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Original article

Reconstruction of a large-scale outbreak of SARS-CoV-2 infection in Iceland informs vaccination strategies

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ABSTRACT

Objectives: The spread of SARS-CoV-2 is dependent on several factors, both biological and behavioural. The effectiveness of nonpharmaceutical interventions can be attributed largely to changes in human behaviour, but quantifying this effect remains challenging. Reconstructing the transmission tree of the third wave of SARS-CoV-2 infections in Iceland using contact tracing and viral sequence data from 2522 cases enables us to directly compare the infectiousness of distinct groups of persons.
Methods: The transmission tree enables us to model the effect that a given population prevalence of vaccination would have had on the third wave had one of three different vaccination strategies been implemented before that time. This allows us to compare the effectiveness of the strategies in terms of minimizing the number of cases, deaths, critical cases, and severe cases.
Results: We found that people diagnosed outside of quarantine ($\widehat{R} = 1.31$) were 89% more infectious than those diagnosed while in quarantine ($\widehat{R} = 0.70$) and that infectiousness decreased as a function of time spent in quarantine before diagnosis, with people diagnosed outside of quarantine being 144% more infectious than those diagnosed after ≥ 3 days in quarantine ($\widehat{R} = 0.54$). People of working age, 16 to 66 years ($\widehat{R} = 1.08$), were 46% more infectious than those outside of that age range ($\widehat{R} = 0.74$).
Discussion: We found that vaccinating the population in order of ascending age or uniformly at random would have prevented more infections per vaccination than vaccinating in order of descending age,

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without significantly affecting the expected number of deaths, critical cases, or severe cases. **Kristjan E. Hjorleifsson, Clin Microbiol Infect 2022;28:852**

Introduction

More than 160 million cases of SARS-CoV-2 have been diagnosed globally, resulting in more than 3.3 million deaths [1]. The first case of SARS-CoV-2 infection in Iceland was confirmed on February 28, 2020, and as of May 14, 2021, a total of 6526 people have been diagnosed in the country. The third wave of SARS-CoV-2 in Iceland consisted of 2783 confirmed cases and was characterized by a single genetic clade, colloquially referred to as the blue clade (Table S2), traced back to a person who entered the country in August 2020. The third wave was contained by January 2021 through nonpharmaceutical interventions [2] (Supplementary methods).

Every diagnosed case was contact traced, and recent contacts were placed in quarantine. Every PCR-positive sample was sequenced (Supplementary methods) within 36 to 48 hours of sample collection, and the results were fed back to the contact tracing team [3].

Understanding the differences between distinct groups of persons in epidemic outbreaks is key to employing targeted containment measures. By reconstructing the chain of events in an entire outbreak, we can observe these differences directly. Furthermore, a case-by-case replay of outbreaks enables us to model the effect vaccinations would have had on the outbreaks had vaccinations been administered beforehand.

In this study, we construct a model of the third wave of SARS-CoV-2 in Iceland. This constitutes the largest study to date reconstructing a single outbreak with complete contact tracing and sequence data.

