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.

COVID-19 herd immunity by immunisation: are children in the herd?

Published Online
April 19, 2021
https://doi.org/10.1016/
S1473-3099(21)00212-7

The scourge of COVID-19 has been global, but the most affected subgroups in the population have largely been older people and individuals with comorbid conditions that predispose them to increasingly severe disease and poor outcomes. Overall, the disease burden in children has been reasonably mild, even in those with comorbidities, such as oncological conditions. Protection from severe disease in children might be related to a lower expression of host factors required for viral replication, and to differences in the magnitude and timing of innate or adaptive immune responses. Data for recorded COVID-19 cases show that only 7% of children younger than 18 years with severe disease required intensive care, whereas 53% of adults who had severe disease required intensive care.[1–3] Multisystem inflammatory syndrome in children, arguably the most dreaded presentation, typically presents between 3 and 6 weeks after SARS-CoV-2 exposure.[4] Most patients at presentation have a negative nasopharyngeal RT-PCR but are positive for serology. This temporal association and low PCR positivity rate suggest a postinfectious mechanism rather than acute viral infection. Children of African or Hispanic race or ethnicity are more frequently affected, whereas children of Asian or White race or ethnicity appear to be less often affected,[5,6] and genetic susceptibility might account for this over-representation. The reasonably low incidence of COVID-19 in the general population of children, the unusual manifestation with multisystem inflammatory syndrome in older children and adolescents, and the absence of epidemiological data that incriminates children in the transmission of SARS-CoV-2, pose important immunological, ethical, and economic conundrums that require careful examination before the deployment of any COVID-19 vaccine in children.

The following clinical observations are relevant for formulating COVID-19 vaccines for deployment in children.

First, from an immunological perspective, the milder spectrum of disease in children might correlate with SARS-CoV-2 antigen processing and immunopathogenesis in children. Few immunological studies in children with multisystem inflammatory syndrome report abnormal immunophenotypes of plasmablasts,[7,8] elevated SARS-CoV-2 IgG, and proinflammatory cytokines.[8] Current vaccines that are authorised for emergency use, approved or in development, do not have a safety or immunogenicity profile in children. In the absence of a better understanding of the pathogenesis of this condition, using the same approach for delivering vaccines as in adults could exacerbate the incidence of this hyperinflammatory condition.

Second, from a public health perspective, it will be necessary to immunise children if they are a major source of SARS-CoV-2 transmission and if the candidate vaccines block transmission. However, epidemiological reports up to now suggest that young children have a high likelihood of developing COVID-19 via household transmission, once a family member tests positive for COVID-19.[1] There is little evidence of secondary infection from children to others in the transmission pathways of COVID-19. Although emerging data suggest that some candidate vaccines can block transmission, vaccinating children cannot be justified if it is to give direct protection despite minimal burden of disease or to help to block transmission if children do not constitute a substantial reservoir for transmission. For other infections that can be prevented by vaccine, such as invasive pneumococcal disease, immunisation of children not only prevented infections in children, but also conferred indirect benefit by decreasing disease in older people, because of its effect on carriage reduction and blockage of transmission.[9] For COVID-19, the reverse might be the case, with adults having to be vaccinated to confer protection on young children.

Third, from an ethical perspective, there is a balance between risk and benefit in offering a COVID-19 vaccine to children that will offer minimal or no direct benefit to the recipient, no benefit to the public, and as yet, unknown medium-term and long-term risks to the recipient. Other important considerations include the economic and practical considerations in deploying a new vaccine into the routine childhood immunisation programmes. Without additional data and public enlightenment on the benefits of immunising young

children, this deployment could further threaten childhood immunisation coverage that is already precariously low in several settings.

Finally, because individuals are not equally susceptible and contagious, our current target to vaccinate 65–70% of the population to archive herd immunity might be an overestimate.[10] If young children are excluded, there will be more vaccines available for the more epidemiologically susceptible subgroups. Initiating efficacy trials in youths aged 12–18 years is a welcome development, but a new strategy might ultimately be required for immunising younger children, should this become necessary.

I declare no competing interests.

Stephen Obaro
stephen.obaro@unmc.edu

University of Nebraska Medical Center, Omaha, NE 68198, USA

1 Castagnoli R, Votto M, Licari A, et al. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr* 2020; **174:** 882–89.

2 Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review. *EClinicalMedicine* 2020; **24:** 100433.

3 US Centers for Disease Control and Prevention. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. *Morb Mortal Wkly Rep* 2020; **69:** 343–46.

4 Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: a systematic review. *EClinicalMedicine* 2020; **26:** 100527.

5 Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med* 2020; **383:** 347–58.

6 Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children—United States, March–July 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 1074–80.

7 Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* 2020; **369:** eabc8511.

8 Carter MJ, Fish M, Jennings A, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med* 2020; **26:** 1701–07.

9 Tsaban G, Ben-Shimol S. Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: a systematic review of the literature. *Vaccine* 2017; **35:** 2882–91.

10 Fontanet A, Cauchemez S. COVID-19 herd immunity: where are we? *Nat Rev Immunol* 2020; **9:** 1–2.

Vaccine development lessons between HIV and COVID-19

The SARS-CoV-2 pandemic has many parallels to the early days of the HIV epidemic. Both began with efforts to identify the causative pathogen, followed by rapid development of diagnostics, animal models, therapeutics, and preventive vaccines. After targeting of the gp120 and gp160 HIV envelope proteins proved ineffective, development of candidate vaccines to prevent HIV expanded to encompass DNA and viral vector vaccines, with the intent of inducing both humoral and cellular immunity. In recent years, mRNA has been harnessed as a newer platform for the development of candidate HIV vaccines.[1] Advancing the evidence from HIV vaccines, research supporting vaccines against other pathogens has also influenced SARS-CoV-2 vaccine design, including structure-based design of stabilised epitope-scaffold proteins for respiratory syncytial virus,[2] DNA vaccines for MERS-CoV,[3] and ongoing global molecular surveillance for the design of influenza vaccines.[4] Collectively, the knowledge gained through these preclinical, manufacturing, and clinical development experiences has allowed for a rapid pivot to apply these approaches to SARS-CoV-2 vaccine research. The success of several large efficacy trials of HIV candidate vaccines has been used to advance SARS-CoV-2 vaccine research and development via existing public–private partnerships and networks such as the HIV Vaccine Trials Network and their established connections with local investigators and community advocates.

The most noteworthy difference between responses to SARS-CoV-2 and HIV is the time to authorisation and rollout of effective preventive vaccines. Emergency use authorisation of initial vaccines against COVID-19 was granted by the US Food and Drug Administration and European Medicines Agency less than 1 year after initial publication of the genetic sequence of SARS-CoV-2. By stark contrast, after more than 30 years of research, only six efficacy trials of candidate HIV vaccines have been completed,[5] of which only one showed partial efficacy in preventing acquisition of new HIV-1 infection (risk lowered by 31%).[6] Much of this discrepancy is due to inherent biological differences between HIV and coronaviruses, such as HIV's substantially higher mutation rate due to reverse transcription and evasion of immune responses after HIV integration into the host genome. Nonetheless, there is much that can be learned