Workers leave a garments factory in Gazipur, Bangladesh, 3 February 2022.

POLICY FORUM

End COVID-19 in low- and middle-income countries

Vaccines are changing the course of the COVID-19 pandemic, but in grossly uneven ways. Low- and middle-income countries (LMICs) face considerable obstacles in both receiving and distributing doses. To limit virus transmission, its devastating impacts, and opportunities for further mutations, this must change. Until it does, nonpharmaceutical interventions such as masking must remain a priority. *Science* invited global experts to highlight research and innovations aimed at quickening the end of COVID-19 in LMICs. **—Brad Wible**

Contributions to COVID-19 research and innovation

By **Amrita Ahuja**[1] *and* **Ahmed Mushfiq Mobarak**[2]

Although it is common knowledge that LMICs have suffered severe pandemic-related economic consequences, less well known is that many of their pioneering research and innovation efforts have helped mitigate pandemic impacts and shape policy globally, including in high-income countries (HICs). Prominent examples include genome sequencing in South Africa, which led to early identification of the Omicron variant; vaccine development of both injectable and intranasal Covaxin in India; and trials of fluvoxamine, an existing drug repurposed for treatment of COVID, in Brazil. Models integrating economic and epidemiological concerns for cost-benefit analyses of lockdown policies were first developed for LMIC contexts (*1*), and household survey data collected in LMICs highlighted the large losses to income, employment, market access, and food security during the pandemic (*2*). These influenced discourse around the nature and length of economic and social restrictions globally.

Masking guidelines from the World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC) remained unclear months into the pandemic. A randomized controlled trial involving 347,000 adults in rural Bangladesh that successfully encouraged consistent mask use showed substantial declines in symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission. This has since informed masking policy across contexts, from South Asian villages to US schools, and influenced revisions to WHO and CDC masking guidelines. Other studies in LMICs have generated insights on how to encourage adherence to public health behaviors such as social distancing and vaccination. Many frugal innovations to contain COVID-19 spread—such as methods to reach and persuade remote populations regarding new public health behaviors—were originally tested in West Africa during the Ebola crisis (*3*). One of the first population-wide, representative-sample pooled polymerase chain reaction testing efforts was done in Punjab, Pakistan, resulting in algorithms for efficient large-scale pooled testing (*4*). Targeted lockdowns based on color-coded viral spread risk factors were implemented in Pakistan starting in April 2020 and then adopted elsewhere (*5*). Studies in LMICs alerted policy-makers about the special risks the pandemic posed to migrants, women, and children; to mental health; and to routine health care (*6*).

These innovations are products of a strong research infrastructure emerging in many LMICs, exemplified by the abilities to (i) conduct trials and surveys in community settings at massive scale and rapid pace and (ii) combine tools from public health and social sciences to understand the interplay of the disease and social environments. These advantages could be leveraged further—for example, to provide evidence on issues like disease transmission pathways and externalities, and individual and community impacts of alternate vaccine doses, testing approaches, and therapeutics for early treatment of disease.

Different environments lead researchers to ask different questions. Supporting high-quality research in a range of environments addresses a wider set of critical questions and creates a broader and stronger array of tools and strategies for pandemic management. Research investments in LMICs would facilitate cost-effective provision of global public goods for ending the pandemic not only in LMICs, but everywhere.

Lessons from India in April 2021

By **Gagandeep Kang[3]**

In April 2021, the second wave of the SARS-CoV-2 pandemic in India moved inexorably from the west and north to the east and south. Hospitals in northern India had no beds, oxygen was in short supply, and health systems were unable to cope. The scale of infection was documented by a survey showing seropositivity increasing from just over 20% in January 2021 to 67% in June–July 2021 (*7*). Because vaccine supply was a constraint until July, the bulk of the antibody acquisition was likely to be from infection.

