g. individuals aged ≥60 years or with impaired immunity). Another limitation of this study is although understanding the duration of the humoral response is essential toward determining immunogenicity obtained with vaccination, antibody testing is not currently recommended to assess immunity after vaccination against SARS-CoV-2.

The incidence of adverse reactions was not rare (35.9%), being the most common symptom headache (26.1%). This result was not in accordance with previous finding from another study performed with CoronaVac where the most common symptom was injection site pain.[7] Compared with other COVID-19 vaccine candidates, such as viral-vectored vaccines or DNA/RNA vaccines, the occurrence of fever (3.2%) with CoronaVac was relatively low.[5,20,22]

Previous studies suggested that antibodies against SARS-CoV-2 were maintained for at least 4 months.[26,27] Khoury et al.[9] found that the decay of neutralizing titer in vaccinated subjects over the first 3–4 months after vaccination was at least as rapid as the decay observed in convalescent subjects. However, the SIREN study supported the hypothesis that the new licensed vaccines will provide high degree of immunity of prevention from symptomatic infection with SARS-CoV-2 for working-age adults for an average of 7 months.[28]

In this study, we observed that the humoral immunity is sustained 96.1% after 3 months; however, the levels of antibody titers obtained in this study should not be used as a correlate of protection because the protective level of antibody titer was not established to date.

As a conclusion, in this study of immunogenicity of an inactivated SARS-CoV-2 vaccine, we found that two consecutive doses of CoronaVac were well tolerated with minor adverse reactions and were highly immunogenic in HCWs. As expected, the amount of antispike antibodies decreased after 3 months following the second dose of vaccine, and the difference was statistically significant ($p < 0.001$). The antibody level itself might not be the key for an intact immune response; however, it is highly predictive of immune protection and will assist in developing new vaccination strategies to control the pandemic. The durability of humoral responses against SARS-CoV-2 on vaccination needs to be further clarified with a longer follow-up time.

Author statements

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Ethical approval

Ethics approval was obtained from Institutional Clinical Research Ethics Committee (Approval number: 2021/02/01).

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Competing interests

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.01.011.

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Original Research

At odds? How European governments decided on public health restrictions during COVID-19

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ABSTRACT

Objectives: This study aimed to understand how politics, economics, and public health restrictions affected each other during the COVID-19 pandemic.
Methods: We use seemingly unrelated regressions on a monthly data set of government approval ratings, the stringency index, the time-dependent reproduction number (R), and unemployment, allowing the residuals in each regression to be correlated with each other. We also conduct sensitivity tests using weekly data and the growth in polls.
Results: The study covers 27 European countries from April 2020 to April 2021. A unit increase in the R and COVID-19 cases per million increases the stringency index by 23.742 and 4.207, respectively; a unit increase in stringency boosts the incumbent's popularity by 0.384; the poll positively affects the stringency index; stringency has negative effects on the R; and the poll and stringency index have opposite effects on unemployment.
Conclusion: Political and economic pressures did not hinder the government from introducing stronger measures.

Background

COVID-19 has had an unprecedented impact on public health, causing a mass outbreak accompanied by a considerable number of deaths. Where the number of patients with COVID-19 soared past the capacity of a nation's healthcare system, patients with COVID-19 could not be treated with proper management, and the death rate increased steeply.[1] Moreover, the medical repercussions of the pandemic reached beyond the patients who were directly affected by the disease: by limiting patient access to hospitals, the pandemic has led to delays in treatment and diagnoses for diseases other than COVID-19 as well.[2]

Containing the spread of the virus-induced disease was, therefore, a central task for many governments across the world in 2020 and 2021. To contain the infectivity of COVID-19, national governments imposed a range of restrictions from the mandatory wearing of masks to more stringent restrictions such as lockdowns. Public health decisions, however, were also inevitably interlocked with economic as well as political considerations. On the one hand, politicians have been penalized in the polls for steep rises in infection.[3] On the other hand, the very restrictions that were seen as effective for curbing the infection of COVID-19 were arguably afflicting the economy[4–6] and politically agitating citizens.[7] In March 2021, Prime Minister Modi announced a sudden national lockdown on India, for instance, severely damaging the economy. Citizens did not comply with lockdown restrictions, leading Modi to eventually ease the lockdown, and India's COVID-19 situation spiraled out of control.[9]

As vaccinations rolled out, some scholars had prematurely predicted that social distancing would be over by the fall of 2021.[7] However, although vaccines may have reduced both the number of new infections and the severity of the illness,[4] the rise of the much more infectious Omicron variant and the possibility that yet another highly infectious virus may arrive at our doorsteps in the coming years call for an enhanced readiness against global pandemics. We contend, therefore, that a thorough investigation of the determinants of COVID-19 health restrictions is still wanting. Indeed, echoing previous fears about the politicization of public health policies,[10] some medical doctors have cautiously raised

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concerns that the field of medicine is becoming "co-opted into a political program of population control,"[11] even urging public health scientists to "play politics."[12] If we are unable to resolve this state of disquietude, the next pandemic might just have to be fought with an army of disillusioned and politicized medical professionals.

An impending question, therefore, is whether political concerns had really hindered the timely implementation of necessary public health restrictions. In an attempt to unpack the possible standoff between politics and public health, we carefully analyze the relationship between unemployment figures, government approval ratings, infectivity status, and the stringency of non-pharmaceutical interventions to understand the real impact of strong restrictions such as lockdowns on political and economic considerations and vice versa. Acknowledging the mutually endogenous nature of variables, we compare fixed effects models with seemingly unrelated regression (SUR) models that evaluate the relationship among the empirical equations.

Methods

To estimate the determinants of our four dependent variables (government approval ratings, the stringency index, the time-dependent reproduction number, and unemployment), we first conduct four fixed effects models using the monthly averages of the variables. However, if fixed effects models could account for country-specific baseline variations, they do not address the possibility that the error terms of each regression may be correlated with one another. Therefore, we also use SUR models allowing the residuals in each regression to be correlated with each other. As sensitivity tests, we apply the same set of analyses using the weekly averages of the variables.

Data source and study population

Our study compares 27 European countries from April 2020 to April 2021. The full list of countries is available in the appendix (Appendix, Table A1). The time-dependent reproduction number, *R*, is defined as the number of secondary infections that arose from a typical primary case in a completely susceptible population[6] and is used as a measure of infectivity. Our article uses Arroyo-Marioli's (2021) real-time estimates of the effective reproduction number.[12] In addition to the reproduction number, our models also include the number of new cases per million. By doing so, we could compare the government's sensitivity to the reproduction number and raw number of new cases. For the population of interest, we also gathered poll data concerning the public's approval of their government. These data were drawn from the Poll of Polls data set,[15] which uses a statistical method called the Kalman filter to aggregate polls from different sources: a series of measurements taken over time are combined to accurately estimate the popularity of an incumbent at a given point in time.[16] To estimate the public's support of their government, we used the public's intention to vote for the incumbent party in the case of majority parliamentary governments, the public's intention to vote for the largest party in the case of coalition governments, and the public's approval of the incumbent president in the case of presidential systems. To measure the restrictiveness of a government's COVID-19 policies, we use the Stringency Index developed by Oxford University's Blavatnik School of Government.[17] Finally, we use the seasonally adjusted unemployment data from Eurostat to account for the economic considerations behind public health restrictions during the pandemic.[18] Unlike other data, which are available on a daily basis, unemployment data were only available by month.

Our main models use monthly averages, and we drop the first 2 months that represents the start of the virus, so the data could have high variability. As a result, our data set includes around 340 observations of monthly unemployment, the public's approval of its government, the stringency index, and the time-dependent reproduction number over a period of 12 months.

Main analysis

First of all, the relationship between the independent and dependent variables varies considerably depending on country-specific contexts. Depending on whether a polity is a multiparty system or a two-party system, for instance, the baseline level of support for the incumbent (or largest incumbent) party would vary considerably. To account for this variation, we first use a set of fixed effects models. However, the variables we seek to analyze are also causally intertwined. Unemployment can affect the approval ratings, the stringency index, and the reproduction number; approval ratings can affect the stringency index and the reproduction number; the stringency index could affect unemployment, approval ratings, and the reproduction number; the reproduction number could affect unemployment, approval ratings, and the stringency index. As a result, if we independently conduct regressions using one of these variables as the dependent variable and the others as the independent variables, the error terms could be biased by the correlation among the independent variables as

Table 1
The results of fixed effect and SUR models with monthly data set.

	Model 1 Poll	Model 2 Stringency	Model 3 R	Model 4 Unemployment
	Coefficient	Coefficient	Coefficient	Coefficient
Fixed effect model				
$Poll_{t-1}$		−0.685* (−1.427, 0.056)	0.000 (−0.005, 0.006)	−0.054*** (−0.083, −0.024)
$Stringency_{t-1}$	−0.005 (−0·045, 0.035)		−0.008***, (−0.009, −0.007)	−0.010** (−0.018, −0.002)
R_{t-1}	0.254 (−0.968, 1.476)	5.432*** (1.501, 9.363)		−0.557*** (−0.769, −0·345)
$Unemployment_{t-1}$	−1.186*** (−2.040, −0.332)	−9.297*** (−11.747, −6.847)	0.108*** (0.066, 0.151)	
New cases per Mil.	−0.728*** (−1.222, −0.234)	3.590*** (2.139, 5.041)		−0.086*** (−0.145, −0.028)
Constant	41.741*** (36.275, 47.207)	125.965*** (88.312, 163.618)	0.790*** (0.418, 1.161)	10.106*** (8.618, 11.593)
SUR				
$Poll_{t-1}$		1.805*** (1.435, 2.176)	0.025** (0.002, 0.047)	−0.243*** (−0.270, −0.217)
$Stringency_{t-1}$	0.384*** (0.308, 0.461)		−0.016*** (−0.025, −0.007)	0.099*** (0.080, 0.118)
R_{t-1}	0.662 (−1.727, 3.050)	23.742*** (17.904, 29.581)		−0.210 (−0.799, 0.380)
$Unemployment_{t-1}$	−3.938*** (−4.373, −3.504)	7.084*** (5.580, 8.588)	0.110** (0.020, 0.199)	
New cases per Mil.	−1.044** (−2.051, −0.037)	4.207*** (2.276, 6.138)		−0.338*** (−0.588, −0.089)
Constant	37.765*** (31.049, 44.480)	−85.914*** (−110.671, −61.158)	0.505 (−0.280, 1.289)	10.010*** (8.315, 11.705)
N	342	343	343	340

Notes: *N is the sample size.* * indicates $P < 0.10$, ** indicates $P < 0.05$, and *** indicates $P < 0.01$.95% of confidence intervals are in the parentheses. New cases per million is logged variable.

Table 2
The results of Fixed Effect and SUR models with weekly dataset.

	Model 5 Poll	Model 6 Stringency	Model 7 R
	Coefficient	Coefficient	Coefficient
Fixed effect model			
$Poll_{t-1}$		−0.033 (−0.814, 0.748)	−0.012** (−0.025, −0.000)
$Stringency_{t-1}$	0.008 (−0.033, 0.049)		−0.014*** (−0.017, −0.012)
R_{t-1}	−0.237 (−1.281, 0.808)	−7.600*** (−10.688, −4.513)	
Ln (New cases per Mil.)	−0.789*** (−1.282, −0.297)	3.071*** (1.631, 4.511)	
Constant	33.805*** (31.447, 36.163)	59.256*** (29.678, 88.833)	2.372*** (1.922, 2.822)
SUR			
$Poll_{t-1}$		2.386*** (2.221, 2.551)	0.060*** (0.055, 0.066)
$Stringency_{t-1}$	0.399*** (0.372, 0.426)		−0.027*** (−0.030, −0.025)
R_{t-1}	12.307*** (11.224, 13.390)	−20.724*** (−23.554, −17.894)	
New cases per Mil.	−0.243** (−0.317, −0.168)	1.092*** (0.864, 1.319)	
Constant	−6.562*** (−8.927, −4.196)	7.206*** (2.227, 12.186)	0.915*** (0.788, 1.042)
N	1593	1595	1622

Notes:N is the sample size. *$P < 0.10$, **$P < 0.05$, and ***$P < 0.01$95% of confidence intervals are in the parentheses. New cases per million is logged variable.

well as by reverse causality. To account for the range of new COVID-19 cases number, we treated the number as log scale. To accommodate this causal complexity, we use SURs to allow the error terms of these regressions to be correlated with one another.

Sensitivity tests

As sensitivity tests, we run the same set of models using weekly averages instead of monthly (Table 2). These tests allow us to compare long-term vs short-term considerations. Because unemployment data were only available on a monthly basis, unemployment is excluded in weekly model. Another set of sensitivity tests run the same models using monthly averages of the growth rate in polls rather than the absolute values of polls (Appendix, Table A1). Because of country-specific political contexts, some countries have inherently higher or lower polls than others; by using the growth in polls, we can discard such country-specific differences.

Results

The included nations and their baseline characteristics are described in the Appendix (Table A1). Table 1 reports the results of each regression derived with the fixed effects (top) and SUR (bottom) models. As expected, the error terms of dependent variables are significantly correlated (Appendix, Table A2), affecting both the size and significance of the variables. Consequently, we will be using the SUR models in our analysis. In Model 1, the SUR indicates that the stringency index, unemployment rate, and number of new cases of previous month affect the poll in the present month. A unit increase in stringency raises the poll by 0.384, a 1% increase in unemployment reduces the incumbent's popularity by 3.938, whereas one-unit increase of COVID-19 case reduces the poll by 1.044. By contrast, the reproduction number has no significant effect on the polls. In Germany, for instance, the first wave of stringent restrictions substantially increased the public's support of the incumbent government, whereas the reproduction number had no clear effect on the polls (Fig. 1a). In Model 2, higher reproduction numbers, more new COVID-19 cases, greater unemployment, and better polls all result in more stringent public health restrictions. A 0.1 increase in the reproduction number raises stringency by 23.742, one-unit increase of COVID-19 case pulls the stringency up by 4.207, a 1% increase in unemployment increases stringency by 7.084, and a unit increase in polls creates a 1.805 hike in the stringency index. In Models 3 and 4, the reproduction number and unemployment are each understandably affected by the other variables. As expected, the reproduction number decreases by 0.016 as the stringency index of the previous month increases by one unit. As the case of Slovenia may illustrate, countries that were slow to implement stringent public health restrictions suffered sharp rises in infectivity (Fig. 1b).

Sensitivity analyses

Table 2 summarizes the results of our alternative analysis using weekly averages. As with the main analysis, there are considerable correlations among the error terms, creating biased estimates for the fixed effects models (Appendix, Table A3). Accordingly, our analysis will again be based on the SUR models. The results closely follow those of the main analysis. As with the monthly analysis, more stringent public health restrictions increase the popularity of the government of 0.399 while suppressing the reproduction number of 0.027, and governments are punished for rising numbers of COVID-19 infections by 0.243. Also confirming the weekly results,

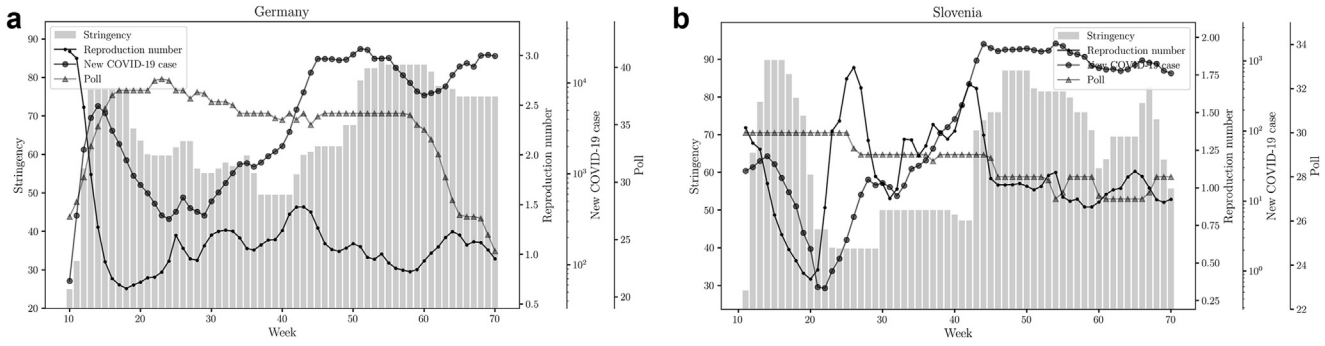

Fig. 1. Time trends (COVID-19 and poll data) in Germany and Slovenia.

higher polls and more COVID-19 cases increase the stringency index by 2.386 and 1.092, respectively. In contrast to the monthly analysis, however, the reproduction number of the previous week has negative effects on the stringency index of the present week. As the responses in Slovakia and Finland illustrate, governments hesitate to conduct strict health policy until there is a large number of new COVID-19 cases, although a rise in the reproduction number precedes a peak of new cases (Fig. 2). Finally, Appendix Table A4 presents the results from our second set of sensitivity tests, using the growth of polls in place of the absolute values. The results do not substantially differ from those of our main analysis.

Discussion

Principal findings

A global pandemic of unprecedented scale, COVID-19 has brought into light the complex, intertwined nature of political behavior during a public health crisis. While a varying intensity of non-pharmaceutical interventions has been introduced at the advice of health experts, restrictions to freedom of movement also negatively affected the economy[4–6] and agitated the citizens under confinement.[7] The public's dissatisfaction with public health restrictions was often so high that they culminated in rule-defying mass demonstrations[19–21] across the globe. Against this background, political decision-makers were arguably under a constant dilemma of whether to prioritize politics or health. The significance of our research, therefore, lies in its attempt to unpack the relationship between political and economic considerations, health restrictions, and health outcomes.

Our main analysis finds that the political dynamics did not hinder stronger public health restrictions, given the same number of new COVID-19 infections. Because the error terms were highly correlated, we used SUR models to analyze the data. First of all, governments imposing more stringent policies were actually rewarded at the polls: a unit increase in the stringency index boosted the incumbent's growth in popularity by 0.384, whereas one additional new case per million reduced the poll by 3.938. Contrary to what the mass demonstrations against COVID-19 restrictions may have led us to believe, the vast majority of the public seems to approve of stronger measures. Second, governments introduced stronger restrictive measures as necessary, even as they suffered from high levels of unemployment. A 0.1 rise in the reproduction number and one additional new case per million raised the stringency index by 23.742 and 4.207, respectively. A unit increase in the polls and a 1% rise in the unemployment rate each resulted in a 1.805 and 7.084 surge in the stringency index. Our empirical analysis indicates that both the public's perception of the incumbent's performance and the government's self-evaluation of their own performance depends heavily on the number of new cases rather than the reproduction number.

Interestingly, the poll affects the reproduction number positively and the unemployment figure negatively. It is possible that this outcome was caused by an exogenous variable such as the government's economic response to the pandemic: expansionary economic policies can increase the popularity of the government while also increasing the reproduction number and reducing unemployment. As our 's focus is on physical public health restrictions rather than economic policies, however, fully explaining Models 3 and 4 is beyond the scope of this article. It also seems that public health restrictions become, in time, less and less popular. Fig. 1a illustrates, for instance, that Germany's first lockdown was more popular in the polls than later restrictions of similar scale.

Furthermore, the results of the sensitivity analysis highlight a potential difference in medium-term and long-term considerations in pandemic decision-making. Yet such an interpretation deserves considerable caution. Because unemployment is not included in the weekly analysis, the apparent differences between weekly and monthly observations may be attributable to the omission of this key variable from the sensitivity tests.

Comparison with other studies

To the authors' knowledge, this is the first study that attempts to unpack the complex interdependence of politics, economics, and public health decisions during the COVID-19 pandemic. Most existing studies analyzing the effectiveness of non-pharmaceutical interventions treat political and economic factors as control variables at best.[22–25] When non-health-related variables did enter the causal framework, scholars have focused on the impact political and economic considerations have on the effectiveness of public health restrictions and vice versa without acknowledging that the causal arrow could head in multiple directions.[26–29] The main innovation of our research is that we explicitly admit the possibility that the variables may be causally intertwined in a multitude of ways: the effect of health restrictions on the reproduction number is contingent on the effect of political and economic factors on the restrictions, which, in turn, is affected by the effect of the reproduction number and the health restrictions have on the political and economic variables.

Limitations of the study

Our study is limited in its scope. First of all, our statistical method is unable to offer detailed analysis about specific countries or periods. Moreover, because data were not readily available in other regions of the world, our study is restricted to comparing 27 European nations, whose long history of democratic political institutions and practices arguably renders them exceptional. As a result, the findings may also have limited external validity outside of this region. Among younger democracies, for instance, the public's support of the incumbent government may have less to do with the

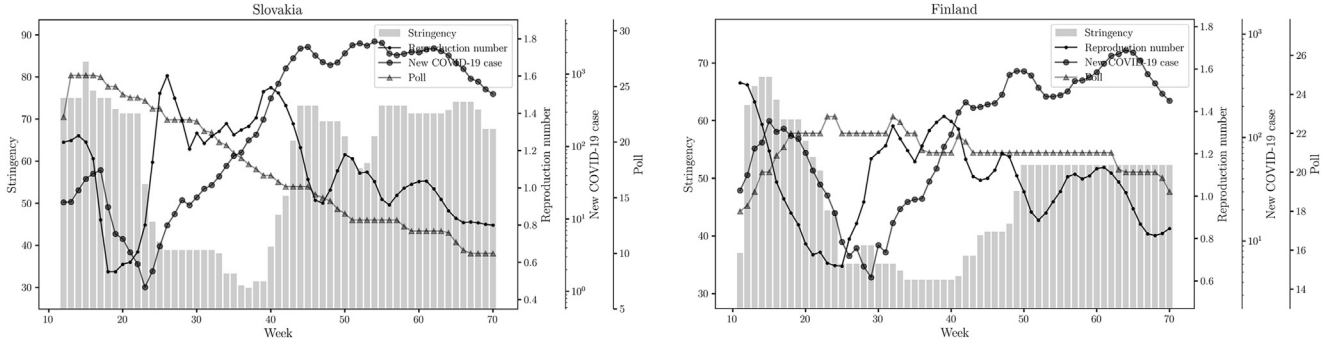

Fig. 2. Governments hesitate to increase restrictions unless there is a clear surge in cases.

efficacy of non-pharmaceutical interventions and more to do with clientelistic linkages. Therefore, to establish whether the relationships we identify could be observed more generally, future studies would need to extend the analysis beyond the European region.

Finally, our study is also limited in its ability to explain the poll's effect on unemployment and the reproduction number. Because of our specific focus on physical—rather than economic—interventions during the pandemic, we have been unable to fully explore the underlying reasons behind the poll's apparent effect on unemployment and infectivity.

Conclusion and policy implications

With new, more infectious variants on the rise; the world is yet to witness a complete end to the prolonged COVID-19 pandemic. Although our study is limited in its geographic scope, it illustrates a novel attempt to disentangle the complex relationship between political and economic considerations and health. As we expected, the popularity of incumbent politicians, unemployment, health restrictions, and the reproduction number are causally intertwined with each other. If health professionals had expressed concerns about the politics surrounding this pandemic,[10,11,29] our study reveals that politicians and health professionals in Europe were not at odds with each other.

Our data illustrate that as a government grows more popular, it could implement more stringent health restrictions, curbing the spread of COVID-19. Moreover, when governments increased the stringency of their policies, they were not punished by the polls; to the contrary, our analysis reveals that politicians were rewarded for their implementation of strict rules. In other words, governments, with greater public support behind their backs, implemented stricter health restrictions that had greater impact on the reproduction number. Although further research must examine the external validity of our findings, these results indicate that the governments and citizens of Europe generally did not demand looser health restrictions for the sake of short-term economic gains.

Author statements

Ethical approval

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Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.02.001.

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Original Research

Combined and interactive effects of alcohol drinking and cigarette smoking on the risk of severe illness and poor clinical outcomes in patients with COVID-19: a multicentre retrospective cohort study

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ABSTRACT

Objectives: Cigarette smoking is an established risk factor for illness severity and adverse outcomes in patients with COVID-19. Alcohol drinking may also be a potential risk factor for disease severity. However, the combined and interactive effects of drinking and smoking on COVID-19 have not yet been reported. This study aimed to examine the combined and interactive effects of alcohol drinking and cigarette smoking on the risk of severe illness and poor outcomes in patients with COVID-19.
Study design: This was a multicentre retrospective cohort study.
Methods: This study retrospectively reviewed the data of 1399 consecutive hospitalised COVID-19 patients from 43 designated hospitals. Patients were grouped according to different combinations of drinking and smoking status. Multivariate mixed-effects logistic regression models were used to estimate the combined and interactive effects of drinking and smoking on the risk of severe COVID-19 and poor clinical outcomes.
Results: In the study population, 7.3% were drinkers/smokers, 4.3% were drinkers/non-smokers and 4.9% were non-drinkers/smokers. After controlling for potential confounders, smokers or drinkers alone did not show a significant increase in the risk of severe COVID-19 or poor clinical outcomes compared with non-drinkers/non-smokers. Moreover, this study did not observe any interactive effects of drinking and smoking on COVID-19. Drinkers/smokers had a 62% increased risk (odds ratio = 1.62, 95% confidence interval: 1.01-2.60) of severe COVID-19 but did not have a significant increase in the risk for poor clinical outcomes compared with non-drinkers/non-smokers.
Conclusions: Combined exposure to drinking and smoking increases the risk of severe COVID-19, but no direct effects of drinking or smoking, or interaction effects of drinking and smoking, were detected.

Introduction

The COVID-19 pandemic is rapidly evolving worldwide.[1,2] The clinical spectrum of COVID-19 appears to be wide, ranging from mild, moderate and severe to critical illnesses.[3] Severe and critical cases are more likely to present with multiple organ dysfunction syndrome, acute respiratory distress syndrome (ARDS) and shock, thus contributing to intensive care unit (ICU) admission, mechanical ventilation (MV) and even death, and posing a serious threat to public health.[4,5] Therefore, the risk factors for severe COVID-19 and

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poor outcomes should be identified to improve the management of COVID-19 in clinical practice.

Several studies have investigated factors related to the severity of COVID-19 and its adverse outcomes. Smoking has received special attention as this is a well-established modifiable risk factor for many diseases.[6] In relation to COVID-19, although the results are contradictory,[7,8] smoking seems more likely to be associated with disease severity, negative progression and adverse outcomes of COVID-19.[9–13] The results from a recent meta-analysis involving 22,939 COVID-19 patients reported that smoking is an independent risk factor for COVID-19 progression, including mortality.[13] Drinking alcohol, a factor closely related to cigarette smoking, has been reported to be associated with poor outcomes of pneumonia patients and critically ill patients.[14–16] However, little attention has been paid to the effects of drinking alcohol on the severity and clinical outcomes of COVID-19.

Alcohol drinking and smoking can cause damage to nearly all body organs and are globally the two most important preventable health risk factors, with an important impact on public health.[17] Based on the report of the Global Burden of Disease study, drinking accounted for nearly 10% of global deaths among populations aged 15–49 years, while smoking accounted for 11.5% of global deaths.[18,19] Furthermore, alcohol drinking and cigarette smoking, as two closely related factors, have various detrimental effects. Alcohol drinking and cigarette smoking have an interactive or combined effect on the treatment of pulmonary tuberculosis, the risk of lung cancer and many digestive malignancies and on all-cause and premature mortality.[17,20–22] However, the association between combined smoking and drinking and COVID-19 has not yet been reported. Therefore, this study aimed to evaluate the combined and interactive effects of alcohol drinking and smoking on the risk of severe illness and poor clinical outcomes in patients with COVID-19, thereby providing a better understanding of the effects of alcohol drinking and smoking exposure in COVID-19 patients.

Methods

Study design and participants

Data from patients with COVID-19 from Sichuan Province and Wuhan City, China, were used in this multicentre retrospective cohort study. All patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were admitted to one of 43 designated hospitals in Sichuan and Wuhan between 14 January and 22 March 2020 were enrolled in the study. All patients with COVID-19 enrolled in this study were diagnosed according to the World Health Organisation (WHO) interim guidelines.[23] SARS-CoV-2 infection was confirmed by laboratory tests using real-time reverse-transcription polymerase chain reaction or high-throughput sequencing. Confirmed cases referred to patients who had positive results on nasal and pharyngeal swab tests.[24]

Clinical data collection

All clinical data on demographic characteristics, underlying comorbidities, laboratory and radiological findings, and treatment and outcome information were retrospectively extracted from the medical records by members of the trained research team. A standardised form, a modified version of the International Severe Acute Respiratory and Emerging Infection Consortium forms, was used for data collection.[25] The confidentiality of the information was maintained by removing personal identifiable information. After careful review of medical records, detailed information on patients' demographic characteristics, pre-existing chronic comorbidities, computed tomographic (CT) images of the chest, laboratory indicators on admission, treatment and outcomes were collected. Data were abstracted and entered into a Microsoft Excel spreadsheet by trained researchers, and the results were then cross-checked by two researchers.

Exposure

Information on the smoking and alcohol drinking history of patients was collected from the electronic medical records. In terms of smoking status, patients were classified as smokers (including former smokers and current smokers) and non-smokers based on the self-reported information. Similarly, in terms of alcohol drinking status, patients were classified as drinkers (including current drinkers and former drinkers) and non-drinkers according to their self-reported information.

Patients were divided into four groups as follows: group one included drinkers/smokers; group two included drinkers/non-smokers; group three included non-drinkers/smokers; and group four included non-drinkers/non-smokers.

Outcomes

The primary outcomes included two important events, one of which was severe illness of COVID-19, and the other was a composite endpoint of all-cause death, ICU admission or invasive/non-invasive MV occurring during hospitalisation. These events were combined into a binary coded composite adverse outcome variable, indicating that at least one of the events occurred during the period of hospitalisation. This composite measure was adopted because all individual components were considered as serious outcomes in a previous study of COVID-19.[26] The disease severity of COVID-19 was evaluated based on the WHO living guidance for COVID-19 management.[27] The clinical classification was as follows:

Critical cases: Defined as patients with ARDS, sepsis, septic shock or other conditions requiring life-sustaining therapies, such as MV or vasopressor therapy.

Severe cases: Defined as patients who met any of the following criteria: (1) respiratory distress ($\geq$30 breaths/min) for adults; (2) oxygen saturation of $\leq$90% at room air; and (3) signs of severe respiratory distress.

Non-severe cases: Defined as patients who did not meet the criteria for diagnosing severe or critical cases.

In line with previous studies,[28] 'severe COVID-19' in our study was defined as patients with severe or critical COVID-19.

The secondary outcomes were defined as the individual events of the primary composite outcome: namely, death (all-cause death after COVID-19 diagnosis), ICU admission and invasive/non-invasive MV during the period of hospitalisation.

Statistical analyses

Continuous variables were expressed as mean (standard deviation) or median (interquartile range [IQR]), as appropriate. Categorical variables were expressed as counts and percentages. Continuous variables were compared using the one-way analysis of variance or Kruskal–Wallis test; categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Bonferroni's correction was used for multiple comparisons. Multivariate mixed-effects logistic regression models were used to explore the association of alcohol drinking and cigarette smoking with outcomes. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated. The details

regarding the statistical methods used are shown in the online Supplementary Material.

Results

Demographic and clinical characteristics

Patients aged <18 years, pregnant women, patients who died on admission to hospital and patients with missing information on smoking and alcohol status were excluded. In total, 1399 patients were included in the final analysis (Fig. 1). As shown in Table 1, the median age of the cohort was 55 years (IQR: 41, 66); 47.9% of patients were men, 60.9% patients were from Wuhan, 56.3% had at least one comorbidity, and the median duration from onset of illness to hospital admission was 10 days (IQR: 5, 16).

Drinkers/smokers, drinkers/non-smokers, non-drinkers/smokers and non-drinkers/non-smokers accounted for 7.3% (n = 103), 4.3% (n = 61), 4.9% (n = 69) and 82.7% (n = 1166) of the total study participants, respectively. Notably, compared with non-drinkers/non-smokers, drinkers/smokers were more likely to be men, younger, live in the epidemic centre region (Wuhan) and have a shorter time from illness onset to hospitalisation. In addition, drinkers/smokers were more likely to show lower CURB-65 (confusion, uraemia, respiratory rate, blood pressure, age ≥65 years) scores on admission, with a higher incidence of hepatic dysfunction complications. Drinkers/non-smokers were less likely to receive antibiotic treatment (39.3% vs. 59.8%; $P = 0.002$) than non-drinkers/non-smokers.

Laboratory and radiological findings

After Bonferroni's correction, the median eosinophil count ($P = 0.006$) and median platelet count ($P = 0.005$) were lower in the drinkers/non-smokers group than in the non-drinkers/non-smokers group. Compared with non-drinkers/non-smokers, the other three groups (drinkers/smokers, drinkers/non-smokers and non-drinkers/smokers) had higher levels of haemoglobin ($P < 0.001$, $P < 0.001$ and $P = 0.001$, respectively) and serum creatinine ($P < 0.001$, $P = 0.005$ and $P = 0.004$, respectively). Moreover, drinkers/smokers had higher levels of creatine kinase ($P < 0.001$) and albumin ($P < 0.001$) than patients in the non-drinkers/non-smokers group. With regard to markers of coagulation function, drinkers/smokers and drinkers/non-smokers showed a slightly longer activated partial thromboplastin time ($P < 0.001$ and $P < 0.001$, respectively) than non-drinkers/non-smokers. In addition, patients in the drinkers/smokers group were more likely to show abnormal findings on radiological CT images (Supplementary Table S1).

Severity and clinical outcomes

The incidence of severe COVID-19 was significantly higher in drinkers/smokers than in non-drinkers/non-smokers (40.8% vs. 29.4%; $P = 0.016$) after Bonferroni's correction. However, no significant difference was observed in the composite outcome (comprised of MV, ICU admission and in-hospital death) or in any of these three outcomes alone (Fig. 2).

Mixed-effects logistic regression analyses

Compared with non-smokers, current smokers and/or former smokers did not have significant associations with severe COVID-19 or composite outcomes. Moreover, current and/or past alcohol consumption were not significant predictors of severe COVID-19 or composite outcomes. By adding the interaction term to the regression models, no interaction effects were observed between smoking and alcohol consumption and severe COVID-19 and poor outcomes (*P*-values of the interaction term of drinking and smoking were 0.30 and 0.10, respectively). With regard to the different combinations of smoking and alcohol drinking status, the present study shows that smoking alone or drinking alone was not associated with severe COVID-19 and composite outcomes. Furthermore, the results show no significant association between drinkers/smokers and an increased risk of composite outcomes. In contrast, drinkers/smokers were more likely to have severe COVID-19 compared with non-drinkers/non-smokers (OR = 1.62; 95% CI: 1.01, 2.60), after adjusting for all potential confounders, including age, sex, Carlson Comorbidity Index, CURB-65 scores, time from illness onset to hospital admission, level of hospital and using centre as a random effect (Tables 2 and 3). However, no significant associations were found between smoking and drinking and any of the secondary outcomes (ICU admission, MV and in-hospital death; Supplementary Tables S2, S3 and S4).

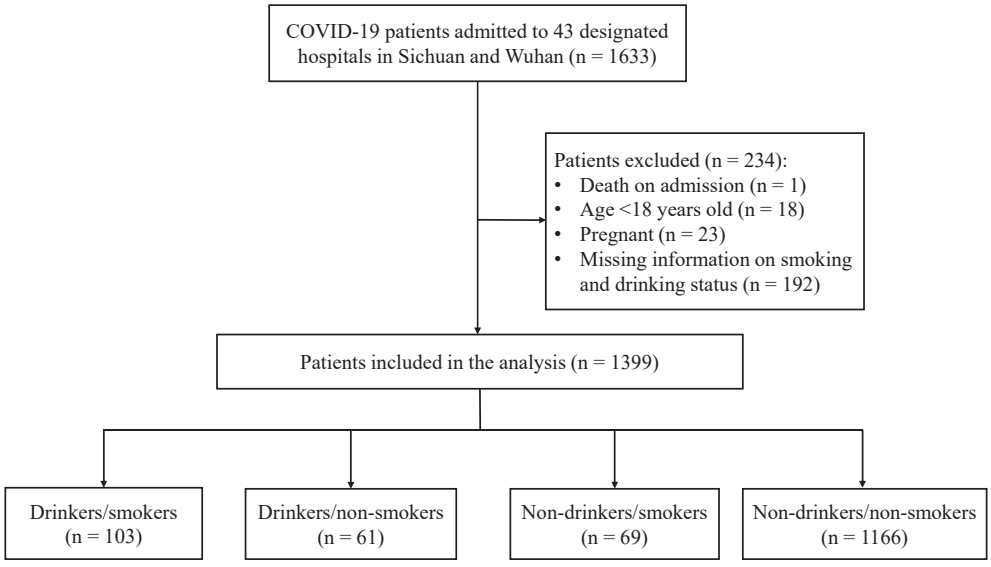

Fig. 1. Flowchart of participants with COVID-19 in this study. The study cohort was divided into four groups based on different combinations of alcohol drinking and smoking status.

Table 1
Demographics and clinical characteristics of COVID-19 patients.[a]

Variables	Drinkers/smokers	Drinkers/ non-smokers	Non-drinkers/ smokers	Non-drinkers/ non-smokers	Total	χ2/H	*P*-value[b]
Total	103 (7.3)	61 (4.3)	69 (4.9)	1166 (82.7)	1399		
Age (years)	48.00 (38.00, 62.00)[c]	48.00 (34.00, 61.00)[c]	56.00 (34.00, 63.50)	56.00 (42.00, 66.00)	55.00 (41.00, 66.00)	16.106	0.001
Male	77 (74.8%)[c]	48 (78.7%)[c]	58 (84.1%)[c]	487 (41.8%)	670 (47.9%)	106.666	<0.001
Region						39.388	<0.001
Sichuan	21 (20.4%)[c]	7 (11.5%)[c]	31 (44.9%))	488 (41.9%)	547 (39.1%)		
Wuhan	82 (79.6%)[c]	54 (88.5%)[c]	38 (55.1%)	678 (58.1%)	852 (60.9%)		
Allergic history	6 (5.8%)	3 (4.9%)	5 (7.2%)	94 (8.1%)	108 (7.7%)	1.404	0.705
CURB-65[d]	0.36 (0.73)[c]	0.43 (0.74)	0.48 (0.72)	0.52 (0.74)	0.50 (0.74)	8.626	0.035
Any comorbidity	53 (52.0%)	32 (52.5%)	36 (52.9%)	662 (57%)	783 (56.3%)	1.701	0.637
CCI[d]	1.37 (2.23)	1.05 (1.53)	1.90 (2.592)	1.51 (2.03)	1.50 (2.06)	4.052	0.256
Complications	62 (60.2%)	30 (49.2%)	39 (56.5%)	679 (58.2%)	810 (57.9%)	2.232	0.526
ARDS	5 (4.9%)	4 (6.6%)	3 (4.3%)	91/1166 (7.8%)	103 (7.4%)	2.261	0.520[e]
Pneumonia	59 (57.3%)	25 (41.0%)	33 (47.8%)	554 (47.5%)	671 (48.0%)	4.869	0.182
Hepatic dysfunction	23 (22.3%)[c]	11 (18.0%)	12 (17.4%)	129 (11.1%)	175 (12.5%)	14.507	0.002
Treatment							
Antiviral treatment	98 (95.1%)	57 (93.4%)	60 (87.0%)	1070 (91.8%)	1285 (91.9%)	3.920	0.270
Antibiotics	54 (52.4%)	24 (39.3%)[c]	39 (56.5%)	697 (59.8%)	814 (58.2%)	11.596	0.009
High-flow oxygen therapy	5 (4.9%)	4 (6.6%)	6 (8.7%)	85 (7.3%)	100 (7.1%)	1.074	0.787[e]
Corticosteroids	17 (16.5%)	11 (18.0%)	23 (33.3%)	307 (26.3%)	358 (25.6%)	8.802	0.032
Time from illness onset to ICU admission, days	14.00 (8.00, 16.00)	6.00 (5.00, 7.00)	23.00 (14.50, 24.00)	11.00 (7.50, 15.50)	11.00 (7.00, 16.00)	3.607	0.307
Time from illness onset to hospital admission, days	6.50 (3.00, 11.00)[c]	7.00 (3.00, 16.00)	9.00 (4.00, 14.00)	10.00 (5.75, 16.00)	10.00 (5.00, 16.00)	22.415	<0.001
Hospital length of stay, days	16.00 (9.25, 21.00)	16.00 (13.00, 23.50)	16.00 (10.00, 24.00)	18.00 (10.00, 27.00)	17.00 (10.00, 26.00)	5.048	0.168
Duration of viral shedding, days	15.00 (9.00, 23.75)	14.50 (11.75, 22.00)	15.00 (9.50, 26.50)	18.00 (12.00, 29.00)	17.00 (11.00, 28.00)	6.374	0.095
Duration of corticosteroids treatment, days	3.00 (1.75, 4.00)	3.00 (2.00, 11.50)	4.00 (1.50, 10.00)	5.00 (3.00, 8.00)	4.00 (3.00, 8.00)	3.403	0.334

CCI, Carlson Comorbidity Index; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; CURB-65, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years.
[a] Data are expressed as median (IQR) or n (%), n/N (%), where N is the total number of patients with available data.
[b] *P*-values comparing four groups are from χ^2, Fisher's exact test or Kruskal–Wallis test. There are post-hoc comparisons.
[c] Indicates $P < 0.017$. Bonferroni's correction was used for multiple comparison with the non-drinkers/non-smokers group.
[d] Shown as mean (standard deviation) because the median of CURB-65 and CCI was '0'.
[e] Fisher's exact test.

