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Understanding the drivers of transmission of SARS-CoV-2

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Despite the recent development of effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), non-pharmaceutical interventions will remain the cornerstone in the battle against COVID-19 for some time. Such interventions are effective but have major societal and economic impacts and should therefore be used as selectively as possible. Quarantine after exposure to a patient with COVID-19 is such a measure. Reported secondary-attack rates among so-called high-risk contacts have varied widely from lower than 1% to 54·9%.[1] In the *Lancet Infectious Diseases*, to better understand these differences, Michael Marks and colleagues explored factors related to onwards transmission of SARS-CoV-2.[2] The authors used data from a randomised controlled trial in Barcelona that assessed the use of hydroxychloroquine as post-exposure prophylaxis.[3] In addition to demographic and epidemiological variables (age, sex, symptoms, type of exposure, and so on) the dataset contained information on viral load as assessed by quantitative PCR for both the index case and the contacts with a positive test. With these data from 282 index cases and 753 contacts, the authors assessed the relationship of viral load and characteristics of cases (age, sex, number of days from reported symptom onset, and presence or absence of fever, cough, dyspnoea, rhinitis, and anosmia) and associations between risk of transmission and characteristics of the index case and contacts.

Marks and colleagues found that the viral load of the index case was strongly associated with the risk of onward transmission (adjusted odds ratio per $\log_{10}$ increase in viral load 1·3, 95% CI 1·1–1·6) and that this risk was higher for household contacts (2·7, 1·4–5·06) than for other types of contact (health-care worker, nursing home worker, or nursing home resident). Additionally, they found a small, but significant, effect for age of the contact person, with older individuals being more at risk of becoming infected. Because the included population of both index cases and contacts consisted mainly of adults aged 27–57 years, more important age effects, such as those for children, might have been difficult to identify. Although the effectiveness of masks is well established,[4,5] in the analysis of Marks and colleagues, self-reported mask use surprisingly did not affect the risk of transmission. Similarly, Ng and colleagues did not find an effect of self-reported mask use on risk of COVID-19 transmission in their analysis of contact tracing data from Singapore.[6] Rather than questioning the usefulness of mask-wearing policies, these results underscore the necessity of a multi-layered comprehensive approach to infection prevention and control.[7] Factors such as consistent and correct use and quality of the mask could not be accounted for in the analysis. Marks and colleagues' finding that the viral load of the index case was a major determinant for onwards transmission does not come as a surprise, since viral load has been previously shown to influence transmission for other respiratory infections such as influenza. The viral load of SARS-CoV-2 is not a fixed characteristic of an individual, but rather shows an evolution over time, peaking around symptom onset. Analyses of transmission pairs for SARS-CoV-2 have previously shown that, similar to viral load, infectiousness peaks around symptom onset.[8] Finally, both viral load and time after symptom onset have been shown to be independently related to infectiousness in viral culture studies.[9]

In people living with HIV, lowering the viral load to an undetectable level has been successfully used as a strategy to prevent onwards transmission. Unfortunately, we are not yet able to actively lower the viral load of a patient with SARS-CoV-2. Nevertheless, the results of Marks and colleagues encourage us to use viral load at time of testing for risk stratification. PCR tests for SARS-CoV-2 can remain positive for a long time after the infectious period. With increased testing and screening of asymptomatic individuals—for example, before international travel—this shedding of non-infectious viral RNA is not only problematic for the individual who was tested, but also for their close contacts who risk unnecessary quarantine. Information on viral load can help to solve this problem. Unfortunately, most commercially available PCR assays are qualitative (giving only a positive or negative result) rather than quantitative (reporting viral load in viral copies per mL). Cycle threshold (Ct) values, the number of amplification cycles needed to obtain a positive result, have been used as a semi-quantitative proxy. Low Ct values correspond to high viral loads. However, the precise correlation between Ct values and

viral load depends on many factors, such as sampling method, gene targets, primers and probes, and possible mutations in target genes. Therefore, Ct values are not systematically comparable. In Belgium, to overcome this challenge of inter-assay variability, the National Reference Laboratory (KU Leuven, Leuven, Belgium) and the National Institute of Public Health (Sciensano, Ixelles, Belgium) have sent all clinical laboratories a series of inactivated samples with a known viral load. These samples can be used to generate an internal calibration curve. Although risk assessments should account for other factors too, such as type of exposure and timing of sample, the standardised reporting of viral load, and thus infectiousness, should facilitate differentiated disease control interventions. Tailored and proportional measures for close contacts are crucial to ensure high compliance, while we wait for vaccine coverage to ramp up and facilitate the return to a more normal life.

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Optimism and caution for an inactivated COVID-19 vaccine

Although the COVID-19 pandemic has caused substantial morbidity, mortality, and social upheaval worldwide, the final months of 2020 heralded the high efficacy and safety results of three phase 3 clinical trials of SARS-CoV-2 vaccines.[1–4] The first COVID-19 vaccine to be approved in the western world, BNT162b2 (Pfizer),[1] was closely followed by mRNA-1273 (Moderna),[2] and the chimpanzee-adenovirus vectored AZD1222 (AstraZeneca–Oxford).[3]

Unfortunately, cold-chain requirements, finite global manufacturing capacity, and insufficient supply are likely to disproportionately affect low-income and middle-income countries (LMICs). Although multilateral agreements have been made to purchase vaccines for LMICs through the COVID-19 Vaccine Global Access Facility, a global collaboration established to provide equitable access to COVID-19 vaccines, only enough doses to vaccinate 250 million people have been purchased to date. Mathematical models indicate there will not be an adequate supply of vaccines available to cover the global population until 2023,[5] further exacerbating health and other disparities in LMICs.

Thus, the early safety and immunogenicity results from Raches Ella and colleagues published in *The Lancet Infectious Diseases*[6] of BBV152, a SARS-CoV-2 vaccine manufactured and produced in India by Bharat Biotech, are a welcome addition to the COVID-19 vaccine landscape. Bharat Biotech, experienced with developing and distributing vaccines to LMICs, is poised to bridge the vaccine disparity gap using the well established inactivated whole-virus vaccine platform. In a multicentre, double-blind, randomised phase 1 trial, investigators enrolled 375 healthy adults in India, who were assigned to receive two doses separated by 2 weeks of BBV152 3 µg with Algel-IMDG (n=100), 6 µg with Algel-IMDG (n=100), or 6 µg with Algel (n=100), or an Algel-only control (n=75). Researchers found the vaccine to be safe and less reactogenic than reported with BNT162b2[1] and mRNA-1273.[2] They found that more than 80% of patients in each vaccine group seroconverted, with at least a four-fold increase in binding antibody titres. Seroconversion occurred by microneutralisation in 88% in the 3 µg Algel-IMDG

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