The cities of Mumbai and Delhi struggled during the first wave in 2020, but the magnitude, severity, and speed during the second wave in April 2021 were on a different scale. Cases had started to increase a few weeks earlier, and scientists had ascribed the rise to a new variant. The government acknowledged the "double mutant" detection, later named the Delta variant, in March but in mid-April 2021 stated that the variant was not established to be more transmissible (*8*). Despite public health researchers emphasizing the need for continued vigilance and genomic surveillance, there were no restrictions on the rallies conducted in key states in preparations for elections. Further, the Kumbh Mela, the world's largest religious gathering, which stretches several weeks, began in April, drawing pilgrims across India to Haridwar to participate in prayers and ritual bathing. There were a million attendees on some days. Testing was advised but not implemented or monitored, and newspapers reported high positivity in returning pilgrims.

As infections exploded, polypharmacy and the inappropriate use of steroids, antibiotics, antivirals, and anti-inflammatories created both shortages and a second epidemic of cases of mucormycosis, not seen at the same scale anywhere else in the world (*9*). SARS-CoV-2 cases and deaths continued to climb, and hospitals converted the greater proportion of their beds to COVID-19 wards. Care for other conditions, such as cancer, could not be accessed by the bulk of the population, and the consequences of the gaps that were created remain to be fully measured (*10*).

Vaccination was initiated in January 2021 backed by electronic registration systems, but supply constraints restricted vaccination to 1 to 3 million doses a day, insufficient to protect the bulk of the population. Unlike the excellent tracking of vaccination, the ability to accurately estimate the scale of morbidity and mortality during the pandemic has been a major gap. Available mortality analyses show that socioeconomic deprivation led to greater excess deaths during the second wave (*11*), but these data are from states with stronger health and data systems, and the full impact on India may only be available with census data on a longer time scale.

India's second wave offers lessons that point the way for the future for LMICs—early signal detection, acknowledgment, and analysis; preparedness of the health system and its supply chains to not only treat the emergent situation but also protect the ability to handle care provisions for other conditions; and the ability to collect, collate, integrate, analyze, and interpret data in real time so that resources can be directed appropriately when needed, and health systems can build an increased understanding of what drove poor and good outcomes.

The economic impact of COVID-19

By **Edward Miguel[4]** *and* **Ahmed Mushfiq Mobarak[2]**

The COVID-19 pandemic is the largest macroeconomic shock the world has seen since the cataclysm of the Great Depression and World War II, with a global decline in gross domestic product of 3% (*6*), far larger than the shock caused by the Great Recession of 2008–2009 or the 1998 Asian financial crisis. LMICs have been especially hard-hit, with an outpouring of quantitative evidence from household surveys documenting adverse effects of the pandemic on economic outcomes and living standards. The majority of households in most LMIC country samples reported sharp drops in incomes, employment, and consumer spending (*2*, *12*) in the early months of the pandemic. Although unemployment rose and earnings dropped in nearly all countries—rich and poor—only among the poorest populations does this translate into widespread hunger with attendant deleterious effects on long-run child growth and cognitive development, whereas in rich countries social safety nets kick in to provide some measure of food security. Fifty-six percent of Rwandans and Sierra Leoneans reported either missing meals or reducing food portion sizes in nationally representative surveys conducted in May–June of 2020 (*2*).

Researchers have documented even broader adverse effects on education, health care access, mental health, and increases in domestic violence (*6*). Partly in response to growing concerns about food security and meeting basic family needs, the first 2 years of the pandemic saw new public social safety net programs like cash transfers introduced in over 200 countries (*13*). Reaching beneficiaries quickly required innovations in delivery, such as machine-learning–based targeting, and low-cost mobile money transfers (*14*).

The adverse effects of pandemic-related lockdowns indicate that it was important to think carefully about balancing disease risk with the risk of hunger and other unintended socioeconomic consequences in deciding on the stringency of lockdowns in LMICs, where the reach of social safety nets is more limited. In addition, epidemiological modeling indicates that benefits of lockdown policies were arguably far smaller in LMICs, given that generally younger populations face lower COVID-19 mortality risk (*1*).