Outbreak reconstruction

Any outbreak of a viral disease has a single progenitor who infects a number of persons, each of whom infects other persons and so forth until the disease is contained or everyone has been infected. These transmissions from person to person form a tree of transmissions with the progenitor as its root. The third wave in Iceland consisted of a single subtree of the global transmission tree of the SARS-CoV-2 pandemic. Despite the extensive data collected on each case, the true transmission tree of the third wave cannot be
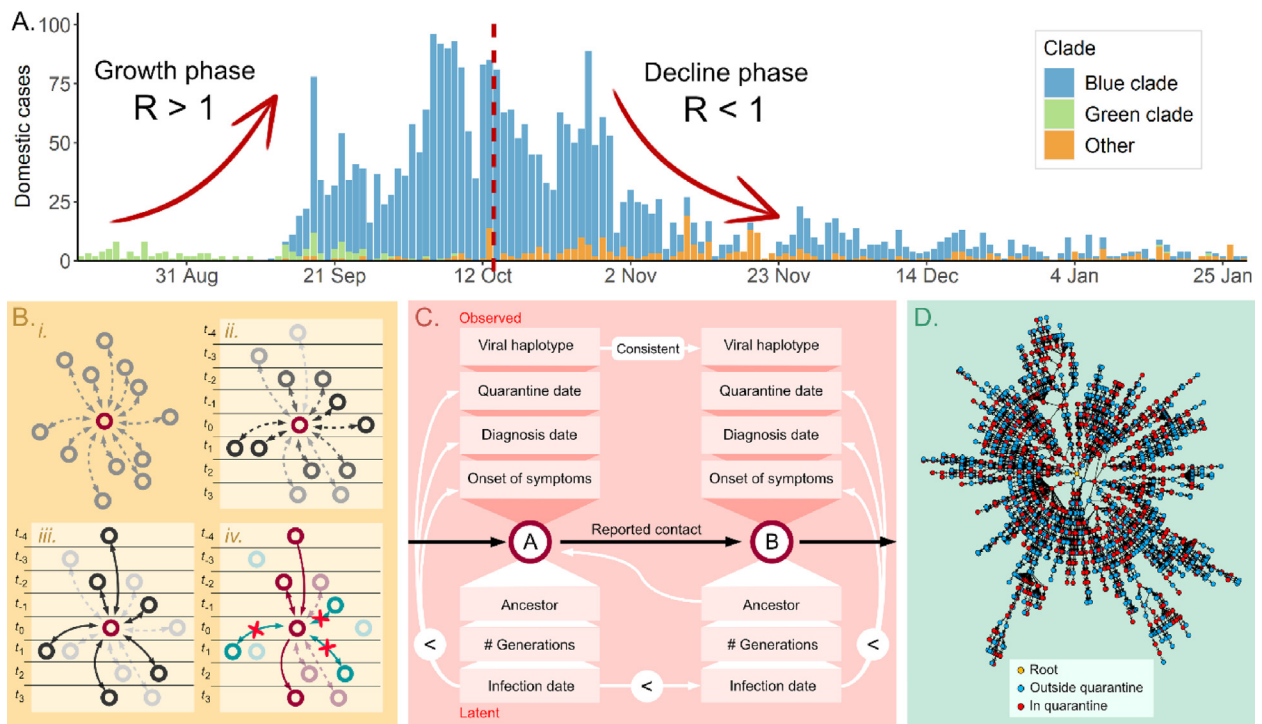

Fig. 1. (A) Daily cases during the third wave of SARS-CoV-2 infections in Iceland, excluding cases diagnosed at the border. On October 15, 2020, $\hat{R}_t$ went below 1 outside of quarantine for the first time and stayed below 1 except for the time period covering the hospital outbreak. Based on this observation, we split the outbreak into a growth phase before October 15 (red dashed line) and a decline phase from then until the end of January 2021. (B) (i) When determining who infected a person, initially all diagnosed cases are equally likely. (ii) Quarantine, diagnosis, and dates of symptom onset make some people more likely than others, assuming specific incubation time and generation time distributions. (iii) Contact tracing data make certain transmissions very likely but do not enable us to disregard others. (iv) Given the viral haplotypes, we can disregard transmissions where the haplotypes are incompatible (i.e. neither is derived from the other) and in some cases determine the direction of the transmission, in cases where de novo mutations occur between generations. (C) We use real-world data and the tree structure to infer the latent data for each diagnosed case. The < symbol indicates that the date on the left needs to precede the date on the right. For each diagnosed person, we infer the ancestor (i.e. the person who infected them), the date of infection, and the number of transmissions separating the ancestor and the person, κ. (D) One instance of a reconstructed transmission tree for the third wave in Iceland.

determined with certainty (Fig. 1B). We extended the Outbreaker2 model [4,5] to infer the transmission tree using data from contact tracing; viral genome sequences; household membership; and times of onset of symptoms, quarantine, and diagnosis (Fig. 1C; Supplementary methods).

Estimating stratified reproduction number using transmission trees

The effective reproduction number R of a disease outbreak denotes how many persons each diagnosed person infects on average. The R at a given time is denoted by R_t, the time-varying reproduction number.

A variety of methods have been proposed to estimate R_t [6–10], all of which attribute the number of cases at time t to cases diagnosed in the preceding days, weighted with the assumed generation time distribution. Reconstruction of transmission trees has been explored previously [4,11–13], most recently with the Outbreaker2 model, which infers the transmission tree of an outbreak using contact data, sequence data, and times of symptom onset. In a transmission tree model, R_t is calculated by averaging the outdegree (i.e. the number of persons they infected) of everyone in the tree at time t (Supplementary methods). Because the data are available on an individual level, we can estimate the reproduction number for distinct groups of people and compare their relative infectiousness.

