Filling the Gap Until Full Vaccine Deployment in the War on Coronavirus Disease-19

Sabrina Mattoli

ABSTRACT

The authorization for emergency use of a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been issued in diverse countries in December 2020, and additional vaccine candidates soon may be cleared for a similar emergency use. If it is reasonable to believe that in some Western countries most people may be vaccinated by the end of 2021, insufficient supplies, access inequities across countries, and deficiencies in enforcing the participatory engagement of communities will present important challenges for the achievement of sufficient vaccination coverage worldwide in less than 2–3 years. A possible strategy for bridging the gap until full vaccine deployment is based on the integration of improved non-pharmaceutical measures and recently authorized pharmaceutical interventions to reduce as much as possible hospitalizations and deaths in the coming months, when recurring infection peaks are expected.

Keywords: COVID-19; Non-pharmaceutical interventions; Pandemic control; SARS-CoV-2; Therapeutic candidate; Vaccine
The authorization for emergency use of the first vaccine candidate against coronavirus disease-19 has been a major leap forward in pursuing pandemic control, and other vaccine candidates may soon be cleared for the same use.

Because of the accelerated development of these vaccine candidates, limited data are, however, available about their efficacy in diverse demographic groups, the magnitude of the protection, the duration of the immunity and the ability to prevent the transmission of the infection to other individuals.

Insufficient supplies, access inequities across countries, and deficiencies in the participatory engagement of communities will present additional challenges for the achievement of sufficient vaccination coverage worldwide in less than 2–3 years.

Optimal integration of non-pharmaceutical and pharmaceutical interventions can minimize the risk of overwhelmed hospitals and increased mortality in high-risk groups until full vaccine deployment.

**DIGITAL FEATURES**

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**COMMENTARY**

Coronavirus disease 2019 (COVID-19) is the clinical syndrome caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in China in December 2019 and spread globally to reach the pandemic level declared by the World Health Organization (WHO) on March 11, 2020. As of December 14, 2020, more than 72 million people have been infected worldwide and over 1.6 million individuals are dead [1].

The initial massive wave of infections has uncovered the vulnerabilities of the healthcare systems of most countries and exposed their weaknesses [2, 3]. To cope with the dramatic situation, many governments have successfully implemented unprecedented measures of widespread lockdown to slow the spreading of the virus and to contain the number of patients requiring hospital admission and treatment in critical care units [4, 5], but such measures have imposed a heavy burden on societies and economies, and have created a large disruption of education systems [6–9]. In the absence of vaccines or reliable pharmaceutical treatments, only non-pharmaceutical interventions such as social distancing, face mask wearing, frequent handwashing, intensive viral testing, isolation of infected individuals and quarantine for traced contacts have been able to mitigate in part the risk of additional uncontrolled resurgence of infection, while allowing the resumption as much as possible of economic and educational activities [10–13]. With the strict implementation and enforcement of such measures in the long term, countries such as New Zealand and Taiwan have almost eradicated COVID-19. In Europe, the easing of social restrictions during the summer months has largely contributed to the reversing of the positive effects of the mitigation measures initially imposed by the governments. Consequently, most European countries are already reporting daily infection numbers comparable to or beyond those of their first peaks, with a second wave rolling over some of them with exponential growth. Other countries, also including the United States of America (USA), are experiencing recurring peaks of infections and deaths because of the inadequate implementation of mitigation measures or their inconsistent application throughout the states.

In the next couple of months, the arrival of the flu season will represent an additional challenge in all countries of the Northern
Hemisphere because the influenza viruses and SARS-CoV-2 cause serious diseases requiring hospitalization in the same groups of individuals [14], and the doses of flu vaccine currently available for the flu season 2020–2021 seems to be insufficient to vaccinate at least all subjects risking serious disease. Moreover, indoor activities that greatly increase the risk of SARS-CoV-2 transmission will become the prevalent activities in colder weather, making containment of the virus spread in the Northern Hemisphere even more difficult in the coming winter [15].

