Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 146 (2021) 110431

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

COVID-19: Does the infectious inoculum dose-response relationship contribute to understanding heterogeneity in disease severity and transmission dynamics?

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Initial infectious inoculum
Viral dose
Public health

ABSTRACT

The variation in the speed and intensity of SARS-CoV-2 transmission and severity of the resulting COVID-19 disease are still imperfectly understood. We postulate a dose-response relationship in COVID-19, and that "the dose of virus in the initial inoculum" is an important missing link in understanding several incompletely explained observations in COVID-19 as a factor in transmission dynamics and severity of disease. We hypothesize that: (1) Viral dose in inoculum is related to severity of disease, (2) Severity of disease is related to transmission potential, and (3) In certain contexts, chains of severe cases can build up to severe local outbreaks, and large-scale intensive epidemics. Considerable evidence from other infectious diseases substantiates this hypothesis and recent evidence from COVID-19 points in the same direction. We suggest research avenues to validate the hypothesis. If proven, our hypothesis could strengthen the scientific basis for deciding priority containment measures in various contexts in particular the importance of avoiding super-spreading events and the benefits of mass masking.

Introduction

The collective image of what constitutes "the COVID-19 epidemic" has been shaped worldwide by the highly mediatized dramatic outbreaks in countries such as China, Italy, Spain, the United Kingdom (UK), the United States (US), and Brazil. However, the significant variation in the speed and intensity of SARS-CoV-2 transmission, and the severity of the resulting COVID-19 are still imperfectly understood. There are still many incompletely explained observations and uncertainties that are crucial in understanding transmission and anticipating the relative impact of containment measures [1].

We think that the importance of the dose of the virus in the inoculum is being neglected and that it is likely that a dose-response relationship (infection intensity) is an important missing link in understanding COVID-19, both as a factor in the severity of disease and transmission dynamics.

Hypothesis

We postulate a dose-response relationship in COVID-19: the "dose of virus in initial inoculum" relates to the severity of disease and intensity of transmission. In our opinion, it is plausible that:

1. At an individual level: "viral dose in inoculum is related to severity of disease (dose-response relationship)".
2. At a cluster level: "severity of disease is related to transmission potential", leading to clusters of mild cases and clusters of severe cases.
3. At a community level: "in certain contexts, chains of severe cases can build up through intensive transmission with high inoculum to severe local outbreaks, which can result in large-scale intensive epidemics; while this is less likely in other contexts".

This theory plays out in practice on these three levels:

a) Individual level: A person infected with a small dose viral inoculum will on average develop milder disease than a person infected with a

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https://doi.org/10.1016/j.mehy.2020.110431
Received 13 July 2020; Received in revised form 22 September 2020; Accepted 23 November 2020
Available online 25 November 2020

high viral inoculum and vice versa. This is independent of other well-known risk factors for severity of disease, mainly old age, and co-morbidities, such as diabetes.

b) Cluster level: A person with asymptomatic infection or mild disease, will on average spread lower dose of the virus, and is less likely to transmit disease; and when the person transmits, the newly infected person is more likely to have mild disease compared to a person infected by a severely ill person, who spreads on average higher doses of the virus. This causes clusters and chains of milder cases or more severe cases.

c) Community level: In certain contexts, such as dense urban centres with a moderate climate, during the season that people live mostly indoors, the potential for intensive transmission and explosive outbreaks is higher than in rural areas, or in regions with a hot and humid climate where people live mostly outdoors. Hence, a cascade of intensive transmission is more likely in certain contexts than in others.

Evaluation of the hypothesis

Evidence from other pathogens

A minimum quantity of infectious particles required to establish infection ("minimum infectious dose") varies across different pathogens; whether this infection subsequently causes disease, and the severity of the disease will depend both on the infectious agent and the host's immune response. Over decades of research, many studies have also consistently shown the importance of the dose of the pathogen in the inoculum in many infectious diseases (Table 1).