In this study, we expand on the size of transmission trees reconstructed in previous studies by analyzing an entire epidemic on a national scale [4,12]. This enables us to quantify the efficacy of quarantine measures and compare the infectiousness of different age groups at different times. Current methods do not consider much of the information we possess (e.g. quarantine times, household data, and the single-introduction nature of the outbreak).

Simulating the effects of vaccination on transmission trees

Vaccination has two distinct goals. First, vaccination protects those at risk, such as the elderly, those with underlying diseases, and front-line workers. Second, it protects the community from future outbreaks. Once the former has been attained, the order in which vaccines should be distributed to the remaining population needs to be decided. Some efforts have been made to simulate the effect vaccination has on the spread of disease [14–16]. These models construct a theoretical wave of infections assuming a compartmental model (e.g. susceptible, infectious, and/or recovered, and variations) and rely on multiple epidemiologic constants. However, by using transmission trees, we can use real-world data to simulate what would have happened if certain persons in the tree had been immune at the time. Thus, we can simulate the effect different vaccine distribution strategies would have had on the third wave.

Methods

Extending the outbreaker model

To make use of our extensive data on each case, we extended the Outbreaker2 [4] model as detailed in the Supplementary Methods.

Simulating vaccination strategies

We selected adults, age ≥16 years, to be immune and removed them and all their downstream transmissions from the tree. By counting the remaining persons in the tree, we obtained a measure of the size of the third wave in Iceland given a particular vaccination distribution, all nonpharmaceutical interventions being identical. This assumes that all transmissions remain the same, except some persons have been immunized and therefore break the chain of transmission. We considered three strategies: vaccinating in order of descending age, in order of ascending age, and uniformly at random.

The adult population was segmented into 10-year age brackets. A person was selected to be immune based on the proportion of their age group vaccinated in the simulation and a given vaccine efficacy (60% for the former dose; 90% for the latter) [17–19]. The outbreak size-point estimates were obtained by averaging the mean outbreak size over all simulations and 95% CIs by taking the 2.5% and 97.5% quantiles. We performed 1000 simulations. We also simulated the expected number of deaths, critical cases, and severe cases using the log-linear fits from Herrera-Esposito et al. [20] and Levin et al. [21] (Supplementary methods). These simulations were not sensitive to the initial cases in the tree (Supplementary methods).

Furthermore, we simulated the effect the actual distribution of vaccines in at-risk groups and front-line workers, at the time of writing, would have had on the third wave (Supplementary methods).

Statistical analysis

We estimated the R of a particular group of persons by averaging the out-degree of everyone in the group over all transmission trees. CIs were obtained by iteratively calculating $\widehat{R}$ with bootstrapping of the persons in the data set. We calculated the ratio of $\widehat{R}$ between distinct groups of persons to estimate the effect size of the difference in infectiousness. Significance was tested by taking the log difference of the bootstrapped $\widehat{R}$ values for the two groups and performing a z-test, using the bootstrapped values to estimate the standard deviation. In addition to bootstrapping, we performed jackknife and permutation tests, with identical results.

We estimated R_t to be the mean out-degree per group of everyone diagnosed in a 4-day sliding window $(t - 4, t]$, such that each person contributed to $\widehat{R}_t$ on 4 days. We obtained the 95% CI with bootstrapping.

Data and source code availability

All sequences used in this analysis are available in the European Nucleotide Archive under accession number PRJEB44803 (https://www.ebi.ac.uk/ena/browser/view/PRJEB44803). The source code for the model construction and analysis is available at https://github.com/DecodeGenetics/COVID19_reconstruction_iceland.

Results

In the third wave of SARS-CoV-2 infections in Iceland, 89% of diagnosed cases shared a single haplotype, traced back to a person who entered the country in August 2020 (Fig. 1A). This initial case accumulated 2783 cases of the same or a derived haplotype over a period of 5 months before being contained. Other clades did not gain foothold during this time, and those cases are not included in this analysis. Vaccinations against SARS-CoV-2 in Iceland started on December 28, 2020, and only 3.6% of the adult population (age ≥16 years) had received at least one vaccine dose when the third wave ended on January 28, 2021.

