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Social Distancing Alters the Clinical Course of COVID-19 in Young Adults: A Comparative Cohort Study

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Background. Social distancing and stringent hygiene seem to be effective in reducing the number of transmitted virus particles, and therefore the infectivity, of coronavirus disease 2019 (COVID-19) and could alter the mode of transmission of the disease. However, it is not known if such practices can change the clinical course in infected individuals.

Methods. We prospectively studied an outbreak of COVID-19 in Switzerland among a population of 508 predominantly male soldiers with a median age of 21 years. We followed the number of infections in 2 spatially separated cohorts with almost identical baseline characteristics with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before and after implementation of stringent social distancing.

Results. Of the 354 soldiers infected prior to the implementation of social distancing, 30% fell ill from COVID-19, while no soldier in a group of 154, in which infections appeared after implementation of social distancing, developed COVID-19 despite the detection of viral RNA in the nasal and virus-specific antibodies within this group.

Conclusions. Social distancing not only can slow the spread of SARS-CoV-2 in a cohort of young, healthy adults but it can also prevent the outbreak of COVID-19 while still inducing an immune response and colonizing nasal passages. Viral inoculum during infection or mode of transmission may be a key factor determining the clinical course of COVID-19.

Keywords. COVID-19; cohort study; SARS-CoV-2; viral inoculum; social distancing.

Coronavirus disease 2019 (COVID-19) is a pandemic disease [1] transmitted from human to human [2] caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in late 2019 in Wuhan, mainland China [3–5]. COVID-19 can have a severe to fatal course, primarily in elderly populations [6], but it also affects children [7] and young adults [8], in which the clinical course has been described to be mild or even asymptomatic [9].

Physical interventions such as social distancing [10, 11], wearing face masks [12] and implementing strict hygiene measures [13] reduce the rate of infection by reducing the transfer of respiratory viruses from infectious to susceptible persons through contact, droplets, or aerosols [14]. These interventions not only lower the chance of infection but also quantitatively reduce the viral inoculum received by the recipient [15, 16] and may change the route of transmission [17] from direct droplet transmission in close proximity to the infecting person [18] to indirect transmission via contaminated surfaces [19]. Higher nasal viral load is associated with worse clinical outcomes for severe acute respiratory syndrome [2, 20], and higher initial viral exposure is associated with more severe disease [21]. To our knowledge, it is unknown if lowering the viral inoculum during infection with SARS-CoV-2 or altering the mode of infection by physical means can affect the clinical course of the disease.

Here, we present an outbreak at a Swiss Army Base with 2 very similar groups infected prior and after the implementation of stringent social distancing and hygiene measures (SDHMs). While both groups showed evidence of infection, the rate of symptomatic COVID-19 among the infected soldiers differed significantly between the 2 groups and was much lower in the cohort where infection occurred after the implementation of these measures.

We provide evidence that SDHMs not only are effective in reducing transmission but also can alter the clinical course of COVID-19 in infected individuals. We hypothesized that the difference in the clinical presentation of infected persons might be due to lower viral inoculum during infection or an altered mode of transmission of the virus, but further studies are needed to answer this question.

