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Open Forum Infectious Diseases

BRIEF REPORT

Assessment of Coronavirus Disease 2019 Intervention Strategies in the Nordic Countries Using Genomic Epidemiology

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We explored how the duration, size, and number of virus transmission clusters, defined as country-specific monophyletic groups in a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) phylogenetic tree, differed among the Nordic countries of Norway, Sweden, Denmark, Finland, and Iceland. Our results suggest that although geographical connectivity, population density, and openness influence the spread and the size of SARS-CoV-2 transmission clusters, the different country-specific intervention strategies had the largest impact. We also found a significant positive association between the size and duration of transmission clusters in the Nordic countries, suggesting that the rapid deployment of contact tracing is a key response measure in reducing virus transmission.

Keywords. COVID-19; genomic epidemiology; Nordic countries; SARS-CoV-2; transmission clusters.

The Nordic countries of northern Europe—Norway, Denmark, Iceland, Finland, and Sweden—are known for their similar demographics and political systems [1]. They have comparable, tax-funded health systems with universal coverage for all citizens and a large extent of management through authorities at the local level [2]. However, during the first year of the coronavirus disease 2019 (COVID-19) pandemic, before widespread vaccination rollout, these countries adopted distinctly different pandemic policies and intervention measures [3]. By mid-March 2020, Norway [4], Denmark [5], and Finland [6] had implemented a national lockdown, including the closing of schools, workplaces, and nonessential businesses, limiting the number of people gathering at home and in public events, and international travel restrictions. Iceland, a small isolated island population, had also implemented comprehensive national measures; however, schools stayed open, subject to infection control interventions [7]. Sweden initially was slower to respond and had a more lenient mitigation strategy relying on recommendations [8] (see Supplementary Information).

Testing was initially recommended to risk groups, severely ill patients, and health personnel in all the Nordic countries due to limited capacity. Iceland and Denmark were the first to get sufficient testing resources to offer widespread testing in the spring of 2020. Denmark continued to have a very high testing rate as a means to prevent transmission. Sweden was the last to initiate extensive testing and did not reach below the World Health Organization-recommended 5% test-positive rate before July 2020 [8]. In Norway, Finland, and Iceland, contract tracing was in place from the start of the pandemic and has remained a key feature of their mitigation strategy. Due to high case numbers, Sweden early on abandoned contact tracing as a national strategy; it was resumed in summer 2020 [2]. Except for Sweden, the countries adopted mandatory quarantine for people exposed to virus and international travelers arriving from areas with widespread transmission. In the autumn of 2020, Norway and Denmark began implementing regional interventions based on local infection levels, while in Sweden and Finland regional differentiation prevailed. At that time, Sweden adopted policy measures that closely resembled that of the other countries.

The Nordic countries provide a "natural laboratory" to compare the impact of COVID-19 intervention strategies [9, 10]. We recently analyzed virus transmission clusters, defined as country-specific monophyletic groups derived from a phylogenetic analysis of the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in the Nordic countries using a genomic data set covering this geographic region [3]. In this study, we use the same transmission clusters to analyze the epidemiological implications of the different intervention strategies used by the Nordic health authorities.

METHODS

The data were generated from [3] by (1) downloading and aligning all available Nordic SARS-CoV-2 genomes from

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GISAID ([www.gisaid.org] with 67 918 Nordic genomes) and (2) the NextStrain global build as of March 22, 2021 (3437 global genomes). Thus, the analyses are based on sequenced genomes obtained between January 2020 and April 2021. Due to markedly different sequencing intensity in the Nordic countries, Sweden—the country with the lowest sequencing intensity—was chosen as the reference for the other countries at a rate of 1.1 genomes per 100 cases. The data set was further subsampled 10 times (referred to here as "replicates") according to prevalence per country, resulting in alignments including between 15 297 and 15 616 SARS-CoV-2 genome sequences. More information on the sequencing data is provided as Supplementary Material 1. For each alignment, a phylogenetic tree was estimated using IQ-TREE v2.0.6 [11] scaled to time using LSD v.03 [12] under a strict molecular clock at a fixed rate of 1×10^{-3} nucleotide substitutions/site per year, and the GTR+Γ substitution model. Transmission clusters were defined as the monophyletic clustering of 2 or more sequences from the same country, and thus they represent putative transmission chains. The duration of a transmission cluster was defined as the time between the last and the first sample. The data set was converted to a weekly time-series format, calculated from the time in a given cluster to most recent common ancestor (TMRCA) from each transmission cluster (see Supplementary Material 2). Analyses were carried out using generalized additive mixed-effects models (GAMM) using restricted maximum likelihood (REML) [13]. We used GAMM for the regression models with country as the explanatory variable and the following outcomes: number of transmission clusters, transmission cluster size (ie, the number of samples in each transmission cluster), and transmission cluster duration. An additional GAMM model was included to assess the association between cluster duration and size. This model included an interaction term between country and number of samples per cluster as the explanatory variable with duration of cluster as the outcome. All models, except those having the number of transmission clusters as an outcome, were also adjusted for the number of transmission clusters and TMRCA with respect to country using splines. Replicate number (1–10) by country (Norway, Sweden, Finland, Denmark, and Iceland) was included as a hierarchical random effect in all models. Goodness-of-fit was determined using Akaike Information Criterion (AIC), R^2, and model residuals conformance to normality. Regression analyses were performed using the GAMM4 package [13], and figures were created using the ggplot2 package [14]. A description of the statistical estimation procedures and results are provided in Supplementary Material 3.

