COVID-19

Weekly Science Review

September 26-October 2

This weekly science review is a snapshot of the new and emerging scientific evidence related to COVID-19 during the period specified. It is a review of important topics and articles, not a guide for policy or program implementation. **The findings captured are subject to change as new information is made available**. We welcome comments and feedback at **covid19-eiu@vitalstrategies.org**.

IN-DEPTH

Dose (inoculum) of SARS-CoV-2 and COVID-19 severity

Main message: Some researchers have suggested that face masks may protect wearers from severe COVID-19 in addition to protecting others. This raises the question of whether the dose of virus may influence how sick someone may become if they get COVID-19. An examination of existing evidence shows

that it is biologically probable that there is a relationship between the size of the viral inoculum—the number of SARS-COV-2 virus particles present at exposure—and COVID-19 severity. In addition, it is mechanistically probable that masks can reduce the amount of virus to which wearers are exposed. This adds weight to existing evidence supporting the role of universal masking in reducing the spread of COVID-19. However, the hypothesis that masks will reduce severity of illness among those who are infected, although biologically plausible, remains unproven.

We **previously wrote** about whether the inoculum of SARS-CoV-2, the virus that causes COVID-19, may influence COVID-19 severity. This raises the question of whether a mask may protect the wearer from severe COVID-19 by reducing viral inoculum. Underlying this question are two core concepts: 1) whether inoculum influences the chance of infection or, if infection occurs, the chance of severe disease, and 2) whether a mask may reduce the inoculum to which the wearer may be exposed.

There is no direct evidence from human challenge studies—in which human volunteers would be deliberately exposed to known quantities of SARS-CoV-2—on the relationship between inoculum of SARS-CoV-2 and the chance of infection and/or COVID-19 severity. There are ethical challenges to performing such studies, especially because the resulting disease may be severe and there is no known cure. It has been reported that **a human challenge trial to assess COVID-19 vaccine efficacy may be performed in the future**, but we are not aware of any completed or planned human challenge study designed to assess the effect of inoculum on SARS-CoV-2 transmission or illness severity nor the level of protection a mask might provide. In the absence of such direct data, other lines of evidence may shed light on this topic:

1. **Infectious and lethal doses have been established for other infectious agents.**
   A century of research on infectious diseases has established that inoculum influences the chance of infection. The idea that the inoculum of SARS-CoV-2 may influence disease severity is also consistent with evidence on the natural

history of a number of viral infections. There are terms for these concepts: the infectious dose is the inoculum required to establish an infection in a susceptible host; the lethal dose is the inoculum that will cause a fatal infection. The ID50 and the LD50, or the doses at which 50% of exposed hosts become infected and die, respectively, have been established for many infectious diseases using animal models. One example of the application of such research is the **classification of some pathogens as potential bioterrorism threats** if the LD50 is particularly low. Animal models of SARS-CoV-2 have shown that the inoculum of SARS-COV-2 can influence the chance of infection and survival. A **preprint study on mice genetically engineered to be susceptible to SARS-CoV-2** showed that survival rates were lower among mice exposed to large inocula of SARS-CoV-2 compared with mice exposed to small inocula. A **hamster model of SARS-CoV-2 transmission** showed that susceptible hamsters separated from infected hamsters by a barrier of surgical mask material were less likely to be infected than hamsters without a barrier. Among hamsters that became infected with SARS-CoV-2, those infected through the barrier developed less severe infections than those without. Human challenge studies on **influenza** and on an **endemic coronavirus** that causes the common cold have shown that smaller inocula are less likely to cause symptoms than larger inocula.

