Reboot biomedical R&D in the global public interest

Inequitable access to the fruits of research during the COVID-19 pandemic highlights the urgency — and feasibility — of overhauling the R&D system.

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COVID-19 diagnostics, therapeutics and vaccines are powerful reminders: health technologies can help to shape the way in which societies control disease. Challenges in ensuring global, equitable access to these fruits of biomedical research and development (R&D) during the COVID-19 pandemic have highlighted the urgency of reorienting the system towards the public interest. The first step is a clearer articulation of what R&D in the global public interest is. That is what we seek to do here.

There are four major concerns about biomedical R&D, despite its impressive technological advances amid profound transformations in how knowledge is generated and used. The first is the lack of medicines in areas where market incentives are inadequate to attract private investment, such as for neglected diseases of poverty, bacterial infections and emerging infectious diseases1. Second is the slow pace of progress in some areas, such as Alzheimer's disease2. Third is the risk of harm, such as adverse drug reactions. The final concern is restricted access to technologies, caused by high prices, insufficient production or inadequate supply3.

These concerns pre-date the emergence of the coronavirus SARS-CoV-2, but the pandemic has underscored the urgency of addressing them. That requires looking beyond just one country or sector.

Biomedical R&D is increasingly global. Historically, it was concentrated in the advanced industrialized countries (excluding traditional medicine). Today, there is rapid growth in low- and middle-income countries (LMICs) in capacity, investment and networks. And, as medicines markets have globalized, people on every continent pay for health technologies – either out of their own pockets or through public and private medical insurance.

Both public and private interests and investments drive R&D. Research is conducted by public laboratories, universities, private firms (small, medium and multinational), non-profit organizations and health-care facilities (public and private). It is funded by taxpayers, philanthropic foundations, private investors, companies and patients. And it is shaped by public policies and agencies, such as those for intellectual property (IP), regulatory standards, procurement, treatment guidelines and reimbursement.

All of these actors can and should reorient the biomedical R&D system to better serve the global public interest (see 'Checklist for R&D in the global public interest'). Concretely, that means answering three questions: why do R&D? How should it be done, and for whom?

Checklist for R&D in the global public interest

Citizens, researchers, governments, intergovernmental organizations, regulators, funders, industry and universities are all stakeholders in public-interest research and development (R&D). They must collaborate to:

• Prioritize public-health needs through structured, inclusive, transparent and informed processes.

• Require that R&D is ethically conducted and scientifically sound.

• Mandate, incentivize and facilitate rapid, open sharing of inputs, processes and outputs.

• Invest in the long term to strengthen scientific, technological and regulatory capacity across all countries.

• Provide timely access to health technologies that are safe, efficacious and offer therapeutic advances.

• Ensure R&D meets the needs of subpopulations such as children, older people and those who might become pregnant.

• Recognize all contributions fairly.

• Share all benefits equitably.

• Build affordability, availability and suitability into the R&D process. ###

Why? Priorities

R&D should respond to priority health needs — such as for new antibiotics — as well as advancing knowledge or responding to intellectual curiosity. However, there is still a lack of systematic approaches to setting R&D priorities. Without them, the market will decide on the basis of the greatest financial return and the lowest risk. Well-organized interest groups will drown out less-powerful voices. The result? Of more than 56,000 candidate products currently under development, 57% are for cancerous tumours. Only 0.5% are for the neglected tropical diseases that affect nearly 2 billion people.

Investigator-driven research is the norm for early-stage discovery. But history has demonstrated the value of strategic efforts to translate science into solutions that ultimately affect people's health. For example, during the Second World War, governments drove the successful mass production of penicillin and development of malaria drugs4. Such 'mission-oriented' approaches require public stewardship5.

Because setting priorities involves value judgements, it must not be done by technical experts alone. Instead, priorities need to be set through processes that are transparent, adaptable and inclusive6. These can and must engage citizens, and account for the needs of patients and disadvantaged groups7.

Most R&D priorities transcend borders. Yet priority-setting arrangements across countries are inadequate. Countries that have the greatest burdens of neglected diseases, for example, have had little input. Instead, priorities are largely funded and decided by high-income country donors8. Furthermore, priority-setting requires 'gap analyses' of existing technologies and ongoing R&D. Such information, often opaque and fragmented, requires significant resources to gather and interpret.