Although the optimal design of lockdown policies may have been less clear for LMICs, there is no doubt that there remains an urgent need to promote vaccine take-up, masks, and other preventive behaviors in all countries—both poor and rich.

Doses of COVISHIELD vaccine manufactured by Serum Institute of India are administered in Mumbai, India, 3 May 2021.

Scale up production of COVID-19 vaccines in LMICs

By **Gregg S. Gonsalves**[5,6,7] *and* **Saad B. Omer**[8,9]

As of 15 February 2022, 4.27 billion people around the world had been fully vaccinated against COVID-19. However, vaccine distribution has been highly inequitable, with 45 countries having vaccinated less than 10% of their population, another 105 nations having offered a primary series (i.e., the initial two doses without boosting) to less than 40%, and 20 countries not having enough doses to vaccinate even their elderly citizens and health care workers (*15*). The COVID-19 Vaccines Global Access (COVAX) facility, founded in April 2020, was meant to ensure equitable vaccine access in LMICs, but though it had promised to deliver more than 2 billion doses globally to the neediest nations by the end of 2021, it struggled to supply even less than half of the shots promised for LMICs (*16*). COVAX initially suffered from a lack of financial support from HICs, and by the time it obtained sufficient resources, a substantial number of vaccine supplies had been claimed by HICs through direct agreements with manufacturers. Even before the trials of the current COVID-19 vaccines had been completed, many were warning about this kind of vaccine nationalism, in which HICs were signing advance purchase agreements with manufacturers for hundreds of millions of doses, restricting future access to potential vaccines by poorer countries (*17*). Although health systems constraints and vaccine hesitancy have been raised by some as key barriers in improving access to COVID-19 vaccines, these notions have been challenged by others (*18*). Other actors, including major nongovernmental organizations, the Joint United Nations Programme on HIV/AIDS, WHO, individual scientists, clinicians, and public health experts, made alternative proposals to expand access to COVID-19 vaccines, by waiving intellectual property protections, sharing technology, and expanding manufacturing capacity for COVID-19 vaccines through production hubs supported by WHO or by government-owned, contractor-operated facilities (*19*). As 2021 came to a close, these proposals were stalled, with little support from governments in HICs and resistance from the key vaccine companies that would be the required partners in technology transfer. This evident policy paralysis in the quest for global vaccine access is imperiling hundreds of millions of lives, risking the development of new variants of SARS-CoV-2, and delaying the worldwide recovery from this pandemic. As we enter the third year of COVID-19, unless there are new commitments to scale up production and access to vaccines to all who need them, we may be back again in 2023, with numerous additional and preventable deaths to answer for. Although Afrigen Biologics and Vaccines in Cape Town, part of the WHO COVID-19 vaccine technology transfer hub for the region, recently announced it has been able to copy and produce Moderna's messenger RNA (mRNA) vaccine, this was done without support from the company. However, scientists from around the world, including those from the US National Institutes of Health who were involved with the initial work on these immunogens, did assist on the project, which sped progress along (*20*). This is a small step forward. Meanwhile, BioNTech, the co-manufacturer of Pfizer's mRNA vaccine, has been accused of undermining the efforts by Afrigen and the WHO vaccine hub (*21*). If HIC vaccine manufacturers are unwilling to help scale up COVID-19 vaccines, at the very least, they have to get out of the way of others who are trying to do so.

Is vaccine hesitancy a problem?

By **Arjun Kharel**[10] *and* **Shana Warren**[11]

COVID-19 vaccine acceptance rates are generally higher in LMICs than in HICs. Studies conducted in 2020 found average acceptance rates across 24 LMICs in Asia, Africa, and South America significantly higher (80%) than in the United States (65%) and across seven HICs in Europe (74%) (*18*, *22*, *23*). This acceptance gap is consistent with attitudes toward childhood immunizations prior to the pandemic; 95% of respondents in South Asia and 92% in Africa believe vaccines to be safe, in contrast to 72% for North America, 73% for Northern Europe, and only 59% for Western Europe (*24*).

