Perspective

Low-dose and oral exposure to SARS-CoV-2 may help us understand and prevent severe COVID-19

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A B S T R A C T

Background: The effectiveness and sustainability of current public health interventions designed to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission remain of great concern in many settings, especially in the absence of a transmission-preventing vaccine.
Hypothesis: It was hypothesized that a more targeted set of interventions focusing on preventing severe coronavirus disease 2019 (COVID-19), rather than SARS-CoV-2 transmission, would be less disruptive to society. To identify these, it would be helpful to better understand how the infecting dose of SARS-CoV-2 and its route of infection influence the clinical outcome, immunological protection, and likelihood of onward transmission.
Proposal: It is suggested that carefully controlled human infection model (CHIM) studies involving intranasal and oral administration of progressively increasing doses of SARS-CoV-2, starting with low levels, to healthy young adult volunteers may be the most expeditious and definitive way to answer these questions. Such studies would differ in objective from CHIM proposals designed to expedite vaccine development, although the latter might be adapted to address some of the questions raised here.
Implications: Results from the studies proposed here could help elucidate the relationship of infection to COVID-19 and thereby provide a scientific basis for more targeted and sustainable application of public health control measures, and inform the design of improved immunotherapeutics and more targeted vaccine development.

Where efficiently applied, a broad range of restrictive non-pharmaceutical interventions (NPI) has succeeded in preempting or mitigating explosive outbreaks of coronavirus disease 2019 (COVID-19) hospitalizations and deaths in many settings. Elsewhere, it has proven difficult to fully implement, maintain, or reimpose these interventions. Much of the public reluctance lies in their huge social and economic consequences, exacerbated by the failure of political leaders to convincingly advocate for these measures. We suggest that three other factors contribute:

1. The vast majority of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections does not result in severe morbidity, much less mortality. Although some individual- and population-level risk factors have been identified, it is not possible to predict individual outcomes.

2. Definitive evidence regarding the effectiveness of individual control measures is lacking.

3. There is a perception in some settings that the only way to gauge the effectiveness of NPI (such as face-masks) lies in their ability (or not) to prevent the transmission of SARS-CoV-2, rather than in their ability to prevent severe disease.

To help address these, a carefully designed research program involving human challenge studies might help us refocus our medium-term public health goals and control measures, and guide the design of novel immunotherapeutics and vaccines.

We learned early in the pandemic that SARS-CoV-2 transmissibility was much greater and with a longer infectious incubation period than for most other respiratory viral infections, and that all age groups could suffer severe disease. Given COVID-19's ability to overwhelm hospital capacity and healthcare systems and the success of broadly targeted lockdown efforts in Wuhan, it was logical to initially focus on the elimination of SARS-CoV-2 transmission. While other countries in East Asia controlled transmission with narrowly targeted approaches, each built on

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historical experience with severe acute respiratory syndrome (SARS) and used extensive digital contact-tracing abilities that may not be acceptable in many settings (Huang et al., 2020).

We also learned that SARS-CoV-2 infection fatality rates were approximately 0.3–0.7% (Rajgor et al., 2020). While lower than SARS (10%) and Middle East respiratory syndrome (MERS) (35%), these are higher than influenza (~0.05%; Centers for Disease Control and Prevention, 2020a). Of course, average figures mask the wide range of COVID-19 case-fatality rates in different age and risk groups. In a recent Danish population-based survey of SARS-CoV-2 PCR-positive individuals presenting with mild to moderate respiratory symptoms, those with ≥3 co-morbidities and/or older than 80 years of age had a case-fatality rate of ≥17% (Reilev et al., 2020). Such high rates, coupled with the sheer explosiveness of COVID-19 hospitalized cases over a short period of time, merited extraordinary control measures. The same study reported no deaths among the large portion of the population <50 years old with ≤1 co-morbidity. This is consistent with a Centers for Disease Control and Prevention (CDC) report (Garg et al., 2020) indicating that 85–90% of patients hospitalized with COVID-19 possess one or more identifiable comorbidity, and also with population-based seroprevalence studies reporting that 88–98% of SARS-CoV-2 infections require no medical attention (To et al., 2020; Stringhini et al., 2020).

These observations highlight the desirability of focusing on the prevention of severe COVID-19. The main reason is pragmatic: if host or environmental risk factors significantly differ for SARS-CoV-2 infection versus severe disease, NPI might be tailored more specifically, efficiently, sustainably, and less painfully for society as a whole.

Recalibration of the goal could also help put in context hypothetical or ambiguous statements from scientific studies. These are not infrequently translated into alarming newspaper headlines such as "SARS-CoV-2 could be spread in sea air" (Robbins, 2020) or by "the distant windborne spread of the virus wafting from untreated sewage" (Fang et al., 2020), "virus is detectable on surfaces for hours" (Van Doremalen et al., 2020), and "no evidence people can't be re-infected" (World Health Organization, 2020). These are reminiscent of the 19th century theory attributing communicable diseases to insidious, virtually inescapable miasma. The reframed, potentially more reassuring question would become, "What is the evidence that any of these are likely to lead to severe disease?"