Better priority-setting is possible. For example, during the 2015–16 Zika epidemic in Brazil, local associations of mothers of children affected by congenital Zika virus syndrome participated directly in setting national research priorities9,10. The World Health Organization (WHO) Global Observatory on Health R&D collates and publishes online, open-access analyses of ongoing R&D for all therapeutic areas (see go.nature.com/3hnxxhi).

During the COVID-19 pandemic, the WHO has regularly convened funders and scientists to identify global R&D priorities and track their progress. To address priorities that are

specific to LMICs, 77 research organizations spanning all world regions launched the COVID-19 Clinical Research Coalition. In their joint 2019 Global Action Plan for Healthy Lives and Well-being for All, United Nations agencies committed to supporting countries that wish to develop locally owned research agendas (see go.nature.com/3jsntnc).

But there is much more that public authorities and research funders can do to make informed, inclusive priority-setting processes the norm.

How? Ethical, sound, open, fair

All biomedical R&D must be ethical and scientifically sound. Authoritative, international ethics guidelines already exist for research involving human participants. Practices do not always meet these standards, however, nor is monitoring reliable. Increased outsourcing to contract-research organizations and the globalization of clinical trials requires close oversight to manage risks11. This is particularly important when authorities have limited experience with new technologies or research regulation12. COVID-19 has further demonstrated the value of regulators collaborating internationally to pool information and expertise; a good example is the African Vaccine Regulatory Forum.

Duplicative research also raises ethical questions. Careful replication is essential for sound science. But duplication that is not part of validation exposes human participants to avoidable risks; it wastes funds, time and human resources. Open science improves efficiency and accelerates scientific progress. How? By the timely sharing of research inputs (such as specimens, compound libraries and data sets with appropriate protections), processes (such as protocols, trial designs and cost data) and outputs (including trial results and publications).

Current arrangements are inadequate for ensuring such openness, however, despite widespread recognition of its value. For example, the majority of clinical-trial outcomes are not reported on time13. This is despite steady progress following clear governmental and funder policies that require all trials to be registered and their results made public14.

COVID-19 has prompted important steps forward. One is the publication of vaccine trial protocols15 and large-scale collaboration and data sharing through the WHO Solidarity and UK RECOVERY therapeutics trials16. Another is the huge increase in open sharing of genomic sequencing data on SARS-CoV-2 that enables scientists to track how, where and when the virus is changing17.

Significant changes in rules and incentives are needed to secure the rapid, open sharing of inputs, processes and outputs18. For example, IP rights can be too upstream (limiting research methods), too wide (for strategic reasons) and too strong (hard to license)19. It is in the public interest to maximize freedom to innovate, access to knowledge and follow-on research. But these require the stewardship of IP throughout the R&D process. Various initiatives to license, pool or innovate without IP demonstrate what such stewardship can look like. It is crucial to govern IP to maximize the societal benefits of knowledge, not merely to generate new inventions20.

Furthermore, those contributing to value creation must get fair recognition and share in its benefits21. Such contributions are broader than is often recognized. They can include funding, scientific expertise, infrastructure, formalized IP and traditional knowledge. Individuals or communities provide data, samples and participate in trials.

Consider these inequities. LMICs that hosted COVID-19 vaccine trials received fewer doses per capita than did high-income countries22. South African researchers publicly shared

genomic sequencing data on the Omicron variant of SARS-CoV-2 through the GISAID database, enabling product developers to jump-start potential adaptations to pre-existing drugs and vaccines, but without guarantees that those products will be accessible to South Africa.

Change is feasible, albeit arduous. The 2011 WHO Pandemic Influenza Preparedness Framework painstakingly crafted a political bargain between public and private actors. It commits governments to share influenza samples openly in exchange for industry guarantees to provide certain volumes of the vaccines or other products that firms develop using the samples23. Under the framework, countries have shared more than 1,300 samples, and the WHO has secured legally binding commitments from industry for 420 million vaccine doses in the event of an influenza pandemic24. Another notable effort is the Council on Health Research for Development's Research Fairness Initiative. This self-assessment tool enables research partners to examine and improve their benefit-sharing arrangements.