RESULTS

We divided the data set into number of transmission clusters per week. First, we compared the number of transmission clusters between the different countries (see Supplementary Figure 1 and METHODS for more details regarding the regression models). This revealed that Sweden had significantly more transmissions clusters ($P < .001$) than Denmark, which in turn had significantly more than Norway ($P < .001$). The number of transmission clusters in Finland was comparable to Norway ($P = .878$). The fewest number of transmission clusters were found in Iceland ($P < .012$), but the smoothing spline did not fit the data properly ($P = .906$) due to the low number of cases.

We next compared transmission cluster size (ie, the number of samples per cluster) among the different Nordic countries. These analyses suggest that transmission cluster size did not differ significantly between Sweden and Denmark ($P = .895$). However, transmission clusters were significantly smaller ($P < .001$) in Norway compared with Sweden and Denmark, with Finland having significantly smaller clusters compared with Norway ($P < .001$). Iceland's model was not found to be significant ($P = .898$) most likely due to the small sample size. Figure 1 shows the log-transformed number of samples per transmission cluster (ie, transmission cluster size) with respect to TMRCA, together with regression model lines, for each Nordic country and all replicates. During the autumn and winter months of 2020 (September through December) we see an increase in transmission cluster size, with the exception of Finland and Iceland (Figure 1).

We also compared transmission cluster duration between the Nordic countries. This did not significantly differ between Sweden and Denmark ($P = .269$) who, in turn, had significantly more enduring transmission clusters than the other Nordic countries ($P < .002$). There was no significant difference between Norway and Finland ($P = .503$), whereas Iceland's model was again not significant ($P = .887$) due to the low number of cases. Figure 2 shows that the duration of the transmission clusters drops when the winter months approach the end of 2020. Finally, we also observed a significant positive association ($P < .001$) between transmission cluster size and cluster duration.

DISCUSSION

We examined how the number, size, and duration of SARS-CoV-2 transmission clusters differed among the Nordic countries. The presence of many samples within a cluster could imply that primary cases are responsible for forward transmission of subsequent cases. Alternatively, it could mean that infection from primary cases spread to multiple people within the cluster. Accordingly, Sweden had the largest number of transmission clusters and, together with Denmark, the most enduring. Moreover, our results also point to an increase of COVID-19 transmission clusters during winter, which could be due to the cold winter climate leading to increased indoor-based activities and thus increased contact frequencies for transmission [15]. Alternatively, the increased spread of SARS-CoV-2 during the winter months could result from more relaxed COVID-19

