ORIGINAL ARTICLE

Spread of SARS-CoV-2 in the Icelandic Population

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ABSTRACT

BACKGROUND

During the current worldwide pandemic, coronavirus disease 2019 (Covid-19) was first diagnosed in Iceland at the end of February. However, data are limited on how SARS-CoV-2, the virus that causes Covid-19, enters and spreads in a population.

METHODS

We targeted testing to persons living in Iceland who were at high risk for infection (mainly those who were symptomatic, had recently traveled to high-risk countries, or had contact with infected persons). We also carried out population screening using two strategies: issuing an open invitation to 10,797 persons and sending random invitations to 2283 persons. We sequenced SARS-CoV-2 from 643 samples.

RESULTS

As of April 4, a total of 1221 of 9199 persons (13.3%) who were recruited for targeted testing had positive results for infection with SARS-CoV-2. Of those tested in the general population, 87 (0.8%) in the open-invitation screening and 13 (0.6%) in the random-population screening tested positive for the virus. In total, 6% of the population was screened. Most persons in the targeted-testing group who received positive tests early in the study had recently traveled internationally, in contrast to those who tested positive later in the study. Children under 10 years of age were less likely to receive a positive result than were persons 10 years of age or older, with percentages of 6.7% and 13.7%, respectively, for targeted testing; in the population screening, no child under 10 years of age had a positive result, as compared with 0.8% of those 10 years of age or older. Fewer females than males received positive results both in targeted testing (11.0% vs. 16.7%) and in population screening (0.6% vs. 0.9%). The haplotypes of the sequenced SARS-CoV-2 viruses were diverse and changed over time. The percentage of infected participants that was determined through population screening remained stable for the 20-day duration of screening.

CONCLUSIONS

In a population-based study in Iceland, children under 10 years of age and females had a lower incidence of SARS-CoV-2 infection than adolescents or adults and males. The proportion of infected persons identified through population screening did not change substantially during the screening period, which was consistent with a beneficial effect of containment efforts. (Funded by deCODE Genetics–Amgen.)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused clusters of severe respiratory illness in Wuhan, China, in late 2019.[1] By January 2020, the virus had been isolated and sequenced,[2,3] which revealed close relationships to coronaviruses such as SARS-CoV-1[4,5] and MERS-CoV.[6] As of March 31, researchers had deposited 3095 SARS-CoV-2 sequences in a repository (Global Initiative on Sharing All Influenza Data; GISAID).[7] As of April 4, a total of 1,051,635 persons in 208 countries were reported to be infected by SARS-CoV-2, which causes coronavirus disease 2019 (Covid-19), a disease that had led to more than 75,000 deaths.[8] Although the number of new cases has decreased drastically in China, it has rapidly increased in Europe and the United States, with the total number of deaths associated with Covid-19 in Italy, Spain, France, and the United States exceeding that in China.[9] On March 11, 2020, the World Health Organization (WHO) announced that Covid-19 should be characterized as a pandemic.[10] At great economic cost, many countries have adopted unprecedented measures to curb the spread of the virus, such as large-scale use of isolation and quarantine, closing borders, imposing limits on public gatherings, and implementing nationwide lockdowns.

Early reports from China and Italy indicated that SARS-CoV-2 causes illness of varying degrees,[11,12] with females and children being underrepresented among cases, especially among severe and fatal cases. It is unclear whether this is because females and children are less likely to be infected by SARS-CoV-2 or because Covid-19 is less likely to become symptomatic after infection in these demographic groups.

The first SARS-CoV-2 infection in Iceland was confirmed on February 28, 2020, in a person who had just returned from northern Italy before that region had been designated as a high-risk area by the Icelandic authorities. Iceland is an island with 364,000 inhabitants, with only one major gateway into the country, the international airport through which 7 million travelers pass each year. On March 19, all travel outside Iceland was designated as high risk. By March 31, a total of 1308 persons in Iceland had tested positive for SARS-CoV-2.[13]

In this study, we used two strategies for SARS-CoV-2 testing in Iceland — targeted testing of persons at high risk for infection and population screening — which provided a gauge of success of measures implemented to curb the spread of the virus. We also sequenced the genomes of SARS-CoV-2 from samples obtained from some persons who had tested positive in order to establish the origins of the specific virions spreading in Iceland and to determine how the virus has mutated as it has spread.

Methods

Study Oversight and Design

The study, which was sponsored by deCODE Genetics–Amgen, was approved by the National Bioethics Committee of Iceland. A flowchart outlining the milestones in the study is shown in Figure 1.

Targeted Testing of Persons at High Risk

Targeted testing began on January 31, 2020, and involved persons who were deemed to be at high risk for SARS-CoV-2 infection. Included in this group were mainly persons who were already symptomatic (cough, fever, body aches, and shortness of breath) and who were returning to Iceland from countries or regions that were classified by the health authorities as being at high risk or who had been in contact with infected persons.

Population Screening

Population screening for SARS-CoV-2 was initiated on March 13 and was open to all residents of Iceland who were symptom-free or who had mild symptoms of the common cold, which is prevalent in Iceland at this time of the year. Registration for the test was performed online. Sample collection was carried out in Reykjavik, the capital of Iceland. Hence, the majority of participants resided in the capital area. During sample collection, a health care worker administered a questionnaire regarding the participant's recent travels, contacts with infected persons, and symptoms compatible with Covid-19.

To evaluate the sampling method of the population screening, we also invited 6782 randomly chosen Icelanders between the ages 20 and 70 years to participate through a telephone text message sent between March 31 and April 1. Of these invitees, 2283 (33.7%) had participated by April 4. Of the invited persons, 2797 (41.2%) were male; of the invitees who participated in the study, 864 (37.8%) were male. Data from the open-

invitation subgroup and random-sample subgroup were evaluated separately.