2. **For some infectious agents, including SARS-CoV-2, a relationship between viral load and disease severity has been described.**
   We **previously presented evidence** on the relationship between viral load, or the amount of virus carried by an individual, and disease severity. There is evidence that high viral load is associated with severe disease and/or mortality for many respiratory viruses, including **influenza, respiratory syncytial virus** and both **SARS-CoV** and **MERS-CoV** (the viruses that cause SARS and MERS, respectively). There is new evidence on the relationship between SARS-CoV-2 viral load and COVID-19 severity: among patients hospitalized with COVID-19, those with higher viral loads have **more severe symptoms** and are **more likely to die**. However, this is not proof of a relationship between inoculum and

disease severity. The relationship between inoculum and viral load is not well understood and, in these studies, viral load was not measured at the moment of infection. Host factors such as a person's immunologic function play an important role in how well an individual's body fights the virus, so these factors are likely to mediate the relationship between inoculum and viral load. In addition, high viral load may be a result of severe disease

3. **Epidemiologic studies suggest that viral inoculum may influence the severity of human disease.**
Although human challenge studies have not been conducted for many infectious diseases, some studies have used proxies of inoculum size to assess the relationship between inoculum and disease severity. For example, closer or more frequent contact with an infected person may expose a susceptible host to a larger inoculum; some studies have assessed the relationship between type of contact and disease severity. In Guinea-Bissau, the **rate of death among children with measles** was higher among children who were likely infected by other children within their households than among children who were the first cases within their households. In a study on a potential treatment for chickenpox, **children infected by household contacts had more severe symptoms** than children who were the first cases in their households. During an **outbreak of SARS within a housing estate in Hong Kong** in 2003, the rate of death was higher among SARS patients who lived geographically closer to the index case than among SARS patients who lived farther away. It is possible that reductions in inoculum through hygiene practices such as hand-washing can mediate disease severity. In a **randomized controlled trial that studied the effects of hand-washing education on the incidence of respiratory infections** among 20,000 participants in the U.K., those who received hand-washing education were less likely to develop symptoms of respiratory illness and, when they did develop symptoms, those symptoms were milder and shorter-lasting compared with the symptoms of those who did not receive hand-washing education. The implications of the findings of all of these studies are not just that inoculum can influence disease severity (as has been established by laboratory

research on animals and controlled studies involving human volunteers) but that the influence may be strong enough to make a measurable difference in the severity of clinical disease among people living in the community.

4. **There are data on COVID-19 severity from different settings and time periods in which mask use was more or less common.**
   Data from the COVID-19 pandemic have been used to support the theory that masks may protect wearers from severe COVID-19. Rates of mask use around the world have increased as the proportion of SARS-CoV-2 infections estimated to be asymptomatic has increased and recommendations have been implemented. There are examples of COVID-19 outbreaks in crowded settings in which people wore masks (including in a meat processing plant and on a cruise ship) and rates of asymptomatic infections were high. One study showed a correlation between higher levels of population masking and lower rates of death due to COVID-19. However, caution must be exercised when comparing data from different populations collected at different times because a) variations in diagnostic capacity can influence estimations of disease severity and b) there are many location-specific factors that may influence disease severity. These include viral factors such as strain lethality, host factors such as comorbidities and demographics, and environmental factors such as treatment availability and access to medical care.

The second underlying question, in addition to whether inoculum influences disease severity, is whether a mask may reduce the inoculum to which the wearer may be exposed. Although there is strong evidence that widespread use of nonmedical masks in the community prevents the spread of COVID-19, mask recommendations emphasize the importance of source control, that is, reducing the respiratory droplets exhaled into the air by potentially infectious people. In comparison with evidence from health care settings that medical masks and respirators protect wearers, there is less evidence that non-medical masks worn in the community protect wearers from infection. However, recent analyses of existing data on other respiratory infections and studies on

the **filtering capacity of nonmedical masks** have demonstrated biologic and mechanistic plausibility that nonmedical masks may reduce the amount of virus to which wearers are exposed.