Discussion

Following a review of the medical literature, to the best of the authors' knowledge, this is the first multicentre, retrospective, cohort study to explore the combined and interactive effects of alcohol drinking and smoking on the risk of severe illness and poor clinical outcomes in patients with COVID-19. In this study, it was observed that patients who smoked and consumed alcohol were more likely to experience severe illness when diagnosed with COVID-19 compared with patients who did not smoke or drink alcohol. However, smoking alone or drinking alone, or the co-existence of both, was not associated with poor clinical outcomes. In addition, we did not observe any interactive effects of drinking and smoking on the severity and poor clinical outcomes of COVID-19.

Smoking is a well-established risk factor for many diseases and is the leading cause of death among middle-aged and older men.[19] However, the association between smoking and COVID-19 has never been clearly evaluated. The results from existing studies are inconsistent, with most studies reporting smoking as a risk factor for severe COVID-19.[11,29,30] A possible explanation for this phenomenon might be the different distribution of important social and clinically relevant variables between smokers and non-smokers. Hence, in this study, we used multivariable mixed-effects logistic regression models to minimise the potential bias. No significant association was found between smoking and severe COVID-19 and poor clinical outcomes. This result is consistent with Ho et al.,[31] who did not observe a significant association between smoking (current or former) and the risks of in-hospital mortality, ICU admission or invasive MV. Conversely, the results from Dai et al.[32] and Adrish et al.[33] show that smoking is associated with a higher risk for developing critical illness and death in hospitalised COVID-19 patients. It is worth emphasising that the results, so far, mainly come from cross-sectional studies or retrospective studies, with relatively small sample sizes. The non-significant correlations obtained might be associated with other uncontrolled factors. The inconsistent results of existing studies may be due, at least partially, to differences in the study participants, study design, follow-up duration and data analysis, in addition to other unknown reasons. However, the exact duration and number of cigarettes smoked per day have not been reported in most studies. The inconsistent results are partially attributed to the difference in exposure dose and duration. To explain the association between smoking and COVID-19, further well-designed and population-based prospective studies are necessary. In addition, the hypothesis that nicotine may be protective against severe COVID-19 makes the association between smoking and COVID-19 more complex.[34] To better understand the relationship between smoking and COVID-19, clinical trials on nicotine are warranted.

In terms of alcohol drinking, to the best of the authors' knowledge, only a few studies have explored the association of alcohol consumption with severe COVID-19 and poor clinical outcomes in COVID-19 patients.[32,35,36] Similar to the findings in the present study, Liu et al.[35] and Dai et al.[32] show that drinking alcohol is not related to the severity of COVID-19. The current finding, that drinking is not related to the severity of COVID-19, is consistent with results from previous studies. In addition, we observed that alcohol consumption was equally unrelated to poor clinical outcomes, including in-hospital death, MV and ICU admission of hospitalised COVID-19 patients, although some important confounding factors were adjusted. Considering the amount of alcohol

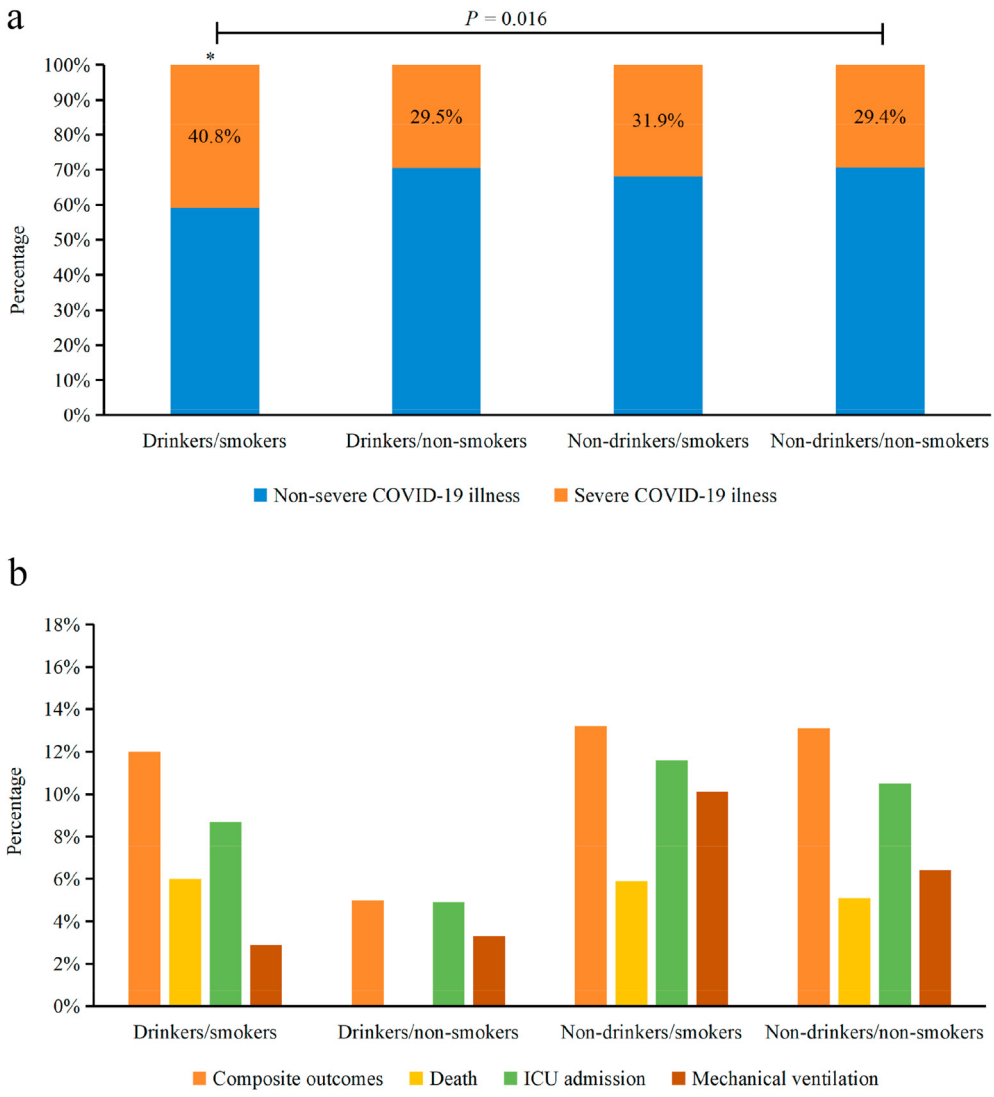

Fig. 2. (a) Disease severity of COVID-19, grouped by alcohol drinking and smoking status. (b) Outcomes of COVID-19 grouped by alcohol drinking and smoking status. There are post-hoc comparisons. * $P < 0.017$. Bonferroni's correction was used for multiple comparison with the non-drinkers/non-smokers group. ICU, intensive care unit.

consumed, the results from Fan et al.'s study, based on a larger sample size, show that heavy drinkers with obesity were more likely to have worse COVID-19 clinical outcomes.[36] Existing evidence demonstrating the association between alcohol consumption and COVID-19 is limited; it remains unclear whether alcohol drinking increases the risk of severe COVID-19 and poor clinical outcomes in COVID-19 patients. In the future, researchers should pay more attention to exploring whether alcohol drinking volume and time are associated with the severity and poor clinical outcomes of COVID-19.

Patients who smoke and drink alcohol are more vulnerable to COVID-19. Smoking can alter the structure of the respiratory tract and decrease the immune response, both systemically and locally within the lungs, increasing the risk of infections.[37] Furthermore, smoking has been shown to upregulate the expression of angiotensin-converting enzyme two receptor in the lungs,[38] which is associated with increased SARS-CoV-2 attachment and entry into the alveolar epithelial cells,[39] indicating a possible high-risk factor for COVID-19. Similarly, alcohol consumption, another important health risk factor, has been shown to alter the release of cytokines and functions of the barrier and ciliary fibres, thereby changing the defence capabilities of the airway epithelial host.[40] Alcohol can also change the function of alveolar macrophages, affect the recruitment of neutrophils, weaken the phagocytosis of neutrophils to pathogens, and reduce the production and release of neutrophils into the circulating blood. Previous studies confirmed that consumption of alcohol causes an increased susceptibility to airway bacterial and viral infections, regardless of the exact underlying mechanism.[41] Although the specific mechanism is not clear, it is likely that alcohol consumption also plays an important role in SARS-CoV-2 infection. In addition, both alcohol consumption and smoking trigger the production of the following substances, leading to oxidant stress: nitric oxide, carbon monoxide and phenolic free radicals, which have proven proinflammatory[42–44] and could increase the likelihood of adverse clinical outcomes of COVID-19. Therefore, given their adverse effects on the lungs and immune system, as well as based on the results of previous studies on other bacterial and viral lung infections, it is reasonable to believe that, despite the lack of data, alcohol consumption and smoking may contribute to the COVID-19-related risk. Although the present study did not find interactive effects between smoking and drinking on COVID-19, combined exposure to drinking and smoking

Table 2
Mixed-effects logistic regression models with centre as a random effect for severe COVID-19.

Variables	Severe COVID-19[a]		Unadjusted	Adjusted
	No, *n* (%)	Yes, *n* (%)	OR (95% CI)	OR (95% CI)
Drinking[b]				
Non-drinkers	361 (29.5)	863 (70.5)	1.00 (reference)	1.00 (reference)
Current drinkers	38 (35.5)	69 (64.5)	1.33 (0.76, 2.34)	1.00 (0.52, 1.92)
Former drinkers	22 (38.6)	35 (61.4)	1.28 (0.84, 1.97)	1.15 (0.67, 1.95)
Drinkers (current/former)	60 (36.6)	104 (63.4)	1.30 (0.91, 1.86)	1.09 (0.69, 1.72)
Smoking[c]				
Non-smokers	357 (29.4)	859 (70.6)	1.00 (reference)	1.00 (reference)
Current smokers	43 (35.0)	80 (65.0)	1.68 (0.93, 3.02)	1.68 (0.84, 3.38)
Former smokers	21 (42.9)	28 (57.1)	1.27 (0.85, 1.89)	1.24 (0.76, 2.03)
Smokers (current/former)	64 (37.2)	108 (62.8)	1.38 (0.98, 1.93)	1.35 (0.87, 2.10)
Combined drinking and smoking[d]				
Non-drinkers/non-smokers	339 (29.4)	816 (70.6)	1.00 (reference)	1.00 (reference)
Drinkers/non-smokers	18 (29.5)	43 (70.5)	0.95 (0.53, 1.69)	0.89 (0.48, 1.64)
Non-drinkers/smokers	22 (31.9)	47 (68.1)	1.13 (0.67.1.91)	1.12 (0.64, 1.99)
Drinkers/smokers	42 (40.8)	61 (59.2)	1.56 (1.02, 2.40)	1.62 (1.01, 2.60)
Interaction of drinking and smoking				
P for interaction[e]			0.39	0.30

CI, confidence interval; CCI, Carlson Comorbidity Index; CURB-65, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years; OR, odds ratio.
[a] Severe COVID-19: including severe subtype and critical subtype.
[b] Adjusted for age, sex, smoking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[c] Adjusted for age, sex, drinking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[d] Adjusted for age, sex, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[e] The *P* value represents the multiplicative interaction of drinking and smoking.

Table 3
Mixed-effects logistic regression models with centre as a random effect for composite poor outcome.

Variables	Composite poor outcome[a]		Unadjusted	Adjusted
	No, *n* (%)	Yes, *n* (%)	OR (95% CI)	OR (95% CI)
Drinking[b]				
Non-drinkers	1077 (87.2)	158 (12.8)	1.00 (reference)	1.00 (reference)
Current drinkers	100 (93.5%)	7 (6.5)	1.29 (0.59, 2.84)	0.90 (0.35, 2.30)
Former drinkers	49 (86.0)	8 (14.0)	0.53 (0.24, 1.18)	0.45 (0.18, 1.13)
Drinkers (current/former)	149 (90.9)	15 (9.1)	0.78 (0.44, 1.38)	0.61 (0.30, 1.25)
Smoking[c]				
Non-smokers	1075 (87.6)	152 (12.4)	1.00 (reference)	1.00 (reference)
Current smokers	110 (89.4)	13 (10.6)	1.41 (0.64, 3.08)	1.37 (0.53, 3.54)
Former smokers	41 (83.7)	8 (16.3)	0.94 (0.51, 1.73)	1.07 (0.52, 2.22)
Smokers (current/former)	151 (87.8)	21 (12.2)	1.08 (0.66, 1.77)	1.16 (0.62, 2.18)
Combined drinking and smoking[d]				
Non-drinkers/non-smokers	1017 (87.2)	149 (12.8)	1.00 (reference)	1.00 (reference)
Drinkers/non-smokers	58 (95.1)	3 (4.9)	0.38 (0.12, 1.26)	0.29 (0.08, 1.03)
Non-drinkers/smokers	60 (87.0)	9 (13.0)	1.02 (0.49, 2.10)	0.81 (0.27, 1.82)
Drinkers/smokers	91 (88.3)	12 (11.7)	1.04 (0.55, 1.99)	0.91 (0.45, 1.84)
Interaction of drinking and smoking				
P for interaction[e]			0.20	0.10

CI, confidence interval; CCI, Carlson Comorbidity Index; CURB-65, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years; ICU, intensive care unit; OR, odds ratio.
[a] Composite poor outcome: including death, ICU admission or mechanical ventilation.
[b] Adjusted for age, sex, smoking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[c] Adjusted for age, sex, drinking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[d] Adjusted for age, sex, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[e] The *P* value represents the multiplicative interaction of drinking and smoking.

significantly increased the risk (OR = 1.62; $P < 0.05$) for severe COVID-19, indicating that drinkers/smokers may be prone to developing severe COVID-19. However, the role of combined exposure to smoking and alcohol drinking as risk factors for severe COVID-19 among hospitalised COVID-19 patients is a preliminary finding; hence, further investigation of these results is necessary.

The present study has several notable strengths. To the best of the authors' knowledge, this is the first study to investigate the interaction and combined effects of alcohol drinking and smoking on severe COVID-19 and the clinical outcomes of COVID-19 patients in China. In addition, this was a multicentre study, with a relatively large number of patients. The results reveal that drinkers/smokers had a higher risk of developing severe COVID-19 than non-drinkers/non-smokers.

The present study also has some limitations. First, the status of cigarette smoking and alcohol consumption was self-reported by the patients. Therefore, it is prone to recall bias. Second, the study had a retrospective observational design. Thus, the observed findings should be interpreted carefully because residual confounding cannot be entirely ruled out. For instance, obesity has been confirmed as an important risk factor for the severity and prognosis of COVID-19 patients;[45] however, the information required to determine obesity was not collected, as body mass index data were missing. Third, exposure levels to alcohol and smoking were not provided; therefore,

the dose–response relationship with COVID-19 cannot be explored. Fourth, a previous study has shown that the smoking rate in hospitalised patients with COVID-19 was lower than that of the general population.[46] The present study only included a hospital-based population, which likely led to a greater imbalance between the number of patients in each group, thus possibly affecting the results and limiting the generalisation of results to other populations. Finally, because of the rapid and strict measures taken by the Sichuan provincial government to combat COVID-19, the sample size of most designated hospitals in Sichuan was relatively small. This limited the ability to control for hospital variability using hospital as a random effect. Therefore, further data are required that are more representative of the global population to validate these preliminary findings.

Conclusions

In conclusion, combined exposure to alcohol drinking and smoking is linked to severe COVID-19; however, drinking alone or smoking alone had no direct effects, and both drinking and smoking had no interaction effects. Intervention strategies for alcohol consumption and smoking are recommended to decrease the risk of severe COVID-19.

Author statements

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Ethical approval

This study was approved by the Biological and Medical Ethics Committee of West China Hospital (approval number: 2020-304 and 2020-126) and the Ethic Committee of Renmin Hospital of Wuhan University (approval number: WDRY2020-K068). Administrative permission to access the raw data was granted by administrators of each hospital. The study was a retrospective cohort design, and the data used in the study were anonymous, so the requirement for informed consent was waived.

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Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.01.013.

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Letter to the Editor

COVID-19 booster vaccination has not decreased access for low-income countries

The Food and Drug Administration and Centers for Disease Control and Prevention have clarified their stance in support of booster vaccinations for COVID-19. However, there are legitimate ethical concerns that booster campaigns in higher-income countries may limit access to primary vaccinations in lower-income countries.[1] Specifically, ethical arguments have suggested that implementation of booster campaigns will limit the available vaccine supply in other countries.[1]

Because vaccine access depends on factors beyond adequate supply, we hypothesized that booster campaigns might not exacerbate disparities for low-income countries. The purpose of this study was to determine how booster vaccination campaigns in higher-income countries have affected primary vaccination rates and survival in low-income countries.

International vaccination information from *Our World in Data* was queried for daily booster administrations and primary vaccinations.[2] Countries were categorized into low-income, lower middle-income, upper middle-income, and high-income cohorts based on current World Bank classifications. Temporal trends of COVID-19 booster vaccinations in higher-income countries were compared to concurrent temporal trends of COVID-19 primary vaccination rates in low-income countries. New infections and death rates due to COVID-19 among these cohorts after booster vaccine implementation were also analyzed.

Vaccination reports from 224 countries and territories were available. Booster vaccinations started as early as July 2021. During the 16 weeks since booster campaigns have been implemented, there have been 52 million booster vaccines administered in higher-income countries.

Contrary to widespread concerns, low-income countries have continued to increase primary vaccinations concurrently with higher-income countries implementing booster campaigns (Fig. 1). During these 16 weeks, low-income countries increased their primary vaccination rate by 257%, outpacing the rates of high- and upper middle-income countries. High-income countries had a 280% increase in new cases of coronavirus infection, whereas low-income countries have had only a 145% increase in new cases of coronavirus infection during the booster campaign interval. High-income countries had a 368% increase in coronavirus deaths, whereas low-income countries have had only a 152% increase in coronavirus deaths during the booster campaign interval.

Global vaccine inequity is a perennial problem, and this has been underscored by the COVID-19 pandemic. To date, nearly half of the population of high-income countries has had at least one dose of vaccination, compared to 1 in 27 people in low-income countries.[3] Of the total 17.9 billion vaccine doses available worldwide, high-income countries have secured more than the total procurement of all upper middle-, lower middle-, and low-income countries combined.[4]

Despite these alarming figures, claims that vaccine booster campaigns by higher-income countries will constrain the supply of vaccines in lower-income countries remain unproven.[1] Although global initiatives have been implemented to mitigate distribution inequity, vaccine vials often go unused. For example, African nations have had to destroy nearly half million doses of expired vaccines since the beginning of the pandemic.[5] Reports of unused vaccines in low-income countries demonstrate that there are additional challenges beyond merely ensuring adequate supply to these regions.

The top of the supply chain includes vaccine research, development, manufacturing, and production. The lower end of the supply chain requires infrastructure for transportation, storage, delivery, and administration. These downstream supply chain components have become the current barriers to adequate vaccine access in lower-income countries. For example, mRNA vaccines require transportation and storage in freezing temperatures until injection. Ensuring that transportation lines and storage centers have the technology to provide uninterrupted temperature of −70 °C throughout the downstream supply chain can be challenging and expensive.

Given the lack of pre-existing infrastructure, significant healthcare spending has been necessary to adequately meet COVID-19 vaccine demand in low-income countries. Prior to the current pandemic, only 11% of countries in Africa and Southeast Asia had established adult vaccination programs.[6] During the COVID-19 pandemic, high-income countries increased their healthcare spending by only 0.8% to vaccinate 70% of their populations, whereas low-income countries increased healthcare spending by 56.6% for significantly lower vaccination rates.[3]

Continued efforts are necessary to enhance supply chain infrastructure for the delivery and administration of vaccines in low-income countries. However, these results demonstrate that global booster campaigns have had no detrimental impact on primary vaccination rates in low-income countries. Continued vigilance is necessary to monitor resource utilization and ensure that booster

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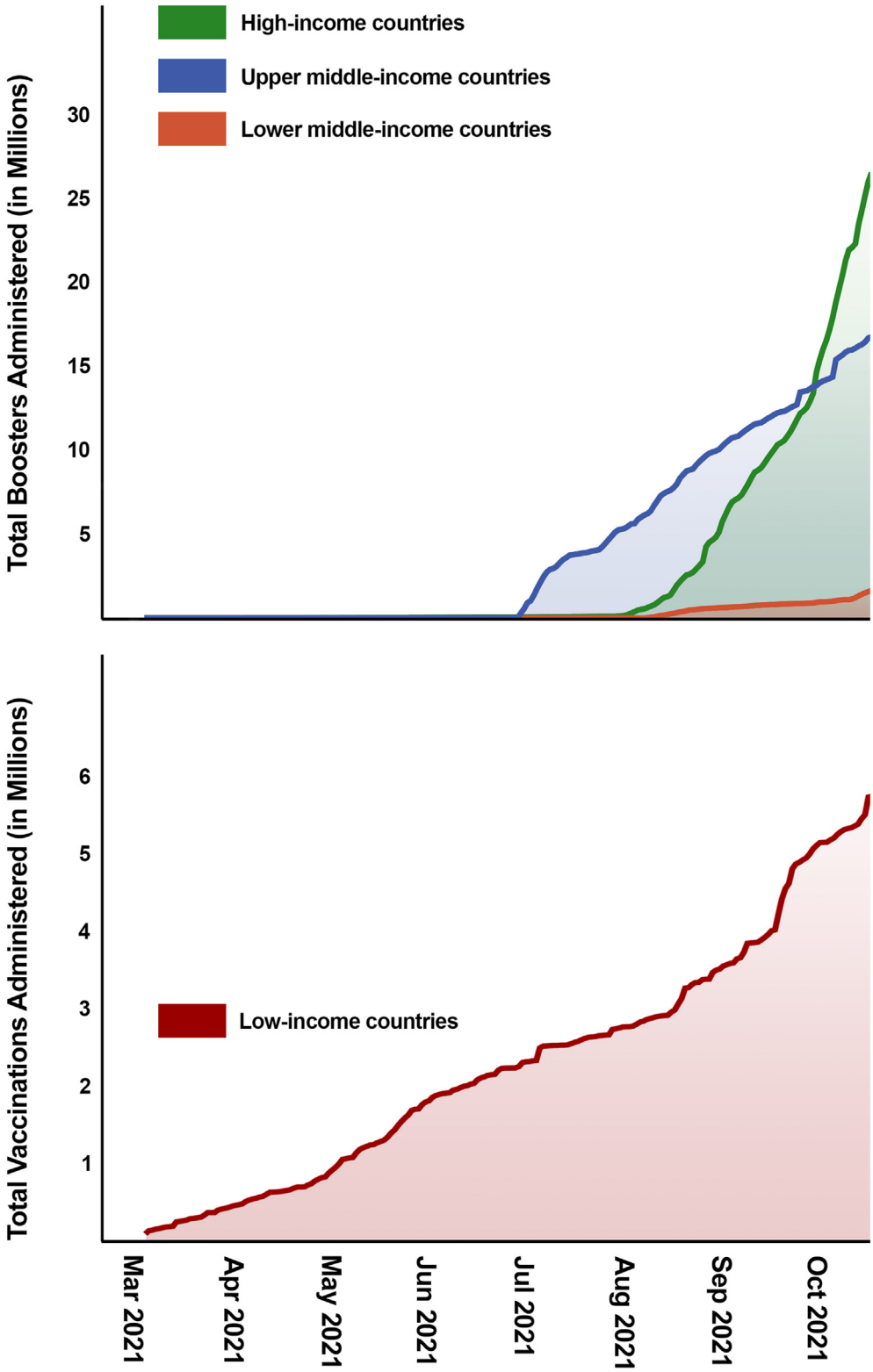

Fig. 1. Trends in low-income vaccination new rates versus higher-income booster vaccination rates.

vaccination campaigns do not disrupt primary vaccination efforts in vulnerable regions.

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Letter to the Editor

COVID-19 vaccine uptake in the US is hampered by mistrust from Black and Latinx communities

As of November 7, 2021, the Centers for Disease Control and Prevention (CDC) has gathered racial/ethnic data on 65% of the COVID-19 cases and 85% of the COVID-19 deaths in the United States. Consistent with previous findings, these data confirm that Black and Latinx individuals have been disproportionately affected by the COVID-19 pandemic. When comparing the proportion of cases to the proportion of the population, data indicate that Latinx individuals, who comprise 18.5% of the population, have 27.6% of the nation's COVID-19 cases. Using the same method, we see that Black individuals, who comprise 12.5% of the population, have 13.5% of the nation's COVID-19 deaths.[1]

These disparities are mirrored in COVID-19 vaccine uptake. One study, based on data from the American Community Survey, found relative uptake rates through March 31, 2021, 1.3 times higher for White adults compared with Black adults (IQR, 1.1–1.6 times) and 1.3 times higher for White adults compared to Latinx adults (IQR, 1.1–1.6).[2,3] These findings suggested that the estimated vaccine uptake among Black and Latinx adults (29%) was one-third lower than among White adults (43%). In light of these disparities, campaigns must be designed to promote vaccine uptake among these two racial/ethnic groups.[4,5]

Vaccine messaging for the Black and Latinx communities presents a challenge. Not only do these groups have suspicions about the vaccine (safety, side effects), but they mistrust the messengers delivering pro-vaccine messages (e.g., Dr. Fauci, CDC, World Health Organization). Black individuals, in particular, question experts' claims about the virus, and the reasons driving COVID-19 policies.[6] This mistrust is understandable in light of the Tuskegee experiments, which were perpetrated by educated, White, health professionals.[7]

To increase vaccine uptake in the Black and Latinx communities, we must earn the trust of these communities.[8] We must remember that these groups were egregiously mistreated in the years of Donald Trump.[9] We must address vaccine concerns and encourage vaccination, using evidence-based, clear communication. We must select appropriate spokespersons for our vaccine uptake mission, as receptivity is higher when using same-race messengers.[10] We must assist community leaders in debunking fake news about the virus and create helplines and apps for the communities.[11] We must approach these two communities as heterogeneous entities, and design vaccine messaging accordingly.

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Conflicts of interest

The author declares no conflicts of interest.

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Original Research

COVID or not COVID: attributing and reporting cause of death in a community cohort

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ABSTRACT

Objectives: In Germany, deaths of SARS-CoV-2–positive persons are reported as 'death related to SARS-CoV-2/COVID-19' to the Robert Koch Institute, Germany's main infectious disease institution. In 177 COVID-19–associated deaths reported in Regensburg, Germany, from October 2020 to January 2021, we investigated how deaths following SARS-CoV-2 infection were reported and whether cases with a death attributed to SARS-CoV-2 (COVID-19 death [CD]) differed from cases with a reported death from other causes (non–COVID-19 death [NCD]).
Study design: This was an observational retrospective cohort study.
Methods: We analysed descriptive data on the numbers of cases, deaths, age, sex, symptoms and hospitalizations. We calculated odds ratios (ORs) with 95% confidence intervals (95% CIs) and performed Chi-squared/Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for comparison of medians.
Results: Deaths attributed to COVID-19 occurred primarily in elderly patients. The mortality rate and the case fatality ratio (CFR) increased with age. The median age and the prevalence of risk factors were similar between CD and NCD. Respiratory symptoms and pneumonia at the time of diagnosis were associated with death reported as CD. The odds of CD attribution in cases hospitalized because of COVID-19 were 6-fold higher than the odds of NCD (OR: 6.00; 95% CI: 1.32 to 27.22).
Conclusions: Respiratory symptoms/pneumonia at the time of diagnosis and hospitalization due to COVID-19 were associated with attributing a death to COVID-19. Numbers of COVID deaths need to be interpreted with caution. Criteria that facilitate attributing the cause of death among SARS-CoV-2 cases more uniformly could make these figures more comparable.

Introduction

The SARS-CoV-2 pandemic has a severe impact on health systems and economies.[1] While the total burden of disease due to COVID-19 is difficult to quantify, the number of deaths attributed to COVID-19 is often used as a surrogate parameter and is regarded as crucial in assessing the severity of the pandemic. Far-reaching consequences for societies worldwide are derived from these figures. Numbers of deaths are often related to the total number of cases (case fatality ratio [CFR]) or to the total number of infections (infection fatality ratio [IFR]), of which the latter is challenging to assess.

In individual cases, it is difficult to determine whether SARS-CoV-2 infection was the direct cause of death, significantly contributed to death or merely coincided with death.[2] Autopsy studies typically comprise small sample sizes of mainly hospitalized patients.[3,4] In a recent study on deaths during the first COVID-19 wave in 2020 in Munich, Germany, autopsies were performed in only 11% of verified fatal COVID-19 cases.[5] To date, there are no uniform criteria to differentiate deaths likely caused by COVID-19 ('due to') from deaths coinciding with COVID-19 ('together with')

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in SARS-CoV-2–infected persons. Thus, deaths of SARS-CoV-2–positive persons are reported to the Robert Koch Institute (RKI) as 'death related to SARS-CoV-2/COVID-19' (according to § 6 of the German Act on Protection Against Infectious Diseases [Infektionsschutzgesetz, IfSG]). Comparisons of international and even national figures need to be handled with caution as determining the cause of death might vary between countries, across time and between individual practitioners and local institutions.[6–8]

In the present study, we focused on deaths in SARS-CoV-2–positive cases in Regensburg, Germany, that occurred during the second COVID-19 wave. Specifically, we aimed to investigate how cases of death following SARS-CoV-2 infection were reported to the public health authorities and whether cases with a death attributed to SARS-CoV-2 ('due to SARS-CoV-2/COVID-19') differed from cases with a death reportedly not caused by SARS-CoV-2 ('together with SARS-CoV-2/COVID-19').

Methods

We collected epidemiologic data on COVID-19 cases in Regensburg residents during the second COVID-19 wave (October 12th, 2020, to January 24th, 2021) and retrospectively analysed cases and deaths. We report absolute numbers of cases and deaths, attack rate, CFR and COVID-19–specific mortality according to age group and sex. Within the study period, cases were included by the date of reporting and deaths were included by the reported date of death.

Case definitions, symptoms/clinical conditions and risk factors at the time of diagnosis

We applied the case definition of COVID-19/SARS-CoV-2 according to criteria specified by the RKI.[9] The following symptoms/clinical conditions and risk factors (RFs) were recorded at the time of case investigation (using the RKI/Äsculab21 reporting software) and analysed retrospectively: sore throat, cough, pneumonia, rhinitis, acute respiratory distress syndrome (ARDS), respiratory disorder requiring ventilation, dyspnoea, fever, general feeling of illness, diarrhoea, smell disorder, taste disorder, tachycardia and tachypnoea; cardiovascular disease, diabetes mellitus, liver disease, neurological/neuromuscular disease, immunodeficiency/HIV, kidney disease, chronic lung disease and cancer. Furthermore, data on status and cause of hospitalization were assessed.

Attribution of the cause of death

Reported deaths in SARS-CoV-2–positive cases were classified as deaths caused by COVID-19 (*COVID-19 death [CD]*) or deaths from a different cause (*non–COVID-19 death [NCD]*) primarily based on notifications by the reporting physician. If the cause of death was not clearly stated by the reporting physician, cases were classified using clinical information from discharge letters and death certificates. Clinical criteria for CD were COVID-19 as a diagnosis in a discharge letter from hospital, a diagnosis of pneumonia, ARDS, morphological findings in computed tomography, multiorgan failure or thromboembolic events stated in medical records or the death certificates associated with a positive polymerase chain reaction (PCR) result for SARS-CoV-2. CD or NCD was categorized by one author (M.L.).

In 28 deaths primarily not reported as having been due to COVID-19, SARS-CoV-2 or COVID-19 was stated as part of the order of events in the death certificate or medical reports. These deaths were reclassified resulting in 137 CDs and 32 NCDs. For 8 deaths, no death certificates were available and those cases were excluded from further analysis (Fig. 1). The retrospective analysis was done by B.L. in a blinded manner.

Statistics

We analysed descriptive data on the numbers of cases, deaths, age, sex, symptoms and hospitalizations. To assess associations, we calculated odds ratios (ORs) with 95% confidence intervals (95% CIs). A Chi-squared/Fisher's exact test was used for categorical variables, and the Wilcoxon rank-sum test was performed for comparison of medians (level of significance for both tests $P < 0.05$). All analyses were done using Microsoft Excel 2016 and SPSS, version 26.0.

Results

A total of 6649 cases were reported to the Regensburg Public Health Department during the study period. Overall, 177 deaths occurred in this period in patients with a SARS-CoV-2 infection. Initially, 109 deaths (61.2%) were reported as having been caused by COVID-19, whereas 68 deaths (38.4%) were reported as NCD. No deaths occurred in individuals younger than 56 years. Therefore, we limited our analysis to cases older than 50 years (2569 cases). The overall CFR based on all COVID-associated deaths was 2.7% (2.1% based on attributed CD), and the CFR among persons aged ≥50 years was 6.9%. Basic descriptive data, symptoms at diagnosis and RFs for all cases ≥50 years and CD and NCD cases separately are shown in Table 1.

Age and sex distribution, CFR and COVID-19–related mortality

We analysed the age and sex distribution of cases and CFR and COVID-19–related mortality according to age group. Most cases were reported among individuals aged 50–59 years (n = 1003, 39% of cases ≥50, Fig. 2 a). Most deaths occurred among individuals aged 80–89 years (n = 86, 48.6%). Women showed a slightly greater number of deaths than men (n = 95 [53.7%] vs. n = 82 [46.3]). Figures per 100,000 individuals per age group (Fig. 2 b) showed that the highest incidence of cases and deaths occurred among persons older than 90 years, with deaths increasing with age. At the same time, the CFR increased in an almost linear fashion (Fig. 2 c). The attack rate was lowest in the group aged 70–79 years, and it peaked among those aged >90 years (7.2%). The age-specific COVID-19–attributed mortality was highest in the age group >90 years, amounting to 1.7% of all COVID-associated deaths and 1.3% of CD. In summary, the attack rate, mortality and CFR increased with age.

Case characteristics of cases ≥50 years of age, CD and NCD cases

There was no significant difference in age between CD and NCD cases (median age = 86 vs. 83 years, interquartile range [IQR]: 80 to 90 vs. 79.3–89 years; $P = 0.32$). Most deaths occurred in the group aged 80–90 years in CD and NCD, with a comparable sex distribution (Fig. 3). The median time from the date of report (as a proxy for the date of diagnosis) to death did not differ significantly between CD and NCD (9.0 vs 8.5 days; IQR: 5.0–15.5 vs 3.0–14.75 days; $P = 0.18$).

A total of 286 of 2569 cases (11.1%) were hospitalized, 133 cases (5.2%) because of COVID-19 and 105 cases (4.1%) due to a different cause; in 48 cases (1.9%), the cause was not reported. Of 137 CDs, 65 cases (47.4%) were hospitalized: 42 cases (30.7%) due to COVID-19 and 14 cases (10.2%) due to a different cause (cause not reported in 9 cases [6.5%]). In NCDs, 12 of 32 cases (37.5%) were hospitalized: 3 cases (9.4%) due to COVID-19, and 6 cases (18.8%) due to a different cause (cause not reported for 3 cases [9.4%]).

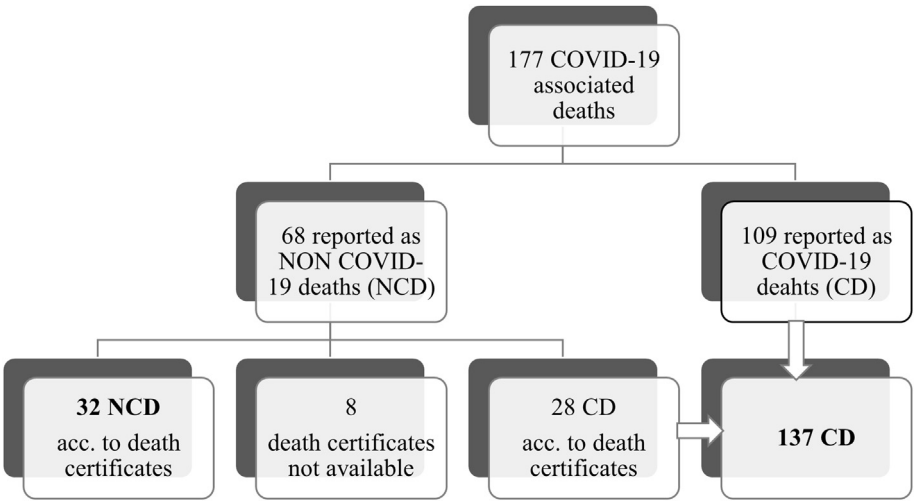

Fig. 1. Assignment of deaths to COVID death (CD) and non–COVID-19 death (NCD) group.

Table 1
Case characteristics of all reported cases ≥50 years of age, COVID-19 deaths and non–COVID-19 deaths[a].

Study period	October 12, 2020, to January 24, 2021			
		All reported cases ≥ 50 years of age	CD	NCD
	Number [n] (%)	2569 (100)	137 (100)	32 (100)
	Male [n] (%)	1137 (44.3)	63 (46)	16 (50)
	Female [n] (%)	1432 (55.7)	74 (54)	16 (50)
	Mean age [y] (median; IQR)	67.3 (63; 56–80)	84.4 (86; 80–90)	82.8 (83; 79.3–89)
	Mean time from date of report to death [days] (median; IQR)	–	11.6 (9; 5–15.5)	8.9 (8.5; 3–14.75)
	Hospitalized [n] (%)	286 (11.1)	65 (47.4)	12 (37.5)
	▪ due to COVID-19	133 (5.2)	42 (30.7)	3 (9.4)
	▪ due to a different cause	105 (4.1)	14 (10.2)	6 (18.8)
Symptoms at diagnosis [n] (% of all cases/deaths)	Cough	662 (25.8)	21 (15.3)	0 (0)
	General feeling ill	587 (22.8)	22 (16.1)	7 (21.9)
	Fever	521 (20.3)	27 (19.7)	4 (12.5)
	Rhinitis	356 (13.9)	3 (2.2)	0 (0)
	Sore throat	312 (12.1)	4 (2.9)	0 (0)
	Taste disorder	189 (7.4)	5 (3.6)	0 (0)
	Odour disorder	143 (5.6)	0 (0)	0 (0)
	Dyspnoea	60 (2.3)	22 (16.1)	1 (3.1)
	Diarrhoea	60 (2.3)	3 (2.2)	0 (0)
	Pneumonia	43 (1.7)	30 (21.9)	1 (3.1)
	ARDS	9 (0.4)	4 (2.9)	1 (3.1)
	Respiratory disorder requiring ventilation	4 (0.2)	2 (1.5)	0 (0)
	Tachypnoea	4 (0.2)	2 (1.5)	0 (0)
	Tachycardia	3 (0.1)	2 (1.5)	0 (0)
Risk factors [n] (% of determinable /investigated RF)	Cardiovascular disease	1108 (77.9)	93 (85.3)	16 (72.7)
	Neurological/neuromuscular disease	379 (27.4)	52 (48.6)	13 (56.5)
	Diabetes mellitus	350 (25.3)	29 (27.1)	6 (28.6)
	Chronic lung disease (COPD)	210 (15.3)	25 (23.6)	4 (20)
	Kidney disease	176 (12.8)	30 (28.8)	7 (35)
	Cancer	155 (11.3)	18 (17)	5 (25)
	Liver disease	77 (5.6)	9 (8.7)	2 (10)
	Immunodeficiency, incl. HIV	74 (5.4)	5 (4.8)	0 (0)

IQR = interquartile range; COPD = chronic obstructive pulmonary disorder; ARDS = acute respiratory distress syndrome.
[a] CD = COVID-19 deaths; NCD = non–COVID-19 deaths.

