Rethinking Global Pharmaceutical Policy

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Part II: Reforms

We arrive finally at the heart of the book. Each of the following six chapters describes a family of reform proposals – a set of ways in which policies and practices that currently shape the creation and distribution of pharmaceutical products might be revised so as to alleviate the global health crisis.

At times, exploration of these options will require us to get well down into the weeds. The reader thus might find helpful, at the outset, a map showing how the various adjustments we will discuss could work together. The rows in the following table correspond to the factors, discussed in Chapter 2, that currently prevent us from fully exploiting the potential power of drugs. The columns then show which members of each family of reforms would be useful in addressing those impediments. (The names of some of the reforms may be mysterious at this point, but they will become clear soon enough.)

	Chapter 5: Modifying Markets	Chapter 6: Differential Pricing	Chapter 7: Voluntary Licensing	Chapter 8: IP Reform	Chapter 9: Carrots	Chapter 10: Sticks
Misalignment		Managed differential pricing		Adjusting IP laws of high-income countries	Grants; Prizes	Social-responsibility index
Inaccessibility	Expediting drug approvals	Managed differential pricing	Authorized generics	Adjusting IP laws of low and middle-income countries	Conditional grants	Price regulation; Benefit sharing; Social-responsibility index
Substandard & Falsified Drugs	Surveillance		Quality control			Social-responsibility index
Pharmaceutical Hesitancy	Cultivating Receptivity		Market Shaping			Social-responsibility index

Chapter 5: Modifying Markets

(version 3.2, January 5, 2025)

Of the many tragic situations we have examined, especially galling are those in which safe and effective drugs capable of preventing or curing diseases already exist, authorized manufacturers of those drugs stand ready to sell them to the residents of all countries, and funds are available to cover such sales – and yet, for some reason, the drugs are not getting into the bodies of the people who could benefit from them. Breakdowns of this sort should not be hard to solve; we would need simply to identify the blockages and remove them. Everyone would win.

This chapter addresses opportunities of this sort. Section A considers solutions to one of the impediments discussed in Chapter 2 – delays in the processes for approving drugs for distribution. Section B discusses some technical solutions to the scourge of SFMPs. Section C explores various possible responses to the growing problem of pharmaceutical hesitancy.

Two words of caution at the outset: As will soon become apparent, elimination of these blockages proves less straightforward than one might expect. Nor could even perfect application of this strategy fully solve the health crisis. Nevertheless, many lives could be saved through adoption of the initiatives discussed here.

A. Expediting Approvals

Chapter 2 showed that one of the reasons why the residents of poor countries sometimes do not have access to the vaccines and therapies they need is that the drugs in question have not been approved by the relevant regulatory authorities. For obvious reasons, we should strive to overcome this state of affairs. To do so, we need first to identify its causes.

For some of the newer drugs, the reason is that, although the firm that developed the drug has applied for marketing approval in LMICs, the National Medicines Regulatory Authorities (NMRAs) in those countries have not granted those approvals. For a small subset of the drugs in this category, the cause is that a NMRA has reviewed the application and concluded that the data submitted by the applicant are insufficient to demonstrate that distribution to the country's residents would be safe and efficacious. For a much larger subset, the reason is that the regulatory authority in the LMIC has not yet rendered a decision.

The principal cause of the slow pace at which many of the NMRAs currently work should not be surprising: most simply lack sufficient trained staff and facilities to move faster.[1] But other forces also seem to be at work. One is the reluctance of many regulators

[1] Many studies emphasize this factor. See, for example, Live Storehagen Dansie, Walter Denis Odoch, and Christine Årdal, "Industrial Perceptions of Medicines Regulatory Harmonization in the East African

in LMICs to defer to the judgments of regulators in UICs. This in turn is attributable partly to simple nationalism, partly to suspicion (rooted in awareness that, historically, developed countries have often treated the residents of the global south as guinea pigs), and partly to the applicants' failure to submit evidence from clinical trials that realistically represent the demographic and environmental conditions in LMICs.[2]

At least occasionally, another consideration also intrudes: Aware that approval of a drug will trigger a statutory obligation on the part of the country's public-health service to buy it and then distribute it to the country's residents, the regulators deliberately tarry. This dynamic is difficult to verify, but informal reports from the officials with whom we have been working in some of these countries lend it credence.

Yet another factor compounds the slow pace of the regulatory authorities: the innovator firms sometimes wait months or years after receiving marketing authority in the United States and Europe before even applying for such authority in some developing countries. Nor once the applications are filed do the firms always pursue them with vigor; they sometimes wait months to respond to queries from the regulators.[3]

A final factor: In a surprisingly large number of cases, innovator firms never apply for marketing authorization in many developing countries. When asked why, their executives typically point to several cumulative considerations. First, the profits they could earn through sales of their products in those countries, even if marketing approval were prompt, are modest, largely because of the poverty of most of the potential purchasers. Second, the costs associated with filing and pursuing applications to the NMRAs are high, in part because they have different procedures and requirements, thus necessitating the preparation of many separate dossiers and requiring the companies to respond to idiosyncratic queries.[4] Finally, the notoriously slow pace of the approval processes in many developing countries (discussed above) shortens the interval between the commercial launch of their products and the moment when they are likely to face competition from generics, thereby further reducing their potential profits. The net effect: seeking marketing authorization in small developing countries is often not worth their while.

To summarize, the distressingly low percentage of the infectious-disease drugs approved for use in rich countries that are also approved for use in poor countries is traceable to four intertwined factors: (1) the NMRAs in poor countries sometimes refuse to approve drugs; (2) the approval process in most developing countries is slow and

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Community," *PLoS ONE* 14, no. 6 (2019).; World Health Organisation. Improving the quality of medical products for universal access. https ://www.who.int/medicines/regulation /fact-figures-qual-med/en/.

[2] See, e.g., Michelle D. Gavin, "What the African Medicines Agency Needs Most to Succeed," *Think Global Hearh* (2021).

[3] See, e.g., Vincent Ahonkhai et al., "Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization," *PLoS ONE* 11, no. 11 (2016).

[4] See, e.g., Kirti Narsai, Abeda Williams, and Aukje Kaija Mantel-Teeuwisse, "Impact of Regulatory Requirements on Medicine Registration in African Countries - Perceptions and Experiences of Pharmaceutical Companies in South Africa," *South Medical Review* 5, no. 1 (2012).

expensive; (3) pharmaceutical firms sometimes delay seeking approval in poor countries; and (4) firms sometimes do not apply for approval in some countries.

The most obvious way in which we might address this cluster of factors would be to improve the processes used by the NMRAs when assessing applications. Specifically, we could and should increase their ability to hire well-trained staff, harmonize their application requirements and procedures (thereby reducing the costs borne by pharmaceutical firms when seeking approvals in multiple countries) and, when possible, enable applicants to obtain approvals from regional agencies, rather than national ones (thereby further reducing regulatory costs).

Fortunately, reform initiatives of all of these sorts are already underway in many parts of the developing world – albeit slowly. In Africa, the establishment of an African Medicines Agency [AMA], modeled loosely on the EMA, is gradually progressing. As of this writing, 27 (of the 55) African countries have ratified the treaty underpinning the AMA, and Rwanda has been chosen as the host country. Hopes are high that some of the most populous countries (e.g., Nigeria, Kenya, and South Africa) will join, and that the agency will soon become operational.[5]

Meanwhile, many African countries have begun collaborating in regional organizations – all operating under the auspices of the African Medicines Regulatory Harmonization Initiative (AMRH) – to harmonize and improve their regulatory systems.[6]

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[5] See Sara Jerving, "Rwanda Chosen to Host the African Medicines Agency," *Devex* (2022), https://www.devex.com/news/rwanda-chosen-to-host-the-african-medicines-agency-103653.; African Union, "The African Union Holds the First Ordinary Session of the Conference of the States Parties to the African Medicines Agency (Ama) Treaty," news release, June 4, 2022, 2022, https://au.int/en/pressreleases/20220604/african-union-holds-first-ordinary-session-conference-states-parties-african; Linda Nordling, "Where Next for the African Medicines Agency?," *Research Professional News* (2022), https://www.researchprofessionalnews.com/rr-news-africa-pan-african-2022-9-where-next-for-the-african-medicines-agency/.; Muyuka Antoinette, "Ratifying the African Medicines Agency Treaty," *PATH* (2024), https://www.path.org/our-impact/articles/ratifying-the-african-medicines-agency-treaty/.

[6] The portal for the AMRH is https://www.nepad.org/programme/african-medicines-regulatory-harmonisation-amrh. The initiative is a programme of the African Union and has been funded and guided by a host of international organizations: Pan-African Parliament (PAP), World Health Organization (WHO), Bill and Melinda Gates Foundation, World Bank (WB), UK Department for International Development (DFID) and US Government-PEPFAR and the Global Alliance for Vaccines and Immunization (GAVI). See Bakani Mark Ncube, Admire Dube, and Kim Ward, "Establishment of the African Medicines Agency: Progress, Challenges and Regulatory Readiness," *Journal of Pharmaceutical Policy and Practice* 14 (2021). For reports on the progress of the initiative, see Alexander R. Giaquinto et al., "Improving Access to Quality Medicines in East Africa: An Independent Perspective on the East African Community Medicines Regulatory Harmonization Initiative," *PLoS Med* 17, no. 8 (2020); Jane H. Mashingia et al., "Eight Years of the East African Community Medicines Regulatory Harmonization Initiative: Implementation, Progress, and Lessons Learned," ibid. Among its fruits is the African Union Model Law on Medical Products Regulation, which has now been adopted in twenty-five countries. See *AU Model Law on Medical Products Regulation*, NEPAD, https://www.nepad.org/publication/au-model-law-medical-products-regulation (last visited Oct. 14, 2021). For a summary of the model law, see INCREASING ACCESS TO HIGH-QUALITY, SAFE HEALTH TECHNOLOGIES ACROSS AFRICA: AFRICAN UNION MODEL LAW ON MEDICAL PRODUCTS REGULATION, AUDA-NEPAD, https://path.azureedge.net/media/documents/APP_au_model_law_br.pdf (last visited Oct. 14, 2021). For recommendations concerning its implementation at both national and regional levels, see IMPLEMENTING THE AFRICAN UNION MODEL LAW AT THE REGIONAL AND NATIONAL LEVEL,

The process has proceeded most rapidly in the East African Community (EAC), but not far behind is the Southern African Development Community (SADC).[7] The dimensions of improvement include: harmonizing technical requirements and guidelines for applications and conducting at least portions of the review processes on regional, rather than national, levels.[8] Two benefits of the harmonization are already apparent: the average time for regulatory approvals has dropped, and the costs to pharmaceutical firms of obtaining approvals in multiple national markets is declining.[9]

In Latin America, there is, as yet, no counterpart to the African Medicines Agency. However, harmonization and collaboration analogous to those organized by the AMRH are proceeding under the auspices of the Pan American Network for Drug Regulatory Harmonization [PANDRH], established in 1998 by the Pan American Health Organization [PAHO]. Through its leadership, the national NMRAs in Latin America have exchanged technical documents, shared training programs, and are moving (haltingly) toward consistent use of the Common Technical Document. AVISA, the MNRA for Brazil, is now sophisticated, and the agencies for the other five designated "regulatory authorities of regional reference" (Argentina, Chile, Colombia, Cuba, and Mexico) are not far behind. But the national and regional agencies for the smaller and poorer countries (including Bolivia, considered in Chapter 2), lag.[10]

Among the LMICs in Southeast Asia, harmonization and modernization have proceeded further, in large part because of a series of initiatives under the auspices of the Association of Southeast Asian Countries [ASEAN].[11] Since 1997, a Pharmaceutical Product Working Group, chaired by Malaysia, has catalyzed the adoption of a regional

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NEPAD, https://path.azureedge.net/media/documents/Implementing_the_AU_Model_Law_brief_October_2016.pdf (last visited Oct. 14, 2021).