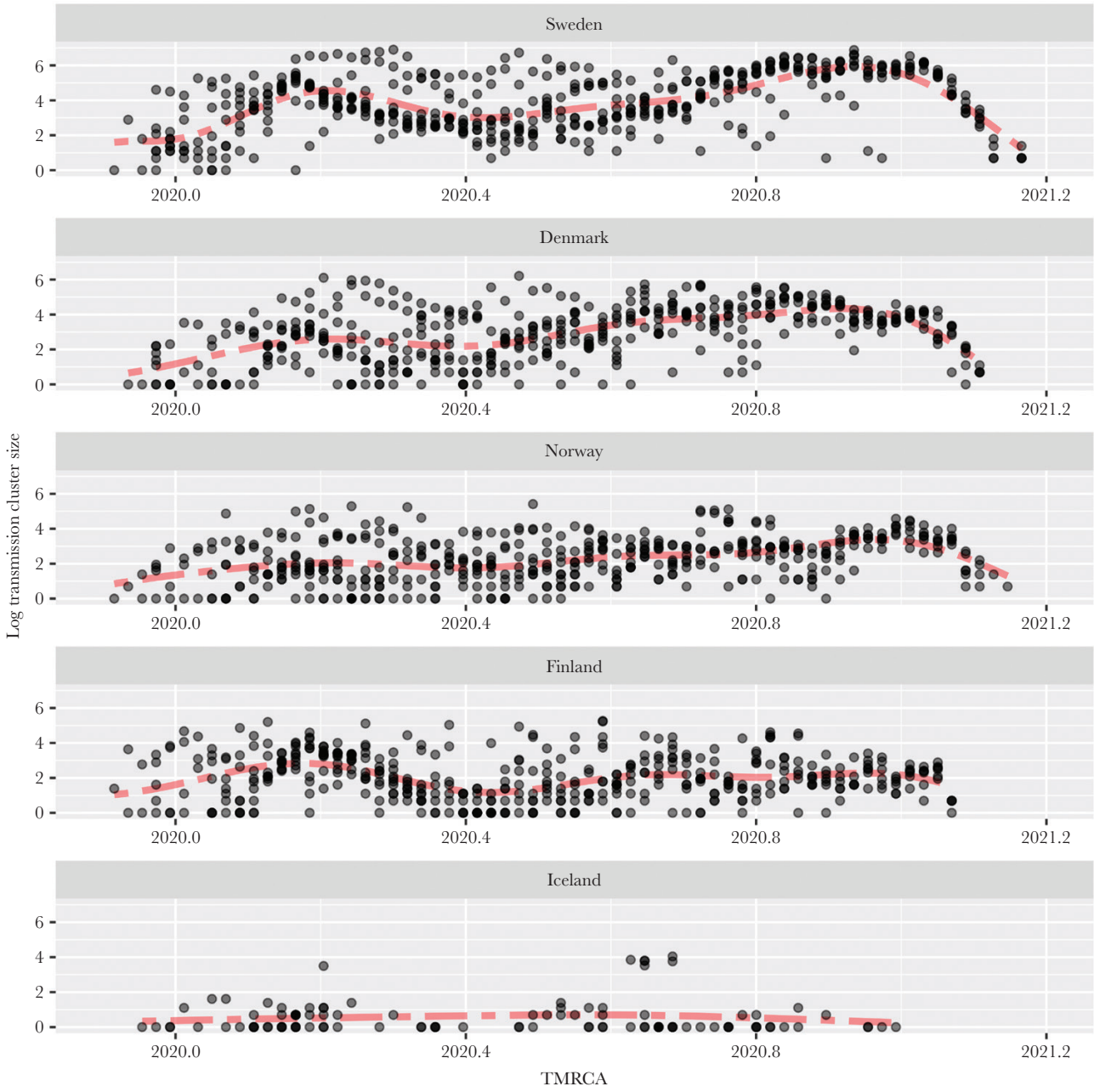


Figure 1. The (log transformed) size of transmission clusters (ie, number of cases per transmission cluster, vertical axis) for replicates 1–10 with respect to the time to most recent common ancestor ([TMRCA] horizontal axis) for the Nordic countries. The red dashed line represents the regression model averaged over all replicates.

intervention measures during the autumn [3]. It is notable that transmission cluster size and duration decreased towards the end of 2020 in concordance with an increase in the governmental stringency index for the Nordic countries [3]. Hence, although climate and change of season influence behavior and contact frequency, our analyses suggest that the adopted intervention measures also effectively reduced virus transmission.

The largest transmission clusters were found in Sweden and Denmark, whereas the size of the transmission clusters in Norway and Finland were significantly smaller and more similar. Iceland differed in general from the other Nordic countries with substantially fewer COVID-19 cases, which can most likely be ascribed to the country's small population and isolated location. It is interesting to note that although Sweden had more transmission clusters (Supplementary Figure 1), their duration and size was not significantly different from the clusters obtained from Denmark. Although we have tried to adjust for bias in sequencing intensity by using subsampled SARS-CoV-2 sequence data from each country in the regression models (Supplementary Material 1), some bias may persist due to country-specific strategies for selecting cases for sequencing. In particular, Swedish transmission clusters could