To summarize the state of existing evidence, widespread mask use prevents SARS-CoV-2 transmission. Masks reduce the amount of virus exhaled into the environment by wearers. If a susceptible person comes into contact with SARS-CoV-2, it is possible that their own mask will further reduce the size of the inoculum they receive. And it is likely that a smaller inoculum of SARS-CoV-2 will reduce the chance of infection or, if infection does occur, reduce the chance of severe COVID-19. Thus, although the degree to which inoculum size versus other factors may influence the risk of severe COVID-19 is not known, it is clear that mask wearing by all is an effective way to protect everyone from COVID-19.

FAQ

How is vaccine safety monitored in the U.S.?

Safety of any therapy or preventive measure such as a vaccine is fundamental to how risks and benefits are balanced. There are several levels of monitoring and surveillance built into the U.S. medical and public health system to ensure safety for all vaccines used in the U.S., including any vaccine authorized for emergency use or approved for licensure for COVID-19.

Data on safety and **adverse events (possible side effects)**, ranging from pain and redness at the injection site to fever or more serious systemic post-vaccination events, are one of the main considerations reviewed by the U.S. Food and Drug Administration (FDA) and its independent advisory committees prior to approving or authorizing use of a vaccine. These same safety data from clinical trials are what guide the Advisory Committee on Immunization Practices (ACIP) and the U.S. Centers for Disease Control and Prevention (CDC) on how to use

the vaccine in different groups of people. ACIP also routinely considers post-market safety data once a vaccine is in use, and may modify recommendations for dosing and schedule.

For COVID-19, given the paramount task of ensuring that any vaccine that is authorized or approved is safe and effective, a separate Vaccine Safety Technical Subgroup was formed in May 2020 to support safety review both while vaccines are in development and when they may be authorized or approved for use. This includes moving toward standardized definitions for adverse events to better capture safety data, while still considering so-called adverse events of special interest: a subset of adverse events that often require additional attention based on who is experiencing the adverse event (e.g., pregnant women, children) or adverse events that differ based on the type of vaccine being considered (e.g., mRNA vs viral vector).

Once a vaccine is approved or authorized for use and is being given to recipients, the focus will shift. Safety monitoring will partly include analysis of safety data from ongoing routine voluntary and passive reports, and also use established early warning and surveillance systems to continually monitor for safety issues. Currently, these efforts are led by the CDC and FDA, with the largest system for early detection of safety issues being **the Vaccine Adverse Event Reporting System** (VAERS). This data system collects reports of adverse events submitted by anyone who gives or receives any vaccine and suspects that a reaction has occurred. VAERS data are updated and reviewed daily, and analyses are performed regularly to detect unusual or unexpected patterns that may indicate an underlying problem. Other systems include the **Vaccine Safety Datalink (VSD)**, a collaboration between CDC and eight large health care organizations that allows for proactive monitoring of vaccine-related data, and **the Clinical Immunization Safety Assessment (CISA) project**, which serves as a research partnership between CDC and medical centers to further assess vaccine-associated health risks. Although VAERS does not provide access to medical records, this **FDA publication** describes how scientists can access data and medical records in VSD to gain further insight on events similar to those reported in VAERS. During emergencies such as the current COVID-19

pandemic, when large numbers of a new vaccine may be given in a short period of time, a network of 62 vaccine safety coordinators across the country is activated to work with CDC to enhance baseline vaccine safety activities. This heightened level of attention to vaccine safety was part of the response to the H1N1 influenza pandemic in 2009.

For COVID-19 specifically, while vaccine supply may be limited at first and only sufficient to be administered to special populations such as health care personnel, other systems are being created to actively seek out data rather than waiting for it to be passively submitted. These include the Vaccine Safety Assessment for Essential Workers (V-SAFE), a smartphone-based web survey platform that will prompt vaccine recipients to submit health check information through text or email daily for the first week after receiving a vaccine and weekly for six weeks after vaccination to cover the most critical window during which adverse events are most likely to occur. This data can then be linked to a call center and incorporated into VAERS if necessary. It remains to be seen if special registries created by vaccine manufacturers themselves will also contribute to efforts to ensure that the public has access to a safe and effective vaccine.