All participants who tested positive for SARS-CoV-2 were required to self-isolate until 10 days after fever had subsided or until they tested negative, and all contacts of these participants were required to self-quarantine for 2 weeks. (Details regarding these measures are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) In addition to isolating participants who had tested positive and quarantining those at high risk for infection, the Icelandic authorities, on March 16, initiated a ban on gatherings of more than 100 persons and stated that social distancing of at least 2 m should be maintained. On March 24, gatherings were restricted to no more than 20 people; to protect the elderly and other groups who are at increased risk for serious illness from Covid-19, health authorities promoted self-isolation and banned visits to nursing homes and hospitals. To date, although universities and colleges have been closed since March 16, day care centers and elementary schools have remained open. The Icelandic authorities have not restricted international travel but have required that returning Icelanders go into quarantine. On March 19, all travel outside Iceland was designated as high-risk.

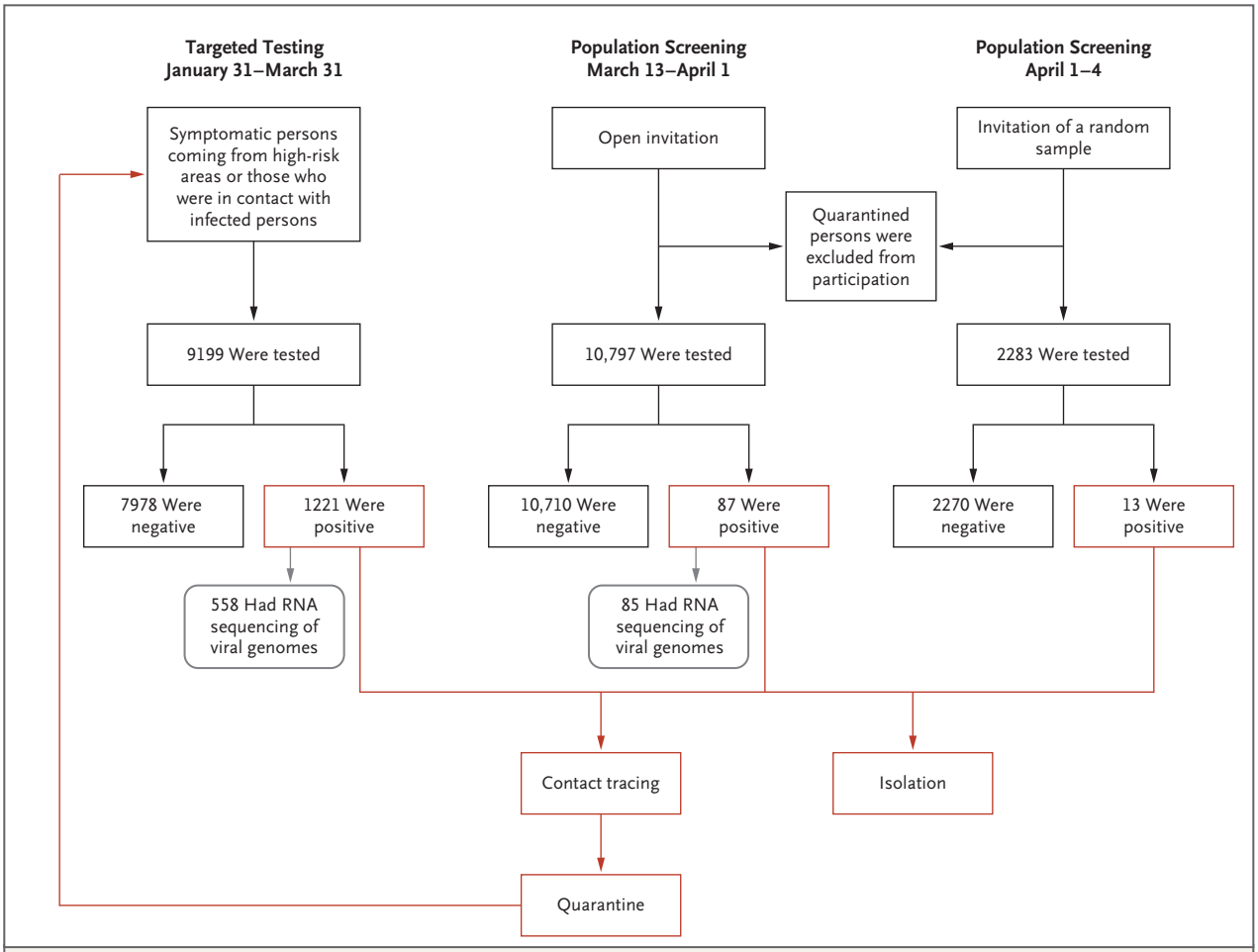


Figure 1. Study Design for Targeted Testing and Population Screening.

In Iceland, targeted testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began on January 31, 2020, and involved persons who were deemed to be at high risk for infection (i.e., those who were symptomatic, had traveled to high-risk countries, or had contact with infected persons). In the population screening, data from the open-invitation subgroup and random-sample subgroup were evaluated separately.

TRACKING OF SARS-COV-2 INFECTIONS

All the participants who tested positive for SARS-CoV-2 were contacted by telephone by a team designated by the authorities to track their infection. The participants were asked about their symptoms and onset, recent travels, and previous contacts with infected persons. They were also asked to identify everyone with whom they had been in contact during the 24 hours before they had noticed their first symptom and to indicate the duration and degree of intimacy of the contact. All registered contacts were interviewed by telephone, asked about their symptoms, and requested to go into 2 weeks of quarantine. Those with symptoms and those in whom symptoms developed in quarantine were tested for SARS-CoV-2.

ACQUISITION AND PREPARATION OF SAMPLES

We obtained nasopharyngeal and oropharyngeal samples and combined them into a single tube for each participant before RNA isolation. Viral RNA from all samples was isolated within 24 hours, either at the Department of Clinical Microbiology Laboratory at Landspitali–National University Hospital of Iceland (LUH) or at deCODE Genetics. Both extraction methods are based on an automated magnetic bead-purification procedure. Testing for SARS-CoV-2 was performed either at LUH or deCODE Genetics with the use of similar quantitative real-time polymerase-chain-reaction (qRT-PCR) assay methods (see the Supplementary Appendix).

