measure in children and adolescents—eg, to what extent are unhealthy patterns of physical growth and micronutrient deficiencies in childhood also reflected in brain growth and cognitive capabilities, and can interventions to promote healthier growth and reduce micronutrient deficiency also achieve better learning outcomes?

The usual way of thinking about growth in late adolescence is as the endpoint of earlier investments in younger children, with the belief that all will be right as long as early growth is alright. Highlighting that healthy early growth trajectories can falter with age, this study reinforces the importance of promoting healthy growth across the developmental years. Newer views conceptualise growth in adolescents from an intergenerational perspective.[6] This view appreciates that, beyond earlier interventions, investments in school-aged children that promote healthy eating and physical activity, access to quality learning environments, gender equality, and older age at first pregnancy not only benefit the growth and development of children and adolescents, but can also be considered investments in the healthy growth and development of the next generation of young children.

I declare no competing interests.

Susan M Sawyer
susan.sawyer@rch.org.au

Department of Paediatrics, University of Melbourne, Melbourne, VIC 3052, Australia; Population Health Group, Murdoch Children's Research Institute, Melbourne, VIC, Australia; and Centre for Adolescent Health, Royal Children's Hospital, Melbourne, VIC, Australia

1 WHO. Reducing stunting in children: equity considerations for achieving the Global Nutrition Targets 2025. Geneva: World Health Organization, 2018.
2 NCD Risk Factor Collaboration. Height and body-mass index trajectories of school-aged children and adolescents from 1985 to 2019 in 200 countries and territories: a pooled analysis of 2181 population-based studies with 65 million participants. *Lancet* 2020; **396:** 1511–24.
3 Swinburn BA, Kraak VI, Allender S, et al. The global syndemic of obesity, undernutrition, and climate change: the *Lancet* Commission report. *Lancet* 2019; **393:** 791–846.
4 Popkin BM, Corvalan C, Grummer-Strawn LM. Dynamics of the double burden of malnutrition and the changing nutrition reality. *Lancet* 2020; **395:** 65–74.
5 Hawkes C, Demaio AR, Branca F. Double-duty actions for ending malnutrition within a decade. *Lancet Glob Health* 2017; **5:** e745–46.
6 Patton GC, Olsson CA, Skirbekk V, et al. Adolescence and the next generation. *Nature* 2018; **554:** 458–66.

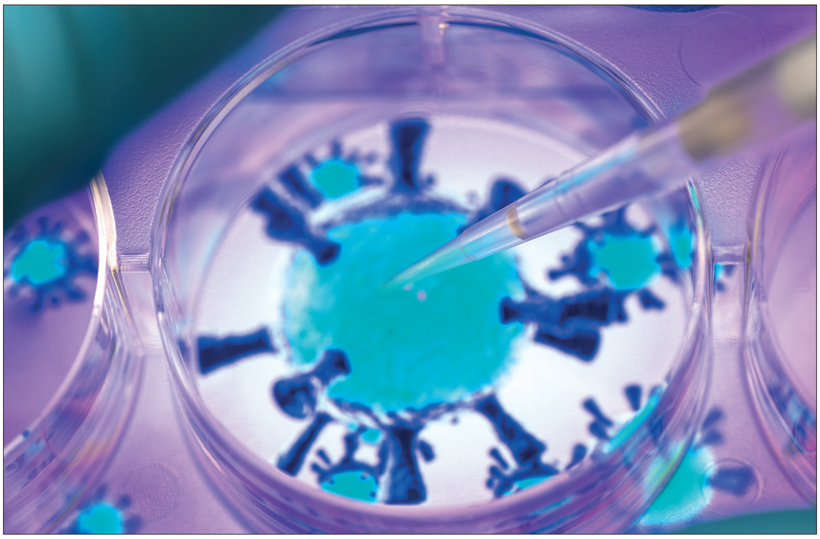
What can we expect from first-generation COVID-19 vaccines?

Published **Online**
September 21, 2020
https://doi.org/10.1016/S0140-6736(20)31976-0

A first generation of COVID-19 vaccines is expected to gain approval as soon as the end of 2020 or early 2021. A popular assumption is that these vaccines will provide population immunity that can reduce transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and lead to a resumption of pre-COVID-19 "normalcy". Given an initial reproduction number of around 2·2,[1] which has since been revised to as high as about 4, and taking into account overdispersion of infections,[2] perhaps about 25–50% of the population would have to be immune to the virus to achieve suppression of community transmission.[1–3]

Multiple COVID-19 vaccines are currently in phase 3 trials with efficacy assessed as prevention of virologically confirmed disease.[4] WHO recommends that successful vaccines should show disease risk reduction of at least 50%, with 95% CI that true vaccine efficacy exceeds 30%.[5] However, the impact of these COVID-19 vaccines on infection and thus transmission is not being assessed. Even if vaccines were able to confer protection from disease, they might not reduce transmission similarly.