Human volunteer challenge studies conducted with influenza and coronaviruses have empirically shown a dose-dependent increase in the occurrence and severity of the disease. Similarly, animal model studies conducted for a range of human pathogens have consistently demonstrated these same features. Epidemiological studies most often show:

1. Close contact with the primary case increases chances of infection and increases the severity of the disease.
2. Primary cases with a severe disease generate more severe disease in secondary cases which generate more severe disease in tertiary cases.
3. Single cases are often less severe than cases occurring in clusters, such as within families, retirement homes, military barracks, and other confined environments.

There is also an abundance of veterinary research showing a dose-dependent outcome of viral infections, and their further transmission [25,26].

Emerging evidence from SARS-CoV-2/COVID-19

In COVID-19, a potential dose-response relationship is especially difficult to prove, as it may be dwarfed by the very strong correlation between severity of the disease and advanced age and co-morbidities.

Despite that difficulty, emerging evidence consistent with a dose-response relationship between the infecting dose and disease severity has been recently observed in three clusters of individuals that were exposed to diverse inocula and developed divergent clinical forms of COVID-19 disease [27]. The potential infecting doses were determined by the extent of physical distancing and precautionary measures that the individuals followed. It was evident that in the clusters which did not follow physical distancing or other precautions, such as wearing masks, a larger proportion of individuals developed severe disease, whereas only asymptomatic or mild disease was seen in the cluster where exposure had been low [27].

The severity of the disease following transmission from pre-symptomatic/mild cases has been documented. Some studies have shown that transmission from a pre-symptomatic person (who later developed a mild disease) resulted in mild diseases in the secondary cases, which is concordant with our hypothesis [28]. It has also been documented that transmission from children, with mild disease, also resulted in mild disease in secondary cases [29–31].

Table 1
Evidence from various pathogens on the importance of the dose of the initial inoculum.

Pathogen	Observations
Influenza	• Viral dose-dependent increase in severity of symptoms in human volunteer challenge studies with different influenza strains [2–4]. • Dynamic transmission models suggest that with a small initial dose of the virus, the disease progresses through an asymptomatic course, for an intermediate value, it takes a typical course, and for a large initial dose of the virus, the disease becomes severe [5]. • Severe disease possibly correlated with higher infectious doses in the 1918–19 influenza "Spanish flu" pandemic [6]. • The duration of viral shedding of influenza A(H1N1)pdm09 is determined by the severity of the disease [7]. • Asymptomatic patients or "silent spreaders" may contribute little to the transmission [8].
Coronaviruses	• For SARS, higher nasopharyngeal viral load correlated with proximity to the index patient [9], severity of disease, and amount of virus shed [10]. • High nasopharyngeal viral loads correlated with disease severity, poorer outcomes, and mortality also seen in MERS [11]. • A dose-response relationship of Human Coronavirus 229E (HCoV-229E) with severity of infection in human volunteer challenge studies [12].
Human Immunodeficiency Virus (HIV)	• The probability of getting infected varies according to the routes of transmission (with highest risk from blood transfusion) and depends significantly on the infectious dose [13]. • High volume of the viral inoculum leads to shorter incubation periods and faster disease progression [14]. • The relation between viral load in the blood (cut-off 1500 copies/mL) and the chances of heterosexual transmission has been repeatedly and convincingly shown in studies with discordant couples [15,16].
Measles	• Higher initial doses associated with more severe disease and higher mortality in secondary (multiple) cases that arise from index cases within the house environment than single cases that arise from an index case outside the house [17], presumably because of exposure to a higher initial dose [18]. • Secondary cases infected through a severe case have higher mortality and these severe cases have shorter incubation periods [17].
Tuberculosis (TB)	• More secondary infections from TB-infected persons who are sputum smear-positive than from persons who are culture-positive only [19]. • Higher doses of infectious particles are more likely to result in tuberculosis [20]. • Dose-dependent infectivity in studies using ultra-low doses of *M. tuberculosis* aerosols in animal models [21]. • Evidence from TB in patients from the US point in the same direction [22,23].
Streptococcus pneumoniae	• The development of bacterial pneumonia more likely when the dose of the inoculum exceeds a threshold of host immune response and antibacterial protection. • A relationship between the dose and the development of pneumonia in animal models [24].

