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Perspective

Do superspreaders generate new superspreaders? A hypothesis to explain the propagation pattern of COVID-19

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ABSTRACT

The current global propagation of COVID-19 is heterogeneous, with slow transmission continuing in many countries and exponential propagation in others, where the time that it took for the explosive spread to begin varied greatly. It is proposed that this could be explained by cascading superspreading events, in which new infections caused by a superspreader are more likely to be highly infectious. The mechanism suggested for this is related to viral loads. Exposure to high viral loads may result in high-intensity infection, which exposes new cases to high viral loads. This notion is supported by experimental veterinary research.

The patterns of propagation of the severe acute respiratory syndrome (SARS) outbreak of 2003 were not explained by conventional epidemic models that assumed homogeneity of infectiousness. Instead, the existing datasets were best matched by models that used negative binomial distributions, in which a small proportion of cases were highly infectious (Lloyd-Smith et al., 2005; McDonald et al., 2004; Shen et al., 2004). Data and modelling supported the existence of superspreaders, which played a crucial role in propagating the disease by being very efficient at transmitting SARS-CoV-1, such that in the absence of super-spreading events most cases infected few, if any, secondary contacts (Stein, 2011). Almost a decade later the Middle East respiratory syndrome coronavirus (MERS-CoV) emerged, with analogous infection dynamics involving superspreading events (Hui, 2016).

Similarly, early modelling and data suggest that a small proportion of cases of COVID-19 were responsible for most transmissions, which is evidence that superspreaders also play an important role in SARS-CoV-2 (MacKenzie, 2020; Frieden and Lee, 2020). Explanations for this superspreader status include high viral shedding due to poor immunocompetence, underlying diseases or co-infection, or elevated contact rate due to active social behaviour (Bassetti et al., 2005; Lloyd-Smith et al., 2005; McDonald et al., 2004; Shen et al., 2004; Wong et al. 2015).

The propagation of SARS-CoV-2 has shown it to be heterogeneous at a global scale (data publicly shared by the World Health Organization and Johns Hopkins University). After the virus started to be reported outside of China, cases were infecting fewer people than expected compared with the rate of spread in China. Nonetheless, by the end of February, when over 50 countries outside China had confirmed the infection, South Korea, Italy and Iran presented notable spread. During the first month of viral propagation in south Korea there were two to three reports of new infections per day. However, the rapid spread began after one case was linked to 3,900 secondary cases in Daegu (Shim et al., 2020).

In Italy, the rapid surge of cases began in a cluster in Lombardy after an infected man was hospitalised without precautionary measures and infected other patients (mostly elderly people) and health workers. Apparently, there was no calm period in Iran, where the first two reported cases were fatal. Two weeks later there were 1,500 cases, and after 1 month there were >17,000 reported infections. A few weeks later, several other countries underwent a similar exponential growth in the number of cases, despite many of them taking drastic measures to control the pandemic. A notable case was the USA, where the infection propagated slowly from 20 January to early March, when the daily growth in the number of cases suddenly went from being of one digit to surpassing 30%, remaining above that geometrical growth rate for almost 20 days. This explosive spread began in New York

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City, where the number of cases reached 20,000 in just over 2 weeks. In contrast, the infection propagated at a slow to moderate pace in most countries such as Thailand, Singapore, Egypt, Finland, Japan, Australia, and many others. In general, there have also been contrasts in the apparent case-fatality rate (deaths/reported) depending on the speed of propagation, being much lower in countries with slow spread (e.g. 0.1% in Singapore, 1.4% in Australia and 1.8% in Thailand) compared with those where the transmission was notably high (e.g. 14% in Italy, 12% in Spain, 7% in USA). This difference might be too large to be solely explained by detection bias.