SEQUENCING

We performed reverse transcription and multiplex PCR on the basis of information provided by the Artic Network initiative (https://artic.network/) to generate complementary DNA and sequencing libraries using the NEBNext Ultra II kit (New England Biolabs). All samples were sequenced on Illumina MiSeq sequencers with the use of 300-cycle MiSeq v2 reagent kits (Illumina). Details regarding sequencing are provided in the Supplementary Appendix.

ANALYSIS OF SEQUENCING DATA

We aligned amplicon sequences to the reference genome of the SARS-CoV-2 (GenBank number, NC_045512.2)[2] using the latest Burrows–Wheeler Aligner (BWA-MEM) and variants called with sequencing utilities bcftools[14] (see the Supplementary Appendix). The mutations that are listed in Table S3 in the Supplementary Appendix were used to define clades with the use of the joint calling from the Graphtyper.[15] For network analysis of haplotypes, we generated a median-joining network[8] of SARS-CoV-2 sequences using data from our sequencing effort in Iceland and from GISAID that were available on March 22 (Table S4). To reduce noise in the network, an imputation step was implemented for sequences with missing nucleotides at sites where other sequences varied, in which the missing nucleotide was imputed to the consensus variant for the clade to which it was assigned on the basis of nonmissing sites.

STATISTICAL ANALYSIS

We used a likelihood ratio method to calculate 95% confidence intervals of fractions with the Clopper–Pearson exact method when the estimated fraction was 0 or 1, as implemented in the R package binom (https://CRAN.R-project.org/package=binom). For comparisons of demographic characteristics (sex and age) and symptoms between groups, we used the likelihood ratio method and logistic regression to estimate 95% confidence intervals of odds ratios. In the logistic regression, we used the testing status for SARS-CoV-2 as the response and included the variable assessed as a covariate. In assessing the difference in test status according to sex, we used an indicator for an age of less than 10 years as a covariate. (The setting of the age threshold at 10 years was arbitrary.) We did not adjust confidence intervals for multiple testing.

RESULTS

SARS-COV-2 INFECTION

On April 4, 2020, among the 9199 persons who were targeted for testing, 1221 (13.3%) tested positive for SARS-CoV-2. Through population screening, positive results were reported for 100 of 13,080 participants (0.8%; 95% confidence interval [CI], 0.6 to 1.0); positive test results were reported for 87 of 10,797 persons (0.8%; 95% CI, 0.6 to 1.0) who accepted the open invitation for testing and 13 of 2283 persons (0.6%; 95% CI, 0.3 to 0.9) who were invited at random (Table 1 and Fig. 2). The percentage of infected participants that was determined through population

screening remained stable for the 20-day duration of screening (Fig. 2F).

Sample collection for population screening began on March 13, and the first positive test results were communicated to the Icelandic health authorities on March 15 (Fig. S2). Because of this timing and rapid changes in the definition of high-risk areas by the Icelandic authorities, we report the targeted testing in two phases: early-phase testing (January 31 through March 15) and later-phase testing (March 16 through 31).

INITIATION OF TESTING

In the early targeted testing, 65.0% of the participants who tested positive for SARS-CoV-2 had recently traveled outside Iceland. In the later phase, 15.5% had recently traveled outside the country (Table 1 and Fig. S3). Similarly, the proportion of participants in the population screening and who had recently traveled outside the country also fell rapidly during the study period. Overall, 23.0% of those with positive test results through population screening had recently traveled, in contrast to 8.7% of those who tested negative.

Of the participants who tested positive from the early targeted-testing phase and who had traveled, 86.1% had visited areas designated as being at high risk by the end of February (China and the Alps mountain regions in Austria, Italy, and Switzerland), whereas only 1 of the participants with a positive test identified through population screening had traveled to a high-risk area. The quarantining of persons arriving from these high-risk regions accounted for the very low proportion of participants in the population-screening group who had recently traveled. On the other hand, 12 of 87 participants (13.8%) with positive tests in the screening group had recently traveled to the United Kingdom, as compared with 1.8% of those who tested negative, which suggests relatively early spread of the virus in the U.K. population.

In the early phase of targeted testing, 40.1% of the participants who tested positive reported having had contact with a known infected person, as compared with 60.2% in the later phase of targeted testing. However, only 6.9% of the participants in the population-screening group reported having had contact with an infected person, probably because infected persons and their contacts were in isolation and therefore not eligible for the population screening.

SYMPTOMS OF DISEASE

Among the participants with positive results for SARS-CoV-2, symptoms of Covid-19 were reported by 93% of those in the overall targeted-testing group and by 57% of those in the overall population-screening group. However, 29% of participants who tested negative in the overall population-screening group also reported having symptoms. Reports of symptoms became less common among participants in the population screening during the study period (Fig. S4).

AGE AND VIRAL SUSCEPTIBILITY

The mean (±SD) age of persons who were targeted for testing overall (40.3±18.4 years) was similar to the mean age (39.7±18.0 years) in the overall population-screening group (Fig. 2A through 2C). In the two data sets, those who tested positive were older and had a narrower age distribution than the full-participant data set (Table 1). Of the 564 children under the age of 10 years in the targeted testing group, 38 (6.7%) tested positive, in contrast to positive test results in 1183 of 8635 persons who were 10 years of age or older (13.7%). In analyses involving participants up to 20 years of age, we observed a gradual increase with older age in the percentage who tested positive (Fig. S5). In the population-screening group, the difference was even more marked: none of the 848 children under the age of 10 years tested positive, as compared with 100 of 12,232 persons (0.8%; 95% CI, 0.7 to 1.0) 10 years of age or older.

SEX AND VIRAL SUSCEPTIBILITY

In the overall targeted-testing and population-screening groups, more females were tested than males (60.5% and 55.1%, respectively) (Table 1). However, in the targeted testing, the percentage of males who tested positive was greater than that of females (16.7% vs. 11.0%), for an odds ratio of 1.66 (95% CI, 1.47 to 1.87). In the population screening, the relative difference between the sexes was similar (0.9% vs. 0.6%), for an odds ratio of 1.55 (95% CI, 1.04 to 2.30) (Fig. 2D and Fig. S6).