SARS: Severe Acute Respiratory Syndrome, MERS: Middle East Respiratory Syndrome, US: United States.

Immunological evidence: Immune responses to SARS-CoV-2—implications of the role of the dose of the initial inoculum on viral clearance

The expression of COVID-19 in an individual is related to the exposure to SARS-CoV-2 and the competency of one's immune system. Effective immune responses against viral infections largely depend on the early innate responses and the downstream cascade that eventually help to control viral replication and induces adaptive immune responses. However, several viruses including SARS-CoV-2 have developed mechanisms to inhibit or evade these initial innate responses. Knowledge on immune response to SARS-CoV-2 is summarised in Table 2 and key differences between immune responses in mild and severe COVID-19 in Table 3.

We postulate that the dose of the initial viral inoculum can partly explain the differences in the immune responses elicited in mild and severe COVID-19 (Fig. 1). A low dose of SARS-CoV-2 initial inoculum is likely to trigger a cascade of immune responses that leads to downstream viral clearance. It is also more likely that a smaller dose of viral inoculum will stimulate a protective immune response and hence result in milder disease, while a higher dose of the viral inoculum will evade the immune response and/or create chaos in the immune system leading to more severe disease [37]. Dose-dependent variations in downstream activation of different components of the innate immune response have been demonstrated earlier. Low doses of pathogens are possibly cleared by primary innate immune responses (such as IFN-III), which are less inflammatory in their action [38]. Higher doses evade this initial response and trigger a delayed response of secondary lines of defence (such as IFN-I) over broader areas of tissues and often trigger inflammation, which leads to severe disease [38].

It is plausible that low doses of SARS-CoV-2 activate the innate immunity component of the immune system which responds with moderate levels of protective cytokines and IFN pathway activation. Additionally, the virus further activates the adaptive immunity component and causes early apoptosis of viral-infected cells by CTLs and NK cells and robust anti-viral neutralizing antibody responses, which eventually lead to mild or indolent disease. In contrast, high doses of SARS-CoV-2 initial inoculum block or delay the activation of the IFN pathway and cause an elevated pro-inflammatory cytokine response which may lead to cytokine storms. The high dose of the initial inoculum also may lead to high dose induced immune suppression, causing downstream apoptosis of CTLs and NK cells leading to lymphocytopaenia, inefficient T and B cell responses (due to "functional exhaustion"), and impaired neutralizing antibody responses all leading to severe COVID-19.

Interestingly, asymptomatic patients appear to have weaker immune responses to SARS-CoV-2 infection [39]. In persons who are asymptomatic or have mild disease, exposure to SARS-CoV-2 induces cellular immune (T cell) responses even without sero-conversion (SARS-CoV-2 specific antibodies), especially in familial contact with infected individuals [40,41]. Index cases for most of these secondary cases resulting in mild or asymptomatic disease also experience mild/moderate COVID-19 [40]. These robust memory T cell responses even without the presence of antibodies may be protective against further or recurrent SARS-CoV-2 infections.

In our opinion, these observations could be correlated to lower doses

Table 2
Key observations of immune responses against SARS-CoV-2 in mild and severe COVID-19.