[7] See Mawien Arik et al., "Optimizing the East African Community's Medicines Regulatory Harmonization Initiative in 2020–2022: A Roadmap for the Future," *PLOS Medicine* 17, no. 8 (2020).; Tariro Sithole et al., "Evaluating the Success of Zazibona, the Southern African Development Community Collaborative Medicines Registration Initiative," *Therapeutic Innovation & Regulatory Science* 54 (2020).; Tariro Sithole et al., "Evaluation of the Good Review Practices of Countries Participating in the Southern African Development Community: Alignment and Strategies for Moving Forward (Part 1)," *Frontiers in Medicine* 8 (2021): 2; "Evaluation of the Review Models and Approval Timelines of Countries Participating in the Southern African Development Community: Alignment and Strategies for Moving Forward (Part 2)," *Frontiers in Medicine* 8 (2021).

[8] See Margareth Ndomondo-Sigonda et al., "The African Medicines Regulatory Harmonization Initiative: Progress to Date," *Medical Research Archives* 6, no. 2 (2018).

[9] See, e.g., ibid.; Scofield, Ian (2017) African Regulatory Harmonization Project Cuts Drug Approval Times and Saves Scarce Resources, https://pink.pharmamedtechbi.com/PS119932/African-Regulatory-Harmonization-Project-Cuts-Drug-Approval-Times-And-Saves-Scarce-Resources; Hiiti Sillo et al., "Coming Together to Improve Access to Medicines: The Genesis of the East African Community's Medicines Regulatory Harmonization Initiative," *PLoS Med* 17, no. 8 (2020).

[10] An extensive review of the progress and limitations of these various initiatives can be found in PAHO, "Regulatory System Strengthening in the Americas: Lessons Learned from the National Regulatory Authorities of Regional Reference," (2022). For a briefer treatment, see Adam Istas, "Regulatory Convergence and Harmonisation Activities in Latin America," *Journal for Clinical Studies* 11, no. 4.

[11] The member countries of the association are Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Viet Nam.

Common Technical Dossier and substantially reduced differences among both the substantive requirements and the procedures employed by the MNRAs of the ten countries. Recently, "joint assessment projects," in which multiple MNRAs within the association evaluate a particular drug simultaneously and collaboratively, have both reduced the burdens born by applicants and improved the quality of the evaluations conducted in the poorer countries.[12] Partly as a result, the approval processes typically take less time in ASEAN countries than in African countries.[13]

All of these initiatives are moving in the right direction, albeit at moderate speed. If possible, we should pick up the pace. For the most part, responsibility for acceleration lies with the governments of developing countries. One relatively easy step they might take would be to charge applicants higher fees. The various LMIC MNRAs currently vary considerably in the degrees to which they are dependent on general government revenues or application fees to fund their operations.[14] But even those that rely entirely on fees typically charge applicants far less than their counterparts in UICs. In Latin America, for example, the fees currently charged by the six National Regional Authorities of Regional Reference for processing applications for new pharmaceutical products are far below the fees charged in the United States.[15]

Figure 2: Application Fees in Latin American Countries

	New Product Fee (USD)	New Product Fee (USD) per 100,000 population	Proportion of the agency's budget derived from user fees
FDA (USA)	2,942,965	873	
ANVISA (Brazil)	58,709	27	50%
INVIMA (Colombia)	9,773	19	100%
COFEPRIS (Mexico)	7,429	6	32%
CECMED (Cuba)	2,620	23	36%
ISP (Chile)	1,359	7	54%
ANMAT (Argentina)	645	1	100%

In light of the reluctance that the firms have already shown to seek marketing authorization in LMICs, it might seem perverse to advocate increasing the fees they would

[12] For a detailed study of the initial stages in this process, see Ruth Lätzel, "Development of the Asean Pharmaceutical Harmonisation Scheme: An Example of Regional Integration" (Rheinischen Friedrich-Wilhelms-Universität Bonn, 2007). For briefer discussions of the current status of the harmonization process, see Ming Xu et al., "Regulatory Reliance for Convergence and Harmonisation in the Medical Device Space in Asia-Pacific," *BMJ Global Health* 7 (2022); Valerio Reggi, "Regulatory Reliance for Convergence and Harmonisation in the Medical Device Space in Asia-Pacific," *Med Access @ Point Care* 1, no. 1 (2017); Sannie Siaw Foong Chong et al., "Asia Partnership Conference of Pharmaceutical Associations (Apac) Report on Regulatory Agility Implemented during the Covid-19 Pandemic: Inspiring Partnerships and Recommendations for the Way Forward," *Therapeutic Innovation & Regulatory Science* (2022).

[13] See Abhishek Tongia, "The Drug Regulatory Landscape in the Asean Region," *Regulatory Focus* (2018).

[14] See Margareth Ndomondo-Sigonda et al., "Medicines Regulation in Africa: Current State and Opportunities," *Pharm Med* 31 (2017): 390-91.

[15] Source: PAHO, "Regulatory System Strengthening in the Americas," 15, 39.

need to pay. However, representatives of pharmaceutical firms commonly express a willingness to pay higher fees "to fund a system that is robust, predictable, accountable, and transparent, with a single point of contact."[16] A possible way of capitalizing on their willingness would be to quantify the dimensions on which they wish to see improvement in the MNRA's processes and then to deposit a portion of each (increased) application fee into an escrow account. If the agency achieved the targets within a prescribed period, it would collect the money; if not, the applicant would get it back. The obvious advantage of this strategy would be to increase the amounts that the agencies could use to hire, train, and retain the staff that they so desperately need.

Other players in the pharmaceutical industry could also help upgrade the MNRAs. For example, institutional donors could increase their contributions. Many governments and NGOs have already contributed substantial amounts of money and expertise to accelerate the harmonization initiatives summarized above. The contributors include the World Health Organization, the World Bank, the Gates Foundation, the European Union, several individual European countries, and the African Union.[17] They could do even more – in particular, by increasing funding for regional initiatives.

The regulatory agencies in UICs could also help. Already, the EMA and FDA offer training programs for staff members of the developing-country NMRAs; they could increase the scale of those programs.

The pharmaceutical firms could also contribute. One way in which a firm could provoke improvement in the regulatory process would be to commit to offering a discount on the price it charged for a particular drug if marketing approval were forthcoming within a specific time period. Among other things, this would mitigate the reluctance of some LMIC MNRAs to add to the list of drugs that the ministries of health must purchase and distribute. (We'll return to this controversial option in Chapter 6.)

The World Health Organization is another crucial actor in this ecosystem. The WHO already runs three related programs intended to assist the NMRAs of LMICs to process applications accurately and expeditiously. The best known is the "prequalification" program [PQP], first launched in 2001. Under its auspices, WHO scientists assess the safety and efficacy of drugs, using data submitted to the agency by pharmaceutical firms using standardized applications, and issue reports of their findings. The WHO's assessments are widely considered highly accurate. Thus, although they are not legally binding on any party, they are frequently relied upon by LMIC MNRAs, procurement agencies, and donors. More recently, the WHO has launched two "collaboration" programs, designed to provide additional assistance to participating MNRAs. Under the "Collaborative Registration Procedure" [CRP], a participating

[16] Arik et al., "Optimizing the East African Community's Medicines Regulatory Harmonization Initiative in 2020–2022: A Roadmap for the Future," 9.

[17] See Sithole et al., "Evaluation of Review Models, Part 2," 1324.; Victoria Palmi Reig, Béatrice Durvy, and Martin Harvey Allchurch, "Eu Mobilizes Cooperation with the African Medicines Agency," *DIA Global Forum* (2022), https://globalforum.diaglobal.org/issue/july-2022/eu-mobilizes-cooperation-with-the-african-medicines-agency/.; Mashingia et al., "Eight Years of the East African Community Medicines Regulatory Harmonization Initiative: Implementation, Progress, and Lessons Learned."

pharmaceutical firm submits to a participating MNRA exactly the same dossier that it previously submitted to the WHO to secure prequalification. The MNRA officials are able to rely upon that information (confident that it has already been deemed adequate by the WHO), and in addition are encouraged to consult informally with the WHO when making their own assessments of the suitability of the drug at issue for their own country's population.[18] The "SRA Collaborative Registration Procedure" [SRA CRP] provides a similar channel to assist LMIC MNRAs when assessing drugs previously approved by one of the "stringent" national or regional regulatory authorities (typically the agencies of major UICs)[19] that meet public health needs even if they do not meet the criteria for WHO prequalification.[20]

All of WHO's initiatives are commendable, but they are not comprehensive. Because the prequalification procedure is limited to drugs that are on the WHO's Essential Medicines List or that are recommended in WHO treatment guidelines, it cannot be used to accelerate deployment of most novel drugs. More generally, the prequalification process is costly and lengthy, especially for vaccines and generics.[21] The potential reach of the CRP is even more limited. The potential reach of the SRA CRP is much broader, but thus far it has been used infrequently. As of 2021, only 88 SRA-CRP applications had been submitted and only 59 approved. Most pertained to HIV, malaria, contraception, or hemophilia.[22] Of the SRAs, only the EMA and the regulatory agency of the United Kingdom have been active participants.

The solutions to these limitations seem straightforward: the WHO should expand the scope of its prequalification procedure; publicize the availability of the two collaborative registration procedures to LMICs; and encourage additional SRAs (including the FDA in the United States) to participate more actively in the SRA CRP. The FDA, in turn, should step up.

In combination the set of reforms outlined above would increase substantially the sets of efficacious drugs available to the residents of poor countries. Everyone, including the pharmaceutical firms, would benefit.

B. Surveillance

Like rats in cities (or endemic viruses), SFMPs (substandard and falsified medical products) are probably impossible to eliminate completely. But we can and should reduce the number. One promising tactic would be to examine drugs periodically during their

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[18] See Stefanie Haas, "The Who Collaborative Registration Procedure for Medicines in Developing Countries" (Rheinischen Friedrich-Wilhelms-Universität Bonn, 2015).

[19] The procedure for identifying these "stringent regulatory authorities" and a list of the current members of the group is available at https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs.

[20] See Alexandra Vaz et al., "Who Collaborative Registration Procedure Using Stringent Regulatory Authorities' Medicine Evaluation: Reliance in Action?," *Expert Review of Clinical Pharmacology* 15, no. 1 (2022).

[21] See Ahonkhai et al., "Speeding Access to Vaccines and Medicines," 5-6.; Mary Moran et al., "Registering New Drugs for Low-Income Countries: The African Challenge," *PLoS Med* 8, no. 2 (2011).

[22] See Vaz et al., "Sra Collaborative Registration Procedure," 12.

journeys from manufacturers to patients, thus enabling us to identify the bad versions when they appear and then to purge them. Many systems that would enable surveillance of this sort already exist, and more are in the offing. The challenge is to develop adaptations of one or more of these systems that would work throughout the world.