VIRAL HAPLOTYPES

We sequenced SARS-CoV-2 RNA extracted from 643 samples; of these samples, we obtained coverage of more than 90% of the SARS-CoV-2 genome from 581 samples and more than 67% from 605

Table 1. Study Participants in Targeted Testing or Population Screening for SARS-CoV-2, According to Timing.

Variable	Targeted Testing January 31–March 15		Population Screening March 13–April 1		Targeted Testing March 16–31		Random-Sample Population Screening April 1–4	
	All Persons (N=1924)	SARS-CoV-2 Positive (N=177)	All Persons (N=10,797)	SARS-CoV-2 Positive (N=87)	All Persons (N=7275)	SARS-CoV-2 Positive (N=1044)	All Persons (N=2283)	SARS-CoV-2 Positive (N=13)
SARS-CoV-2 positivity — no. (%)	177 (9.2)	—	87 (0.8)	—	1044 (14.4)	—	13 (0.6)	—
SARS-CoV-2 sequencing performed — no. (%)	—	157 (88.7)	—	59 (67.8)	—	361 (34.6)	—	0
Male sex — no. (%)	835 (43.4)	92 (52.0)	5004 (46.3)	46 (52.9)	2795 (38.4)	516 (49.4)	864 (37.8)	9 (69.2)
Mean age — yr	40.0	44.4	38.6	40.8	40.4	41.3	45.4	50.5
Any international travel — no. (%)	—	115 (65.0)	939 (8.7)	20 (23.0)	—	162 (15.5)	11 (0.5)	0
Specific country of international travel — no.*								
China (high-risk area)	—	1	2	0	—	0	0	0
Austria (high-risk area February 29)	—	43	16	0	—	34	0	0
Italy (high-risk area February 29)	—	45	7	1	—	3	0	0
Switzerland (high-risk area February 29)	—	9	11	0	—	2	1	0
United Kingdom	—	7	193	12†‡	—	44	0	0
United States	—	7	160	3	—	18	1	0
Denmark	—	2	90	1	—	2	2	0
Germany (high-risk area March 12)	—	1	36	1	—	2	0	0
Spain (high-risk area March 14)	—	0	142	1‡	—	34	3	0
The Netherlands	—	0	26	2†	—	5	1	0
Poland	—	0	45	1	—	0	0	0
Other	—	0	247	0	—	14	4	0
Known contact with infected person — no. (%)	—	71 (40.1)	281 (2.6)	6 (6.9)	—	629 (60.2)	60 (2.6)	1 (7.7)

Reported any symptoms — no. (%)‡	—	153 (86.4)	3579 (33.1)	51 (58.6)	—	985 (94.3)	271 (11.9)	6 (46.2)
Reported specific symptoms — no.	—	78	3579	51	—	950	271	6
Distribution of symptoms reported — no. (%)								
Fever	—	38 (42.1)§	410 (3.8)	17 (19.5)	—	491 (48.8)§	21 (0.9)	0
Cough	—	23 (25.5)§	1769 (16.4)	32 (36.8)	—	313 (31.1)§	87 (3.8)	3 (23.1)
Body aches	—	26 (28.8)§	537 (5.0)	19 (21.8)	—	310 (30.8)§	43 (1.9)	1 (7.7)
Headache	—	21 (23.3)§	1,086 (10.1)	18 (20.7)	—	239 (23.7)§	89 (3.9)	2 (15.4)
Sore throat	—	15 (16.6)§	1,558 (14.4)	26 (29.9)	—	123 (12.2)§	107 (4.7)	0
Rhinorrhea	—	14 (15.5)§	1,784 (16.5)	24 (27.6)	—	126 (12.5)§	139 (6.1)	4 (30.8)
Fatigue¶	—	12 (13.3)§	—	—	—	207 (20.6)§	—	—
Loss of smell or taste‖	—	2 (2.2)§	—	—	—	116 (11.5)§	13 (0.6)	1 (7.7)
Other	—	14 (15.5)§	911 (8.4)	15 (17.2)	—	254 (25.2)§	88 (3.9)	3 (23.1)

* On March 19, all travel outside Iceland was designated as high-risk.
† One person traveled to the United Kingdom and the Netherlands.
‡ One person traveled to the United Kingdom and Spain.
§ Information regarding symptoms was not collected for participants who tested negative in the targeted testing. Symptoms were not recorded for all the participants who were targeted for testing. Therefore, for the early targeted-testing group, we used the formula: 100(symptom count/78×[153/177]), and for the later targeted-testing group, we used the formula 100(symptom count/950×[985/1044]).
¶ Participants were not queried about fatigue in the population screening.
‖ Participants were not queried about loss of smell or taste in the open-invitation phase of the population screening.