Immune response	Key observations in COVID-19 [2,32–36]
Innate	
Cytokines/ chemokines	• Increased plasma levels of pro-inflammatory cytokines and chemokines (especially IL-2, IL-6, IL-10, and TNFα in severe cases) compared to mild cases or healthy controls. • The host pro-inflammatory response hypothetically induces an immune pathology resulting in uncontrolled dysregulation of the immune system. • Rapid course of ALI and ARDS occurring in severe disease including massive cytokine and chemokine release, the so-called "cytokine storm". • An increase in serum cytokine/chemokine levels and neutrophil-lymphocyte-ratio (NLR) correlated with the severity of COVID-19, implicating hyper-inflammatory responses in pathogenesis and adverse outcomes.
Interferon (IFN) type I/III	• Patients with severe COVID-19 demonstrate remarkably impaired IFN-I activation as compared to mild or moderate cases. • Lack of robust IFN-I/III signatures from infected cell lines, primary bronchial cells, and a ferret model.
Adaptive	
T cells, B cells, and NK cells	• Lymphocytopaenia and modulation in lymphocyte balance associated with a decrease in levels of circulating CD4+ cells, CD8+ cells, B cells, and NK cells; and a decrease in monocytes, eosinophils, basophils, and total neutrophils have been commonly observed to be directly correlated with disease severity and death. • Upon entry, SARS-CoV-2 viral peptides enable the development of virus-specific effector and memory T cells, and patients with mild disease present with normal or slightly higher T and NK cell counts. • The cause of peripheral T cell loss in moderate to severe COVID-19 is unclear. Direct infection of T cells has not been reported (which occurs in MERS-CoV infections) [34] although evidence on this is accumulating. • Lymphocyte responses postulated to be influenced by the dose of the virus.
Antibodies	• SARS-CoV-2 infection also involves T and B cell immunity and anti-viral neutralizing antibody responses; delayed in severe patients. • IgM primary antibody response observed within the first week following symptoms while IgG antibodies follow and are assumed to retain a life-long immunity. High serum antibody levels have been associated with more severe disease.
Apoptosis	• CTL responses lyse virus-infected tissue cells in mild patients. • It has also been proposed that apoptosis of lymphocytes induces lymphocytopaenia in critically ill patients.

IL: Interleukin, IFN: Interferon, TNFα: Tumour Necrosis Factor (alpha), ICU: Intensive Care Unit, ALI: Acute Lung Injury, ARDS: Acute Respiratory Distress Syndrome, NK: Natural Killer, CTL: Cytotoxic T-Lymphocyte.

Table 3
Key differences between immune responses to mild and severe COVID-19.

Immune response	Mild COVID-19	Severe COVID-19
Innate		
Cytokines/ chemokines	Elevated cytokines/ chemokines but limited pro-inflammatory responses	Highly elevated cytokines/ chemokines with more pro-inflammatory responses eventually leading to "cytokine storms"
Interferon (IFN) type I/ III	Possible activation of IFN pathway	Delayed or blocked activation of IFN pathway
Adaptive		
T cells, B cells, and NK cells	Normal or slightly increased T cells (no lymphocytopaenia)	Decreased T cells, NK cells, and eosinophils (lymphocytopaenia and eosinopaenia)
Neutralizing antibodies	Anti-viral neutralizing antibody response	Inefficient T&B cell response (exhaustion) and delayed neutralizing antibody response
Apoptosis	Early apoptosis of virus-infected cells by CTL (CD8+) and NK cells causing viral clearance	Delayed apoptosis of CTL (CD8+) and NK cells

IFN: Interferon, CTL: Cytotoxic T-Lymphocyte, NK: Natural Killer.