Cough (25.8%), general feeling of illness (22.8%) and fever (20.3%) were the most common symptoms reported among all cases (Table 1). Cough was not reported as a symptom at the time of reporting in NCD and was less frequent in CD (15.3%) than in all cases ≥50 years (25.8%). Fever was less common in NCD as an initial symptom (12.5% vs 19.7% in CD and 20.3% in all cases). Pneumonia and dyspnoea were more frequent as an initial symptom in CD (21.9% and 16.1%, respectively) than in NCD (3.1% and 3.1%, respectively) and among all cases (1.7% and 2.3%, respectively). ARDS was equal for CD and NCD (2.9% and 3.1%). RFs were not determinable or not investigated in a large proportion of cases (mean 47.6% for all RF in cases older than 50 years, 22.7% in CD, and

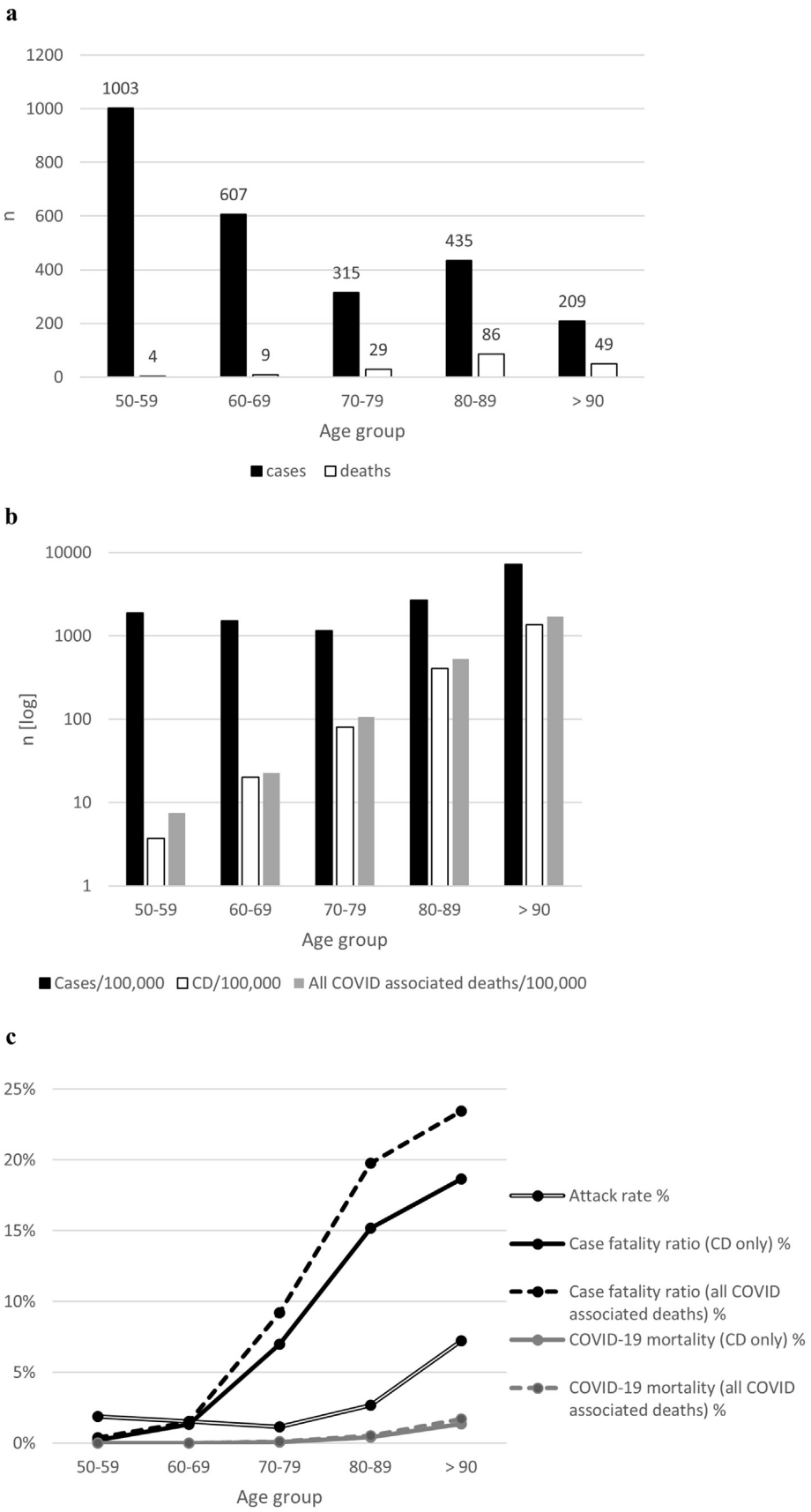

Fig. 2. Distribution of COVID-19 cases ≥50 years of age and deaths. (a) numbers of cases and deaths by age group. (b) Numbers of cases and deaths per 100,000 per age group (logarithmic scale) (c) Attack rate, case fatality ratio (CFR) and COVID-19 associated mortality per age group.

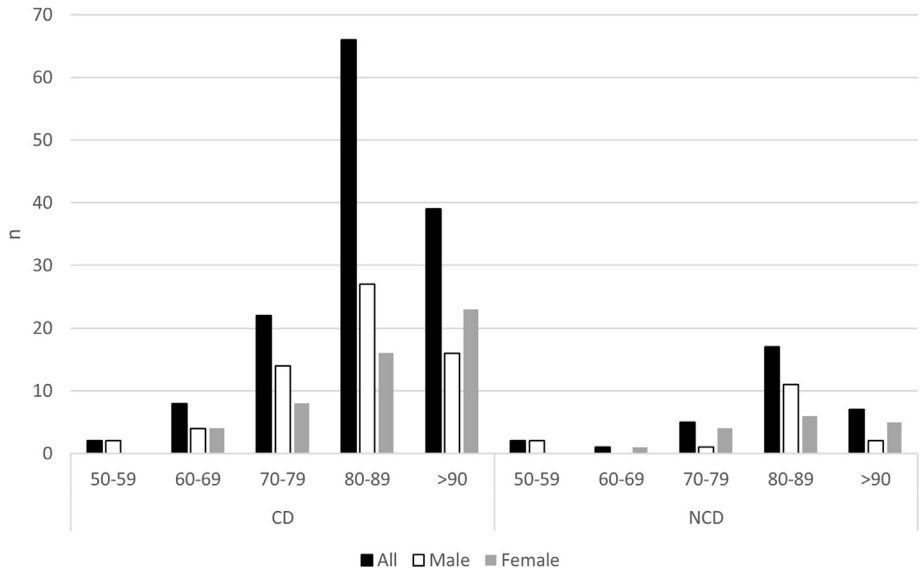

Fig. 3. Sex distribution of deaths per age group in COVID death (CD) and non–COVID-19 death (NCD).

35.2% in NCD). The leading RF in all cases with determinable RF was cardiovascular disease (77.9%), being more frequent in CD (85.3%) than in NCD (72.7) and among all cases aged ≥50 years (77.9%). Apart from immunodeficiency/HIV, all RFs were more frequent in CD than in all cases aged ≥50 years.

Association of symptoms/clinical conditions, RF and hospitalization with CD and NCD

For further analysis, CD and NCD were compared with respect to symptoms at diagnosis, RFs and hospitalization (Table 2). An association with CD was observed for pneumonia (OR: 8.69; 95% CI: 1.14 to 66.32; $P = 0.01$) and cough ($P = 0.02$). Dyspnoea was more frequent in CD (22/115 vs 1/31; OR: 5.93; 95% CI: 0.77 to 45.74; $P = 0.08$). Cardiovascular disease as an RF was not significantly associated with CD (OR: 2.18; 95% CI: 0.74 to 6,41; $P = 0.21$). Hospitalization due to COVID-19 was associated with CD compared to hospitalization due to a different cause (OR: 6.00; 95% CI: 1.32 to 27.22; $P = 0.01$), but not hospitalization itself (OR: 1.33; 95% CI: 0.58 to 3.07; $P = 0.50$).

Discussion

The present study represents a retrospective analysis of a cohort from Regensburg, Germany. We focused on deaths in patients with SARS-CoV-2 during the second COVID-19 wave (October 2020 to

Table 2
Association of different symptoms, risk factors (RFs) and hospitalization at the time of reporting with CD and NCD[a].

		Odds (yes/no) of CD vs NCD	OR (95% CI)	*P* value (Chi^2/Fisher's exact test)
Symptoms	Pneumonia	30/107 vs 1/31	8.69 (CI: 1.14 to 66.32)	0.01
	Fever	27/110 vs 4/28	1.72 (CI: 0.56 to 5.31)	0.34
	Dyspnoea	22/115 vs 1/31	5.93 (CI: 0.77 to 45.74)	0.08 (Fisher's)
	Cough	21/116 vs 0/32	–	0.02 (Fisher's)
	General feeling ill	22/115 vs 7/25	0.68 (CI: 0.26 to 1.77)	0.432
	Taste disorder	5/132 vs 0/32	–	0.59 (Fisher's)
	Sore throat	4/133 vs 0/32	–	1.00 (Fisher's)
	ARDS	4/133 vs 1/31	0.93 (0.10–8.64)	1.00 (Fisher's)
	Diarrhoea	3/134 vs 0/32	–	1.00 (Fisher's)
	Respiratory disorder requiring ventilation	2/135 vs 0/32	–	1.00 (Fisher's)
	Rhinitis	3/134 vs 0/32	–	1.00 (Fisher's)
	Tachycardia	2/135 vs 0/32	–	1.00 (Fisher's)
	Tachypnoea	2/135 vs 0/32	–	1.00 (Fisher's)
	Odour disorder	0/137 vs 0/32	–	–
Risk factors (calculated for determinable/investigated RF)	Cardiovascular disease	93/16 vs 16/6	2.18 (0.74–6,41)	0.21 (Fisher's)
	Neurological/neuromuscular disease	52/55 vs 13/10	0.73 (0.29–1.80)	0.49
	Diabetes mellitus	29/78 vs 6/15	0.93 (0.33–2.63)	0.89
	Chronic lung disease	25/81 vs 4/16	1.24 (0.38–4.03)	1.00 (Fisher's)
	Kidney disease	30/74 vs 7/13	0.75 (0.27–2.07)	0.58
	Cancer	18/88 vs 5/15	0.61 (0.20–1.90)	1.00 (Fisher's)
	Liver disease	9/95 vs 2/18	0.85 (0.17–4.28)	1.00 (Fisher's)
	Immunodeficiency/HIV	5/99 vs 0/20	–	1.00 (Fisher's)
Hospitalization		65/61 vs 12/15	1.33 (0.58–3.07)	0.50
	due to COVID-19	42/14 vs 3/6	6.00 (1.32–27.22)	0.01

RF = risk factor; 95% CI = 95% confidence interval; ARDS = acute respiratory distress syndrome; OR = odds ratio.
If expected frequency in 2x2 table was <5, *P* value is stated according to Fisher's exact test.
[a] CD = COVID-19 death; NCD = non–COVID-19 death.

January 2021). Overall, mainly elderly and old patients died from COVID-19 or died in association with COVID-19. The attack rate and mortality increased with age, and the CFR culminated in a maximum of 23.4% calculated for all COVID-associated deaths aged ≥90 years. Pneumonia and cough at the time of diagnosis were significantly associated with death reported as CD. The odds for CD in cases hospitalized because of COVID-19 increased 6-fold compared to NCD. Time from diagnosis/date of report to death did not differ between the two groups. Thus, respiratory symptoms/pneumonia at the time of diagnosis and hospitalization due to COVID-19 seem to be associated with attributing deaths to COVID-19.

Taking only deaths with CD into account, the overall CFR of 2.1% in Regensburg was rather low compared to the literature.[10,11] If the CFR was based on all COVID-19–related deaths, it was 2.7%, which is slightly higher than in the first COVID-19 wave in spring 2020, which showed a CFR of 2.1%.[12] The observed increase in CFR, attack rate and mortality with age is well documented for COVID-19 in Europe and the US.[13,14]

In our cohort, we found that a number of deaths were initially not reported as CD to the public health authorities despite conflicting information in medical records or death certificates. Taking into account the information provided by death certificates, we reclassified nearly 16% of deaths in our cohort as CD. Divergent information between death reports and death certificates or discharge letters may reflect uncertainty in attributing the cause of death, particularly in older patients with comorbidities.

Studies on COVID-19–related deaths have mainly focused on hospitalized patients.[3,4,15] Studies attempting to identify associations of epidemiologic or clinical features with attribution of cause of death in general have been scarce.[16] Several RFs for death in COVID-19 cases have been identified thus far.[17,18] However, the presence of one or more RFs does not allow us to differentiate between CD and NCD as most of them are frequently present in elderly patients. Accordingly, we could not find significant differences in RFs between CD and NCD. Dyspnoea is described in the literature as a predictor of disease severity and death in COVID-19 patients.[17,19] We found significant associations with CD attribution only for pneumonia and cough.

Our study has several limitations. First, this is a retrospective study with a relatively small sample size. RFs and symptoms were collected as part of infection control investigations at one time point only and were provided by the individual case. The data on risk factors are incomplete due to the lack of verification and missing data. Associations of symptoms and cause of death attribution showed wide CIs. We did not adjust for potential confounding factors. To our knowledge, the autopsy rate in our cohort was 0, and no standard characteristics have been defined to decide, how deaths may be attributed to COVID-19 in different populations (e.g., outpatients) and timeframes after infection. Information from death certificates varied qualitatively and did not support a firm attribution of the cause of death in every case. Hence, our study cannot make solid statements about causes of death but only about the attribution of COVID-19 and its association with symptoms/clinical conditions and RF reported at the time of the first notification of the case. Generally, there is no unambiguous data source for the attribution of a death to SARS-CoV-2 infection as clinical assessments in discharge letters or death certificates (and even autopsies) must be regarded as arbitrary to some extent. So the number of deaths caused by COVID-19 has to be interpreted with caution.

To conclude, we have in a (cautious) exclusion process identified a number of deaths which were not attributed to COVID-19 in the judgement of the treating physician. There are some clinical characteristics present in this group which support our findings that not every death in a patient with a positive SARS-CoV-2 PCR is caused strictly by SARS-CoV-2. On the other hand, asymptomatic (undiagnosed) fatalities may be missed and misclassification of deaths has to be assumed. Defined criteria might at least facilitate attributing the cause of death more uniformly and comparing death counts in different regions and countries. Efforts have to be made to improve the quality of the data on the suspected cause of death in the absence of widely used autopsies. Clinicians should be encouraged to deliver complete reports of clinical conditions in deceased patients and a complete and logical chain of causation in filling in death certificates. Awareness of the described problem and further research on the topic are necessary.

Author statements

Ethical approval

Not applicable.

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Competing interests

None declared.

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Short Communication

Diagnostic precision of local and World Health Organization definitions of symptomatic COVID-19 cases: an analysis of Mexico's capital

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ABSTRACT

Objectives: Case definitions are vital in a pandemic to effectively identify, isolate, and contact trace, particularly where testing is slow, scant, or not available. While case definitions have been developed in the COVID-19 pandemic, their diagnostic properties have not been adequately assessed. This study's objective is to determine the diagnostic properties of local and World Health Organization (WHO) COVID-19 case definitions in the large metropolitan area of Mexico City.

Methods: We calculated the diagnostic properties of five COVID-19 definitions (three of the Mexican government and two of the WHO) using open data of suspected COVID-19 cases in Mexico City from March 24th, 2020, until May 15th, 2021.

Results: All 2,564,782 people included in the analysis met the WHO suspected case definition (sensitivity: 100%, specificity: 0%). The WHO probable case definition was met by 1.2%, while the first and second Mexican suspected case had sensitivities of 61% and specificities of 61% and 67%, respectively. Confirmed case by epidemiological contact had a low sensitivity (32%) but slightly higher specificity (81%).

Conclusions: Case definitions should maximize sensitivity, especially in a high-transmission area such as Mexico City. The WHO suspected case definition has the potential for detecting most symptomatic cases. We underline the need for routine evaluation of case definitions as new evidence arises to maximize their usefulness.

Introduction

Epidemiologic case definitions for a disease are vital in surveillance during epidemics. In this context, the aim of a case definition is to be highly sensitive as to miss the fewest true cases of the disease. In low-income countries, case definitions are valuable to make decisions on isolation, contact tracing, and monitoring disease trends since definitive tests might be scarce, unavailable, and highly expensive.[1] During the COVID-19 pandemic, the World Health Organization (WHO) released case definitions for suspected, probable, and definitive COVID-19 cases, which have been periodically updated.[2] Countries also released definitions with irregular updating, even though they should be revised according to new scientific evidence as to increase their diagnostic value.[1–4]

Mexico released the first version of its COVID-19 suspected case definition in March 2020, with the aim of determining who should be tested. Only one in ten ambulatory suspected COVID-19 patients would be tested, as well as all hospitalized ones. An update in the case definition was published in August 2020 with minor changes, but the testing strategy remained the same.[3,4] Considering this deliberate undertesting, suspected case definitions become especially important to account for disease undercounting, initiate contact tracing (which has not been a feature of Mexico's pandemic response, but is elsewhere), and starting individual treatment. An important caveat is that the people who design these definitions are in many cases not the same people that have to apply them on the field. Thus, dissociation could occur between intended and actual use.

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Mexico City is a large metropolitan area with 9,209,944 habitants.[5] In this analysis, we calculated the diagnostic properties of the definitions of COVID-19 cases of Mexico's Ministry of Health (from now on, simply Mexico) and those of the WHO to determine their adequacy for epidemiological monitoring purposes.

Methods

We used open data from the Mexico City government for reported cases of suspected COVID-19 between March 24th, 2020, and May 15th, 2021.[6] We calculated the diagnostic properties (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], positive likelihood ratio, and negative likelihood ratio), as well as post-test probabilities of five different epidemiological COVID-19 case definitions: three issued by Mexico for COVID-19 surveillance purposes (suspected case, updated suspected case definition, and suspected case 'confirmed' by epidemiological linkage to a laboratory-confirmed case) and two WHO-recommended definitions (suspected and probable).[2–4]

A comparison between these definitions is provided in Table 1. Mexico's COVID-19 suspected case definition was issued in March 2020 and included anybody seeking care for at least one of the following symptoms starting within the 7 previous days: cough, dyspnea, fever or headache; with at least one of the following: myalgia, arthralgia, sore throat, thoracic pain, rhinorrhea, polypnea, or conjunctivitis.[3] COVID-19 suspected case definition was updated by Mexico in August 2020 (adding chills, anosmia, and dysgeusia and expanding the period of symptoms onset from 7 to 10 days).[4] The case definition for COVID-19 confirmed by epidemiological linkage to a laboratory-confirmed case (anyone meeting the COVID-19 suspected case criteria that have had contact with a laboratory-confirmed case within the previous 14 days).[4] We substituted contact with 'confirmed case' with contact with an 'individual with respiratory symptoms,' as only information on this variable was available.[6] Mexico's COVID-19 case definition is the same case definition used for surveillance activities of seasonal Influenza. Only one in ten symptomatic ambulatory patients is tested, while all hospitalized patients are tested, and no asymptomatic testing occurs.[3] There are no pre-established criteria on which ambulatory patients are tested for SARS-CoV-2, and decisions about testing depends heavily on clinical judgment and tests availability on sentinel sites. The revised WHO COVID-19 case definitions for suspected (which includes a set of different options of clinical and epidemiological criteria, as shown in Table 1) and probable cases (which requires the presence of the clinical criteria in suspected cases: acute onset of fever and cough OR acute onset of any three or more of the following symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status in combination) in combination with chest imaging showing findings suggestive of COVID-19 disease, which we replaced with the variable 'clinical diagnosis of pneumonia' since no data on chest imaging were available.[2–4]

Since all tested patients in Mexico are symptomatic, the diagnostic gold standard for our calculation of the diagnostic properties of case definitions was having either a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) or a positive antigen test. Post-test probabilities of COVID-19 were calculated using the daily proportion of positive molecular or antigen tests and graphed using 7-day rolling means.

All analyses were performed with R, version 4.0.0.

Results

A total of 2,564,782 people were registered in the Mexico City open database during the study period. There were 631,342 (24.6%) cases confirmed by RT-PCR or antigen test and 1,932,440 (75.3%) negative tests.

Both Mexican definitions of suspected COVID-19 cases had similar diagnostic properties, with slightly better characteristics in the updated definition (Table 2). All patients met the WHO definition of suspected COVID-19 case, with a perfect sensitivity, specificity of 0%, PPV of 25%, and NPV of 0%. Meanwhile, the WHO case definition for probable COVID-19 was met by very few patients (30,839, 1.2%), showing a sensitivity of 3%, specificity of 99%, PPV of 66%, and NPV of 76%. It is noteworthy that all patients that did not meet the probable case definition met the suspected case definition.

Post-test probability varied greatly according to the pretest probability and the definition utilized, with a mean probability of 39% (standard deviation [SD]: 15) for the first Mexican case definition, 43% (SD: 15) for the second definition, 41% (SD: 15) for the Mexican definition of confirmed case by epidemiological contact, 30% (SD: 13) for the WHO definition of suspected case, and 54% (SD: 16) for the WHO definition of probable case. Post-test probabilities along the study period for each definition are shown in Fig. 1.

Discussion

Epidemiological case definitions are indispensable for surveillance but are riddled with challenges. When tallying COVID-19 cases according to case definition, changing it can increase the number of cases several-fold.[7] We observed that the three COVID-19 case definitions used by Mexico have poor sensitivity (32–61%) in contrast to the WHO suspected case definition. This has the obvious implication that Mexico's suspected case definition is not being used as intended (as a screening test to decide who should be considered for testing). Considering that theoretically it should have a sensitivity of 100%, it is fortunate that it is not being used as planned, as almost 40% of currently observed cases would be missed.

A suspected case definition that is not met by many confirmed cases is not useful, for epidemiologic purposes or otherwise. Our analysis underlines the importance of this, as Mexico is a country that tests a small percentage of symptomatic people. In our context, suspected cases based on symptoms should include all but asymptomatic individuals as the WHO suspected case definition does and be formally counted and included in epidemiologic surveillance, as most do not have access to confirmatory tests.

Thus, the high sensitivity of the WHO suspected case definition could potentially reduce case subestimation and should be preferred when guiding testing decisions in Mexico City and elsewhere. We consider results would be similar if we replicated the analysis country wide; unfortunately we do not have the data to do so.

As only symptomatic people are being tested, clinical judgment remains key and patients should be retested in case of a negative result if prevalence remains high.[8] Point-of-care tests might be very useful in these contexts, as their low cost allows for repeated testing.[8]

Strengths and limitations

Our study has several limitations. We did not have information on several variables, such as anosmia, dysgeusia, and radiological imaging. The incidence of anosmia and/or dysgeusia in Mexican COVID-19 patients is unknown, but elsewhere it has been reported in 35%.[9] This could improve the sensitivity of Mexico's second definition. Only one in ten ambulatory patients is tested, and these patients could differ in ways that we are unable to account for, such as subjective disease severity. Furthermore, false-negative tests are well known and limit

Table 1
Comparison of Mexican Ministry of Health and World Health Organization (WHO) COVID-19 case definitions.

Mexican Ministry of Health COVID-19 definitions			WHO COVID-19 definitions	
Suspected case (March 24, 2020 definition)	Suspected case (August 25, 2020 definition)	Confirmed case by epidemiological link (August 25, 2020 definition)	Suspected case of SARS-CoV-2 infection	Probable case of SARS-CoV-2 infection
Any person that presented in the last seven days any one of these symptoms: cough, dyspnea, fever or headache AND at least one of the following: - Myalgias - Arthralgias - Sore throat - Chest pain - Rhinorrhea - Polypnea - Conjunctivitis	Any person that presented in the last ten days any one of these symptoms: cough, dyspnea, fever or headache AND at least one of the following: - Myalgias - Arthralgias - Sore throat - Chills - Chest pain - Rhinorrhea - Polypnea - Conjunctivitis - Anosmia - Dysgeusia	Any person that presented in the last ten days any one of these symptoms: cough, dyspnea, fever or headache AND at least one of the following: - Myalgias - Arthralgias - Sore throat - Chills - Chest pain - Rhinorrhea - Polypnea - Conjunctivitis - Anosmia - Dysgeusia **AND** Contact with a laboratory-confirmed COVID-19 case during the last 14 days.	One of three options must be met, A through C: A. A person who meets the clinical **AND** epidemiological criteria: Clinical criteria: 1. Acute onset of fever **AND** cough; **OR** 2. Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness, fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status. **AND** Epidemiological criteria: 1. Residing or working in a setting with high risk of transmission of the virus: for example, closed residential settings and humanitarian settings, such as camp and camp-like settings for displaced persons, any time within the 14 days before symptom onset; **OR** 2. Residing in or travel to an area with community transmission anytime within the 14 days before symptom onset; **OR** 3. Working in health setting, including within health facilities and within households, anytime within the 14 days before symptom onset. **B**. A patient with severe acute respiratory illness (SARI: acute respiratory infection with a history of fever or measured fever of $\geq$38 C°; **AND** cough; with onset within the last 10 days; **AND** who requires hospitalization). **C.** An asymptomatic person not meeting epidemiologic criteria with a positive SARS-CoV-2 antigen −detecting rapid diagnostic test (Ag-RDT)	One of the four options must be met, A through D: **A.** A patient who meets clinical criteria of suspected case AND is a contact of a probable or confirmed case or is linked to a COVID-19 cluster. **B.** A suspected case (described earlier) with chest imaging showing findings suggestive of COVID-19 disease. C. A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause. D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND who was a contact of a probable or confirmed case or linked to a COVID-19 cluster.

Table 2
Diagnostic properties of COVID-19 epidemiological case definitions in Mexico City.

Definition		Positive RT-PCR or antigen test	Negative RT-PCR and antigen test	Properties	
Mexico's first suspected case definition	Yes	383,951	746,930	Sens	61%
				Spec	61%
				PPV	34%
	No	247,391	1,186,510	NPV	83%
				LR+	1.56
				LR-	0.64
Mexico's second suspected case definition	Yes	382,560	643,748	Sens	61%
				Spec	67%
				PPV	37%
	No	248,782	1,289,692	NPV	84%
				LR+	1.85
				LR-	0.58
Mexico's confirmed case by epidemiological contact	Yes	199,587	359,748	Sens	32%
				Spec	81%
				PPV	36%
	No	431,755	1,573,692	NPV	78%
				LR+	1.68
				LR-	0.84
WHO's suspected case definition	Yes	631,342	1,933,440	Sens	100%
				Spec	0%
				PPV	25%
	No	0	0	NPV	0%
				LR+	1
				LR-	*
WHO's probable case definition	Yes	20,285	10,554	Sens	3%
				Spec	99%
				PPV	66%
	No	611,057	1,922,886	NPV	76%
				LR+	3
				LR-	0.98

LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; RT-PCR: real-time reverse-transcriptase polymerase chain reaction; Sens: sensibility; Spec: specificity; WHO: World Health Organization.

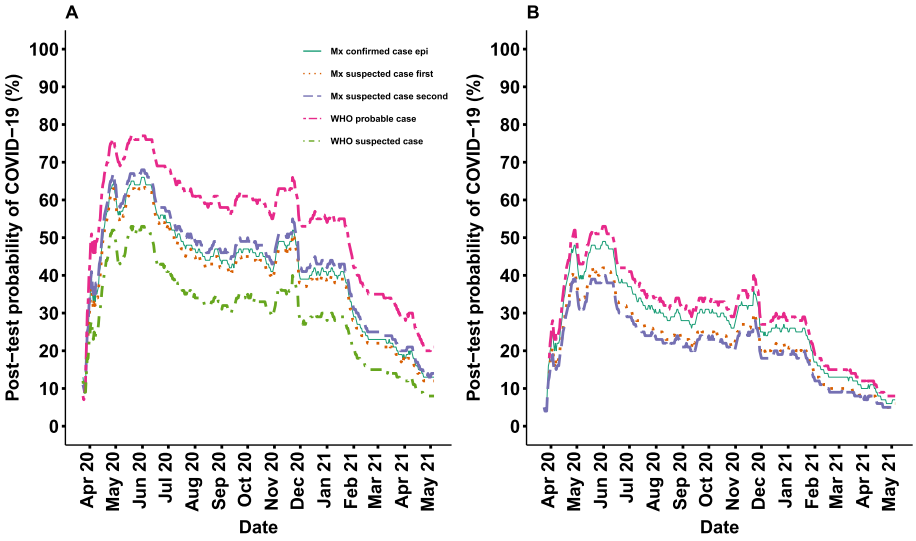

Fig. 1. Post-test probability of COVID-19 according to several case definitions. A) shows post-test probabilities in case of meeting a given case definition. B) shows post-test probabilities in case of not meeting the case definition. Mx confirmed case epi: Mexico's definition of confirmed case by epidemiological contact; Mx suspected case first: Mexico's first suspected case definition; Mx suspected case second: Mexico's second suspected case definition; WHO probable case: WHO's probable case definition; WHO suspected case: WHO's suspected case definition. Gold standard was considered to be either a positive molecular or antigen SARS-CoV-2 test. As WHO's suspected case definition had a negative predictive value of 0%, it does not appear in B). WHO: World Health Organization. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

our definition of gold standard.[10–12] This is especially important given the high post-test probability observed throughout the study period (>10%). Accounting for false-negative tests would increase the post-test probability, and thus, a negative test would not rule out the disease in high-prevalence areas such as this.

Conclusion

Our analysis supports that case definitions should be formally evaluated as to ensure their usefulness. Those with low sensitivity, especially in places with high disease burden and/or limited testing,

should not be used. Given its high sensitivity, places in need of a local definition should adopt the WHO suspected case definition.

Author statements

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Ethical approval

This study did not require ethics board approval because it used publicly available anonymized data, with no interaction between the researchers and individuals.

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None.

Competing interests

None.

Data availability

Data are freely available at the official Mexico City government COVID-19 website.[6] Code used for the analyses is available at https://github.com/isaac-nunez/covid19_case_definition.

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Letter to the Editor

Fast COVID-19 vaccine effectiveness estimation on the basis of recovered individual propensity to be vaccinated

Since March 2020, the study of COVID-19 pandemic contagion data has been perceived as relevant by a wide audience composed not only of epidemiologists and specialized personnel but also of press offices, independent agencies, and ordinary people. There is therefore a strong need to provide clear information understandable to a wide unspecialized public. Vaccine efficacy, in terms of risk reducing of infection/hospitalization/death, is usually estimated by the Government Centers for Disease Control (CDC) through multivariate analysis (e.g. [1,2]); however, these statistical methods are often incomprehensible to the general public. To provide immediate information to the general (unqualified) public, the CDCs of different nations (e.g. [3–5]), as well as several prestigious press offices (e.g. [6]), have published epidemiological data and statistics on dedicated Web pages and dashboards.

The main purpose of this article is to point out to the CDCs of the various governments, as well as to independent agencies and press offices, the need and advantages of correcting incidence data of the infection, as well as to propose a practical equation to calculate vaccine effectiveness, based on the count of recovered subjects who have not yet been vaccinated. This equation can be used to accompany data on infection incidence aimed at the general public, as well as an "easy-to-access" formula to be used for the official and institutional communication of the CDCs.

Relative risk reduction (RRR) can be defined as follows:

$$\mathrm{RRR} = (\mathrm{Pn} - \mathrm{Pv})/\mathrm{Pn}; \tag{1}$$

where *Pn* and *Pv* denote the probability of SARS-CoV-2 infection in the subpopulations of unvaccinated and vaccinated individuals, respectively. Usually, *Pn* and *Pv* are estimated by the respective incidence values; nevertheless, this produces a bias in *RRR* estimation depending on various factors. Among these, a major bias source consists in the failure in excluding the recovered individuals from the count of unvaccinated population, whose consequence is a systematic underestimation of vaccine efficacy. In fact, if the vaccinated population were compared with the unvaccinated one, but inclusive of the healed subjects, the degree of susceptibility to infection would be biased because a part of the unvaccinated is instead immunized from the previous infection.

An unbiased vaccine efficacy estimate is provided by (Appendix 1):

$$RRR = 1 - \frac{N_V \cdot ((1 - V) - G \cdot E_G \cdot (1 - P_R))}{N_N \cdot V} \tag{2}$$

where RRR = vaccine efficacy, N_V = positive cases among vaccinated, N_N = positive cases among unvaccinated individuals; V = fraction of vaccinated population, G = fraction of recovered population, E_G = recovery immunization efficacy, P_R = propensity of the recovered individuals to vaccination, P_R = probability(vaccination | recovery), and N_V and N_N denote the numbers of detected positive individuals in a certain time interval (e.g. 128 positive in a certain day); all other variables represent probabilities or fractions of the unit; therefore, they are positive real numbers less than 1 (e.g. $E_G = 0.85$; $G = 0.1$, etc.).

Such equation allows to easily estimate vaccine effectiveness in terms of reducing the risk of diagnosing SARS-CoV-2 infection for different values of the propensity of the recovered individuals to vaccination. If we assume that E_G = RRR, then equation 2 becomes:

$$\mathrm{RRR} = (\mathrm{R} \cdot (1 - \mathrm{V}) - \mathrm{V})/(\mathrm{R} \cdot \mathrm{G} \cdot (1 - \mathrm{Pr}) - \mathrm{V}); \tag{3}$$

where R = Nv/Nn.

In the proposed equation, the contagion reduction risk (RRR in case of vaccine, E_G in case of recovery) may be defined as the value, averaged over the population and a time interval, of the relative reduction in the probability of contracting the infection at each contact or occasion of contagion.

The propensity of recovered individuals to undergo vaccination is affected by the technical time to vaccinate (of several months), as well as by postponing the decision or give up (propensity stricto sensu). We suggest to CDCs to provide updated *Pr* values to allow correcting effectiveness estimates according to Eq. (2) within the framework of a simplified analysis.

To illustrate the advantages related to the proposed correction, we have applied such method to simulated data whose solution is already known, according to the scenario illustrated in Fig. 1A, where likely values have been assigned to vaccine and recovery efficacy: $RRR = E_g = 0.8$.

By way of example, biased RRR values (Eq. (1)) and corrected ones, by means of Eq. (2), for each age class, have been compared (Fig. 1B).

For the week 4–10 October 2021, corrected and uncorrected SARS-CoV-2 contagion incidence values have been compared in Fig. 1C and 1D. This latter figure provides a valid example of diagram possibly aimed to a wide unspecialized audience to be published in dedicated Web pages or dashboards.

In summary, we point out to the CDCs of various nations the importance and the need of correcting contagion incidence data (e.g. tables, diagrams etc.), as well as risk reduction estimates by means of Eq. (2), on the basis of the propensity of recovered individuals to vaccination to disseminate immediate and explanatory information regarding COVID-19 vaccine effectiveness.

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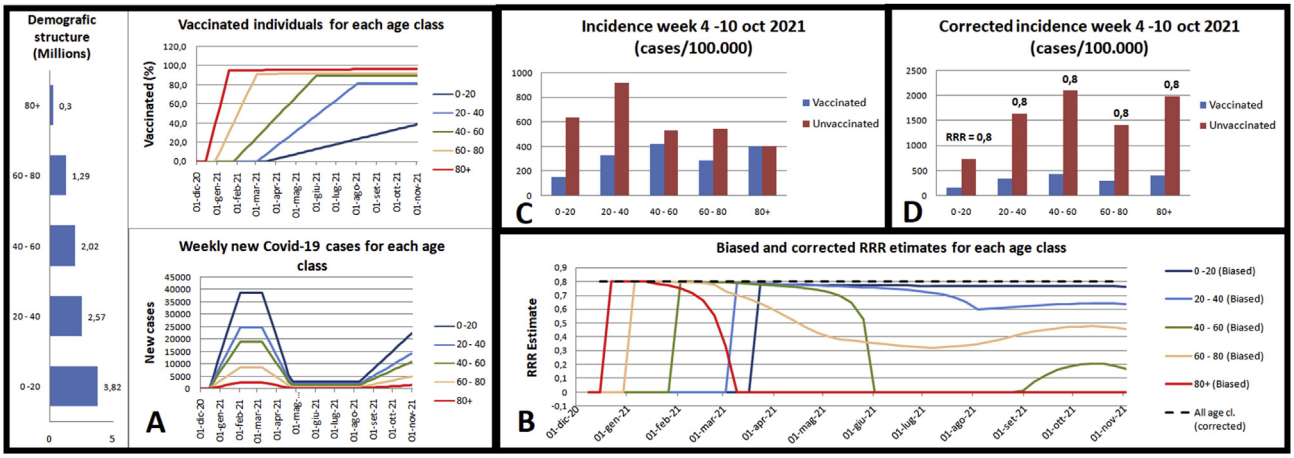

Fig. 1. **(A)** Simulated scenario of epidemic diffusion in population showing the illustrated demographic structure. Weekly new infected individuals and cumulative vaccinated ones are illustrated for several age classes. In this simulation, we have assumed that the propensity of infected people to vaccination is equal to zero within 5 months from positive diagnosis and then it increases according to a linear law for the successive 6 months. **(B)** Estimations of *RRR* calculated according to Eq. (1) (biased vales) and by means of Eq. (2) (corrected) for several age classes. Should be noted as, for some age class, the *RRR* estimates significantly decay after the first wave, whereas the corrected estimation is constant and equal to the true value (0.8). **(C)** Weekly incidence values detected during the simulated epidemic outbreak (week October 4–10, 2021), calculated without excluding recovered unvaccinated individuals from unvaccinated population and **(D)** by excluding them. Should be noted as, for age classes exhibiting highest vaccination ratios, the uncorrected incidence values for unvaccinated individuals approach that of vaccinated ones. Namely, in the age class of over 80, these assume the same value.

Appendix I. Derivation of Equation 2

Let denote by:

P_{op} = number of population individuals
S_V = number of susceptible vaccinated individuals
S_N = number of susceptible unvaccinated individuals

$$S_V = P_{op} \cdot V \cdot (1 - RRR). \tag{A1}$$

Here we have assumed that recovered and never-infected individuals, if vaccinated, exhibit the same degree of immunization.

$$S_N = P_{op}((1 - V) - G \cdot E_G \cdot (1 - P_R)). \tag{A2}$$

As when a population fraction is infected in a certain interval time, it results: $N_V/N_N = S_V/S_N$; therefore, after substitution of S_V and S_N with the terms in Eqs. A1 and A2, respectively, and after simple manipulations, Eqs. 2 and 3 are derived.

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Original Research

Gambling and online trading: emerging risks of real-time stock and cryptocurrency trading platforms

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ABSTRACT

Objectives: Online platforms enable real-time trading activities that are similar to those of gambling. This study aimed to investigate the associations of traditional investing, real-time stock trading, and cryptocurrency trading with excessive behavior and mental health problems.
Study design: This was a cross-sectional population-based survey.
Methods: The participants were Finnish people aged 18–75 years (N = 1530, 50.33% male). Survey asked about monthly regular investing, real-time stock-trading platform use, and cryptocurrency trading. The study had measures for excessive behavior: gambling (Problem Gambling Severity Index), gaming (Internet Gaming Disorder Test), internet use (Compulsive Internet Use Scale), and alcohol use (Alcohol Use Disorders Identification Test). Psychological distress (Mental Health Inventory), perceived stress (Perceived Stress Scale), COVID-19 anxiety, and perceived loneliness were also measured. Background factors included sociodemographic variables, instant loan taking, and involvement in social media identity bubbles (Identity Bubble Reinforcement Scale). Multivariate analyses were conducted with regression analysis.
Results: Within the sample, 22.29% were categorized into monthly regular investors only, 3.01% were investors using real-time stock-trading platforms, and 3.59% were cryptomarket traders. Real-time stock-trading platform use and cryptocurrency trading were associated with younger age and male gender. Cryptomarket traders were more likely to have an immigrant background and have taken instant loans. Both real-time stock-trading platform use and cryptomarket trading were associated with higher excessive behavior. Cryptomarket traders especially reported higher excessive gambling, gaming, and internet use than others. Cryptomarket traders reported also higher psychological distress, perceived stress, and loneliness.
Conclusions: Regular investing is not a risk factor for excessive behavior. However, rapid online trading platforms and applications were significantly more commonly used by participants reporting excessive behavior and mental health problems. The strong association between cryptomarket trading and excessive behavior in particular underlines the need to acknowledge the potential risks related to real-time trading platforms.

Introduction

Real-time trading applications and platforms, such as Robinhood, have recently caused concerns over the gamification in investing. Investor Warren Buffett said the apps were bringing casino-like behavior to the stock market.[1] Although the similarities between investing and gambling have been discussed for a long time,[2,3] new forms of online apps and platforms have created a new need for empirical research in this area. These apps and platforms offer fast and easy entry into diverse investing opportunities and risks, and they are also potentially attractive to people manifesting excessive behaviors. Recently, discussions have focused on potential gambling risk in day trading and cryptocurrency trading.[4,5]

Online apps and platforms such as Robinhood, eToro, and Plus500 have opened the doors of day trading for many. Robinhood states that their mission is to "democratize finance for all."[6] Users

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are allowed to trade stocks in real time and often without commission. Such apps and platforms also offer high-risk investing options such as leverage (using borrowed capital) which multiplies both wins and losses and carries a risk of losing all of one's own capital in forced liquidations. Cryptocurrency trading apps and platforms (e.g., Binance and Phemex) enable 24/7 real-time trading of cryptocurrencies such as Bitcoin and Ethereum with leverages up to more than one hundred. Cryptocurrency trading is estimated to be the fastest growing market in the world.[4] Economists have considered cryptocurrency trading to be a highly speculative, lottery-like activity.[7]

Researchers have suggested people might have discovered new trading apps and platforms while at home due to the COVID-19 pandemic and the temporary collapse of markets in March 2020.[8,9] Some people may also have looked for new types of gambling opportunities and activities owing to the lack of sporting events, especially in the beginning of the COVID-19 crisis in Spring 2020.[5] At that point, many of the regular gambling activities were closed, including much of sports betting. An economic analysis in 37 equity markets showed that during COVID-19, investing increased more in countries that have more gambling opportunities.[10] This calls for attention to analyze different forms of investing and trading. Also, the COVID-19 pandemic has been a major psychological, social, and economic stressor for people. Hence, it is important to investigate the correlates of mental health to these new forms of investing and trading.

In the financial sector, there is a continuum from investing to speculation. Speculation refers to forms of financial actions that are shorter term and higher in risk. These include day-trading, inexpensive but volatile penny stocks, and the use of financial instruments such as shorting, leverage, and derivatives.[2,11,12] Even though a relationship between gambling and financial speculation has long been noted, according to a systematic review by Arthur, Williams, and Delfabbro, there is relatively little empirical research on the topic.[2] Economic studies suggest gamblers and gambling-like investors have similar sociodemographic and psychological profiles, with the less wealthy individual making riskier decisions to rise out of poverty.[3] However, one Canadian study found that high-risk stock-traders were more likely to be male, self-employed, or employed full-time and to have higher income than gamblers.[2] Studies suggest that personal risk factors, such as risk-taking, sensation-seeking, and overconfidence, are similar for both gambling and stock trading.[2,13] Trading is also found to be more common among males.[14,15]

There are very few studies on users of real-time trading apps and platforms. A recent study based on a sample drawn from Amazon's Mechanical Turk found that cryptocurrency trading strongly correlates with problem gambling severity.[16] Another recent study based on a sample of gamblers from the panel of Prolific found that cryptocurrency trading was associated with a wider range of gambling activities.[4] A Korean study found out that bitcoin investors reported higher rates of excessive gambling than share investors.[17] There is also a general lack of studies investigating the relationship between day trading and gambling. A South Australian study found that day-traders were involved in skill-based gambling and had a higher rate of problem gambling than non-traders.[11] A Dutch study on investors showed that investors who had gambling problems were more speculative, traded more frequently, and invested more often in derivatives and leveraged products.[18]

This study aimed to investigate the associations of traditional investing, real-time stock trading, and cryptocurrency trading with excessive behaviors and mental health problems. Our research questions were the following: 1) What background factors are associated with regular investing and real-time trading using online platforms and 2) how different types of investing are related to excessive behaviors and mental health problems.