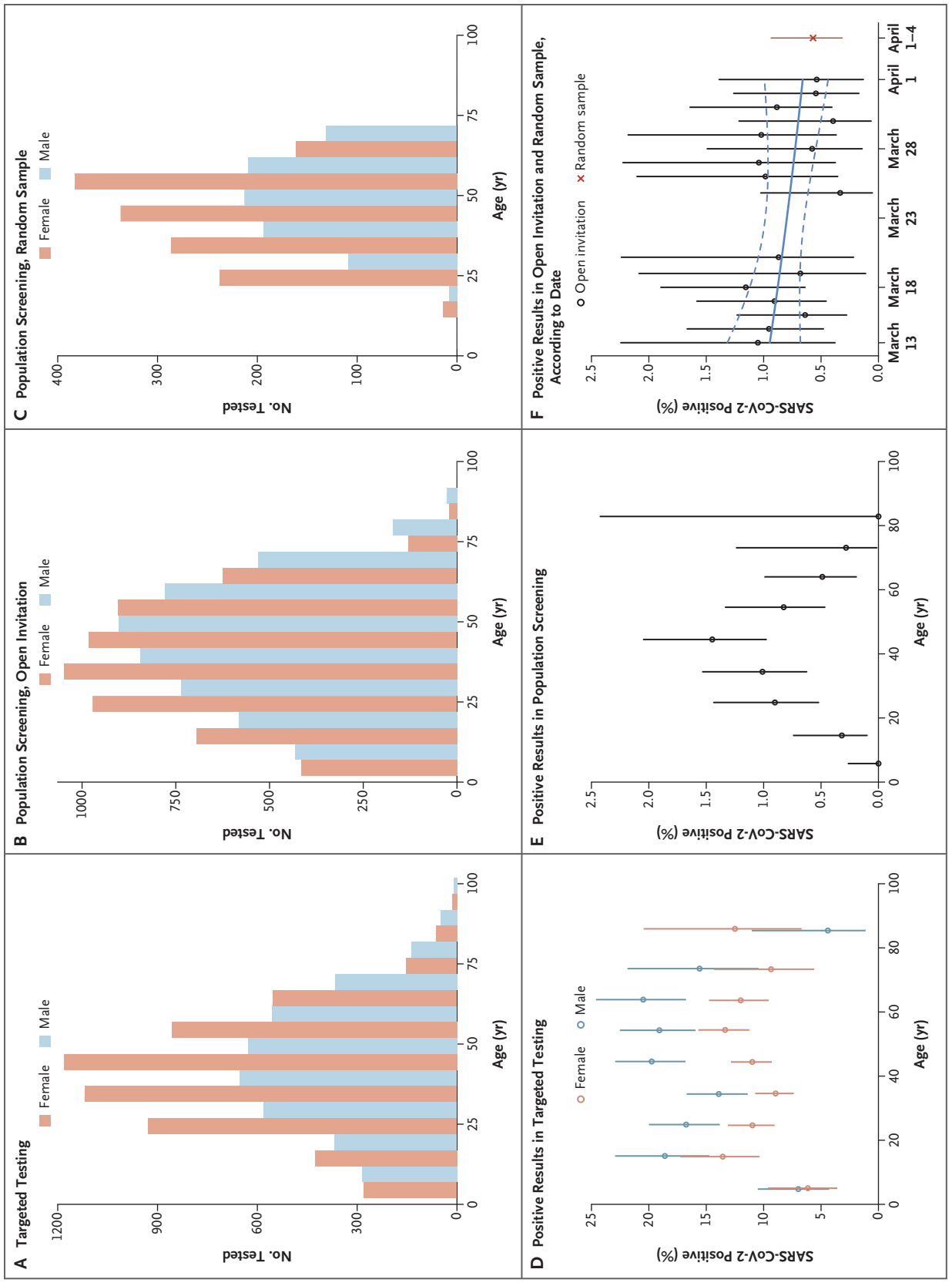

A Targeted Testing
Female
Male
No. Tested
Age (yr)
B Population Screening, Open Invitation
C Population Screening, Random Sample
D Positive Results in Targeted Testing
SARS-CoV-2 Positive (%)
E Positive Results in Population Screening
F Positive Results in Open Invitation and Random Sample, According to Date
Open invitation
Random sample
March 13
March 18
March 23
March 28
April 1
April 1–4

Figure 2 (facing page). Distribution of Targeted Testing and Population Screening for SARS-CoV-2 and Percentages of Positive Results, According to Age and Sex.

Shown is the distribution according to age and sex among all the participants in the study who were targeted for testing for the presence of SARS-CoV-2 (Panel A), among those who participated in the open invitation of the population screening (Panel B), and among those who participated in the random sample (Panel C). Also shown are the percentages of participants who tested positive stratified according to sex in the targeted-testing group (Panel D) and in the population-screening group (Panel E). In addition, the percentage of participants who tested positive in the population screening is shown according to sampling date in the open invitation (black) and the random sampling (red) (Panel F). The solid blue curve in Panel F indicates the logistic-regression line, and the dashed lines indicate the 95% confidence intervals (CI) of the logistic regression. The logistic-regression slope corresponds to a change of –2% (95% CI, –5 to 1) in the infection rate per day. The vertical bars indicate 95% confidence intervals for age groups (in Panels D and E) and for individual dates (in Panel F).

samples. We called 409 sequence variants, 291 of which were not found in the GISAID database (Fig. 3A). (GISAID accession numbers are provided in the Supplementary Appendix.) We used clade-informative mutations (Table S3) to assign haplotypes to persons: 518 from the targeted-testing group and 59 from the population-screening group (Table 2, Fig. 3C, and Fig. S7).