Can dogs detect COVID-19?

It was recently reported that travelers to the international airport in Helsinki, Finland, may be **screened for COVID-19 by dogs** that smell samples of sweat collected from travelers' necks. Dogs have also been used to **screen travelers for COVID-19 at airports in the United Arab Emirates**. Although this may appear to be an unusual way of screening for COVID-19, there is precedent for using dogs to detect diseases. Dogs have an extraordinary sense of smell that far eclipses human abilities. They can be trained to signal when they detect a particular scent, they can perform their duties quickly and efficiently, and their diagnostic performance can be compared with the results of other tests. Dogs may detect either pathogen-specific chemical changes or changes in the metabolism of host cells so

they can be trained to determine if a sample has a pathogen in it or if a person has a particular disease. Dogs have successfully learned to determine whether people had lung or breast cancer by smelling their breath, to diagnose children in The Gambia with asymptomatic malaria infections by smelling their socks and to detect the presence of a specific type of bacteria in stool samples.

In Germany, eight dogs were trained to detect, with a high degree of accuracy, SARS-CoV-2 in respiratory samples from patients hospitalized with COVID-19. Other dogs around the world are in training, including the Medical Detection Dogs at the London School of Hygiene and Tropical Medicine and dogs at the University of Pennsylvania's School of Veterinary Medicine Working Dog Center. In terms of the safety of the dogs and the people with whom they have contact, there have been few reported cases of pets infected with SARS-COV-2; dogs are thought to be at very low risk even if exposed to the virus. In addition, training programs have stated that dogs will not make direct contact with the people they screen and will be carefully monitored.

Weekly Research Highlights

Note: US CDC also publishes a COVID-19 Science Update

Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis

(JAMA Pediatrics, Sept. 25, 2020)

Main message: A recent systematic review and meta-analysis summarized information on the relative susceptibility of children and adolescents compared to adults based on 32 contact tracing and population screening studies. Compared to adults, children and adolescents were about 60% as likely to

contract COVID-19 (OR 0.56, 95% CI 0.37 – 0.85, based on 14 contact tracing studies). Among the eight studies where children were grouped by age, children were 50% as likely to contract the virus compared to adults (OR 0.52, 95% CI 0.33 – 0.82) but there was no significant difference between adolescents and adults.

- To minimize bias based on the fact that children appear to be more likely to have asymptomatic infection of COVID-19, contact tracing studies were only included if all contacts were tested using PCR.
- Results from the population screening studies were not combined in a meta-analysis. However, of the 14 studies, four found that children had significantly lower rates of infection and the rest found no significant differences (though in all cases the risk ratio was <1). Results from these studies should be interpreted with caution as population screening studies cannot distinguish between differences in susceptibility and differences in exposure.
- Three contact tracing studies in schools (Ireland, Australia and Singapore) found little transmission in schools. This might indicate that children are less involved in transmission of the virus, but there is not yet sufficient evidence either way.
- The susceptibility of children and adolescents to COVID-19 has important implications for opening and closing schools during the current COVID-19 pandemic. Overall, the results suggest that children under 10 are less susceptible than adults, but the evidence is less clear about adolescents. This is the best evidence we have to date on this issue. However, despite their best efforts to eliminate major sources of bias, the authors note that many of the studies included were of low or moderate quality and therefore results should be interpreted with caution.

Immune Responses to SARS-CoV-2 Infection in Hospitalized Pediatric and Adult Patients

(Science Translational Medicine, Sept. 21, 2020)

Main message: Researchers systematically documented immunological response measures among patients hospitalized with COVID-19 at a single urban medical center in New York. Pediatric patients (children and young people age <24 years, n=65) had less severe illness than adult patients (people aged 24 years and older, n=60). Both pediatric and adult patients developed measurable cytokine, antibody and T-cell responses, but there were clear age-related trends. Adult patients developed more robust cellular and humoral immune responses than children and young people with COVID-19. In contrast, concentrations of some cytokines were higher among pediatric patients compared to adults. Differences in the type of immune response may contribute to the differences in relative severity of illness observed between adults and younger people with COVID-19.