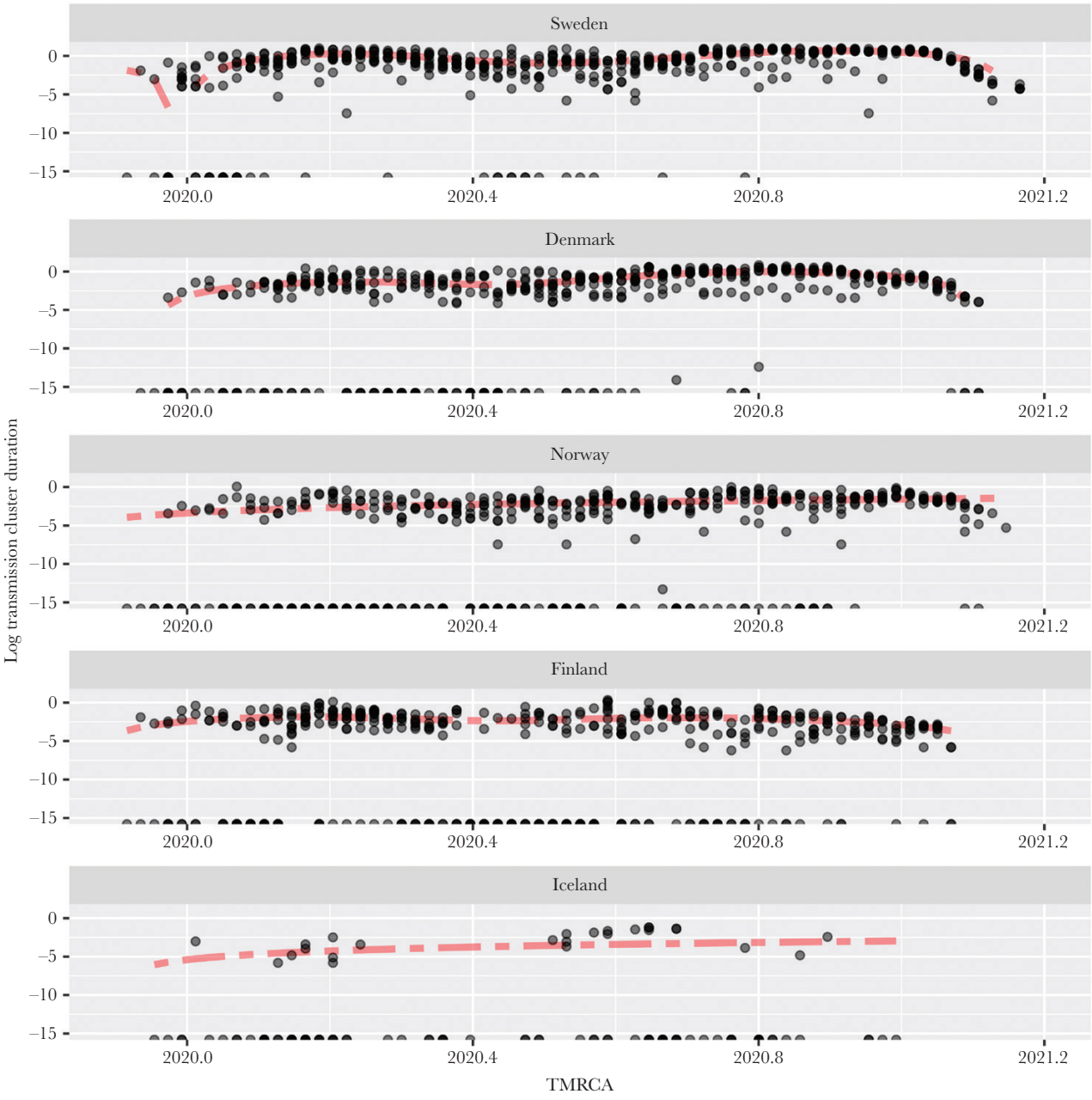


Figure 2. The (log transformed) transmission cluster duration (difference between last and first sample, vertical axis) for replicates 1–10 with respect to time to most recent common ancestor ([TMRCA] horizontal axis) for the Nordic countries. The red dashed line represents the regression model averaged over all replicates.

be underestimated in terms of both size and duration due to the low ratio of genomic SARS-CoV-2 sequence data to each reported case (1.1 genomes per 100 cases). Alternatively, the more stringent intervention policies implemented in Denmark compared with Sweden could have reduced the total number of infections, whereas the enduring transmission clusters could be due to the higher population density in Denmark, making it harder to break the transmission chains. Denmark also focused less on contact tracing compared with the other Nordic countries with the exception of Sweden. The significant association between transmission cluster size and duration is compatible with both of these explanations. Finland and Iceland had the transmission clusters with the shortest duration, with Iceland's duration significantly shorter than Finland's.