Methods

Participants and procedure

Gambling in the Digital Age Survey was targeted to Finnish speakers in mainland Finland in April 2021. The survey focused on gambling and addictive behavior. Participants (N = 1530) were 18–75 years old (M = 46.67; SD = 16.42), and 50.33% of them were male (n = 770), 49.41% were female (n = 756), and 0.26% reported other gender (n = 4). The participants were from all major areas of Finland: 35.29% were from Helsinki-Uusimaa region, 21.50% from Southern Finland, 24.84% from Western Finland, and 18.37% from Northern and Eastern Finland.

Data collection was administrated by Norstat, and all respondents answered the survey online. Participants were drawn from Norstat's Web-based panel. The response rate for the survey was 34.60%, and the median response time for the full survey was 18 min. Comparison of the sample to the Finnish population aged 18 to 75 years was conducted using population census figures provided by Statistics Finland in StatFin service (https://www.stat.fi/tup/statfin/index_en.html). Gender distribution of the sample was almost identical to the population aged 18 to 75 years according to statistics provided by statistics Finland (50.33% vs 50.20% male). Also, in terms of age, the sample matched the Finnish population aged 18 to 75 years (mean age = 46.67 vs 46.89). There were slightly more participants from the Helsinki-Uusimaa region in the sample than in the population (35.29% vs 30.94%) and less participants from Northern and Eastern Finland (18.37% vs 23.16%). The sample also included a higher percentage of people having at least a BA degree from a university than in the population (38.50% vs 27.28%).

The data quality protocol for the project was stored on the Open Science Framework website prior to the data collection. Data quality checks involved attention checks, patterned responses checks, rapid responses checks, and nonsensical responses checks.[19,20] Open-ended comments were also checked to further evaluate possible biased motives in response patterns.

The study was approved by the academic ethics committee of Tampere region in Finland in March 2021. All participants agreed to voluntarily participate in the surveys and were informed about the aims and purpose of the study.

Measures

Types of monthly investing and trading were categorized based on three questions: “How often have you practiced investing (e.g., investing in stocks or funds)?” “How often do you use services suitable for real-time investing (e.g., eToro, Plus500)?” and “How often have you traded in cryptomarkets (e.g., Binance, BitPanda)?” We created a categorical variable on the basis of participants' monthly investing and trading activity: non-investors (0), regular investors who do not use online platforms for stock or cryptocurrency trading (1), investors using real-time stock-trading platforms but not trading in cryptomarkets (2); and cryptomarket traders (3).

We used the Problem Gambling Severity Index (PGSI) to measure excessive gambling.[21,22] The PGSI has been widely used to assess problem gambling in the general population rather than in clinical settings.[23,24] For the purpose of the study, respondents were asked about their gambling during the previous 6 months

(e.g., "Have you felt that you might have a problem with gambling?"). The response choices were 0 (*never*), 1 (*sometimes*), 2 (*most of the time*), and 3 (*almost always*). A higher score on the scale indicates more excessive gambling. The scale had excellent internal consistency measured with McDonald's omega ($\omega = 0.95$, see details in Table 1).

We used the Internet Gaming Disorder Test (IGDT) to measure excessive gaming. The IGDT is a short 10-item screen that has been used to assess internet gaming disorders.[25] The measure includes statements about excessive behaviors in gaming during previous 6 months for the purposes of this study (e.g., "Have you risked or lost a significant relationship because of gaming?"). Answer choices were 0 (*never*), 1 (*sometimes*), and 2 (*often*). Higher scores of the scale indicate higher levels of excessive gaming. The scale had good internal consistency ($\omega = 0.89$).

We measured excessive internet use with the 14-item Compulsive Internet Use Scale (CIUS).[26] The CIUS has been widely used and validated in previous studies on excessive internet use.[27,28] The CIUS is designed as an addiction screener and includes measures that are similar to other addictions scales, such as those on withdrawal (e.g., "Do you think about the internet, even when not online?"). Responses are rated on a five-point scale from 0 (*never*) to 4 (*very often*). Higher scores on the scale indicate higher levels of excessive internet use. The scale had excellent internal consistency ($\omega = 0.95$).

We measured excessive alcohol use with the Alcohol Use Disorders Identification Test (AUDIT-C). The AUDIT-C is a widely used screener for excessive drinking.[29,30] Three items of AUDIT-C measure frequency of drinking, heavy drinking, and units per drinking occasion. Responses to each item are assigned risk points from 0 to 4. Higher scores on the scale indicate higher risk for excessive drinking. The scale showed good internal consistency ($\omega = 0.81$).

Table 1
Characteristics of study variables.

Categorical variables	*n*	%			
Monthly investing					
No	1088	71.11			
Regular investors	341	22.29			
Real-time platform users	46	3.01			
Cryptomarket traders	55	3.59			
Male	770	50.33			
Age<40 years	579	37.84			
Higher education	589	38.50			
Working	806	52.68			
Income>3000€/month	528	34.51			
Children	896	58.56			
Immigrant background	52	3.40			
Instant loans	292	19.08			
Continuous measures	*M*	*SD*	Range	*n* of items	ω
Social media identity bubbles (IBRS-9)	30.38	10.74	9–63	9	0.90
Excessive gambling (PGSI)	1.31	3.33	0–25	9	0.95
Excessive gaming (IGDT)	1.34	2.64	0–20	10	0.89
Excessive internet use (CIUS)	8.79	9.65	0–52	14	0.95
Excessive alcohol use (AUDIT-C)	3.58	2.69	0–12	3	0.81
Psychological distress (MHI-5)	12.40	4.73	5–30	5	0.89
Perceived stress (PSS)	13.61	7.04	0–40	10	0.89
COVID-19 anxiety (C-19-ANX)	18.89	7.34	6–42	6	0.88
Perceived loneliness (R-UCLA-3)	1.76	1.77	0–6	3	0.86

SD, standard deviation; IBRS-9, 9-item Identity Bubble Reinforcement Scale; PGSI, Problem Gambling Severity Index; IGDT, Internet Gaming Disorder Test; CIUS, Compulsive Internet Use Scale; AUDIT-C, Alcohol Use Disorders Identification Test; MHI-5, 5-item Mental Health Inventory; PSS, Perceived Stress Scale; C-19-ANX, COVID-19 anxiety scale; R-UCLA-3, Revised UCLA Loneliness Scale.

We measured psychological distress using the 5-item Mental Health Inventory (MHI-5). The MHI-5 is a short version of the original 38-item inventory including items on anxiety, depression, positive affect, and emotional control (e.g., "How much of the time, during the last month, have you felt downhearted and blue?").[31] It has been widely validated as an accurate screener for mood disorders in general population.[32–34] Responses were given on a scale from 1 (*none of the time*) to 6 (*all of the time*). Two items on positive affect were reverse coded. The measure had good internal consistency ($\omega = 0.89$).

Perceived stress was measured with the 10-item Perceived Stress Scale that was developed as a screener for psychological stress.[35,36] Items of the scale ask about uncontrollable and stressful events during the last month (e.g., "How often have you been upset because of something that happened unexpectedly?"). Answer options ranged from 0 (*never*) to 4 (*very often*). A higher score on the scale indicates higher perceived stress. The measure had good internal consistency ($\omega = 0.89$).

COVID-19 anxiety was assessed using a scale based on the 6-item Spielberger State–Trait Anxiety Inventory (STAI-6).[37] The COVID-19 anxiety scale screens anxiety state during the COVID-19 pandemic.[38] Respondents were asked to evaluate their feelings about the COVID-19 crisis during the past seven days with six statements (e.g., "I feel tense"). The response scale for each statement ranged from 1 (*does not describe my state at all*) to 7 (*describes my state completely*). The scale had good internal consistency ($\omega = 0.88$).

Loneliness was measured with a 3-item loneliness scale adapted from the standard Revised UCLA Loneliness Scale.[38–40] The scale includes three statements about perceived loneliness (e.g., "How often do you feel isolated from others?"). Answer options were 0 (*almost never*), 1 (*sometimes*), or 2 (*often*). Higher scores indicate higher levels of perceived loneliness. The measure had good internal consistency ($\omega = 0.88$).

Background and control variables included sociodemographic variables. Options for gender included categories for male (n = 770), female (n = 756), and other (n = 4). Dummy variables were created to indicate participants who were male and those younger than 40 years. We also used dummy variables for income (more than 3000€/month) and having children. Immigrant background was assessed with the question: "Was your mother or father born abroad?" We also asked respondents whether they have taken any instant loans (i.e., pay-day loans). Instant loans were included in the data because they are considered major economic stressors that can lead to long-term financial difficulties.[41,42]

Social media identity bubbles were measured with the 9-item Identity Bubble Reinforcement Scale.[43] This measure involves statements on social identification, homophily with others online, and reliance on information coming from others on social media. This type of bubble behavior is an important form of herd behavior, and bubble behavior has been recognized in cryptomarket trading as well.[9,44,45] Possible responses ranged from 1 (*does not describe me at all*) to 7 (*describes me completely*). Higher scores on the scale indicate higher involvement in social media bubbles. The measure had excellent internal consistency ($\omega = 0.90$).

Our survey also included questions on activities during the COVID-19 pandemic. Measured items were gambling in general, gaming, cryptocurrency trading, and social media profile updates. Response options were the following: *I have not engaged in this activity*, *no change*, *decreased*, and *increased*. We report descriptive findings on these measures in the results section to provide additional information about activities of investors during the COVID-19 era.

Statistical analyses

Statistical analyses were carried out using Stata, version 16, software. We report descriptive findings on different types of investing and other behaviors during the COVID-19 pandemic. Statistical modelling focused first on the analysis of background factors associated with different types of investing. This was conducted with multinomial logistic regression using non-investors as a reference group. Table 2 reports relative risk ratios (RRRs), standard errors (SE), and the statistical significance of results (p). RRRs are interpreted as odds ratios (ORs) in binary logistic regression (RRRs >1 indicate higher risk, and RRRs <1 indicate lower risk).

Associations of different types of investing and excessive behavior and mental health problems are analyzed using negative binomial regression owing to the overdispersion of scales measuring excessive behavior. Hence, negative binomial regression provides a better alternative for the analysis of skewed outcome variables. A similar method of analysis was selected for all eight outcome variables reported in Tables 3 and 4 for the sake of comparability. Robustness checks were conducted by running the analyses with ordinary least squares regression, but the main results concerning types of investing remained the same. For these reasons, we report only the results based on the main analyses.

Tables 3 and 4 report the incidence-rate ratios (IRRs). IRRs are interpreted as ORs (an IRR >1 indicates higher risk, and an IRR <1 indicates lower risk). We first report unadjusted models (model 0) without control variables, indicating only the associations of types of investing with excessive behavior and mental well-being. Full models adjusted for number of confounding factors.

Results

Within the sample, 22.29% of participants were categorized into monthly regular investors only, 3.01% were investors using real-time stock trading platforms, 3.59% were cryptomarket traders, and the rest were non-investors.

Multinomial logistic regression models were used to analyze background factors associated with these three categories of investing in comparison to non-investors (Table 2). Male gender was associated with all forms of investing, especially real-time stock market platform use (RRR = 6.24, $P < 0.001$) and cryptocurrency trading (RRR = 5.06, $P < 0.001$). Younger age and higher income were associated with all types of investing. Regular investing was more common among those with higher education (RRR = 1.48, $P = 0.005$) and employment (RRR = 1.42; $P = 0.015$). Cryptomarket traders were less likely to have children (RRR = 0.49, $P = 0.045$) and more likely to have an immigrant background (RRR = 3.47, $P = 0.008$). Instant loans were less common among regular investors (RRR = 0.47, $P < 0.001$) and more likely among cryptomarket traders (RRR = 2.53; $P = 0.005$) than among non-investors.

Respondents were asked about their activities during the COVID-19 pandemic (from March 2020 to April 2021) in comparison to their previous activities. Of all respondents, 4.58% reported increased gambling during the COVID-19 pandemic; 13.07% reported increased gaming, 2.55% reported increased cryptocurrency trading, and 6.93% reported increased their social media updates. These figures were higher especially among real-time stock trading platform users, and of them, 13.04% reported increased gambling, 23.91% reported increased gaming, and 15.22% reported increased frequency of social media updates. Of cryptomarket traders, 47.27% reported increased purchases of cryptocurrencies.

Table 3 reports the findings on associations of excessive behaviors and different types of investing. As indicated by results for model 0, regular investing was not associated with any of the excessive behaviors. However, regular investors did report higher excessive internet use than non-investors (IRR = 1.18; $P = 0.037$). Real-time trading app users reported higher excessive gaming (IRR = 2.12; $P = 0.016$), higher excessive internet use (IRR 1.57; $P = 0.018$), and higher excessive alcohol use (IRR = 1.39, $P = 0.003$) than did non-investors. Similarly, cryptomarket traders reported higher excessive gambling (IRR = 5.98; $P < 0.001$), higher excessive gaming (IRR = 4.21; $P < 0.001$), higher excessive internet use (IRR 2.43; $P < 0.001$), and higher excessive alcohol use (IRR = 1.35, $P = 0.004$) than did non-investors. Full models adjusted a number of background factors, but the main results did not change. Both real-time stock-trading platform users and cryptomarket traders reported higher excessive behavior than non-investors and regular investors. Cryptomarket trading had very high IRRs. All types of investing were associated with excessive internet use. In comparison to non-investors, only real-time stock trading platform users reported higher excessive alcohol use than non-investors.

Table 4 reports the findings of associations between mental well-being and different types of investing. The results for model 0 demonstrate that cryptomarket traders reported higher distress (IRR = 1.18, $P = 0.001$), higher stress (IRR = 1.24, $P = 0.004$), higher COVID-19 anxiety (IRR = 1.16, $P = 0.007$), and higher perceived loneliness (IRR = 1.37, $P = 0.025$) than did non-investors. Regular investors and real-time platform users did not differ from non-investors. Full models showed that cryptomarket traders reported higher psychological distress (IRR = 1.11; $P = 0.035$), higher perceived stress (IRR = 1.16; $P = 0.043$), and higher perceived loneliness (IRR = 1.32, $P = 0.044$) than did non-investors.

Discussion

This study investigated users of real-time trading apps and platforms. Analyses based on a sample of adult population in

Table 2
Multinomial logistic regression model on correlates of different types of monthly investing.

	Regular investors				Real-time platform users				Cryptomarket traders			
	RRR	95%	CI	P	RRR	95%	CI	P	RRR	95%	CI	P
Male	1.36	1.05	1.77	0.022	6.24	2.73	14.26	<0.001	5.06	2.44	10.47	<0.001
Age<40 years	2.32	1.70	3.18	<0.001	3.82	1.83	7.95	<0.001	7.66	3.47	16.87	<0.001
Higher education	1.48	1.13	1.95	0.005	1.40	0.73	2.70	0.310	0.90	0.47	1.70	0.738
Working	1.42	1.07	1.89	0.015	0.63	0.31	1.26	0.192	1.79	0.88	3.63	0.107
Income>3000€/month	2.50	1.84	3.40	<0.001	3.19	1.48	6.86	0.003	3.48	1.75	6.93	<0.001
Children	1.22	0.90	1.65	0.195	0.69	0.34	1.41	0.314	0.49	0.25	0.98	0.045
Immigrant background	0.80	0.37	1.72	0.573	0.37	0.05	2.90	0.340	3.47	1.38	8.73	0.008
Instant loans	0.47	0.32	0.71	<0.001	1.05	0.48	2.29	0.903	2.53	1.33	4.80	0.005
Social media identity bubbles	0.99	0.98	1.00	0.154	1.03	1.00	1.06	0.059	1.00	0.97	1.03	0.926

*Reference category, no monthly investing.
RRR, relative risk ratio; CI, confidence interval.

Table 3
Negative binomial regression models on associations of different types of monthly investing and excessive behavior.

	Gambling				Gaming				Internet				Alcohol			
	IRR	95%	CI	P	IRR	95%	CI	P	IRR	95%	CI	P	IRR	95%	CI	P
Model 0																
Investing (ref. no)																
Regular investors	0.77	0.55	1.08	0.130	0.90	0.69	1.17	0.441	1.18	1.01	1.38	0.037	1.02	0.92	1.12	0.731
Real-time platform users	1.96	0.90	4.26	0.089	2.12	1.15	3.89	0.016	1.57	1.08	2.28	0.018	1.39	1.12	1.73	0.003
Cryptomarket traders	5.98	2.98	12.01	<0.001	4.21	2.44	7.28	<0.001	2.43	1.73	3.42	<0.001	1.35	1.10	1.65	0.004
Full model																
Investing (ref. not)																
Regular investors	0.76	0.54	1.07	0.111	0.87	0.67	1.13	0.298	1.17	1.00	1.36	0.045	0.96	0.87	1.06	0.436
Real-time platform users	2.08	0.96	4.52	0.064	1.87	1.05	3.31	0.033	1.63	1.15	2.30	0.006	1.20	0.97	1.49	0.087
Cryptomarket traders	4.61	2.25	9.42	<0.001	2.62	1.55	4.43	<0.001	1.91	1.38	2.65	<0.001	1.14	0.93	1.39	0.219
Male	1.43	1.08	1.89	0.012	1.48	1.20	1.83	<0.001	0.83	0.74	0.94	0.003	1.38	1.27	1.49	<0.001
Age<40 years	1.55	1.15	2.09	0.004	2.37	1.87	3.00	<0.001	2.16	1.88	2.48	<0.001	0.99	0.91	1.09	0.902
Higher education	0.70	0.53	0.94	0.017	0.95	0.76	1.18	0.630	1.02	0.90	1.16	0.767	0.85	0.78	0.92	<0.001
Working	1.24	0.93	1.67	0.143	1.13	0.91	1.41	0.284	1.07	0.94	1.22	0.297	1.12	1.03	1.22	0.006
Income>3000€/month	0.77	0.56	1.06	0.104	0.73	0.56	0.94	0.014	0.84	0.73	0.98	0.026	1.11	1.01	1.22	0.034
Children	0.82	0.62	1.10	0.186	0.71	0.56	0.89	0.003	0.85	0.74	0.97	0.017	0.82	0.75	0.90	<0.001
Immigrant background	1.09	0.52	2.26	0.825	1.21	0.70	2.07	0.495	1.47	1.06	2.03	0.022	0.88	0.71	1.10	0.253

IRR, incidence-rate ratio; CI, confidence interval.

Table 4
Negative binomial regression models on associations of different types of monthly investing and mental well-being.

	Distress				Stress				COVID-19 anxiety				Loneliness			
	IRR	95%	CI	P	IRR	95%	CI	P	IRR	95%	CI	P	IRR	95%	CI	P
Model 0																
Investing (ref. no)																
Regular investors	0.97	0.93	1.02	0.250	0.94	0.88	1.00	0.056	0.97	0.93	1.02	0.265	0.88	0.77	1.01	0.075
Real-time platform users	1.01	0.90	1.12	0.898	0.95	0.81	1.12	0.578	1.04	0.92	1.17	0.524	1.10	0.80	1.51	0.550
Cryptomarket traders	1.18	1.07	1.30	0.001	1.24	1.07	1.43	0.004	1.16	1.04	1.29	0.007	1.37	1.04	1.81	0.025
Full model																
Investing (ref. not)																
Regular investors	0.99	0.95	1.04	0.694	0.97	0.91	1.03	0.331	0.97	0.92	1.02	0.242	0.97	0.84	1.11	0.617
Real-time platform users	0.99	0.90	1.11	0.922	0.96	0.83	1.13	0.654	1.03	0.92	1.15	0.656	1.14	0.84	1.55	0.397
Cryptomarket traders	1.11	1.01	1.22	0.035	1.16	1.00	1.34	0.043	1.08	0.97	1.20	0.158	1.32	1.01	1.74	0.044
Male	0.96	0.92	0.99	0.020	0.91	0.86	0.96	<0.001	0.94	0.90	0.98	0.002	0.87	0.78	0.97	0.013
Age<40 years	1.15	1.10	1.20	<0.001	1.22	1.15	1.30	<0.001	1.16	1.11	1.21	<0.001	1.26	1.11	1.42	<0.001
Higher education	1.04	1.00	1.09	0.030	1.01	0.95	1.06	0.864	1.07	1.03	1.12	0.002	1.11	0.99	1.24	0.080
Working	0.99	0.95	1.03	0.543	1.00	0.94	1.06	0.968	1.02	0.98	1.07	0.249	0.89	0.80	1.00	0.050
Income>3000€/month	0.89	0.85	0.93	<0.001	0.86	0.81	0.92	<0.001	0.92	0.87	0.96	<0.001	0.71	0.62	0.82	<0.001
Children	0.92	0.88	0.95	<0.001	0.89	0.84	0.95	<0.001	0.96	0.91	1.00	0.044	0.78	0.69	0.88	<0.001
Immigrant background	1.10	1.00	1.20	0.056	1.16	1.00	1.33	0.045	1.14	1.03	1.26	0.014	1.16	0.88	1.52	0.282

IRR, incidence-rate ratio; CI, confidence interval.

Finland compared non-investors and regular investors to real-time trading platform users and cryptocurrency traders. According to our results, males, younger individuals, and those with a higher education were more likely to engage in all forms of investing. Cryptomarket traders were more likely to have taken instant loans and less likely to have children. Results showed that both real-time trading platform use and cryptomarket trading were associated with higher scores of addictive behavior measures. Especially cryptomarket traders reported significantly higher scores in excessive gambling, gaming, internet use, and alcohol use. Cryptomarket traders also reported higher scores in different measures on mental health problems.

Considering previous economic studies, it is not surprising that males engage in risky economic activities.[14,15] Specifically, cryptomarket traders were more commonly younger males. This could be, at least partly, explained by personality and preference factors, such as high excitatory value and orientation toward a specific economic goal.[46] The results are aligned with those of previous studies on the association between cryptomarket trading and excessive gambling.[4,16,17] We also found strong associations between cryptomarket trading and excessive gaming and internet use that has not been reported in previous studies.

Cryptomarket traders reported higher scores in psychological distress, stress, and perceived loneliness. These difficulties may have been exacerbated during the COVID-19 pandemic owing to concerns over economics, health, and social isolation.[47] Prior studies have shown that mental health problems are related to higher risk-taking online.[48] Hence, it is conceivable to at least hypothesize that people with existing mental health problems would be more susceptible to taking economic risks on online platforms.

Under unusual and unexpected circumstances brought by COVID-19, people have rushed into stock markets and looked for alternative activities. Cryptocurrencies have been in the spotlight and gained attention in the media and social media. As noted in economic literature, there is a continuum from investing to speculation, and most speculative forms of investing are often related to

day-trading.[2,11] During the COVID-19 pandemic, the markets have certainly been more unpredictable, but at the same time, people have had the opportunity provided by the platforms to practice day-trading. Our results call for more studies on how investing turns into gambling given the use of these platforms.

Our study is limited to Finland, and findings are based on self-reported measures and a cross-sectional design. No implications of causality can thus be drawn from the results. Also, our data are limited by relatively few participants using platforms for real-time trading and cryptomarket trading. Despite these limitations, we were able to demonstrate that real-time trading apps are used by people manifesting excessive behaviors. More research attention should therefore be directed toward these speculative forms of investing as a specific form of gambling. Future studies should also investigate in detail different forms of cryptocurrency investing and trading that were beyond the scope of our study.

Trading platforms enable making a large volume of transactions quickly and relatively effortlessly, making impulsive and high-risk short-term actions possible. The results of this study indicate that users of these platforms reported higher scores in excessive behaviors. Although our study did not focus on potential long-term impacts of these platforms, it would be important to recognize that these platforms are potentially attractive to those individuals who are struggling with behavioral addictions. User awareness training may be needed for individuals using such trading platforms to increase awareness of the risks involved.

Author statements

Ethical approval

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Competing interests

None of the authors have a conflict of interest to declare.

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Original Research

‘I don't want my son to be part of a giant experiment’: public attitudes towards COVID-19 vaccines in children

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ABSTRACT

Objectives: This qualitative study explored public attitudes to COVID-19 vaccines in children, including reasons for support or opposition to them.
Study design: This was a qualitative study using online focus groups and interviews.
Methods: Group and individual online interviews were conducted with a diverse sample of 24 adults in the United Kingdom to explore their views on the issue of COVID-19 vaccination in children. Data were analysed using a framework approach.
Results: COVID-19 vaccination in children was framed as a complex problem (a ‘minefield’). Six themes emerged to explain participants views: (1) uncertainty over whether children can catch, transmit or be severely harmed by COVID-19; (2) lower risk tolerance for unknown longer term effects of the vaccine in children; (3) association of the vaccine programme with government's handling of the pandemic; (4) local social norms as a driver of hesitancy; (5) vaccinating children as a way to protect vulnerable adults; and (6) children's vaccination as parental choice.
Conclusions: COVID-19 vaccination in children is perceived by members of the public as a complex issue, and many are torn or hesitant about the idea. Public health communications will need to combat this hesitancy if vaccine uptake for children is to be pursued as a public health policy.

Introduction

The question of whether to vaccinate children against COVID-19 remains a controversial issue globally, with no current consensus in the public health community.[1] Many public health opinion articles have tended to focus on mandatory vaccination in children, despite mandating being unlikely or even counter productive.[2–4] However, many of the arguments raised are also relevant for optional vaccination in children. Arguments that have been made in favour include a potential contribution to overall population (‘herd’) immunity, preventing rare but severe disease in children, reducing transmission from children to adults, priming children's immune response to future (re-)infection and helping to keep schools open.[2] Arguments made against tend to focus on the fact that children are significantly less prone to serious outcomes from COVID-19 and that it is necessary to obtain substantial safety data before widespread use amongst (non-clinically vulnerable) children.[3] The level of public acceptability of COVID-19 vaccines in children is a key criterion that determines eventual uptake.[5]

Findings from public opinion surveys are mixed, with little consensus over the level of support for COVID-19 vaccinations in children.[6–8] Surveys have begun to explore reasons behind public attitudes to COVID-19 vaccines in children, with the most common reasons in support including to prevent the spread of COVID-19 or to prevent their children from catching COVID-19, and the most common reasons against include concerns over long-term side-effects and the belief that children are unlikely to get very ill from COVID-19.[8] There is a dearth of qualitative research on public attitudes to COVID vaccines in children. However, qualitative research has explored hesitancy around vaccinations in children generally (i.e. not specifically related to COVID-19) have found that it is a complex decision affected by a range of factors, including experiences, emotions, routine ways of thinking, information sources, peers/family, risk perceptions and trust.[9] Also, research is starting to emerge on COVID-19 vaccine attitudes in adults – with views falling on a ‘continuum of vaccine hesitancy’, from full acceptance though to refusal.[10] In a previous study, we found that decisions

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concerning COVID-19 adult vaccinations were influenced by a number of facilitators, including an emergent social norm around vaccination and the perceived 'need' for vaccines to end the pandemic, and barriers, including concerns over side-effects and a preference for 'natural immunity'.[11] This article explores the participants' attitudes towards COVID-19 vaccination in children, including the reasons behind their views.

Methods

Sample and recruitment

Participants were recruited as part of the qualitative component of an ongoing, longitudinal mixed methods study exploring public views on the COVID-19 pandemic in the United Kingdom. More details about the methodology can be found in previous publications.[12–14] In this article, we report on data from a rapid round of four focus groups and three one-to-one interviews with a total of 24 participants. The study was initially designed as a focus group study. However, the decision to include three individual interviews was made on pragmatic grounds (where participants were either the only ones to turn up to a given focus group or contacted the researcher after focus groups had been conducted expressing an interest to still take part).

Data were collected between 1 July and 25 July 2021. At the time in the United Kingdom, the Joint Committee on Vaccination and Immunisation released an official recommendation on 19 July that COVID-19 vaccinations should be offered only to children aged ≥12 years with certain underlying health conditions, and not to all children aged 12–15 years.[15] This decision prompted much debate in the scientific community, given a number of countries, such as the United States, for example, had already approved the vaccine for general use in 12 to 15-year-olds.[16]

Participants were initially recruited to the full study from March to July 2020 and were all UK-based adults aged ≥18 years. Recruitment for the study took place via a combination of social media advertising and snowball recruitment (e.g. Facebook advertisements, online free advertisements, and Twitter). Purposive sampling was used to seek as diverse a range of ages, genders, race/ethnicities, UK locations, and social backgrounds as possible, although the limitations of the final sample are discussed below as well as in previous publications.[12–14] Full demographic summary details are provided in Table 1.

Participants who had signed up for the full study were invited to take part in focus groups and interviews as a rapid response to the issue of vaccinations in children (a topic preset by the researcher). All focus groups had an average of five participants per group, and focus groups and interviews took place remotely via videoconferencing (Zoom) and lasted approximately 1 h. All participants gave verbal and written consent to be recorded, and audio recordings were then anonymised transcribed. The final sample size was determined largely because of opportunity sampling from the main participant pool for the full study (all 24 participants who responded to the recruitment email for the present study were included). Despite the fact that only 24 of 57 total participants in the participant pool responded to the recruitment email for the present study (in part due to the time sensitive nature of the study and the need to conduct focus groups at short notice), as Table 1 shows, the final sample was diverse. Questions were guided by a semistructured schedule built around the research question and literature mentioned previously, particularly focused on participants' reasons for their views on whether or not they were favourable towards COVID-19 vaccination in children. Sample questions included 'do you think children should be offered the COVID-19 vaccine?' What, if any, concerns do you have about vaccinating children for COVID-19 and what are the reasons for these concerns? Ethical approval was granted by (anonymised for peer review) research ethics committees, and all participants gave informed written consent and had their data anonymised.

Table 1
Demographic characteristics for participants in this report.

Characteristic	*n* (%)
Gender	
Female	10 (42)
Male	14 (58)
Age range	
20s	8 (33)
30s	7 (29)
40+	8 (33)
Did not say	1 (05)
Ethnicity	
White	13 (54)
BAME (Black and Asian Minority Ethnic)	11 (46)
Has child/ren	
Yes	7 (29)
No	17 (71)
Own vaccination status/intention[a]	
Vaccinated	19 (79)
Not vaccinated	4 (17)
Undisclosed	1 (04)

[a] Vaccination status intention was coded as two groups: (1) 'vaccinated' (i.e. those who had received at least one dose of a vaccine at the time of data collection); (2) 'Not vaccinated' (those who at the time of data collection had not received at least one dose of a vaccine at the time of data collection; NB: all participants in the sample had received an offer for a first dose by the time of data collection).

Data were analysed in accordance with a framework analysis approach.[17] Analysis followed the five main stages of the framework approach: data familiarisation (reading/re-reading transcripts), identifying key themes or codes in initial transcripts, indexing (identifying consistencies and applying codes across transcripts), charting (drawing up a visual data matrix of themes across transcripts), and data mapping (interpretation of the themes matrix).[17] Analysis followed the coding was performed using NVivo (version 11.4.3, QRS).

Results

COVID-19 vaccination in children as a 'minefield'

Overall, the issue of COVID-19 vaccination in children was framed as a complex issue. Although there was a spectrum of views represented, few participants were unequivocally in favour of COVID-19 vaccination for children. Those with relatively few reservations tended to be non-parents who argued they had less 'stake' in the issue and that they would support vaccination in children only if it had been approved as safe. All parents ($n = 7$) in our study expressed hesitancy and concerns, with one stating outright they did not agree with vaccinating children against COVID-19. However, most participants framed the issue as 'tricky', 'a grey area' or a 'minefield':

> *I just think it's a grey area. I can't really decide which way is best to be honest, there's like pros and cons to each side … I'm unsure on the whole matter. I think it's a minefield.* [Participant 1, male, 30s, non-parent, vaccinated]

Six themes emerged to explain participants' views: (1) Uncertainty over whether children can catch, transmit or be severely harmed by COVID-19; (2) lower risk tolerance for unknown longer term effects of the vaccine in children; (3) Association of the vaccine programme with government's handling of the pandemic; (4) Local social norms as a driver of hesitancy; (5) Vaccinating children as a

way to protect vulnerable adults; (6) Children's vaccination as parental choice. Participants tended to weigh up these factors simultaneously and struggled to disentangle them to provide a definitive answer as to whether or not children should be offered a vaccine.

Uncertainty over whether children can catch, transmit or be severely harmed by COVID-19

One prominent theme concerned participants' uncertainty over the extent to which children could either themselves catch, suffer from, and transmit COVID-19:

> *It's a tricky one. I think there's so much like discrepancy on that the data with COVID in children … I still don't even know like when I'm teaching if kids are spreading the virus.* [Participant 3, male, 20s, non-parent, not vaccinated]

This led to some to argue that because of this uncertainty, they were not sure if vaccinations were necessary or that more time was needed to see exactly how the virus (including new variants) was impacting children:

> *It feels like is it necessary for them, when it's not initially affecting children. But then you have got this delta variant which does seem to be have more children testing positive. … It's hard because you feel like you need a bit of time to see*. [Participant 8, female, 30s, parent, vaccinated]

Those who were more opposed to vaccination in children were more likely to emphasise that COVID-19 was something that children were not at high risk of dying from or being 'severely impacted biologically' (Participant 10, male, 20s, non-parent, not vaccinated) or were even 'prone to' (Participant 11, female, 30s, parent, not vaccinated). They also emphasised that because children had 'young' and healthy immune systems they were more able to fight the virus 'naturally':

> *When you are young natural immune system is really strong … and that if you take care of your lifestyle and eat healthy that should, for now be sufficient than actually going for this jab.* [Participant 9, male, 40+, non-parent, vaccinated]

Some participants were inclined to be more favourable to the idea of vaccinating older children ('teenagers') because they felt they were more likely to transmit the disease compared to younger children ('they are out and about a bit more' [Participant 4, male, 40+, non-parent, vaccinated]) and they thought there was 'more evidence they spread the virus' (compared with younger children; Participant 3, male, 20s, non-parent, not vaccinated).

Lower risk tolerance for unknown longer term effects of the vaccine in children

Many participants were 'apprehensive … that the risks of the vaccine are possibly higher than the risks of them if they were to have Covid' (Participant 8, female, 30s, parent, vaccinated). Parents in particular seemed to have a lower risk tolerance for vaccines in children compared with in adults, with this apprehension being due largely to concerns over potential and unknown future side-effects:

> *Although I have been vaccinated, I wouldn't want my son to be vaccinated. Although there has been research done, I know it is quite early days, so I would rather take the risk of him getting Covid than the risk of him having the vaccine … I still feel that some point in the future they will discover something [about the vaccine] that affects children more than adults.* [Participant 15, female, 40+, parent, vaccinated]

Although as described previously, participants tended to feel children were *less* biologically susceptible to the virus because of their young body and immune system, some felt that they were potentially *more* biologically susceptible to any potential adverse side-effects of the vaccine precisely because their body was young and still developing:

> *I don't think there is a need for any type of fluid going into a child's body. … Because even with adults, the side effects you've noticed from taking the vaccine and children are more vulnerable and more [at] risk.* [Participant 2, male, 30s, non-parent, vaccinated]

As with the previous theme, participants focused on the need for more clarity or evidence:

> *There is not enough data to show how effective the vaccines are for children or what the implications may be and so maybe waiting for more government information and scientific data to backup that it's important that children get vaccinated before we make these decisions.* [Participant 20, female, 30s, parent, vaccinated]

Participants tended to emphasise that the vaccines, in their view, had not been 'fully tested at the moment' (Participant 6, male, 40s, parent, vaccinated). As one parent put it: 'I don't want my son to be part of a giant experiment' (Participant 15, female, 40+, parent, vaccinated).

Local social norms as a driver of hesitancy

Social norms, particularly local social norms (i.e. the views and beliefs of immediate network of family, friends and close others) appeared to strongly influence participants' views:

> *Speaking to friends with children we seem to all feel similar. We wouldn't want our children to be vaccinated, because we feel that if they get Covid hopefully they won't be too ill.* [Participant 15, female, 40+, parent, vaccinated]

> *I have a young nephew … and the consensus in our family is that no he shouldn't have it [the vaccine], and the consensus amongst friends who have children is also hesitancy to do this … Its far too early.* [Participant 13, male, 40s, non-parent, vaccinated]

These social norms often related to the factors discussed previously – uncertainty around COVID-19 in children ('hopefully they won't be too ill') and lower risk tolerance for unknown longer term effects ('it's far too early'). Participants also felt that there was or would be a wider social norm around hesitancy or even opposition towards vaccination in children:

> *I think a lot of people would be upset if they started saying you know that our children are going to have their nasal flu jab and we're going to be offering a Covid jab as well in schools.* [Participant 3, male, 20s, non-parent, not vaccinated]

Association of the vaccine programme with government's handling of the pandemic

A number of participants, particularly those more hesitant to the idea of vaccines in children, tended to frame their views in relation

to what they saw as a lack of trust or confidence in the (UK) government's handling of the pandemic:

> *How can you trust the government or how much confidence do the public have with the government, now that the damage has been done, how can the public restore confidence … are parents prepared to take a risk for their own children?* [Participant 2, male, 30s, non-parent, vaccinated]

One particular concern was over how a vaccination programme would be implemented and whether it would be handled poorly as had been, in their view, the contact tracing and testing programmes in schools:

> *If they [the government] were having to vaccinate children, they were planning to do some kind of rollout of testing in schools, but they couldn't even organise that. Like it was literally left up to schools … I think it does come back down to that all of the systems that are in place are really shoddy and like test and trace we know, has been proven it doesn't work they spent billions [of pounds] on it … it ultimately comes down to trust.* [Participant 3, male, 20s, non-parent, not vaccinated]

Vaccinating children as a way to protect society (as collective responsibility)

Some participants argued that vaccinating children might be beneficial to society by contributing to the overall population ('herd') immunity. Only one parent discussed this theme but acknowledged being torn when it came to their own children:

> *It's important to do what we can to get out of the pandemic situation but it much harder when it's your children. I have very mixed feelings about it.* [Participant 8, female, 30s, parent, vaccinated]

Other participants tended to frame vaccination as a way of protecting transmission to the more vulnerable in society, including their grandparents, thereby implying that they felt that although children may not 'suffer' from COVID-19, they can spread it nonetheless:

> *I think it would be a good idea to vaccinate children. I know they say children don't suffer so much when they get the virus if they catch it, but then to me its who they interact with at the end of the day, so you know they are going to go home to their parents who then go to work for example, or they are going to see their grandparents – and so to me I would be better if it was rolled out to try and flatten it down as much as possible.* [Participant 4, male, 40+, non-parent, vaccinated]

These participants were mostly non-parents who caveated their views by emphasising that they themselves were not parents and as such stated or implied that they had less say (or stake) in the decision.

Children's vaccination as parental choice (as individual responsibility)

Hesitancy around whether or not children should be vaccinated was often framed in terms of vaccination as an individual choice – in this instance, the choice of the individual parents. Those without children often suggested they felt they were 'not in a position to comment or judge' (Participant 1, male, 30s, non-parent, vaccinated) and that 'it's better to leave this decision to those who have children I think' (Participant 19, male, 20s, non-parent, vaccinated). Participants acknowledged that there was a lot of responsibility for parents in making the decision, implying that a 'wrong' decision could be costly:

> *It is quite concerning when it's your children you are responsible for their health and want the best for them – and you don't want to make the wrong decision for them.* [Participant 5, female, 20s, non-parent, vaccinated]

One distinction that some participants made was between the ability of older children ('teenagers') to be able to make more informed decisions for themselves, compared with younger children who were too young to understand the issue:

> *It comes down to people's perception of like, you know, they are children and they can't make decisions and the parents have to make decisions on whether they want to or not, whereas teenagers actually can form their own decision.* [Participant 3, male, 20s, non-parent, not vaccinated]

Discussion

This study found that participants framed COVID-19 vaccination in children as a complex issue, or 'minefield'. Although a spectrum of views was found, most participants tended to be uncertain or hesitant about the idea, concluding that there was no straightforward answer. This corresponds with broader research on vaccine attitudes, which suggests that hesitancy is a nuanced concept, and one which occurs on a spectrum (and that hesitancy should not be conflated with opposition or 'anti-vax' sentiment).[10,18] Findings also provide some context and nuance to existing surveys, which, overall, suggest that there is a significant proportion of people, including parents, who remain uncertain as to whether children should be given a COVID-19 vaccine.[6–8]

Six main themes, or factors, shaping public attitudes to COVID-19 vaccines were identified. First, there was uncertainty over whether children can catch, transmit or be severely harmed by COVID-19. This uncertainty partly reflected genuine scientific uncertainty that still exists, particularly around children's role in transmission[19] but also may have been compounded by the confusion caused by changing messages and policies they experienced (e.g. around school testing and isolation policies). Existing research suggests that the perception of mixed messages can have a negative effect on pandemic mitigation measures.[14] In the face of such uncertainty, participants tended to couch their views in affective terms (of a 'feeling' they had).[20] Second, there was generally a lower risk tolerance for unknown longer term effects of the vaccine in children. Whereas participants generally felt children were less susceptible to COVID-19, they felt they were more susceptible to long-term potential side-effects of the vaccine compared with adults. Parents suggested that they needed to see more evidence of testing and safety in children in order to feel confident. Thirdly, local social norms were a driver of hesitancy. Research suggests that social norms play a significant role in adherence to COVID-19 health behaviours,[21] including vaccine uptake.[22] Participants were strongly influenced by their own social networks, including for parents, other parents, where for many, there is currently a culture of hesitancy around vaccination for COVID-19 in children. Fourth, participants views were often framed in terms of trust in government;

specifically, the extent to which they felt that the UK government could be trusted to successfully extend the vaccination programme to children (based on what they perceived as past failures over, for example, contact tracing). Lack of trust or confidence in government has been shown to be a big predictor of adherence to COVID-19 mitigation measures.[14,23] Fifth, those who were more in favour tended to emphasise the potential role of COVID-19 vaccines for children in reducing overall infection rates, possibly by bringing up population ('herd') immunity. In this sense, individual vaccinations were framed as a collective act – in line with a common justification of adult vaccination.[13,24] Conversely, many participants also framed children's vaccination as one of individual choice and responsibility. Non-parents tended to emphasise that the overall issue of whether vaccination should be made available for children was one that parents had a greater say or stake in. Parents tended to emphasise how difficult the issue was and how much responsibility they felt over the potential decision of whether or not they would have their child vaccinated. Thus, many may have a lower risk tolerance, meaning that even those parents very accepting of vaccination in adults were more undecided or hesitant over whether vaccination in children was currently desirable.