- Researchers enrolled 125 patients admitted for COVID-19 at the Montefiore Health System in New York between March 13 and May 17, 2020, including 65 pediatric and 60 adult patients. They compared clinical features and outcomes and measured cytokine, antibody and T-cell responses. Patients with conditions that might affect their immune responses were excluded.
- Pediatric patients had milder illness and better outcomes including a shorter hospital stay (6.4 days vs. 14.8 days), less need for mechanical ventilation (7.7% vs. 36.7%) and lower risk of death (3.1% vs. 28.3%). COVID-19-associated multisystem inflammatory syndrome in children was diagnosed in 20 pediatric patients, all of whom survived.
- Patients of all ages showed evidence of an innate immune response, measured by the presence and level of inflammatory proteins. There was a statistical trend for higher levels of some of these cytokines, particularly interleukin-17A and interferon-γ, among younger patients. The authors suggest that these nonspecific immune modulating proteins may contribute to protecting children from more severe and fatal manifestations of COVID-19.

- Both pediatric and adult patients also mounted adaptive antibody and cellular immune responses specifically targeting SARS-CoV-2, the virus that causes COVID-19. Adult patients developed higher levels of antibodies and more robust T-cell responses than were seen in pediatric patients. In fact, the highest levels of neutralizing antibodies occurred in adult patients with the most severe disease—those who required mechanical ventilation or died in hospital. Researchers suggest that severely ill adults, having mounted strong antibody responses on their own, might benefit little from treatments such as convalescent plasma.
- The study provides important information about some differences in innate and adaptive immune responses among patients of different ages hospitalized with COVID-19. This study might be too small to detect all of the important differences that characterize the immune responses to COVID-19 in pediatric and adult patients. Its single geographic location and short time frame could limit the generalizability of the study findings. It is also possible that some important immunological differences between age groups were not anticipated or measured and that some other factor accounted for the statistical associations described.

COVID-19 Trends Among School-Aged Children — United States, March 1–September 19, 2020

(MMWR, early release Sept. 28)

Main message: Many children are back in school in some parts of the country, and others are anticipating possibly returning to in-person learning in the coming months. Researchers at the U.S. Centers for Disease Control and Prevention (CDC) analyzed data on COVID-19 cases among children 5 to 17 years old to better inform decision-making about activities that affect children and adolescents. Overall, mortality and hospitalization for school-aged children remained low. From March to September 2020, incidence among adolescents aged 12 to 17 years was twice that

of children aged 5 to 11 years. Multiple layers of mitigation strategies—including wearing masks, watching distance and washing hands—will be necessary to keep teachers, staff, students and their families safe. Monitoring trends of multiple indicators in such cases and testing parameters can guide the best use of mitigation strategies.

- Laboratory-confirmed cases of COVID-19 are reported to the CDC. From March 1 to Sept. 19, there were 277,285 cases of COVID-19 reported among school-aged children (5 to 17 years old) in the U.S.
- Average weekly incidence for adolescents aged 12 to 17 years was 37 per 100,000 population compared to 19 per 100,000 population for younger school-aged children (5 to 11 years old). Testing volume and test positivity peaked for school-aged children in July, and subsequently decreased and plateaued by early September, although these indicators may again be increasing. From the cases for which race and ethnicity data was available, Latinx children accounted for 46% of cases among younger school-aged children and 39% of cases among adolescents. Overall, 3,240 (1%) of school-aged children with COVID-19 were hospitalized and 404 (0.1%) required ICU admission. There were 51 COVID-19-related deaths reported in this age group from March 1 to Sept. 19.
- Since testing has not been prioritized among those with mild or no symptoms (as is often the case in children), the total case numbers may be an underestimate. Data for race/ethnicity, symptoms, and some other demographic factors were often reported incompletely

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