THE CENTER FOR POLICY IMPACT IN GLOBAL HEALTH

OPEN CONSULTANTS

Reforming the research and development ecosystem for neglected diseases, emerging infectious diseases, and maternal health

提高被忽视疾病、新发传染病和孕产妇健康产品开发效率的健康和经济效益

AUTHORS:作者

Marco Schäferhoff,[1] Gavin Yamey,[2] Osondu Ogbuoji,[2] Ayodamope Fawole[2], Armand Zimmerman,[2] Ipchita Bharali,[2] Shingai Machingaidze,[3] Ernesto J. Ortiz,[2] Mosa Moshabela,[4] Ming Xu[5]

1: Open Consultants, Berlin 柏林 Open咨询公司

2: Center for Policy Impact in Global Health (CPIGH), Duke University, Durham, North Carolina, USA 美国北卡罗来纳州达勒姆杜克大学全球健康政策影响中心（CPIGH）

3: Global health consultant 全球健康顾问

4: School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa
南非德班夸祖鲁-纳塔尔大学护理与公共卫生学院

5: Department of Global Health, School of Public Health & Institute for Global Health and Development, Peking University, Beijing, China
中国北京，北京大学公共卫生学院全球卫生系及全球卫生与发展研究所

TABLE OF CONTENTS目录

Acknowledgements: We thank all key informants for generously sharing their expertise and relevant data. We also thank Luca Pusceddu from Open Consultants and Jane Claire Anderson from CPIGH for their editorial and organizational support in fnalizing this study. We thank Agata Rocka from Rocka Design for graphic design of this report.

致谢:我们感谢所有慷慨分享专业知识和数据的所有人。感谢Open Consultants的Luca Pusceddu和来自CPIGH的Jane Claire Anderson为本研究提供的编辑和组织方面的支持。感谢来自Rocka设计公司的Agata Rocka负责本报告的平面设计。

经费:本研究由比尔和梅林达·盖茨基金会的研究经费资助

ACT-A	Access to COVID-19 Tools Accelerator访问 COVID-19 工具加速器
Africa CDC	Africa Centres for Disease Control and Prevention非洲疾病控制和预防中心
AU	African Union非洲联盟
AMA	African Medicines Agency非洲药品管理局
AMRH	African Medicines Regulatory Harmonization非洲药品监管协调
AI	Artificial intelligence 人工智能
AMC	Advanced market commitment预先市场承诺
APA	Advanced purchase agreement预购协议
AVAT	African Vaccine Acquisition Trust非洲疫苗收购信托基金
AVAREF	African Vaccine Regulatory Forum非洲疫苗监管论坛
AVMA	African Vaccine Manufacturing Accelerator非洲疫苗生产加速器
ASEAN	Association of Southeast Asian Nations 东盟
CMA	Conditional marketing authorization有条件的上市许可
CEPI	Coalition for Epidemic Preparedness Innovations防疫创新联盟
CoGs	Cost of goods 药品成本
CPP	Certificate of pharmaceutical product药品证书
CPIGH	Center for Policy Impact in Global Health, Duke University杜克大学全球健康政策影响中心
DALYs	**Disability-adjusted life years 伤残调整寿命年**
DCTs	Decentralized clinical trials分散式临床试验
DHTs	Digital health technologies数字医疗技术
DHVI	Duke Human Vaccine Institute杜克人类疫苗研究所
EAC	East African Community东非共同体
EDEN	Efficacy Discriminating Educated Network
EIDs	Emerging infectious diseases新发传染病
EMA	European Medicines Agency欧洲药品管理局
EUA	Emergency use authorization紧急使用授权
FDA	US Food and Drug Administration美国食品和药物管理局
FIND	Foundation for Innovative New Diagnostics创新诊断基金会
FGHI	Future of Global Health Initiatives全球健康倡议的未来
Gavi	Gavi, the Vaccine Alliance疫苗联盟 Gavi
GAO	US Government Accountability Office美国政府问责局
GBT	WHO Global Benchmarking Tool世界卫生组织全球基准工具
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria全球抗击艾滋病、结核病和疟疾基金
GMP	Good Manufacturing Practice良好生产规范
HCTs	Human challenge trials人体挑战试验
HECT	Highly Efficient Clinical Trials高效临床试验 人用药品注册技术要求国际协调会议
HIC	High-income country高收入国家
HPV	Human papillomavirus人类乳头瘤病毒
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use人用药品注册技术要求国际协调会议

ICMRA	International Coalition of Medicines Regulatory Authorities国际药品监管机构联盟
IRB	Institutional review board机构审查委员会
KI	Key informant主要信息提供者
KII	Key informant interview主要信息提供者访谈
LIC	Low-income country低收入国家
LiST	Lives Saved Tool挽救生命工具
LMICs	Low- and middle-income countries中低收入国家
mAbs	Monoclonal antibodies单克隆抗体
MCM	Medical countermeasure医疗对策
MH	Maternal health产妇保健
ML	Maturity level成熟度
NCDs	Non-communicable diseases非传染性疾病
NDs	Neglected diseases被忽视的疾病
NRA	National regulatory authority国家监管机构
PACs	Post-approval changes批准后的变更
PAVM	Partnership for African Vaccine Manufacturing非洲疫苗生产伙伴关系
PE&E	Preeclampsia and eclampsia先兆子痫和子痫
PEPFAR	U.S. President's Emergency Plan for AIDS Relief美国总统艾滋病紧急救援计划
PPH	Postpartum hemorrhage产后出血
PPR	Pandemic preparedness and response大流行病的准备和应对
PRIME	PRIority MEdicines scheme优先药品计划
PQ	WHO prequalification of medicines世卫组织药品预认证
PRV	Priority review voucher优先审查凭证
R&D	Research and development研究与开发
REC	Regional economic community区域经济共同体
RSV	Respiratory syncytial virus呼吸道合胞病毒
RWD	Real world data真实世界数据
SCA	Synthetic control arm合成对照臂
SRA	Stringent regulatory authority严格的监管机构
SSA	Sub-Saharan Africa撒哈拉以南非洲
SADC-MRH	Southern African Development Community Medicines Regulatory Harmonization南部非洲发展共同体药品监管协调机构
SRH	Sexual and reproductive health性健康和生殖健康
TB	Tuberculosis结核病
TLD	Tenofovir, lamivudine, and dolutegravir替诺福韦、拉米夫定和多罗替拉韦
TLE	Tenofovir, lamivudine, and efavirenz替诺福韦、拉米夫定和依非韦伦
tWLA	Transitional WHO-listed authority过渡性世卫组织列名机构
WHO	World Health Organization世界卫生组织
WLA	WHO-listed authority世卫组织列名机构

EXECUTIVE SUMMARY概要

Aims, methods, and analytic framework

The long timelines, high attrition rates, and high costs of global health research and development (R&D) are impeding the development of new health technologies. This study examines the key shifts in the R&D ecosystem that could help overcome these problems and accelerate the discovery and development of new tools for neglected diseases (NDs), emerging infectious diseases (EIDs), and maternal health (MH) over the next 20 years. The analysis is based on insights and data from:

全球医药研发（R&D）时间长、损耗率高、成本高，阻碍了新医药技术的开发。本研究探讨了研发生态系统的有助于克服这些困难的关键转变，并在未来 20 年内加快发现和开发治疗被忽视疾病 (ND)、新发传染病 (EID) 和孕产妇健康 (MH) 的新工具。该分析基于以下方面的见解和数据：

A workshop with over 30 senior policy actors who are engaged in global health R&D policymaking, held in London on August 8-9, 2023, which had strong representation from low- and middle-income countries (LMICs). At this workshop, we shared and received feedback on our proposed study approach and elicited participants' views on the likely shifts in the R&D ecosystem that could drive efficiencies. A second virtual meeting was held in February 2024 to discuss our findings.