The availability of a vaccine against SARS-CoV-2 has been considered of paramount importance for pandemic control. Following accelerated development, Phase 3 testing of some vaccine candidates is currently under way [16]. On the basis of data from the ongoing large-scale clinical trial [17], one of these vaccine candidates (BNT162b2) has been found to be effective and safe enough for the release of an emergency-use authorization (EUA) or equivalents in the United Kingdom (UK), Canada, and the USA at the beginning of December 2020. BNT162b2 and other vaccine candidates may soon be cleared for a similar emergency use in other countries, but there are limited data about long-term safety, efficacy in high-risk demographic groups, the magnitude of the protection, and the duration of the vaccine immunity [18, 19]. In fact, it may take years to achieve the necessary vaccination coverage at the global level because, on the basis of the results of antibody testing, it has been estimated that at least 5 billion people worldwide (including almost 200 million Americans) would need to be vaccinated in order to achieve community protection and end the pandemic [19]. High-risk individuals may account for up to 30% of this population [20], and frontline health and social workers also need to be vaccinated as soon as possible. Even if there were sufficient health care resources and appropriate facilities to make it possible to vaccinate 100,000 people a day, as estimated by the Robert Koch Institute for Germany [21], after 180 days (6 months) only 18 million people would have received a single dose of one of the potentially available vaccines (all injectable and most requiring 2 doses to achieve sufficient protection). In Germany, where vaccination centers are ready to start, pending the authorization of the European Medicines Agency, 8 months of intensive vaccination efforts would be required to vaccinate all the already identified high-risk groups [21, 22]. Insufficient supplies and access inequities across countries [23] will present additional important challenges for the achievement of sufficient vaccination coverage in other parts of the world, particularly low-income countries, in less than 2–3 years. Deficiencies in enforcing the participatory engagement of communities by governments may also significantly delay vaccine uptake worldwide [24].

Considering the most recent information about the dynamic of virus spreading, and the fact that asymptomatic and pre-symptomatic individuals represent an important proportion of the potential spreaders and super-spreaders [25, 26], personal protective measures such as physical distancing and mask-wearing could still be required for the next 2 years, while awaiting the establishment of sufficient immunization by vaccination. It may be necessary to extend such a requirement even beyond 2 years because it has not yet been tested if vaccinated people can still be infected and transmit the infection. Moreover, in keeping with published projections [13], governments may need to impose prolonged or intermittent periods of sustained distancing, with temporary closure of schools and businesses, to contain virus spreading when and where case numbers rebound over the next 2 years. Repeated cycles of such restrictions are scarcely sustainable and would certainly hinder the future socio-economic recovery from the pandemic [27], even when supported by the development of appropriate financial and social programs [28]. A possible option for bridging the gap until full vaccine deployment is the planning and implementation of strategies based on the integration of improved non-pharmaceutical measures and recently authorized pharmaceutical interventions to reduce as much as possible hospitalizations and deaths in the coming months.

In terms of non-pharmaceutical interventions, some studies have estimated the
feasibility, health impact, and economic effects of diverse strategies. A new model based on the analysis of mobile-phone data [29] has demonstrated that there are cost-effective measures to contain the spread of SARS-CoV-2 in COVID-19 hot spots while limiting the damage to economic segments highly affected by the pandemic, such as restaurants and stores, and that these data, which accurately predict the risks of visiting identified locations of infection, might be used to refine and calibrate social-distancing policies (i.e., optimal occupancy reduction, opening of multiple food distribution centers to reduce densities in high-risk stores, good ventilation of high-risk but essential workplaces). In another recent study [30], Colbourn and colleagues tested the health and economic outcomes of population-wide testing, contact tracing, and isolation strategies in the UK by combining mathematical and economic models. They found that these strategies can be used cost-effectively to suppress SARS-CoV-2 outbreaks quickly, and then prevent new outbreaks and deaths without the need for other lockdowns, when testing and tracing programs are scaled-up sufficiently during the initial lockdown.