The existing and foreseeable systems fall into two broad categories. Systems of the first type rely on verifying the authenticity of the drugs that, at the end of the chain, are delivered to consumers. In simple variants of this approach, manufacturers embed visible or "scratchable" codes in their packages. The ultimate purchaser of a packet uses his or her cell phone to transmit an image of the code to the manufacturer and receives, in response, a text message indicating whether its contents are authentic. Systems of this sort include Sproxil (developed in Nigeria) and Pharmasecure (developed in Nigeria and India).[23]

Far more complex and effective members of this category are the comprehensive "track and trace" systems that, since the turn of the century, have been established in many jurisdictions. In such regimes, an authorized manufacturer of a properly registered product assigns a unique identifier to every package it produces and sells – a process known as "serialization." Thereafter, every wholesaler, distributor, and dispenser who has custody of the package records when and from whom it was acquired and when and to whom it is transferred. In some systems, those intermediaries also record the conditions under which the package was stored when in their possession. If all goes well, this process ensures that each package finally delivered to a patient is what it purports to be.

The United States is currently in the late stages of deploying a system of this sort. When fully operational, every manufacturer of a pharmaceutical product distributed in the U.S. will be obliged to attach a durable "Product Identifier" (PI) to every unit of the product it sells. Each PI will contain an expiration date, lot number, and "standardized numerical identifier." All intermediaries ("trading partners") will be required to use those PIs to "validate" every shipment they receive. All transactions must be recorded in a standardized electronic format – thereby making it possible to "track" every unit as it moves from manufacturer to customer. Equally important, retention of those records makes it easy to "trace" the series of hands through which any packet has previously passed. Comprehensive "traceability," in turn, will make it possible to identify (and then quarantine) drugs that have entered the chain through illicit channels.[24]

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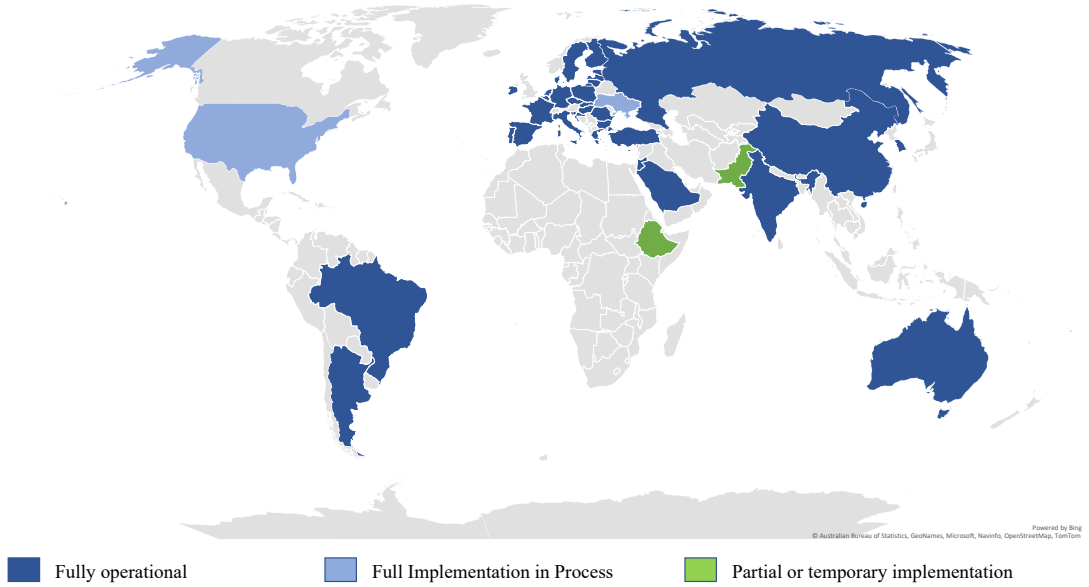
[23] *See* Huma Rasheed, Ludwig Höllein, and Ulrike Holzgrabe, "Future Information Technology Tools for Fighting Substandard and Falsified Medicines in Low- and Middle-Income Countries," *Frontiers in Pharmacology* 9 (2018): 3; Matthew Wall, "Counterfeit Drugs: 'People Are Dying Every Day'," *BBC News*, September 26, 2016 2016.; Jennifer Kite-Powell, "Pharmasecure Uses Mobile Device and Id Codes to Take on Counterfeit Drug Problem," *Forbes*, February 16, 2012.

[24] For a detailed description of the obligations of all of the members of the distribution chain, see U.S. Food and Drug Administration, "Are You Ready for the Drug Supply Chain Security Act," January 19, 2022, available at https://www.fda.gov/drugs/drug-supply-chain-security-act-dscsa/are-you-ready-drug-supply-chain-security-act. Access to the formal Draft Guidance advising companies of their obligations can be obtained through https://www.federalregister.gov/documents/2022/07/06/2022-14342/drug-supply-chain-security-act-standards-for-the-interoperable-exchange-of-information-for-tracing. Descriptions and assessments of the emerging system include Elona Gjini and Albert I. Wertheimer, "Review of Drug Quality and Security Act of 2013: The Drug Supply Chain Security Act (Dscsa)," *Innovations in Pharmacy* 7, no. 3 (2016).

The development of this system has been onerous and expensive. The 2013 Drug Supply Chain Security Act, which launched the initiative, gave the FDA 10 years to implement it. The deadline was recently pushed back to November 27, 2024. As of this writing, uncertainty concerning how the new system will mesh with extant licensing requirements and how small-scale dispensers of drugs will be integrated into the system suggest that full deployment is not imminent.[25]

In many other countries and regions, similar "track and trace" systems are either already operational or will soon become so. The map on the following page shows the locations of the principal programs.[26]

Figure 3: "Track and Trace" Systems



Unfortunately, the systems adopted by the various countries and regions differ significantly in both architecture and rules. For example, India, Brazil, China, and the European Union currently use a "Point-of-Dispense Verification" approach, in which intermediaries are not required (at least in the absence of "cause") to record transactions.[27] That approach is less burdensome but also less robust than the comprehensive regimes already in place in Turkey, Russia, and Saudi Arabia and soon to be implemented in the United States and Brazil.[28] Another example: in the Chinese system, inclusion of the

[25] See Joseph T. Kannarkat, Michael W. Denham, and Ameet Sarpatwari, "Improving Drug Supply Chain Security," *JAMA Health Forum* 5 (2024).

[26] The data underlying locations and classifications of the systems were derived from: https://vertassets.blob.core.windows.net/image/d9999998/d9999998-6807-4356-852d-902ef3e9453d/_kztyrworldmap.pdf;

[27] See Joeke Kootstra and Tineke Kleinhout-Vliek, "Implementing Pharmaceutical Track-and-Trace Systems: A Realist Review," *BMJ Global Health* 6 (2021).

[28] See ICMRA, "Recommendations on Common Technical Denominators for Traceability Systems for Medicines to Allow for Interoperability," (2021), 19, 32-34.; Michael Pisa and Denise McCurdy, "Improving Global Health Supply Chains through Traceability," (Washington, D.C.: Center for Global Development, 2019), 15.

expiration date and batch number in the product identification information is optional, not mandatory.[29] With respect to aggregation, again the EU is lenient, requiring serialization only at the unit level; by contrast, India requires the application of unique ID numbers, not just to individual units, but also to the larger bundles that are typically used to ship products.

Because, for the reasons we have seen, a large percentage of pharmaceutical markets move across national borders, differences of these sorts both increase the costs borne by all parties of complying with the requirements and can undermine the ability of distributors and dispensers in one country to determine the provenances of drugs manufactured in another country.[30]

Efforts are currently underway to increase interoperability among the various systems. For example, a consortium of manufacturers, MNRAs, and NGOs recently released a report outlining a set of features that, if shared by all systems, would augment their compatibility; the World Health Organization issued a similar call.[31] Most likely, the coming decades will witness a process of harmonization of the "track and trace" systems analogous to (and just as slow as) the process described in the preceding section in which the drug-approval processes of individual countries are converging.

Systems of the second type rely, not upon verifications of authenticity, but instead upon testing the chemical composition of medicines at various points in the distribution chain. The most reliable of the technologies employed for this purpose is High-performance liquid chromatography ("HPLC"). Because of its complexity, HPLC testing must be done by trained personnel in laboratories.[32] Somewhat less complex and more portable is the "MiniLab," developed in the 1980s by the Global Pharma Health Fund (and subsequently updated periodically).[33] Some relatively new systems of this type use a combination of portable scanners (relying on Raman, near-infrared, or Fourier-transform Infrared ("FTIR") spectroscopy) and portable digital libraries (containing the spectral profiles of authenticated drugs) to determine, in the field, whether pills contain the

[29] See ICMRA, "Recommendations on Common Denominators," 22.

[30] See Pisa and McCurdy, "Improving Health Supply Chains," 16.

[31] See ICMRA, "Recommendations on Common Denominators."; WHO, "Policy Paper on Traceability of Medical Products," (2021).

[32] For a description of HPLC technology and its suitability to poor countries, see Ludwig Hoellein and Ulrike Holzgrabe, "Development of Simplified Hplc Methods for the Detection of Counterfeit Antimalarials in Resource-Restraint Environments," *Journal of Pharmaceutical and Biomedical Analysis* 98 (2014).

[33] *See, e.g.,* Ifeyinwa Fadeyi et al., "Quality of the Antibiotics—Amoxicillin and Co-Trimoxazole from Ghana, Nigeria, and the United Kingdom," *American Journal of Tropical Medical Hygiene* 92 (2015).(comparing HPLC testing and the MiniLab); Gesa Gnegel et al., "Surveillance for Substandard and Falsified Medicines by Local Faith-Based Organizations in 13 Low- and Middle-Income Countries Using the Gphf Minilab," *Scientific Reports* 12 (2022).; Stephanie Kovacs et al., "Technologies for Detecting Falsified and Substandard Drugs in Low and Middle-Income Countries," *PLoS ONE* 9, no. 3 (2014): 8-9.; Albert Petersen, Nadja Held, and Lutz Heide, "Surveillance for Falsified and Substandard Medicines in Africa and Asia by Local Organizations Using the Low-Cost Gphf Minilab," *PLOS ONE* 12, no. 9 (2017).

ingredients they purport to contain.[34] Finally, a few portable systems rely on paper chromatography.[35]

Type-1 systems dovetail with intellectual-property law. In other words, they facilitate detection of pills that have been produced or distributed by companies lacking legal rights to do so. Their capacity to ensure that the drugs delivered to patients are up to par are thus dependent upon the quality-control measures that the authorized manufacturers employ. Type-2 systems instead determine whether tested medicines have the right amount of active ingredients (and are uncontaminated by unwanted substances), regardless of whether they have been lawfully manufactured.

In most instances, the two approaches will lead to the same results, but not always. Most importantly, drugs that are safe and efficacious but unauthorized (for example, because they were produced by a generic manufacturer that lacks marketing approval in the jurisdiction in question) are more likely to be detected (and purged) by Type-1 systems, whereas authorized drugs that have degraded (for example, because of improper storage) are more likely to be detected (and purged) by Type-2 systems. Thus, other things being equal, the former is somewhat better for pharmaceutical firms, while the latter is somewhat better for patients.