We inferred a transmission tree using data on every person in the third wave diagnosed before December 1, 2020, totalling 2522 people (Fig. 1D). Of these, 91 had an incomplete or missing haplotype but were included because of contact tracing. This data set contains 91% of the 2783 persons who were ever diagnosed

with this clade. Contact tracing data, quarantine status, and onset of symptoms were available for everyone in the dataset. A total of 1275 persons (51%) were diagnosed while in quarantine, and 1964 (78%) had reported contact with prior cases. In addition, 1738 persons (69%) were symptomatic at the time of diagnosis, and 187 (7%) never showed any symptoms. An average of 303 persons (12%) in the model had more than one transmission between them and their ancestor, indicating the presence of undiagnosed cases (Supplementary methods). Outbreaker2 estimated the observed cases to be 87% of the total number (95% CI, 83%-91%; Table S5).

Effect of contact tracing-informed quarantine on effective reproduction number

Persons diagnosed outside of quarantine were 88.8% more infectious (95% CI, 70.9%–109.2%; $p = 2.8 \times 10^{-32}$) than those diagnosed while in quarantine. Furthermore, the time from the start of quarantine to a positive PCR test had a significant effect on infectiousness. Persons diagnosed after 1 or 2 days in quarantine were 66.6% more infectious (95% CI, 49.3%–85.2%; $p = 4.0 \times 10^{-19}$) than those diagnosed after ≥ 3 days. Additionally, those diagnosed outside of quarantine were 144.4% more infectious (95% CI, 116.8%–174.1%; $p = 2.5 \times 10^{-50}$) than those diagnosed after ≥ 3 days. The estimated reproduction numbers are listed in Table 1.

Effective reproduction number varies with age

Adults age ≥ 16 years were 59.5% more infectious than children age ≤ 15 years (95% CI, 41.6%–83.4%; $p = 1.7 \times 10^{-12}$). Those of working age (age 16–66 years) were 45.9% more infectious (95% CI, 27.7%–65.4%; $p = 1.6 \times 10^{-8}$) than those outside of that age range.

Estimating time-varying reproduction number

We calculated $\widehat{R}_t$, stratified by whether people were in quarantine at the time of diagnosis. Fig. 2A shows three peaks in $\widehat{R}_t$ outside of quarantine, corresponding to two superspreading events and one outbreak in a hospital.

An outbreak has (at least) two phases

Any outbreak has at least one growth phase and one decline phase. The mean out-degree is > 1 during a growth phase and <1 during a decline phase. The $\widehat{R}$ of different groups during the decline and growth phases of the third wave are shown in Table 1. All comparisons reported remain significant in the growth phase and decline phase, except there is no significant difference between the infectiousness of those of working age and those outside of working age in the decline phase (23.8%;

95% CI, −3.3% to 56.3%; $p = 0.08$). Full results of the comparisons are shown in Table S1.

Simulating vaccination strategies

We modelled three vaccination strategies on the adult population age ≥ 16 years to investigate the difference in infectiousness between age groups: vaccinating by order of descending age, order of ascending age, and uniformly at random. We then estimated what the size of the third wave would have been for different levels of vaccination. For each strategy, we iteratively increased the proportion of the adult population vaccinated, both starting at 0% and assuming a starting point of 29%. The second starting point reflects the actual vaccinations of persons at high risk and frontline workers in Iceland as of April 28, 2021. We found no significant difference in the number of deaths, critical cases, and severe cases between the vaccination strategies (Table S7; Fig. S5).

Fig. 3 shows the mean size of the outbreak for the three strategies, assuming the first person in the transmission tree is unvaccinated. These simulations are not sensitive to the initial cases in the transmission tree (Supplementary methods; Figs. S1–4). Table 2 shows the lowest proportion of adults who would have needed to be vaccinated such that the final size of the third wave would have been 100 persons (4% of the observed outbreak) on average.