COVID-19 has demonstrated the feasibility of more-open R&D and wider sharing of its benefits. The GISAID platform makes genomic data openly available, while protecting certain rights of contributors to seek benefits derived from the data shared25. The drug firm AstraZeneca committed to transfer technology and forgo profit from sales of the COVID-19 vaccine it jointly developed with the University of Oxford, UK, for the duration of the pandemic. The WHO created the COVID-19 Technology Access Pool, a platform for technology holders to share IP, knowledge and data with potential product manufacturers. The UN-backed Medicines Patent Pool has negotiated licences with the drug makers Pfizer and Merck for COVID-19 treatments to be sold as low-cost generic drugs in 95 and 105 LMICs, respectively; a number of middle-income countries are excluded, however. The COVID-19 Moonshot, a "spontaneous, open, global, Twitter-fuelled collaboration" to discover and develop therapeutics for COVID-19 without patenting them, is moving towards identifying clinical-trial candidates this year26.

Despite all this, there are clearly global inequalities in access to COVID-19 countermeasures. These demonstrate that much broader uptake of open science and benefit sharing are still needed, as is more learning-by-doing and regular exchange.

Finally, as COVID-19 has shown, investment in scientific, regulatory and technological capacity must be a higher political priority in countries at all levels of development (see go.nature.com/34trtjv). North–south initiatives for capacity-strengthening and technology transfer have operated over many years. Yet concerns remain about power disparities and measurable impact27. An evaluation of the Wellcome-funded African Institutions Initiative, a network of 7 research capacity-building consortia across 18 African countries, found benefits in a more nationally driven, network-based approach28. A group of partners has established a WHO technology-transfer hub for messenger RNA vaccines in South Africa as a multilateral, transparent mechanism to build capacity to use new technologies in LMICs; other regions have expressed interest in doing the same. Perhaps the pandemic will bolster national willingness to make the sustained investments required for adequate institutional capacity.

For whom?

Health technologies need to be safe, efficacious and high quality. Many national and international standards and institutions exist to rigorously assess the safety and efficacy of new technologies, regulate manufacturing quality and ensure adequate tracking of adverse

events after a technology reaches the market. Yet significant debate remains on how exactly to carry out these duties12.

Regulators need to collaborate more if technologies are to improve health quickly across different global contexts. This includes finding ways to share or accept data across borders to reduce delays. Requirements to conduct clinical trials domestically — despite relatively low numbers of cases — delayed regulatory approval of COVID-19 vaccines in Japan before it hosted the summer Olympic Games in 202129.

A review of regulations for accelerated regulatory approval of products in emergencies found more than 50 pathways in 24 countries30. Important advances have been made, such as the WHO initiative to assess health technologies collaboratively with national regulators to speed up decision-making (see go.nature.com/3mgek7d). Regional efforts include the creation of the European Medicines Agency in 1995 and of the African Medicines Agency in 2021. Further development is needed.

Currently, regulators do not always require evidence of a therapeutic advance before granting approval, nor are sufficient longer-term studies necessarily conducted after a product is marketed31. Instead, they should require concrete improvements, such as increased efficacy, reduced toxicity, fewer adverse reactions or improved patient adherence. And they should ensure that interventions address subpopulations such as children, older people or those who might become pregnant.

To address these challenges, the use of health-technology assessment has been expanding worldwide: it often involves conducting cost–benefit analyses of competing technologies to inform policy32. For example, several European countries require evidence of therapeutic advance for a medicine to qualify for reimbursement33. Nevertheless, more rules, incentives and financing are needed to ensure technologies benefit all groups.

In addition, there needs to be more emphasis on how upstream R&D decisions affect affordability and availability. For products with potentially lucrative markets, such as cancer treatments, low prices have not been an objective of commercial R&D. This can place treatments totally out of reach for most3.

In a few areas, affordability and availability are core objectives34. The Drugs for Neglected Diseases initiative, for instance, has specified price targets for drugs in advance in design specifications, and has licensed IP to encourage competition between manufacturers7. Some COVID-19 R&D projects also aim for global access, such as the COVID-19 Moonshot26, the unpatented Corbevax vaccine developed at Baylor College of Medicine in Houston, Texas, and vaccines for which R&D was largely funded by the Coalition for Epidemic Preparedness Innovations (CEPI)35. It is crucial to learn from these efforts.

