Social distancing alters the clinical course of COVID-19 in young adults: A comparative cohort study

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Key points:

We observed an outbreak of COVID-19 among two very similar cohorts with 508 soldiers in Switzerland: There is evidence that social distancing not only reduced transmission of the virus but also prevented infected soldiers from developing COVID-19.

Abstract

Background: Social distancing and stringent hygiene seem 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 two 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 nose 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 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 key factors determining the clinical course of COVID-19.

Keywords: COVID-19, Cohort study, SARS-CoV-2, viral inoculum, social distancing

Introduction

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 the 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 two very similar groups infected prior and after the implementation of stringent social distancing and hygiene measures (SDHMs). While both groups show evidence of infection, the rate of symptomatic COVID-19 amongst the infected soldiers differed significantly amongst the two groups and was much lower in the cohort where infection happened 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 hypothesize 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.

Materials and Methods

We recruited soldiers stationed at a Swiss Army Base in Airolo between March 25 and April 14, 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 simultaneously. Data collection, as well as clinical follow-up, ceased on May 3, 2020.

RT-qPCR in triplicate for SARS-CoV-2 targets was performed on all nasopharyngeal swab samples. Detailed descriptions of sample collection and PCR can be found in the Supplementary Appendix.

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, USA) were used to measure IgM and IgG titers. Kits from Euroimmun (Luebeck, Germany) were used to measure IgA titers. Serological data normalization and validation (Figure S2) is described in the Supplementary Appendix.

Data were analyzed with R Statistical Software (www.r-project.org) 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 two by approximately 3 km distance and 200 m of elevation. Minimal contact occurred between company 1 and the other companies. The demographic characteristics of all three 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 March 11, 2020, we diagnosed the first patient suffering from COVID-19 in company 3; we refer to this date as day 1 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 three 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 (e.g., 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 PCR-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 (April 14th), we cross-sectionally sampled 363 asymptomatic soldiers of all three 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%): seven (8.7%) produced a positive nasopharyngeal swab and seven exhibited evidence of a SARS-CoV-2–specific immunological response (one 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 PCR and 59.2% and 66.7% had a positive serology. None of the soldiers tested on that day presented symptomatically in our clinic nor 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 symptomatically for COVID-19, more than 30% of this population must have been infected asymptomatically but still developed a detectable immune response. Infection of these soldiers is likely to have happened 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 amongst all soldiers with evidence of exposure to SARS-CoV-2 either by PCR or serology was significantly lower (p=0.02, 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 for 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 non-participants. Thus, the reported fractions of infected likely represent the true prevalence within the cohorts.

To exclude an ongoing infection of 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 has not been introduced by the selection process. Hence infection of 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.

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 PCR, 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 six symptomatic COVID-19 cases in this population. Five had been negative by nasopharyngeal PCR 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 four days but recovered without obvious sequelae. Despite the high reported prevalence of thromboembolic 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 one 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 two spatially separated groups with almost identical baseline characteristics but different clinical courses. While one 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 social distancing and hygiene measures (SDHMs) were enforced in all companies nine 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 were identified in all groups (Figure 1B). While 40% of the infected in companies 2 and 3 developed COVID-19, none of the 13 infected in company 1 suffered from COVID-19. Strict enforcement of SDHMs prior to infection therefore reduced the rate of COVID-19 amongst 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 non-pharmacological interventions have to our knowledge not been known to reduce the fraction of patients suffering of COVID-19 amongst those who are infected prior to this study.

Although all three companies were very similar demographically, all members of 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 courses is controversial ranging from 4% of a highly selected and exposed group in Shanghai [26], 18% on the Diamond Princess cruise ship [27] up to 75% [28,29] of cross-sectional studies, some even reporting clusters of entirely asymptomatic cases [30]. This large range of the rate of symptomatic COVID-19 amongst infected might reflect the differential implementation of measures to prevent exposure to the virus or the mode of infection; as observed between the two groups reported in this study.

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

SDHMs 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 surface. 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 amongst those infected. These findings suggest, that reducing the viral inoculum might not only lead to a reduced probability of infection but also could cause favor an asymptomatic infection while still being able to induce an immunological response at least in a proportion of the infected. However, our study has not directly studied the effect of viral inoculum on the clinical course of an infection with SARS-CoV-2 but shows the profound effect 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 co-morbid population). Studies involving more heterogeneous populations under similar physical separation measures currently show a sero-prevalence of 6.9% amongst the population of 20-49 year olds [32], which is much higher than what expected based upon COVID-19 case numbers. It remains to be clarified if asymptomatic infection protects from future re-infection and thus if herd immunity can be induced via asymptomatic infections before a vaccine is broadly available.