Discussion

Quarantine has been assumed to slow the spread of infectious diseases, but the extent to which it is effective has been difficult to quantify because doing so requires data on the individual level. We found that mandated quarantine significantly decreased the spread of the third wave of SARS-CoV-2 infections in Iceland, with persons diagnosed outside of quarantine being 89% more infectious than those diagnosed while in quarantine. Furthermore, we observed that contact tracing is time critical by comparing the infectiousness of people diagnosed after a short quarantine to that of those diagnosed after a longer quarantine. Lastly, we found that people of working age played a key role in the generation of the third wave in Iceland, most likely resulting from more frequent contact among this age group, compared with older persons who may be retired.

We found that vaccinating persons in order of ascending age or uniformly at random would have prevented more transmissions per vaccination than vaccinating in descending order of age in the third wave in Iceland. Our estimates of the final size of the outbreak are sensitive to the assumed vaccine efficacy. However, the relative difference between the modelled vaccination strategies is independent of efficacy. Recent studies suggest that vaccinated persons who become infected have a lower viral load [22] and may be less likely to infect others [23]. This is not taken into account here.

Table 1

Number of people in different groups diagnosed in the growth phase (until October 15, 2020) and decline phase (after October 15, 2020) of the third wave of SARS-CoV-2 infections in Iceland and their estimated effective reproduction number $\widehat{R}$

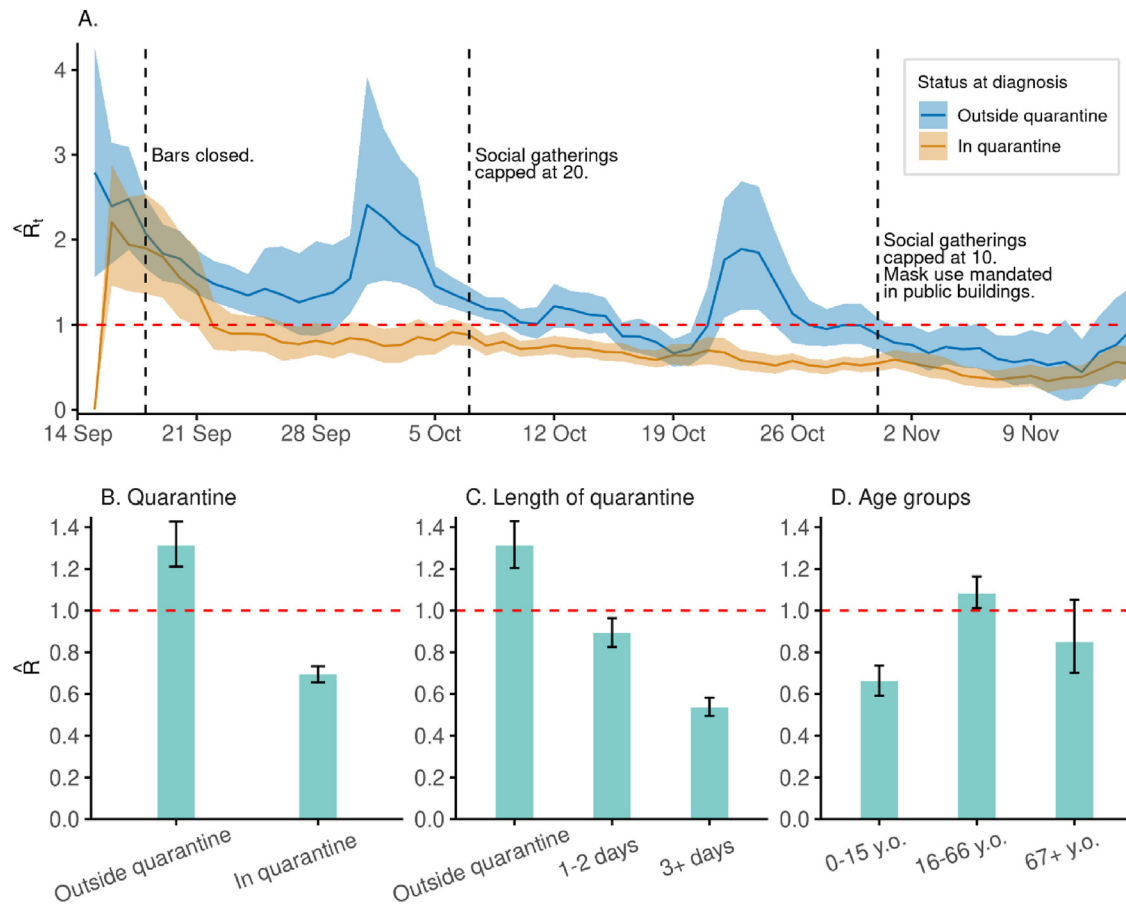| Group	Overall		Growth phase		Decline phase	
	n (%)	$\widehat{R}$	n (%)	$\widehat{R}$	n (%)	$\widehat{R}$
Whole sample	2522 (100)	1.00	1442 (100)	1.17 (1.09–1.27)	1080 (100)	0.77 (0.70–0.85)
Outside of quarantine	1247 (49)	1.31 (1.21–1.43)	776 (54)	1.45 (1.32–1.62)	471 (44)	1.08 (0.93v1.25)
In quarantine	1275 (51)	0.69 (0.66–0.73)	666 (46)	0.84 (0.78–0.91)	609 (56)	0.53 (0.49v0.57)
Short quarantine	564 (22)	0.89 (0.83–0.96)	340 (24)	1.02 (0.93–1.13)	224 (21)	0.70 (0.62–0.78)
Long quarantine	711 (28)	0.54 (0.50–0.58)	326 (23)	0.66 (0.58–0.74)	385 (36)	0.43 (0.39–0.48)
Adults (age ≥ 16 y)	2164 (86)	1.06 (0.98–1.12)	1269 (88)	1.22 (1.13–1.32)	895 (83)	0.82 (0.74–0.91)
Children (age 0–15 y)	358 (14)	0.66 (0.59–0.73)	173 (12)	0.80 (0.69–0.93)	185 (17)	0.53 (0.45–0.62)
Working age (16–66 y)	1921 (76)	1.08 (1.01–1.16)	1171 (81)	1.25 (1.15–1.37)	750 (69)	0.82 (0.73–0.92)
Outside of working age	601 (24)	0.74 (0.66–0.84)	271 (19)	0.83 (0.74–0.92)	330 (31)	0.66 (0.54–0.81)