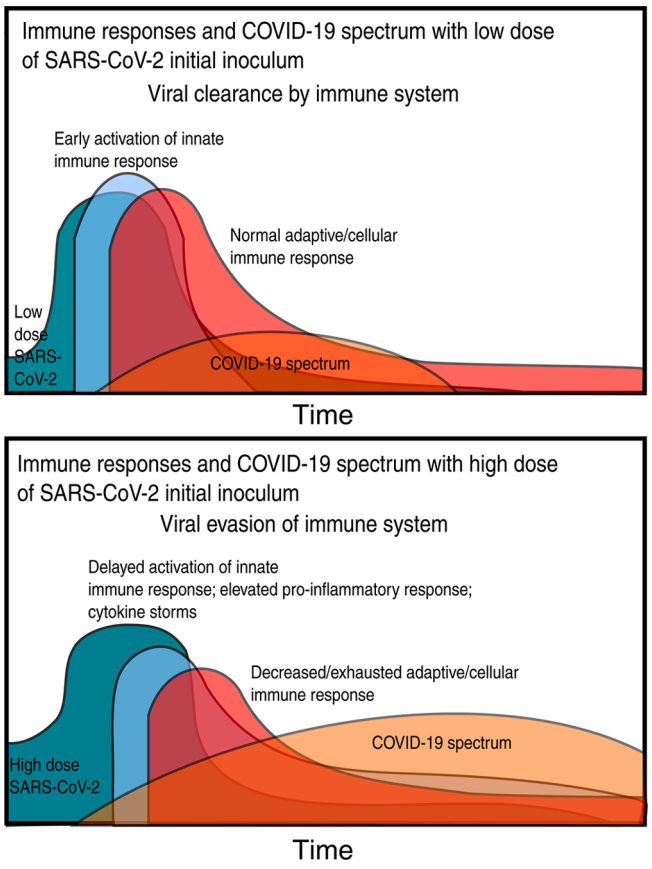

Fig. 1. The role of the dose of the initial viral inoculum on the immune system leading to mild/severe disease (based on immune responses observed in mild versus severe COVID-19) [Adapted from Ref. [42]]. Top panel: Low dose of the SARS-CoV-2 initial inoculum elicits an early innate immune response (INF pathway; elevated cytokines/chemokines; limited pro-inflammatory response) and normal adaptive/cellular response leading to early clearance of the virus with a limited spectrum of COVID-19 and mild disease. Bottom panel: High dose of the SARS-CoV-2 initial inoculum delays or blocks innate immune response (limited INF pathway; highly elevated cytokines/chemokines; elevated pro-inflammatory response leading to "cytokine storms") and decreased or exhausted adaptive/cellular response leading to viral evasion of the immune system with increased spectrum of COVID-19 and severe disease.

of exposure to SARS-CoV-2 and strengthen the importance of the dose of the initial viral inoculum in downstream immune responses.

The inoculum theory provides a logical explanation for several "incompletely explained observations" in COVID-19 epidemics

Super-spreading events have been documented all over the world, typically in crowds or confined spaces. Transmission is especially plausible while infected persons are singing or talking loudly, particularly in poorly ventilated spaces [43,44]. An online database (https://bit.ly/3ar39ky) created by the London School of Hygiene & Tropical Medicine (LSHTM) lists several such events [45]. It is estimated that 1–20% of infected individuals (super-spreaders) result in 80% of secondary cases [46–49].

There is anecdotal evidence that health workers with low-risk profile developed severe COVID-19 when infected during high exposure contacts such as intubation of a COVID-19 patient leading to intensive coughing [5,50–52].

COVID-19 has spread especially fast and explosively in colder climates such as North Italy, France, Belgium, and New York and less explosively or later in hot and humid climates. Colder climates with mostly indoor events in closed environments create a more conducive context for exposure to a high dose of virus, than hotter climate where people live mostly outdoors, and where aerosols diffuse more rapidly [53]. However, air-conditioning systems, especially those that recirculate air, may create indoor environments with high potential for dense contamination and transmission. Evidence on the high likelihood of airborne transmission of SARS-CoV-2 is accumulating [54,55].

Although asymptomatic transmission of SARS-CoV-2 has been well documented, an asymptomatic person might well have a lower potential for spreading the virus in the absence of coughing and sneezing.

Table 4 lists some of the incompletely explained observations and their possible explanation through the hypothesis.

However, there remain other puzzling observations, such as the limited role of children in the transmission of SARS-CoV-2 [57–61], the paradoxical relationship between the length of the incubation period and severity of COVID-19 [62,63], and the role of air pollution in SARS-CoV-2 transmission [64]. We contend that these observations are compatible with the inoculum hypothesis, but potentially confounded by immunological particularities which are not yet fully understood.

Proposed research avenues

Several studies could be undertaken to further validate our postulate. In our opinion, this hypothesis can be more convincingly explained through epidemiological studies rather than clinical or immunological

Table 4
Some incompletely explained observations in the SARS-CoV-2 transmission and COVID-19 disease that may be explained by the hypothesis.