2023 年 8 月 8-9 日，我们在伦敦与 30 多位参与全球健康研发决策的资深政策制定者举行了一次研讨会，来自中低收入国家（LMICs）的代表参加了此次研讨会。在这次研讨会上，我们分享了我们建议的研究方法并收到了反馈意见，还征求了与会者对改革研发生态系统提高效率的看法。2024 年 2 月举行了第二次虚拟会议讨论我们的发现。

Key informant (KI) interviews with over 60 key informants (KIs) worldwide, held between August 2023 and March 2024. We interviewed a broad range of KIs, including from academia, bilateral and multilateral health agencies, pharmaceutical companies, research funding agencies, regulatory agencies, product development partnerships, non-government organizations, foundations, and regional alliances. In addition, we organized regional consultations in Africa, Asia, and Latin America to better understand regional ecosystem needs. Over 60 additional stakeholders were consulted in this regional consultation process.

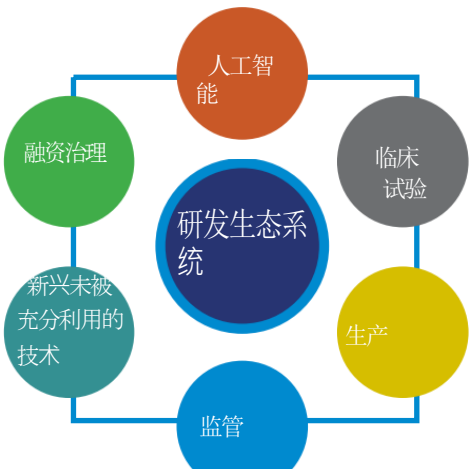
在 2023 年 8 月至 2024 年 3 月期间与全球 60 多名关键信息提供者（KIs）进行了访谈。我们采访了来自学术界、双边和多边卫生机构、制药公司、研究资助机构、监管机构、产品开发伙伴、非政府组织、基金会和区域联盟。此外，我们还在非洲、亚洲和拉丁美洲组织了地区磋商，以更好地了解地区研发生态系统的需求，期间，我们还咨询了另外 60 多个利益相关方，对同行评议的文献和灰色文献进行文献综述。

A review and synthesis of the peer-reviewed and grey literature.

The analytic framework used for the study examined the R&D ecosystem across six key dimensions, which we validated with stakeholders at the London workshop (Figure ES1).

研究中使用的分析框架从六个关键方面考察了研发生态系统，我们在伦敦研讨会上与利益相关者对这六个方面进行了验证（图 ES1）。

图ES1: 研发生态系统的六大维度



Our study has three key limitations. First, the evidence on potential efficiency gains from ecosystem shifts is still nascent and some of it comes from high-income countries (HICs) and from studies on non-communicable diseases (NCDs). These findings cannot always be easily translated to NDs, EIDs, and MH in LMICs. Second, our paper does not address the transformations needed in R&D for NCDs in LMICs, even though the burden of NCDs will continue to grow in these countries over the next 20 years. Third, this report does

not analyze delivery systems, which were beyond the scope of our study, but which are essential to ensure access to new health tools.
我们的研究有三个主要局限性。首先，有关生态系统转变可能带来的经济效益的证据仍处于萌芽阶段，其中一些证据来自高收入国家（HIC）和有关非传染性疾病（NCD）的研究。这些发现并不总能轻易地转化为中低收入国家的被忽视疾病、新发传染病和孕产妇保健（ND, EID, MH）。其次，我们的论文并没有涉及低收入国家在非传染性疾病研发方面所需的转变。
第二，我们的报告没有涉及低收入与中等收入国家在非传染性疾病研发方面所需的转型，尽管这些国家的非传染性疾病负担在未来 20 年内将继续加重。第三，本报告没有分析交付系统，这超出了我们的研究范围，但该系统对确保获得新的医疗工具至关重要。

Key findings on efficiencies and their policy implications

对于效率及其政策启示的主要发现

APPLYING ARTIFICIAL INTELLIGENCE (AI) TO PRODUCT DEVELOPMENT在产品研发中运用人工智能

Given its potential to drive major efficiencies, there is huge interest in applying AI to global health R&D. AI has been applied across the whole product development spectrum, including new target identification, drug candidate selection, protein structure prediction, molecular compound design and optimization, and clinical trial design, conduct, and analysis. AI can accelerate discovery and preclinical research and reduce its costs. The standard time for screening, identifying, and validating target molecules is 3-5 years, with costs of up to US$10 million; with AI, the discovery phase can be shortened to less than 12 months.
鉴于人工智能具有推动重大创新的潜力，人们对将人工智能应用于全球卫生研发兴趣浓厚。人工智能已
人工智能已被应用于整个产品开发领域，包括新靶点识别、候选药物选择、蛋白质结构预测、分子化合物设计和优化以及临床试验设计、实施和分析。人工智能可以加速发现和临床前研究，并降低其成本。筛选、确定和验证目标分子的标准时间为 3-5 年，成本高达 1 千万美元；有了人工智能，发现阶段可缩短到 12 个月以内。

There are also examples of AI tools that have lowered discovery costs by a factor of up to 50. Compared with traditional screening approaches, AI tools can improve
screening and thus the quality of candidates, leading to less attrition during the clinical phase. AI tools have been used to identify truly novel compounds, which resulted in promising new drug candidates that are currently being tested in clinical trials. There is also a valuable role for AI platforms in drug repurposing and in identifying combination therapies; such platforms have identified optimal drug combinations (e.g., for COVID-19) faster and at lower cost compared with conventional approaches. AI platforms can predict trial success with high accuracy, which could reduce the costs of the clinical phase, e.g., one AI prediction tool, trained on 55,600 unique Phase 2 clinical trials over 7 years, predicted the probability of moving to Phase 3 with 79% accuracy.
也有人工智能工具将发现成本最多降低 50 倍的例子。与传统筛选方法相比，人工智能工具可以提高筛选效率，从而提高候选药物的质量，减少临床阶段的损耗。人工智能工具已被用于识别真正的新型化合物，从而产生了目前正在进行临床试验候选新药。人工智能平台在药物再利用和确定联合疗法方面也发挥着重要作用；与传统方法相比，这类平台能以更快的速度和更低的成本确定最佳药物组合（如 COVID-19）。人工智能平台可以高精度地预测试验成功与否，这可以降低临床阶段的成本，例如，一个人工智能预测工具在 7 年内对 55,600 项独特的 2 期临床试验进行了训练，预测进入 3 期临床试验的概率的准确率高达 79%。
However, AI has several limitations. If it is rolled out inequitably, AI could augment inequalities between LMICs and HICs. African researchers have therefore called for a research agenda on AI grounded in the African context to determine locally relevant strategies for its development and use. Most of the data feeding into AI tools comes from HICs and there is very little data on the use of AIfor R&D for NDs.
然而，人工智能也有一些局限性。如果推进得不公平，人工智能可能会加剧低收入和中等收入国家与高收入国家之间的不平等。因此，非洲研究人员呼吁制定一项立足于非洲国情的人工智能研究议程，以确定适合当地的人工智能发展和使用战略。为人工智能工具提供的大部分数据来自高收入国家，而关于将人工智能用于被忽视疾病研发的数据却很少。