Fig. 2. (A) $\widehat{R}_t$ for those diagnosed while in quarantine and those diagnosed outside of quarantine, respectively. The shaded area represents the 95% CI for the mean, and the dashed lines show the dates of social restrictions imposed. (B) Effective reproduction number of those diagnosed outside of quarantine compared with those diagnosed in quarantine. Error bars reflect the 95% CI of the mean. (C) Effective reproduction number of those diagnosed outside of quarantine, those diagnosed after 1 to 2 days in quarantine, and those diagnosed after $\geq$3 days in quarantine. (D) Effective reproduction number stratified by age.

The effect of vaccination on the spread of the disease has been studied with classical modelling approaches based on susceptible, infectious, and/or recovered models and variations thereof. These models can yield insights, but uncertainty remains as to how contacts, dependency between age of contacts, and variability due to superspreading events should be modelled. By reconstructing the third wave from real-world data, we circumvented these limitations by removing the behavioural modelling assumptions and simulating vaccinations directly on the transmission tree.

Our results show no significant difference in the expected number of deaths, critical cases, or severe cases between the modelled strategies. This implies that it is possible to minimize the number of cases without increasing the mortality or hospitalization rates. One possible explanation is that, although older persons are more likely to develop severe disease, the vaccination of younger persons prevents transmission to older people.

Since the data were collected, SARS-CoV-2 variants have emerged that have been shown to be more infectious than previous ones, particularly the Delta variant (B.1.617.2). Like vaccine efficacy, this increased infectiousness would only affect the final size of the outbreak, but the relative difference between the strategies is independent of baseline infectiousness. Recent studies have considered vaccine efficacy (VE) against SARS-CoV-2 infection and whether VE against the Delta variant is reduced. A study from Qatar [24] based on convenience samples showed lower VE against all infections (symptomatic and asymptomatic) of the Delta variant for BNT162b2 (Pfizer; 53.5% VE), whereas no reduction was observed

for mRNA-1273 (Moderna; 84.8% VE). Additionally, a recent survey-based study from the UK [25] revealed decreased VE against all infections of the Delta variant for ChAdOx1 nCoV-19 (Oxford-AstraZeneca; 67% VE), but no significant reduction for BNT162b2 (Pfizer; 80% VE). Based on these results, we believe that our findings would also apply to the Delta variant.