Challenge studies in vaccinated primates showed reductions in pathology, symptoms, and viral load in the lower respiratory tract,[6,7] but failed to elicit sterilising immunity in the upper airways. Sterilising immunity in the upper airways has been claimed for one vaccine, but peer-reviewed publication of these data



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are awaited.[8] There have been reports of virologically confirmed SARS-CoV-2 re-infection of previously infected individuals, but the extent of such re-infection is unclear.[9] Whether re-infection is associated with secondary spread is unknown.

The immunological correlates of protection from SARS-CoV-2 infection and COVID-19 have yet to be elucidated. Pre-existing neutralising antibody seemed to have afforded protection against re-infection in people on board a fishing vessel where there was an outbreak of SARS-CoV-2 with a high infection attack rate.[10] In animal models, passive antibody transfer protected against COVID-19,[11,12] whereas neutralising antibody correlated with protection after inoculation.[13] However, the roles of mucosal immunity, other biological antibody activities (eg, antibody-dependent cellular cytotoxicity), and T cells in protection conferred by natural infection or passive immunisation are unclear.

The prevalence and duration of neutralising antibody responses after natural infection remain to be defined by gold-standard neutralisation assays that use live virus rather than pseudotype neutralising assays or non-functional ELISA assays.[14] The duration of protection against re-infection with seasonal human coronaviruses might last for less than a year.[15] Middle East respiratory syndrome coronavirus (MERS-CoV) re-infection occurs in dromedary camels, the natural host of that virus.[16] Whether re-infected camels are as infectious as those with primary infections is not known. The observation that MERS-CoV is enzootic in dromedary populations despite high (>90%) seroprevalence in juvenile and adult camels implies that virus transmission may not be functionally interrupted by previous infection. Also relevant is how influenza vaccines can reduce disease transmission,[17] whereas inactivated polio vaccines are effective at protecting from disease but have less effect on reduction of faecal shedding of poliomyelitis virus[18] and thus possibly on transmission.

These observations suggest that we cannot assume COVID-19 vaccines, even if shown to be effective in reducing severity of disease, will reduce virus transmission to a comparable degree. The notion that COVID-19-vaccine-induced population immunity will allow a return to pre-COVID-19 “normalcy” might be based on illusory assumptions.

Another important consideration is COVID-19 vaccine allocation strategy. First principles would preferentially allocate vaccine supplies to people at high risk of severe morbidity and mortality. Preliminary model-informed analyses support this theoretical inference.[19] However, vaccine allocation perspectives in addition to utilitarian considerations are important. The US National Academy of Medicine’s *Preliminary Framework for Equitable Allocation of COVID-19 Vaccines* identified other foundational criteria, such as equal regard, mitigation of health inequities, fairness, and transparency, that should also determine vaccine allocation.[20] Alongside the risks of severe morbidity and mortality and of disease transmission, this framework stipulates two additional criteria for equitable vaccine allocation—namely, risks of acquiring infection and of negative societal impact.[20] Front-line health-care and essential workers, such as school teachers, belong in both these latter groups.

Policy makers must be vigilant of the possible impact of vaccine hesitancy.[21] In the COVID-19 response, the activities of some politicians have been incompatible with science and risk further eroding vaccine confidence among the general public. The potential disruption of a proportion of people declining vaccine uptake could be substantial. The likely heterogeneity of such abreactions to vaccination roll-outs between countries and across partisan divides within nations should not be underestimated. Finally, if international travel were to fully recommence, vaccine allocation to different countries with varying means of access will require careful deliberation, based on moral grounds and because no country will be truly protected from COVID-19 until virtually the entire world is.[22]

Notwithstanding these caveats, COVID-19 vaccines are needed, even if they have minimal impact on transmission and despite the challenges of vaccine allocation. What such vaccines are likely to achieve might not be herd immunity. If so, strategies for how we use such vaccines would have to be based on other considerations. Will vaccines that protect healthy young adults also protect groups vulnerable to severe disease such as older adults and those with comorbidities? Influenza vaccines are less effective in older populations than in younger populations, partly due to immune senescence,[23] which might similarly affect COVID-19 vaccines. However, the so-called original antigenic sin in influenza vaccines that arises from sequential infections by or vaccinations with antigenically closely related strains[24] is not relevant to coronaviruses. If COVID-19 vaccines have acceptable effectiveness in reducing morbidity and mortality in high-risk groups, they would have an important role, irrespective of impact on transmission and population immunity. If high-risk populations can be shielded by vaccination, COVID-19 control measures could be recalibrated. Crucially, it will be important to communicate to policy makers and the general public that first-generation vaccines are only one tool in the overall public health response to COVID-19 and are unlikely to be the ultimate solution that many expect.

We declare no competing interests.