Comprehensive Type-1 systems have proven to be highly effective. One of the first systems of this sort was launched in Turkey. It has resulted in dramatic declines in the incidence of SFMPs in that country. Additional benefits of Type-1 systems include: curbing reimbursement fraud (the principal objective of the regime in Turkey); enabling rapid recalls of bad batches (using the "tracking" function); and improved inventory management.[36]

Unfortunately, successful implementation of a Type-1 regime requires three things. First, substantial financial resources. The technology required for unit-level serialization is expensive, as are the devices used by intermediaries and dispensers to track those units. Next, the willingness and ability of all intermediaries and dispensers in the jurisdiction to

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[34] See Kovacs et al., "Technologies for Detection," 8.; Lukas Roth et al., "Global Landscape Assessment of Screening Technologies for Medicine Quality Assurance: Stakeholder Perceptions and Practices from Ten Countries," *Globalization and Health* 14 (2018).; Tomoko Kakio et al., "Survey to Identify Substandard and Falsified Tablets in Several Asian Countries with Pharmacopeial Quality Control Tests and Principal Component Analysis of Handheld Raman Spectroscopy," *American Journal of Tropical Medicine and Hygiene* 98, no. 6 (2018). An example of a venture using this approach is RxAll, which currently has preliminary deployments in five other African countries). *See*, *e.g.*, Eillie Anzilotti, "'This Startup Built a Device to Figure out If Prescription Drugs Are Fake," *Fast Company*, https://www.fastcompany.com/90323372/this-startup-built-a-device-to-figure-out-if-prescription-drugs-are-fake.; *Instant Drug Testing*, RXALL, https://www.rxall.net. (last visited Oct. 14, 2021).

[35] See Hui-Han Chen et al., "Cost Savings of Paper Analytical Devices (Pads) to Detect Substandard and Falsified Antibiotics: Kenya Case Study," *Medicine Access @ Point of Care* 5 (2021); Yusuke Hattori et al., "Device-Independent Discrimination of Falsified Amoxicillin Capsules Using Heterogeneous near-Infrared Spectroscopic Devices for Training and Testing of a Support Vector Machine," *Applied Spectroscopy* 75, no. 10 (2021): 1252.

[36] See Parmaksiz, Koray. "Political and Economic Drivers of Medicine Quality: Main Drivers of Success of the Pharmaceutical Track and Trace System in Turkey." July 2018. Thesis, Vrije Universiteit Amsterdam.

participate. Finally, the capacity of the national or regional regulatory authorities to monitor compliance and to enforce the rules of the road. The magnitude of these requirements helps explain why most of the countries shown in Figure 3 in which Type-1 systems are either already operational or under construction are either UICs or upper-middle-income countries.

Type-2 systems have fewer benefits, but are far less expensive and are much easier to deploy incrementally. For the near future, therefore, most LMICs will be obliged to rely on the second approach.

As indicated above, a variety of technologies could be employed to construct a Type-2 system. None is ideal. The most accurate (HPLC) is expensive and slow. The most portable and inexpensive (the paper-based systems) are unreliable.

Our view is that, on balance, the best of the currently available technologies for use as the primary line of defense in low and middle-income countries is near-infrared (NIR) scanning. Each scanner is moderately expensive (roughly 800 USD), but is capable of testing an enormous number of drug samples. (No one knows for sure, but a common estimate is 40,000.) The smartphone that houses the software necessary to drive the system and the library of the spectral profiles of authorized drugs costs roughly 200 USD – bringing the total cost of a system to 1000 USD. Testing requires no reagents or other supplies, and can be done without destroying or degrading the samples. Thus, despite the substantial upfront cost, the average cost of a test is very low. Conducting a test requires only a few minutes. Most importantly, if kept up to date, an NIR system is remarkably accurate. Many comparative studies have now been conducted of the various Type-2 technologies. All of them rate the NIR technology highly.[37]

Relying on those studies, we have been collaborating with some other institutions to deploy pilot projects employing NIR technology in two countries: Namibia and Malawi. Our own contributions to this venture have been made under the auspices of Global Access in Action, a research program at Harvard University.[38] The other institutions with whom we have been working are: Global Good (an NGO funded by Bill Gates that originally developed the technology used in the system); the Mission for Essential Drugs and Supplies (MEDS), a faith-based organization in Nairobi that distributes medicines throughout East Africa, which has assumed now responsibility for refining and managing the system); Innospecta, the manufacturer of the scanners; the Ministry of Health and Social Services

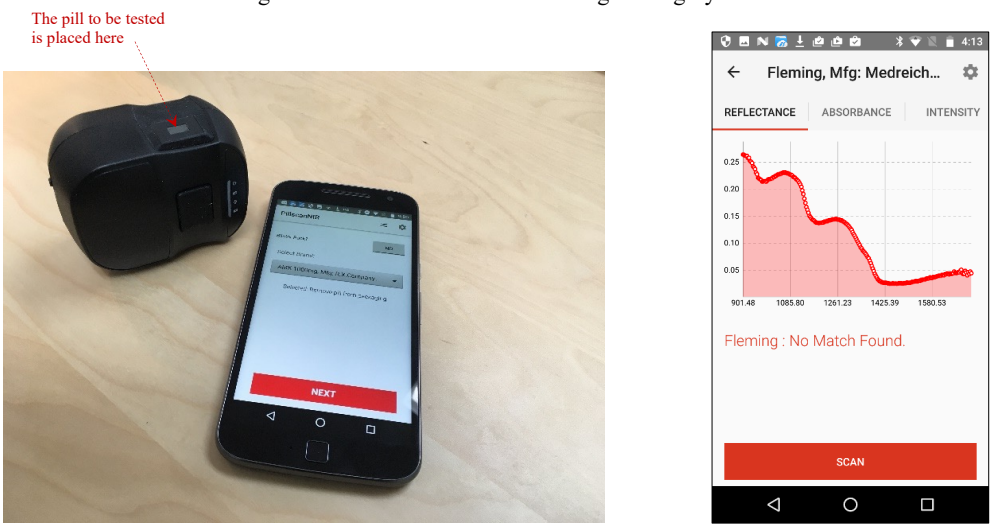
[37] See Nantasit Luangasanatip et al., "Implementation of Field Detection Devices for Antimalarial Quality Screening in Lao Pdr—a Cost-Effectiveness Analysis," *PLOS Neglected Tropical Diseases* 15, no. 9 (2021): 12-13.; P.H. Ciza et al., "Comparing the Qualitative Performances of Handheld Nir and Raman Spectrophotometers for the Detection of Falsified Pharmaceutical Products," *Talanta* 202 (2019): 477.; Wenbo Wang et al., "Evaluating Low-Cost Optical Spectrometers for the Detection of Simulated Substandard and Falsified Medicines," *Applied Spectroscopy* 74, no. 3 (2020): 332.; Stephanie Kovacs et al., "Technologies for Detecting Falsified and Substandard Drugs in Low and Middle-Income Countries," *PLoS ONE* 9, no. 3 (2014): 8, 10.; Moussa Yabré et al., "Detection of Falsified Antimalarial Sulfadoxine-Pyrimethamine and Dihydroartemisinin-Piperaquine Drugs Using a Low-Cost Handheld near-Infrared Spectrometer," *Journal of Analytical Methods in Chemistry* 2022 (2022): 6.

[38] Information concerning Global Access in Action is available at https://globalaccessaction.org.

of Namibia; the Pharmacy, Medicines and Poisons Board of Malawi; the London School of Hygiene and Tropical Medicine; the Infectious Diseases Data Observatory; and most recently the World Health Organization.

A photograph showing one of the scanners used in this system and its associated smartphone appears on the left side of Figure 4, below. To test a pill, the operator removes it from the container (typically a box or jar) in which it was delivered, places it on the small translucent window located on the top of the scanner, uses the software housed in the phone to select from a menu the product that the pill purports to be, and touches a button labelled, "Scan." Less than 10 seconds later, the screen of the smartphone shows the result. If the spectral profile generated by the scan matches the profile (contained in the smartphone's database) of an authenticated version of the product in question (within the tolerances permitted by the software), that result is "Match Found." If not, the screen informs the operator (using a red font): "No match found."

Figure 4: PillScan Near-Infrared Drug Testing System



In either event, the operator then uses the camera of the smartphone to take a photograph of the label on the container from which the pill was taken. A geotagged and time-stamped copy of that photograph is associated with the data generated by the scan and recorded by the phone. To minimize opportunities for corruption, the operator cannot delete or alter any of this data. When the operator returns to a location with access to the Internet, the data is uploaded to a central database.[39]

In 2019, we accompanied government inspectors, first in Namibia and then in Malawi, on unannounced surveillance trips in which they used these devices to conduct

[39] A more detailed description of this procedure in contained in the Operating Manual for the system, which is available at ____.

random samples of drugs on the shelves of urban hospitals and rural pharmacies. The devices performed well – and brought to light one batch of degraded cancer drugs.

To be sure, technology of this sort will do little good unless it is deployed as part of a comprehensive testing protocol. At the request of the Namibia Medicines Regulatory Council, we prepared such a protocol. An abridged version is set forth on the opposite page.[40]

[40] A complete version is available at ____.

Figure 5:

Standard Operating Procedure for Device Use and Data Collection and Management
April 2018

1. Use of the Devices

1.1. The Devices should be deployed at points of maximum supply chain vulnerability to penetration by falsified medicines.

1.1.1. Officials in the NMRC are in the best position to locate those points. Examples may include ports of entry, warehouses that collect significant quantities of medicines, health facilities that obtain medicines from multiple sources, or remote community pharmacies. …

1.2. Devices should be used only by persons ("Users") who have received training from Global Good or the Namibia Medicines Regulatory Council ("NMRC") in their correct use and storage.

1.2.1. Upon successful completion of this training, each User will receive a unique ID number, which he or she should include in all written reports associated with scans that result in "No Match Found" determinations….

2. Management of Suspected Falsified Medicines

2.1. When the scan of a pill results in a "No Match Found" determination, the scanned pill should be placed in a plastic bag along with a completed User Form filled out by the User who performed the scan. The User should then add to the bag an appropriate number of additional pills from the same batch to ensure that the laboratories doing confirmatory testing have a sufficient number of samples. ….

2.2. The NMRC should arrange for additional testing to eliminate user or Device error and confirm that a sample is, in fact, falsified. The optimal sequence of confirmatory testing is as follows:

2.2.1. The sample should be subjected to a second NIRS scan at the NMRC Laboratory to ensure that the scan performed in the field was not an aberration.

2.2.2. If the second NIRS scan also results in a "No Match" determination, then the sample should be subjected to HPLC testing at the NMRC Laboratory.

2.2.3. If the HPLC test indicates that the sample fails to meet the applicable quality standard, then the sample must be forwarded to MEDS for further testing. …

2.2.4. If the third NIRS scan also results in a "No Match" determination, then the sample should be subjected to HPLC testing at MEDS.

2.3. The NMRC should establish, promulgate and periodically review a Quarantine Policy….

2.4. Once a medicine is confirmed to be falsified, its distributors and suppliers should be instructed to cease its distribution and supply. Site inspections should be conducted to ensure compliance with this provision. Individuals who continue to distribute or supply confirmed falsified medicines should be informed of the legal consequences of their actions, and their licenses may be suspended or revoked in accordance with the Medicines and Related Substances Control Act 2003.

2.5. …. If the source of the medicine is a supplier known to the NMRC, this supplier should be removed from national tender lists.

2.6. Confirmed falsified medicines should be reported to the drug regulatory authority of the country of origin stated on the label of the falsified product.

The fate of this particular system remains uncertain. The onset of the COVID-19 pandemic forced suspension of the two pilot projects in Namibia and Malawi. We are now in the process of attempting to restart those programs and are currently in discussions with representatives of other subSaharan African countries concerning potential deployments in their jurisdictions. Meanwhile, the World Health Organization determined that the fruits of the initial tests of the system were sufficiently impressive that it commissioned MEDS to conduct training programs in several Schools of Pharmacy in Africa. The result is that many members of the next generation of pharmacists will be ready to deploy it.