METHODS

We recruited soldiers stationed at a Swiss Army Base in Airolo between 25 March and 14 April 2020. Patients not feeling fit for service were required to report to our clinic and were promptly isolated and tested for COVID-19 by nasopharyngeal swabs. Additionally, asymptomatic soldiers were sampled cross-sectionally as indicated in Figure 1. Nasopharyngeal swabs, as well as serum samples, were taken
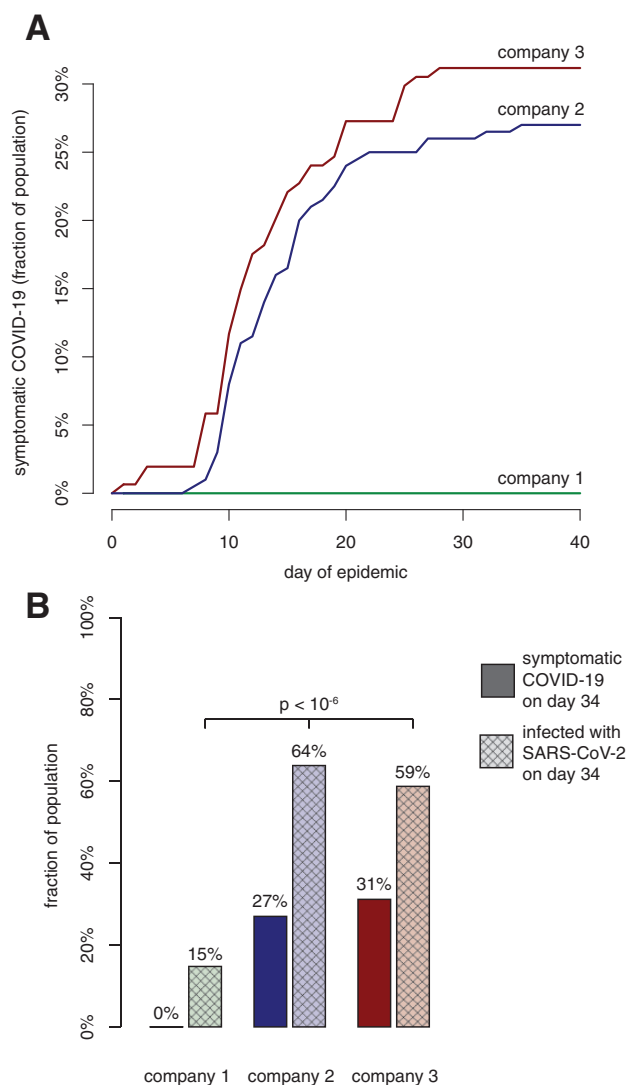

A

B

Figure 1. *A*, Epidemic curve of patients with COVID-19 as a fraction of the total population of the 3 companies. While company 1 (green), organizationally and spatially separated from the others, had no case of COVID-19, companies 2 (blue) and 3 (red) show a very similar course where one-third of the population were symptomatic for COVID-19. *B*, Symptomatic cases of COVID-19 and rate of infection among the 3 companies. The rate of infected persons was significantly smaller in company 1 than in the other companies (Fisher's exact test) and was determined on day 34 by combined nasopharyngeal swab and serological testing; a person was considered infected if either returned a positive result. The fraction of symptomatic patients among the infected was significantly larger in companies 2 and 3 than in company 1 (*P* = .02). Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

simultaneously. Data collection, as well as clinical follow-up, ceased on 3 May 2020.

Reverse transcriptase–quantitative polymerase chain reaction (RT-qPCR) in triplicate for SARS-CoV-2 targets was performed on all nasopharyngeal swab samples. Detailed descriptions of sample collection and RT-qPCR can be found in the Supplementary Appendix and Supplementary Figure 1.

The immune response against SARS-CoV-2 was measured by commercial enzyme-linked immunosorbent assay kits used according to the manufacturer's instructions. Kits from Epitope Diagnostics Inc (San Diego, CA) were used to measure immunoglobulin (Ig) M and IgG titers. Kits from Euroimmun (Luebeck, Germany) were used to measure IgA titers. Serological data normalization and validation (Supplementary Figure 2) are described in the Supplementary Appendix.

Data were analyzed with R Statistical Software (www.r-project.org R Foundation for Statistical Computing, Vienna, Austria) version 3.6.1. Specificity and sensitivity analyses were calculated using Epi version 2.4.0.

This study was approved by the ethical commission of the Republic and Canton of Ticino (Comitato Etico Cantonale; BASEC Nr 2020-00623 CE 3609). All procedures involving human participants were conducted in accordance with the ethical standards of the Declaration of Helsinki and its amendments. Written informed consent was obtained from every included patient and participant in their native language (German, French, or Italian) after oral education. Study participation was voluntary and not enforced by any means.

RESULTS

We observed a COVID-19 outbreak at a Swiss Army base in Airolo. Three companies (508 soldiers) were stationed at the base (Table 1). While companies 2 and 3 shared the same barracks and their soldiers had abundant contact with each other, sharing the same kitchen and communal areas, company 1 was based at barracks separated from the other 2 companies by a distance of approximately 3 km and 200 m of elevation. Minimal contact occurred between company 1 and the other companies. The demographic characteristics of all 3 companies (Table 1) were similar, with a median age of 20.4 years (range, 18–28 years). Due to a stringent recruitment process, soldiers with severe health-related constraints are generally excluded from military service. Company 1 consisted exclusively of male soldiers, while 12% of companies 2 and 3 were women. Some of the soldiers, instructors, and other personnel at the base were stationed in separate units and therefore grouped as "other." They were excluded from further analysis due to group heterogeneity and segmentation into various subgroups with a very low sample size each.