Nevertheless, our analysis of the evidence, together with the experience of KIs interviewed for this project, shows that AI is already transforming the global health R&D ecosystem. While AI offers unprecedented opportunities for drug discovery, AI tools have the potential to optimize the entire product development process (from “end to end”), which could substantially reduce future R&D costs, accelerate R&D timelines, and lead to new medicines.
尽管如此，我们对证据的分析以及为本项目采访的主要信息提供者的经验表明，人工智能已经在改变全球卫生研发生态系统。人工智能为药物研发提供了前所未有的机遇。同时，人工智能工具还有可能优化整个产品开发流程（从 “端到端”），从而大幅降低未来的研发成本，加快研发进度，并开发出新药。

WE RECOMMEND FIVE KEY REFORMS:关键改革建议

1. Leverage the substantial efficiencies and benefits of AI in drug discovery and preclinical research: global health R&D funders should increase their investment in AI-based companies.
充分利用
利用人工智能在药物发现和临床前研究中的巨大效率和优势
全球健康研发
资助者应增加对人工智能公司的投资。

2. Expand the use of AI for epidemic and pandemic preparedness: use AItools to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library.
扩大人工智能在流行病和大流行病防备方面的应用：
利用人工智能工具预测重点病原体的蛋白质结构，以协调建立疫苗库

3. Further assess and leverage the potential of AI in clinical research: using AI in the prediction of clinical trial outcomes, for example, can lead to cost savings.

Significantly strengthen existing regulatory frameworks for AI in global health.

进一步评估和利用人工智能在临床研究中的潜力：例如，在预测临床试验结果时使用人工智能可以节省成本。
例如，利用人工智能预测临床试验结果可以节约成本。
大力加强全球卫生领域人工智能的现有监管框架。
大力加强全球卫生领域人工智能的现有监管框架

4. Enable LMICs to meaningfully participate in AI-driven R&D and build respective capacity and expertise: Without such participation, existing inequalities in global health will be widened. Partnerships between AI companies—which are mostly based in HICs—and LMIC researchers will be important. Efforts to develop an African-led AI research agenda should be supported.

4. 使中低收入国家能够有意义地参与人工智能驱动的研发，并建立各自的能力和专业知识，否则双方差距会进一步加大。

人工智能公司(主要位于高收入国家)和中低收入国家研究人员之间的合作将非常重要。应该支持制定非洲主导的人工智能研究议程的努力。

5. Significantly strengthen existing regulatory frameworks for AI in global health.
大力加强全球医疗事业人工智能运用的监管框架

INNOVATIONS IN CLINICAL TRIAL CONDUCT临床试验行为的创新

Clinical trials are essential in showing that a product is effective and safe. New health tools for NDs, EIDs, and MH should ideally be trialed in LMICs, where the burden of disease is highest, ensuring inclusive and representative selection of trial participants. Yet the vast majority of trials are conducted in HICs. In addition, traditional trial designs are expensive, lengthy, and have low success rates. The good news is that advances in trial conduct are now driving efficiencies and the COVID-19 pandemic validated many of these advances, e.g., trial networks were critical to the rapid development of vaccines, while platform trials like RECOVERY helped usher in COVID-19 therapies.
临床试验对于证明产品的有效性和安全性至关重要。理想情况下，针对被忽视疾病疾病（ND）、新发传染病（IED）和孕产妇保健（MH）的新医疗工具应在疾病负担最重的中低收入国家试用，以确保试验参与者的选择包容性和代表性。然而，绝大多数试验都是在高收入国家进行的。此外，传统的试验设计成本高、耗时长、成功率低。好消息是，试验行为的进步正在提高效率，COVID-19大流行验证了其中的许多进步，例如，试验网络对疫苗的快速开发至关重要，而RECOVERY等平台试验帮助引入了COVID-19疗法。

Innovations in trial conduct can be categorized into technological innovations, e.g., digital clinical trials (DCTs) and open source trials software; innovative trial designs, e.g., master protocols (such as platform trials) and real world evidence; and trial networks. There is good evidence—mostly from HICs—that DCTs can reduce trial costs, timelines, and the number of patients needed in a trial and can improve recruitment and retention of participants. It is unclear whether the findings can be generalized to LMICs. Platform trials can drive efficiencies by shortening trial duration, evaluating more treatments per trial, reducing the number of patients required per trial (by up to 70%), and increasing the proportion of programs that accurately recognize an effective treatment. Using real-world data and evidence can lead to savings of US$10 million to US$20 million per trial, depending on how much synthetic control arms are used to replace traditional control arms. Clinical trial networks can drive efficiencies by using existing sites instead of creating new ones, recruiting patients more quickly and reliably, and reducing the number of patients needed by sharing control groups with other trials. Furthermore, the ability to rapidly test product candidates during outbreaks relies on the existence of effective and inclusive regional clinical trial networks that are kept “warm” in between infectious disease outbreaks.
试验行为方面的创新可分为技术创新，例如数字临床试验(DCT)和开源试验软件、创新试验设计，如主协议(如平台试验)和真实试验以及还有试验网络。良好迹象表明（大多来自高收入国家）数字临床试验可以降低试验成本、时间表和试验所需的患者数量，并可以改善参与者的招募和保留。目前尚不清楚这些发现是否可以推广到中低收入国家。平台试验可以通过缩短试验持续时间、每次试验评估更多的治疗方法、减少每次试验所需的患者数量(最多可减少70%)来提高效率，并增加准确识别有效治疗方案的项目比例。使用真实世界数据和证据可为每次试验节省1000万至2000万美元，这取决于使用多少合成控制臂来取代传统控制臂。临床试验网络可以通过使用现有的站点而不是创建新的站点提高效率，更快更可靠地招募患者，并通过与其他试验共享对照组来减少所需患者的数量。此外，在传染病爆发期间快速测试候选产品的能力取决于传染病爆发期间是否存在有效和包容的地区临床试验网络。

Capacity for conducting even traditional trials is currently limited in LMICs, and there are barriers to rolling out trial innovations in these settings (e.g., the high complexity of platform trials and maintaining data quality and privacy in DCTs). Nevertheless, we believe capacity building eforts should include innovative approaches.