Given the important role that public and philanthropic funders have in all areas of R&D (and ultimately as purchasers of medicines), much more can be done to build conditionalities into health innovation. As well as stipulations about IP, supply and pricing, requirements can include transparency and reinvestment of profits into research. Public-interest research funders could work together on affordability.

Finally, high-quality health technologies must be available and appropriately designed for where and when people need them. Much of this lies outside the control of R&D actors, but not all. For example, IP can be licensed to develop new products or adapt existing ones to better suit different contexts, as happened with the HIV drug dolutegravir. The US drug firm ViiV Healthcare licensed patents on dolutegravir to the Medicines Patent Pool, which enabled generic-drugs manufacturers to combine it with two other therapies in a single pill to

make treatment easier for people to take. This is now the WHO-recommended first-line therapy. Technology transfer can enable multiple manufacturers to prevent shortages and secure supply, as for AstraZeneca's COVID-19 vaccine. Developers can also submit registration dossiers promptly in all countries where products are needed36.

Including these considerations in research-funding models could make health technologies more widely available.

Seize the day

We recognize that reorienting the system towards the public interest is hard. First, nationalism is not easy to align with global health concerns. Taxpayer-financed funders often have industrial, economic and political objectives, as well as health and science ones, such as competitiveness, job creation or boosting exports. Competition between nations, as witnessed in the scramble for COVID-19 vaccine doses, can undermine the willingness to cooperate.

Yet international agreements can structure cooperation to meet each country's needs37, as shown by the influenza framework. International agreements could require contributions of human, financial, cultural and knowledge resources to R&D efforts in return for fair recognition and access to benefits, thereby serving the self-interest of all countries38.

Second, public and private interests are not always aligned. Maximizing returns on private investment is often counter to dedicating resources to unprofitable diseases or ensuring universal affordability of medicines; openly sharing data or IP can dent competitiveness.

But COVID-19 has demonstrated that public funding and stewardship can reduce the R&D costs and risks borne by the private sector39 — for example, by making affordability or data transparency more feasible. Sharing knowledge or technology is more realistic, albeit not guaranteed, when it has been co-produced by public and private actors. For example, CEPI subsidized R&D and technology transfer for US-based drug firm Novavax's COVID-19 vaccine. The first regulator-approved doses of this vaccine have been produced in India, with priority supply going to developing countries through the COVAX programme. A creative combination of regulation, incentives and persuasion can align private objectives with the global public interest.

These fundamental governance challenges are not new. Many efforts have been made to address them. These often focus on specific therapeutic areas such as neglected diseases, antibiotics and pandemics, or cover groups of countries or parts of the R&D process (basic research, discovery, translation, development, regulatory review, production, pricing and distribution). Alternatively, they might focus on certain means to achieve specific ends (an international treaty, a global R&D fund, declarations on ethical research or platforms for data sharing)38.

In this article, we have taken a step back and sought to articulate a more holistic vision. COVID-19 has both exposed the shortcomings of the R&D system and offered concrete examples of how we can and must reorient it to meet the global public interest. The 1948 Universal Declaration of Human Rights recognizes people's right to "share in scientific advancement and its benefits". If not now, when?

References

1. Pedrique, B. *et al. Lancet Glob. Health* **1**, E371–E379 (2013).

2. Bachurin, S. O., Bovina, E. V. & Ustyugov, A. A. *Med. Res. Rev.* **37**, 1186–1225 (2017).

3. Morgan, S. G., Bathula, H. S. & Moon, S. *BMJ* **368**, L4627 (2020).

4. Gross, D. & Sampat, B. *Crisis Innovation Policy from World War II to COVID-19*. NBER Working Paper 28915 (National Bureau of Economic Research, 2021).

5. Mazzucato, M. *Mission-Oriented Research & Innovation in the European Union* (European Commission, 2018).

6. Montorzi, G., De Haan, S. & IJsselmuiden, C. *Priority Setting for Research for Health: A Management Process for Countries* (Council on Health Research for Development, 2010).