The goal of better targeting interventions is aspirational, and would be facilitated by answering some basic research questions as outlined below.

Can we identify biologically low-risk populations?

Within the CDC study, 10–15% of putatively 'low-risk' individuals contracted severe disease (Garg et al., 2020), raising questions as to whether any group is intrinsically at low risk. Most striking were deaths of young Chinese medical personnel in the Wuhan outbreak, yet at least some were apparently associated with deep inhalation of high doses of SARS-CoV-2 while performing intubations (Penn Medicine News, 2020). High attack rates of severe COVID-19 in prisons and retirement homes may also be attributable to higher viral dose exposures. Research on behavioral or environmental risk factors of severe disease cases in otherwise low-risk populations could strengthen the case that the vast majority of individuals within some populations is indeed biologically low risk.

Is the infectious dose an important determinant of COVID-19 severity?

Separate studies with mouse-adapted MERS coronavirus (Li et al., 2017) and SARS coronavirus (Roberts et al., 2007) assessed disease severity across dose ranges spanning 10^3 and 10^6 the 50% tissue culture infectious dose ($TCID_{50}$), respectively. While the highest dose levels proved uniformly lethal, the lowest 1 and 2–3 dose levels, respectively, were still infectious but did not result in mortality or significant weight loss.

Similarly, recent studies with SARS-CoV-2 in the Syrian hamster model suggested that low infectious doses, despite eventually leading to replication to high titers in the respiratory tract, nonetheless resulted in reduced disease severity compared to higher doses (Imai et al., 2020; Lee et al., 2020). Intriguingly, the use of facial masking material between hamster cages resulted not only in less frequent transmission, but those that were infected had much more mild disease (Chan et al., 2020).

In a controlled human infection model (CHIM) testing doses of H1N1 influenza virus (Memoli et al., 2015) over a 10^5-fold range of $TCID_{50}$ titers, clinical symptoms in those that were infected were much more prevalent at the highest two doses. The severity of illness and median days of symptoms were positively associated with dose titer. Abnormal pulmonary computed tomography scans were apparent only at the highest two doses. Another CHIM examining doses of H3N2 influenza virus over a 10^4-fold range of $TCID_{50}$ titers noted that only the highest two doses elicited mild to moderate influenza (Han et al., 2019). In addition, intriguing observations correlating extensive mask wearing with lower COVID-19 case-fatality rates in different populations support the hypothesis that besides reducing the risk of transmission of SARS-CoV-2, mask wearing may also decrease the severity of COVID-19 in those who are infected by reducing the infectious dose (Gandhi and Rutherford, 2020).

Is the route of infection an important determinant of COVID-19 severity?

Adenoviruses 4 and 7 cause pneumonia when infection occurs via the airways, but not when acquired through the gastrointestinal tract, despite replicating efficiently. This behavior is the basis for licensed wild-type-based adenovirus vaccines, of proven high level of safety and efficacy when administered orally (Couch et al., 1963). Diarrhea and SARS-CoV-2 shedding are frequently reported to precede other COVID-19 symptoms, and although the virus can be detected in stools by PCR in half of patients, the incidence of gastrointestinal symptoms is limited (Mao et al., 2020). Might these findings and the common detection of SARS-CoV-2 in stool in the absence of symptoms reflect oral ingestion? Could oral ingestion, and/or low exposure doses, account at least partly for the wide prevalence of asymptomatic infections?

In the Syrian hamster model, oral inoculation with what would be a high intranasal dose of SARS-CoV-2 could establish a subclinical respiratory infection in only a subset of animals. These animals showed no weight loss and exhibited decreased lung histopathology scores and viral loads compared to animals that had been intranasally infected with a dose 10^3-fold lower (Lee et al., 2020).

Do low doses or the route of administration affect the viral titer achieved, as well as the amount, route, and duration of viral shedding?

Understanding the relationship between the infectious dose, resultant viral titer, and clinical outcome could allow quantitative differences in PCR diagnostic results to be meaningfully interpreted (Mandavilli, 2020). The shedding parameters are presumably major determinants of the probability of further transmission, and perhaps of its clinical consequences.

Do low doses or the route of administration elicit qualitatively different immune responses than those seen with higher doses?

Mild and severe COVID-19 may be accompanied by marked differences in various aspects of the innate and adaptive immune responses, and it has been postulated that the dose of the initial viral inoculum can partly explain these differences (Van Damme et al., 2020). However, we are not aware of any direct evidence that this is the case.

Do low doses or an alternate route of administration protect against COVID-19?

One study conducted 30 years ago examined whether mild and asymptomatic infections with common cold coronaviruses affect-ed the clinical severity of a subsequent infection with the same virus. This study utilized a CHIM model with coronavirus 229E and concluded that reinfection with the same virus resulted in milder disease (Callow et al., 1990).