As with all qualitative studies, the generalizability of the findings is limited. In addition, because of the rapid nature of the call for participation from the participant pool, the sample size was smaller than in previous rounds of data collection – although the total sample was deemed sufficient for the purposes of the analysis. Also, because of the pragmatic decision to include a small number of interviews, saturation of themes may not have occurred here. A larger number of one-to-one interviews might have explored themes that did not emerge in the group setting (perhaps due to desirability or conformity bias). Future research plans to follow ongoing views on this topic, and more one-to-one interviews will be considered.

There are a number of potential policy implications of this study. For example, many countries are yet to offer COVID-19 vaccines to children (including in the United Kingdom to all 5- to 11-year olds). If high uptake amongst children is deemed by a country's public health policymakers to be important to contribute to a reduction of COVID-19 rates or keep the virus 'under control', then it is important for the reasons for hesitancy to be better understood – particularly amongst parents as key stakeholders. To improve uptake, public health authorities need to ensure clear public communication that emphasises that vaccines have strong scientific evidence to suggest they are safe and effective in children (as demonstrated by a growing number of global childhood vaccinations) and that vaccines are developed by scientific and medical research (i.e. should not be seen as 'political'). Also, uptake might be improved by emphasising the collective benefits that vaccination can have (even where the vaccinated person – e.g. most children – is at relatively low individual risk of serious outcomes). The value of emphasising the collective, 'greater good' in COVID-19 policies have been found elsewhere, for example, contact tracing and isolation.[13] Finally, it is important for public health to recognise that not all members of the public, including parents, are supportive of COVID-19 vaccinations in children, and recognising it as an act that is of collective significance (e.g. to help 'protect vulnerable adults') but which is fundamentally seen as a 'personal choice'; as research on attitudes towards adult vaccinations have shown, any measures or messages that are perceived to be too strong or are perceived to infringe too greatly on individual choice could ultimately prove counter productive.[25]

It is important to note that the science of COVID-19 vaccines is rapidly evolving,[1] and public attitudes are doing so with them – social norms around vaccination in children is variable across countries and over time and that additional research will be needed to explore any future attitudinal changes.

Author statements

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Letter to the Editor

Inequalities associated with emergence of Delta SARS-CoV-2 variant of concern (B.1.617.2) in England: awareness for future variants

Health inequalities associated with COVID-19 in England were investigated soon after the initial peak of infections[1] generating significant public and political discussion. The recent report from the Commission on Race and Ethnic Disparities[2] generated further discourse as has vaccine inequalities on both a domestic[3] and global[4] scale. Delta was first detected in India in December 2020,[5] with the first UK cases identified in April 2021; the variant emerged over the following months to later become the dominant strain among all sequenced cases in England.

We analysed available data on ethnicity, age group, sex and deprivation based on the Index of Multiple Deprivation (IMD) for all cases of the delta variant of SARS-CoV-2 (B.1.617.2) with a specimen date between 1 April and 30 September 2021. The IMD is a geographical deprivation measure based on a range of factors including income, crime, employment and health within a lower super output area (LSOA) containing around 1500 people. LSOAs are ranked based on their IMD score from the most to least deprived. We have categorised these scores into quintiles, with Q1 = most deprived and Q5 = least deprived.

Fig. 1 shows our main findings across these four key demographics. An immediate disparity is seen in ethnicity and deprivation with significantly higher rates in Asian and other ethnic groups as delta emerged in England; over time, these rates fluctuated, but since June 2021, the rate amongst other ethnic groups consistently remained the highest. Since the first detection, delta rates were highest amongst the more deprived populations, with little difference between Q3 and Q5 but a marked gap between Q3 to Q2 and Q1, respectively, showing an increase in burden

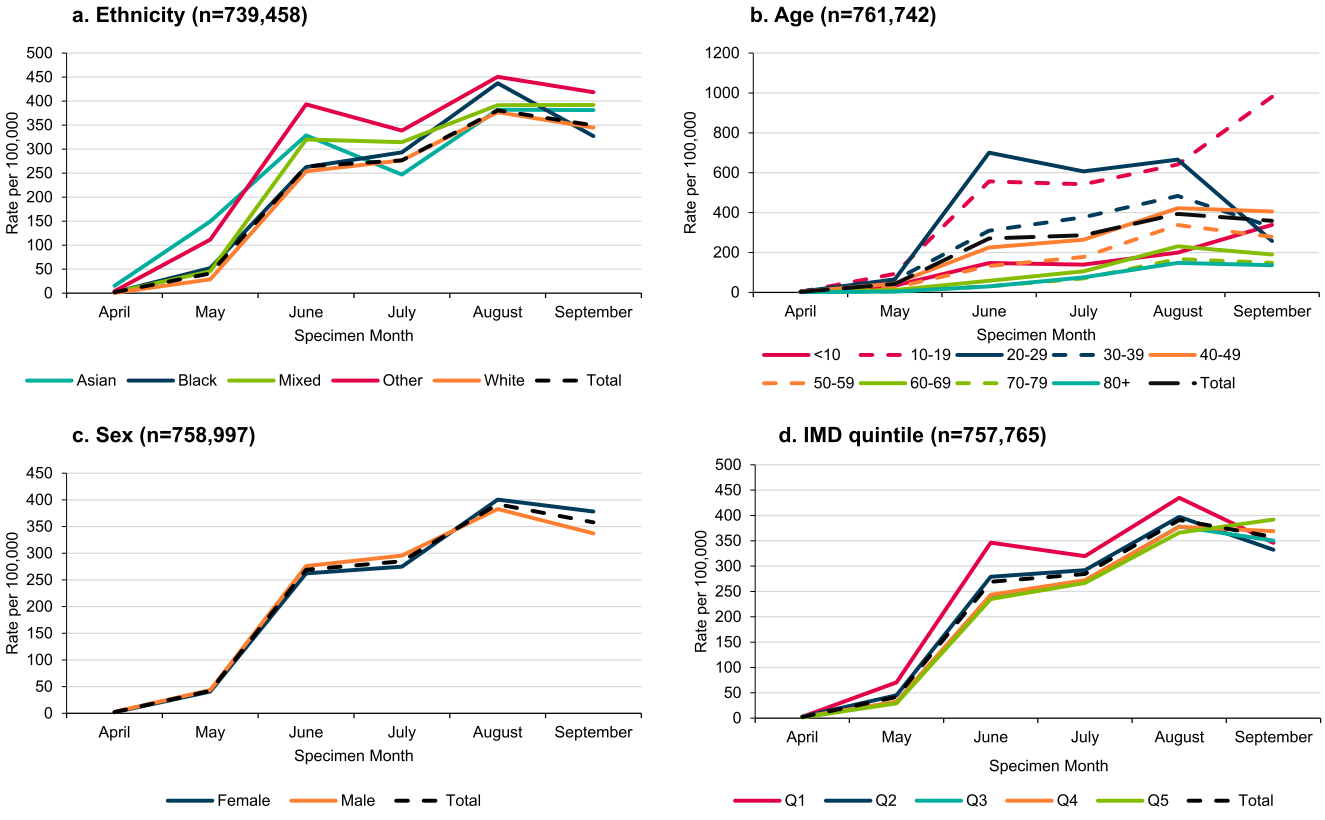

Fig. 1. Rates of SARS-CoV-2 delta variant cases by ethnicity, age, sex and deprivation, England April - September 2021.

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amongst the most deprived. The highest rates occurred amongst 10- to 29-year olds, with increasing rates in 10- to 19-year olds likely reflecting the lack of vaccination in this age group and the return of schools. There is little difference in rates between sex.

Although the highest rates were amongst the most deprived, the distribution of delta cases by IMD quintile groups is different to that observed overall. Overall cases of COVID-19 (regardless of variant) have a linear distribution in relation to deprivation, whereas proportion and rates of delta in Q3-5 are very similar with a step change to Q2 and again to Q1. There is however a smaller gap between the least and most deprived with 22.4% of delta cases in Q1 versus 18.7% in Q5, compared to 24% of all cases in Q1 versus 16.3% in Q5.

Furthermore, the observed distribution of delta cases by IMD was different across age groups; in cases aged <20 years, the distribution reversed over time. In June, 26.6% were in Q1 versus 19.3% in Q5, but by September, this had changed to 17.9% in Q1 versus 24.1% in Q5. In 20- to 29-year olds, 23.5% of cases were in the most deprived areas compared to 15.5% in the least deprived with this gap increasing over time. The distribution of cases aged 30–59 years and $\geq$ 60 years has changed from a linear distribution with a higher proportion in Q1 to being equally distributed across quintile groups.

In summary, emergence of the delta variant of SARS-CoV-2 demonstrated a disproportional effect on more deprived communities, younger populations and ethnic groups other than white, prior to becoming the dominant variant. These disparities were observed despite the vaccination programme shifting the age distribution of cases with a much greater difference in proportion between the most and least deprived young adults compared to overall delta infections. As more variants such as Omicron (B.1.1.529) emerge, detailed surveillance is needed to monitor inequalities during the initial emergence phase and focus public health strategies.

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Letter to the Editor

It is not the time to relax yet: masks are still needed for the Omicron variant of SARS-CoV-2

Since the first case of Coronavirus disease 2019 (COVID-19) was found in Wuhan, China, on December 31, 2019, this pandemic went on to affect more than 267 million people worldwide.[1] Although the Delta variant remains the leading cause of infection, the Omicron (B.1.1.529) variant of concern, which is associated with enhanced transmissibility and evasion to vaccine-induced immunity, now emerged as a new public health threat.[2,3]

Currently, 25.7% of fully vaccinated Americans received their boosters as of December 2021.[4] However, alterations of 37 amino acids in the Spike (S) protein in Omicron variant may have rendered it with resistance and blunts the potency of neutralizing antibodies.[5] A recent study by *Cele* et al. from Africa Health Research Institute has indicated the Omicron escapes antibody neutralization elicited by the Pfizer BNT162b2 mRNA vaccine by 41-fold in comparison to ancestral D614G in FRNT50 assay.[6] Also, to investigate immune evasion mediated by Omicron, researchers from Vir Biotechnology, Switzerland, have compared the variant's neutralizing ability in all existing vaccines (mRNA-1273, BNT162b2, AZD1222, Ad26.COV2.S, SputnikV, BBIBP-CorV) using plasma obtained from COVID-19 convalescent or vaccinated individuals. It has found mRNA-1273 (Moderna) exhibits highest neutralization of Omicron followed by BNT162b2 (Pfizer), with Sputnik V (Russia) showing diminished to non-existent neutralization.[7] Meanwhile, another recent study found that in comparison to Delta variant, Omicron replicates and infects 70 times faster in human bronchus.[8] Although the vaccines protect people well against severe progression of the disease, its effectiveness on prevention of the new Omicron variant remains under investigation. Therefore, non-pharmaceutical interventions (NPIs), such as mask-wearing, remain essential to mitigate the COVID-19 infection. Recently, a 6-month-long cluster-randomized trial has revealed intervention measures to make people wear surgical mask correctly can reduce the prevalence ratio (PR) for COVID by 11%; the outcome has most significant impact for age group>60 as it successfully reduced the PR by 35%.[9] According to a recent published meta-analysis, mask-wearing reduces the risk of COVID-19 infection by 81%.[10] These studies indicate that mask provides an additional low-cost and easy-to-implement physical barrier to effectively minimize the infection risk of severe acute respiratory coronavirus 2.

In conclusion, while it is important to continue promoting the vaccination among population in developing countries and underserved areas, mask-wearing and other NPIs are still effective preventive methods with low cost and easy access in current COVID-19 pandemic, especially with the emergence of the more infectious Omicron variant.

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Short Communication

Lessons learned from the investigation and management of an outbreak of *Shigella flexneri* associated with a restaurant in London, 2019–2020

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ABSTRACT

Background: Foodborne outbreaks of *Shigella flexneri* infection are uncommon in the UK. In November 2019, the United Kingdom Health Security Agency investigated an outbreak of *S. flexneri* associated with a fast-food restaurant in London.

Methods: Epidemiological investigations included case ascertainment and interviewing suspected cases using enhanced surveillance questionnaires. Whole-genome sequencing (WGS) was used for characterisation of human isolates. Environmental investigations included a review of food safety processes at the implicated restaurant, administration of exposure questionnaires and stool sampling of staff.

Results: Between November 2019 and February 2020, 17 cases were confirmed as part of the outbreak by WGS in London. Among these, 15 were linked to the implicated restaurant. A review of the food safety processes at the restaurant was satisfactory. Despite initial suboptimal coverage of stool screening of staff, all staff members working at the restaurant during the sampling period were screened and an asymptomatic food handler tested positive for *S.flexneri* with the outbreak WGS profile. The individual underwent microbiological clearance, and no further cases were reported. It was not possible to confirm the direction of transmission for the community cases or the staff member.

Conclusion: We report an outbreak of *S. flexneri* in a fast-food restaurant in London with previous inspection ratings indicating good compliance with food safety and hygiene standards. WGS was crucial in identifying cases linked to the outbreak. This outbreak highlights the importance of prompt testing of food handlers in outbreaks suspected to be associated with food businesses.

Introduction

Shigellosis is a gastrointestinal infection caused by four species of the bacteria *Shigella*: *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri* and *Shigella sonnei*. Clinical presentation ranges from asymptomatic carriage to acute watery diarrhoea with bloody stools, abdominal pain and fever.[1] While death due to complications is rare in developed countries, shigellosis accounts for over 164,000 deaths globally.[2] The primary routes of transmission are person-to-person spread and through contaminated food and water.[3]

Approximately 2,000 shigellosis cases are reported annually in England and Wales; around a third are caused by *S. flexneri*.[4] Historically, travel to high-incidence countries accounted for the majority of shigellosis in England. However, the epidemiology has shifted in the last decade with increasing numbers linked to sexual transmission in men who have sex with men.[5,6] Foodborne *S. flexneri* outbreaks in England are rare.

Outbreak investigation

In 2019, the South London Health Protection Team (SLHPT) at the United Kingdom Health Security Agency (UKHSA), which

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existed as Public Health England at the time, initiated an investigation after being alerted to three *S. flexneri* cases confirmed by a local hospital laboratory. The first case was reported on 19th November, 2019, with two subsequent cases on 20th November, 2019. An outbreak control team (OCT) was convened to coordinate investigations and management.

As per usual arrangements, stool samples submitted by those with diarrhoeal illness were tested by local hospital laboratories. Isolates of confirmed Shigella species were referred to the UKHSA for confirmation and whole-genome sequencing (WGS). A confirmed case was defined as being infected with *S. flexneri* serotype 1b that had a genome sequence within a5 single-nucleotide polymorphism (SNP) single linkage cluster of the outbreak-specific WGS profile. Of note, outside of the outbreak cluster, the nearest isolate in the UKHSA archive had a sequence that was 64-SNPs different from the WGS profile of the outbreak strain.

Initial investigations identified 15 confirmed cases of *S. flexneri* between 19th November, 2019, and 4th December, 2020. Of these, 13 reported consuming a meal from the same fast-food restaurant during their exposure period. Of the remaining two, one could not provide a reliable history of exposure in spite of attending the implicated venue regularly and the other reported not visiting or eating food from the restaurant (Fig. 1). No other common exposures were identified. The majority of confirmed cases were male (59%) with a mean age of 17 years (range: 4–60). Symptom onset dates ranged from 10th November, 2019, to 24th December, 2020. Most cases reported symptoms of diarrhoea, vomiting, fever and abdominal pain. Six cases were admitted to hospital; no deaths were reported.

Following the identification of the potential link to the fast-food premises, Local Authority Environmental Health Officers (EHO) visited and undertook a review of food safety measures. The inspection did not identify any issues of concern, either in the food preparation or hygiene practices. At the time of the inspection, no staff members reported feeling unwell. Based on the initial inspection findings, the EHOs judged environmental swabs or food sampling was not required. The restaurant was awarded the highest possible food hygiene rating of five, indicating that hygiene standards were assessed as 'very good' by the Food Standards Agency's criterion.[7] Following a review of the epidemiological information and the EHO's findings, the OCT recommended stool sampling for staff in December 2019. Staff samples were tested at a UKHSA regional laboratory for culture and identification of *Shigella* species. Among 61 members of staff, 22 (36%) submitted a stool sample and all samples returned negative results for *Shigella* species.

A further community case with a possible link to the restaurant was then reported to the SLHPT on 23rd January, 2020. They had consumed a takeaway meal from the franchise, although the specific outlet was unconfirmed. However, it met the definition of a confirmed case and there was no other obvious source of infection. Following this case, the EHOs revisited the restaurant to inform the management and reinforced the need for stool sampling by highlighting the Food Standards Agency's - "Food Handlers: Fitness to Work" guidance.[8] An additional 32 staff members submitted a sample, and of these, one staff sample returned a positive result for *S. flexneri* on 27th January, 2020, which was also identified as being serotype 1b, falling within 5-SNPs of the main outbreak profile.

Following the positive result, the staff member was excluded from work until microbiological clearance was obtained. The staff member did not report any diarrhoeal symptoms in the recent past and had not travelled abroad. Given the lack of symptoms and travel history in the staff member, it was not possible to determine the direction of transmission.

Lessons learnt

This incident highlights how outbreaks of *S. flexneri* linked to low-risk food businesses can occur in resource-rich settings, and symptoms may be severe. Robust epidemiological and microbiological surveillance systems ensured the rapid detection and timely investigation of the outbreak.

For the initial cluster of 15 cases up to December 2019, the OCT considered several hypotheses relating to the source of the outbreak. These included a foodborne source through a contaminated food item or infected food handler and an environmental source through common touch points contaminated by an infected customer or staff member. EHOs believed that environmental contamination was unlikely owing to the restaurant's robust cleaning procedures, and the fact that three cases had received delivered meals, and therefore had not entered the premises. Contamination of a specific food item was deemed unlikely as the fast-food outlet was part of a franchise, and no cases were reported

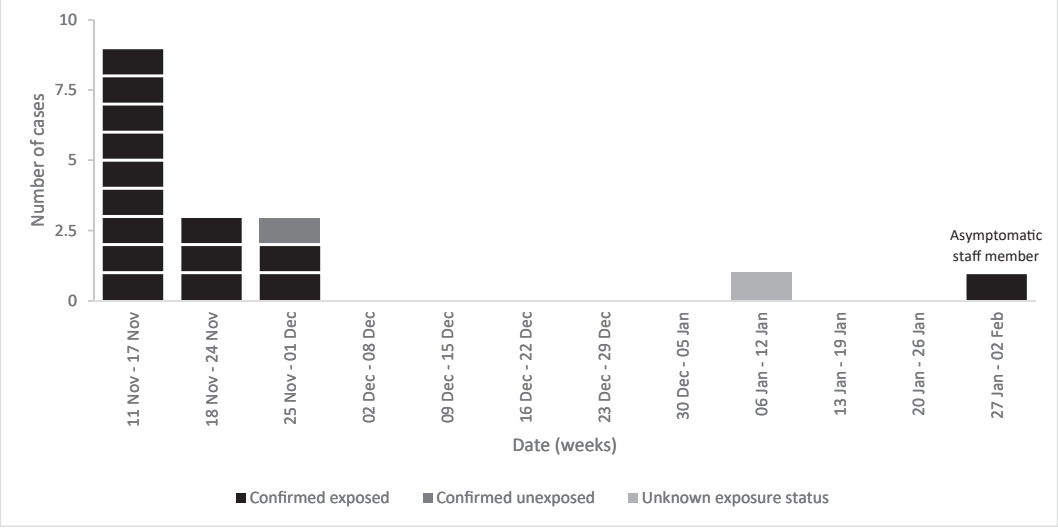

Fig. 1. Epidemic curve of cases by week of sampling.

in other outlets that utilised the same food supply chain. In view of this, the OCT agreed that the most likely source was one or more food handlers and therefore recommended stool sampling of all food handler staff members at the restaurant regardless of symptom status.

However, there were several operational challenges in obtaining stool samples from staff in a timely manner. The National Shigella Guidance specifically recommends testing of symptomatic contacts in risk groups,[9] but the outbreak appeared to have ended by the time the restaurant was identified as the common link. EHOs felt there were little grounds to mandate stool sampling and pursued a voluntary approach in discussion with the management team of the restaurant. This entailed providing information to staff explaining the rationale for stool sampling and the supply of stool sample kits that staff could take home and return directly by post to the UKHSA laboratory. However, compliance was limited and only 22 of 61 staff members had submitted a stool sample by the end of December 2019.

It is important to note that Local Authorities have legal powers under the Health Protection Regulations 2010 to request co-operation in taking samples.[10] While EHOs can invoke legal powers to protect public health, such decisions may be deemed intrusive and challenged by an affected business. In scenarios where the public health risk is deemed to be low or minimal by the EHOs, the conventional approach is to work collaboratively with local businesses to mitigate risks without resorting to legal enforcement. In this instance, the OCT agreed with the EHOs' approach as the outbreak appeared to have finished.

Following the additional case reported on 23rd January, 2020, the OCT agreed that an asymptomatic food handler source was increasingly likely and emphasised the need for stool sampling of all staff members. Owing to the limited returns of postal stool sample kits, the EHOs agreed with the restaurant's management team to implement an alternative approach, whereby the management team monitored the return of stool samples to the venue. Staff members who did not return samples were appropriately followed up. Samples were returned to the regional UKHSA laboratory for testing by courier. This model increased compliance substantially.

This incident highlighted the need for clear coordination and monitoring of stool sampling where it is deemed necessary and that a voluntary approach that relies on staff to return samples is unlikely to succeed. Active engagement from the resturant's management team was crucial in ensuring high compliance in a timely manner. Identification and effective management of the asymptomatic food handler likely mitigated the ongoing public health risk to consumers. Crucially, EHOs should provide robust advice on safe handling and storage of returned stool samples, ensuring there are no concerns for food safety. EHOs should also liaise with the restaurant management to understand the workforce and identify challenges to the investigation, including shift patterns, levels of education, language barriers and disabilities of staff.[7]

The 2017 National Shigella Guidance states that testing for *S. flexneri* should only be conducted when contacts in risk groups are symptomatic. There is no additional guidance for management of outbreaks. We recommend this guidance is strengthened by considering the testing of asymptomatic food handlers in outbreak situations where appropriate. This would give EHOs a stronger mandate when engaging with implicated food businesses. In instances where the restaurant management team are not sufficiently engaged, Health Protection Teams and EHOs should not hesitate to apply legal powers to mitigate ongoing public health risks.

Author statements

Ethical approval

Not required.Surveillance data were used in this article, without the need for the collection of additional information.

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Competing interests

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Editorial

Living with endemic COVID-19

After 2 long years, the COVID-19 pandemic has now led to more than 304 million confirmed infections and more than 5.4 million deaths, as well as causing significant societal disruption worldwide.[1] Unfortunately, the pandemic has not run its course, with many countries still in the grip of the latest wave of infections caused by the Omicron variant. That said, the world is in a different, and better, place now than a year ago, with multiple effective vaccines and new therapeutic options currently available, stronger testing and surveillance infrastructure and better knowledge of public health measures that work. Indeed, Dr Tedros Adhanom Ghebreyesus, Director General of the World Health Organization, has sounded an optimistic note that this may be the year we end the pandemic.[2]

For some countries, there is an increasing belief that the pandemic will tail off in the coming year based on their achievement of high levels of vaccine coverage. Thoughts naturally now turn toward contemplating life beyond COVID-19. It is highly unlikely at the present time that SARS-CoV-2 will be eliminated from human populations but instead will become one of the endemic human coronaviruses. The two key questions many people are wondering are as follows: when will the pandemic end? and how do we live with COVID-19?

Defining when exactly the pandemic will end is not easy. An epidemiologic definition is when the pathogen becomes well established with sustained transmission in human populations. Some add the caveat that the infections become more predictable, and usually (but not always) less severe. Infections will settle to an "equilibrium" where the incidence of infections reaches a stable baseline, possibly with seasonal variations.

An endemic disease can still have serious consequences. Take the examples of malaria, HIV, tuberculosis and other infectious diseases that are endemic worldwide. In 2020, there were an estimated 241 million cases of malaria worldwide and around 627,000 deaths.[3] Outbreaks and sporadic infections will continue to occur, particularly in population groups with little or no immunity from either past infection or immunisation. We know some population groups will be more vulnerable (such as the elderly, the very young and those with certain pre-existing health conditions),[4] as exemplified by malaria, where most of the infections occur in children aged <5 years. Public health measures postpandemic must continue to focus on protecting the vulnerable.

We also know certain groups will suffer significant health inequality with infectious disease. These include those who have limited access to health resources or experience greater disadvantage due to a variety of socio-economic and other risk factors.[5] These health inequalities were evident in the last 2 years, particularly amongst marginalised ethnic or faith communities, the homeless, substance misusers, migrants and refugees and others, and most certainly will continue. There will be an ongoing need for public health efforts to try and address these entrenched health inequalities.

We need to be careful in how we communicate 'endemicity' to the general public. Could the public perceive this to mean that the infection is now somehow mild and inconsequential like the common cold? If so, this could lead to relaxation of protective behaviours that help to keep infections in check. It is well recognised that risk perceptions have a powerful influence on health-related behaviours.[5] For many, 'living with COVID' may mean going back to the prepandemic normal ways of living. This desire to return to familiar old ways of living is understandable but also risks recreating the same conditions of vulnerability. Effective risk communication, particularly in the social media age, is therefore both a challenge and necessity.[6]

Instead of returning to the old ways, it may be desirable to establish new norms for living with COVID. For example, could a greater appreciation of the airborne and fomite routes of transmission and the necessary precautions needed help societies minimise future burdens of winter respiratory viral illness? Could behavioural changes such as more ubiquitous use of face coverings, social distancing, better hand hygiene, and people more readily self-isolating when ill, also help curb the spread of these diseases? Similarly, the lessons learned around the need for better ventilation in high-risk indoor settings may help not just reduce respiratory infections but also air pollution–related illnesses. That said, the possibility of widespread public 'pandemic fatigue' may present a significant barrier and lead to lower adherence to such protective behaviours.[7]

Undoubtedly, some of the public health interventions introduced in the pandemic era will probably need to cease, such as the mass test and trace programmes that were implemented at great cost in the United Kingdom totalling £27 billion over 2 years[8] simply because of their unsustainability and questionable cost-effectiveness in the longer term.

There is therefore value now in considering now what (if any) new norms are needed, as well as what are the societal costs entailed and benefits that may accrue from them. Without deliberate intent, it is likely that we will revert to the old norms.

On a final note, whilst we may speak of a time beyond the pandemic, we are still very much in the midst of one. We are not out of it yet. At the present time, the world continues to grapple with the Omicron variant. Fortunately, infections with the current Omicron variant appears to be less severe in populations with high levels of immunity, but it remains a dangerous disease for unvaccinated populations and for vulnerable high-risk population groups.[9]

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There also remains the risk of new variants emerging, including ones that will evade population immunity. Whilst viruses usually tend to evolve into less virulent forms, and we may hope the severity of future infections will attenuate; there is no guarantee that a more virulent form will not emerge. Public health systems will need to be vigilant and ready to respond in a timely way should that happen. In the meantime, vaccines remain our best bet out of the pandemic, and global efforts are still needed to achieve global vaccine coverage.

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Letter to the Editor

Money for a vaccine? Pay incentives as a solution to increase vaccination rates during the COVID-19 pandemic

The fight against coronavirus cannot be solved in one single country. This is a global problem. It can only be solved together and everywhere. Vaccination against COVID-19 is one of the most effective, affordable, and cost-effective ways to protect the population from COVID-19 disease and its complications. We propose a potential solution at the present time to increase the number of people vaccinated. Specifically, we report an example from Russia.

Mass vaccination in Russia started in December 2020, however, due to various circumstances; the authorities are constantly looking for new mechanisms to stimulate citizens to vaccinate.

By November 2021, only 33% of the population in Russia was vaccinated, according to the RBC (RosBiznesConsulting). The reason for this is the reluctance of the population to get vaccinated. The level of herd immunity is estimated by the authorities at 49%, but to stabilize the situation with the coronavirus, it should be 90–95%.[1]

An urgent need was to educate citizens about the need for vaccination to overcome conservatism and fear of vaccination.

The authorities want to stimulate citizens by introducing mandatory QR codes for intercity transport, cafes, and non-food stores. One of the incentives is economic.

Thus, Moscow will continue to stimulate the vaccination of the population. The authorities plan to return to the practice of drawing valuable prizes among those who were vaccinated. This experience has already shown good results and aroused the interest of the population because not only cash prizes were raffled off but even apartments, as pointed out by the Mayor of Moscow.[2]

In Russia, the authorities concluded that the best way to encourage people to participate in the coronavirus vaccination is through financial incentives. The authorities decided to start by encouraging the elderly.

In older citizens, the disease can proceed with significant complications and lead to death. In Moscow, older citizens are encouraged to vaccinate. From October 12, Muscovites older than 65 years who have been vaccinated against COVID-19 will be able to choose in what form to receive an incentive—in the form of a gift set or a payment in the amount of 10 thousand rubles, in accordance with the order of the mayor of the city.

The program of financial incentives for the elderly to vaccinate began on 23 June. Gifts are awarded to those who will be vaccinated with the first component before December 31 and then fully complete the vaccination. Gift sets, which include medical devices and hygiene products, have already been given out to 240 thousand vaccinated pensioners.[3] In the regions of Russia, measures are also being taken, such as one-time cash payments after vaccinations to pensioners older than 60 years.

In addition, the Russian Ministry of Health proposes to stimulate the physicians involved in vaccination with cash payments. To maintain high rates of vaccination, as well as to motivate health workers to conduct outreach work among citizens, it is proposed to provide material incentives for health workers involved in the vaccination of the population as support measures.[4]

Current research does not provide a clear answer regarding the use of pay incentives to increase vaccination rates. Previous experimental research has shown that pay incentives do not always increase vaccination interest.[5] However, it is critical to inquire as to the nature of the reward. In the experiment's case, the maximum reward was €200, it was in Germany, and it was not focused on pensioners.[6] It is currently available in Moscow for 10,000 rubles, or about €120, which is a lower amount but significantly higher for Russian pensioners in relation to their pensions. The average pension in Russia is about €190,[7] whereas in Germany it is about €900.[3] Unfortunately, we do not yet have precise data on how many Moscow pensioners have been motivated to vaccinate as a result of the newly established financial incentive. All we know is that in the last two months, approximately 800,000 people in Moscow have been vaccinated for the first time.[8] Unfortunately, no information on the age profile is available at this time.

Rewarding vaccination raises several ethical concerns, which were raised by many academics and experts when the scheme was first discussed and implemented in countries.[9] Most of the world's economies were forced to go into lockdown for at least part of last year and this year, at a significant cost. Unfortunately, many countries are failing to achieve herd immunity, and solutions are being sought to address this issue. Some countries are even talking about and implementing mandatory vaccination, which is causing a lot of controversies because opponents of mandatory vaccination claim it restricts their freedom and rights.

We believe that focusing on rewarding the older population, which is the most affected by the COVID-19, with a significant one-time financial reward, such as one full month's worth of pension, will generate enough interest that many countries will achieve herd immunity and, as a result, the economy will save financial resources by implementing this measure. The lockdown cost countries a huge amount of resources and significantly increased the debt in many of them. Furthermore, retired people are frequently in a position where they do not have much money to spare, and the money invested in them will go back into the economy. We therefore eagerly await any credible data from Moscow on the success of the

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financial incentive in this city, to assess whether offering a substantial sum for pensioners can avoid the next wave and return to normalcy in many countries. We believe that focusing only on pensioners with financial incentives is the right strategy to use in the countries where herd immunity has not yet been achieved.

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Letter to the Editor

Possible drawbacks of relying only on molecular testing for diagnosing SARS-CoV-2 infections

We read with interest the article of Smith and colleagues,[1] who concluded that it should be widely communicated to the public that molecular assays are superior to lateral flow tests (LFT) in symptomatic people with suspected severe acute respiratory coronavirus 2 (SARS-CoV-2) infection. Although widespread diagnostic testing remains a major cornerstone in strategies aimed at limiting or preventing the transmission of SARS-CoV-2 in the community, we are willing to highlight some limitations in preventive policies exclusively based on a molecular approach.

The first limitation is the current availability of molecular tests, which remains rather limited around the world. According to updated data from a survey by the American Association of Clinical Chemistry (AACC), the vast majority of clinical laboratories, which responded all around the world (i.e., nearly 80%) are still facing hard challenges in providing routine SARS-CoV-2 testing or increasing their testing capacity (most difficulties were attributed to recruiting staff and obtaining supplies).[2] Therefore, widespread sole use of molecular testing cannot be considered a feasible or effective solution, at least not presently, since these types of assays will not be accessible by many patients worldwide, neither they will permit the generation of timely test results, thus leaving several laboratories plagued by a dramatic backlog of samples to be processed.[2] Providing rapid results is especially important given the emergence of new SARS-CoV-2 variants of concern (e.g., delta or lambda) that are associated with higher and longer periods of infectivity compared to the prototype strain that originally emerged in Wuhan in 2019,[3] which requires the adoption of tests with the capability of rapid viral detection, especially in subjects with higher viral load.

The diagnostic performance of LFTs and laboratory-based SARS-CoV-2 antigen immunoassays is a second aspect that must be considered. Although we would all agree that molecular testing is still characterized by higher diagnostic sensitivity for detecting SARS-CoV-2 mRNA, it seems important to reaffirm that a positive test does not always translate into real infectiveness. Several lines of evidence attest that subjects with a positive molecular test but low viral load (e.g., above 30–32 cycle thresholds) detected 1–2 weeks after the onset of symptoms have a very low, virtually meaningless risk of being infective and capable of transmitting the virus, as reflected by the negativity of viral cultures.[4] The positivity with molecular tests in these subjects may hence be attributable to residually low viral load, which is unlikely to be sufficient for infecting other people, or to the shedding of non-viable SARS-CoV-2 genetic material present within or outside the host cells, which is not associated by any infective potency.

Replacing genetic testing with antigen immunoassays in symptomatic subjects seems the best strategy for rapid and widespread screening and/or diagnosis of SARS-CoV-2 infections. A meta-analysis has recently concluded that the pooled diagnostic sensitivity of SARS-CoV-2 antigen testing in subjects with onset <7 days of typical symptoms of coronavirus disease 2019 (COVID-19) is as high as 84% compared to molecular tests,[5] thus underpinning that these tests represent a trustable means for large population screening, especially during sudden emergence of large local outbreaks.

In conclusion, we do not agree with the concept that the use of LFTs and laboratory-based SARS-CoV-2 antigen immunoassays should be discouraged to the public, but we rather proffer that the use of (rapid) antigen tests shall be incorporated into validated algorithms aimed at filling the still important gaps that testing programs experience when relying only on SARS-CoV-2 molecular testing, especially when demand is high.

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Review Paper

Public attitudes and influencing factors toward COVID-19 vaccination for adolescents/children: a scoping review

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ABSTRACT

Objective: This study aimed to systematically clarify attitudes and influencing factors of the public toward COVID-19 vaccination for children or adolescents.
Study design: This was a scoping review.
Methods: This scoping review screened, included, sorted, and analyzed relevant studies on COVID-19 vaccination for children or adolescents before December 31, 2021, in databases, including PubMed, Elsevier, Web of Science, Cochrane Library, and Wiley.
Results: A total of 34 studies were included. The results showed that the public's acceptance rate toward COVID-19 vaccination for children or adolescents ranged from 4.9% (southeast Nigerian mothers) to 91% (Brazilian parents). Parents' or adolescents' age, gender, education level, and cognition and behavior characteristics for the vaccines were the central factors affecting vaccination. The vaccine's safety, effectiveness, and potential side-effects were the main reasons affecting vaccination.
Conclusions: Realizing current public attitudes of COVID-19 vaccination for adolescents or children can effectively develop intervention measures and control the pandemic as soon as possible through herd immunity.

Introduction

The COVID-19[1] is a new strain of coronavirus called as a severe acute respiratory syndrome coronavirus (SARS-CoV-2) or COVID-19. COVID-19 was first discovered and wildly spread in Wuhan, China, in December 2019. So far, the global COVID-19 pandemic has been complex.[2] COVID-19 adapts to new human hosts and produces mutant individuals with different characteristics from their ancestral strains, such as Alpha (B.1.1.7), Delta (B.1.617.2), etc.[3] These mutant individuals continue to cause damage and waves of pandemic around the world. All by August 2021,[4] persistent COVID-19 pandemic has generated more than 4,500,000 deaths worldwide. Since the first pandemic spread, experts have always stressed the importance of personal protective measures (e.g. home quarantine, wear masks, and disinfecting).[5] However, in essence, these physical protective measures cannot eliminate the virus and restore people's everyday life. Similarly, it is also impossible for the public to abide by protective measures for many years.

Herd immunity[6,7] is an important measure to control the pandemic situation as soon as possible from protecting susceptible individuals through a significant enough immune individual in the group. The COVID-19 vaccines' development and application may be the effective roads to curb the pandemic spread and then realize herd immunity.[6] As we know, the Pfizer-BioNTech COVID-19 vaccine was emergently approved and put into use in the United States on December 11, 2020. After that, a variety of vaccines with reasonable safety and effectiveness (Oxford-AstraZeneca, Moderna's mRNA-1273, Sinovac's CoronaVac, etc.) displayed a fantastic speed of research and development. All by January 2022,[8] nearly 134 vaccines remain in clinical development. Existing studies reported that the messenger RNA vaccine (specifically reference Pfizer-BioNTech COVID-19) showed excellent reliability to reach the global vaccine demand against COVID-19.[9] Even so, we found that adults varied degrees of hesitation about the vaccine, and the acceptance rate ranged from 29.4% to 86% in COVID-19 vaccination studies over the past few months.[10] The majority of people hesitated because of COVID-19 vaccines' safety

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and side-effects, which remains a principal problem for children. Today, lots of evidence about the vaccines' safety and effectiveness among children is provided, and Food and Drug Administration (FDA) urgently approved Pfizer-BioNTech COVID-19 vaccines for application among adolescents on May 10, 2021,[11] and among children aged 5–11 years on October 29, 2021.[12] Experts have repeatedly stressed that child protection remains the key to reducing infection rates. Once a vaccine is available, vaccinating young people and children is necessary.[13] However, there was no high acceptance rate in Pan's[14] report. Most parents were skeptical and unwilling to receive emergency-approved vaccines. With the continuous fermentation of COVID-19 pandemic, the pace of vaccine development has also increased, appearing the new progress in public willingness to vaccinate children.

Until now, COVID-19 vaccination remains essential for achieving herd immunization to reduce the pandemic burden.[15] Vaccination hesitancy has been identified as a significant public health crisis. Whereas, we conducted a rapidly scoping review for the latest studies in recent months to clarify the public (including adults, parents, and adolescents themselves) attitudes and influencing factors toward COVID-19 vaccination for adolescents or children and provide information or advice for public institutions to better implement immunization plans. Considering the vaccines' rapid development and application, we mainly included studies after Pfizer-BioNTech COVID-19 vaccine first emergency approval among adults to present the latest views.

Methods

Protocol and registration

We conducted a scoping review according to PRISMA Extension for Scoping Reviews (PRISMA-ScR)[16] (see supplementary documents). Furthermore, we preregistered on OSF Registries (osf.io/qw985). The study's questions are as follows:

1 What are the public attitudes toward COVID-19 vaccination for adolescents or children after COVID-19 vaccination approval among adults? Is there any difference between before and after approval COVID-19 vaccination for adolescents?
2 What are the influencing factors about COVID-19 vaccination for adolescents or children?

Information sources

We searched databases including PubMed, Wiley, Web of Science, Elsevier, and Cochrane Library to obtain relevant literature about the public attitudes toward COVID-19 vaccines for adolescents or children before December 31, 2021. Moreover, we searched the reference list of the included literature to find missed literature. The search strategy of Web of Science is as follows:

TS=((Corona OR "SARS-CoV-2" OR "COVID 19" OR 2019 nCov) AND (vaccine OR vaccination) AND (children OR kid OR teen OR juvenile OR teenagers OR adolescent OR youth) AND (hesitancy OR accept OR demand OR willingness OR antivaccine OR anti-vaccine OR reject OR rejection OR resistance OR refuse OR refusal))

Study selection

We imported retrieved literature into Endnote 9.1 and removed the duplicate; two researchers screened the title and abstract according to the principle of PICOs (P: participants; I: intervention; C: control; O: outcome; s: study design) and cross-checked. After initial screening, we downloaded full texts. Two researchers read full texts for rescreening, and the third researcher decided on conflicts.

Eligibility criteria

Included studies were produced since 2021, only in English. The study population consisted of adults aged >18 years, adolescents, children, and parents (grandparents and other guardians were defined as parents in this study). Articles with incomplete or incorrect content, repeated data studies, commentary studies, and letters to editors without data were excluded to improve the included literature's quality.

Data charting process

We extracted relevant data through Excel (Microsoft Corporation), including the study's first author, study setting, study time, country, recruitment, study population, sample size, children or adolescents' age, COVID-19 vaccination acceptance rate, and subjective reasons or related factors associated with vaccination.

Collate, summarize of results

According to the extracted content, study characteristics and influencing factors toward COVID-19 vaccines were presented in tables to clarify this scoping review's subject. In addition, the figures described influencing factors of high frequency.