目前，在中低收入国家开展传统试验的能力有限，而且在这些环境中推广试验创新也存在障碍（例如，平台试验的高复杂性以及在 DCT 中维护数据质量和隐私）。尽管如此，我们认为能力建设工作应包括创新方法。

WE RECOMMEND TWO KEY REFORMS:两大改革建议

1. Research funders and agencies should support sustained, long term efforts to build clinical trial networks that have the capacity to adopt innovative approaches, leveraging capacities already built. These networks need be kept active in between epidemics/pandemics.

2. Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, institutional review boards (IRBs), data safety boards, and regulators to become familiar with these designs. As innovative trial designs become more widespread in LMICs, operational lessons need to be shared so that implementation barriers can be tackled and best practices adopted.

1. 研究资助者和机构应支持建立临床试验网络的持续、长期努力，使其有能力采用创新方法，并利用已经建立的能力。流行病/大流行之间这些网络需要保持活跃。

2. 低资源环境下采用平台试验和其他主协议将要求资助机构、机构审查委员会、数据安全委员会和监管机构熟悉这些设计。随着中低收入国家的创新的试验设计越来越多，需要分享业务经验，以便解决实施困难并采用最佳做法。

BUILDING MANUFACTURING CAPACITY IN LMICs打造中低收入国家产能

Multiple high-level regional eforts, such as the Partnership for African Vaccine Manufacturing (PAVM), are now underway to increase manufacturing capacity in LMICs and enable these countries to become self-sufficient in making their own health products. Building such capacity has taken on new urgency to ensure that LMICs can manufacture medical countermeasures (MCMs) in the next pandemic rather than relying on donations from HICs. In addition, diagnostics experts interviewed for this study highlighted the lack of production capacity for diagnostics in LMICs and noted that the market for diagnostics is dominated by just a few major players.

如非洲疫苗制造伙伴关系(PAVM)等多个高级别项目目前正在进行以提高中低收入国家的制造能力，使这些国家能够生产自己的医疗产品。这种能力建设势在必行，以确保中低收入国家能够在下一次大流行病中拿出医疗对策，而不是依靠高收入国家的捐赠。此外，接受本研究采访的诊断专家指出中低收入国家缺乏诊断产品的生产能力，并指出诊断产品市场仅由少数主要参与者主导。

Traditional manufacturing is expensive. Innovative modular manufacturing approaches and optimized production processes for mRNA technologies could help to drive these costs down, speed up production, and globalize manufacturing. Modular facilities have a small footprint, so capital costs are much lower compared to traditional manufacturing sites. Optimized production processes for mRNA technologies have much lower operational costs because of high yields, reduced reagent use, and efficient design. Optimized mRNA production processes can save over 60% (about US$70 million) of the annual cost of goods for the production of 100 million vaccine doses compared to conventional mRNA manufacturing. These savings could lower mRNA vaccine production costs to US$0.5 per dose. An optimized mRNA production process ofers several other advantages—the fexibility to quickly switch from making one vaccine to another, scalable production, and integration of product development with large-scale manufacturing. Such integration is especially useful during pandemics, supporting a rapid response in line with the target of the Coalition for Epidemic Preparedness Innovations (CEPI) to develop a vaccine against the next Disease X within 100 days (“100 days mission”).

传统制造业成本高昂。创新的模块化制造方法和优化生产mRNA技术的进程可以帮助降低这些成本，加快生产和全球化制造业。模块化设施占地面积小，因此与传统设施相比，资本成本要低得多。优化的mRNA技术生产流程因其产量高、减少试剂的使用，和有效的设计大大降低了运营成本。与传统的mRNA制造相比，生产1亿剂疫苗，优化的mRNA生产过程可以节省成本的60%以上(约7000万美元)，将mRNA疫苗的生产成本降低到每剂0.5美元

mm These savings could lower mRNA vaccine production costs to US$0.5 per dose.
这些节省将mRNA疫苗的生产成本降低到每剂0.5美元

。优化的mRNA生产过程还提供了其他几个优势——灵活切换： 从生产一种疫苗快速切换到另一种疫苗；易升级以及整合产品开发的大规模制造业。这种整合能力在大流行病期间特别高效，支持根据流行病防范创新联盟(CEPI) (" 100天任务")：在100天内研制出针对下一种X疾病的疫苗的目标。

While modular mRNA sites ofer substantial benefts compared with traditional manufacturing, their full potential for LMICs still needs to be tested over the coming years. And there are several fnancial, political, and technical challenges to be addressed in creating sustainable markets and local demand. Despite these challenges, we believe that **investments in regional and sub-regional manufacturing in LMICs accompanied by regulatory strengthening would have a substantial public health impact and is a critical component of global pandemic preparedness and response (PPR)**.

尽管与传统制造方式相比，模块化 mRNA具有巨大优势，但其在低收入国家的全部潜力仍有待未来几年的检验。在创造可持续的市场和本地需求方面，还有一些融资、政治和技术挑战。尽管如此，我们还是相信在加强监管的同时，对中低收入国家的区域和次区域制造业进行投资，将对公共卫生产生重大影响，也是全球大流行病防备和应对（PPR）的重要组成部分。

WE RECOMMEND FOUR KEY REFORMS:

1. Donors need to support the creation of manufacturing capacity in LMICs over the long term. Building such capacity is part of planning for sustainable business models and creating market demand for routine immunization. Gavi, the Vaccine Alliance (Gavi) recently launched the African Vaccine Manufacturing Accelerator (AVMA), which will provide up to US$1 billion for creating sustainable vaccine production capacity on the African continent. Other funders must also be willing to subsidize manufacturing in LMIC regions and to guarantee procurement from LMIC manufacturers to create sustainable markets. They should make financial commitments and set concrete purchasing targets to enable the creation of sustainable production across regions, including Africa.
2. LMICs should also commit to buying products manufactured by LMICs, such as through advanced purchase agreements, to help create sustainable markets.
3. The multiple benefits of optimized mRNA production processes and modular production need to be leveraged. Such production approaches can be established faster and produce vaccines at much lower cost than conventional approaches. Nevertheless, supply chain problems (e.g., with reagents and other inputs) still need to be resolved.
4. While the construction of mRNA-based production sites should continue, diversified manufacturing is needed to enable production of existing licensed products across regions, including routine non-mRNA vaccines, drugs, and diagnostics. Building this capacity will also require a stronger focus on technology transfer, licensing agreements, and sharing of intellectual property (IP).