GEOGRAPHIC VIRAL ORIGIN

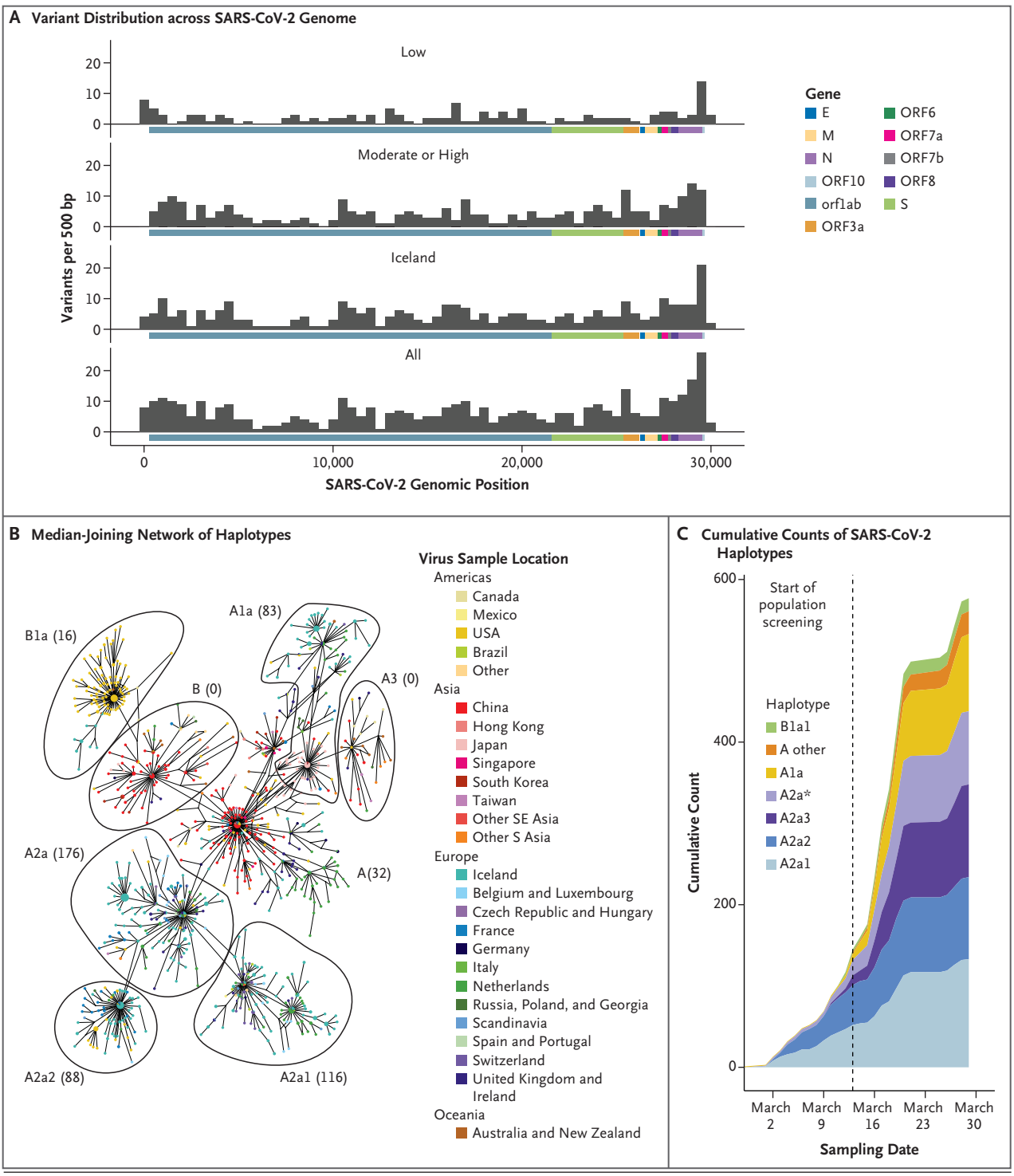
To shed further light on the geographic origin of the SARS-CoV-2 infections in residents of Iceland, we generated a median-joining network of 1547 complete viral sequences (513 from complete viral genomes from Icelanders and 1034 from other populations around the world) (Fig. 3B). Several viral lineages have emerged during the 3 to 4 months since the original outbreak in China, with an average of five mutations separating the lineages from the founding haplotype from Wuhan (the central haplotype of clade A). Although the sequencing efforts vary considerably among populations, it is clear that the geographical distribution of clades is highly structured. Thus, A and B haplotypes are common in East Asia, whereas the B1a haplotype appears to be at the center of the outbreak on the West Coast of the United States, and A2a and its descendants are almost exclusively found in European populations.

COMPOSITION OF HAPLOTYPES

The haplotypes of SARS-CoV-2 infections observed in Iceland cluster into several diverse clades (Fig. 3B). To estimate the number of introductions of the SARS-CoV-2 virus to Iceland, we searched for infected persons who had traveled internationally or had an unknown source of infection. This led us to 363 persons for whom viral genomes had been sequenced. These genomes clustered into 42 distinct clades, which provided a lower boundary on the number of individual introductions.

Of the 157 sequenced virions obtained during the early targeted testing, 143 were in the A2 clade (Table 2 and Fig. S7). By the time we initiated the population screening, all travelers who had returned from ski resorts in the Alps had been requested to self-quarantine and were not eligible for participation, which resulted in a substantially different composition of haplotypes. For example, the A2a2 haplotype, which was most commonly seen in travelers coming from Austria in the early phase of targeted testing, was much less frequent in travelers in the population screening. The A1a haplotype was more common in the general population than in those who received targeted testing, with a total of 23 of 59 haplotypes among participants in the population-screening group, as compared with only 8 of 157 haplotypes in the early-targeted testing.

The composition of haplotypes changed substantially from early targeted testing to later targeted testing. The A2a1 and A2a2 haplotypes, which had collectively made up 103 of 157 haplotypes (65.6%) in the early-targeted testing, were reduced to 115 of 361 haplotypes (31.9%) in the later-targeted testing, mostly because of the increased frequency of the A1a and other A2a-derived haplotypes. This change probably meant that population screening identified clusters of infected persons who seeded infection from areas that had not been designated as high risk, such as the United Kingdom. The relatively high prevalence of A1a and A2a clades in the later-targeted testing group was unsurprising: the targeted testing had been extended to include those who had traveled to additional high-risk areas, and population screening had identified cases that could be used to inform tracking efforts. The A2a3a and A2a2a haplotypes were the two most common haplotypes in Iceland; of



the 577 persons who provided samples that were sequenced, the A2a3a haplotype was found in 78 (13.5%) and the A2a2a haplotype was found in 45 (7.8%).

HAPLOTYPE ANALYSIS OF CONTACT-TRACING NETWORKS

Haplotype analysis that was based on SARS-CoV-2 sequences overlaid on contact-tracing net-

Figure 3 (facing page). Distribution of Variants across the SARS-CoV-2 Genome, a Median-Joining Network of Haplotypes, and Cumulative Counts from Targeted Testing and Population Screening.

Panel A shows the distribution of variants across the SARS-CoV-2 genome. The genes of SARS-CoV-2 are E (envelope small membrane protein), M (membrane protein), N (nucleoprotein), S (spike protein), and ORFs (open reading frames) 10, 1ab, 3a, 6, 7a, 7b, and 8. The different subsets that were considered included all variants, variants only observed in Iceland, and variants that were determined by the variant effect predictor to have a low effect (synonymous variants), a moderate effect (missense variants), or a high effect (loss-of-function variants). Panel B shows a median-joining network of 802 haplotypes from 1547 SARS-CoV-2 sequences (of which 513 are from Iceland). Each circle represents a different sequence type, in which the size of the circle reflects the number of carrier hosts, and the lines between circles represent one or more mutations that differentiate the sequence types. Circles are colored according to the regions where samples were obtained. The principal clades are outlined and labeled, with the number of sequences from Icelanders shown in parentheses. Haplotypes from clade A are not outlined. Panel C shows the cumulative counts of SARS-CoV-2 haplotypes from targeted testing and population screening as a function of sampling date. A2a* refers to all A2a haplotypes except A2a1, A2a2, and A2a3. The dashed vertical line indicates the start of the population screening.

works[16] showed concordance between the contacts identified by the tracking team and those based on viral sequences (Fig. 4A). Of the 369 pairs of persons found through contact tracing, 295 were consistent with the sequence data (i.e., their haplotypes differed by strictly less than 3 mutations).