On 11 March 2020, we diagnosed the first patient suffering from COVID-19 in company 3; we refer to this date as day 1

Table 1. Baseline Characteristics of the Study Population on 31 March 2020

	Company 1	Company 2	Company 3	Others	All
Soldiers, n	154	200	154	76	584
Males, n (%)	154 (100)	174 (87)	138 (90)	60 (79)	526 (90)
Age, years	20.4 (18–27)	20.4 (18–28)	21.0 (18–27)	20.6 (19–54)	20.6 (18–54)
COVID-19,[a] n (%)	0 (0)	54 (27)	48 (31)	4 (5.3)	107 (18)
Exposed to SARS-CoV-2,[b] n/N (%)	13/88 (15)	83/130 (64)	30/51 (59)	22/57 (39)	148/326 (45)
Date of first exposure to SARS-CoV-2	Between 31 March and 14 April	Before 18 March	Before 11 March	Variable	…
COVID-19	Not affected	Affected		…	…

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Symptomatic patients between 11 March and 3 May 2020.

[b]On 14 April, by positive serology test for immunoglobulin A, G, or M or detection of SARS-CoV-2 in nasopharyngeal swabs.

of the outbreak. In the following weeks, we observed an epidemic in companies 2 and 3 as depicted in Figure 1A, while company 1 had no cases. On day 9, it became clear that the disease was widely spreading within companies 2 and 3; both units were put under quarantine, and hygiene measures were rigidly enforced across all 3 companies. Soldiers had to keep a distance of at least 2 m from each other at all times, and in situations where this could not be avoided (eg, military training), they had to wear a surgical face mask. A distance of 2 m was enforced between the beds and during meals. All sanitary facilities were cleaned and disinfected twice daily. Symptomatic soldiers were immediately separated and required to report to our clinic where they were tested for COVID-19 using nasopharyngeal swabs. Strict separation of the unaffected company 1 from the other companies was enforced.

Until data censoring on day 54, 29% (102/354) of companies 2 and 3 suffered from RT-qPCR-confirmed symptomatic COVID-19. None of the 154 soldiers from company 1 was diagnosed with COVID-19 (Figure 1A). All soldiers with symptoms compatible with a respiratory infection, or who did not feel fit for service, were required to present at our clinic. Additionally, symptoms as well as vital parameters were assessed daily in the unaffected company 1. It is thus unlikely that we missed a symptomatic case of COVID-19. We tested 15 symptomatic soldiers from company 1 for COVID-19; all were negative.

On day 35 of the outbreak (14 April), we cross-sectionally sampled 363 asymptomatic soldiers of all 3 companies as well as other units on the army base by nasopharyngeal swabs, serological testing, and a systematic questionnaire. Of the 88 tested soldiers of the unaffected company 1, we found evidence of active or past exposure to SARS-CoV-2 in 13 soldiers (15%; 95% confidence interval, 8–24%): 7 (8.7%) produced a positive nasopharyngeal swab and 7 exhibited evidence of a SARS-CoV-2–specific immunological response (1 soldier was double positive). In the affected cohort we found evidence of exposure to SARS-CoV-2 in 64% of company 2 and 59% of company 3 (Figure 1B): 20.6% and 37.2% tested positive by RT-qPCR and 59.2% and 66.7% had a positive serology. None of the soldiers tested on that day presented symptomatically in our clinic or

showed symptoms in our daily assessments during the following 19 days of follow-up despite daily assessment. Viral concentrations were lower than in symptomatic patients (Figure 3) but still detectable. Since 29% of the soldiers of companies 2 and 3 had previously presented with symptoms of COVID-19, more than 30% of this population must have been infected asymptomatically but still developed a detectable immune response. Infection in these soldiers is likely to have occurred after the implementation of SDHMs, given that these measures were implemented 25 days prior to the testing date.

The fraction of symptomatic patients with COVID-19 among all soldiers with evidence of exposure to SARS-CoV-2 either by RT-qPCR or serology was significantly lower (P = .02, Fisher's exact test) in company 1 (0/13, 0%) than in companies 2 and 3 (45/113, 40%). Companies 2 and 3 not only had an increased rate of infection but soldiers in these companies also had a higher probability of developing COVID-19 when infected. More than 50% of the soldiers of all companies could be sampled; however, 36% of company 1 and 42% of companies 2 and 3 either refused to participate or were not available (Figure 2). Our sample is likely to be representative of all companies, since we sampled a high proportion of the population and we are not aware of any possible selection bias possibly introduced by the nonparticipants. Thus, the reported fractions of infected likely represent the true prevalence within the cohorts.