1.捐助方需要长期支持中低收入国家提高制造能力。建设这种能力是可持续的商业模式、为常规免疫接种创造市场需求规划的关键。疫苗联盟 (Gavi) 最近启动了非洲疫苗制造加速器 (AVMA)项目，将提供高达 10 亿美元的资金用于在非洲建立可持续的疫苗生产能力。其他资助者也必须愿意为中低收入和贫困地区的生产提供补贴，并保证从中低收入和贫困地区的生产商采购，以创造可持续的市场他们应做出资金承诺并制定具体的采购目标，以便在包括非洲在内的各地区建立可持续生产。
2. 中低收入国家也应承诺购买中低收入国家生产的产品，如通过预先采购协议，以帮助创造可持续市场。
创造可持续市场。
3. 需要充分利用优化的 mRNA 生产流程和模块化生产的多重优势。这种生产与传统方法相比速度更快、生产疫苗的成本更低。然而供应链问题（如试剂和其他投入）仍有待解决。
4. 在继续建设基于 mRNA 的生产基地的同时，还需要进行多样化生产，以便能够跨地区生产现有的许可产品，包括常规非 mRNA 疫苗、药物和诊断产品。建设这种能力还需要更加重视技术转让、许可协议和知识产权共享。

INCREASING THE USE OF NEW AND UNDERUSED HEALTH INNOVATIONS扩大使用新兴未被充分利用的技术

Our analysis of new and underused innovations focused on mRNA and monoclonal antibodies (mAbs).
我们对新兴和未充分利用的创新技术的分析重点是 mRNA 和单克隆抗体 (mAbs)。

The COVID-19 pandemic validated two platform technologies for vaccines that were based on decades of prior research. The first was the mRNA platform, used by Moderna and Pfizer-BioNTech to develop their COVID-19 vaccines, and the second was the viral vector platform, used by Oxford University/AstraZeneca and Johnson & Johnson in developing their COVID-19 vaccines. During the pandemic, these platforms received large amounts of funding and streamlined regulatory approval. KIs argued that mRNA is now garnering the most attention given its potential applications towards a range of diseases, including NDs, EIDs, and certain cancers. mRNA platforms are suited for speed and are highly versatile, which is especially valuable during pandemics. They can be proactive rather than reactive to a pathogen, and have been successfully applied to a previously unknown pathogen. mRNA vaccines could potentially help overcome delivery challenges for NDs and EIDs by being thermostable, single dose, or delivered nasally, though this will require intensified R&D. As mentioned above, there are now multiple attempts to build regional self-sufficiency in mRNA manufacturing capacity. However, mRNA is not a panacea—the chances of developing mRNA vaccines against some pathogens are low.
COVID-19 大流行验证了基于数十年研究的两种疫苗平台技术。第一个是 mRNA 平台，由 Moderna 和 Pfizer-BioNTech 用于开发其 COVID-19 疫苗；第二个是病毒载体平台，由牛津大学/阿斯利康和强生用于开发其 COVID-19 疫苗。在新冠大流行期间，这些平台获得了大量资金和简化的监管审批。关键信息提供者们认为，mRNA 目前备受关注，平台速度快，用途广泛适用于各种疾病，包括 ND、EID 和某些癌症。mRNA 疫苗可以主动而非被动地应对病原体，并已成功应用于以前未知的病原体。mRNA 疫苗可以通过恒温、单剂量或鼻腔给药等方式帮助克服 ND 和 EID 的给药难题，但这需要进行深入的研发。如上所述，目前已有多地尝试建立mRNA生产能力以满足本地需求。然而，mRNA 并非万能药--针对某些病原体开发 mRNA 疫苗的可能性很小。

mAbs have come of age in clinical medicine, with more than 100 mAbs licensed over the past 30 years to treat, prevent, and cure NCDs. However, only seven mAbs have been licensed for infectious diseases. Developing mAbs for EIDs would offer many benefits, including (i) primary prophylaxis while waiting for vaccines to be developed; (ii) immediate protection during the time it takes for an individual to mount a response after vaccination; (iii) passive immunity to patients who do not mount an adequate immune response to vaccines or who are vaccine hesitant; (iv) reducing transmission by reducing viral load; and (v) the potential for stockpiling.
mAbs 在临床医学中已进入成熟期，在过去 30 年中，已有 100 多种 mAbs 获得治疗、预防和治愈非传染性疾病的许可。然而，只有七种 mAbs 获得了治疗传染病的许可。为新发传染病（EID）开发mAbs将带来许多益处，包括：(i) 在等待疫苗研发时提供初级预防；（ii）在等待产生反应期间提供及时保护；(iii) 在病人对疫苗没有产生充分免疫反应或对疫苗犹豫时提供被动免疫； (iv)通过减少病毒载量来降低传播率；以及(v)储存mAbs的潜力。

WE RECOMMEND FOUR KEY REFORMS:4大关键改革建议

1. Given that mRNA platforms have significant comparative advantages over more traditional technologies, investments should be scaled up in mRNA technologies for NDs, EIDs, and MH.

2. It is critical for LMICs to be able to produce their own mRNA technologies. The global health community needs to further strengthen its ongoing support to strengthen mRNA production capacity in LMICs. The patent holders for many of the production inputs needed for mRNA are mostly in HICs, which contributes to existing equity gaps. Addressing this barrier requires a combination of stronger sharing of IP and technology transfer agreements. A major barrier facing LMICs in making mRNA vaccines is the IP constraints attached to lipid nanoparticles, a critical component of the technology—a lipid needs to be available without the IP constraints.

3. New approaches are needed to bring down the production costs of mAbs, e.g., by linking discussions of building manufacturing capacity for mRNA to mAb production in LMICs.

4. There is no example of scaled up mAbs in LMICs, yet we saw with antiretroviral therapies that it is possible to introduce expensive drugs in a relatively fast manner and see costs fall quickly. While the financial environment for mAbs is currently severely constrained, there is an opportunity to pilot their wide-scale introduction; COVID-19 was a missed opportunity to do so. RSV mAbs could be a game changer—a low-cost RSV mAb is believed to be underdevelopment—and could serve as a product for the global community to rally around.

1. 鉴于 mRNA 平台与更传统的技术相比具有显著的比较优势，因此应加大对用于 ND、EID 和 MH 的 mRNA 技术的投资。

2. 中低收入国家应该能够生产自己的 mRNA 技术。全球医药界需要进一步加强当前的支持力度以提高中低收入国家的 mRNA 生产能力。mRNA 所需的许多生产资料的专利持有者大多在高收入国家，这加剧了现有的公平差距。消除这一壁垒需要加强知识产权共享与技术转让协议。中低收入国家在制造 mRNA 疫苗时面临的一个主要障碍是技术的关键组成部分脂质纳米颗粒的知识产权限制。--需要提供不受知识产权限制的脂质。

3. 需要新的方法来降低 mAb 的生产成本，例如，将 mRNA 生产能力建设的讨论与低收入国家的 mAb 生产联系起来。

4. 目前还没有在中低收入国家扩大 mAb 生产规模的实例，但我们从抗逆转录病毒疗法中看到，有可能以相对较快的速度引进昂贵的药物，并使成本迅速下降。虽然目前 mAbs 的融资环境受到严重制约，但仍有机会试点大范围引入这种药物；COVID-19 就是一个错失良机的例子。据信，一种低成本的 RSV mAb 尚处于开发阶段，RSV mAb 可能会改变游戏规则，成为让全球大团结的典范。

In parallel, the case for using mAbs in LMICs needs to be further assessed. From an equity perspective, there needs to be a strong push for developing, producing, and using mAbs in LMICs and for generating evidence on effectiveness and cost effectiveness in different settings.