During the second half of 2020, Sweden adopted stricter COVID-19 intervention policies, which were more on par with Norway and Finland [3]. However, the number of cases remained high. This may point to some inertia regarding COVID-19 policies, such that the attitudes in the population and consequences from early COVID-19 intervention strategies persisted for some time after the new measures were introduced. A study using Google mobility data suggests that

the overall population-based response in Sweden was less strong compared with its neighboring countries, even as the situation aggravated [8]. Because Norway and Finland are similar to Sweden in terms of demographics, location, climate, and governance, our results demonstrate the effects of the variable COVID-19 control measures adopted and the timeliness of the rollout of these measures. Norway, Finland, and Denmark experienced a similar disease burden, although Denmark recorded significantly more cases and transmission clusters. This could in part be due to far more intensive SARS-CoV-2 sequencing. We observed a similar pattern in our previous study [3], in which both Denmark and Sweden had the most importation events (as well as the most exportation events). The duration of transmission clusters in Norway and Finland was significantly shorter compared with Denmark and Sweden. It is notable that the Norwegian and Finnish strategies focused on municipality-based rigorous contact tracing, isolation, and quarantining with the aim to clamp down transmission.

Our results suggest that reducing transmission cluster duration through effective contact tracing could also reduce transmission cluster size. In particular, the shorter duration of transmission clusters in Norway and Finland may reflect the effectiveness of the strategies deployed in those countries. More importantly, a growing number of transmission clusters would likely imply an increase in the genetic diversity of SARS-CoV-2, while the presence of transmission clusters of extended length better enable the virus to evolve [16].

The SARS-CoV-2 Alpha variant of concern (Pangolin lineage B.1.1.7) was first discovered in the United Kingdom and was associated with an increase in infectivity [17]. It is interesting to note that we did not see any dramatic change in transmission cluster size or duration associated with the introduction of the Alpha variant (see Supplementary Figure 2). With the exception of Iceland, both the duration and number of cases increased in all countries from mid-2020 onwards, with cases dropping at the end of 2020 (Figures 1 and 2) and not contemporaneous with the rise of the Alpha variant. The lack of any clear resurgence associated with the emergence of the Alpha variant likely reflects the impact of the COVID-19 control policies in place [3], again emphasizing their importance in controlling the pandemic.

The strategies implemented by Norway, Finland, and Iceland seem to have been more successful in reducing both the number and the size of their transmission clusters than those in Denmark and Sweden. Since Sweden is a geographical neighbor to Norway and Finland (Denmark is located on the European continent neighboring Germany), our findings highlight the importance of local measures in controlling the spread of SARS-CoV-2. However, it is unclear to what extent geographical location or strict COVID-19 strategies are responsible for the lower burden of COVID-19 in Norway, Finland, and Iceland compared with Sweden and Denmark. It is likely that national COVID-19 numbers mask variation within countries, particularly between low- and high-density regions. Controlling outbreaks in Denmark may be more challenging because it is a small country, located on the European continent, with a population density 5 to 40 times larger than the other Nordic countries. In contrast, the pattern in Iceland may reflect that it is an island with a substantially smaller population and low population density, located far away from other countries, and thus easier to get early control of the pandemic [7]. Our findings from Iceland resembled those of other small island nations [18].

CONCLUSIONS

Using a genomic epidemiology-based approach, we found that SARS-CoV-2 transmission cluster size and duration differed markedly among some of the Nordic countries. Norway, Sweden, and Finland are neighboring countries with similar demographics, political systems, and climate, and our findings highlight the influence of intervention strategies in controlling the spread of COVID-19. It is interesting to note that Denmark implemented more similar COVID-19 intervention strategies to Norway and Finland, but it did not reduce the spread of COVID-19 to the same extent as other Nordic countries, which may reflect its location on the European continent and relatively high population density. Hence, our results suggest that disease intervention strategies should be adapted to the specific geographic and demographic factors of each country to more effectively reduce the transmission and evolution of SARS-CoV-2.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Author contributions. All authors have read the manuscript and approved the final version of the manuscript

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