Regardless of the fate of this particular initiative, an LMIC lacking a "track-and-trace" system would be well advised to adopt a chemical-testing regime of this general sort. The cost of instituting such a regime would of course vary with the size of the country's population, but in any event would be small in proportion to the country's overall public-health budget and could be deployed in a few months. The technology and the software already exist. The only significant hurdles would be training the inspectors and crafting a protocol like the one summarized in Figure 5.

Such a regime would not only enable the inspectors to detect many SFMPs and prevent them from reaching consumers, but would also facilitate identification of the manufacturers of those products and the channels through which the products are entering the distribution chain – which in turn would help the governments purify the tender process and the networks of distributors. The net result: many lives would be saved and much misery could be avoided.

Manufacturers of legitimate drugs would also plainly benefit from a systematic chemical-testing regime. Awareness of that potential benefit should prompt the manufacturers to lend a hand in creating one. They could do so in at least two ways. First, they could donate to LMICs the funds necessary to acquire the NIR scanners and the associated smartphones. Second, each time a manufacturer produced a new batch of a drug, it could provide the organization charged with maintaining the library of authenticated spectral profiles (e.g., MEDS in the PillScan system) a profile of a pill representative of the new batch. That would considerably reduce the logistical burdens borne by the organization and enable more rapid updating of the library.

This concludes our analysis of Type-2 surveillance systems. As indicated above, a Type-1 ("trace-and-trace") system would be even better at eliminating SFMPs. The fact that, in the short term, the cost and complexity of a Type-1 system place it beyond the means of most LMICs does not mean that the interests of LMICs should not be taken into account when designing them. As we have noted, consortia of UIC governments and pharmaceutical firms are currently working to harmonize their regimes through the identification of common technologies and protocols. Unfortunately, LMICs currently have little or no voice in the harmonization process. The reason this exclusion matters is that modest adjustments in the technologies and protocols chosen might make it considerably easier for LMICs in the long term to avail themselves of the emerging global regime. Examples of issues in which LMICs have a stake follow:

- *Technology*. For obvious reasons, LMICs would prefer a system that relied as much as possible upon existing, widely distributed devices (e.g., smartphones) to one that used bespoke devices (like the customized scanners employed Hong Kong).[41]
- *Connectivity*. Limitations on the reliability and geographic scope of broadband access in most LMICs[42] would put a premium on a track-and-trace system that either allows the data generated by intermediaries and rural pharmacies to be uploaded through a low-bandwidth network or enables the data to be stored by those parties until broadband service is available. Those same limitations would likely make it difficult for LMICs to employ a system that relied on blockchain technology.[43]
- *Labels*. Thus far, all of the countries that have adopted Type-1 systems have opted to use two-dimensional bar codes, rather than active or passive RFID tags, to track units of drugs. That is probably the right choice, but it is possible that LMICs would prefer the semi-automated tracking that RFID tags enable.[44]
- *Alarms*. Because of the limited human resources of regulatory authorities in LMICs, they would likely benefit from an automated warning system of the sort now in place in Turkey.[45]
- *Aggregation*. In many LMICs, the first lines of defense against SFMPs are the Central Medical Stores, through which pallets of packages of drugs typically pass on their way to distributors and dispensers. The job of the CMS inspectors would be eased by an aggregation requirement of the sort currently in place in India, which would facilitate rapid tracing of the pallets.

This list is surely not comprehensive. Many other features of the emerging global regime could undoubtedly be adjusted in ways that would either advantage or disadvantage the LMICs that, eventually, join the regime. Our recommendation is not that, on each issue, the interests of the LMICs ought to prevail, but rather that, before the fluid gels, the

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[41] See Kootstra and Kleinhout-Vliek, "Implementing Track-and-Trace Systems."; Pisa and McCurdy, "Improving Health Supply Chains," 11..

[42] See https://blogs.worldbank.org/digital-development/africas-connectivity-gap-can-map-tell-story; https://www.weforum.org/agenda/2021/07/latin-america-caribbean-digital-access/; https://www.oecd.org/digital/broadband/lac-digital-toolkit/toolkit-text-chapter1.htm; https://blogs.worldbank.org/latinamerica/poor-digital-access-holding-latin-america-and-caribbean-back-heres-how-change-it; https://www.iadb.org/en/news/least-77-million-rural-inhabitants-have-no-access-high-quality-internet-services; https://www.unescap.org/sites/default/files/1%20Broadband-Infrastructure-in-the-ASEAN-9-Region.pdf

[43] For a description of the potential advantages of the use of blockchain in track-and-trace systems, see Patrick Sylim et al., "Blockchain Technology for Detecting Falsified and Substandard Drugs in Distribution: Pharmaceutical Supply Chain Intervention," *JMIR Research Protocols* 7, no. 9 (2018). https://www.modality-solutions.com/blockchain-applications-in-pharmaceutical-serialization/..

[44] See Alberto Coustasse et al., "Could the Pharmaceutical Industry Benefit from Full-Scale Adoption of Radio-Frequency Identification (Rfid) Technology with New Regulations?," *Perspectives in Health Information Management* (2016).

[45] See Kootstra and Kleinhout-Vliek, "Implementing Track-and-Trace Systems.".

designers are at least aware of how their decisions will affect the global south. Then, if appropriate adjustments are feasible and affordable, they can be made before it is too late.

C. Cultivating Receptivity

How might vaccine hesitancy be reduced – and thus the beneficial impact of vaccines be increased? Considered below are the four most plausible possibilities.

1. Mandates

The most obvious potential strategy is to require people to be vaccinated – i.e., to overcome hesitancy with compulsion. The approach has been employed many times since vaccines first became available. Some of the mandates have been adopted by national governments. For example, in the United Kingdom, the Vaccination Act of 1853 required that all infants be vaccinated against smallpox during their first three months of life.[46] More often, mandates have been adopted and enforced at the local level – for example, by the municipal health departments of Montreal and Milwaukee in response to nineteenth-century smallpox outbreaks[47] and, in 2022, by the health department of Beijing in response to a surge of COVID cases when the Chinese national government began to lift the strict quarantine rules with which it had originally sought to combat the pandemic.[48]

Some mandates have been enforced with traditional criminal penalties: imprisonment or cumulative fines. In other cases, governments have denied unvaccinated persons access to resources over which the government has either complete or partial control – such as public education, public employment, membership in the military, or permission to fly on commercial airlines. Although systems of the latter sort might plausibly be described as "nudges," rather than mandates, in practice the affected persons rarely think of them this way. Because, typically, they constrict access to materials or opportunities to which people previously had unfettered access, they are generally perceived as mandatory.[49]

Mandates have an important advantage: They have proven in practice to increase sharply the rates of vaccination. However, they have two related disadvantages. First, they provoke resistance, sometimes resulting in violence. Typically, such resistance is isolated. But it occasionally becomes widespread, even deadly. For example, the Montreal and

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[46] See Robert M. Wolfe and Lisa K. Sharp, "Anti-Vaccinationists Past and Present," *BMJ* 325, no. 7361 (2002).

[47] See Jonathan M. Berman, "When Antivaccine Sentiment Turned Violent: The Montréal Vaccine Riot of 1885," *CMAJ. Canadian Medical Association journal* 193, no. 14 (2021).; Judith W. Leavitt, "Politics and Public Health: Smallpox in Milwaukee, 1894-1895," *Bulletin of the history of medicine* 50, no. 4 (1976).

[48] See Helen Davidson, "Vaccines Are Key to China's Zero-Covid Exit but Scepticism Poses Challenge," *The Guardian*, December 2, 2022 2022; Yaqiu Wang, "China's Use of Force and Coercion to Drive up Its Covid-19 Vaccination Rate Is Not the Answer," *Globe & Mail*, September 28, 2021 2021.

[49] See, e.g., Select Subcommittee on the Coronavirus Pandemic U.S. House of Representatives, "After Action Review of the Covid-19 Pandemic: The Lessons Learned and a Path Forward," (2024), 336-48. Cf. Kahneman and Tversky on baseline issues.

Milwaukee mandates, just mentioned, provoked riots.[50] During the COVID-19 pandemic, truckers became increasingly angry at requirements that the be vaccinated before entering Canada. Finally, in February of 2022, they "paralyzed downtown Ottawa and the area around Parliament, parking their vehicles in intersections and across busy thoroughfares," prompting the mayor to decline a state of emergency.[51] Even in Beijing, where one might assume that compliance with governmental edicts would be the norm, intense resistance to the vaccine mandate prompted the city to reverse course quickly.[52]

Second, mandates seem to intensify general distrust of government – and that distrust can be long-lasting. Thus, even if a mandate is effective in increasing inoculation rates with response to a particular outbreak, it is likely to increase public resistance to vaccines in general in the future.[53]

In addition to these prudential concerns, mandates are troubling when measured against some conceptions of civil liberties. This issue is complicated by the fact that, as we have seen, vaccines usually benefit, not only the person vaccinated, but also society at large – by reducing transmissions and fostering herd immunity. Forcing people to accept vaccines on the latter ground is no more problematic, morally, than other legal regimes aimed at promoting social welfare – such as speed limits on highways. But to the extent vaccine mandates are justified by the benefit they provide to the people who are vaccinated, they implicate the longstanding unease concerning the legitimacy of "paternalistic" regulations – such as requirements that motorcyclists wear helmets. That unease is especially salient when the regulation at issue compels people to acquiesce in intrusions into their bodies. This is not to say that we should automatically avoid initiatives that trigger this unease; some forms of paternalism are defensible. But the discomfort raises the stakes. The arguably problematic character of the dimension of vaccine mandates that are rooted in the attitude that the government knows better than the citizen what is in his or her best interest suggests that, before adopting them, we should at least be confident that they will be efficacious. For the reasons sketched above, that confidence is sometimes weak.

2. Incentives

The second possible strategy for mitigating vaccine hesitancy is to rely on carrots, rather than sticks. Instead of compelling people to be vaccinated, the government can offer them rewards. In the simplest version of this approach, each vaccinated person (or occasionally each person who transports someone else to the vaccination site) is given a sum of money, typically modest in amount (e.g., between USD25 and USD100). In a more complex version, each vaccinated person is entered into a lottery from which he or she

[50] See Berman, "The Montréal Vaccine Riot."; Leavitt, "Smallpox in Milwaukee."

[51] Ian Austen and Isai Vjosa, "Ottawa Declares a State of Emergency as Protests against Pandemic Measures Spread across Canada," *New York Times (Online)* (2022).

[52] See Yanzhong Huang, "The Short-Lived Covid-19 Vaccine Mandate in Beijing," *Think Global Health*.

[53] See, e.g., U.S. House of Representatives, "Review of the Covid-19 Pandemic," 340-45.

might receive a more substantial sum of money.[54] Governments are not the only institutions that can employ this tactic. During the COVID-19 pandemic, private businesses in many countries offered vaccinated persons rewards of various sorts: donuts, cheesecakes, discounts on restaurant meals, marijuana joints, arcade games, the right to drive a few laps on a NASCAR track, and so forth.[55]

Prior to the pandemic, both scholars and policymakers disagreed sharply concerning the wisdom of using incentives to increase the willingness of people to be vaccinated – or to engage in analogous activities. Some argued that offering material rewards was the most efficient way to induce people to get vaccinated. Others argued that such incentives do little good and indeed can backfire by corroding selfless motivations and augmenting doubts concerning the merits of the vaccines. (If they are so beneficial, why must you pay people to take them?)[56]

The pandemic itself triggered a substantial set of empirical studies designed to test these competing views. Some of those studies used surveys to ascertain whether people thought that incentives would affect their willingness to get vaccinated or "boosted"; others relied on "natural experiments" – comparing rates of vaccination in sets of people offered incentives and in otherwise comparable sets of people not offered incentives. As one might expect, the results of these studies were not altogether consistent. Most, however, support the following generalizations: Programs in which vaccinated persons were enrolled in lotteries featuring small probabilities of very large rewards had minimal in any impact (positive or negative) on vaccination rates.[57] By contrast, programs in which vaccinated persons were paid small but certain sums of money increased vaccination rates modestly – and had no measurable adverse impacts of the sorts that the skeptics had feared.[58] Those

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[54] A survey of programs of these two sorts can be found at National Governors Association, "Covid-19 Vaccine Incentives," (2021), https://www.nga.org/publications/covid-19-vaccine-incentives/.