7. Drugs for Neglected Diseases initiative. *15 Years of Needs-Driven Innovation for Access* (DNDi, 2019).

8. Beyeler, N., Fewer, S., Yotebieng, M. & Yamey, G. *BMJ Glob. Health* **4**, e001209 (2019).

9. Gadelha, P., Lima, N. T., Rangel, V. F. & Stabeli, R. *Policy Focus* **13**, 23–26 (2016).

10. Silva, L., Albuquerque, M. & Mayrink, M. F. *Saúde em Debate* **45**, 861–870 (2021; in Portuguese).

11. da Silva, R. E., Amato, A. A., Guilhem, D. B. & Novaes, M. R. C. G. *Int. J. Clin. Trials* **3**, 1–8 (2016).

12. Coleman, C. H. *et al. Dev. World Bioeth.* **15**, 241–247 (2015).

13. DeVito, N. J., Bacon, S. & Goldacre, B. *Lancet* **395**, 361–369 (2020).

14. Moorthy, V. S., Karam, G., Vannice, K. S. & Kieny, M. P. *PLoS Med.* **12**, e1001819 (2015).

15. Doshi, P. *BMJ* **371**, m4058 (2020).

16. Burki, T. K. *Lancet Respir. Med.* **8**, 1178–1180 (2020).

17. Swaminathan, S. *Nature* **588**, 583–585 (2020).

18. Munos, B. *Clin. Pharmacol. Ther.* **87**, 534–536 (2010).

19. Mazzoleni, R. & Nelson, R. R. *J. Econ. Issues* **32**, 1031–1052 (1998).

20. WHO Council on the Economics of Health for All. *Governing Health Innovation for the Common Good* (World Health Organization, 2021).

21. Lazonick, W. & Mazzucato, M. *Ind. Corp. Change* **22**, 1093–1128 (2013).

22. Ramachandran, R., Ross, J. S. & Miller, J. E. *JAMA Netw. Open* **4**, e2134233 (2021).

23. Fidler, D. P. & Gostin, L. O. *JAMA* **306**, 200–201 (2011).

24. World Health Organization. *Pandemic Influenza Preparedness Framework: 18-month Progress Report, 1 January 2020–30 June 2021* (WHO, 2021).

25. Shu, Y. & McCauley, J. *Euro Surveill.* **22**, 30494 (2017).

26. von Delft, F. *et al. Nature* **594**, 330–332 (2021).

27. Chu, K. M., Jayaraman, S., Kyamanywa, P. & Ntakiyiruta, G. *PLoS Med*. **11**, e1001612 (2014).

28. Cochrane, G. *et al. The African Institutions Initiative: Insights from the First Four Years* (RAND Corporation, 2014).

29. Kosaka, M., Hashimoto, T., Ozaki, A., Tanimoto, T. & Kami, M. *Lancet* **397**, 2334–2335 (2021).

30. Simpson, S., Chakrabarti, A., Robinson, D., Chirgwin, K. & Lumpkin, M. *npj Vaccines* **5**, 101 (2020).

31. Wieseler, B., McGauran, N. & Kaiser, T. *BMJ* **366**, L4340 (2019).

32. Oortwijn, W., Broos, P., Vondeling, H., Banta, D. & Todorova, L. *Int. J. Technol. Assess. Health Care* **29**, 424–434 (2013).

33. Panteli, D. *et al. Health Syst. Transit.* **18**, 1–122 (2016).

34. Muñoz, V., Visentin, F., Foray, D. & Gaulé, P. *Sci. Public Policy* **42**, 315–338 (2015).

35. Lurie, N., Saville, M., Hatchett, R. & Halton, J. *N. Engl. J. Med.* **382**, 1969–1973 (2020).

36. Moran, M., Guzman, J., McDonald, A., Wu, L. & Omune, B. *Registering New Drugs: The African Context* (George Inst. for International Health, 2010).

37. Keohane, R. O. *After Hegemony: Cooperation and Discord in the World Political Economy* (Princeton Univ. Press, 1984).

38. WHO Consultative Expert Working Group on Research and Development. *Financing and Coordination. Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination* (World Health Organization, 2012).

39. Moon, S., Alonso Ruiz, A. & Vieira, M. *N. Engl. J. Med.* **385**, 193–196 (2021).

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