与此同时，还需要进一步评估在中低收入国家使用 mAbs 的可行性。从公平的角度来看，需要大力推动在中低收入国家开发、生产和使用 mAbs，并就不同环境下的疗效和成本效益提供证据。

ACCELERATING REGULATORY REFORMS加快监管改革

Poor regulatory systems are a major barrier to providing safe, high quality, effective tools for NDs, EIDs, and MH. Globally, only 57 countries (around 3 in 10) have regulatory systems that are strong enough to perform core functions. Weak regulatory capacity is a key reason for the large time gap in market authorization of health products between LMICs and HICs. One study estimated that there is lag of 4 to 7 years between first submission for regulatory approval, which is usually to a regulator in a HIC, and final approval in Sub-Saharan Africa (SSA). The study found that the World Health Organization (WHO) prequalification of medicines

Globally, only 57 countries have regulatory systems that are strong enough to perform core functions全球只有57个国家的监管系统足以履行核心职能.

(PQ) processes and national regulatory authorities (NRAs) often repeated assessments of quality, safety, and efficacy already performed by stringent regulatory authorities and that manufacturers did not prioritize market access in LMICs, slowing down rapid access.
监管体系不完善阻碍了为ND、EID 和 MH 开发提供安全、优质、有效工具。全球只有57个国家（约十分之三）的监管体系足以履行核心职能。监管能力薄弱导致中低收入国家与高收入国家在保健产品市场授权方面存在巨大时间差。据一项研究估计，，从首次（通常是向高收入国家的监管机构）提交监管审批申请到最终在撒哈拉以南非洲地区（SSA）获得批准的时间间隔为 4 到 7 年。研究发现，世界卫生组织（WHO）的药品预认证（PQ）流程和国家监管机构（NRAs经常重复严格的监管机构已经进行过的质量、安全性和传染性评估，制造商没有优先考虑低收入和中等收入国家的市场准入，从而减缓了快速准入的速度。

Three sets of regulatory reforms have helped to accelerate introduction of new, quality-assured, effective health tools in LMICs. The frst was regulatory harmonization and reliance. Second, there were efforts to strengthen regional and national regulatory capacity. The third was a set of regulatory reforms triggered by the COVID-19 pandemic, such as rapid scientifc advice and review (in Europe, such advice and review was reduced from 40-70 days to 20 days), rolling reviews, and accelerated marketing authorization.

有三套监管改革措施有助于加快中低收入国家引进新的、有质量保证的、有效的保健工具。首先是监管的统一和依赖。其次是努力加强地区和国家监管能力。第三是由 COVID-19 大流行引发的一系列监管改革，如快速科学建议和审查（在欧洲，这种建议和审查从 40-70 天缩短到 20 天）、滚动审查和加速上市授权。

Multiple studies have shown that harmonization and reliance mechanisms, such as the use of reference agencies and joint reviews, can accelerate market authorization by limiting duplicative assessments. But KIs emphasized the lack of legislation for reliance in countries that also do not have capacity to fulfll the range of regulatory functions; in addition, the implementation of reliance is often done poorly. There is substantial potential to further deepen the collaboration between NRAs.

多项研究表明，监管协调和依赖机制，如使用参考机构和联合审查，可以通过限制重复评估来加快市场授权。但关键信息提供者们强调，一些国家缺乏关于依赖机制的立法，也没有能力履行一系列监管职能；此外，依赖机制的执行情况往往不佳。但进一步深化国家监管机构之间的合作还有很大潜力。

WE RECOMMEND THREE KEY REFORMS:三大改革建议

1. Regulatory capacity gaps need to be gradually and strategically addressed. LMICs should assess their current regulatory systems using the WHO benchmarking tool and allocate more funding to these systems. HICs should provide technical and financial support to national and regional regulatory agencies to ensure that these agencies can effectively perform core regulatory functions. Partnerships between regulatory authorities in HICs and those in LMICs, such as twinning or joint assessments, will also be critical to building capacity and achieving efficiency gains. African countries with more advanced NRAs should support less advanced countries. For example, Tanzania, a country with a regulatory system that has reached maturity level (ML) 3, has supported Rwanda's NRA in recent years.

2. Any efforts to strengthen manufacturing capacity need to be accompanied by investments in regulatory systems.

3. WHO PQ of medicines was introduced at a time when regulatory systems were very weak, but this situation has changed to a certain degree; while the WHO PQ system is currently still needed, there should be more flexibilities. Countries and global procurement agencies should increasingly accept reviews from WHO-Listed Authorities (WLAs) and/or transitional WLAs (tWLAs) as an alternative to WHO PQ.

1. 监管能力方面的差距需要逐步从战略角度加以解决。中低收入国家应利用世卫组织的基准工具评估其当前的监管系统，并为这些系统划拨更多资金。高收入国家应向国家和地区监管机构提供技术和资金支持，确保这些机构能够有效履行核心监管职能。高收入国家监管机构与低收入国家监管机构之间的伙伴关系，如结对或联合评估对于能力建设和实现高效益也至关重要。拥有较先进的国家监管机构的非洲国家应支持较落后的国家。例如，监管体系已达到成熟度 (ML) 3 级的坦桑尼亚近年来就为卢旺达的国家监管机构提供了支持。
2. 在加强制造能力的同时，还需要对监管系统进行投资。

3. 世卫组织的药品预认证PQ 是在监管体系非常薄弱的情况下引入的，但这种情况已在一定程度上发生了改变；虽然目前仍需要世卫组织的 PQ 体系，但应该有更多的灵活性。各国和全球采购机构应越来越多地接受世卫组织列名机构（WLAs）和/或过渡性世卫组织列名机构（tWLAs）的审查作为世卫组织 PQ的替代性选择。

IMPROVING THE FINANCE AND GOVERNANCE OF R&D FOR NDs, EIDs, AND MH改善ND、EID和MH产品研发的融资和治理

Product development for NDs, EIDs, and MH faces a constrained funding environment. Our previous research, in 2020, found a substantial funding gap for ND R&D (about US$2.6 billion per year), and our new research points to persisting R&D funding gaps.[1] Policy Cures Research found that funding for ND R&D declined in recent years. Industry only accounted for 13% of funding for ND R&D between 2007 and 2022, and funding from LMICs remained highly limited in this timeframe. Furthermore, even after the worst pandemic in a century, donors did not provide the US$3.5 billion requested by CEPI for its "100 days mission" at its 2022 replenishment. While funding for sexual and reproductive health R&Dgrew from 2018 to 2021 (totaling US$593.7 million in 2021), only a small share of this funding was for MH tools and the share declined over time.