Another recently proposed approach deserving consideration is the government-supported repurposing of hotels to isolate and monitor individuals potentially infected and asymptomatic and those with mild symptoms of COVID-19 [31]. The aim is to reduce the risk of within-household transmission and hospital admissions. Prioritizable individuals could be those who live in multi-generational families or with subjects at risk of severe COVID-19 because of concomitant pathologies, and those who live alone and who might benefit from food provision and practical aid. The medical sheltering sites in Los Angeles County and the COVID hotels in Italy are examples of the effective implementation of this strategy by local and national governments of democratic countries, which in so doing are aiming to replicate the positive results obtained with similar strategies in countries such as China and Taiwan.

The availability of vaccines will urge governments to address the additional challenge of how to prevent SARS-CoV-2 outbreaks generated by the importation of cases from countries where the implementation of the vaccination campaign is ineffective or delayed. It has been demonstrated that travel restrictions can decrease the rate of case importation or exportation only if imposed during the early phase of an epidemic [32]. In the case of a pandemic, testing at the point of entry, contact tracing, and quarantine remain the most effective containment measures. The risk of importation can be mitigated by starting vaccine distribution in regions where the estimated risk is higher because of the high numbers of foreigners and commuters, and then move to the regions that are highly connected to the high-risk regions [32].

In terms of pharmaceutical interventions, most trials have been planned to test the effectiveness of therapeutic candidates in advanced COVID-19, when patients are already hospitalized, while very few studies have addressed early interventions for the prevention of hospitalization [33]. Following the negative results obtained in trials testing the efficacy of hydroxychloroquine as post-exposure prophylaxis [34, 35], only the very recent clearance of two monoclonal antibody-based therapeutic candidates for emergency use in the United States (bamlanivimab and the combination casirivimab and imdevimab) and the release of interim authorization for bamlanivimab in Canada have given an option to keep people infected with SARS-CoV-2 out of hospital. Bamlanivimab (LY-CoV555) is a recombinant, neutralizing human monoclonal antibody directed against the spike protein of SARS-CoV-2, and capable of blocking viral attachment and entry into human cells. The clearance of bamlanivimab is based on the interim results of the ongoing BLAZE-1 randomized, double-blind, placebo-controlled trial conducted at 41 centers in the USA, and including 452 patients who had a positive SARS-CoV-2 test within 3 days before infusion of the active ingredient or the placebo and who presented with mild or moderate symptoms [36]. About 70% of the patients had at least one risk factor for severe COVID-19, defined as an age of ≥ 65 years, a body mass index of ≥ 35, or the presence of at least one relevant coexisting illness. In the post hoc
analysis examining hospitalization among the patients aged 65 years or older and with a body mass index of 35 or more, 4 of 95 (4%) were hospitalized in the LY-CoV555 group and 7 of 48 (15%) were hospitalized in the placebo group. Only one patient in the placebo group was admitted to an intensive care unit. The manufacturer of bamlanivimab (Eli Lilly) has anticipated manufacturing up to 1 million doses (700 mg per dose) by the end of 2020 for worldwide use if cleared for emergency use in other countries.

Casirivimab (formerly REGN10933) and imdevimab (formerly RGN10987) are the active ingredients of the Regeneron investigational antibody combination REGEN-COV2 (formerly REGN-COV2). This is a combination of two monoclonal antibodies that bind to different binding sites of the spike protein of SARS-CoV-2 and alter its structure to prevent viral attachment and entry into human cells. The combination is designed to prevent mutations that may lead to future treatment unresponsiveness. According to the press release of the Food and Drug Administration (available at https://www.fda.gov/media/143894/download) the data supporting the EUA are based on an ongoing randomized, double-blind, placebo-controlled clinical trial in 799 non-hospitalized adults with mild to moderate COVID-19 symptoms, receiving a single intravenous infusion of 1 of 2 different doses of the antibody combination (2400 mg and 8000 mg) or placebo within 3 days of obtaining a positive SARS-CoV-2 viral test. As of December 14, 2020, the data are not yet published in peer-reviewed journals but are publicly available at https://www.regeneroneua.com/clinicaldata. In the trial, patients at high risk are defined as patients who meet at least one of the following criteria: “Have a body mass index (BMI) ≥ 35, chronic kidney disease, diabetes, immunosuppressive disease (immuno-compromised), are currently receiving immunosuppressive treatment, are ≥ 65 years of age, are ≥ 55 years of age AND have cardiovascular disease or hypertension or chronic obstructive pulmonary disease/other chronic respiratory disease, are 12–17 years of age AND have a BMI ≥ 85th percentile for their age and gender based on CDC growth charts, or sickle cell disease or congenital or acquired heart disease or neurodevelopmental disorders (e.g., cerebral palsy) or a medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), or asthma, or reactive airway or other chronic respiratory disease that requires daily medication for control.” For these patients, hospitalizations and emergency room visits occurred on average in 3% of 151 patients treated with the active combination (3% of 70 patients who received 2400 mg and 2% of 81 patients who received 8000 mg) compared with 9% of 78 placebo-treated patients.