To exclude an ongoing infection in company 1 prior to the implementation of SDHM, we tested 23 asymptomatic soldiers by nasopharyngeal swabs and serology (Figure 2) on day 20— thus, 11 days after implementation of these measures. None had a serological response and no viral RNA was detected in their nasopharyngeal swabs (Figure 3), excluding an infection of more than 12.2% of company 1 at day 20 with a confidence level of 95% (exact binomial test) at that day. Although the sample of 23 patients was not drawn randomly (the group of soldiers were about to be deployed), a relevant bias most likely was not introduced by the selection process. Hence, infection in company 1 most likely occurred after day 20 and thus after implementation of SDHMs, while both companies 2 and 3 had cases of COVID-19 prior to this date.
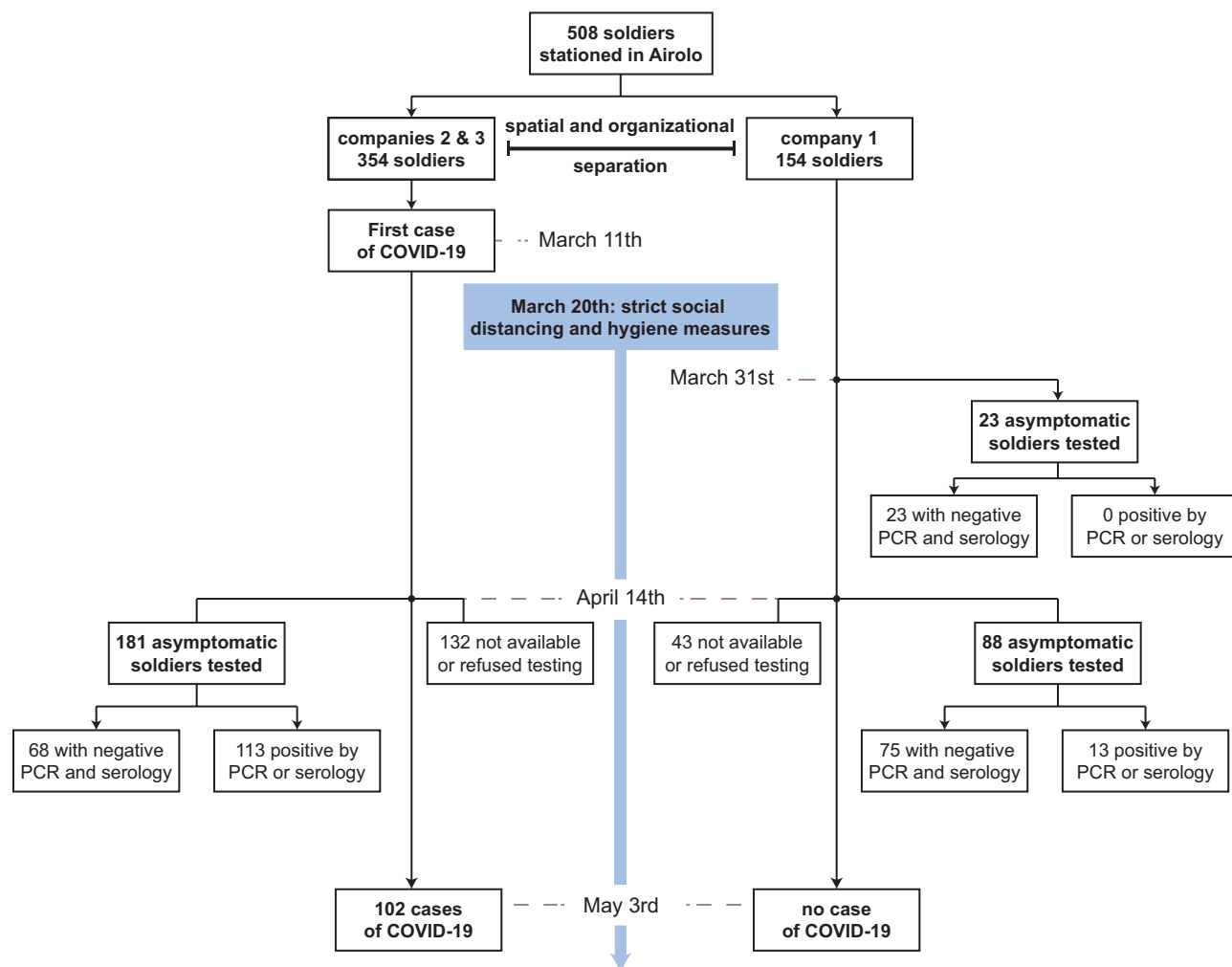
Figure 2. Flowchart of the study. A total of 354 soldiers of companies 2 and 3 were spatially and organizationally separated from 154 soldiers of company 1. On 11 March, the first case of COVID-19 was diagnosed in the left cohort; thus, infection in this group must have occurred prior to or on this date. On 20 March, strict social and hygiene measures were implemented in both cohorts. On 31 March, 23 asymptomatic soldiers from company 1 were tested, of whom all showed negative serology and PCR. On 14 April we conducted a cross-sectional testing on all soldiers who agreed to take part in our study. From company 1, 88 soldiers were tested; 13 were positive by PCR or by serology. Of 181 asymptomatic soldiers from companies 2 and 3, 113 were positive by either serology or PCR. We continued to follow up both cohorts for 19 more days; none of the tested soldiers developed COVID-19 during this time. While in companies 2 and 3 102 cases of COVID-19 were diagnosed, company 1 remained without cases. This finding infers a profound impact of social distancing and stringent hygiene measures on the outbreak of COVID-19 in an infected cohort. While companies 2 and 3 were infected prior to the enforcement of such methods, nearly one-third of all soldiers developed COVID-19 and a high level of seroconversion was observed; the cohort to the right was infected after 31 March and thus after the enforcement of social distancing and hygiene measures. Despite 15% asymptomatically infected soldiers in company 1 on 14 April, we did not observe a single case of COVID-19 in this cohort. This demonstrates that enforcing social distancing before infection can lead to milder clinical courses of COVID-19. Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