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Conflict of interest: None

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Tables

Table 1: Baseline characteristics of the study population on March 31, 2020

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

[1] symptomatic patients between March 11 and May 3, 2020

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

Figure Legends

Figure 1 Legend: (A) Epidemic curve of patients with COVID-19 as a fraction of the total population of the three companies. While company 1 (green), organisationally and spatially separated from the others, had no case of COVID-19, companies 2 (blue) and 3 (red) show a very similar course where a third of the population have been symptomatic for COVID-19. (B) Symptomatic cases of COVID-19 and rate of infection amongst the three companies. The rate of infected persons is 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 as infected if either returned a positive result. The fraction of symptomatic patients amongst the infected is significantly larger in companies 2 and 3 than in company 1 (p=0.02).

Figure 2 Legend: Flowchart of the study. 354 soldiers of companies 2 and 3 were spatially and organisationally separated from 154 of company 1. On March 11, the first case of COVID-19 was diagnosed in the left cohort, thus infection of this group must have occurred prior or on this date. On March 20, strict social and hygiene measures were implemented in both cohorts. On March 31, 23 asymptomatic soldiers from company 1 were tested, of which all showed negative serology and PCR. On April 14 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 further 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 a third of all soldiers developed COVID-19 and a high level of seroconversion was observed, the cohort to the right was infected after March 31 and thus after the enforcement of social distancing and hygiene measures. Despite 15% asymptomatically infected soldiers in company 1 on April 14, 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.

Figure 3 legend: Nasopharyngeal viral concentration of the three cross-sectional samplings of asymptomatic participants versus samplings at the day of presentation of 21 symptomatic patients (bright red). The first cross-sectional study of 41 asymptomatic soldiers of the affected company 3 on day 14 of the epidemic is shown in green, 20 of these asymptomatic soldiers have a viral load comparable to symptomatic patients. The study of 23 asymptomatic soldiers of the unaffected company 1 at day 20 is shown in blue (all negative), and the final sampling of all companies at day 34 in gray with lower viral loads.