[55] See "The Best Coupon for Freebies Is Your Vaccination Card -- Wsj," *Dow Jones Institutional News* (2021).; James Dator, "Talladega Superspeedway's Covid Vaccination Incentive Was Genius," *SB Nation*, May 17, 2021 2021.; Dover International Speedway, "Race to End Covid," https://www.racetoendcovid.org/event/dover-international-speedway/.

[56] See, e.g., Ana Santos Rutschman, "Vaccine Hesitancy across Time," *North Carolina Journal of Law and Technology* 23 (2022): 38ff.; see William Seitz, *Can Vaccination Incentives Backfire? : Experimental Evidence That Offering Cash Incentives Can Reduce Vaccination Intentions in Some Contexts*, ed. Eiji Yamada and Satoshi Shimizutani, Can Vaccination Incentives Backfire? (Washington, District of Columbia: The World Bank, 2023).

[57] See Acharya B, Dhakal C. Implementation of state vaccine incentive lottery programs and uptake of COVID-19 vaccinations in the United States. JAMA Netw Open. 2021;4(12): e2138238; Robertson C, Schaefer KA, Scheitrum D. Are vaccine lotteries worth the money? Econ Lett. 2021; 209:110097; Walkey AJ, Law A, Bosch NA. Lottery-based incentive in Ohio and COVID-19 vaccination rates. JAMA. 2021;326(8):766–7; Dave D, Friedson AI, Hansen B, Sabia JJ. Association between statewide COVID-19 lottery announcements and vaccinations. JAMA Health Forum. 2021;2(10):e213117.; Lang D, Esbenshade L,Willer R. Did Ohio's vaccine lottery increase vaccination rates? A pre-registered, synthetic control study. J Exp Political Sci. 2023;10(2):242–60.; Barber A, West J. Conditional cash lotteries increase COVID-19 vaccination rates. J Health Econ. 2022; 81:102578. [Recheck]

[58] See Hwang Kim and Vithala R. Rao, "Vaccination Diffusion and Incentive: Empirical Analysis of the Us State of Michigan," *Frontiers in public health* 9 (2021); Florian H. Schneider et al., "Financial Incentives for Vaccination Do Not Have Negative Unintended Consequences," *Nature (London)* 613, no. 7944 (2023); Yin Wang et al., "Guaranteed Cash Incentives Boosted Covid-19 Vaccinations of Young Adults: Evidence from

increases were most noticeable among poor people, unemployed people, and racial minorities.

The implication seems to be that, at least if the rewards are kept at levels that are affordable, incentives cannot entirely eliminate vaccine hesitancy. However, they are net beneficial and thus should be employed.

3. Improving Information

As indicated above, several of the factors that contribute to vaccine hesitancy pertain to the quality or credibility of the information that is provided to people considering vaccination. A promising strategy for reducing hesitancy would thus be to improve the information to which people are exposed. Possible techniques for doing so might be gleaned from efforts that were undertaken during the COVID-19 pandemic to enrich and purify the informational environment. In retrospect, four such efforts stand out.

First, most national governments sought both to educate the public and to neutralize the flow of vaccine misinformation and disinformation by disseminating as broadly as possible unbiased, scientifically sound information concerning all aspects of the pandemic, including the power of vaccines to prevent infections or reduce their severity. In the United States, for example, the Center for Disease Control created and regularly updated a website providing general advice about COVID-19, an upbeat survey of the "Benefits of Getting Vaccinated," and vaccination guidelines for members of specific groups (such as pregnant women).[59] Similar sites were created by the government of South Africa,[60] the Ministry of Health and Family Welfare in India,[61] and many other public health ministries.

Second, some national governments punished people or organizations that created or distributed false information. The government of Malaysia, for example, used two ambiguous criminal statutes to pursue disseminators. The first forbade "improper use of network facilities"; the second "statements conducive to public mischief."[62] As early as

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West Virginia: Study Examines Cash Incentives for Covid-19 Vaccinations among Young Adults in West Virginia," *Health Affairs* 43, no. 5 (2024); Charlene A. Wong et al., "Guaranteed Financial Incentives for Covid-19 Vaccination: A Pilot Program in North Carolina," *Archives of internal medicine (1960)* 182, no. 1 (2022).

[59] For some of the relevant pages of this site, see https://www.cdc.gov/covid/vaccines/stay-up-to-date.html; https://www.cdc.gov/covid/vaccines/benefits.html; https://www.cdc.gov/covid/vaccines/pregnant-or-breastfeeding.html.

[60] See https://www.gov.za/covid-19/vaccine/vaccine.

[61] See https://covid19dashboard.mohfw.gov.in.

[62] The relevant portions of the two provisions follow: Section 233 of the Communications and Multimedia Act (1998) provides that "any person who uses network facilities or network service or applications service to make any comment, request, suggestion, or other communication, which is false, with intent to annoy, abuse, threaten or harass another person commits an offense" and further provides that the penalty thereof shall be "a fine not exceeding 50,000 ringgit or to imprisonment for a term not exceeding one year or to both and shall also be liable to a further fine of 1000 ringgit for every day during which the offense is continued after conviction." Section 505 of the Penal Code provides that "Whoever makes, publishes, or circulates any statement, rumor or report with intent to cause, or which is likely to cause, fear or alarm to the public, or to any section of the public, whereby any person may be induced to commit an offense against the state or

July of 2020, the Royal Malaysia Police, collaborating with the Malaysian Communications and Multimedia Commission, "opened 266 investigation papers relating to COVID-19 false information, of which 17 individuals have been found guilty, 12 have been issued warning notices, 13 are still undergoing the trial process, while the remaining 172 are still under investigation."[63] Analogous statutes were deployed – although typically less aggressively – in Germany, Hungary, and Singapore.[64]

Third, a few national or state medical boards disciplined physicians who initiated or augmented a stream of disinformation. In the United Kingdom, for example, one doctor was "struck off" the medical register after a tribunal found that she not only had repeatedly argued publicly that vaccines were ineffective or unsafe, but also had encouraged parents to falsify the "red books" containing the immunization records of their children.[65] In Texas, a doctor was fined $500 for prescribing hydroxychloroquine as a treatment for COVID and failing to explain its potential side-effects.[66]

Last but not least, some of the social-media companies attempted to curtail the dissemination of false or misleading information through their platforms. Facebook, for example, engaged independent fact-checking organizations to help identify misinformation pertaining to COVID and then (a) attached warning labels to posts containing such misinformation and (b) deleted posts that, in its judgment, contributed to the risk of physical harm or imminent violence (such as messages advocating drinking bleach as a cure for the disease or President Trump's assertion that children are "almost immune" to the virus).[67] Equally important, Facebook established a site ("Coronavirus Information Center") containing curated, unbiased information concerning the pandemic (including the potential of vaccines to curb it) and from various angles directed users to that site. Soon

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against the public tranquility shall be punished with imprisonment which may extend to two years or with fine or with both." Hanis Wahed, "Misinformation and Disinformation during Covid-19: The Effects and the Relevant Laws in Malaysia.," *International Journal of Law, Government and Communication* 5, no. 21 (2020): 206.

[63] Harris Zainul and Farlina Said, "The Covid-19 Infodemic in Malaysia: Scale, Scope and Policy Responses," (Institute of Strategic and International Studies (ISIS) Malaysia Policy Paper, 2020), 29. For a discussion of this policy two years later, see Norazlinda Hj Mohammad et al., "Fake News and Misinformation: Covid-19 & Challenges Confronted by Malaysian's Ministry of Health," *International Journal of Academic Research in Business and Social Sciences* 12, no. 5 (2022): 1286.

[64] See Raffael Heiss et al., "How Have Governments and Public Health Agencies Responded to Misinformation during the Covid-19 Pandemic in Europe?," *COVID-19 Health System Response Monitor (HSRM)* (2021), https://eurohealthobservatory.who.int/monitors/hsrm/analyses/hsrm/how-have-governments-and-public-health-agencies-responded-to-misinformation-during-the-covid-19-pandemic-in-europe.; Miriam Berger, "Singapore Invokes 'Fake News' Law in Push against Anti-Vaccine Website," *Washington Post*, October 25, 2021.; Melinda C Mills and Jonas Sivelä, "Should Spreading Anti-Vaccine Misinformation Be Criminalised?," *BMJ* 2021 (2021).

[65] See Clare Dyer, "Gp Is Struck Off after Comments Made to Parents About Vaccines," *BMJ (Online)* 382 (2023).

[66] See Y. Tony Yang and Sarah Schaffer DeRoo, "Disciplining Physicians Who Spread Medical Misinformation," *Journal of public health management and practice* 28, no. 6 (2022).

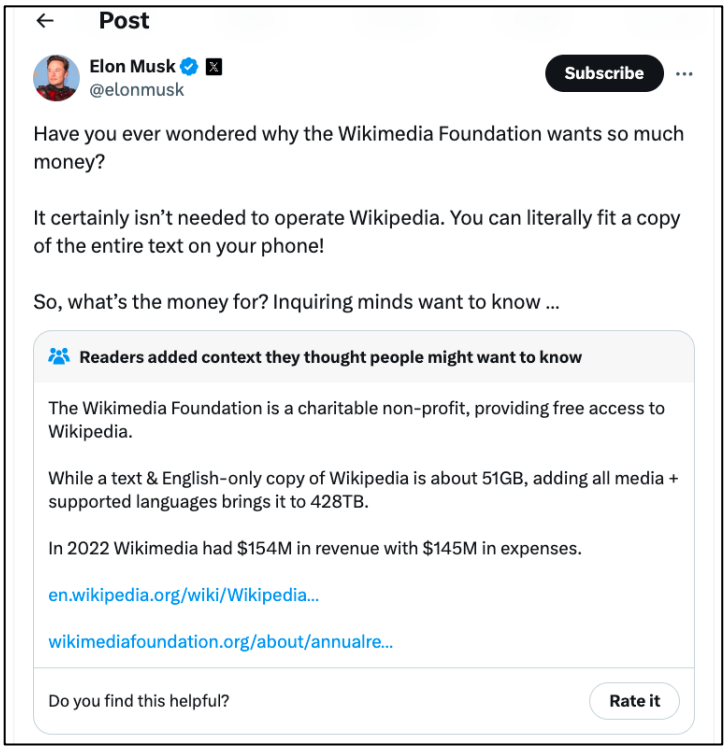
[67] See Dawn Carla Nunziato, "Misinformation Mayhem: Social Media Platforms' Efforts to Combat Medical and Political Misinformation," *First Amendment Law Review* 19 (2020): 38-41.

thereafter, Twitter implemented a similar combination of policies.[68] In addition, Twitter created a system called "Birdwatch," in which subscribers were encouraged to volunteer to assess the accuracy of other subscribers' posts. Once the judgment of these monitors had been verified, they were able to attach publicly visible "notes" to problematic posts, providing either discrediting or contextual information. When Elon Musk purchased Twitter, he dismantled most of its systems for detecting and blocking misinformation. However, he retained – and indeed expanded – Birdwatch, renaming it "Community Notes."[69]

The second and third of these four initiatives seem, in retrospect, to have had minimal impact – largely because they were not deployed on sufficiently large scales. The governments of most countries were reluctant to follow the lead of Malaysia in criminalizing disinformation, on the ground that doing so would encroach excessively on freedom of speech. The reluctance was especially strong in the United States, where freedom of speech receives constitutional protection. Even in jurisdictions that adopted such prohibitions, prosecutions were rare. Similar concerns explain the rarity with which physicians were disciplined for spreading inaccurate information about vaccines. In most of the small number of cases in which disciplinary proceedings were initiated, no sanction was ultimately imposed.[70] The minority of doctors who disseminated anti-vax messages

[68] See ibid., 43-47.