The effectiveness of nonpharmaceutical interventions can largely be attributed to changes in human behaviour. Quantifying this effect remains challenging. By leveraging the extensive data collected for diagnosed persons in the third wave of SARS-CoV-2 infections in Iceland, we created a model that allowed us to observe the differences in infectiousness of distinct groups of people.

Although the data collected are extensive, some cases went undiagnosed. Serologic measurements after the first wave of SARS-CoV-2 infections in Iceland [3] estimated that diagnosed cases were 56% of the total and another 14% were quarantined but undiagnosed. In addition, 95% of people quarantined in the third wave ($n = 21\,225$) were PCR tested upon leaving quarantine. Due to this and the higher availability of PCR tests, we expect that at least 70% of cases in the third wave were diagnosed and therefore included in the transmission tree. Outbreaker2 estimated that 87% of cases were diagnosed, but this estimate does not include undiagnosed persons who did not infect others.

The vaccination of a population serves two distinct purposes: first, to prevent death and severe illness in groups at high risk, and second, to curb the spread of the virus in the population. We
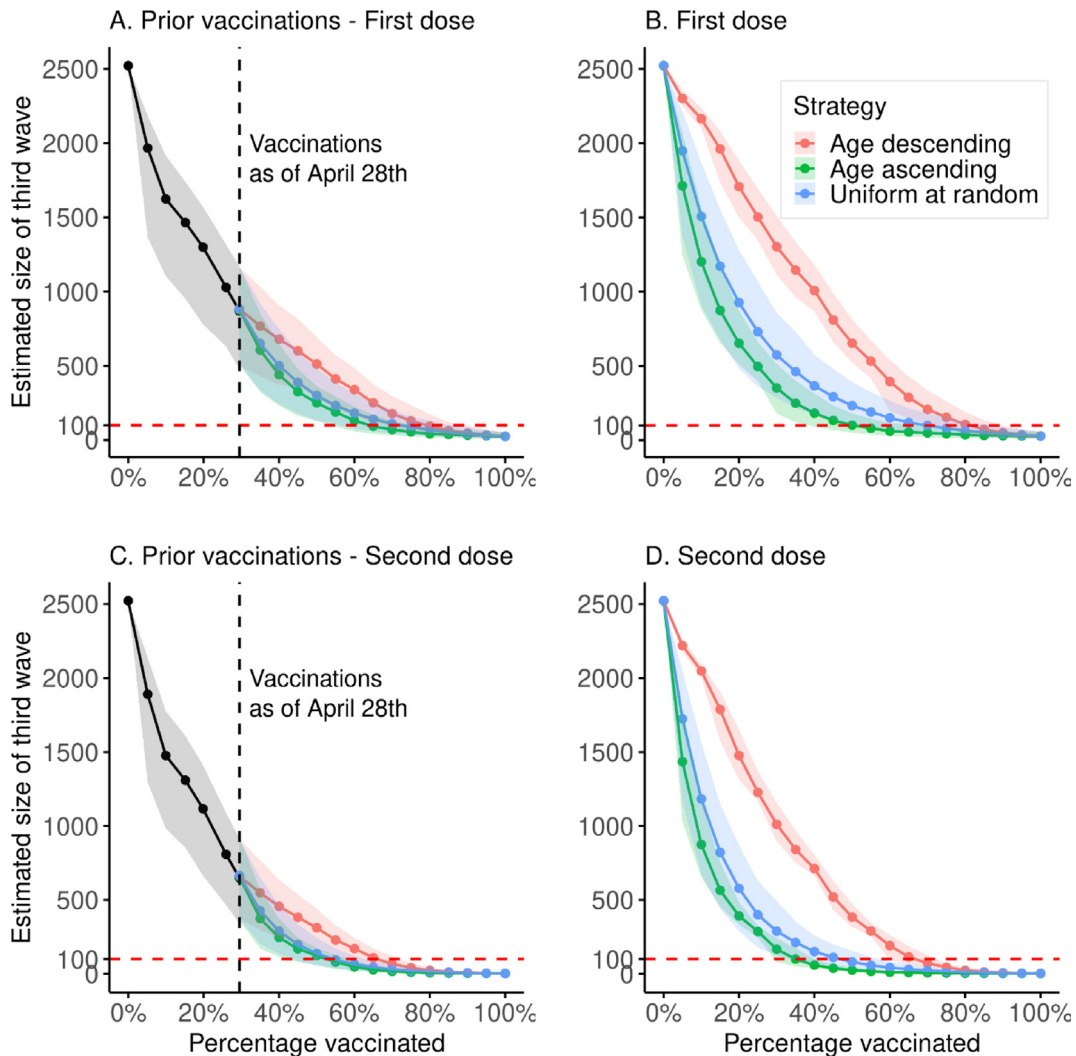
Fig. 3. Simulations of the estimated final size of the third wave at a given population prevalence of vaccination. Solid lines show the mean size of the outbreak, and shaded areas represent 2.5% to 97.5% quantiles. As a benchmark, we compared the vaccination strategies by the lowest proportion of adults who would have needed to be vaccinated such that the final size of the third wave would have been 100 persons (4% of the observed outbreak) on average. (A) Using the actual vaccination scheme for at-risk groups and front-line workers, up to 29% of the adult population, and using three separate vaccination strategies from 29% to 100%: age-descending, age-ascending, and uniformly at random. Modelled vaccinations beyond the 29% mark are assumed to have an efficacy of 60%. (B) Simulations of the size of the third wave, assuming 60% vaccine efficacy, under the three different vaccination strategies, starting with no vaccinations and concluding with 100% of the adult population vaccinated. (C) Same simulation as in (A), but all vaccinations are assumed to have an efficacy of 90% (both first and second dose administered). (D) Same simulation as in (B), but assuming 90% vaccine efficacy.