Figure 1

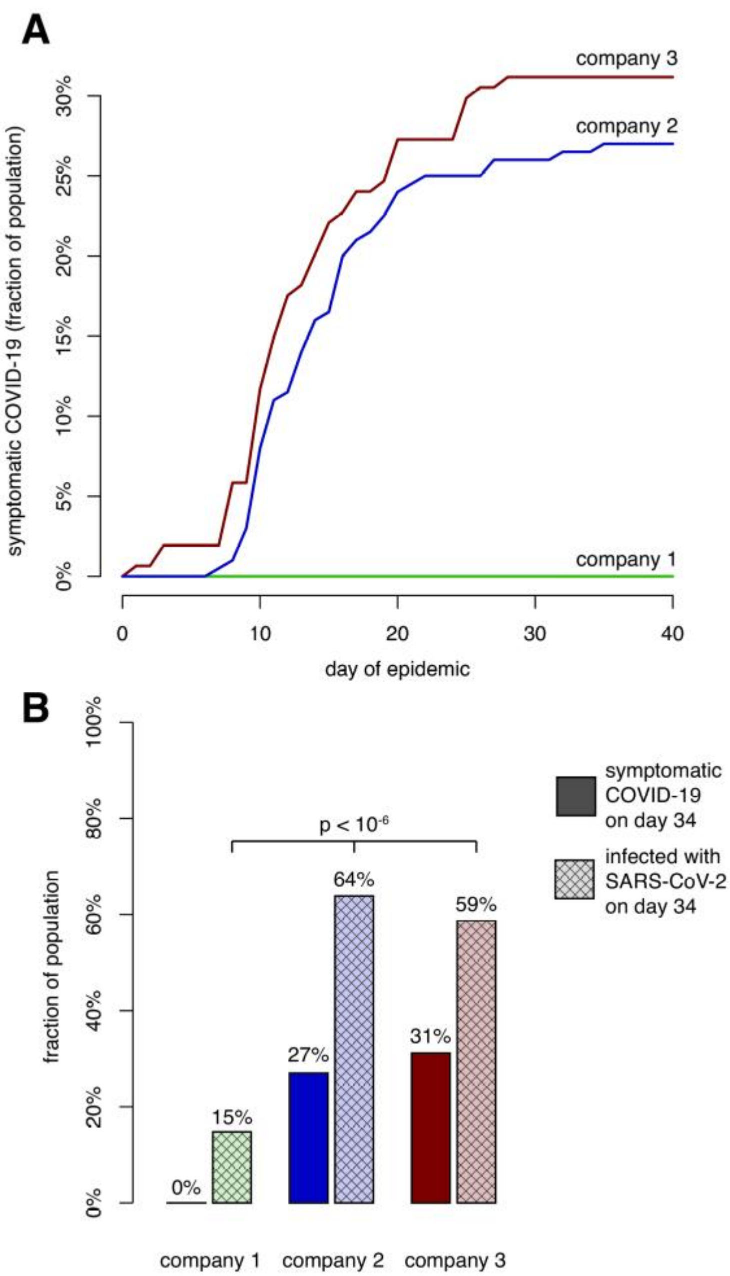
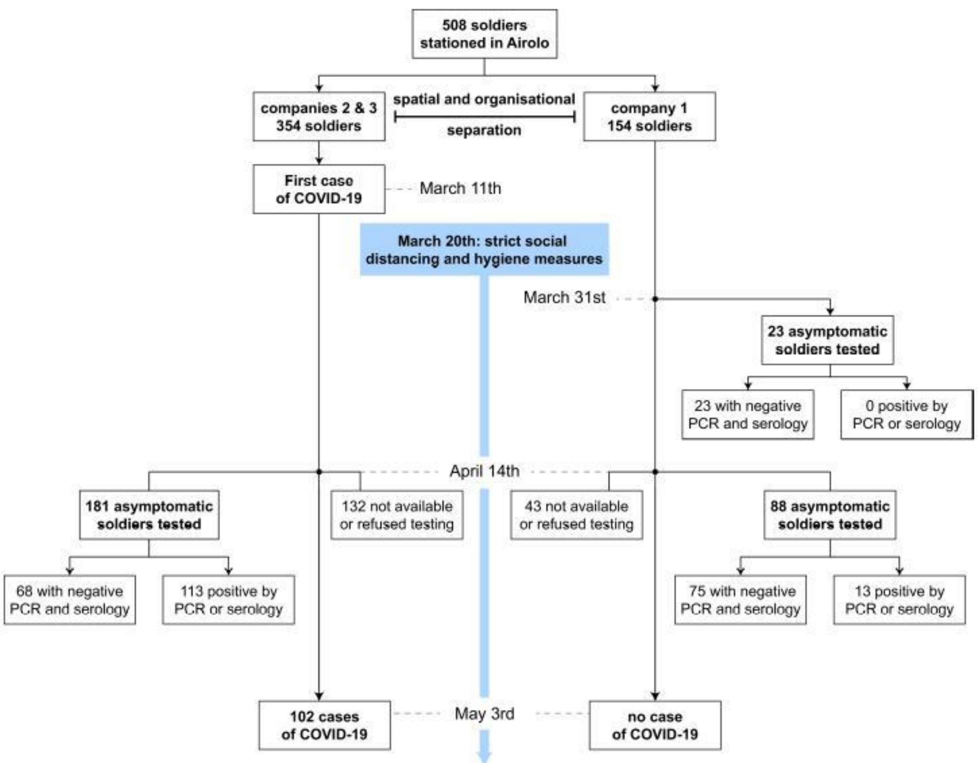
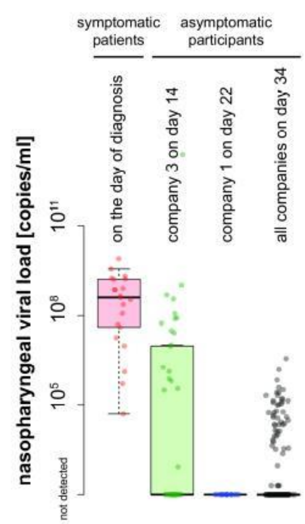

A
company 3
company 2
company 1
symptomatic COVID-19 (fraction of population)
0%
5%
10%
15%
20%
25%
30%
0
10
20
30
40
day of epidemic
B
fraction of population
0%
20%
40%
60%
80%
100%
p < 10-6
0%
15%
27%
64%
31%
59%
company 1
company 2
company 3
symptomatic COVID-19 on day 34
infected with SARS-CoV-2 on day 34

Figure 2



508 soldiers stationed in Airolo
companies 2 & 3 354 soldiers
spatial and organisational separation
company 1 154 soldiers
First case of COVID-19
March 11th
March 20th: strict social distancing and hygiene measures
March 31st
23 asymptomatic soldiers tested
23 with negative PCR and serology
0 positive by PCR or serology
April 14th
181 asymptomatic soldiers tested
132 not available or refused testing
43 not available or refused testing
88 asymptomatic soldiers tested
68 with negative PCR and serology
113 positive by PCR or serology
75 with negative PCR and serology
13 positive by PCR or serology
102 cases of COVID-19
May 3rd
no case of COVID-19

Figure 3



nasopharyngeal viral load [copies/ml]
not detected
10⁵
10⁸
10¹¹
symptomatic patients
asymptomatic participants
on the day of diagnosis
company 3 on day 14
company 1 on day 22
all companies on day 34