It appears that SARS-CoV-2 spreads gradually within a region unless a chain reaction of transmission is triggered. Independent superspreading events due to individual variation cannot explain this large-scale heterogeneous pattern of transmission. The occurrence of superspreaders may not be at random and may depend on other superspreaders. It is proposed that infections caused by contact with superspreaders are more likely to result in new superspreaders than those caused by transmission from a less infectious individual. The mechanism by which this would be possible is by exposure to differential viral load. The primary mode of transmission of SARS-CoV-2 appears to be through exposure to respiratory droplets and direct contact with infected individuals and their contaminated environment (Xiao et al., 2017; van Doremalen et al., 2020). Droplets may contain a few or a million viral particles, and this differential load determines how much the environment is contaminated and the infective dose a susceptible person is exposed to. A case with a high intensity of infection has the potential of being a superspreader due to high viral shedding. Susceptible people exposed to this hypothetical superspreader would be exposed to a high viral dose. Infections resulting from exposure to high loads of virus are expected to be of high intensity, as a large quantity of viral particles initiating replication in synchrony might overwhelm the mechanisms of resistance, and the poor control of viral replication may therefore result in a new potential superspreader.

This hypothesis has support from veterinary research. For example, in a recent study, calves were experimentally infected by bovine viral diarrhoea virus (an RNA *Pestivirus* that is transmitted via droplets) at three different viral doses (Strong et al., 2015). The outcome of infection was dose dependent, with animals given a higher dose developing severe disease and more pronounced viral replication and shedding. Moreover, sentinel calves housed with the low-dose-infected group did not become infected, despite viral shedding being confirmed. Other experimental infections also found that viral dose positively correlated with disease severity and viral shedding in other virus-domestic animal systems such as feline viral rhinotracheitis in cats (Gaskell and Povey, 1979), low pathogenic avian influenza virus in chickens (Zarkov and Bochev, 2008) and equine influenza in horses (Mumford et al., 1990).

Under the hypothesis posited here, cases with low-to-moderate intensity of infection would mainly yield new infections of low-to-moderate severity and viral shedding in people who are not in risk groups. Occurrence of cases of high-intensity infection could result in new cases that are of high viral replication, generating a 'domino effect'. The severity of disease caused by high viral loads is expected to be high. This would be due to extensive cell damage caused by large amounts of virus and also due to the resulting immune response. The virulence arising from an infection by SARS-CoV-2 is related to inflammatory self-damage (Qin et al., 2020), and it is expected that an infection initiated by a large number of viral particles would generate a stronger immune response compared with infections caused by a low viral dose. Therefore, a case resulting from exposure to high viral loads has the potential to develop severe disease and also of being highly infectious. It was found that the severity of disease in MERS patients was positively correlated with viral load (Min et al., 2016), and the same was recently reported for COVID-19 (Liu et al., 2020; Zou et al., 2020).

It could be argued that individuals with higher viral loads are more likely to be hospitalised or die, and therefore less likely to contribute to community transmission as superspreaders. However, it should be considered that the outcome of an exposure to a high viral dose largely depends on the tolerance (ability to reduce the damage of an infection) of an individual (Råberg et al., 2009). Given equal resistance (ability to limit the infection), exposure to high viral loads will result in severe disease in the less tolerant and high infection intensity with few manifestations in the more tolerant. The latter case is of special concern because in these individuals the clinical signs would be mild or absent, and therefore likely to be undetected, exposing many people to high viral loads. On the other hand, severe cases may be important sources of disease in hospitals (Wang et al., 2020). For example, in Argentina, 17% of the cases reported to date are healthcare workers (Infobae, 2020). Therefore, the presence of superspreaders in hospitals could make them nodes, where cascades of superspreading events emerge, which is consistent with what was observed in Lombardy.

Disease is traditionally studied as a binary outcome: infected or non-infected. The concepts presented here alert us to the value of studying disease as a continuous variable (i.e. infection intensity) (Beldomenico and Begon, 2010). Measuring the intensity of an infection is crucial because it may be related to the virulence as well as infectiousness. There are many studies of different viral diseases in which the length of viral shedding is recorded, yet very few produced data on the viral shedding load. The hypothesis posited here needs to be tested by empirical and theoretical studies, but this requires that data on viral load (viraemia and shedding) are urgently collected. If superspreaders generate new superspreaders by exposing susceptible people to large viral loads, this mechanism should be immediately acknowledged and considered in the responses being undertaken. In particular, emphasis should be placed on the isolation or strict distancing of people of risk groups, as they would not only have more chances of developing a more severe disease (with the potential of overwhelming the health system) but they could also be sources of high viral loads. In addition, aggressive contact tracing and testing would allow quick identification of tolerant superspreaders, who might be key elements of propagation.

Conflict of interest

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