At the end of the exponential growth phase of the epidemic on day 14 of the outbreak (5 days after implementing SDHMs) we used nasopharyngeal swabs and serology to sample a group of 41 asymptomatic soldiers in the heavily affected company 3. By RT-qPCR, 20 tested positive for SARS-CoV-2; and 3 tested positive by serology. Over the following weeks, we followed up on these soldiers and registered 6 symptomatic COVID-19 cases in this population. Five had been negative by nasopharyngeal RT-qPCR for SARS-CoV-2 during our sampling, while only one had had a borderline positive result without a quantifiable virus load. The remaining 19 soldiers who tested

positive for SARS-CoV-2 by nasopharyngeal swab on that day never developed COVID-19 and remained asymptomatic. Nasopharyngeal virus quantities were comparable to those of symptomatic patients (Figure 3), suggesting similar infectivity.

We treated more than 100 young, previously healthy, adult patients with COVID-19 at our clinic; all were treated symptomatically. No patient died, was admitted to the intensive care unit, or needed mechanical ventilation. One patient was referred to a hospital with interstitial pneumonia requiring oxygen supplementation for 4 days but recovered without obvious sequelae. Despite the high reported prevalence of thromboembolic
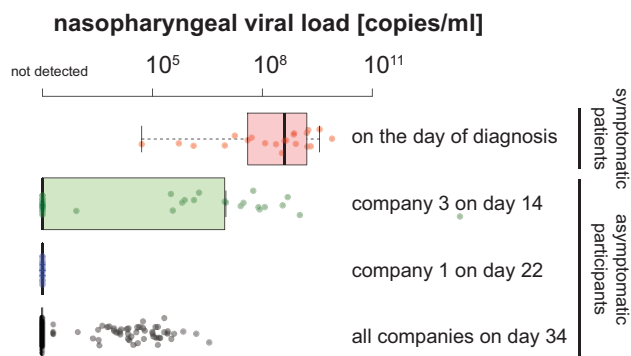
nasopharyngeal viral load [copies/ml]

Figure 3. Nasopharyngeal viral concentrations of the 3 cross-sectional samplings of asymptomatic participants versus samplings at the day of presentation of 21 symptomatic patients (first row). The first cross-sectional study of 41 asymptomatic soldiers of the affected company 3 on day 14 of the epidemic is shown in the second row; 20 of these asymptomatic soldiers had a viral load comparable to symptomatic patients. The study of 23 asymptomatic soldiers of the unaffected company 1 at day 20 is shown in the third row (all negative), and the final sampling of all companies at day 34 is shown in the last row with lower viral loads.

complications among severely ill patients with COVID-19 [8], we observed no thromboembolic complications in our population, although pharmacological thrombosis prophylaxis was only used in 1 case (the hospitalized patient). However, mechanical thrombosis prophylaxis was applied by encouraging physical training and involvement in cleaning and disinfection measures.