[69] See Yang Gao, Maggie Mengqing Zhang, and Huaxia Rui, "Can Crowdchecking Curb Misinformation? Evidence from Community Notes," (2024). An example of this system in action is shown below.



[70] See David Robert Grimes and Trisha Greenhalgh, "Vaccine Disinformation from Medical Professionals—a Case for Action from Regulatory Bodies?," *Journal of evaluation in clinical practice* 30, no. 4 (2024).

probably were unmoved by solemn but toothless hortatory statements by their professional associations.[71] Against this backdrop, it is highly unlikely that either of these initiatives reduced materially the volume of misinformation and disinformation available to the public.

By contrast, the first of the four strategies surely did some good. Traffic to the governmental sites providing information about vaccines, boosters, and so forth was robust. However, the beneficial impact of those sites was undercut in many countries by partisanship and the associated politization of the pandemic. People persuaded that nefarious motives underlay the governmentally sponsored vaccination programs were disinclined to trust information provided by the government concerning the merits of the vaccines.

Assessment of the net impact of the multifaceted campaigns by the social-media platforms is more difficult. On one hand, millions of misleading posts were either deleted or burdened with warning labels, and some of the people who repeatedly contributed such posts (including world leaders) were at least temporarily banned from the platforms.[72] In addition, Twitter's crowdchecking program prompted many of the authors of the posts to which cautionary "community notes" were attached to retract them.[73] One the other hand, the limited resources that the platforms devoted to the centralized filtration systems resulted in long delays in the attachment of warning labels to misleading posts.[74] And Twitter's intriguing distributed system was hampered by a design defect: The community notes became publicly visible only after a diverse set of other contributors had endorsed them. The result, again, was substantial delays between the times when problematic messages were first posted and when the cautionary commentary emerged. During the interim, much damage was done.[75]

Recent studies attempting to measure the overall effect of the social-media companies' efforts are discouraging. One concluded:

> Our findings suggest that Facebook's policies may have reduced the number of posts in antivaccine venues but did not induce a sustained reduction in engagement with antivaccine content. Misinformation proportions both on

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[71] An example of such a statement is the following from the Federation of State Medical Boards in the United States: "Physicians who generate and spread COVID-19 vaccine misinformation or disinformation are risking disciplinary action by state medical boards, including the suspension or revocation of their license. Due to their specialized knowledge and training, licensed physicians possess a public trust and therefore have a powerful platform in society, whether they recognize it or not. They also have an ethical and professional responsibility to practice medicine in the best interests of their patients and must share information that is factual, scientifically grounded and consensus-driven for the betterment of public health. Spreading inaccurate COVID-19 vaccine information contra responsibility, threatens to further erode public trust in the medical profession and puts all patients at risk." Ibid.

[72] See Nunziato, "Misinformation Mayhem," 39.

[73] See Gao, Zhang, and Rui, "Crowdchecking."

[74] See Nunziato, "Misinformation Mayhem," 41-43.

[75] See Gao, Zhang, and Rui, "Crowdchecking."; Center for Countering Digital Hate, "Rated Not Helpful: How X's Community Notes System Falls Short on Misleading Election Claims," (2024).

> and off the platform appear to have increased. Furthermore, it appears that antivaccine page administrators especially focused on promoting content that outpaced updates to Facebook's moderation policies: The largest increases appear to have been associated with topics falsely attributing severe vaccine adverse events and deaths to COVID-19 vaccines.[76]

Another found that, even if Facebook's policies did reduce the availability on its platform of *false* information, they did nothing to curb content "suggesting" that vaccines were harmful to health. Such "vaccine-skeptical" material was disseminated extremely widely and had an enormous adverse impact on public confidence in vaccines. "For example, a single vaccine-skeptical article published by the Chicago Tribune titled, 'A healthy doctor died two weeks after getting a COVID vaccine; CDC is investigating why,' was seen by >50 million people on Facebook (>20% of Facebook's US user base) and received more than six times the number of views than all flagged misinformation combined."[77]

So what lessons can be distilled from these experiments concerning future efforts to improve the informational environment pertaining to vaccines? To begin with, we should probably not attempt to suppress misinformation and disinformation by imposing sanctions – either criminal or professional – on the parties who create it. A large enough penalty, combined with a high enough probability of its imposition, might prompt individuals or organizations to hesitate before contributing to the flow of misinformation and disinformation. However, the unease with which most governments regard suppression of vaccine-critical speech and with which most physicians' organization regard disciplining doctors for expressing unorthodox views is both strong and well-founded. Increasing penalties far enough to make a significant impact thus seems both impracticable and unwise.

By contrast, it would make good sense for public-health officials to continue to devote substantial resources to the aggregation and publication of unbiased information concerning vaccines of all sorts. The beneficial impact of those efforts could be increased if, somehow, the credibility of the relevant government offices could be enhanced. In the current political environment, that would not be easy, but any of the following strategies could help:

a) The most obvious is that the public-health officials should be more willing to acknowledge the <u>degree</u> of empirical support for their recommendations – and to update as appropriate changes in the levels of support. Typically, the government websites urge visitors to act in a particular fashion (get vaccinated; get "boosted"; etc.) without any indication of the strength of the evidence underlying the instruction. Although this has the advantages of simplicity and clarity, it has the disadvantage of providing little guidance to people trying to balance competing considerations. Even more seriously, it corrodes the

[76] David A. Broniatowski et al., "The Efficacy of Facebook's Vaccine Misinformation Policies and Architecture during the Covid-19 Pandemic," *Science advances* 9, no. 37 (2023).

[77] Jennifer Allen, Duncan J. Watts, and David G. Rand, "Quantifying the Impact of Misinformation and Vaccine-Skeptical Content on Facebook," *Science* 384, no. 6699 (2024).

government's credibility when new studies require adjustment or retraction of recommendations.[78]

b) As indicated above, in some countries the recommendations of public-health officials concerning vaccination have been undercut by adverse commentary from religious leaders. To avoid this effect, the officials can and should consult, whenever possible, with relevant religious leaders prior to announcing their recommendations. For example, providing Muslim leaders evidence that makes clear that a vaccine does not contain any pork products could reduce the probability of post-release critical commentary.

c) A more radical approach would entail restructuring public-health ministries to make them more independent of both the executive and the legislative branches of national governments. For this purpose, the history of fiscal management may be instructive. Over the course of the twentieth century, most national governments found that, to avoid debilitating inflation, it was essential to insulate their central banks from political control. The degree and ways in which this was achieved varied, but today in most developed countries, the task of managing the currency is left to respected economists, appointed for long terms, who are not accountable to political leaders. In the United States, this system (and the consensus upon which it has rested) is now under siege, but in most countries its wisdom continues to be widely recognized.[79] Reduction of the partisanship that increasingly taints the formulation of public-health policies could be facilitated by restructuring public-health ministries along similar lines. Specifically, the procedures for appointing or removing the officials who determine vaccine policy could be revised to resemble the procedures for appointing central bankers. In the United States, such a reform is extremely unlikely in the near term, but in other jurisdictions it may be more feasible. One major benefit would be to endow decisions and publications of public-health officials with some of the credibility that accompanies adjustments of monetary policy by central banks.

d) A final way of augmenting the credibility of vaccine-related information disseminated through official channels would be to increase the role placed by entities other than national governments. The obvious candidate for such a role would be the World Health Organization. Indeed, during the COVID-19 pandemic, the WHO did maintain a site analogous to the nation-specific sites described above.[80] Currently, the information provided by the WHO

[78] The recently released report by the Select Committee of the U.S. House of Representatives overstates this problem somewhat, but it does identify several instances in which the reluctance of the CDC (and other officials) to provide nuanced discussions of the degree of empirical support for their recommendations concerning COVID vaccinations eventually undercut their credibility. See U.S. House of Representatives, "Review of the Covid-19 Pandemic," 296-300, 46-47.

[79] See Alejo Czerwonko, "A Lesson from Emerging Markets: Why Central Bank Independence Is So Important," (World Economic Forum, 2024).

[80] See https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.

concerning vaccines for other diseases is much less fulsome and user-friendly,[81] but with sufficient funding, they could be brought up to levels comparable to that associated with COVID. (Ideally, an initiative of this sort would be combined with more general structural reforms designed to increase the credibility of the WHO in general – but exploration of that topic would take us far afield.)

We come finally to the potential roles of the social-media platforms. As indicated above, several of the extant platforms developed and implemented filtration systems that were moderately beneficial in reducing the presence or influence of false assertions pertaining to COVID-vaccines. Looking forward, all platforms could deploy such systems with respect to misleading statements pertaining to vaccines of all sorts, if they have not done so already. The beneficial effect of those systems could be increased in three ways:

a) The most obvious is that each platform could increase the resources devoted to filtration. That would increase the percentage of misleading posts that are either labelled or removed. Equally important, it would decrease the delays that currently impede the efficacy of the filters.
b) All platforms could experiment with ways to refine the pioneering crowdchecking system first developed by Twitter. Among other things, they could devise ways of making critical comments visible to the public sooner, without sacrificing the quality control that the current version of Community Notes is designed to maintain.
c) Some platforms could employ architectures that encourage subscribers to develop and deploy other systems that would reduce the density of misinformation in their feeds. Currently, the leader in this respect appears to be Bluesky, which enables users to create custom feeds using the open-source AT Protocol.[82] One subscriber has already used this feature to build a "custom feed in Python that filters posts based on keywords" associated with anti-vax messaging – and then made available to other subscribers a tutorial concerning how to implement and improve upon this technique.[83] More sophisticated custom filters are likely to be developed and shared if Bluesky's market share continues to grow.

In combination, the initiatives outlined above could enhance significantly the quality of the information to which most people are exposed pertaining to vaccines. That, in turn, would help reduce vaccine hesitancy.

Once again, however, it would be a mistake to put too much stock in these reforms. The volume of the river of misinformation pertaining to vaccines is now so high that no

[81] Examples: On HPV, see https://www.who.int/news/item/04-10-2024-who-adds-an-hpv-vaccine-for-single-dose-use. On dengue, see https://www.who.int/news-room/questions-and-answers/item/dengue-vaccines.

[82] See https://atproto.com.

[83] See Tilde Thurium, "Detecting Vaccine Misinformation in a Custom Bluesky Feed, Using Launchdarkly and Openai," https://launchdarkly.com/blog/bluesky-custom-feed-llm-feature-flag/.

combination of dikes will be able to control it altogether. And while competition among platforms may facilitate the emergence of platforms like Bluesky that (at least thus far) have been able to minimize the levels of empirically unfounded anti-vax messaging, the same dynamic will likely continue to produce platforms like Truth Social, where anti-vax messaging is rife. In the latter, what the World Health Organization has called an "infodemic" will continue.