Yet LMICs are not a homogeneous bloc; there is substantial variation in vaccine acceptance rates between and within LMICs (*18*, *24*–*27*). Studies in sub-Saharan Africa, South Asia, and Latin America and the Caribbean find a higher degree of COVID-19 vaccine hesitancy among people with less education, and those who are elderly and have lower levels of trust in the health care system (*25–27*). National governments and international agencies must develop context-specific strategies to reach out to different segments of the population within and across countries in the LMICs.

Building trust and mitigating misinformation will remain pivotal to translating vaccine acceptance into uptake, and convincing hesitant segments of the population. Vaccine acceptance rates may fluctuate with every bit of misinformation and media reports of side effects or potential side effects, however small the odds of those side effects may be (*18*). Coherent messaging through trustworthy sources like local health care professionals will remain important (*18*).

As COVID-19 vaccination progresses in LMICs, there are good reasons to be optimistic about translating acceptance to uptake; 79% of Brazilians, 67% of Indians, and 64% of Indonesians have received at least one dose (*28*). Recent surveys in 19 sub-Saharan African countries have found that 78% of respondents had received or planned to receive a COVID-19 vaccination (*25*). These successes demonstrate that hesitancy is not a widespread problem in LMICs when supply is readily available.

Although vigilant efforts to track and counter misinformation to address hesitancy must continue, the data suggest that broadly speaking, vaccine acceptance rates in LMICs are sufficiently high that hesitancy should not be used as an excuse to delay or downsize vaccine shipments. If vaccine doses are being wasted within LMICs, the solution likely requires investments in the supply chain logistics, because LMIC populations are likely to take vaccines when they have access.

Overcoming last-mile vaccine delivery challenges

By **James Dzansi[12], Niccolo Meriggi[13,14], Ahmed Mushfiq Mobarak[2], Maarten Voors[15]**

Making the COVID-19 vaccine easily accessible to everyone, everywhere is the most promising solution to end this pandemic (*29*). Beyond distributing vaccines to every country based on their needs, ensuring access for every individual within each country requires investing in infrastructure for domestic distribution. Many LMICs face substantial challenges in last-mile delivery of vaccines, especially to people living in more remote, rural, low-density areas. These are the countries with deficiencies in both health system capacity and in transportation infrastructures, which jointly make it more difficult for citizens to access vaccination centers. Data that we collected in Sierra Leone show that a trip to a vaccination center for a person residing in a rural community is $6 and 1.5 hours, on average, each way. In a place where over 56% of the population lives hand-to-mouth with less than $1.25 per day, such a transportation cost is prohibitive. Thus, what may at first appear to be vaccine hesitancy and explain why doses get wasted in fact reflects the real constraints on accessibility.

Leaving remote populations unvaccinated exposes the entire world to the risk of new virus mutations. We should therefore prioritize development of creative solutions that enhance access for all LMIC citizens. The good news is that domestic distribution capabilities can be fast to establish, affordable, and cost-effective. LMICs have considerable prior experience with mass immunization campaigns that have led to high levels of childhood vaccine coverage (*18*).

Several countries, including Ghana, Liberia, India, Pakistan, and Sierra Leone, have started experimenting with the concept of "mobile vaccination teams" that take batches of vaccines closer to where people live, to make getting jabs more convenient (*30*, *31*). These can involve nurses visiting remote villages with doses, backed by community mobilizers to sensitize the local population and leaders, and gather people for efficient vaccine administration. Such models have been applied successfully in the past: "outreach clinics" to provide immunization services to hard-to-reach subpopulations are cited as an important factor in eliminating measles in The Gambia (*32*).

Such frugal innovations can be cost-effective solutions to the accessibility issue, but public health officials, researchers, and nongovernmental organizations need to further experiment with these models, to understand whether small financial incentives or other complementary services can improve efficacy (*33*). To achieve vaccine equity, supplying doses of COVID-19 vaccines to LMICs needs to be supplemented with creative efforts to reach remote, underserved areas within each country.