ND、EID 和 MH 的产品开发面临着严峻的资金环境。我们之前在 2020 年进行的研究发现被忽视疾病研发资金缺口巨大（每年约 26 亿美元）。而我们的新研究表明研发资金缺口持续存在。Policy Cures Research 发现近年来ND研发资金短缺， 2007至2022 年间，工业仅占 ND 研发资金的 13%，而来自中低收入国家的资金在这一时期内仍然非常有限。此外，即使在百年来最严重的疫情之后，捐助方也没有在 2022 年为 CEPI 的 "百日任务 "提供所需的 35 亿美元。虽然从 2018 年到 2021 年，用于性健康和生殖健康研发的资金有所增长（2021 年总额为 5.937 亿美元），但其中只有一小部分资金用于 MH 医疗工具，且这一比例随着时间的推移而下降。

WE RECOMMEND FOUR KEY REFORMS:四大改革建议

1. A priority review voucher (PRV) should be created in Europe, hosted by the European Medicines Agency. Introduced in 2007, the US PRV program awarded more than 60 vouchers by 2024, contributing to the development of new medicines for neglected diseases, such as Chagas and tuberculosis. US vouchers were sold for US$100 million each, creating a substantial though insufficient financial incentive for developers. An EU voucher would provide an additional incentive of US$100 million to US$200 million, which investors say would be a meaningful stimulus. The introduction of the voucher could have a substantial impact, especially if it is part of a larger strategy for neglected disease research andisintegrated with other EU mechanisms, such as PRIME (the PRIority MEdicines scheme).

2. Volume guarantees should remain a key mechanism to promote access to new health tools. There needs to bethinking on how to best expand the use of these guarantees while managing associated risks (overreliance on such guarantees can create a moral hazard).

3. Rather than targeting individual research projects, such as individual clinical trials, R&Dfunders also need to invest in the underlying research ecosystem. A system-wide approach would include investments in clinical trial infrastructure, capacities for discovery and preclinical research, and local manufacturing.

1. 欧洲应设立优先评审券 (PRV)，由欧洲药品管理局负责管理。美国于 2007 年推出了PRV，到 2024 年，已发放了 60 多张优先评审券，促进了恰加斯病和结核病等被忽视疾病新药的开发。美国的PRV以每张 1 亿美元的价格出售，为开发者提供了巨大的经济激励，尽管还有待提高。欧盟的PRV将提供 1 亿至 2 亿美元的额外激励，投资者认为这将是一个有意义的刺激。优先评审券的实行，如果作为被忽视疾病研究战略的一部分、并与 优先药物计划（PRIME）等其他欧盟机制相结合可能会产生重大影响。
2. 数量保障仍应是促进获得新的保健工具的关键机制。需要思考如何以最佳方式扩大这些担保的使用范围，同时管理相关风险（过度依赖这些担保可能会造成道德风险）。
3. 研发资助者不能只针对单个研究项目，比如单个临床试验，还需要投资于基础研究生态系统。全系统方法将包括对临床试验基础设施、发现和临床前研究能力以及本地生产的投资。

LMIC governments need to increase their own funding for health R&D. This will be important to advance product development for NDs, EIDs, and MH.

5. The overarching R&D ecosystem would be improved by stronger regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing.

4.中低收入国家政府需要增加自己的卫生研发资金，这对于推动 ND、EID 和 MH 的产品开发非常重要。

5.加强区域优先事项的确定、建立区域和次区域临床试验、监管系统和产品生产中心将改善总体研发生态系统。

Conclusions: towards a reformed R&D ecosystem

结论：打造革新的研发生态系统

Our analysis of key shifts and innovations across six major domains of the R&D ecosystem for NDs, EIDs, and MH found that many of these advances hold great potential for accelerating R&D, lowering its costs, and reducing attrition rates (Figure ES2). Changes in the ecosystem could also reduce manufacturing costs and speed up regulatory approval. Bringing new products to market at a faster pace and at lower cost could also help to relieve fnancial pressures on global health funders both upstream and downstream.

我们对 ND、EID 和 MH 研发生态系统六个主要领域的关键转变和创新进行了分析，发现其中许多进步都蕴含着加速研发、降低研发成本和减少流失率的巨大潜力（图 ES2）。生态系统的变化还可以降低制造成本、加快监管审批。以更快的速度和更低的成本将新产品推向市场也有助于减轻全球健康领域上下游资助者的财务压力

Our second working paper models the impact of these efficiencies in the R&D ecosystem.[1] In that second paper, we apply the Portfolio to Impact (P2I) modeling tool to the product candidate pipeline for NDs, EIDs, and MH to estimate the likely launches and the development costs and timelines of these launches. The P2I model is based on standard, historical attrition rates, cycle times, and costs per phase for a range of different product types (archetypes), such as simple and complex vaccines, new chemical entities, and repurposed drugs. In addition to the P2I modeling, we estimate the public health and economic impact resulting from these product launches. In our modeling, we frst assumed that R&D uses traditional approaches (i.e., without the kinds of efficiencies that ecosystem shifts can bring). Second, we repeated the modeling but changed the model parameters (e.g., cycle times, costs per phase) to refect the efficiency gains of ecosystem changes and innovations.

我们的第二篇工作报告以研发生态系统的这些效率建模。其中，我们将 “从组合到影响”（P2I）建模工具应用于 ND、EID 和 MH 的候选产品管线，以估算可能的发布时间以及这些产品发布的开发成本和时间表。P2I 模型基于一系列不同产品类型（原型）的标准历史损耗率、周期时间和每个阶段的成本，如简单和复杂疫苗、新化学实体和再利用药物。除了P2I 模型外，我们还估算了这些产品发布对公众健康和经济的影响。在我们的模型中，首先假设研发采用传统方法（即没有生态系统变化可能带来的各种生态效应）；然后，我们重复了建模过程，但改变了模型参数（例如周期时间、每个阶段的成本），以反映生态系统变化和创新带来的效率提升。