Results

Selection of sources of evidence

According to the literature screening flowchart shown in Fig 1, 34 studies were finally included. After removing the dropout and loss of follow-up caused by various reasons, 85,608 subjects (54,703 parents and adults, 30,905 adolescents) were left.

Study characteristics

All included studies described survey methods and outcome indicators in detail. Table 1 shows the primary characteristics. There were 33 cross-sectional surveys and one cross-sectional survey combined with semistructured interviews.[24] Most studies were online surveys; only seven studies[17,18,22,23,32,44,45] completed questionnaires by face-to-face or paper. All study populations were from one country; 15 of these studies[17,22,23,29,33,35–38,40–44,50] were based on data from Asia, one[18] from Africa, seven[19,20,27,28,39,46,47] from North America, one[32] from South America, seven[21,26,30,31,34,45,48] from Europe, two[24,49] from Oceania, and one[25] from the Eurasian continent.

In terms of study time, 20 studies[31–50] were collected after commencing the national childhood COVID-19 vaccination program, and the data of adolescents came from these.[44–50] The recruitment methods are briefly described as follows: five studies[17,32,37,44,45] used convenient sampling, two studies[20,39] included data from representative regions, two studies[23,29] used purposive sampling, two studies[27,28] used non-probability quota-based sampling, three studies[19,35,38] used snowball sampling, four studies[18,22,31,47] used random sampling, one study[36] was cluster

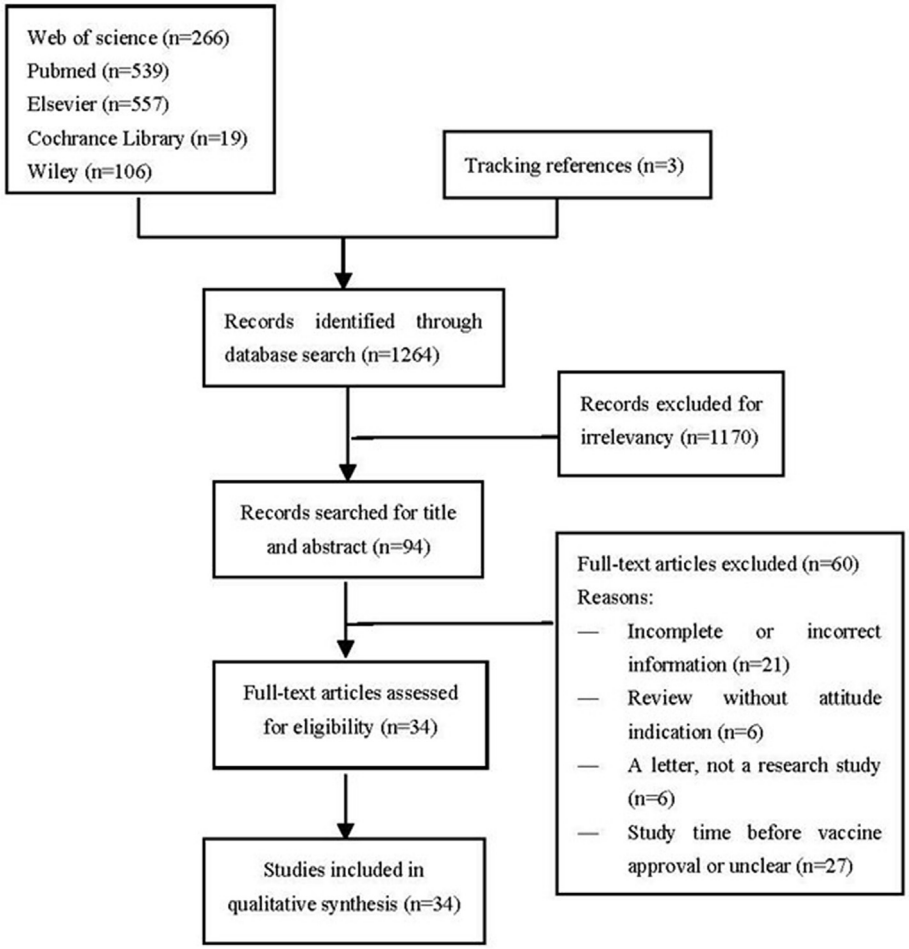

Fig. 1. Literature screening flowchart.

sampling, populations of five studies[21,34,40,43,50] were from participant pool or other registered research centers/database, seven studies[24–26,30,33,41,42] were recruited through online platforms (via Facebook, WhatsApp, mail, Wen-Juan-Xin, etc.) or visits, and three studies[46,48,49] did not mention specific recruitment methods.

Public attitudes toward COVID-19 vaccination for adolescents or children

All studies reported the acceptance rate of vaccination for children in the study population. One study[44] reported parents' and adolescents' acceptance rates (we separately analyzed the data), and one study[31] reported three child age levels' acceptance rates (we selected the median of the three for analysis). The acceptance rate ranged from 4.9% (southeast Nigerian mothers) to 91.0% (Brazilian parents), and the median acceptance rate was 53.70% (47.60%, 70.40%). As a reference, the median acceptance rate of 28 studies reported adults' or parents' attitudes was 60.20% (46.78%, 70.03%) and seven studies reported by adolescents was 50.40% (49.60%, 72.10%). At the same time, we analyzed the data before and after the commencement of the national adolescent's COVID-19 vaccination program. The median before the approval was 49.43% (43.55%, 60.78%), and the median after the approval was 64.20% (48.95%, 80.20%). Even if the data have high heterogeneity, it can provide a reference in this study.

Influencing factors toward COVID-19 vaccination for adolescents or children

According to the studies reported, we summarized and charted the influencing factors of acceptance and hesitation for COVID-19 vaccine among the study population, divided into related factors (single factors or multifactor statistical analysis; Table 2) and related reasons (qualitative data; Table 2). Meanwhile, we summarized high-frequency factors and reasons as shown in Figs. 2 and 3.

Sociodemographic or personal characteristics

Twenty-four studies depicted sociodemographic or personal characteristics in vaccination attitudes for adolescents or children (Table 2). Female,[27,28,33,43,49] low household income,[28,32,34,39,43,45,49] parents with lower educational level,[21,28,32,34] and non-native[27,39,40] were more likely to hesitate, whereas older parents[17,30,38] and children[38,47,48,50] were associated with vaccination acceptance. Similarly, parents who worked for health care were associated with vaccination for children,[25,30,36,38] and freelance[34] or part-time jobs[20]parents were more hesitant about vaccination; Asian parents[28] and adolescents[47] were more likely to vaccination. In addition, other factors such as the number of children,[32,36,37] children who attended in-person school or daycare,[27] and rural residence[36] were related factors affecting children's vaccination. Adolescents with remote, poor schools,

Table 1
Study characteristics.

First author	Study setting	Recruitment	Study time	Country	Study population	Sample size	Age of the child (year)	Acceptance rate
Bader A. Altulaihi[17]	A cross-sectional, paper questionnaire	Convenience sampling	After adult approval	Saudi Arabia	Parents	333	≤18	53.70%
Awoere T. Chinawa[18]	A cross-sectional, face-to-face survey	Simple random sampling in hospital	After adult approval	Southeast Nigeria	Mothers	577	Baby	4.90%
Kristine M. Ruggiero[19]	A cross-sectional, online survey	Snowball sampling	November 2020 to January 2021	The United States	Parents	427	≤18	49.45%
Robin M. Humble[20]	A cross-sectional, online survey	Representatively sampling survey	December 10 to 24 2020	Canada	Parents	1702	0–17	63.10%
Marco Montalti[21]	A cross-sectional, online survey	Personnel of the local public health service	December 2020 to January 2021	Italy	Parents	4993	≤18	60.40%
Xiao Wan[22]	A cross-sectional, paper questionnaire	Two-stage stratified random sampling	December 2020 to February 2021	Korea	Parents	468	3–6	86.75%
Haifa Aldakhil[23]	A cross-sectional, face-to-face survey	Non-probability purposive sampling	January to February 2021	Saudi Arabia	Mothers	270	≤7	43.77%
S. Evans[24]	A cross-sectional, online survey, and open interview	Via paid and unpaid social media advertisements	January to February 2021	Australia	Parents	1094	≤18	48.30%
Meltem Yılmaz[25]	A cross-sectional, online survey	Via Facebook, WhatsApp, and mail groups	February 2021	Turkey	Parents	1035	≤17	36.30%
Nuno Fernandes[26]	A cross-sectional, online survey	Institutional email and online social networks (e.g. Facebook)	January to March 2021	Portugal	Adults and parents	649	–	60.00%
Chloe A. Teasdale[27]	A cross-sectional, online survey	Non-probability quota-based sampling	March to April 2021	The United States	Parents	1119	4.7 (2.0, 8.5)	61.90%
Chloe A. Teasdale[28]	A cross-sectional, online survey	Non-probability quota-based sampling	March to April 2021	The United States	Parents	2074	≤12	49.40%
Takeshi Yoda[29]	A cross-sectional, online survey	Purposive sampling	April 2021	Japan	Parents	1100	0–15	42.90%
Mateusz Babicki[30]	A cross-sectional, online survey	Via Facebook.com social network, promoting and disseminated in groups	May 2021	Poland	Parents	4432	≤18	44.10%
Pierre Verger[31]	A cross-sectional, online survey	Randomly selected	May 2021	France	Adults	2533	≤17	62.70% for adolescents ; 48.30% for school children ; 30.90% for preschoolers
Leonardo Evangelista Bagateli[32]	A cross-sectional, face-to-face survey	Convenient sampling in hospital	May to June 2021	Brazil	Parents	501	≤17	91.00%
Mei-Xian Zhang[33]	A cross-sectional, online survey	Wen-Juan-Xing platform without random	June 2021	China	Parents	1788	13.7 ± 3.2	46.50%
Stefano Zona[34]	A cross-sectional, online survey	The Crowd Signal platform	July to August 2021	Italy	Parents	1799	12–17	26.50%
Jian Wu[35]	A cross-sectional, online survey	Snowball sampling	August 2021	China	Parents or grandparents	16,133	3–18	82.61%
Yunyun Xu[36]	A cross-sectional, online survey	Cluster sampling	July to August 2021	China	Parents	917	–	68.90%
Mohammed Samannodi[37]	A cross-sectional, online survey	Convenience sampling	June to July 2021	Saudi Arabia	Parents	581	0–17	63.90%
Mohamad-Hani Temsah[38]	A cross-sectional, online survey	Snowball sampling	After adolescent approval	Saudi Arabia	Parents	3167	≤18	47.60%
Britt McKinnon[39]	A cross-sectional, online survey	Representatively sampling survey	May to June 2021	Canada	Parents	809	2–17	87.60%
Sarah Musa[40]	A cross-sectional, online survey	A database of adolescents	May to June 2021	Qatar	Parents	4023	13.4 ± 1.1	82.10%

Yulia Gendler[41]	A cross-sectional, online survey	Via public Facebook pages of parents' groups	June 2021	Israel	Parents	520	12–15	70.40%
Konstadina Griva[42]	A cross-sectional, online survey	Via Facebook, WhatsApp and mail, social media posts, self-referral and by recruiting past participants	June to July 2021	Singapore	Parents	233	12–18	84.10%
Sayaka Horiuchi[43]	A cross-sectional, online survey	Registered Research Center	May to June 2021	Japan	Parents	1200	3–14	64.70%
Soo-Han Choi[44]	A cross-sectional, face-to-face survey	Convenient sampling	May to June 2021	Korea	Parents	226	≤18	64.20%
					Adolescents	117	10–18	49.60%
Mina Fazel[45]	A cross-sectional, paper questionnaire	General sampling in school	May to July 2021	England	Adolescents	27,910	9–18	50.10%
Don E. Willis[46]	A cross-sectional, online survey	–	May 2021	The United States	Adolescents	345	12–15	42.00%
Adam A. Rogers[47]	A cross-sectional, online survey	Stratified random sampling	June 2021	The United States	Adolescents	916	12–17	50.40%
Anna Zychlinsky Scharff[48]	A cross-sectional, online survey	–	May to June 2021	Germany	Adolescents	903	14.6 ± 2.3	78.30%
Elke Humer[49]	A cross-sectional, online survey	–	June to July 2021	Austria	Adolescents	564	16.34 ± 1.33	53.00%
Ateret Gewirtz-Meydan[50]	A cross-sectional, online survey	Participants' pool	May to June 2021	Israel	Adolescents	150	12–18	72.10%

smoking, and time in media[45] or television[46] were associated with vaccine hesitation.

Cognition and behavior characteristics for the vaccines

Twenty-five studies depicted the cognition and behavior characteristics for the vaccines in vaccination attitudes for adolescents or children (Table 2). Parents' willingness to get themselves vaccinated,[20,29,30,33,35,38,41,44,47,50] positive or negative attitudes,[17,23,25,26,35,36,41] history of taking influenza vaccine,[17,19,20,30,35,41] impact of social vaccination programs,[30,31,44] and high risk for their children to COVID-19[18,22,30] were related factors affecting children's vaccination. Next, accessing information about COVID-19 vaccines from community workers[35] or the World Health Organization[38] were associated with vaccine acceptance and from web/social media[21] or unofficial media[43] were associated with vaccine hesitation. The attention to COVID-19 vaccine–related information[22,23,30,47] was also a related factor. In addition, compulsory vaccination policy,[21,30] general favorability to vaccination,[31] trusting doctors,[24,35] and COVID-19's tested or infected histories[40,44] affected willingness to vaccinate children.

Reasons associated with vaccination

Twenty-one articles reported reasons associated with COVID-19 vaccination for children, see Table 2 for details; the main reasons for acceptance or hesitancy are shown in Fig. 3.

We found that most of them were associated with the vaccine characteristics among relevant reasons. Most people accepted the vaccine because of its protective effects[17,24,25,35] or they believed in the vaccines' safety and effectiveness.[22,25,34,36] They were afraid that their children would be infected in the future,[22,36] and they would spread the virus to people around them.[22] Nevertheless, 17 articles pointed out that parents and adolescents were reluctant to vaccinate as they were worried about the vaccine's safety, effectiveness, and potential side-effects. Meanwhile, some people believed that children were at a low risk,[27,28,35,39,40] and COVID-19 vaccine lacked sufficient information and evidence.[17,24,25,37–39]

Moreover, a small number of people preferred to vaccinate as they followed medical advices[21,34] or mandatory policies,[21,37] the vaccines were provided free of charge,[35] insufficient supply,[17] and they could contribute to national epidemic prevention and control.[17,25] Equally, a small number of people were reluctant to vaccinate because of their personal beliefs[21,27,28] or they had no time to vaccinate their children.[17]

Discussion

This scoping review updates 34 recent studies on the public attitudes toward COVID-19 vaccination for adolescents or children. We found that the public's willingness to vaccinate children was not high, and the median acceptance rate was 53.70%. This rate is lower than the 61.40% vaccination rate for parents.[14] Snehota's systematic review[51] mentioned that percentage of people's intention to vaccinate themselves was 75%, which is also much higher than this study's results. Meanwhile, the results showed that the vaccination willingness of different study populations remained different. The median vaccination rate for children among adults and parents was 60.20%, whereas the median acceptance rate among adolescents was 50.40% (in particular, these studies' time was after children's COVID-19 vaccination program). This may be because adolescents do not fully understand COVID-19 vaccine and did not experience adequate vaccination plans' publicity like parents. In addition, the results showed that the acceptance rate after approval for children's COVID-19 vaccination was higher than

Table 2
Attitudes and individual factors of COVID-19 vaccines vaccination among adolescents/children.

First author	Related factors	Related reasons	Acceptance/hesitancy
Bader A. Altulaihi[17]	1. Parents aged between 31 and 40 years; 2. Children age group was 4–12; 3. Had a history of taking the seasonal influenza vaccine; 4. The scores of negative attitude scale.	1. Highly effective in protecting their children from COVID-19; 2. Contributed to the control of COVID-19; 3. Adequate supply of COVID-19 vaccination.	Acceptance
	The scores of positive attitude scale	1. Lack of information and evidence; 2. Severe side-effects; 3. The protection of COVID-19 vaccines will only last for a short time; 4. Child was afraid of vaccination; 5. Lack of time.	Hesitancy
Awoere T. Chinawa[18]	1. Believed they could be infected with the COVID-19; 2. Aware of someone that died from COVID-19.	–	Acceptance
Kristine M. Ruggiero[19]	Already or planned to vaccinate their child against influenza this season	Vaccine side-effects and safety	Hesitancy
Robin M. Humble[20]	1. Parents employed part-time; 2. Parents who spoke English; 3. Children did not receive the influenza vaccine prepandemic; 4. Parents had low intention to vaccinate themselves; 5. Lacked confidence in the safety of COVID-19 vaccines; 6. If vaccines had not yet been tested in children.	–	Acceptance
Marco Montalti[21]	1. Children aged 6–10 years old; 2. Parents aged ≤29 years, with low educational level; 3. Rely on information found in the Web/social media; 4. Dislike mandatory vaccination policies.	1. Rely on medical advice; 2. Mandatory vaccination policies.	Acceptance
	–	Followed personal beliefs, Web/social media, or celebrities	Hesitancy
Xiao Wan[22]	1. Female parents; 2. High risk for their children to COVID-19; 3. Often pay attention to the COVID-19 vaccine–related information; 4. Believed in the safety of the COVID-19 vaccine; 5. Thought the COVID-19 vaccine could prevent COVID-19.	1. Worried about their children being infected in the future; 2. Spreading the virus to people around them; 3. Quarantined after being infected; 4. Believed in the safety and effectiveness of vaccines.	Acceptance
	–	1. Vaccine side-effects, safety, and effectiveness; 2. Had contraindication to vaccination.	Hesitancy
Haifa Aldakhil[23]	1. Not know where to get vaccination; 2. Not know where to access good/reliable information; 3. Not think vaccine was effective and necessary; 4. Not think the vaccine was safe or concerned about side-effects; 5. Someone else told their child had a bad reaction and was not safe; 6. Heard or read negative media associated with vaccine hesitancy toward childhood immunizations.	–	Hesitancy
S. Evans[24]	–	To parent is to protect, for children have health issues	Acceptance
	Lower trust in doctors	1. Vaccine risks were higher and benefits are lower; 2. To parent is to protect, for child's ill health would be further compromised; 3. Unclear advice.	Hesitancy
Meltem Yılmaz[25]	1. Parents are healthcare workers; 2. Parents' willingness to receive the vaccine and positive attitudes (participate in the COVID-19 vaccine trial, participate in the COVID-19 vaccine trial, etc.).	1. Need for COVID-19 control; 2. The benefits of the COVID-19 vaccine outweighing its potential harm; 3. To protect their own families and others.	Acceptance
	–	1. Lack of sufficient scientific studies; 2. Concerned about safety and side-effects; 3. Potential inefficacy of the vaccine due to mutations.	Hesitancy
Nuno Fernandes[26]	Positive beliefs and attitudes toward the vaccine	–	Acceptance
	–	Possible adverse side-effects effectiveness of the vaccine	Hesitancy
Chloe A. Teasdale[27]	Children attend in-person school or daycare	–	Acceptance
	1. Female parents; 2. Non-Hispanic Black parents.	1. Safety and effectiveness of COVID-19 vaccination; 2. Children are at low risk; 3. Medical; 4. Religious or philosophical reasons.	Hesitancy
Chloe A. Teasdale[28]	Asian parents	–	Acceptance Hesitancy

	1. Female parents; 2. lower education; 3. Household income $25,000.	1. Potential safety and effectiveness; 2. Children are at low risk; 3. Religious or medical reasons.	
Takeshi Yoda[29]	Parents' willingness to get themselves vaccinated	–	Acceptance
	–	Vaccine side-effects, vaccine safety, and effectiveness	Hesitancy
Mateusz Babicki[30]	1. Female parents; 2. Older parents; 3. Parents are healthcare workers; 4. Parents vaccinated themselves against COVID-19; 5. Mandatory vaccinations; 6. History of vaccinations in child; 7. COVID-19 vaccination campaign for children; 8. Assessment of COVID-19 severity and the risk among children.	–	Acceptance
	1. COVID-19 vaccination was unsafe for children; 2. The same applies to the number of concerns.	1. Concerned about complications that may arise in the future; 2. The effectiveness of the preparation used.	Hesitancy
Pierre Verger[31]	1. Trust in institutions, sensitivity to social pressure, and general favorability to vaccination (for adolescents); 2. Low perception of the risks of COVID-19 vaccines, general favorability to vaccination, and sensitivity to social pressure (for school children); 3. General favorability to vaccination, fear of contracting COVID-19, and trust in institutions (for preschoolers).	–	Acceptance
Leonardo Evangelista Bagateli[32]	1. Parents' young age; 2. ≥2 children in the house; 3. Lower educational level; 4. Low household income.	Serious side-effects and safety of the vaccines	Hesitancy
Mei-Xian Zhang[33]	1. Female parents; 2. Younger child; 3. Lower scores of knowledge about COVID-19 vaccination; 4. Lower awareness of the permission of vaccinating children; 5. Hesitancy to inoculate themselves.	–	Hesitancy
Stefano Zona[34]	–	1. Confidence on safety and efficacy of pediatric vaccines; 2. Confidence in health institutions.	Acceptance
	1. Parents aged ≤40 years; 2. Parents with a secondary school or three-year degree; 3. Parents are freelancers; 4. Family income <€28,000; 5. An erroneous perception of the risk of COVID-19 as the disease.	–	Hesitancy
Jian Wu[35]	1. Married; 2. Total family income last year between 9 and 14 ten thousand; 3. Rejected to Category 1 vaccines; 4. Accessed information about the COVID-19 vaccines from community workers; 5. Low COVID-19 vaccine conspiracy; 6. Guardian's vaccination behavior; 7. The importance of vaccinating teenagers.	1. Prevention of COVID-19; 2. Vaccines free of charge.	Acceptance
	1. Worried about the safety of general vaccines; 2. Low trust in doctors; 3. Vaccine developers.	1. Teenagers' young age; 2. Worried about the safety of vaccines; 3. Believed that the risk of infection was low.	Hesitancy
Yunyun Xu[36]	In Shandong: 1. Female parents; 2. ≥2 children raised. In Zhejiang: 1. Rural residence; 2. ≥2 children raised.	1. If the vaccine was proven to be safe; 2. A low risk of side-effects; 3. For reducing the risk of COVID-19 infection.	Acceptance
	In Shandong: 1. Yearly household incomes ≥120,000RMB; 2. Parents were medical workers; 3. General attitudes of Parental Attitudes toward Childhood Vaccines (PACV). In Zhejiang: 1. Behavior; 2. Safety and efficacy; 3. General attitudes of PACV.	Vaccine side-effects, unknown effects, and effectiveness	Hesitancy
Mohammed Samannodi[37]	–	1. Adequate information about vaccines; 2. Compulsory vaccination.	Acceptance
	≥5 children raised	1. Poor awareness about the effectiveness of the vaccine on children;	Hesitancy

(*continued on next page*)

Table 2 (*continued*)

First author	Related factors	Related reasons	Acceptance/hesitancy
		2. Vaccine approval process was fast, so the safety of the vaccine was not assessed adequately; 3. Heard that blood clots were a common side-effect of the vaccine.	
Mohamad-Hani Temsah[38]	1. Parents received the COVID-19 vaccine themselves; 2. Kids were aged 12–18 years; 3. Older parents; 4. Had an educational level of high school or less; 5. Native; 6. Relied on the Saudi MOH website information.	–	Acceptance
	1. Parental COVID-19 hesitancy; 2. Parents are healthcare workers; 3. Parents were hesitant about the COVID-19 vaccine.	1. Inadequate safety information; 2. Worried about side-effects.	Hesitancy
Britt McKinnon[39]	1. Annual household income <$100,000; 2. Non-nationals; 3. Racialized parents.	1. Lack of information about the vaccine safety and potential side-effects; 2. Believed that their child would not get seriously ill from COVID-19.	Hesitancy
Sarah Musa[40]	1. Younger children; 2. Non-nationals; 3. Previously COVID-19 infected.	–	Hesitancy
Yulia Gendler[41]	1. COVID-19 vaccination status of the participants; 2. Higher mean levels of vaccine literacy; 3. More positive perception of the vaccine; 4. Lower perceived vaccine hesitancy.	–	Acceptance
Konstadina Griva[42]	1. Male parents; 2. Individuals with lower risk perception of COVID-19; 3. Lower perceived benefits of the vaccines; 4. Higher vaccination concerns and perceptions of higher personal necessity for the COVID-19 vaccine.	–	Hesitancy
Sayaka Horiuchi[43]	1. Trusted in sources of COVID-19 related information other than government/public organization or public news media; 2. Female gender either of parent or child; 3. Parents aged <34 years; 4. Lower household income; 5. Parents are unemployed; 6. Lower perceived risk of infection; 7. Younger children; 8. Mothers with lower satisfaction to social relationships.	COVID-19 vaccines adverse reaction and safety	Hesitancy
Soo-Han Choi[44]	1. High confidence of COVID-19 vaccines safety; 2. Parents' willingness to vaccinate themselves; 3. Awareness of the need for children's COVID-19 vaccination.	–	Acceptance
	History of tested for COVID-19 in themselves or family members	–	Hesitancy
Mina Fazel[45]*	1. From deprived socio-economic contexts; 2. Higher rates of home rental vs. homeownership; 3. School locations were more likely to be in areas of greater deprivation; 4. Smoke or vape; 5. Spent longer on social media; 6. Felt that they did not belong in their school community; 7. Lower levels of anxiety and depression.	–	Hesitancy
Don E. Willis[46]*	Spent more hours of TV watched during school days	–	Hesitancy
Adam A. Rogers[47]*	1. Older adolescents; 2. More education; 3. Higher income; 4. Asian American and Latinx youth; 5. More COVID-19-related anxiety; 6. High vaccine-related concerns; 7. Parent and peer vaccination norms.	–	Acceptance

Anna Zychlinsky Scharff[48]*	Concerned about the safety and efficacy of the vaccine 1. Older adolescents; 2. Parents or guardians with no college educated.	Vaccine's perceived safety –	Hesitancy Acceptance
Elke Humer[49]*	1. Migration background; 2. Female adolescents.	–	Hesitancy
Ateret Gewirtz-Meydan[50]*	1. Older adolescents; 2. Had both parents vaccinated; 3. Social media use. Higher distress over the effects of the vaccine	– 1. Not know enough about the harms that a vaccine has in the long run; 2. Not trust the drug companies that the vaccine will be safe; 3. Believed the virus is not dangerous; 4. Doubt the safety of the vaccine in the short term.	Acceptance Hesitancy

*Influencing factors for adolescent population; the rests are adults or parents.

before (64.20% vs. 49.43%). This shows the official vaccination programs' influence on the public, and the public attitudes toward vaccination will also change over time. Even if vaccination for adolescents was approved, the results about vaccination intention remained not high. A low COVID-19 vaccination rate cannot satisfy the herd immunity criteria, which may prolong the pandemic. In the later stage, providing multiparty publicity or intervention measures is the key to improving vaccination.

Clarifying factors affecting vaccination intention is the key to improving children's vaccination coverage. Thirty-four studies reported the influencing factors or reasons associated with vaccination intention. These results may play a specific role in developing immunization plans and controlling COVID-19 pandemic.

In sociodemographic characteristics' factors of the high frequency, parents' and adolescents' age, gender, and education level were related factors affecting vaccination and hesitant vaccination. Nehal's research[52] also mentioned the three. Older adolescents or parents were associated with receiving vaccines. Whereas, we can formulate publicity strategies according to the vaccinated objects' age, such as increasing publicity frequency for younger people and strengthening health education for parents with lower grade children. Next, females were also an important factor in receiving and hesitating vaccination. Due to the critical position of women in decision-making on children's vaccination, we should consider them in the development of the vaccine promotion strategies.[53] Moreover, parents with low educational levels were associated with hesitation to vaccinate, and these populations also need to be considered when formulating vaccination plans. We can improve their understanding through the internet, television, other media, and home visits by community service center staffs.[54]

Parents' willingness to get themselves vaccinated was the most common factor affecting acceptance and hesitancy for the vaccine's cognition and behavior characteristics. People with negative attitudes or low confidence in vaccines also caused vaccine hesitation. Healthcare centers should improve the cognition, behavior, and attitudes of vaccinated people and carry out regular public education activities to effectively improve the acceptance rate of vaccines.[55] In addition, taking the influenza vaccines' histories was relevant in accepting the vaccine. Parents who have previously vaccinated adolescents with influenza had a higher acceptance of the vaccine, providing us with relevant experience. We also could identify and implement multilevel strategies about COVID-19 relying on influenza's experience to maximize COVID-19 vaccination rates.[56] Second, among the reasons for qualitative data, parents or adolescents accepted vaccines because they relied on medical advice and considered that it could contribute to control of COVID-19. However, there are many ways to get medical advice. Especially in the age of information explosion, it is difficult for people to distinguish obtained information's accuracy and timeliness. Therefore, the official departments and media should strengthen the publicity to ensure that adolescents and parents get correct and adequate information about COVID-19 vaccination.[54,57] Another result was people's cognition and understanding of childhood vaccination. Some refused vaccination because they deemed children were at low risk, and others accepted for fear of infection among their children. According to current studies, the advantages of COVID-19 vaccine outweighed the disadvantages. Therefore, improving parents' knowledge and cognitive ability is also necessary to enhance vaccination rate.[58] Next, the pandemic risk rate in the study area was also the basis for parents' choice, which we should consider in promoting vaccines. Different vaccination rates should be planned for different strategies and strive for full coverage. Moreover, some people refused vaccination because of their personal beliefs, whereas relevant departments can seek help from religious or ethnic institutions to reduce the conspiracy

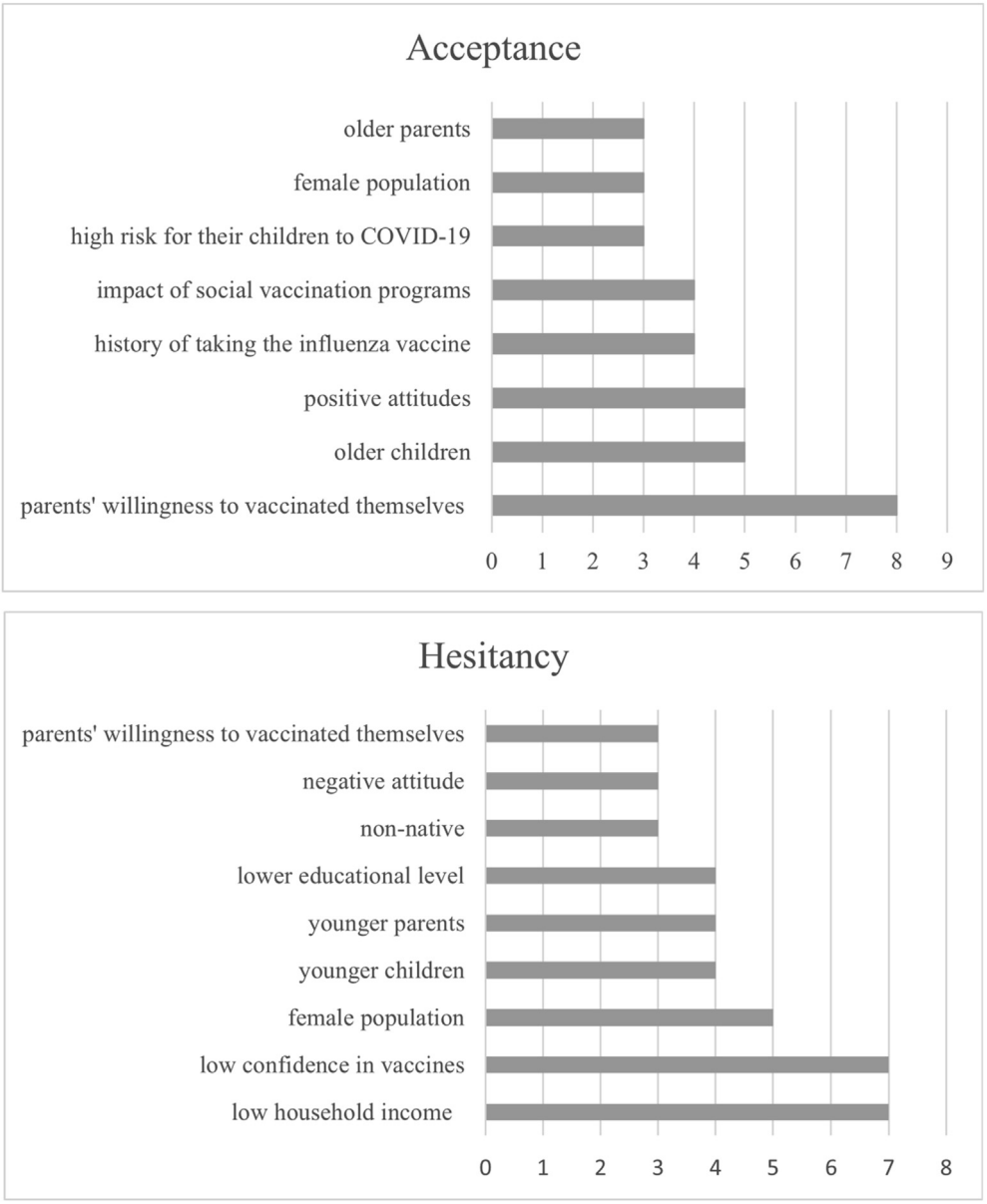

Fig. 2. Factors associated with the vaccine acceptance and hesitation.

theories spread and implement the immunization plans as far as possible on-premise of respecting beliefs.[59]

Vaccine characteristics were essential factors affecting parents' or adolescents' attitudes among the vaccination reasons. One of the characteristics that people were concerned about the most was COVID-19 vaccines' safety and efficacy. There has been sufficient evidence about the vaccines' development and application in the population. Nevertheless, most hesitant people mentioned the lack of evidence. In addition to the inconvenience of personal communication, healthcare departments should increase publicity and follow-up of COVID-19 vaccine knowledge to ensure that parents and adolescents have adequate and correct access to information, including advertisements on “we media” and streaming media.[54] Similarly, although some people were encouraged to receive COVID-19 vaccine through compulsory and free policies, most people hesitated to get the vaccine because of side-effects. However, most reported adverse events in children were mild and transient, and <1% of children needed medical care.[60] Hence, it is imperative to make adolescents and parents trust healthcare centers and increase their vaccines’ recognition to improve the vaccination rate.[61]

Limitations

Based on this, we summarized and sorted out published studies. Although our results reported the global data, there may be insufficient inclusion and loss of data as languages are all in English. Second, almost all studies included were cross-sectional surveys, which cannot track and update the public opinions and lead to limitations in our inference. Moreover, some studies did not detail specific situations for children of different ages. Still, they contained infants' and young children's data, which may impact results. Future research could focus more on COVID-19 vaccines'

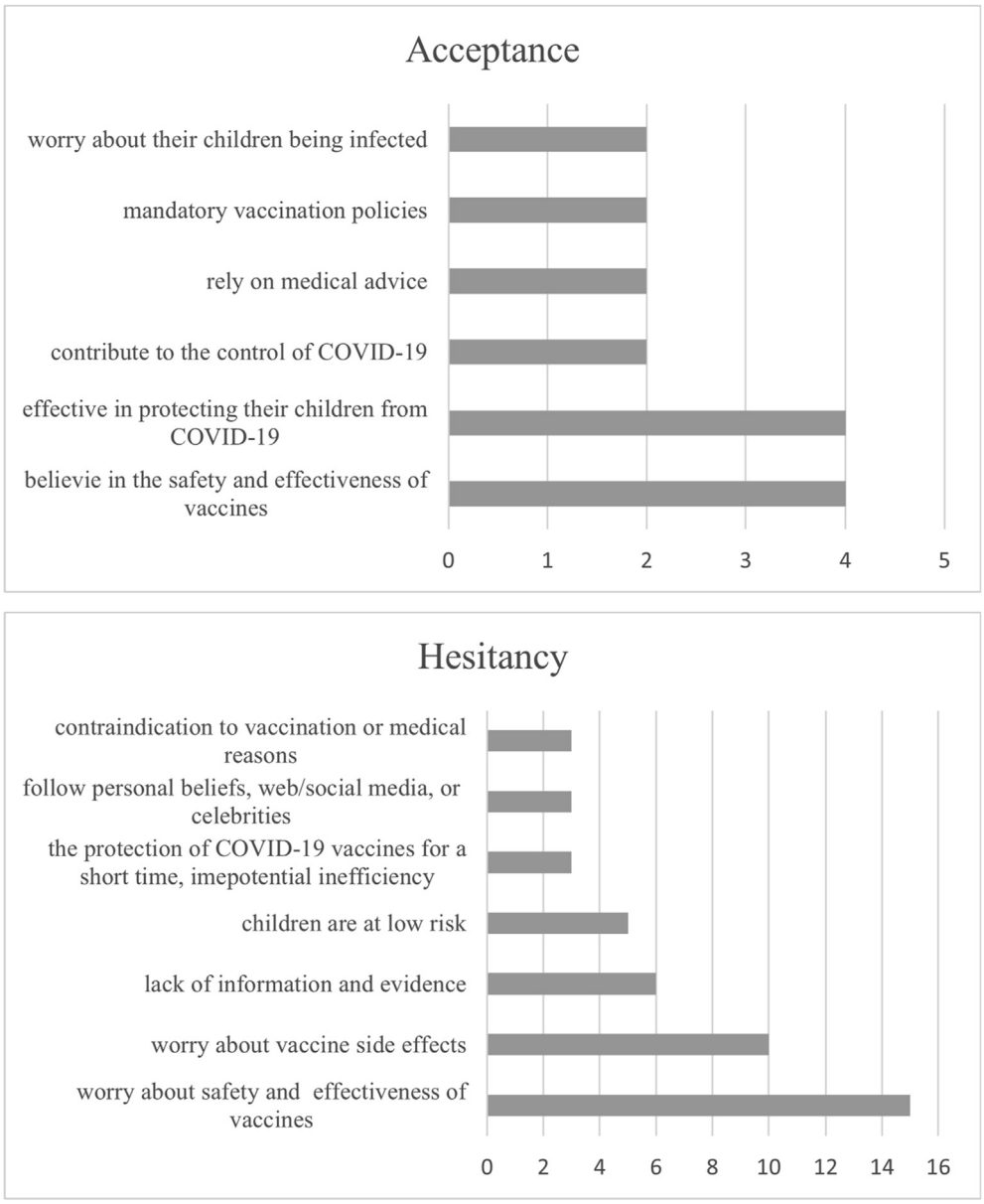

Fig. 3. Reasons associated with the vaccine acceptance and hesitation.

development and application in special crowds to improve produced vaccines' utilization rate.

Conclusions

The above stated the acceptance rate and influencing factors toward COVID-19 vaccination for children or adolescents among adults, parents, and adolescents. The survey data showed that people's willingness to vaccinate children was weak. At the same time, the vaccine's cognition, behavior, and vaccine characteristics were the central influencing factors. Thus, the government should base on scientific data and fully consider individual experiences during the vaccine promotion.[62] The specific situations shall be analyzed and improved according to local and individual conditions. In the future, we can mobilize multiple sectors (healthcare centers, communities, schools, etc.) to improve vaccination rates by providing multilevel interventions for children and parents, controlling COVID-19 pandemic's development as soon as possible, and returning to everyday life.

Author statements

Ethical approval

None sought.

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Competing interests

None declared.

Informed consent statement

Not applicable.

Data availability

The author confirms that all data generated or analyzed during this study are included in this published article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.02.002.

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Original Research

Reasons for participation and non-participation in colorectal cancer screening

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ABSTRACT

Objectives: The aim of the present analysis is to identify the reasons for accepting or rejecting the invitation to be screened by the Faecal Immunochemical Test as part of the free Danish screening programme for colorectal cancer (CRC).
Study design: A cross-sectional representative survey of 15,072 Danish citizens aged 50–80 years was collected in 2019 via a Web-based questionnaire administered by Statistics Denmark. Among the net sample of 6807 respondents (45%), 177 were excluded because of current treatment for colorectal disease.
Methods: To determine the reasons for accepting or refusing the invitation to be screened for CRC, a latent class analysis was conducted, which allowed participants to provide several reasons for acceptance or rejection of screening.
Results: The most important reason for participating in CRC screening was the active public programme. A further reason for participation was the perceived risk for CRC, mainly in combination with the public programme. The reasons for participation did not differ between individuals who had participated and those who intended to participate when offered. Among participants who declined screening, the most frequent reasons were that they forgot to participate or that they were concerned about the unpleasant test procedure. Among individuals who intended to decline screening, a perceived low risk for CRC was the most frequently cited reason.
Conclusions: Recommendation from a general practitioner (GP) was not given as a frequent reason for CRC screening participation which is discussed as a challenge to participation rates in population based screening program The main reasons reported for non-participation in CRC screening (i.e. forgot to participate or the unpleasant test procedure) might be addressed by a stronger endorsement from GPs.

