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important new contribution with high-quality statistical methods that allow quantification of independent risks. However, the data are not fully representative of the general population, excluding those with mild or no symptoms and instead reflecting consultation patterns, with over-representation of women and older people but fewer smokers.<sup>7</sup> Lower thresholds for presentation (eg, among women) could dilute test positivity compared with groups who might present only if they are more severely ill. It is also possible that there are unmeasured confounders—eg, social and workplace exposures, interactions, and behaviours, which might explain increased risk in some groups.

Unlike other reports,<sup>8</sup> this study suggests that sex differences in poor outcomes from COVID-19 are at least in part related to differential infection susceptibility. The role of ethnicity in greater susceptibility and poorer prognosis is a growing concern and deserving of further study. It seems that most comorbidities (except chronic kidney disease), although important for predicting prognosis, do not have a major part in susceptibility to infection. Regarding the results on smoking, it is likely that they could reflect consulting patterns and higher rates of non-infectious cough among smokers than non-smokers. Smoking seems important as a risk factor for poor prognosis,<sup>4</sup> but studies are conflicting, and the association merits further investigation. The one major modifiable risk factor is obesity, which presents a double problem of increasing susceptibility to infection, as well as the risk of severe consequences.<sup>9</sup>

However, what is fundamentally clear is that whatever the specific risk factors, the COVID-19 pandemic exacerbates existing socioeconomic inequalities, and this needs both exploration and mitigation in the coming months and years.<sup>10</sup> As the UK prepares to

loosen lockdown measures, knowing who is most at risk of infection is vital. This study highlights the more susceptible subgroups among those with relevant symptoms, although we cannot be sure why they are more susceptible. Population-level studies with testing among random samples of the general population (irrespective of symptoms), as well as accurate antibody tests of past infection, are urgently needed.

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## Asymptomatic SARS-CoV-2 infection

The pandemic spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of COVID-19, has placed lives and economies of many countries under unprecedented stress. Many countries have shut schools and workplaces and imposed physical distancing to reduce virus transmission, in an effort to prevent the number of COVID-19 cases from overwhelming health-care systems. Such measures, however, are not economically

sustainable. Schools and workplaces will have to be reopened. An important challenge for returning to normality is the prevalence of asymptomatic infection and the question of whether such individuals could sustain community virus transmission.<sup>1</sup> As the health community debates and examines the epidemiological significance of asymptomatic individuals, such cases present unique opportunities to gain insight into COVID-19 pathogenesis.

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In *The Lancet Infectious Diseases*, two independent studies by Sakiko Tabata and colleagues<sup>2</sup> and Ivan Fan-Ngai Hung and colleagues<sup>3</sup> have focused on the COVID-19 outbreak on board the *Diamond Princess* cruise ship in February, 2020, to retrospectively and prospectively compare asymptomatic with presymptomatic infection. Screening for viral shedding of all individuals on board was done when the ship was docked in Japan and those who tested positive were hospitalised. Individuals who tested negative and who returned to their country of residence were further quarantined and monitored for infection. These control measures provided an opportunity for clinical studies of asymptomatic infection. A previous study found that half of the 634 passengers who screened positive for SARS-CoV-2 while on board the ship were asymptomatic,<sup>4</sup> although whether these individuals remained asymptomatic until infection resolution was not prospectively determined.

Of the 43 individuals positive for SARS-CoV-2 on RT-PCR who were asymptomatic at admission to a hospital in Tokyo, Japan, ten developed COVID-19, including severe pulmonary disease.<sup>2</sup> Of the 215 asymptomatic individuals who returned to Hong Kong for further quarantine and were enrolled in the study by Hung and colleagues,<sup>3</sup> eight became RT-PCR positive and three of them eventually developed symptoms; a ninth individual was seropositive for SARS-CoV-2 and had abnormalities on chest CT scan but remained asymptomatic. The individuals in both studies were monitored until discharge from isolation. Neither of the studies, however, were able to identify the time of initial exposure to the virus that led to infection. Because RT-PCR positivity can persist for weeks and is subject to sampling error,<sup>5</sup> the comparison between asymptomatic and symptomatic cases could be confounded by the difference in time from virus exposure.

Notwithstanding this limitation, these studies describe two remarkable features. First, the presence of comorbidities did not appear to increase susceptibility to symptomatic infection or even disease outcome in these studies. Instead, older age appeared to be the only demographic factor that differentiated symptomatic from asymptomatic outcome in the individuals in Hong Kong,<sup>3</sup> as well as differentiating severe from mild cases in the Japanese hospital.<sup>2</sup>

Second, about 50% of asymptomatic individuals showed radiographic abnormalities, including ground-glass opacities on chest CT scans.<sup>2,3</sup> The Hong Kong

group also observed that patients with CT scan abnormalities had higher concentrations of SARS-CoV-2 spike protein and nucleoprotein antibodies than those with normal CT scans, regardless of whether they were symptomatic or asymptomatic.<sup>3</sup> These findings suggest that the anatomy and extent of infection might not differentiate symptomatic from asymptomatic cases. A quantitative comparison of the extent of abnormalities in the chest radiographs or CT scans between those with symptomatic and presymptomatic infection would have been informative, but this analysis was not carried out in these studies. Nonetheless, these findings suggest that some individuals can tolerate a certain extent of lower respiratory tract infection without developing any symptoms.