The two antibody-based therapeutic candidates can be administered to adults and pediatric patients of 12 years of age or older with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19. These patients include those who are 65 years of age or older or those who have concomitant disorders that are known to increase the risk of severe disease. The antibody therapy should be administered as soon as possible after a positive COVID-19 test and within 10 days of symptom onset. Neither treatments are authorized for hospitalized patients. They may be associated with worse clinical outcomes when administered to hospitalized individuals with COVID-19 requiring high-flow oxygen or mechanical ventilation. Because of their efficacy in preventing emergency room visits and hospitalizations of infected high-risk people, bamlanivimab and REGEN-COV2 can represent acceptable pharmaceutical options for bridging the gap until full vaccine deployment, unless safety issues emerge in the coming months, and taking into account that the clearance of these therapeutic candidates is currently based on limited evidence. There are, however, drawbacks such as the cost (high doses of antibody are very expensive) and the method of administration (intravenous infusion). For this reason, prioritizable high-risk groups could mainly include older individuals who are less likely to respond to vaccination, and in particular long-term care facility residents, who are also experiencing the highest mortality rate.
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REFERENCES

1. The Center for Systems Science and Engineering at the Johns Hopkins University. Tracking COVID-19. https://systems.jhu.edu. Accessed 26 Nov 2020.

2. Shamasunder S, Holmes SM, Goronga T, et al. COVID-19 reveals weak health systems by design: why we must re-make global health in this historic moment. Glob Public Health. 2020;15(7):1083–9.

3. Sturmburg JP, Tsasis P, Hoemeke L. COVID-19—an opportunity to redesign health policy thinking. Int J Health Policy Manag. 2020. https://doi.org/10.34172/ijhpm.2020.132 (Online ahead of print).

4. Flaxman S, Mishra S, Gandy A, et al. Estimating the effects of non-pharmaceutical intervention on COVID-19 in Europe. Nature. 2020;584(7820):257–61.

5. Hsiang S, Allen D, Annan-Phan S, et al. The effect of large-scale anti-contagion policies on the COVID-19 pandemic. Nature. 2020;584(7820):262–7.

6. Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): a review. Int J Surg. 2020;78:185–93.

7. Li Y, Mutchler JE. Older adults and the economic impact of the COVID-19 pandemic. J Aging Soc Policy. 2020;32(4–5):477–87.

8. National Bureau of Economic Research. Working Papers on Pandemic-Related Research 2020. https://www.nber.org/wp_covid19.html. Accessed 12 Nov 2020.

9. Clarke L, Chalkidou K, Ruiz F. Flatten the curve without flattening the economy: How to stop COVID-19 from causing another catastrophe for health in low- and middle-income countries. Center for Global Development. April 6, 2020. https://www.cgdev.org/blog/protect-livelihoods-covid-19-prevent-another-health-catastrophe-low-and-middle-income-countries. Accessed 12 Nov 2020.

10. Ferguson NM, Laydon D, Nedjati-Gilani G, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Imperial College COVID-19 Response Team, London. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf. Accessed 16 Mar 2020.

11. World Health Organization, WHO Regional Director for Europe. Statement—Risk of COVID19 resurgence is never far away, but now we know how to target the virus instead of targeting society. 20 August 2020. https://www.euro.who.int/en/media-centre/sections/statements/2020/statement-risk-of-covid19-resurgence-is-never-far-away-but-now-we-know-how-to-target-the-virus-instead-of-targeting-society. Accessed 25 Aug 2020.

12. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schuenemann HJ, COVID-19 Systematic Urgent
Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020;395(10242):1973–87.

13. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science. 2020;368(6493):860–8.

14. Maltezou HC, Theodoridou K, Poland G. Influenza immunization and COVID-19. Vaccine. 2020;38(39):6078–9.

15. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. Ann Rev Virol. 2020;7:83–101.

16. Corum J, Wee SL, Zimmer C. Coronavirus vaccine tracker. The New York Times. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html. Accessed 12 Nov 2020.

17. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BTN162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2034577 (Online ahead of print).

18. Callaway E. What Pfizer's landmark COVID vaccine results mean for the pandemic. Nature. 2020. https://doi.org/10.1038/d41586-020-03166-8 (Online ahead of print).

19. Bloom BR, Nowak GJ, Orenstein W. “When will we have a vaccine?” – Understanding questions and answers about Covid-19 vaccination. N Engl J Med. 2020;383:2202–4.

20. Clark A, Jit M, Warren-Gash C, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health. 2020;8(8):e1003–17.

21. Mayer-Kuchuk F. Up to 100,000 vaccinations a day should be possible. Badische Zeitung 2020 Nov 24. https://www.badische-zeitung.de/bis-zu-100-000-impfungen-am-tag-sollen-moeglich-sein. Accessed 24 Nov 2020.

22. Beaumont P. Covid-19 vaccine: who are countries prioritizing for first doses? The Guardian 2020 Nov 18. https://www.theguardian.com/world/2020/nov/18/covid-19-vaccine-who-are-countries-prioritising-for-first-doses. Accessed 18 Nov 2020.

23. Mullard A. How COVID vaccines are being divvied up around the world. Nature. 2020. https://doi.org/10.1038/d41586-020-03370-6 (Online ahead of print).

24. Burgess RA, Osborne RH, Yongabi KA, et al. The COVID-19 vaccines rush: participatory community engagement matters more than ever. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)32642-8 (Online ahead of print).

25. Fang FC, Benson CA, Del Rio C, et al. COVID-19 lessons learned and questions remaining. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa1654 (Online ahead of print).

26. Center for Disease Control and Prevention. The science of masking to control COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/downloads/science-of-masking-full.pdf. Accessed 16 Nov 2020.

27. Tisdell CA. Economic, social and political issues raised by the COVID-19 pandemic. Econ Anal Policy. 2020;68:17–28.

28. Alwan NA, Burgess RA, Ashworth S, et al. Scientific consensus on the COVID-19 pandemic; we need to act now. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)32153-X (Online ahead of print).

29. Chang S, Pierson E, Koh PW, et al. Mobility network models of COVID-19 explain inequities and inform reopening. Nature. 2020. https://doi.org/10.1038/s41586-020-2923-3 (Online ahead of print).

30. Colbourn T, Waites W, Panovska-Griffiths J, et al. Modelling the health and economic impacts of population-wide testing, contact tracing and isolation (PTTI) strategies for COVID-19 in the UK. Preprints with The Lancet posted on SSRN Oct 6, 2020. Available at https://ssrn.com/abstract=3627273 or https://doi.org/10.2139/ssrn.3627273.

31. Dickens BL, Koo JR, Wilder-Smith A, Cook AR. Institutional, not home-based, isolation could contain the COVID-19 outbreak. Lancet. 2020;395:1541–2.

32. Wells CR, Sah P, Moghadas SM, et al. Impact of international travel and border control measure on the global spread of the novel 2019 coronavirus outbreak. Proc Natl Acad Sci USA. 2020;117(13):7504–9.

33. Forrest JI, Rayner CR, Park JJH, Mills EJ. Early treatment of COVID-19 disease: a missed opportunity. Infect Dis Ther. 2020;9:715–20.

34. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as post-exposure prophylaxis for Covid-19. N Engl J Med. 2020;383:517–25. 

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35. Mitjà O, Corbacho-Monné M, Ubals M, for the BCN-PEP-CoV2 Research Group, et al. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMo2021801 (Online ahead of print).

36. Chen P, Nirula A, Heller B, for the BLAZE-1 Investigators, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMo2029849 (Online ahead of print).