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer worldwide and accounts for 10% of all new cases of cancer. Furthermore, it is the fourth most common cause of death from cancer.[1] In Denmark, the overall age-standardised incidence of colon cancer is 22.6 per 100,000 population and rectal cancer is 13.0 per 100,000 population. CRC impacts men and women equally, and the risk increases with age. However, recent studies have shown that the incidence of CRC is increasing in younger age groups, particularly in high-income countries. These findings highlight the importance of early detection strategies[2] because survival depends on the stage at which cancer is diagnosed, with later-stage diagnosis leading to poorer survival chances.[1]

In Denmark, all citizens aged ≥50 years are invited to participate in screening for CRC every 2 years. Participation is free of charge, and the invitation for the Faecal Immunochemical Test (FIT) is sent by ordinary mail, including information on incidence and treatment options, a graphics-supported instruction on sampling, all material needed for the faecal test and a prepaid return envelope.[3] If the FIT indicates the presence of blood in faeces, individuals are subsequently invited to a free colonoscopy at their local hospital. Despite the free screening programme, around 40% of Danish citizens do not participate when they are initially invited.[4]

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A systematic review on participation in publicly available CRC screening programmes summarised the barriers to screening as 'fear of cancer', 'not knowing how to conduct the test', 'mental health' and 'lack of knowledge about the test', and the facilitators to screening as 'being supported by general practitioners (GPs)' and 'knowing someone who has participated in the CRC screening programme'.[5] A study from the United States reported that the two main reasons for not participating in a screening programme based on guaiac-based Faecal Occult Blood Test (g-FOBT) were not wanting to handle stool and not wanting to keep the cards with the stool sample in the hands,[6] a result that was also reported from Saudi Arabia.[7] Similar results were reported in two previous UK studies.[8,9] A more recent Scottish study compared perceptions about the g-FOBT with those about the newer FIT test, which requires only single-time sampling and the stool is stored in an opaque plastic test.[10] In this study, respondents perceived FIT as more convenient and less unpleasant to handle than the FOBT. However, some information appears to indicate that the FIT procedure may continue to be a reason for rejecting the screening as people feel uncomfortable taking a faecal test.

Another consistent finding is that physicians' recommendation to participate leads to an increase of uptake.[11–13] Analysis from the 2000 US national health survey interview suggests that low screening participation appears to be because of lack of awareness and inadequate health provider counselling, rather than poor patient acceptance.[14]

Health literacy and knowledge about the risk for CRC play complex roles in the decision to participate in CRC screening. A systematic review on health literacy in screening found only limited evidence for the relationship between health literacy and CRC screening.[15] In a nationwide survey from Saudi Arabia, where participants were asked about knowledge and intention to participate in CRC screening, no significant correlation was found between knowledge and willingness to undergo screening. However, a systematic review on the factors affecting patients' adherence to publicly funded CRC screening found that perceived relevance of CRC screening is the most important factor within the subthemes of knowledge and relevance, which was mentioned in 13 studies.[5]

Many of the previous studies on CRC screening have been based on the more demanding FOBT procedure and have had small numbers of participants, which has limited the possibilities of studying the relative importance of different barriers and facilitators. The aim of the present analysis was to identify the reasons for accepting or rejecting the invitation to be screened for CRC by FIT.

Methods

This study used a cross-sectional survey based on a representative group of 15,072 Danish citizens aged 50–80 years. Data were collected in 2019 through a voluntary Web-based standardised questionnaire (see online supplementary material) administered by the official Danish data authority (Statistics Denmark, www.DST.dk), and sociodemographic data were obtained from a national registry. Two reminders were sent through digital mail. Representativity is gained by using the random sample method, and anonymity is ensured as no identifiable personal data were provided from Statistics Denmark. Among the gross sample, 6807 persons (45%) returned a completed questionnaire. Of these, 6185 had been offered screening for CRC, whereas 622 reported not having received a screening offer. Within these groups, a total of 177 participants were subsequently excluded because of ongoing treatment for colorectal disease (see Fig. 1). All analyses are based on either the 6008 respondents who had been offered screening or the 622 individuals who had not been offered screening.[3]

According to the Act on a Biomedical Research Ethics Committee System in Denmark, the project was not a biomedical research project and did not need an ethics committee's approval. Data include information that could potentially identify individuals, and the project is therefore registered at the University's Research and Innovation Office (SDU-RIO: 10.155), and data handling is in accordance with the General Data Protection Regulation from (EU) 2016/679.

The main outcome variable was uptake of the screening invitation, which was asked by a single-item question (no/yes). In the group where screening had not been offered, the question was asked if the respondents intended to participate when the screening test was offered (no/yes). Register information included gender, highest educational attainment and age.

The potential reasons for participating or not participating in the CRC screening programme that could be selected by respondents in the questionnaire were developed and pilot tested by the authors and were analysed separately depending on screening participation. The following response options were offered to the respondents who stated that they had accepted or intended to accept the offer for CRC screening: 'I think you ought to participate when the offer is given to you', 'The earlier you start treatment, the better the chance to be cured', 'To reduce the risk of getting CRC, I want to be sure that I am not on my way to get CRC', 'I would regret it, if I said no, and later developed CRC', 'I know several people close to me who have been diagnosed with CRC', 'I believe that my risk for developing CRC is high' and 'My doctor recommended that I should participate'. On the other hand, those who had not participated or had indicated that they did not intend to participate in CRC screening were presented with the following response options: 'I think the risk of a false alarm, and the worries it brings along, is too high', 'There is no one in my closest family diagnosed with CRC', 'I do not want to do the faecal test sample', 'I want to live today and not think about what the future may bring', 'I believe that my risk for developing CRC is small', 'I don't like the thought of potentially having a colonoscopy', 'I don't think the benefits outweigh the harms in this screening offer', 'I am nervous that they will find out that I have CRC' and 'I do not think that the screening will help prevent CRC'. Respondents could choose multiple reasons from the given options as well as fill out an additional open text category ('other reason').

Statistical analyses were conducted using STATA V16. To explain the reasons for accepting or refusing the CRC screening invitation, latent class analyses were conducted so that several interdependent reasons could be selected for acceptance or rejection of the screening test. This analysis involved segmenting the population in mutually exclusive latent classes, where each class contained reasons for participation and non-participation with a similar correlation pattern but dissimilar to those in different classes.[16] One model was used for the reasons for participation in CRC screening among people who participated ($n = 4971$), and another model was used for reasons among non-participants ($n = 1037$). Six latent classes were chosen in both models, according to the smallest value of Bayesian information criterion and the Akaike information criterion.[16]

Results

Of the 6008 respondents who had been offered screening, 52.9% were women, which corresponds with the equivalent Danish population in the selected three age decades (Table 1). Respondents were equally distributed between the three 10-year age groups (between 50 and 80 years of age), and 43.8% of the study population had at least a high school education. Compared with the overall Danish population within the respective age range, the mean age of respondents was slightly higher, and survey participants were

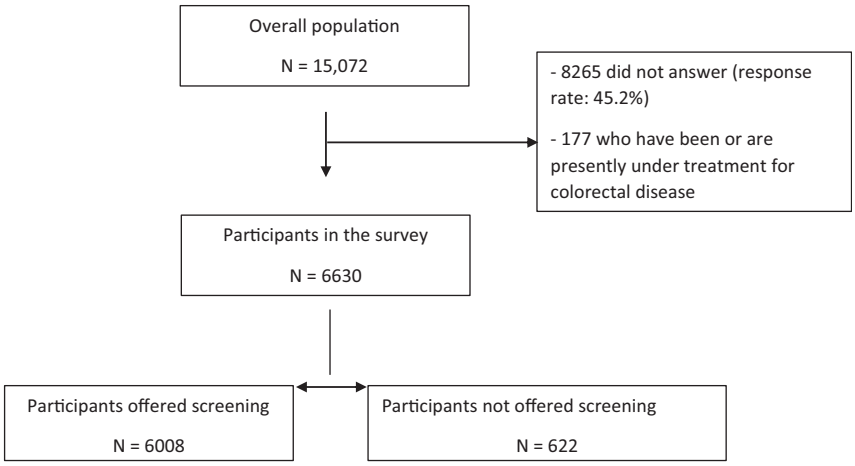

Fig. 1. Study population.

Table 1
Characteristics of the population who received an offer for CRC screening (Subgroup A; n = 6008) and who did not receive an offer for CRC screening (Subgroup B; n = 622).

(A) Subgroup who already had received at least one invitation to CRC screening						
Characteristics	Participants		Non-participants		Total	
	n	%	*n*	%	*N*	%
Overall	4971	82.73	1037	17.27	6008	100.00
Gender						
Female	2701	54.35	475	45.81	3176	52.86
Age group in years						
50–60	1916	38.54	483	46.58	2399	39.93
61–70	1890	38.02	357	34.43	2247	37.40
71–80	1165	23.44	197	19.00	1362	22.67
Education[a]						
Basic school	919	18.49	192	18.51	1111	18.49
High school	2195	44.16	436	42.04	2631	43.79
Vocational	276	5.55	37	3.57	313	5.21
Medium education	1114	22.41	239	23.05	1353	22.52
High education	467	9.39	133	12.83	600	9.99
B) Subgroup who had not received their first invitation to CRC screening						
Characteristics	Intend to accept invitation		Intend to reject invitation		Total	
	n	%	*n*	%	*N*	%
Overall	481	77.33	141	22.67	622	100.00
Gender						
Female	235	48.86	69	48.94	304	48.87
Age group in years						
50–60	166	34.51	29	20.57	195	31.35
61–70	129	26.82	47	33.33	176	28.30
71–80	186	38.68	65	46.10	251	40.35
Education[a]						
Basic school	100	20.79	39	27.66	139	22.35
High school	230	47.82	56	39.72	286	45.98
Vocational	22	4.57	9	6.38	31	4.98
Medium education	92	19.13	24	17.02	116	18.65
High education	37	7.69	13	9.22	50	8.04

CRC, colorectal cancer.
[a] Basic school: primary education; high school: upper secondary education; vocational: technical education and training; medium education: short cycle higher education; high education: long cycle higher education.

slightly better educated. Geographical distribution of birthplace and place of residence within Denmark were similar to the overall Danish population. Additional comparison information is published elsewhere.[3]

When looking at the characteristics of individuals who stated that they had not received the screening offer, no specific educational or age groups emerged. However, considering the subgroup intending to participate when the invitation appeared, participants aged 50–60 years were more likely to respond 'yes' to the screening offer, whereas no association was seen between educational attainment and intention to participate.

In total, 71.5% of all participants indicated that the reason 'I think you ought to participate when given the offer' was relevant for them, making this the most common choice (Table 2). This response was followed by 'The earlier you start treatment, the better the chance to be cured', 'to reduce the risk of getting CRC', 'I want to be sure that I am not on my way to get CRC' and 'I would regret it, if I said no and later developed CRC'; all these single

Table 2
Reasons for participating in screening for CRC (FIT) among those who have been screened (n = 4971) and those who intend to be screened when they get the offer (n = 482).

Reasons for participating	Have been screened (n = 4971)		Intend to be screened (n = 482)	
	n	%[a]	n	%[a]
I think you ought to participate when given the offer	3554	71.5	278	57.7
The earlier you start treatment, the better the chance to be cured	2116	42.6	199	41.3
To reduce the risk of getting CRC	2114	42.5	206	42.7
I want to be sure that I am not on my way to get CRC	1956	39.4	178	36.9
I would regret it, if I said no, and later developed CRC	1832	36.7	167	34.0
I know several people close to me that have been diagnosed with CRC	712	14.3	69	14.3
I believe that my risk for developing CRC is high	108	2.2	12	2.5
My doctor recommended me to participate	103	2.1	15	3.1
Other reasons	64	1.3	20	4.1

CRC, colorectal cancer; FIT, Faecal Immunochemical Test.
[a] Percent is calculated based on the number of individuals giving the reason (multiple reasons allowed).

responses were mentioned by around 40% of survey participants each. The least often mentioned reason (2.1% of participants) was that 'my doctor recommended that I should participate'. The reasons for participation did not differ between individuals who had already been screened and those who were intending to be screened when the invitation arrived.

Among reasons for not participating in CRC screening, 'other reasons' was chosen most frequently (26.0%), followed by 'risk of false alarm' (21.2%), 'no family history of CRC' (18.9%) and 'concerns about the faecal test procedure' (16.0%). When comparing the reasons for non-participation between people who had already received the screening offer and those who intended to reject screening when offered, no differences were observed (Table 3).

Among the 229 non-participants who selected the option 'other reasons', the number of answers provided was 249 (some respondents gave more than one additional reason). The predominant reasons were 'having forgotten to do the test' (21%) and/or 'having been too busy to do the test' (17%). Another 10% explicitly blamed themselves, stating that they had been 'too lazy' or 'too sloppy' or could not 'pull themselves sufficiently together' to get the procedure done, whereas 3% indicated that they had misplaced/lost the sampling equipment. Overall, the group of individuals who claimed that their non-participation in the test was unintentional made up nearly 52% of all responses.

From the latent class analysis for individuals participating in CRC screening, most participants supported the reason 'when the offer is given to you, you ought to participate' (Table 4). In 28% of participants (Class 1), this was the only reason given. In total, 19% of participants stated this reason together with 'the earlier you start treatment, the better the chance to be cured' (Class 4). Further risk-related statements were added to the previously mentioned statements, such as 'To reduce the risk of getting CRC' and 'I want to be sure that I am not on my way to get CRC' and 'I would regret it, if I said no, and later developed CRC', in 22% of participants (Class 5). Furthermore, 6% endorsed all reasons offered and stated additionally that they knew people close to them who had been diagnosed with CRC (Class 6). The statement 'when the offer is given to you, you ought to participate' was not selected as a reason by 20% of participants (Class 3). Finally, 5% of participants chose the response 'I want to be sure that I am not on my way to get CRC' (Class 2).

The results from a latent class analysis for individuals who did not participate in CRC screening showed that 22% of those not participating only chose the reason 'other' (Class 1). In total, 7% stated only that they 'wanted to live today and not think about what the future may bring' (Class 3), whereas 14% were only 'worried about a potential false alarm' (Class 4). No clear pattern emerged in 26% of respondents, but they most often stated that they 'did not want to do the faecal test sample' or 'did not like the thought of potentially having a colonoscopy' (Class 2). In 7% of respondents, several statements were selected, including that 'there is no one in my closest family diagnosed with CRC', that they were 'concerned about false alarm' and that they believed that 'my risk for developing CRC is small' (Class 6; Table 5).

Discussion

The main reason for participation in the CRC public screening programme was the fact that the screening was offered (cited by 72% of screening participants). The results from the latent class analysis showed that in 28% of respondents, this was the only reason for participation; in 41% of respondents, this rationale was mentioned in combination with other reasons connected to risk

Table 3
Reasons for not participating in screening for CRC (FIT) among those who have received the offer to be screened and rejected participation (n = 1037) and those who intend not to be screened when they received the offer (n = 141).

Reasons for not participating	Rejected screening (n = 1037)		Intend to reject screening (n = 141)	
	n	%[a]	n	%[a]
Other reasons	270	26.0	13	9.7
I think the risk of a false alarm, and the worries it brings along, is too high	220	21.2	22	16.4
There is no one in my closest family diagnosed with CRC	196	18.9	37	27.6
I do not want to do the faecal test sample	165	16.0	8	6.0
I want to live today and not think about what the future may bring	159	15.3	28	20.8
I believe that my risk for developing CRC is small	135	13.0	29	21.6
I don't like the thought of potentially having a colonoscopy	123	11.9	14	10.4
I don't think the benefits outweigh the harms in this screening offer	93	9.0	13	9.7
I am nervous that they will find out that I have CRC	75	7.2	8	6.0
I do not think that the screening will help prevent CRC	68	6.6	14	10.4

CRC, colorectal cancer; FIT, Faecal Immunochemical Test.
[a] Percent is calculated based on the number of individuals giving the reason (multiple reasons allowed).

Table 4
Latent class analysis[a] about the reasons for participation among individuals who were screened for CRC when screening was offered (n = 4971).

Probability	Class					
	1	2	3	4	5	6
	0.28	0.05	0.20	0.19	0.22	0.06
Reasons						
I think you ought to participate when the offer is given to you	**1.000**	0.192	0.000	**0.999**	**0.836**	**0.902**
The earlier you start treatment, the better the chance to be cured	0.000	0.000	0.278	**0.548**	**0.948**	**0.992**
To reduce the risk of getting CRC	0.000	0.0174	0.412	0.454	**0.917**	**0.944**
I want to be sure that I am not on my way to get CRC	0.000	**0.999**	0.134	0.430	**0.822**	**0.854**
I would regret it, if I said no, and later developed CRC	0.000	0.000	0.224	0.470	**0.804**	**0.959**
I know several people close to me that have been diagnosed with CRC	0.002	0.020	0.169	0.204	0.082	**0.818**
I believe that my risk for developing CRC is high	0.001	0.000	0.021	0.018	0.000	0.221
My doctor recommended me to participate	0.003	0.002	0.037	0.026	0.009	0.091
Other reasons	0.003	0.003	0.039	0.013	0.003	0.017
Explanations	It is offered	I want to be sure	Only individual risk-related explanations	It is offered and one risk-related explanation	It is offered and more than one risk-related explanation	It is offered, and it reduces the risk and someone in my family has CRC

CRC, colorectal cancer.
[a] Item response probability (bold values indicate item response probability within each class of >0.50.).

Table 5
Latent class analysis[a] about reasons for non-participation among those not participating in screening for CRC when offer was received (n = 1037).

Probability	Class					
	1	2	3	4	5	6
	0.22	0.26	0.07	0.14	0.24	0.07
Reasons						
Other reasons	**1.000**	0.012	0.008	0.051	0.089	0.095
I think the risk of a false alarm and the worries it brings along, is too high	0.000	0.083	0.000	**0.999**	0.000	**0.765**
There is no one in my closest family diagnosed with CRC	0.007	0.114	0.000	0.064	0.340	**0.999**
I do not want to do the faecal test sample	0.017	0.430	0.000	0.064	0.079	0.243
I want to live today and not think about what the future may bring	0.000	0.095	**1.000**	0.127	0.082	0.305
I believe that my risk for developing CRC is small	0.000	0.030	0.000	0.019	0.304	**0.691**
I don't like the thought of potentially having a colonoscopy	0.000	0.273	0.000	0.149	0.040	0.263
I don't think the benefits outweigh the harms in this screening offer	0.000	0.024	0.012	0.136	0.179	0.304
I am nervous that they will find out that I have CRC	0.003	0.228	0.047	0.024	0.010	0.055
I do not think that the screening will help prevent CRC	0009	0.034	0.016	0.087	0.112	0.245
Explanation	Forgot	Don't like the procedure	Living today	Worries about false alarm	No clear structure in reasons	No personal connection own risk and worries of false alarm

CRC, colorectal cancer.
[a] Item response probability (bold values indicate item response probability within each class of >0.50.).

reduction in getting CRC. This observation is supported by results from other countries where screening is not publicly offered and by studies that have found one of the major barriers for participation to be access to free screening.[13–15,17,18]

The reasons for accepting the invitation to the public screening programme did not differ between individuals who had already participated and those who intend to participate. In addition to the screening invitation, risk estimates (reduce the risk, a better chance to be cured) were frequently mentioned as reasons for participation, mostly in combination with the screening invitation. This supports the fact that knowledge and risk estimation of CRC risk are important and a constant driver of participation and intention to participate in CRC screening. Understanding risk estimates is complex and requires advanced health literacy. There is only limited knowledge available on the association of health literacy and cancer screening. One systematic review suggests that health literacy may be a contributing factor for participation in cancer screening; however, evidence is still lacking, and the review concluded that further studies are necessary.[15]

In the present study, recommendation from GPs to participate in the screening programme was not a major reason to participate. This result is in contrast with findings reported by other studies that report inadequate health provider counselling, rather than poor patient acceptance, to be a factor that hampers screening.[14] Also, complete absence of a screening recommendation from physicians is often mentioned as a major barrier to participation.[19,20] However, these results cannot be directly compared with the present data. The current results only provide information about whether respondents perceived a physician recommendation as subjectively relevant to their participation decision. An explanation of the apparent missing association might be that the Danish mail-based screening invitation basically cuts out the GP as the patients' counsellor. With this exclusion, the impact of GPs on CRC screening participation via support and involvement in recruiting participants[5] was precluded. In other studies, it is well documented that a patient-specific reminder or endorsement from a GP has a positive impact on participation rates.[21,22] Furthermore, GPs who support screening programmes are regional promoters to

improve participation.[23] In support of this observation, a study on non-participants in CRC screening found that an endorsement letter or text message from their own GP did encourage participation in individuals who otherwise forgot, procrastinated or were reluctant to collect a stool sample.[24] To enhance knowledge about screening and allow evidence-based decisions about participation, it is important to consider GPs in the process. One possibility would be to inform GPs when patients are invited for CRC screening. In addition, patients' invitations to CRC screening should more clearly suggest that they can contact their GP if they are in doubt about what to do.

For those choosing not to participate in CRC screening, no clear structure indicating one or two homogeneous types of reasons could be identified. One important reason mentioned by people who had already rejected participation was that they forgot to conduct the test and send in the sample, which might be in line with a US survey that found patients' beliefs of having 'no time' or being 'too busy' were important factors for predicting participation in CRC screening.[13] It is assumed that this answer is chosen to omit stating any specific reason. In this context, support from the GP might facilitate the decision-making process of the patient.[25] The second most frequent reason for not participating (26%) was the statement that the patient did not like the test procedure. A subgroup analysis of non-participants expressed that if the FIT was replaced by a blood test, approximately 60% of these non-participants would be happy to undergo screening.[3] Furthermore, fears and worries about the false alarm were mentioned as a reason for not participating. Similar barriers were seen in a US survey.[13] However, in contrast to Ely et al.,[13] the present analysis also asked for reasons why respondents intended to refuse participation when they received the invitation for screening. The most important reason for intending to reject screening was an apparent absence of CRC risk in the family and the estimation that one's own risk to develop CRC was small. Some people may correctly estimate that their present risk for CRC is too low to worry about. However, it is essential that the information provided is easy to understand and enables people to correctly estimate their own risks and benefits of screening, and decide individually, correctly and evidence based whether they should participate in the offer to be screened for CRC.

The current results are based on the Danish situation, where a free-of-cost, biannual, national CRC screening programme is established. It can be expected that most survey participants have already thought about the screening method as they had already received an invitation letter. This regular invitation procedure might increase their interest and ability to estimate their personal CRC risk, and therefore, their reasons to participate or not participate in screening might differ from other countries. Scientific literature on reasons for participation and particular non-participation in CRC screening remains scarce, and validated questionnaires are still missing. It would be worthwhile to repeat this survey in other countries to allow a comparison of results.

The main limitation of this study is the cross-sectional design, which does not allow conclusions on causality. Furthermore, the response rate of 46% may suggest a response rate bias, a specific form of selection bias, which might impact the estimated prevalence of participants. However, this response rate is quite high for a population-based online survey, and the sample was comparable to the total Danish population.[3] Moreover, a bias related to a specific attitude towards CRC screening was not present, as the participants did not know that the survey included questions on CRC screening when they entered the survey and drop-outs during answering sessions were almost zero. An implicit risk in self-reported data is that we cannot exclude a social desirability bias among the stated reasons and stated participation in screening. Finally, the list of potential reasons is not a validated questionnaire, and the predetermined list of potential reasons could have been a limitation, despite the extra option (free text) to state 'other reasons'.

Conclusions

The most important reason for participating in CRC screening was the fact that participants received a personal invitation letter offering a free medical service. In addition to the offer of screening, CRC risk was frequently mentioned by participants, mainly in combination with the offer of screening. Including GPs in the Danish CRC screening process could improve the knowledge level among participants who are in doubt of whether to participate. Such involvement may also reduce participation barriers related to forgetfulness, unpleasant test procedures, and false perceptions on individual risk for developing CRC.

This study provides the following conclusions: (1) the personal letter including an invitation to participate in CRC screening, combined with no out-of-pocket payment, is an important driver to support high participation in the programme; (2) risk estimates are important – to allow inclusion of patient preferences in the decision-making process, information needs to be easy to understand and accessible, regarding both benefits and risks (e.g. intestinal damage during colonoscopy related to CRC screening); and (3) the role of GPs in the CRC screening process needs to be endorsed.

Author statements

Ethical approval

The questionnaire study does not involve human biological material. According to the Act on the Biomedical Research Ethics Committee System in Denmark, the project was therefore not a biomedical research project, and the need for consent was waived (Danish Act on Research Ethics Review of Health Research Projects; §14 stk 2, June 2011). Data include information that could potentially identify individuals, and the project is therefore registered at the University's Research and Innovation Office, and data handling is in accordance with the General Data Protection Regulation (GDPR) from (EU) 2016/679.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and materials

The datasets used and/or analysed in the present study are available from the corresponding author on reasonable request.

Author contributions

All three authors (J.B.N., G.B.B. and A.L.) participated equally in the planning, analysing and writing of the article. All authors read and approved the final article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.puhe.2022.01.010.

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Letter to the Editor

Societal reopening after the COVID-19 pandemic

The COVID-19 pandemic is not over, and in many places around the world, populations are either unable or unwilling to be vaccinated, either because of logistical supply issues or because of vaccine scepticism. Despite these problems with vaccination coverage, there are plans to relax social distancing rules and the wearing of masks throughout Europe. This strategy is likely to be followed by many nations around the world; however, it has the potential to reverse gains that have been attained on COVID-19 control thus far.

The continuing emergence of novel viral variants to which the current vaccines (raised against the original alpha variant) are less effective is a distinct possibility. In addition, there remain huge unvaccinated populations, for example, in Africa, India and Brazil, some of whom it is predicted will not be immunised until 2023. Proposals to irreversible relax current COVID-19 control policies in Europe, without global consensus and for a pandemic of this magnitude, therefore seem to be ill-informed.

Globally, there is an escalating counter-reaction to COVID-19 containment protocols as communities start to question ongoing approaches to the pandemic. This is fuelled by either bored or misinformed social media opinion, often in response to confusing public health messages from both medical authorities and governments.

As this new pressure to liberalise COVID-19 containment policy grows, it is likely that populist politicians around the world will give way to the perceived desire for relaxation of the rules from the general public, who now see few good options from their national leaders. Despite a surge in cases across Africa, for example, in Tanzania, a vaccination programme is not taking place.[1] Furthermore, with business continuing as usual in Zambia, most of the population do not use masks or practice social distancing.[2,3] Hybrid approaches in Kenya and Uganda with intermittent lockdowns need to be further evaluated for effectiveness.[2,3] Moreover, Somalia, in the horn of Africa, has abandoned all COVID-19 containment measures, perhaps because governance and implementation systems remain fragile.[1–4] In South America, Brazil has a leadership that is in COVID-19 denial, despite the country being severely impacted by the pandemic. In the East, India is struggling to cope with COVID-19, both in terms of providing acute medical services and an effective vaccination programme.

So, the authors argue that the 'reopening' of countries and the approval of mass travel is driven by new pressures from the public to counter and question current or previous public health policy.[5] With the notable exception of New Zealand and Australia, where case numbers have, not coincidentally, remained low, these issues seem too great for elected politicians to ignore. In the long run, this is foolhardy, given the potential of viral variants to take hold even in the double-vaccinated sections of society.

The authors recommend that governments think carefully about actioning populist policies that counteract evidence-based public health consensus in the global pandemic.

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Original Research

The 1st year of the COVID-19 epidemic in Estonia: a population-based nationwide sequential/consecutive cross-sectional study

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ABSTRACT

Objectives: The objective of this study was to assess the population prevalence of SARS-CoV-2 and changes in the prevalence in the adult general population in Estonia during the 1st year of COVID-19 epidemic.
Study design: This was a population-based nationwide sequential/consecutive cross-sectional study.
Methods: Using standardised methodology (population-based, random stratified sampling), 11 cross-sectional studies were conducted from April 2020 to February 2021. Data from nasopharyngeal testing and questionnaires were used to estimate the SARS-CoV-2 RNA prevalence and factors associated with test positivity.
Results: Between April 23, 2020, and February 2, 2021, results were available from 34,915 individuals and 27,870 samples from 11 consecutive studies. The percentage of people testing positive for SARS-CoV-2 decreased from 0.27% (95% confidence interval [CI] = 0.10%–0.59%) in April to 0.04% (95% CI = 0.00%–0.22%) by the end of May and remained very low (0.01%, 95% CI = 0.00%–0.17%) until the end of August, followed by an increase since November (0.37%, 95% CI = 0.18%–0.68%) that escalated to 2.69% (95% CI = 2.08%–2.69%) in January 2021. In addition to substantial change in time, an increasing number of household members (for one additional odds ratio [OR] = 1.15, 95% CI = 1.02–1.29), reporting current symptoms of COVID-19 (OR = 2.21, 95% CI = 1.59–3.09) and completing questionnaire in the Russian language (OR 1.85, 95% CI 1.15–2.99) were associated with increased odds for SARS-CoV-2 RNA positivity.
Conclusions: SARS-CoV-2 population prevalence needs to be carefully monitored as vaccine programmes are rolled out to inform containment decisions.

Introduction

During the 1st year of COVID-19 pandemic,[1,2] control measures (non-pharmaceutical interventions, including business and school closures, restrictions on movement, total lockdowns, social distancing) were widely implemented to contain the spread of SARS-CoV-2 and have been effective in curbing the COVID-19 epidemic, but they do not represent desirable long-term strategies. The future trajectory of the COVID-19 pandemic hinges on the dynamics of both viral evolution and population immunity against SARS-CoV-2.

Understanding the future trajectory of this disease requires knowledge of the population-level landscape of immunity, generated by the life histories of the SARS-CoV-2 infection or vaccination among individual hosts.[3] The drivers of future COVID-19 dynamics are complex. However, characterisation of the prevaccination

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prevalence, the change of active infections and development of immunity in the population are vital data elements for adequately projecting the future course of the SARS-CoV-2 epidemic and the effect of containment measures.

In Estonia, as of January 31, 2021, 785,333 SARS-CoV-2 (RNA) tests (58,967 per 100,000 population) were undertaken, and a total of 44,208 (3326 per 100,000) COVID-19 cases were confirmed[4,5] (Fig. 1). The confirmed SARS-CoV-2 case rate was the highest among people aged 15–24 years (4120/100,000), followed by the age group 45–54 years (4053/100,000), and lowest among children younger than 10 years (522 and 1279 per 100,000 among 0- to 4-year olds and 5- to 9-year olds, respectively). By January 31, 2021, of all the confirmed COVID-19 cases, 5.6% ($n = 2471$) had been hospitalised for treatment and 0.9% ($n = 419$) had died.[6]

The first case of COVID-19 was confirmed in Estonia on February 26, 2020.[4] A special digital referral system was developed in mid-March 2020 to simplify the referral process.[6] Individuals who were deemed to be at a high risk for the SARS-CoV-2 infection (symptomatic patients referred by family physicians) and frontline staff members (health care, nursing home, social workers, police, border guard officers with a referral letter from their employer) were all eligible for testing. Testing eligibility was relaxed by July 2020.

On March 13, 2020, a set of lockdown rules was implemented—people were allowed to leave their homes at any time so long as they observed social distancing. By June 2020, the restrictions were gradually eased, but physical distancing requirements, that is, the 2 + 2 rule (up to two people can be in a public place together and at least a 2-m distance must be kept from others[7]), have remained in force. In response to the increase of new case notifications since the last week of July 2020, and attributing the new cases to visiting nightclubs and bars, the Police and Border Guard Board imposed bans on night-time alcohol sales from August 7 (in two counties),[8] and since September 25, a nationwide restriction on the sale of alcohol has been in force. Since the beginning of November 2020, additional measures on the workplace (recommendation to work remotely and cancelling all joint events), in public places and in transport (mandatory mask wearing) were implemented.[9] COVID-19 vaccination started in January 2021.[10]

The evidence of the first year of the COVID-19 epidemic is frequently based on the data from symptomatic patients,[11,12] seroepidemiological studies[13] and modelling.[14,15] Most studies are based on small or selected population samples (e.g., hospital admissions) providing data not representative of the community. To the best of our knowledge, large population-based studies needed

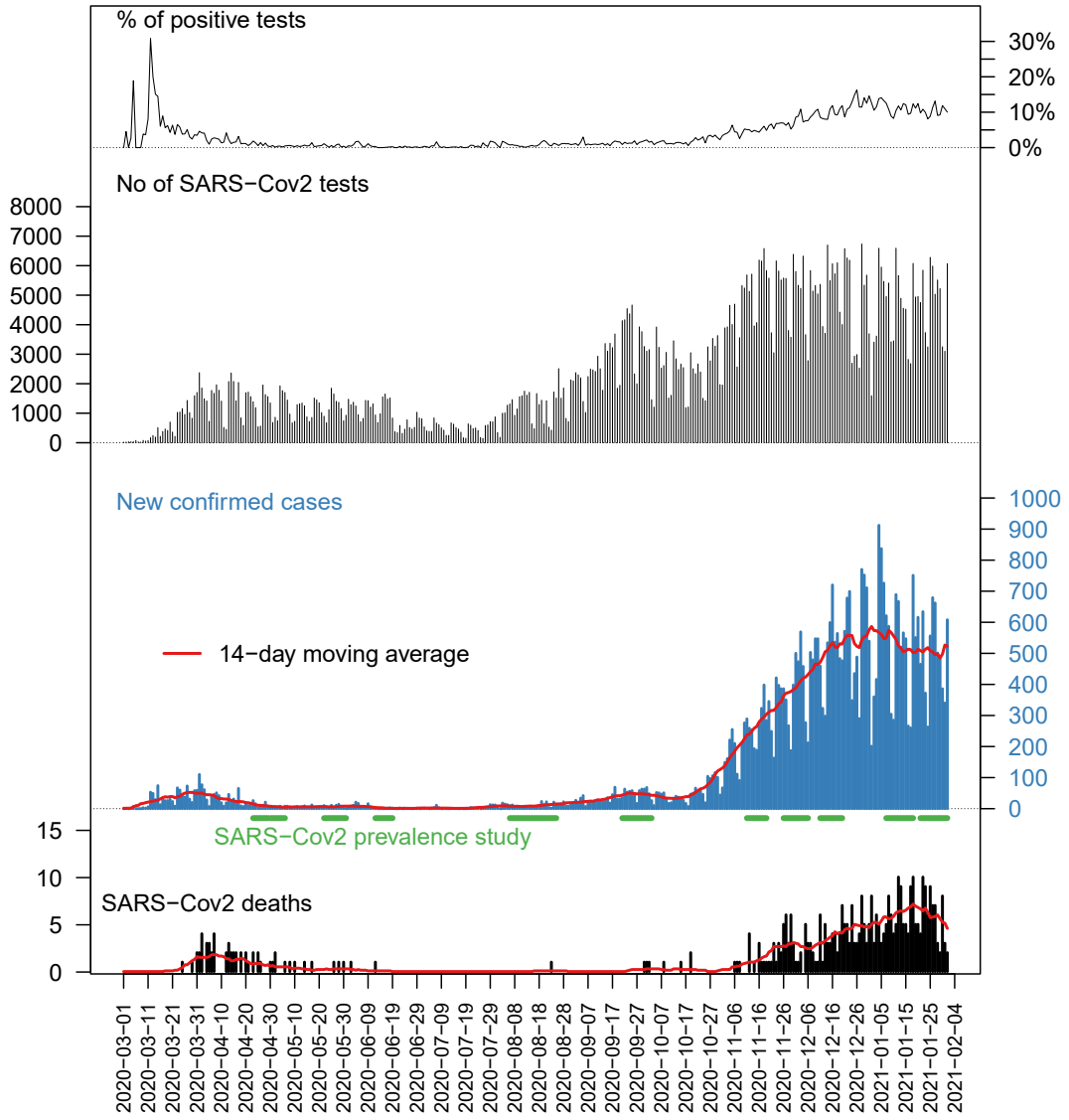

Fig. 1. The COVID-19 epidemic in Estonia: daily numbers of new confirmed cases, the number of tests, proportion of positive tests and the number of deaths, 2020–2021.

to understand risk factors and dynamics and delineate the pre-vaccination course of the COVID-19 pandemic are scarce.[16,17]

In this study, we rely on a national survey designed to be representative of the target population to describe the course of the epidemic over the first year and risk factors for testing positive for SARS-CoV-2 in Estonia (until the end of January 2021).

Methods

Study design

A population-based nationwide sequential/consecutive cross-sectional study was conducted.

Source population

In 2020, the population of Estonia was estimated at 1,326,535 million people (equivalent to 0.02% of the total world population), with 68% of the population living in urban areas. The Estonian language is spoken by roughly 68% of the population, with approximately 28% of the population being Russian speakers.[5] Historically, most of Russians-speaking population is settled in the capital, Tallinn, or the northeastern region of the country (Ida-Virumaa County).[18]

Data source: SARS-CoV-2 community prevalence studies

The data for this work originate from sequential/consecutive nationwide cross-sectional studies. This methodology was chosen on the premise that valid inferences of change in population values can be made on the basis of repeated cross sections within the single population.[19]

The listing of the Estonian Population Registry[20] was used as a sampling frame, and all individuals aged 18 years and older were eligible for study participation.

Using standardised methodology (population-based, random stratified sampling), 11 cross-sectional studies were conducted with data collection during April 23–29, April 30 – May 6, May 22–31, June 11–22, August 6–25, September 21 – October 3, November 11–19, November 26 – December 6 and December 11–20 in 2020 and during January 7–18 and January 21 – February 2 in 2021. For each study, multistage stratified random sampling was used. Primary sampling strata consisted of all counties ($n = 15$), and two most populated cities were considered separately from their respective counties. In each primary sampling stratum, stratified by gender and age (18–39, 40–64 and 65+ years), random samples ($n = 200$ in most regions, $n = 400$ in the three most populated areas) of civilian residents were recruited.

Sample size

The required total sample size for individual SARS-CoV-2 RNA testing studies was estimated based on the upper Clopper-Pearson confidence limit under the assumption of no positive test results. The sample size of 2000 was derived at a 5% level of significance with an upper confidence limit of 0.184%.

Study procedures

Participants were contacted by e-mail (original invitation and up to two reminders) or telephone (for those aged 65 years or older) for completion of a screening questionnaire regarding previous SARS-CoV-2 testing and symptoms of COVID-19. Respondents could take a phone interview in case of any problems with accessing the web questionnaire. A structured questionnaire (based on the instrument recommended by World Health Organization[21]) was used to elicit respondent sociodemographic data, data on the size and age structure of the household, health status and social- and work-related contacts within two weeks before the study.

Referral and registration for SARS-CoV-2 testing at state drive-in sites or home visit by the testing station team (for those study participants unable to access drive-in stations) was undertaken by the study team.

SARS-CoV-2 testing

The nasopharyngeal samples collected were tested for SARS-CoV-2 RNA by quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) at the SYNLAB Laboratory, a private medical laboratory company (SolGent DiaPlexQT Novel Coronavirus (2019-nCoV) Detection Kit CE-IVD). Viral RNA from all samples was isolated within 24 h.

All SARS-CoV-2 test results were entered into the state E-Health service system and communicated back to participants by the authorised staff member of the testing stations. Participants who tested positive for SARS-CoV-2 were required to self-isolate for 14 days since developing symptoms. All those who tested positive were monitored by their own family doctor until recovery.

Statistical analysis

Descriptive statistics (i.e., proportions and means) are presented. SARS-CoV-2 prevalence (the proportion of testing positive) and 95% Clopper-Pearson confidence interval (CI) were calculated, taking into account the sample design. Prevalence rates were calculated using the Estonian population at the beginning of 2020 as a denominator.[17]

A survey-adjusted logistic regression model was applied to explore associations between data collection timing (study round), age, gender, preferred language, region of residence, size and age structure of the household, pre-existing physician diagnosed chronic conditions, body mass index, number of contacts within two weeks before the study and having COVID-19–specific symptoms at the time of study with the SARS-CoV-2 RNA test positivity. Variables identified as statistically significant predictors with a significance level of $P < 0.05$ were inserted into a multivariable logistic model.

We present adjusted odds ratios (ORs) together with the 95% confident estimates. Since the observed prevalence is relatively low (<3%),[22] the ORs found in the logistic regression model approximate the risk ratios reasonably well.

We used the R statistical programming language for the analyses.[23]

The study is registered with the ISRCTN Registry, ISRCTN10182320.

Results

SARS-CoV-2 community prevalence over the first year of the epidemic

A total of 34,915 individuals, including 15,203 males and 19,712 females, participated in the series of cross-sectional studies from April 2020 to February 2021. The age of the study participants ranged from 18 to 96 years (average age = 48.1 years); 85.5% filled the survey in Estonian and 14.2% in Russian language. The average household size among the study participants was 2.7. SARS-CoV-2 prevalence declined at the beginning of the observation period (in April: 0.27%, 95% CI = 0.10%–0.59%; June 2020: 0.00%, 95% CI = 0.00%–0.12%)) and remained low until the end of September 2020

Table 1
Characteristics of the population-based SARS-CoV-2 prevalence studies and respective study participants, Estonia, 2020–2021.