4. Provider Recommendations

Conversation with trusted health-care professionals consistently have been shown to increase people's confidence that vaccines are safe and efficacious and to make them more likely to get inoculated or to get their children inoculated. This effect has been verified for many diseases – including influenza, HPV, and COVID-19.[84]

Unfortunately, such "provider recommendations" are far from universal. Even in developed countries, the percentage of people who have had in-person conversations with a health-care professional concerning the merits of vaccination is low. In developing countries, it is of course lower still. The implication seems clear: To mitigate vaccine hesitancy, we should devise ways of providing more people the opportunity to speak with health-care professionals about their decisions concerning vaccination.

The principal impediment to pursuit of this strategy is the shortage of health-care professionals. This is especially true of physicians. In most high-income countries, there are between 30 and 50 physicians for every 10,000 residents. By contrast, in both India and the Philippines, the number is 7. In most countries in sub-Saharan Africa, the number is less than 3; in some it is less than 1.[85] The density of nurses is somewhat higher. In most developed countries, there are over 80 practicing nurses for every 10,000 residents. Again, however, the numbers in low and middle-income countries are much lower – for example, 17 in India, and 6 in Kenya.[86] In view of the loads already being borne by these professionals, it would be unrealistic to expect that they could increase significantly the number of in-person conversations they had with people considering vaccinating themselves or their children.

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[84] See, e.g., Czerwonko, "A Lesson from Emerging Markets: Why Central Bank Independence Is So Important."; Katherine E. Kahn et al., "Association between Provider Recommendation and Influenza Vaccination Status among Children," *Vaccine* 36, no. 24 (2018); Peng-jun Lu et al., "Association of Provider Recommendation and Offer and Influenza Vaccination among Adults Aged ≥18 Years – United States," ibid., no. 6; Kimberly H. Nguyen et al., "Report of Health Care Provider Recommendation for Covid-19 Vaccination among Adults, by Recipient Covid-19 Vaccination Status and Attitudes - United States, April-September 2021," *MMWR. Morbidity and mortality weekly report* 70, no. 50 (2021); N. Loren Oh et al., "Provider Communication and Hpv Vaccine Uptake: A Meta-Analysis and Systematic Review," *Preventive medicine* 148 (2021); Douglas J. Opel et al., "The Influence of Provider Communication Behaviors on Parental Vaccine Acceptance and Visit Experience," *American Journal of Public Health* 105, no. 10 (2015).; Alric Charmasson et al., "Perceived Impact of Discussions with a Healthcare Professional on Patients' Decision Regarding Covid-19 Vaccine," *Human vaccines & immunotherapeutics* 20, no. 1 (2024).

[85] Estimates provided by the World Health Organization of the density of physicians in every country are available at https://data.who.int/indicators/i/CCCEBB2/217795A. A map showing the differences among countries is available at https://worldpopulationreview.com/country-rankings/doctors-per-capita-by-country.

[86] See https://data.who.int/indicators/i/B54EB15/5C8435F.

Fortunately, in many LMICs, there is one additional group that already conducts many such conversations – and might plausibly be enlisted to conduct more. Although they go by different names in different countries, they are most often known as community health workers (CHWs).[87]

To appreciate the enhanced role that they might play in reducing vaccine hesitancy requires a bit of background. CHWs are laypersons trained in basic disease-prevention and diagnostic techniques. Their backgrounds and responsibilities vary somewhat by country, but in the typical system, their primary role is to visit regularly all of the households in a particular zone, providing the residents services of four types. First, they offer instruction and assistance on a wide variety of topics: birth control, pre-natal care, breast feeding and other dimensions of infant care, nutrition, the use of insecticide-treated bednets, techniques for preventing or managing diarrhea, the use of ARVs to prevent transmissions of HIV from mothers to newborns, and so forth. Second, they gather information concerning the health of each person in each household and record that information using templates on mobile telephones. (That data is then aggregated to track the incidence of diseases and to guide the development of appropriate public-health initiatives.) Third, the CHWs provide on-the-spot treatments to persons suffering from common, easily diagnosed illnesses. Not long ago, this would have been impossible or unsafe. Recently, however, short-course therapeutics for many maternal and childhood diseases have been developed that can be administered safely by appropriately trained laypersons. These include "single-dose albendazole for helminthes, low osmolarity oral rehydration therapy and zinc for diarrhea, artemisinin-based combination therapy for malaria, antibiotics for pneumonia and newborn sepsis, nevirapine for HIV, and depo-provera for family planning."[88] Some of these treatments require drugs. In those instances, the CHWs deliver the drugs directly to the patients and provide instructions concerning their use.[89] Fourth, when CHWs encounter persons suffering from uncommon or complex diseases, they refer such persons to suitable public-health facilities, private clinics, or hospitals and provide advice about how to get there.

Systems of this sort are already in place and working well in several countries. They include the Community Health Agents in Brazil (currently providing basic care to over 120 million people);[90] the Village Health Workers, Maternal Child Health Workers, and the Female Community Health Volunteers in Nepal (currently serving the entire rural population),[91] the Community Health Workers working with Partners in Health in Haiti;[92]

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[87] For a comprehensive survey of CHW systems, and a powerful argument for their expansion, see Prabhjot Singh, *One Million Community Health Workers* (New York: The Earth Institute, Columbia University, 2011).

[88] See ibid., 17.

[89] See ibid., 38.

[90] See James Macinko et al., "Going to Scale with Community-Based Primary Care: An Analysis of the Family Health Program and Infant Mortality in Brazil, 1999-2004," *Social Science Medicine* 65, no. 10 (2007); Singh, *One Million Community Health Workers*, 22.

[91] See Claire Glenton et al., "The Female Community Health Volunteer Programme in Nepal: Decisionmakers' Perceptions of Volunteerism, Payment and Other Incentives," *Social Science & Medicine* 70, no. 12 (2010); Singh, *One Million Community Health Workers*, 42.

[92] See http://www.pih.org/pages/community-health-workers/.

the Barangay Health Workers in the Philippines (providing essential services to the rural population, much of it located on remote islands);[93] the Millennium Villages Community-Based Management for Health system in Uganda;[94] large-scale systems in Nigeria, Ethiopia, and Kenya; and smaller systems in most African countries.

This system has proven remarkably effective in many settings. Several formal reviews have concluded that it leads to dramatic reductions in both mortality and morbidity.[95] A dated but still relevant summary of these studies follows:

> Systematic reviews have concluded that CHWs can safely and effectively deliver health services as diverse as birth control injections; perinatal and neonatal care; case management and prevention of malaria, diarrhea, and acute respiratory infections; and HIV care management. There is also emerging evidence that CHWs can provide mental health care. Meta-analysis of moderate-quality evidence indicates that CHWs can, in comparison to usual care, increase the number of children whose immunizations are up-to-date; promote the initiation of exclusive breastfeeding; increase care seeking for pregnancy-related complications; and improve pulmonary TB cure rates. A Cochrane review using evidence from .randomized controlled trials assessed for quality, indicated that CHWs ultimately provide promising benefits in reducing child morbidity (*RR* = 0.86, 95% CI 0.7–0.99; *p* = 0.03), child mortality (*RR* = 0.75, 95% CI 0.55–1.03; *p* = 0.07), and neonatal mortality (*RR* = 0.86, 95% CI 0.75–0.99; *p* = 0.03) when compared to usual care. Modeling of health system investments in CHWs found that the return was as high as 10:1 when accounting for increased productivity from a healthier population, the

[93] See Warren Dodd et al., "Governance of Community Health Worker Programs in a Decentralized Health System: A Qualitative Study in the Philippines," *BMC Health Services Research* 21 (2021); Ma Leslie Ulmido et al., "Conflicting and Complementary Notions of Responsibility in Caregiver's and Health Care Workers' Vaccination Narratives in the Philippines," *Journal of global health* 14 (2024).; Mikhaela Y. T. Baliola, Margaret R. Golpe, and Leslie V. Advincula-Lopez, "Gains and Challenges of the Barangay Health Worker (Bhw) Program during Covid-19 in Selected Cities in the Philippines," *JOURNAL OF HEALTH RESEARCH* 38, no. 1 (2024).

[94] See Herrick Fisher, Community Health Workers and Millennium Villages, Community Based Management for Health, Presentation to the Ugandan Ministry of Health, April 2, 2009.

[95] See, for example, ZA Bhutta et al., "What Works? Interventions for Maternal and Child Undernutrition and Survival," *Lancet* 371, no. 9610 (2008); Zohra S Lassi, Batool A Haider, and Zulfiquar Bhutta, "Community-Based Intervention Packages for Reducing Maternal and Neonatal Morbidity and Mortality and Improving Neonatal Outcomes," *The Cohrane Library*; Henry Perry et al., "How Effective Is Community-Based Primary Health Care in Improving the Health of Children?," *American Public Health Association*, http://www.future.org/sites/future.org/files/FinalCBPHCReporttoERP-7July2009.pdf; Singh, *One Million Community Health Workers*, 12.

> avoidance of the high costs of health crises, and the economic impact of increased employment.[96]

The potential for CHWs to provide in-person vaccine counselling should by now be apparent. As the foregoing passage indicates, CHWs in some countries already discuss vaccinations with the people they visit. Their role in this regard could easily be expanded.

To be most effective, an initiative of this sort should be accompanied by two reforms. First, in only approximately half of the countries in which these networks are currently established are the CHWs currently authorized to administer the vaccines themselves. As one might expect, inoculation rates rise when the person providing counselling is also empowered to deliver the vaccine. In all jurisdictions, CHWs should be provided the training necessary to deliver vaccines safely – and then any legal impediments to this practice should be removed.

Second, CHWs should receive better training on how to conduct these conversations. Currently, their practices in this regard are uneven. Some of the advice that they provide is well-informed and appropriately delivered – but not all. For example, even in the Philippines, where the Barangay Health Workers are well established and respected, the advice they provide is sometimes imperfect. For example, one recent study reported:

> Our findings also emphasise that caregivers perceive HCWs as dismissive, unavailable or disrespectful in terms of answering questions or concerns about vaccines. This in turn leads caregivers to rely more heavily on other channels for information, such as their own social circle or social and traditional media. However, these channels can function as 'echo chambers.'[97]

Conversations of this sort are unlikely to be effective in overcoming vaccine hesitancy (which, for the reasons discussed above, is currently high in the Philippines).

This problem could be remedied easily. Training programs designed to enable health-care professionals to have constructive conversations about vaccination with their patients already exist in many upper-income countries. Those programs would just need to be adapted to be suitable for CHWs in LMICs – and then made widely available.

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In sum, of the four plausible initiatives that might be employed for mitigating vaccine hesitancy, three should be pursued. If tuned in the ways described above, modest financial incentives, purifications of the relevant sectors of the informational environment,

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[96] Concept Note, "Community Health Workers," Brigham and Women's Hospital (2018), https://www.globalhealthdelivery.org/files/ghd/files/ghd-c11_chw_concept_note.pdf. See also Simon Lewin et al., "Lay Health Workers in Primary and Community Health Care for Maternal and Child Health and the Management of Infectious Diseases," *Cohrane Database of Systematic Reviews*, no. 3 (2010).

[97] Jhoys Landicho-Guevarra et al., "Scared, Powerless, Insulted and Embarrassed: Hesitancy Towards Vaccines among Caregivers in Cavite Province, the Philippines," *BMJ global health* 6, no. 9 (2021): 9.

and augmentation of the roles played by community health workers in providing in-person counselling are all promising. None of these initiatives is a panacea, but in combination they could go far in overcoming this formidable barrier to the consumption of life-saving vaccines.

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