Incompletely explained observations	Possible explanation through the hypothesis
Super-spreading events: Intensive transmission in crowded environments, especially indoor events in poorly ventilated environments [45].	These conditions are favourable for transmission of higher doses of initial infectious inocula, due to intensive exposure over a longer time.
Clusters of severe cases and clusters of mild cases [27].	Primary cases with severe disease result in transmitting higher doses of infectious inocula, while those with mild disease transmit lower doses.
Health care workers with a low-risk profile got severe COVID-19, infected from very sick patients, e.g. during intubation [52].	Proximity to patients with severe disease enables being infected with higher doses of infectious inoculum.
Severe epidemics mostly in dense urban centres.	Primary cases in dense urban centres result in transmission of higher doses of infectious inocula, due to greater proximity and longer duration of exposure, leading to more severe disease in secondary cases.
Less explosive epidemics in countries outside 30°–60° Northern latitude. In sub-Saharan Africa and South and Southeast Asia, the virus spread with a less steep exponential pattern than in Western Europe or the United States.	Colder climates may be more conducive for transmission of higher doses of the virus, as people live mostly indoors. In warmer and humid climates, where people are mostly outdoors, the aerosols may diffuse more rapidly and lead to lower doses of the virus being transmitted.
Many people remain asymptomatic or pauci-symptomatic [56], their proportion seems to increase over time.	Individuals infected with lower doses of infectious inocula possibly remain asymptomatic or develop milder disease due to their immune systems being able to mount a more robust response against a smaller dose of the virus. It is plausible that the current containment measures, such as mass masking and physical distancing result in lower doses being transmitted, which leads to increasing proportions of asymptomatic or mild disease in those who do get infected.

studies which tend to be more biased by simultaneous treatment and clinical management options for COVID-19, and may eclipse the role of the dose of the infectious inoculum related to the severity of disease and mortality.

Field epidemiology studies that assess the severity of COVID-19 in clusters can help identify patterns or chains of disease severity. A combination of contact tracing and in-depth interviews could be used for tracing where and when transmission probably occurred, to determine primary contacts and the duration of exposure with these contacts. Data from these studies can help determine whether this interaction follows chains of mild or severe disease depending on the severity of the disease in the primary contact. Specific circumstances such as whether the exposure was in a poorly-ventilated indoor space versus in an outdoor area, details on the proximity to the primary case, and duration of the exposure to the infectious dose, such as through a brief encounter versus a prolonged meeting, may also correlate with likely infectious dose being transmitted. Analysing these circumstances in conjunction with the severity of the disease of the primary case will facilitate a better understanding of the role of the dose of initial infectious inoculum. Such investigations would be most interesting after super-spreading events involving large numbers of individuals, with subsequent seeding of SARS-CoV-2 in communities.

Such studies could include re-analysis of super-spreading events, from an epidemiological gaze keeping the hypothesis in mind. An analysis of one such super-spreading event in Germany has yielded insights, entirely consistent with our hypothesis [65].

The infectious dose is related to the amount of virus expelled through respiratory droplets/aerosols while an infected individual is coughing/sneezing, but also possibly when talking, laughing, singing etc. An important element for such research is that viral loads in respiratory droplets and aerosols need to be studied, as this is more likely to correlate with the potential dose of the virus in the initial infectious inoculum. This is very difficult, and therefore most current literature focuses on the amount of the virus in nasopharyngeal swabs as an indicator in viral transmission dynamics; however, we think it is a poor substitute. Virological studies, that measure viral load in expelled respiratory droplets/aerosols as a determinant for transmission should be undertaken. Viral culture of the respiratory droplets/aerosols could be done to determine infectious dose which can then be correlated (although crudely) with observed viral loads and for determination of the minimum infectious dose. Further, whether or not secondary infection actually occurs also depends on the duration of exposure to the infectious dose, which is difficult to quantify in virological studies without the use of human volunteer challenge studies. However, since human volunteer challenge studies may pose unnecessary risks to the volunteers until effective antivirals or vaccines become available, similar studies using animal models adapted for SARS-CoV-2 can be designed to explain or refute our hypothesis.