SARS-CoV-2 infection can protect non-human primates against disease, though not reinfection, upon rechallenge. However, rhesus monkeys only exhibit mild disease even upon exposure to extremely high titer challenges (Chandrashekar et al., 2020), and thus represent an imperfect model to study disease attenuation. At present, the nature and extent of protection provided by previous infection in humans is unknown. It is unlikely that a longitudinal observational study, given uncertainties about the dose and nature of the original and subsequent infectious exposures, could determine whether exposure to single or multiple low doses, or by oral ingestion, protects against symptomatic disease. It is promising, however, that an observational study (Sagar et al., 2020) suggested an association between recent cold coronavirus infection and less severe COVID-19.

We propose CHIM studies that would involve young adult volunteers selected for the absence of identifiable co-morbidities and pre-screened for genetic markers associated with severe disease, such as those involving the type 1 interferon pathway (Zhang et al., 2020). These volunteers would be exposed to low doses of SARS-CoV-2 through nasal instillation or oral ingestion in a closely monitored environment. The surveillance duration would

necessarily take into consideration that COVID-19 can result in a prolonged illness, even among persons with milder outpatient illness (Tenforde et al., 2020). In the initial phase, only subjects previously naturally infected would be challenged. The clinical endpoint of such studies would be the induction of asymptomatic or mild disease.

Various investigators have recently proposed CHIM studies in order to expedite clinical testing of COVID-19 vaccines (Eyal et al., 2020; Plotkin and Caplan, 2020). The ethical validity of such studies depends in large part on whether the anticipated public health benefit (and/or individual benefit to study participants) outweighs the risk of contracting severe COVID-19, as such studies must induce sufficiently severe disease to be relevant for the evaluation of vaccine efficacy. Detailed discussion and quantitation of those risks, and how they compare to risks in other CHIM studies or other societal risks, have been detailed extensively by a World Health Organization Advisory Group (Levine et al., 2020) and others (Deming et al., 2020; Eyal et al., 2020; Plotkin and Caplan, 2020) with no need to recapitulate them here.

In contrast, the potential public health benefits from the studies proposed here differ, as they would not be predicated on shortening vaccine development timelines. Instead, the proposed studies could provide a stronger evidence base to allow de-emphasis of NPI not likely to decrease severe disease, and conversely allow more streamlined public health messaging around those that are. If low doses or an alternate route of administration protect against severe disease, even without providing sterilizing immunity, the identification of immune correlates could guide the development of vaccines or immuno-therapeutics specifically aimed at preventing severe disease.

Importantly, direct benefit to patient volunteers may accrue if low-dose and/or oral administration provides immunity against more severe disease. We note that some of the analyses described here might be efficiently incorporated into the development stages of a CHIM whose primary goal is to expedite vaccine development, as sequential dose-ranging studies will be necessary to establish a consistently infectious dose (Levine et al., 2020).

A major limitation is the generalizability of conclusions observed in lower-risk younger subjects to higher-risk popula-tions. Ideally, CHIM participants would progressively include somewhat 'riskier' cohorts as confidence grows in the safety of the

Table 1
How study observations could affect public health control measures and messaging

	Potential observation	Possible practical implications
1	Low-dose infection results in asymptomatic or mild disease and low-titer, short-term viral shedding	• Strengthened and streamlined messaging on the value of masks as a way to minimize the infectious dose received.
2	Previous natural infection provides some protection against symptomatic disease	• Possibility of relaxing certain public health measures in lower-risk groups, while efforts to protect high-risk populations from any infection remain in place. For example: ○ Mask-less outdoor recreation activities for the 'low-risk' population and the previously infected explicitly allowed as long as social distancing is maintained. Social/work interactions allowed if likely to result in only low-dose exposure (due to distancing and/or masks) for lower-risk populations.
3	Oral ingestion of SARS-CoV-2 in CHIM leads to little or no symptomatic disease or shedding	• De-emphasized messaging focused on the risk of contamination from food packaging (ANSES, 2020) and costly efforts to repeatedly disinfect surfaces after every public contact (Centers for Disease Control and Prevention, 2020b).
4	An immune parameter induced by previous coronavirus infection, such as SARS-CoV-2 reactive T-cells (Braun et al., 2020), is closely associated with the prevention of symptomatic disease upon challenge in CHIM	• Targeted vaccine or immunotherapeutic development to elicit, mimic, or enhance this parameter. • Incorporation of this parameter into screening programs to estimate population immunity.
5	Low-dose infection and/or ingestion of SARS-CoV-2 in CHIM provide some protection against disease	• More focused public health messaging around avoiding situations with higher dose exposure. • Prioritization of SARS-CoV-2 vaccine candidates that prevent disease but not reinfection, like rotavirus, especially if they allow natural infections to boost short-lived immunity. • Development pursued of enterically administered live vaccines.

CHIM, controlled human infection model; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

low dose and/or oral administration regime, and as adequate therapies are identified. In addition, the numbers of subjects needed to provide definitive conclusions may require innovative study designs to be feasible. It may be questioned whether CHIM studies, which induce mild disease, are sufficiently predictive of what would happen with severe cases, a general criticism of all challenge models.

We suggest that the acceptance of a refined public health goal focused on clinically severe disease, informed by results from carefully designed observational and CHIM studies addressing the roles of dose and route of administration, could allow the elaboration of more targeted and sustainable, or at least more scientific justifiable, disease control measures (Table 1).

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The authors declare no competing interests.

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