DISCUSSION

We describe an outbreak of SARS-CoV-2 infections in young, healthy soldiers in 2 spatially separated groups with almost identical baseline characteristics but different clinical courses. While 1 cohort was heavily affected by COVID-19, with 102 cases of 354 soldiers (companies 2 and 3), the separated group (company 1) was infected later and had no case of COVID-19 in a total of 154 soldiers until the censoring of data (day 53), despite a liberal testing strategy.

Stringent SDHMs were enforced in all companies 9 days after the first case of COVID-19 was diagnosed. Both companies 2 and 3 had cases of COVID-19 prior to implementation of these measures; however, the unaffected company 1 was infected with SARS-CoV-2 after implementation of social distancing between days 20 and 34 of the outbreak, as evidenced by nasopharyngeal colonization or immunization in 13 asymptomatic soldiers. Several asymptomatically infected cases were identified in all groups (Figure 1B). While 40% of the infected cases in companies 2 and 3 developed COVID-19, none of the 13 infected cases in company 1 suffered from COVID-19. Strict enforcement of SDHMs prior to infection therefore reduced the rate of COVID-19 among those infected. Since we followed up the soldiers for 19 days after testing and soldiers were required to immediately report to our clinic if they became

symptomatic during this period, we can exclude that any of the soldiers tested on that day later developed symptoms: 99% of cases become symptomatic before day 14 after infection [22]. While SDHMs reduce the reproductive number [23, 24], these nonpharmacological interventions have, to our knowledge, not been known to reduce the fraction of patients who fall ill of COVID-19 among those who are infected prior to this study.

Although all 3 companies were very similar demographically, all members of the unaffected company 1 were male soldiers, but approximately 10% of the affected companies 2 and 3 were female. A key role for gender in the spread of the disease is unlikely as other studies have reported no differences in viral shedding between males and females [25].

The literature on the ratio of asymptomatic infections is controversial, ranging from 4% of a highly selected and exposed group in Shanghai [26], 18% on the Diamond Princess cruise ship [27], to up to 75% [28, 29] in cross-sectional studies, some even reporting clusters of entirely asymptomatic cases [30]. This large range of the rate of symptomatic COVID-19 among infected individuals might reflect the differential implementation of measures to prevent exposure to the virus or the mode of infection, as observed between the 2 groups reported in this study.

Companies 2 and 3 showed high infection rates approaching the proposed level of herd immunity of 70% [31]. In company 1, infection occured after the implementation of SDHMs and the rate of infected individuals remained significantly lower. The epidemic might have ceased not only due to the implementation of SDHMs but also due to herd immunity since both factors effectively lower the reproductive numbers of the virus.

Social distancing and hygiene measures have been shown to quantitatively reduce the viral inoculum during infection [15, 16]. The route of transmission might also be changed by SDHMs [17] from direct droplet transmission in close proximity to the infecting person [18] to indirect transmission via contaminated surfaces [19], although the hygiene measures implemented involved regular disinfection of potentially contaminated surfaces. Our data show that SDHMs not only slow infection with SARS-CoV-2 but also can attenuate the clinical course by reducing the rate of symptomatic patients among those infected. These findings suggest that reducing the viral inoculum might not only lead to a reduced probability of infection but also could favor an asymptomatic infection while still being able to induce an immunological response at least in a proportion of the infected. However, our study did not directly explore the effect of viral inoculum on the clinical course of an infection with SARS-CoV-2 but shows the profound effect that SDHMs have thereon.

Since our study population consisted of young, predominantly male adults, our findings might not be applicable to the general population (especially to the elderly and comorbid populations). Studies involving more heterogeneous populations under similar physical separation measures currently

show a seroprevalence of 6.9% among 20–49-year-olds [32], which is much higher than what is expected based on COVID-19 case numbers. It remains to be clarified if asymptomatic infection protects from future reinfection and thus if herd immunity can be induced via asymptomatic infections before a vaccine is broadly available.

Supplementary Data

Supplementary materials are available at *Clinical 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.

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