Table 2
Lowest proportion of adults who would have needed to be vaccinated such that the final size of the third wave would have been 100 persons on average

Model	Proportion of adults vaccinated (%), mean (range)		
	Age, descending	Age, ascending	Uniform at random
Actual vaccinations/first dose	79.2 (67.6—89.4)	64.1 (53.7—75.7)	72.3 (56.1—85.1)
Actual vaccinations/second dose	66.2 (57.1—72.1)	52.8 (42.4—58.4)	54.5 (43.7—63.1)
First dose	81.1 (71.8—89.6)	50.4 (38.5—69.2)	70.0 (50.0—86.5)
Second dose	66.8 (59.9—72.4)	35.0 (29.4—40.1)	47.0 (33.6—57.5)

The former two models use actual vaccination numbers up to the 29% mark and extrapolate from there using the three strategies. The latter two models start from zero.

simulated the effect of three vaccination strategies using four different metrics: the number of infections, severe cases, critical cases, and deaths. Our results demonstrate a negligible difference between the vaccination strategies for the latter three metrics, but a significant difference in the number of infections (Fig. 3). Although our results for the third wave indicate that vaccinating in order of ascending age would have curtailed the outbreak sooner, this may

reflect the age composition of this particular outbreak. Vaccinating the remaining adult population uniformly at random, once high-risk groups have been fully vaccinated, is a more robust strategy, because it removes the dependency between who is vaccinated and their age. When interpreting these results, it is important to keep in mind that they only provide a lower bound on the so-called herd immunity threshold.

Ethics statement

This study was approved by the National Bioethics Committee of Iceland (approval no. VSN-20-070) after review by the Icelandic Data Protection Authority. Consent was not required from the participants in the study.

Transparency declaration

All authors declare no conflicts of interest. No external funding.

Author contributions

K.E.H. and S.R. contributed equally to this article. KEH, SR, PM, and KS designed the study and interpreted the results. ABA, MA, KB, GH, AdJ, AsJ, NK, BK, DNM, LLR, GMS, AS, FJ, OTM, GLN, and JS planned and performed the laboratory work. ESE, RP, MIS, and MT performed the data collection. KEH, SR, HJ, ESE, RF, GG, KRG, AG, BOJ, KSJ, TK, RP, MIS, GS, EAT, BT, MT, AH, HH, IJ, GM, PS, UT, and PM performed the data curation. KEH, SR, HJ, OE, DFG, and PM performed the statistical and bioinformatics analyses. KEH, SR, PM, and KS drafted the manuscript. All authors contributed to the final version of the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.012.

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