Figure 4B shows one of the most complex contact-tracing networks, in which clusters of persons returning from Italy or Austria transmitted the virus to persons in Iceland. The figure shows a network of 14 persons who were infected in Iceland. Haplotype analysis showed that these persons were infected by viruses with the A2a1 haplotype, more commonly imported from northern Italy than from Austria (Table 2). This cluster also contained persons with a mutation that was specific to Iceland. The cluster can be traced to a person who had both mutated and wild-type haplotypes; those whom this person infected had only the mutated haplotype. We searched for persons carrying these mutations who were not associated with this cluster and found two who had probably been infected by

Table 2. Distribution of SARS-CoV-2 Haplotypes, According to Timing of Diagnosis and Internationally Imported or Local Transmission.*

Haplotype	Early Targeted Testing January 31–March 15			Population Screening March 13–April 1			Later Targeted Testing March 16–31		
	Imported	Country of Origin	Local	Imported	Country of Origin	Local	Imported	Country of Origin	Local
	no. (%)		*no. (%)*	*no. (%)*		*no. (%)*	*no. (%)*		*no. (%)*
All haplotypes	101 (100)	IT:42, AT:38	56 (100)	16 (100)	UK:9, US:3	43 (100)	83 (100)	AT:28, UK:23	278 (100)
A2a1	36 (35.6)	IT:29, AT:3	16 (28.6)	5 (31.2)	UK:4, DE:1	8 (18.6)	17 (20.5)	AT:6, UK:4	51 (18.3)
A2a2	33 (32.7)	AT:28, DK:2	18 (32.1)	2 (12.5)	US:2	1 (2.3)	19 (22.9)	AT:9, UK:5	28 (10.1)
A2a3	5 (5.0)	CH:5	11 (19.6)	0		11 (25.6)	5 (6.0)	ES:2	82 (29.5)
A2a	19 (18.8)	IT:11, AT:6	5 (8.9)	2 (12.5)	NL:1, DK:1	1 (2.3)	30 (36.1)	AT:13, UK:10	33 (11.9)
A1a	2 (2.0)	CH:1, IT:1	6 (10.7)	4 (25.0)	UK: 4	19 (44.2)	4 (4.8)	UK:2, ES:2	60 (21.6)
Other clade A	2 (2.0)	UK:1, AT:1	0	2 (12.5)	UK:2	3 (7.0)	2 (2.4)	US:1, UK:1	19 (6.8)
B1a1	4 (4.0)	US:4	0	1 (6.2)	US:1	0	6 (7.2)	US:6	5 (1.8)

* Among the imported haplotypes, each country is represented by a two-letter country code as follows: AT denotes Austria, CH Switzerland, DE Germany, DK Denmark, ES Spain, IT Italy, NL Netherlands, UK United Kingdom, and US United States. For each haplotype, the two most common countries of origin are indicated, followed by the number of participants with that haplotype.