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	Round 7	Round 8	Round 9	Round 10	Round 11
	April 23–29, 2020	April 30 –May 6, 2020	May 22–31, 2020	June 11–22, 2020	Aug 6–25, 2020	Sept 21–Oct 3, 2020	Nov 11–19, 2020	Nov 26–Dec 6, 2020	Dec 11–20, 2020	Jan 7–18, 2021	Jan 21– Feb 2, 2021
Study characteristics											
Total sample	10,209	12,020	21,830	28,034	25,998	22,900	23,187	20,032	23,921	21,063	25,135
Non-contacts (*n*)	4119	6113	12,869	20,133	19,467	15,460	16,322	14,296	17,900	14,957	18,042
Refusals (*n*)	2060	1791	2923	2414	1546	3024	2623	2211	2294	2583	2816
Other non-response (*n*)	1141	981	2538	1615	1813	983	893	688	749	732	1318
Participants (*n*)	2889	3135	3500	3872	3172	3433	3349	2837	2978	2791	2959
SARS-CoV-2 tested (*n*)	2306	2666	2579	2983	2335	2532	2726	2381	2522	2370	2470
Participants characteristics											
Men (*n*, %)	1254, 43.4%	1377, 43.9%	1627, 46.5%	1657, 42.8%	1413, 44.6%	1504, 43.8%	1388, 41,5%	1189, 41,9%	1297, 43,6%	1202, 43,1%	1295, 43,8%
Age (mean, SD, range)	47.7, 15.8, 18-94	46.7, 15.6, 18-94	49.6, 16.7, 18-93	47.5, 15.6, 18-92	47.2, 15.9, 18-94	48.2, 15.8, 18-95	48.7, 15.9, 18-96	49.9, 16.2, 18-94	47.0, 15.8, 18-91	48.1, 16.1, 18-93	48.6, 16.0, 18-93
Size of the household (mean, SD)	2.77, 1.42	2.79, 1.42	2.70, 1.41	2.75, 1.41	2.77, 1.43	2.68, 1.36	2.62, 1.36	2.63, 1.36	2.68, 1.37	2.66, 1.36	2.67, 1.38
Respondent language Russian (yes; *n*, %)	396, 13.7%	432, 13.8%	513, 14.7%	554, 14.3%	380, 12.0%	482, 14.0%	565, 16.9%	411, 14.5%	388, 13.0%	406, 14.6%	428, 14.5%
Smoking (yes; *n*, %)	685, 23.7%	709, 22.6%	762, 21.8%	789, 20.4%	706, 22.3%	681, 19.9%	652, 19.5%	520, 18.3%	600, 20.2%	555, 19.9%	553, 18.7%
Pre-existing chronic disease (yes; *n*, %)	1138, 39.4%	1217, 38.8%	1493, 42.7%	1532, 39.6%	1224, 38.6%	1375, 40.1%	1345, 40.2%	1176, 41.2%	1120, 37.6%	1123, 40.2%	1192, 40.3%
Self-reported COVID-19 symptoms (yes; *n*, %)	1079, 37.4%	1132, 36.1%	1110, 31.7%	1142, 29.5%	1047, 33.0%	1234, 36.0%	1159, 34.6%	1005, 35.4%	1987, 36.5%	939, 33.6%	945, 31.9%
Previous SARS-CoV-2 testing (yes; *n*, %)	143, 4.95%	159, 5.07%	318, 9.09%	308, 7.95%	363, 11.4%	810, 23.6%	1107, 33.1%	1061, 37.4%	1268, 42.6%	1341, 48.1%	1475, 49.9%
Previously tested positive for SARS-CoV-2 RNA (*n*, %)	12, 8.39%	11, 6.92%	16, 5.03%	15, 4.87%	6, 1.65%	14, 1.73%	19, 1.72%	31, 2.92%	43, 3.39%	75, 5.59%	82, 5.56%
SARS-CoV-2 positivity and estimated prevalence											
No of test positives	4	8	2	0	1	5	10	30	31	55	42
Prevalence (%, 95% CI)	0.27% (0.10% –0.59%)	0.17% (0.05% –0.41%)	0.04% (0.00% –0.22%)	0.00% (0.00% –0.12%)	0.01% (0.00% –0.17%)	0.22% (0.08% –0.49%)	0.37% (0.18% –0.68%)	1.34% (0.92% –1.89%)	1.27% (0.87% –1.79%)	2.69% (2.08% –2.69%)	2.05% (1.53% –2.69%)

CI, confidence interval; SD, standard deviation.

Table 2
Risk factors for testing positive for SARS-CoV-2, population-based SARS-CoV-2 prevalence studies, Estonia, 2020–2021.

Variables	Odds ratio (OR)	Lower confidence limit (2.5%)	Upper confidence limit (97.5%)	*P*-value[a]
Data collection timing				
April 23–29, 2020 (base)	1			
April 30–May 6, 2020	0.63	0.13	3.10	
May 22–31, 2020	0.67	0.08	5.39	
June 11–22, 2020	0.00	0.00	0.00	***
Aug 6–25, 2020	0.02	0.00	0.22	**
Sept 21–Oct 3, 2020	0.84	0.16	4.43	
Nov 11–19, 2020	1.44	0.30	6.84	
Nov 26–Dec 6, 2020	5.35	1.25	22.93	*
Dec 11–20, 2020	5.12	1.21	21.73	*
Jan 7–18, 2021	11.07	2.65	46.32	***
Jan 21– Feb 2, 2021	8.48	2.03	35.43	**
Participant Language				
Estonian (base)	1.00			
Russian	1.85	1.15	2.99	*
Size of the household (number of individuals)	1.15	1.02	1.29	*
Reporting symptoms[b] *at the time of study*				
No	1.00			
Yes	2.21	1.59	3.08	***
Region of the country				
Harju County w/o Tallinn (base)	1.00			
Hiiu County	0.91	0.32	2.60	
Ida-Viru County	3.06	1.67	5.59	***
Jõgeva County	0.14	0.02	1.03	
Järva County	0.54	0.14	2.05	
Lääne-Viru County	1.08	0.38	3.04	
Lääne County	0.24	0.05	1.06	
Põlva County	0.13	0.02	1.00	
Pärnu County	0.86	0.37	1.99	
Rapla County	0.38	0.11	1.32	
Saare County	0.93	0.38	2.27	
Tallinn city	1.32	0.74	2.34	
Tartu city	0.87	0.36	2.11	
Tartu County w/o city	0.50	0.17	1.52	
Valga County	0.83	0.19	3.60	
Viljandi County	2.20	0.95	5.12	.
Võru County	1.71	0.74	3.91	

[a] ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.
[b] Participants reporting at least one of the three major symptoms (cough, fever, dyspnoea) or at least two of minor symptoms (fatigue, sputum production, muscle or joint aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea, irritability or confusion).

(0.01%, 95% CI = 0.00%–0.17%) (Fig. 2). Since then, SARS-CoV-2 positivity rates have been increasing from 0.22% (95% CI = 0.08%–0.49%) in September to 1.27% (95% CI = 0.18%–0.68%) in November 2020 and then reaching an all-time high at 2.69% (95% CI = 2.08%–2.69%) by mid-January, 2021. About 34% of individuals (n = 11 879) self-reported experiencing COVID-19 symptoms at study participation (34.8% of participants testing negative, and 52.1% testing positive). Of all people tested for SARS-CoV-2, 190 were RNA-positive (Table 1).

Modelling confirms significant changes in SARS-CoV-2 prevalence over the first year of the epidemic. In comparison to the first survey round (April 23–29, 2020), SARS-CoV-2 RNA prevalence was significantly lower in rounds four (June 11–22: OR = 0.00, 95% CI = 0.00–0.00) and five (August 6–25: OR = 0.02, 95% CI = 0.00–0.22) and started to increase from round 8 (Nov 26 – Dec 6, 2020: OR = 5.35, 95% CI = 1.25–22.9) onward to round 11 (Jan 21 – Feb 2, 2021: OR = 8.48, 95% CI = 2.03–35.4). Furthermore, regions of the country (Ida-Viru County OR = 3.05, 95% CI = 1.67–5.59), increasing number of household members (for one additional OR = 1.15, 95% CI = 1.02–1.29), reporting symptoms of COVID-19 (OR = 2.21, 95% CI = 1.59–3.09) and completion of the survey in Russian (OR = 1.85, 95% CI = 1.15–2.99) were all associated with higher SARS-CoV-2 RNA positivity (Table 2).

Discussion

The nationwide study documents substantial changes in the population prevalence of SARS-CoV-2 RNA in Estonia during the 1st year of the COVID-19 epidemic, with an initial decrease between April and June, 2020. The findings of the post-1st wave of COVID-19 prevalence and decline are in perfect agreement with a community-based SARS-CoV-2 study from England for the period of April to June 2020.[16] In their study, SARS-CoV-2 community prevalence of 0.32% (95% credible interval 0.19%–0.52%) in April 2020 declined to a very low level by the end of June 2020 (0.08%, 95% credible interval 0.05%–0.12%). In Estonia, the short period of very low SARS-CoV-2 prevalence over the summer of 2020 was followed by an initially slow (in September and October) and then escalating increase since November 2020.

This study documents a clear decline in the prevalence of SARS-CoV-2 following the implementation of the nationwide non-pharmacological intervention (NPI) at the beginning of the epidemic. SARS-CoV-2 prevalence remained extremely low for a short period after lifting NPI measures. In the face of mitigation (slowing down transmission) rather than suppression (stopping SARS-CoV-2 community spread) of containment, an exponential increase of new COVID-19 cases occurred at the verge of the 2nd year of the epidemic.

These findings allow us to speculate that, until now, this is a very unforgiving virus. While rigorous and comprehensive NPI measures are clearly effective in stopping transmission, lifting the measures or less stringent implementation will lead to new and sizable outbreaks.

Second, findings from Estonia should be interpreted in the context of the high SARS-CoV-2 testing rate (80,630/100,000),[24] a very low COVID-19 case fatality rate of 0.8% (both, as of March 18, 2021) and no significant excess (all cause) deaths over the first year of the epidemic.[25]

We saw that those with a larger household size were at a higher risk of SARS-CoV-2 infection with no attributable risk either from the age of the individual or from the age structure of the household (very similar to the results of the study from the UK[26]). Ongoing household transmission with occasional spill over to other households could act as an important driver for ongoing transmission[27] and is estimated to be responsible for roughly 70% of SARS-CoV-2 transmission when widespread community control measures are in place.[28]

Our findings of higher SARS-CoV-2 risk among those reporting symptoms characteristic to COVID-19 are clearly not new. Yet, it highlights the need to focus on symptomatic cases rather than mass-testing in the face of resource constraints or competing resource needs (i.e., vaccination). Focus on symptomatic COVID-19 cases has a solid evidence base—the majority of COVID-19 cases are symptomatic (~60–80%)[29] and are significantly more likely to infect their close contacts than their asymptomatic counterparts.[30]

Last but not least, we saw regional and ethnic (main language spoken) differences in SARS-CoV-2 positivity. Disproportionately affected racial and ethnic minority groups have been reported elsewhere (United States,[31] UK,[32]). In Estonia, ethnic disparities are not unique to COVID-19 outcomes.[33] The reasons for ethnic disparities in COVID-19 outcomes are multilayered[32] and underline

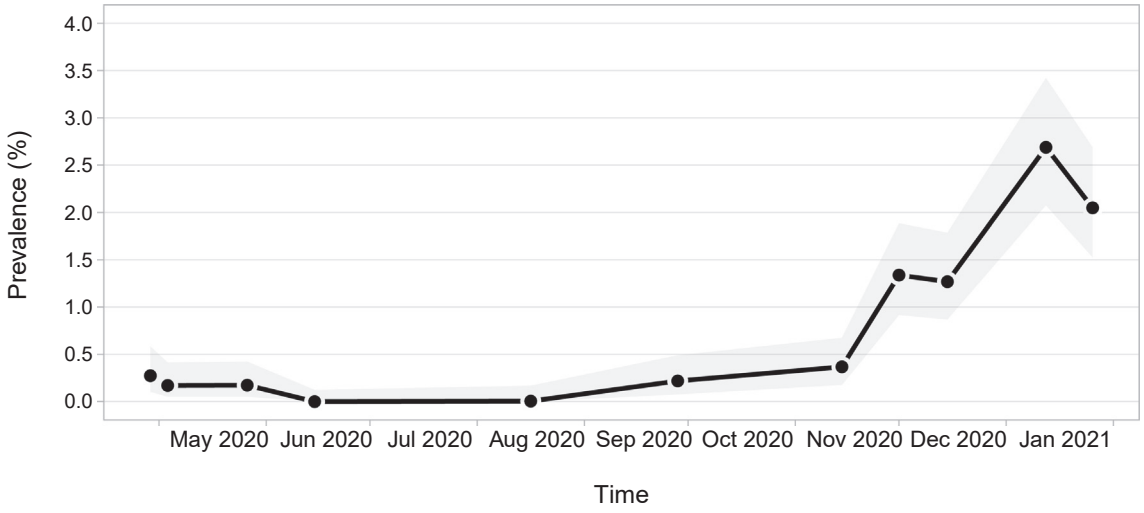

Fig. 2. Percentage of population testing positive for SARS-CoV-2 over time in Estonia during the 1st year of the COVID-19 epidemic 2020–2021. The grey area indicates 95% confidence intervals.

the regional differences in Estonia. Ida-Viru County is in the northeastern part of Estonia bordering the Russian Federation. The overwhelming majority (82%) of residents are Russian speaking. It is important to note that nearly 75% of Russian speakers in Estonia regularly follow TV channels and online media originating from the Russian Federation[34] and are more likely to trust Russian than domestic (Estonian) or EU media.[35] Whether the Russian Federation's pandemic-related disinformation campaign[36] has had some effect on the beliefs and behaviours of the Russian-speaking population in Estonia (and other neighbouring countries with sizable Russian speaking minorities) is unknown at this stage. There are anecdotal reports from Ida-Viru County on residents of declining state-provided COVID-19 vaccines and demands to be vaccinated with the Russian Sputnik vaccine.[37] There is a risk that COVID-19 vaccine uptake will be lower among minority ethnic groups in Estonia, thereby widening the health gap further. COVID-19 risk communication and community engagement is a priority for information provision and to counter misinformation.

In conclusion, a rather limited number of studies have assessed the prevalence of SARS-CoV-2 infection in the general population (seroprevalence,[38,39] SARS-CoV-2 RNA[10,40,41]). Population-based studies assessing temporal changes in SARS-CoV-2 prevalence, either via repeated cross-sectional studies[42] or following subjects longitudinally,[9] are, to our best knowledge, exceedingly rare. It is critically important to create a knowledge base to inform future strategies, and a range of real-life COVID-19 epidemic scenarios over extended periods needs to be documented to assist in understanding the infection risk factors at the individual and population levels. Analyses based on patients in need of hospital treatment, and/or with comorbidities reported during the early phases of the COVID-19 epidemic, were unable to disentangle infection from virulence risks. Yet, primary prevention operates through the control of (the true) infection risk factors.

Our study has several limitations. The degree to which the study is representative of the larger population is influenced by the low response rate and potential selective factors associated with responses. To minimise non-response bias, the prevalence estimates were weighted (age, gender and region) to ensure representativeness of the source population. Yet, there could be other factors for which we did not have detailed information about population distributions which are also associated with testing positive for SARS-CoV-2. The number of people testing SARS-CoV-2 RNA positive in the cross-sectional studies is low, leading to relatively large uncertainty around estimates.

We see the long period of observation and population-based nationwide study design as strengths of our work. Interpretation of changes in SARS-CoV-2 incidence and positivity rates originating from case notification or clinical cases is likely to be confounded by substantial changes in testing practice over time. Our study is based on a series of cross-sectional studies with a standardised methodology and is thereby very unlikely to be influenced by the testing practice. As this evaluation is based upon observing a single population over time, we speculate that selection bias or unmeasured confounders would operate rather uniformly over the period of observation, though presenting a less-threatening trend of SARS-CoV-2 prevalence and analysis of factors associated with SARS-CoV-2 positivity.

Conclusions

The population-based effect of the novel vaccines against SARS-CoV-2 is highly contingent on the infection-blocking (or transmission-blocking) action of the vaccine and population uptake.[8] SARS-CoV-2 population prevalence needs to be carefully monitored to inform containment decisions as vaccine programmes are rolled out.

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Competing interests

The authors report no competing of interest.

Author contributions

Anneli Uusküla - Conceptualisation, Methodology, Writing - Original Draft; Ruth Kalda, Mihkel Solvak, Mikk Jürisson, Krista Fischer, Aime Keis, Kristjan Vassil, Jaak Vilo, Hedi Peterson, Lili Milani, Mait Metspalu - Conceptualisation, Writing - Review & Editing; Meelis Käärik, Krista Fischer, Uku Raudvere, Ene Käärik, Liis Kolberg, Tuuli Jürgenson, Ene-Margit Tiit - Investigation, Data analysis, Writing - Review & Editing; Meelis Käärik, Krista Fischer - Visualisation. All listed authors reviewed and edited the manuscript and approved the final, submitted version. All authors confirm that they had full access to the data in the study and accept responsibility to submit for publication.

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Letter to the Editor

The forgotten people: impacts of COVID-19 on refugees

The evolution of COVID-19 has exposed many shortages in the social, healthcare, and economic systems around the world. This report intends to discuss the COVID-19 impact on an often-neglected population, refugees. The situation of refugees and other marginalized populations including the displaced and asylum seekers depends mainly on their legal situations in host countries.[1] Small fractions of refugees were lucky enough to get permanent residence or citizenship, whereas most refugees face disastrous conditions in reception camps or identification centers on countries' borders, and many of them reside and work without legal documentation. In addition to their traumatic experience with war, persecution, and poverty, refugees suffer in their host countries from overcrowded and unsanitary living conditions, inadequate education and healthcare, discrimination, and xenophobic attitudes.[1] Thus, it should not be unexpected that they are disproportionately affected by the COVID-19 pandemic. A retrospective analysis of COVID-19 outbreaks among refugees in Greece showed that refugees in reception and identification centers were 2.5 and 2.9 times, respectively, more likely to acquire COVID-19 infection than the general population. This is despite that refugees were significantly younger than the general population.[2] It is even widely thought that COVID-19 infections are under-reported among refugees because of their fear of serious ramifications such as deportation.[3] This fear is enhanced by the fact that refugees are often blamed by radical politicians and their supporters for the spread of infections to host communities.[3] Furthermore, it seems that COVID-19 put heavy psychological burdens on refugees, with reports showing higher rates of depression, stress, anxiety, and post-traumatic stress disorders in postpandemic than in prepandemic time among refugees coming from Syria, Iraq, and Uganda.[4–6] Moreover, other drawbacks of the COVID-19 pandemic that affected the population as a whole, including job loss and economic hardships, delayed health care, and educational disruptions, showed exacerbated impacts on refugees.[7] Some countries even used the COVID-19 pandemic as an excuse not to receive or resettle refugees, making them more vulnerable to COVID-19 consequences.[7]

From a global health perspective, the failure to address healthcare inequity can certainly hinder the world's efforts to contain the COVID-19 pandemic. Although the refugee crisis has several intersecting aspects including humanitarian, political, social, and economic aspects, the complexity of this crisis should not distract policymakers from a concomitant health crisis hitting refugees as a consequence of the COVID-19 pandemic. Because solving the refugee crisis is not predicted within the next few years, many urgent policies should be considered to lessen health inequity among refugees during the COVID-19 pandemic. First, to reduce overcrowdedness and allow social distancing, refugees should be resettled and current refugee camps should be renovated and expanded as early as possible. Second, health education, using refugees' own languages, should be promoted. Third, mental health counseling services should be available on a wider scale. Fourth, the World Health Organization and other high-indexed income countries should dispatch more COVID-19 jabs to refugees. These policies should be accompanied by a media campaign aiming to raise awareness about the refugee crisis. More importantly, refugees, themselves, should be incorporated into national and global health plans pertaining to alleviating COVID-19 impacts.[6–8]

In conclusion, addressing health inequity among refugees during the COVID-19 pandemic should be a global health priority. A call to urgent actions seeking to improve the health conditions of refugees should be encouraged by global health specialists worldwide.

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Original Research

The impact of COVID-19 pandemic on the 2020 hepatitis C cascade of care in the Republic of Georgia

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ABSTRACT

Objectives: In 2015, the Republic of Georgia initiated a National Hepatitis C Elimination Program, with a goal of 90% reduction in prevalence of chronic hepatitis C virus (HCV) infections by 2020. In this article, we explore the impact of the COVID-19 pandemic on the 2020 hepatitis C cascade of care in Georgia.
Study design: Retrospective analytic study.
Methods: We used a national screening registry that includes hospitals, blood banks, antenatal clinics, harm reduction sites, and other programs and services to collect data on hepatitis C screening. A separate national treatment database was used to collect data on viremia and diagnostic testing, treatment initiation, and outcome including testing for and achieving sustained virologic response (SVR). We used these databases to create hepatitis C care cascades for 2020 and 2019. Bivariate associations for demographic characteristics and screening locations per year and care cascade comparisons were assessed using a chi-squared test.
Results: In 2020 compared to 2019, the total number of persons screened for HCV antibodies decreased by 25% (from 975,416 to 726,735), 59% fewer people with viremic infection were treated for HCV infection (3188 vs. 7868), 46% fewer achieved SVR (1345 vs. 2495), a significantly smaller percentage of persons with viremic infection initiated treatment for HCV (59% vs. 62%), while the percentage of persons who achieved SVR (99.2% vs. 99.3%) remained stable.
Conclusions: The COVID-19 pandemic had a negative impact on the hepatitis C elimination program in Georgia. To ensure Georgia reaches its elimination goals, mitigating unintended consequences of delayed diagnosis and treatment of hepatitis C due to the COVID-19 pandemic are paramount.
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Introduction

Georgia is a small country in the South Caucasus with a population of 3.7 million and a high prevalence of chronic hepatitis C virus (HCV) infection among the adult population. The national serosurvey in 2015 estimated that HCV viremic prevalence was 5.4%, and more than 150,000 Georgians were infected with HCV.[1] In April of 2015, Georgia initiated a National Hepatitis C Elimination Program, which provides free treatment with direct-acting antivirals (DAAs) for all citizens, and set the ambitious target of a 90% reduction in the prevalence of chronic HCV infection by 2020.[1] As of October 2019, prior to the start of the Coronavirus disease (COVID-19) pandemic, 53% of the estimated number of adults with chronic HCV infection had been identified as part of the elimination program and 78% of them initiated treatment.[2] On average, 1000 persons were initiating treatment each month, which would have

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reduced HCV prevalence by 51% and incidence by 51% by the end of 2020.[3] The progress toward the elimination was substantial, but continued scale-up is needed to reach elimination targets.[4,5]

The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) case in Georgia was reported at the end of February 2020.[6] In response to the emerging pandemic, the Government of Georgia declared a state of emergency on March 21st, which progressed into a full national lockdown on March 30th. The lockdown measures included quarantining all international arrivals, closing borders and airports, restricting movement inside the country, banning mass gatherings, and maintaining closure of all schools, preschools, and universities. These measures were effective at controlling SARS-CoV-2 community spread, with only 1510 cumulative cases reported through September 1, 2020.[6] Cases started to increase again in late September, and the number of COVID-19 cases across the country reached nearly 228,000 by the end of 2020. From November 2020 through January 2021, new restrictions and lockdowns were imposed.

Mitigation strategies deployed to reduce SARS-CoV-2 transmission in Georgia created new challenges for the hepatitis C elimination program. Travel restrictions in Georgia coupled with a suspension of most in-person healthcare delivery further reduced screening efforts and patients' ability to seek care. Despite continued efforts to adapt (e.g., health service providers in Georgia increased the number of DAA pills per prescription, organized delivery of the prescribed medications including for those in quarantine or isolation, implemented distance-based provision of medical care where possible and patients with chronic conditions who were enrolled in the elimination program were asked to visit healthcare facilities every 28 days instead of 14), the monthly number of people tested and treated declined. In this study, we compare the HCV care cascades for 2019 and 2020 to determine the impact of the COVID-19 pandemic on a well-established hepatitis C elimination program in Georgia.

Methods

In 2017, a comprehensive national screening registry was created in Georgia to collect data on hepatitis C screening, including hospitals, blood banks, antenatal clinics, harm reduction sites, and other programs and services.[2] Data from 2015 onward are available in the registry, including date and HCV antibody (anti-HCV) test results, age, sex, and location. A separate treatment database was also created for program monitoring and evaluation, which collects data on demographics, viremia and diagnostic testing, treatment initiation, and outcome including testing for sustained virologic response (SVR), and achieving SVR. In Supplementary Tables 1 and 2, we present a list of different methods used to detect HCV antibodies and HCV viremic infection in Georgia. SVR is always determined by polymerase chain reaction (PCR). All national data from both the screening registry and the treatment database are included in the analysis, linked by patients' unique national ID. All data were deidentified, and national IDs were encrypted prior to analysis.

Care cascades were created and compared for 2020 and 2019 (using data from January 1 to December 31) to evaluate the potential impact of COVID-19 pandemic on the hepatitis C cascades of care in Georgia's hepatitis C elimination program. No major programmatic changes were implemented during 2020 that would have otherwise substantially affected rates of screening or linkage to care. Monthly screening rates were computed, and demographic characteristics and location of screening were compared. For monthly screening rates, those screened multiple times were counted once for each month in which they were screened. For annual comparisons, repeat screeners were counted once per year, using data from the first time an individual was screened in a calendar year. To compare monthly screening for HCV prepandemic and during the pandemic, we calculated the percentage of persons screened in each month of 2020 compared to the same month of 2019.

To analyze linkage to care and treatment outcomes, separate care cascades were created for 2019 and 2020 based on the year in which a person first tested anti-HCV positive. Treatment data were included through February of the year following initial positive anti-HCV result (e.g., February 2020 for those screened positive in 2019) to better capture treatment initiation and SVR testing, which is performed 12–24 weeks after treatment completion. Bivariate associations for demographic characteristics and screening locations per year and care cascade comparisons were assessed using a chi-squared test. We considered findings to be statistically significant if the two-sided *P*-value was <.05. All analyses were performed in SAS, version 9.4 (Cary, North Carolina, USA).

Results

In 2019, 975,416 people were screened for anti-HCV and 21,405 tested positive. Of these, 12,627 were viremic and 7868 were treated for HCV infection. In 2020, 726,735 people were screened, 10,899 tested positive for anti-HCV, 5433 were viremic, and 3188 were treated. The total number of persons who were screened for anti-HCV decreased by 25.5% in 2020 compared to 2019, 59% fewer people were treated (3188 vs. 7868), and 46% fewer achieved SVR (1345 vs. 2495). Compared to the number of persons screened for HCV in 2019, the largest reduction occurred in October of 2020 (46% of 2019 levels), followed by April and November (both 47% of 2019 levels) (Fig. 1). Persons screened for anti-HCV in 2019 and 2020 were similar in age (median age: 41 years vs. 42, respectively) and sex (56.4% vs. 55.4% female). In 2020, we observed an increase in the percentage of persons screened for anti-HCV at blood banks (4.9% vs. 7.1%), antenatal clinics (3.1% vs. 5.3%), and inpatient settings (32.5% vs. 33.4%) and a decrease in the percentage tested in outpatient clinics (57.7% vs. 53.2%) and harm reduction programs (0.6% vs. 0.3%) (*P*-values all <.001; Table 1).

In 2020, among all persons screened for HCV, 1.5% (n = 10,899) were anti-HCV positive, 70.8% of them were tested for viremia, and 70.4% of those tested had HCV infection. Among persons with viremia, 58.7% initiated treatment, 84.6% of whom completed treatment, and 76.5% of them were eligible to be tested for SVR. Among those eligible for SVR, 65.7% were tested and 99.2% achieved SVR (Fig. 2).

Compared to 2019, there were fewer people at each step of HCV cascade of care in 2020. However, in 2020, the percentage of people who completed treatment (84.6% vs. 72.9%) and who were eligible for SVR testing (76.5% vs. 62.6%) was significantly higher than in 2019 (*P*-values all <.001). Conversely, there was a significantly smaller percentage of people who were anti-HCV positive (1.5% vs. 2.2%), tested for HCV viremia (70.8% vs. 78.8%), confirmed to have viremic infection (70.4% vs. 74.8%), initiated treatment for HCV (58.7% vs. 62.3%), and tested for SVR (65.7% vs. 70.0%) in 2020 than in 2019 (*P*-values all <.001). The percentage of persons who achieved SVR (99.2% vs. 99.3%; *P*-value = .64) or discontinued treatment (3.2% vs. 3.3%; *P*-value = .72) was similar in 2020 and 2019, respectively.

Discussion

COVID-19 significantly impacted many aspects of health policy, programs, and healthcare delivery throughout 2020. The Georgian Government acted swiftly in March 2020 to impose restrictions that proved effective at reducing transmission of SARS-CoV-2.[5]

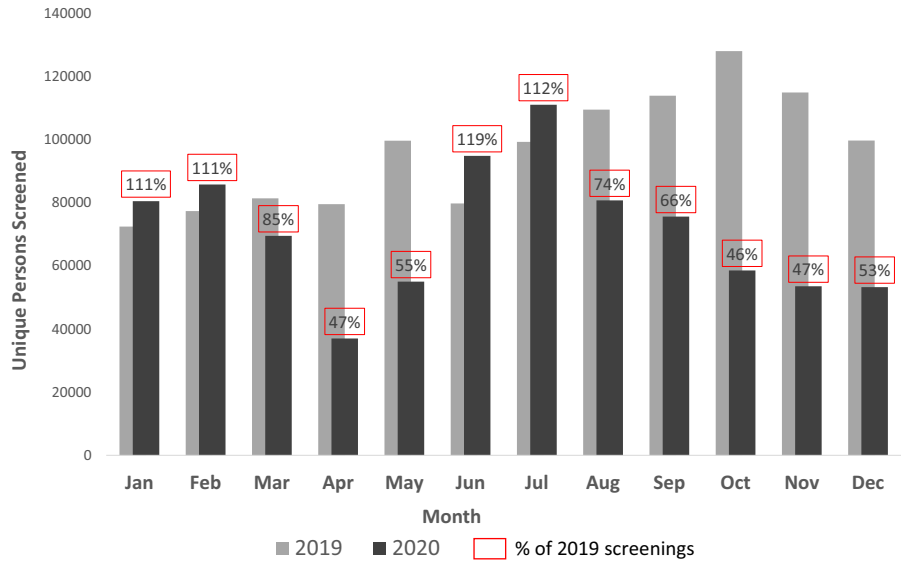


Fig. 1. Monthly hepatitis C antibody screening rates by year, Georgia, 2019–2020. To compare monthly screening for HCV prepandemic and during the pandemic, we calculated the percentage of persons screened in each month of 2020 compared to the same month of 2019.

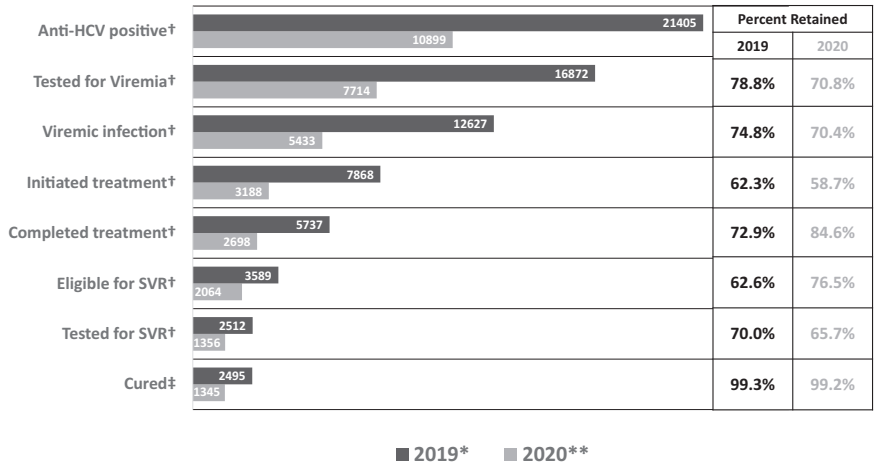
Table 1
Demographic characteristics and hepatitis C screening settings by year, Georgia, 2019–2020.

Characteristic	2019 (n = 975,416)		2020 (n = 726,735)		*P*-value
	n	%	n	%	
Age group, years					
<18	122,130	12.5	77,554	10.7	<.001
18–29	180,744	18.5	138,914	19.1	
30–39	159,241	16.3	124,844	17.2	
40–49	128,174	13.2	94,467	13.0	
50–59	135,263	13.9	96,116	13.2	
≥60	248,851	25.5	194,305	26.8	
Median age, years (IQR)	41 (26, 60)		42 (27, 61)		<.001
Sex					
Female	550,160	56.4	402,489	55.4	<.001
Male	425,256	43.6	324,246	44.6	
Screening setting[a]					
Outpatient	563,000	57.7	387,000	53.2	<.001
Inpatient	317,000	32.5	243,000	33.4	
Harm reduction	5499	0.6	2076	0.3	
Blood bank	48,034	4.9	51,765	7.1	
Antenatal clinic	30,067	3.1	38,231	5.3	
Other	12,033	1.2	5233	0.7	
Region[a]					
Tbilisi	331,094	34.0	238,860	34.3	<.001
Adjara	122,733	12.6	72,844	10.5	
Guria	50,573	5.2	33,310	4.8	
Imereti	143,314	14.7	113,058	16.2	
Kakheti	87,750	9.0	46,533	6.7	
Kvemo Kartli	54,195	5.6	37,124	5.3	
Mtskheta-Mtianeti	14,975	1.5	11,416	1.6	
Racha-Lechkhumi-Kvemo Svaneti	10,848	1.1	2680	0.4	
Samegrelo-Zemo Svaneti	101,022	10.4	66,149	9.5	
Samtskhe-Javakheti	20,598	2.1	38,072	5.5	
Shida Kartli	37,523	3.8	35,723	5.1	

[a] Location of earliest screening in time period; IQR = interquartile range.

While restrictions on population movement and mitigation measures were effective in reducing SARS-CoV-2 transmission, they led to challenges for the hepatitis C elimination program. A similar reduction in access and use of different healthcare services was observed across the Europe.[7,8] Overall, there was a reduction in the number of individuals engaging in and benefiting from the program, hampering progress toward elimination targets. To adapt, the hepatitis C elimination program increased pill counts dispensed, adopted medication delivery systems, and utilized distance-based care (e.g., telemedicine). To continue progress toward hepatitis elimination, the hepatitis C elimination program must further adapt and find strategies to increase the number of people being screened, tested, and treated for HCV infection.

Our analysis showed that in Georgia, screening for anti-HCV was one of the areas most affected by COVID-19 related restrictions. The number of persons screened in April of 2020 was approximately



* 2019 linkage data as of Feb 28, 2020 ** 2020 linkage data as of Feb 28, 2021. Classification based on date of earliest positive antibody test
† Chi-square p-value for year comparison <0.001; ‡ p=0.64; Abbreviations: anti-HCV = antibody to hepatitis C virus, SVR = sustained virologic response

Fig. 2. Comparison of hepatitis C care cascade by year of earliest positive antibody test, Georgia, 2019–2020.

half of what it was the same month of 2019. Restrictions were gradually lifted in late April 2020, and the state of emergency ended in May 2020. Shortly afterward, in June and July, there was a rebound in the number of screening tests conducted. When a second wave of SARS-CoV-2 cases occurred in September of 2020 and new restrictions were imposed, the number of persons screened dropped to approximately 50% of what it had been the year before.[6,9] This effect is likely multifactorial; during times of widespread community COVID-19 transmission and restrictions on movement, people are less likely to access in-person screening services and preventive services. The similar pattern of reduction in testing for HCV at the onset of COVID-19 pandemic and rebound in spring and summer of 2020 was observed in other countries.[10,11] At the same time, the healthcare system diverted attention to the treatment of COVID-19 and away from screening for hepatitis and other conditions. The shared needs of COVID-19 and the hepatitis C elimination program highlight the importance of mitigation measures for SARS-CoV-2 (e.g., vaccination, testing, isolation of cases) to allow recuperation of other healthcare services. It also presents the opportunity to consider alternatives to in-person screening (e.g., at-home testing) and additional outreach to populations disproportionally impacted by restrictions due to the COVID-19 pandemic.

In addition to an overall reduction in the absolute number of persons enrolled in each step of the HCV care cascade, a smaller percentage of people were 1) tested for HCV viremia, 2) treated for HCV, and 3) tested for SVR in 2020 than in 2019. The reduction in viremia and SVR testing could be either consequent to individuals being less likely to seek care in-person from the sites able to conduct this advanced laboratory testing or because diagnostic testing was less readily available at decentralized locations during the COVID-19 pandemic. The existing infrastructure for HCV testing provided a foundation for SARS-CoV-2 assessment in local and regional settings, but resources may have been diverted to focus on SARS-CoV-2 diagnostics. During 2020, there was a shift in the venues where people were screened, with fewer people screened in outpatient settings. While testing in inpatient settings leads to reflex confirmatory testing, the proportion of people linked to treatment is often less than in outpatient settings.[4] Care provided at outpatient primary care sites in Georgia resulted in higher rates of retention in the care cascade.[12] Since identification of people with viremia and subsequent treatment ultimately reduces the rate of further transmission in the population, measures to address deficiencies in these steps in the cascade should be considered.[13]

In 2020, among those screened and tested for viremia, we observed a lower percentage positive for both compared to 2019. This finding could be the result of the advances of hepatitis C elimination program and the fact that a large number of persons are already diagnosed and treated for HCV infection in Georgia. In addition, during the pandemic, population groups with a higher prevalence of HCV viremic infection, such as persons who inject drugs (PWIDs),[14] experienced additional challenges in accessing healthcare services and harm reduction services (HRS), including hepatitis C screening and treatment. In 2020, substantially fewer people were screened for anti-HCV at HRS than in 2019. Lower participation in HCV testing by persons who are at a higher risk for HCV (e.g., PWID) in 2020 could have caused lower HCV viremia positivity than in prepandemic time. Decreases in hepatitis C testing and treatment among PWIDs, in addition to less frequent use of prevention interventions such as needle and syringe programs (NSPs) and opioid substitution treatment (OST), could lead to increases in HCV transmission among PWID, further increasing hepatitis C incidence and prevalence and making it more challenging for Georgia to reach HCV elimination goals.[15,16] It is important to ensure that despite the COVID-19 pandemic, PWID and persons with substance use disorder continue to have low barriers to access HCV treatment and prevention services such as NSPs and OST that are shown to reduce the risk of HCV acquisition.[17]

Our analysis is subject to limitations. The national treatment database, which contains information on all diagnosed persons enrolled in the hepatitis C elimination program, provides accurate treatment-related information on a national level. However, this database has limited ability to explain why persons are lost to follow-up or what are the main reasons for such large reductions in the number of persons in each step of the cascade of care in 2020 compared to 2019. There may have been other factors contributing to a decrease in screening for hepatitis C between 2019 and 2020 unrelated to the COVID-19 pandemic which could not be assessed in this analysis.

Conclusions

In this article, we present the impact that the COVID-19 pandemic has had on reductions in hepatitis C testing and treatment in the hepatitis C elimination program in Georgia. These reductions could lead to an increase in HCV transmission and HCV-related morbidity and mortality and could threaten Georgian progress toward HCV elimination goals. Georgia has committed to

eliminate hepatitis C, and efforts aimed at mitigating unintended consequences of delayed diagnosis and treatment of hepatitis C due to the COVID-19 pandemic are paramount to ensuring Georgia can reach its national hepatitis C elimination goals.

Author statements

Ethical approval

Data for this analysis come from Georgia's National Hepatitis C Elimination Program, which was deemed by the Institutional Review Board of Georgia's National Center for Disease Control (NCDC) to be a public health program activity. The United States CDC determined this activity was not research involving human subject. Some data from this study were presented as the poster presentation at the EASL conference held virtually in June of 2021.

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Competing interests

The authors have no commercial associations or sources of support that may pose a conflict of interest.

Authors contribution

Amiran Gamkrelidze: Conceptualization, Supervision; **Senad Handanagic**: Writing - Original Draft, Review & Editing; **Shaun Shadaker**: Methodology, Software, Validation, Formal analysis, Data Curation, Visualization, Writing - Review & Editing; **Alexander Turdziladze**: Software, Validation, Writing - Review & Editing; **Maia Tsereteli**: Investigation, Supervision; **Vladimer Getia**: Investigation, Validation; **Ana Aslanikashvili**: Investigation; **Sophia Surguladze**: Writing - Original Draft; **Lia Gvinjilia**: Review & Editing, Validation, Project administration; **Tinatin Kuchuloria**: Writing - Original Draft, Review & Editing, Validation, Project administration; **Irina Tskhomelidze**: Writing - Original Draft, Review & Editing, Validation, Project administration; **Paige A. Armstrong**: Conceptualization, Supervision, Writing - Review & Editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.01.040.

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Letter to the Editor

The inseparable link between primary health care and health security

In 2020, an estimated 243.8 million people across 75 countries have been estimated to be in need of humanitarian assistance;[1] this is well above the 134 million assessed in 2018,[2] and has been mainly driven by the COVID-19 pandemic, which has compounded existing needs and fueled new crises.

The impact of each emergency is context-specific and depends on various aspects like the pre-existing vulnerability, the capacity of the affected community to manage the risks, and the severity of the hazard. Given the critical role of primary care in providing essential routine health services, disease surveillance, and implementation of public health measures at the community level,[3] a primary health care oriented health system is key in supporting resilience (defined as the ability to resist, absorb, accommodate and recover from the effects of a shock in a timely and efficient manner).[4]

Global and national health security activities frequently focus mainly on national and central-level structures and institutions, with primary health care underrepresented or absent. Therefore, there is a need to recognise and include primary health care in national health emergency risk management policies, plans and programmes. Similarly, primary health care requires well-defined and recognised roles and functions in emergency prevention, preparedness and response at the regional, district and community levels; roles and functions need to be integrated into health-facility risk management plans and linked with secondary and tertiary care systems.

Essential public health functions, including health promotion, health protection, disease prevention, and surveillance and early warning mechanisms, create a prepared system, which is vital to minimise exposure to health hazards. The community-orientation nature of primary health care makes it well placed to facilitate such activities through work with a range of actors within communities. On the other hand, damaged health care infrastructure and disruption of primary health services result in weak health systems and vulnerable communities with increased health needs. This can, in turn, lead to increased morbidity and mortality due to preventable or treatable conditions. To note that evidence revealed how primary care reduces non-emergency-related mortality and morbidity in humanitarian settings and is particularly important for women, children and people living with chronic health conditions.[5]

COVID-19 could represent a specific momentum for a renewed global commitment to primary health care to contribute to better health outcomes of people at risk of emergencies through prevention, preparedness and readiness for future emergencies. At the same time, ensuring that primary health care services continue to be available in regions experiencing complex emergencies is vital in order to guarantee access to essential health services.

Ensuring accessible, equitable primary health care (PHC) services during emergencies addresses a critical need and human right, while builds a foundation for universal health coverage. Additionally, empowerment of PHC is critical to ensure effective detection, case management and limiting of spread of infectious disease outbreaks by avoiding delay in seeking treatment or access to care because of the disrupted health system.

Primary health care, universal health coverage and health security are intricately connected and require global, national and local actions.

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