*Malik Peiris, *Gabriel M Leung*
gmleung@hku.hk

School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, China

1 Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; **382:** 1199–207.
2 Adam DC, Wu P, Wong JY, et al. Clustering and superspreading potential of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Hong Kong. *Nat Med* 2020; published Sept 17. https://doi.org/10.1038/s41591-020-1092-0.
3 Gomes MGM, Corder RM, King JG, et al. Individual variation in susceptibility or exposure to SARS-CoV-2 lowers the herd immunity threshold. *medRxiv* 2020; published online May 21. https://doi.org/10.1101/2020.04.27.20081893 (preprint).
4 WHO. Draft landscape of COVID-19 candidate vaccines. Sept 9, 2020. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed Sept 13, 2020).
5 Krause P, Fleming TR, Longini I, Henao-Restrepo AM, Peto R, for the World Health Organization Solidarity Vaccines Trial Expert Group. COVID-19 vaccine trials should seek worthwhile efficacy. *Lancet* 2020; **396:** 741–43.
6 van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. *Nature* 2020; published online July 30. https://doi.org/10.1038/s41586-020-2608-y.
7 Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. *N Engl J Med* 2020; published online July 28. https://doi.org/10.1056/NEJMoa2024671.
8 Novavax. Novavax announces positive phase 1 data for its COVID-19 vaccine candidate. Aug 4, 2020. https://ir.novavax.com/news-releases/news-release-details/novavax-announces-positive-phase-1-data-its-covid-19-vaccine (accessed Sept 13, 2020).
9 To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis* 2020; published online Aug 25. https://doi.org/10.1093/cid/ciaa1275.
10 Addetia A, Crawford KHD, Dingens A, et al. Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate. *J Clin Microbiol* 2020; published online Aug 21. https://doi.org/10.1128/JCM.02107-20 (preprint).
11 Chan JF, Zhang AJ, Yuan S, et al. Simulation of the clinical and pathological manifestations of coronavirus disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. *Clin Infect Dis* 2020; published online March 26. https://doi.org/10.1093/cid/ciaa325.
12 Chandrashekar A, Liu J, Martinot AJ, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science* 2020; **369:** 812–17.
13 Yu J, Tostanoski LH, Peter L, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science* 2020; **369:** 806–11.
14 Seow J, Graham C, Merrick B, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *medRxiv* 2020; published online July 11. https://doi.org/10.1101/2020.07.09.20148429 (preprint).
15 Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol Infect* 1990; **105:** 435–46.
16 Hemida MG, Alnaeem A, Chu DK, et al. Longitudinal study of Middle East respiratory syndrome coronavirus infection in dromedary camel herds in Saudi Arabia, 2014–2015. *Emerg Microbes Infect* 2017; **6:** e56.
17 Monto AS, Davenport FM, Napier JA, Francis T. Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. *J Infect Dis* 1970; **122:** 16–25.
18 Davis DC, Lipson MJ, Carver DH, Melnick JL, Robbins FC. The degree and duration of poliomyelitis virus excretion among vaccinated household contacts of clinical cases of poliomyelitis. *Pediatrics* 1958; **22:** 33–40.
19 Bubar KM, Kissler SM, Lipsitch M, Cobey S, Grad YH, Larremore DB. Model- informed COVID-19 vaccine prioritization strategies by age and serostatus. *medRxiv* 2020; published online Sept 10. https://doi.org/10.1101/2020.09.08.20190629 (preprint).
20 National Academies of Sciences, Engineering, and Medicine. Discussion draft of the preliminary framework for equitable allocation of COVID-19 vaccine. Washington, DC: The National Academies Press, 2020.
21 de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *Lancet* 2020; published online Sept 10. https://doi.org/10.1016/S0140-6736(20)31558-0.
22 Emanuel EJ, Persad G, Kern A, et al. An ethical framework for global vaccine allocation. *Science* 2020; **369:** 1309–12.
23 Wagner A, Weinberger B. Vaccines to prevent infectious diseases in the older population: immunological challenges and future perspectives. *Front Immunol* 2020; **11:** 717.
24 Kim JH, Skountzou I, Compans R, Jacob J. Original antigenic sin responses to influenza viruses. *J Immunol* 2009; **183:** 3294–301.

Strategy, coordinated implementation, and sustainable financing needed for COVID-19 innovations

Innovative tools and approaches are needed in the response to the COVID-19 pandemic. But innovation alone is insufficient and requires resources and an overarching strategy for implementation in a planned and coordinated way. Furthermore, it is important to evaluate the effectiveness of innovations before they are implemented in clinical care even in an emergency situation. Unfortunately, this strategic approach is not happening in many parts of the world as the numbers of COVID-19 cases and deaths continue to rise. Since so much innovation is bottom-up and entrepreneurial, it can be unclear how best to evaluate, coordinate, or