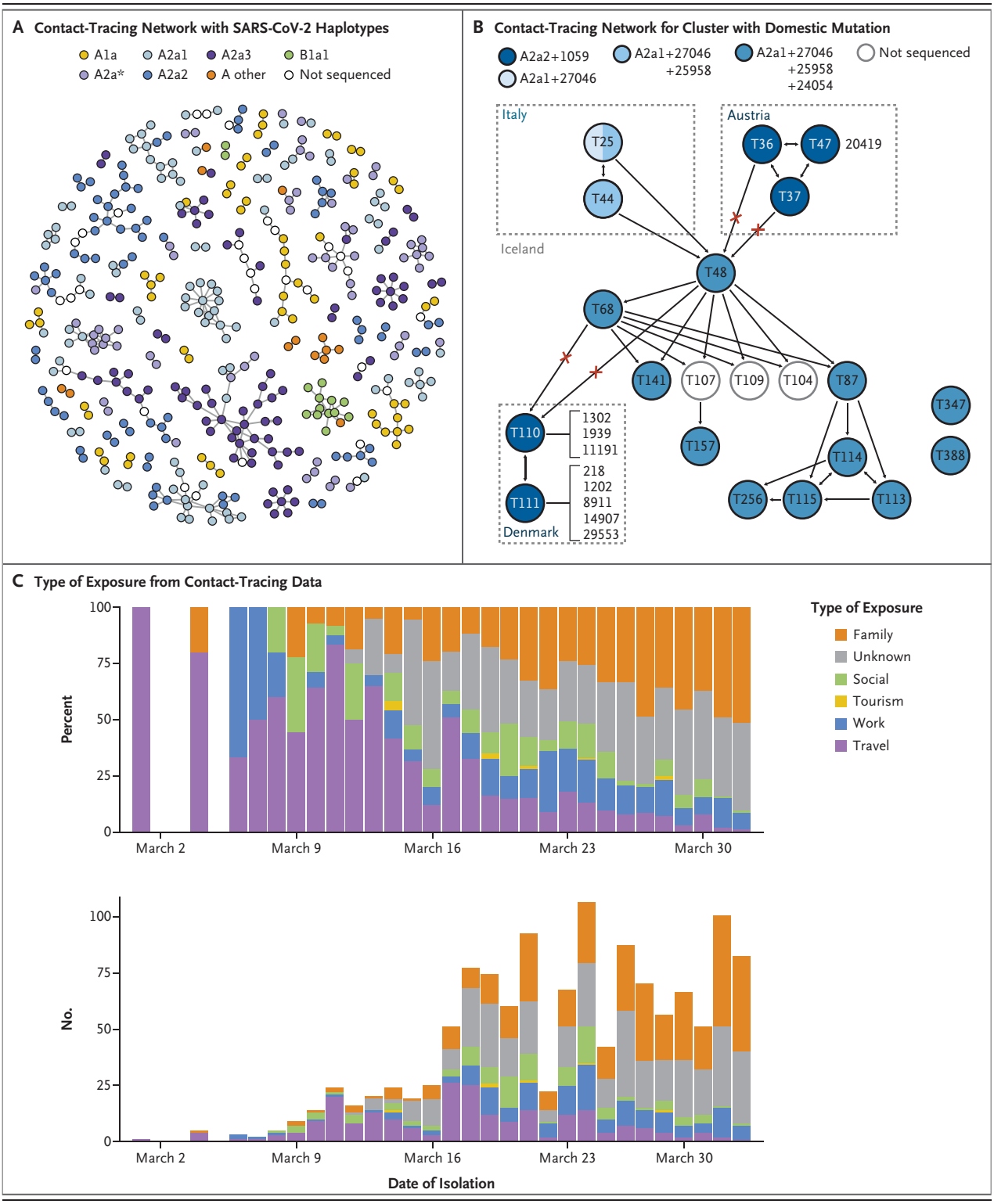

A Contact-Tracing Network with SARS-CoV-2 Haplotypes
A1a
A2a1
A2a3
B1a1
A2a*
A2a2
A other
Not sequenced
B Contact-Tracing Network for Cluster with Domestic Mutation
A2a2+1059
A2a1+27046
A2a1+27046 +25958
A2a1+27046 +25958 +24054
Not sequenced
Italy
Austria
Iceland
Denmark
T25
T44
T36
T47
20419
T37
T48
T68
T141
T107
T109
T104
T87
T347
T388
T110
1302
1939
11191
T157
T114
T111
218
1202
8911
14907
29553
T256
T115
T113
C Type of Exposure from Contact-Tracing Data
Percent
No.
March 2
March 9
March 16
March 23
March 30
Date of Isolation
Type of Exposure
Family
Unknown
Social
Tourism
Work
Travel

Figure 4 (facing page). Overall Clusters in the Contact-Tracing Network, a Network Cluster Including a Novel Domestic Mutation, and Source of Exposure.

Panel A shows an overview of all clusters in the contact-tracing network with SARS-CoV-2 haplotypes. Panel B shows a contact-tracing network for a cluster that included a novel domestic mutation (24054C→T). Person T25 carried both the A2a1a strain and the A2a1a+25958 strain. Contact-tracing networks show infected persons as nodes and a connection between two nodes where a transmission of infection or contact has been established. In cases in which the direction of transmission was ambiguous, a bidirectional arrow is shown. Persons who traveled internationally are indicated in boxes representing their travel destination. The colors of nodes represent the haplotype of the viral strain, either as a clade or a clade plus one or more mutations. Additional mutations are represented by a position number beside each node. The labels on the nodes are identifiers given in increasing order of identification (e.g., T6 is the sixth case reported). Red X marks indicate recorded contacts that are inconsistent with the viral haplotypes carried by each person. Panel C shows the type of exposure from contact-tracing data according to the date of isolation and percentage (top graph) and total number (bottom graph). The type of exposure is classified for each positive case into the following categories: family, unknown, social, work (including schools), tourism (reported working domestically in tourism), and travel (international travel).

someone in the cluster through an unknown contact.

CONTACT TRACING AND EXPOSURE TYPE

We categorized exposure into six categories: family, social, tourism (working in the travel industry in Iceland), work (including schools), travel (international), and unknown and observed a shift in the composition of exposures from international travel and social exposure to familial exposure over time (Fig. 4C).

DISCUSSION

In Iceland, the prevalence of SARS-CoV-2 infection among persons at high risk for infection and the stability of the infection rate in the general population provide grist for both assurance and alarm. The percentage of participants who tested positive in population screening remained stable (0.8%) over the course of 20 days, and the infection rates in the two screening groups (recruited through open invitation and through random sampling) were not substantially different. These results were consistent with a slow spread of SARS-CoV-2 through the Icelandic population.

The lack of increase in the incidence of infection over time may be due to containment efforts by the Icelandic health care authorities and their nimble response to the outbreak abroad. Testing of exposed persons with symptoms had been carried out for 1 month before the first SARS-CoV-2 case was identified in Iceland. Self-isolation, quarantining, and other social-distancing measures may also have helped to prevent an increase in the infection rate.

Although we asked participants who had respiratory symptoms that they described as more than mild not to participate in population screening, close to half the participants reported symptoms, most commonly rhinorrhea and coughing. Thus, a weakness in the design of the population-screening component of the study was that persons who were concerned about potential infection may have been more likely to participate than others. Symptoms were common both in participants who tested positive and in those who tested negative for SARS-CoV-2 in the overall population-screening group. Notably, 43% of the participants who tested positive reported having no symptoms, although symptoms almost certainly developed later in some of them. During the study, the prevalence of symptoms decreased considerably in both testing groups (despite the stability of the SARS-CoV-2 infection rate), probably owing to a general decrease in other respiratory infections, which in turn may have been brought about through measures implemented to decrease the spread of SARS-CoV-2.

Young children and females were less likely to test positive for SARS-CoV-2 than adolescents or adults and males. Whether the lower incidence of positive results in these two groups resulted from less exposure to the virus or from biologic resistance is not known. In other studies, investigators have found that infected children and females were less likely to have severe disease than adults and males, respectively.[11,12]

The haplotype composition of the viruses from persons who were identified through population screening was different from that of viruses infecting persons who tested positive in the early phase of targeted testing, so we conclude that the haplotypes of the virus that were

propagating in the general population came from a different source (as compared with those infecting high-risk persons in the early phase of targeted testing), perhaps brought into Iceland by persons arriving from countries that had not yet been designated as high-risk areas.

Thus, the frequency of the SARS-CoV-2 infection in the overall Icelandic population was stable from March 13 to April 1, a finding that appears to indicate that the containment measures had been working. However, the virus has spread to the extent that unless we continue to test and isolate, track contacts, and quarantine, we are likely to fail in our efforts to contain the virus.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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