Optimizing vaccine dosing in pandemics

By **Denise Garrett[16], Michael Kremer[17], Helen Rees[18], Babatunde Salako[19], Firdausi Qadri[20], Witold Więcek[17]**

COVID-19 highlighted that accelerating vaccine rollout in LMICs during pandemics requires parallel, complementary investments, including vaccine distribution systems, vaccine manufacturing capacity (*34*), and more equitable systems for allocating doses based on health need. We argue that optimizing vaccine dosing can also substantially increase supply, thereby increasing vaccine equity. The strategy has also been used during global vaccine shortages; for example, one-fifth doses were recommended by WHO Strategic Advisory Group of Experts on Immunization (SAGE) and used for yellow fever (*35*) and inactivated polio (*36*) vaccines.

Vaccine developers typically optimize dosage by trading off efficacy with possible side effects, both of which may increase with higher doses. The COVID-19 pandemic created pressure to evaluate preclinical candidates and then produce high-efficacy vaccines quickly, leading to large doses being tested and adopted. Once vaccines were approved, developers faced overwhelming commercial incentives to stick with the approved formulations. Yet from a public health standpoint, during a pandemic and a vaccine shortage, there are large potential benefits from using lower

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Maasai elders don face masks at their homestead in Narok County, Kenya, 10 August 2020.

doses to save supplies, thus allowing more doses to be distributed. This could greatly accelerate vaccination, particularly benefiting those at the end of the queue (mostly people in LMICs). If further booster doses are required or if a new variant emerges against which some vaccines are ineffective, the benefit of fractional dosing would be even higher.

Several published and ongoing studies suggest that lower doses of the more effective vaccines lead to a robust immune response for both primary vaccination and boosters [for a regularly updated review of evidence on fractional dosing and list of ongoing trials see (*37*)]. For some vaccines, doses at one-quarter to one-half the level currently used may be superior to full doses of the less effective vaccines being used in some LMICs (*38*). Lowering doses may also reduce both mild side effects and the risk of serious, rare adverse events seen with these vaccines, thereby increasing vaccine acceptance. Some upper middle- and high-income countries have already authorized reduced doses for boosters and for children, and interviews with decision-makers and researchers in several LMICs suggest great interest in optimizing dosing if research confirms they are beneficial.

International and national regulators and policy-makers should review evidence from lower-dose vaccine trials and decide whether reoptimizing dosing levels (for both primary series and boosters) would likely improve public health in their context. For future pandemics, research on dosage optimization should receive early support as a global public good.

Mobile phone messaging to promote preventive behaviors

Abhijit Banerjee[21], Marcella Alsan[22], Emily Breza[23], Arun G. Chandrasekhar[24], Esther Duflo[21], Paul Goldsmith-Pinkham[25], Benjamin A. Olken[21]

Populations vulnerable to COVID-19 due to conditions of poverty and marginalization often have less access to timely, accurate, and credible information. For the first time in history, most poor people had direct or indirect access to a mobile phone during a global pandemic. This was both an opportunity and a danger: Mobile phones could be used to transmit useful public health messages to the most remote corners of the world. At the same time, individuals were potentially overwhelmed by messaging. In a survey we conducted in West Bengal, India, in May 2020, the average person had received about 20 messages on COVID-19 in the previous 2 days.

In this context, is it possible to use mobile phone messaging to convey information and promote prevention? How best to do it? Using a series of mobile phone messaging interventions across developed and developing countries, we have found that trusted messengers can induce preventive behavior change during a pandemic and are effective even in an information-rich environment or polarized climate.