Studies in animal models for Influenza, MERS, SARS, and Ebola have provided insights into the transmission dynamics of these infections, including dose-response relationships with initial viral inoculum and the immune responses [66,67]. Dose-response models developed for other viruses based on suitable animal model studies are important in predicting realistic outcomes in the transmission and infectivity in humans [68–71]. Developing dose-response models for SARS-CoV-2 can help to assess the outcomes of mitigation and containment measures related to the transmission dynamics and risk of infection [72].

Recent studies using Syrian hamster models of COVID-19 infection have already shown that higher doses of administered SARS-CoV-2 virus led to more severe disease even though viral loads during the ensuing infection did not differ significantly between hamsters infected with high doses versus low doses [73].

Implications for containment measures

It is increasingly becoming clear that totally stopping the transmission of SARS-CoV-2 is extremely difficult in most societies. Strategies to “flatten the curve” have come at a tremendous societal cost, and cannot be maintained over extended periods, despite the virus continuing to circulate, the likelihood of subsequent waves, and covering entire populations with an effective vaccine might take a long time. Therefore, physical distancing, improved hygiene and masking are recommended, and have often been applied as “lockdowns” (of various intensities) [1].

All these measures may not practically be applicable, acceptable and sustainable in all situations. In many countries, a bundle of more selective and targeted containment strategies, with a more acceptable socio-economic cost, are increasingly being defined and implemented. If our hypothesis were proven right, it would strengthen the scientific basis for deciding an appropriate mix of priority containment measures for COVID-19, depending on the phase of the epidemic, the risk profile of the people involved, and the particular context. The dose-response relationship in our hypothesis might contribute to making choices for more feasible containment strategies, considering not only the probability of transmission in relation to the risk profile of the persons (such as the elderly and those with co-morbidities) but also include the potential for high-density infection (the dose of virus in the inoculum), in a given environment and context.

The potential for high-probability high-dose (or high-intensity) transmission is undoubtedly greatest during close contact with an infected person with respiratory symptoms, frequently spreading infected droplets and aerosols, such as during coughing and sneezing. Close encounters with symptomatic COVID-19 patients typically occur in health care settings, in nursing homes, or during home-care for a sick person. Particularly high-risk are medical procedures touching respiratory mucosae, such as during aspiration of respiratory secretions, sampling for PCR tests, and especially during intubation, potentially triggering coughing or sneezing. There is no doubt that strict barrier and hygiene measures in such situations remains a top priority, especially for older health care workers and care givers.

The potential for transmission with a high-dose inoculum is probably also high during prolonged exposure to air containing aerosols and droplets with high viral loads, such as in poorly ventilated crowded spaces, where an infected person is speaking loudly or singing, even if the infected person is asymptomatic. Colder temperatures in such an environment could prolong the viability of the virus in aerosols. One infected person in such crowded places can easily cause intensive transmission in several people. It is thus likely that not only more transmission can occur in these settings, but also that such high-dose transmission will potentially result in more severe disease. This is especially relevant when high-risk persons attend such crowded events (e.g. funerals, religious services, choirs, etc.).

Evidence on the inoculum hypothesis could thus further strengthen the evidence base for the generally recognised priority interventions in health care settings and elderly homes. It would also strengthen the rationale for focusing on gatherings in spaces with environments conducive to super-spreading events, in which the role of ventilation and air-conditioning may have been neglected till now. Too often, avoidance of potential super-spreading events is lumped together in a measure, such as, “gatherings of more than 20 or 50 or 100 people are forbidden,” while the risks are totally different for an open-air gathering (such as walking, playing, or running in public spaces) attended by young people with enough space for physical distancing, as compared to a social gathering with elderly people in a crowded indoor space.