Besides the extent of pulmonary infection, differentiation between symptomatic and asymptomatic outcomes might be related to the type of host response to infection. In the Japanese study (but not in the Hong Kong study), significantly increased serum lactate dehydrogenase was observed in presymptomatic individuals compared with asymptomatic individuals. Lactate dehydrogenase is a marker of pyroptosis, an inflammatory form of programmed cell death.<sup>6</sup> Pyroptosis releases proinflammatory molecules,<sup>6</sup> including IL-1, which we found to be expressed before the nadir of respiratory function and peak expression of other cytokines in a previous study.<sup>7</sup> Pyroptosis could therefore be an initiator of pulmonary inflammation and symptomatic disease.

In conclusion, outbreak investigations that are able to identify asymptomatic and presymptomatic infections have unique opportunities to gain clinical insights into COVID-19 pathogenesis. Such clinical insights will be pivotal for shaping future pathogenesis studies.

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## Vaccine development during global epidemics: the Zika experience



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The North and South American continents experienced a major epidemic of Zika virus in 2015–16, which infected up to 70% of the population in some areas.<sup>1</sup> Until then, Zika virus infection had been considered a benign viral infection with minor health consequences. However, during the 2015–16 epidemic, it was recognised that Zika virus infection can lead to neurological diseases of the peripheral and central nervous systems, including Guillain-Barré syndrome and congenital syndrome, which was initially characterised by microcephaly. The spectrum of clinical presentations of congenital Zika syndrome is still not fully described. Studies have shown that about 20% of babies of mothers exposed to Zika virus during pregnancy who were born with no initial signs of birth defects presented impaired cognitive development and other neurological abnormalities later in life.<sup>2,3</sup> Zika is endemic in all tropical areas of the world, following a pattern of global distribution similar to that of dengue. Nearly half of the global population lives in areas at risk of Zika transmission, and the chance for future Zika epidemics remains very real. 5 years after the 2015–16 outbreak, we still do not have a licensed Zika vaccine despite substantial efforts throughout this time period.<sup>4</sup>

In *The Lancet Infectious Diseases*, Kathryn Stephenson and colleagues<sup>5</sup> report the final results of a phase 1 clinical trial on the safety and immunogenicity of a Zika purified inactivated virus vaccine given via standard, accelerated, or shortened schedules. The authors showed that their Zika vaccine formulation was well tolerated, immunogenic, and did not show signs of inducing any significant adverse medical outcome (eg, Guillain-Barré syndrome) through 52 weeks of follow-up. A two-dose prime–boost regimen of the vaccine, administered either via a standard schedule

(weeks 0 and 4) or an accelerated schedule (weeks 0 and 2), elicited a robust Zika virus neutralising antibody response that peaked 2 weeks after the final vaccination, and then declined to a geometric mean titre of less than 100 by study week 16. The sharp decay in Zika virus neutralising antibody titres might be linked to poor induction of cellular immune responses by the inactivated vaccine.<sup>6</sup> This antigen formulation is still far from an ideal vaccine, and efforts to develop or refine promising Zika vaccine candidates must remain a priority. However, because of the progresses made we might be somewhat better prepared should a new Zika outbreak occur.

Despite low antibody durability after boost, it is possible that the level of immunological memory elicited by this vaccine formulation would allow for a quicker humoral immune response to a Zika infection, as has been shown for other flavivirus vaccines.<sup>7,8</sup> This quick response might reduce levels of replicating virus enough to inhibit fetal infections. Nevertheless, safety issues still need to be addressed.

The small number of participants in Stephenson and colleagues' trial<sup>5</sup> does not allow the risk that this formulation can induce Guillain-Barré syndrome to be completely ruled out. Moreover, it is still uncertain whether low levels of anti-Zika antibody can affect the clinical outcome of dengue infection. Anti-dengue antibodies have been shown to enhance Zika virus infection in in-vitro, ex-vivo, and animal models, but the role of anti-Zika antibodies in dengue infections remains unclear.<sup>9</sup> In an ex-vivo human skin model, low titres of anti-Zika antibodies enhanced dengue infection of macrophages and dendritic cells, suggesting that a vaccine formulation that induces low immunogenicity might increase the risk for severe