Building upon prior research in Indonesia demonstrating that messages delivered by celebrities improved vaccination rates, we worked with the government of West Bengal to develop and disseminate videos that featured Nobel Laureate and West Bengal native Abhijit Banerjee discussing the importance of reporting symptoms to local health workers and social distancing (*39*, *40*). The video messages were sent via text to millions of mobile phone users across West Bengal in randomly selected small geographical areas, and preliminary results suggest the intervention had immediate and lasting effects on reports of symptoms to health workers, self-reported preventive behavior, and mobility. We then used a similar strategy in the United States, partnering with 40 physicians at the Massachusetts General Hospital's Center of Diversity and Inclusion, who recorded video messages on masking and distancing. We tested these videos in experiments involving thousands of participants recruited on online survey platforms and found that the messages affected knowledge of effective prevention, willingness to pay for masks and obtain more information, and self-reported prevention behavior (*41*, *42*).

Encouraged by these results, we sent millions of messages (by text in West Bengal, and via Facebook ads in the US) to encourage people to stay put prior to major holidays in both countries. In the US, we randomly assigned counties to different message penetrations via Facebook. We documented meaningful declines in movement (recorded by mobile phones) and COVID-19 cases in treated areas, underscoring the power of actionable, well-timed messages targeting specific behavior (*43*).

Notably, the exact content of the message, which was also randomized in the first set of experiments, did not make a considerable difference. Furthermore, even in a polarized climate, impacts were similar for all types of recipients, suggesting that specific messages by trusted messengers can still lead to meaningful change at scale.

Promoting mask wearing to reduce COVID-19 infections

By **Jason Abaluck[26], Aleksandra Jakubowski[27], Muhammad Maqsud Hossain[28], Carol Nekesa[29], Edward Miguel[4]**

Masks alone will not eliminate COVID-19 and they are not a substitute for vaccines. But when COVID-19 mortality is high and health systems are strained, masks can potentially save many lives at low cost.

A growing body of laboratory and field studies indicates that masks reduce the public health burden of COVID-19 (*44*). A randomized trial in Bangladesh found that a 29 percentage-point increase in mask use led to a 9% reduction in symptomatic infections over a 10-week period (*45*). The reductions were especially large among the elderly, among whom infections fell by 15 to 35%. But despite this evidence, some people have adopted the viewpoint that everyone will ultimately be infected—especially with highly infectious variants like Omicron—so masks are an unnecessary nuisance that will have no impact on the long-term infection rate. There are two reasons why this view is not right. First, delaying infections gives people more time to become vaccinated, a point especially critical in LMICs where vaccine distribution has been slow. Second, by reducing viral load at transmission, masks may reduce the severity of illness and risk of death when infections do occur (*46*). More generally, masking by symptomatic people may be warranted to reduce transmission of respiratory diseases other than Covid (*47*).

The costs and benefits of masks are not identical at all times and places. The benefits are larger in indoor, crowded areas with poor ventilation. Masking in schools remains complex; though children bear lower morbidity and mortality burden from Covid, masks also prevent secondary infections in the elderly. The long-term impacts of wearing masks in schools on learning are not well-understood, in addition to discomfort costs. Both in schools and elsewhere, the benefits of masking are larger during surges when many people are hospitalized or dying of Covid (and thus where fewer people are adequately vaccinated).

Given masks' low cost and relative ease of use, how can we get people to wear masks when their use is warranted? A preliminary point is that direct observation is necessary to measure mask use due to social desirability bias (*48*): in Kenya, 88% of survey respondents said they wear masks to public places but only 10% of people were observed with masks (*49*), and gaps were even larger in Uganda (*50*). People say they wear masks but promoting adoption at appropriate times is a more serious challenge.

How can we increase actual observed mask use rather than just self-reports? Preliminary findings from Africa suggest that mask distribution alone barely moved the needle on masking in Kenya (*50*) and that pairing mask distribution with education increased take-up by 3 percentage points in the short-term, with this effect fading over time (*51*). Asking people directly to wear masks in public areas led to substantially larger increases in masking in the aforementioned Bangladesh study (29 percentage points). The effectiveness of such reinforcement will of course vary across contexts due to the underlying political situation; in places where there is not active political resistance to mask-wearing, approaching people in public and asking them to put on masks is the most effective strategy to date, but important questions remain about whether this approach will continue to work after multiple waves.

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