Our hypothesis would also strengthen the rationale for mass masking, including well-designed and well-fitting multi-layered home-made masks in public spaces, especially when interacting in poorly ventilated places with other people at a close distance [74–76]. Mass masking remains controversial in many countries; not only for cultural reasons but also since some experts continue to question their effectiveness. However, it likely decreases both the frequency of transmission and the infectious inoculum if a transmission still occurs. It has indeed been

shown that viral loads in respiratory droplets being emitted while talking or breathing out are significantly less when masks are used [77]. It has also been postulated that mass masking not only limits the transmission of the infection, but also protects the wearer from severe disease, by reducing the inoculum that may potentially lead to infection [78]. While masks that are currently being prescribed for the general public (such as home-made cloth masks or commercially available surgical masks) do not completely prevent infection as compared to more specialized FFP2/N95 masks, wearing any type of mask could potentially reduce intensity of exposure and lead to a milder disease [76]. It is thus very plausible that mass masking leads to chains of individuals with asymptomatic or mild disease. Although such chains of asymptomatic or mild disease may seem beneficial in generating community-level immunity [79], whether that is actually possible remains to be elucidated, especially with recent reports of several individuals getting re-infected [80]. Nonetheless, such chains of asymptomatic or mild disease will undoubtadely reduce the burden on the health care system.

Conclusion

In our opinion, the role of the dose of the initial inoculum in the transmission dynamics of SARS-CoV-2 has been neglected. Based on evidence from other infectious diseases and observations from the current SARS-CoV-2 transmission dynamics, immune responses against SARS-CoV-2, and the COVID-19 disease spectrum, we think that the dose-response relationship in the initial viral inoculum plays an important role in the severity of the COVID-19 epidemic. While immunological responses in mild versus severe COVID-19 disease provide valuable information in understanding the role of the dose of the initial inoculum, certain intrinsic immunity components such as the role of mucosae in preventing infection are still a grey area. In addition, it is very evident that a different efficacy of both innate and immune responses, according to age and co-morbid conditions is a confounding factor. This is especially apparent in the younger and older part of the population: the former may better resist a higher dose, while the latter may be more susceptible to a lower dose. All this considerably complicates establishing insights in a dose-response relationship, and has to be carefully separated out in any research.

We propose that additional research will potentially generate insights relevant for prioritising strategies to decrease the impact of the epidemic.

More attention should be given when assessing risk to whether activities are outdoors or indoors, and to the ventilation of the space. This is often neglected by medical experts, who most often have a focus on transmission between individuals, and may give less consideration to the importance of the context and the space in which transmission occurs, than engineers and architects, who also include air circulation and ventilation in their analyses.

This calls for greater involvement of experts on built environments in transmission research. They also should get a stronger voice, along with social scientists, in advising policies and analysing the risks in events and other situations.

Insights on the importance of transmission dynamics, such as while caring for a sick person, or in environments conducive to super-spreading events should also be communicated to the general public, so that “dangerous settings” are more widely identified and avoided or palliated. It may be more important to understand the space, the air circulation and the mix of individuals attending a gathering than the number of people in attendance. There should be greater public awareness that, for instance, a gathering in a poorly-ventilated, noisy, closed, and crowded environment with elderly people speaking loudly is conducive for high-intensity transmission, and that one infected person coughing, singing, or shouting could create a perfect storm, infecting several high-risk individuals with a high inoculum, potentially triggering a cascade of further infections and triggering a local hotspot, with severe COVID-19 cases.

In conclusion, our hypothesis could contribute to more selective, feasible, and sustainable containment strategies to reduce the severity of the COVID-19 epidemic, with a lower or more acceptable societal and economic cost. It specifically would further strengthen the rationale for the importance of avoiding super-spreading events in crowded indoor environments, and for the benefits of mass masking.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Dr. Koen Vercauteren and Dr. Brecht Ingelbeen for useful comments on a previous draft, the teams of the Riposte corona, INRB, Kinshasa and the Belgian Embassy in Kinshasa for welcoming and hosting WVD during his unscheduled extended stay in Kinshasa during the lockdown, March–July 2020.

Authors’ contribution

WVD, RD, RvdP, and GV conceived and designed the study. RD, GV, YA, and WVD searched the literature and screened for new emerging evidence. WVD, RD, and YA drafted successive versions of the manuscript and coordinated inputs from all co-authors. RvdP and GV contributed to writing the manuscript and reviewed successive versions of the manuscript. All authors commented on subsequent versions of the manuscript and approved the final version. WVD attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding statement

No specific funding was provided for this study.

Competing interests

None declared.

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