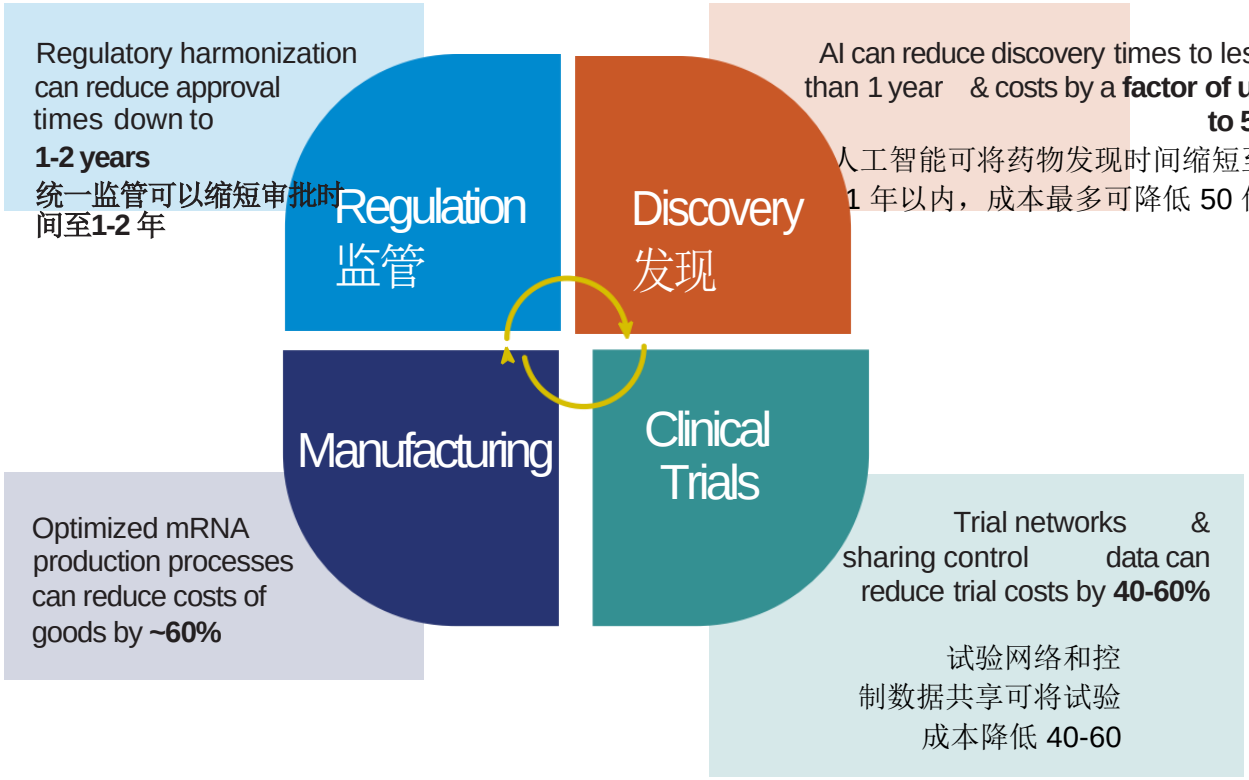
Finally, we believe that investments in R&D for LMICs should be driven by the disease and health priorities that these nations and regions set themselves. The shifts identifed above must link to these priorities if we are to move in the direction of equity. Such shifts in R&D must be accompanied by increased ownership by LMICs and increased investments from LMIC governments, as well as from the private sector and industry players.

最后，我们认为，对中低收入国家的研发投资应由这些国家和地区自己确定的疾病和健康优先事项来驱动。为发展公平的目的，上文确定的转变必须与这些优先事项相联系。研发工作的这种转变必须伴随

着中低收入国家的增强自主权、中低收入国家政府增加投资、以　及私营部门和行业参与者增加投资。

Figure ES2: Potential efficiency gains from shifts in the R&D ecosystem

图 ES2：研发生态系统转变带来的潜在效率收益



左下框 Manufacturing 生产

Optimized mRNA production processes can reduce costs of goods by ~60%

优化的mRNA生产流程可减少60%生产资料成本

SECTION 1

第一节
INTRODUCTION
引言

INTRODUCTION引言

Investing in new health technologies is critical to reducing preventable illness, suffering, and death worldwide. Such technologies have saved tens of millions of lives. A new study by the WHO, for example, suggests that vaccines have saved 154 million lives over the past 50 years, of which 101 million were infant lives saved.[2] And a study by Jamison et al found that about 80% of the decline in the under-5 mortality rate from 1970-2000 across 95 low- and middle-income countries (LMICs) can be explained by the diffusion of new health technologies.[3]
投资新的医疗技术对于在全球范围内减少可预防的疾病、痛苦和死亡至关重要。这些技术挽救了数千万人的生命。例如，世卫组织的一项新研究表明，过去 50 年间，疫苗挽救了 1.54 亿人的生命，其中 1.01 亿人是婴儿。2 杰米森等人的一项研究发现，1970-2000 年间 95 个中低收入国家 5 岁以下儿童死亡率的下降，约有 80% 可以归因于新卫生技术的引入。

In this paper, we analyze how the ecosystem for global health research and development (R&D) should evolve over the next 20 years to accelerate the discovery and delivery of new health tools. Our focus is on product development for neglected diseases (NDs), emerging infectious diseases (EIDs), and maternal health (MH) technologies. We use the G-FINDER project's definitions of NDs, EIDs, and MH (Annex 1).
在本文中，我们将分析未来 20 年全球卫生研发生态系统应如何发展。
3 本文分析了未来 20 年全球健康研发（R&D）生态系统应如何发展，以加速发现和提供新的健康工具。我们的重点是被忽视疾病 (ND)、新发传染病 (EID) 和孕产妇健康 (MH) 技术的产品开发。我们采用 G-FINDER 项目对 NDs、EIDs 和 MH 的定义（附件 1）。
We review the evidence and provide recommendations on the high-impact shifts required in the R&D ecosystem to drive efficiencies to accelerate development and uptake of new health technologies by LMICs. The paper also examines R&D funding approaches and policies that could help deliver the highest impact innovations and save the most lives. It looks at options to close financing gaps and mechanisms to coordinate prioritization of R&D needs and resource mobilization and to ensure equity and ownership of LMICs in the end-to-end development of priority health tools.
我们回顾了相关证据，并就研发生态系统所需的高影响力转变提出了建议，以推动低收入和中等收入国家加速开发和吸收新的卫生技术。本文还探讨了有助于实现最具影响力的创新和挽救最多生命的研发资助方法和政策。本文探讨了弥补资金缺口的各种方案以及协调研发需求优先次序和资源调动的机制，并确保公平和所有权。
本研究借鉴了此前由联合国儿童基金会（UNICEF）开展的一项研究，即 “在全球范围内开发创新工具”。

This study builds on previous research conducted by the Center for Policy Impact in Global Health (CPIGH) at Duke University and Open Consultants. In our previous work, we have focused on the benefits and costs of investing in neglected disease R&D and manufacturing, as well as on measures to leverage efficiencies and expand global access to new health tools.[4,5,6] Our study complements other studies, such as the Wellcome Trust's 2023 report, "Towards a Reformed Research and Development Ecosystem for Infectious Disease," and Policy Cures Research's new report, "The Impact of Global Health R&D: The High Return of Investing in R&D for Neglected Diseases."[7,8]
本研究借鉴了杜克大学全球健康政策影响中心 (CPIGH) 和开放咨询公司之前开展的研究。
和开放咨询公司之前开展的研究为基础。在之前的工作中，我们重点研究了投资于被忽视疾病研发和生产的收益和成本，以及投资于被忽视疾病研发和生产的收益和成本。
4,5,6我们的研究是对其他研究的补充，如惠康基金会的 2023 年报告《迈向改革后的传染病研发生态系统》，以及政策治愈研究的新报告《全球健康研发的影响：投资被忽视疾病研发的高回报》7,8。

Our paper is based on a **literature review** and **key informant interviews (KIIs)** with experts in both high-income countries (HICs) and LMICs. The aim was to identify (a) the key potential ecosystem shifts that would drive efficiencies in R&D, and (b) specific needs for product development and uptake. The study began with a "**validation workshop**"—a

two-day workshop with over 30 senior policy actors who are engaged in global health R&D policymaking, held in London on August 8-9, 2023. In this workshop, which included strong representation from LMICs, we shared and received feedback on our proposed study approach. Workshop participants shared with us their views on the key shifts that are likely to occur in the R&D ecosystem over the next 20 years. The aim of this workshop was to ensure that we understood the views of a wide range of actors in the R&D space and took these into account in our work. Following the workshop, we conducted KIIs with over 60 key informants between August 2023 and March 2024. A second virtual meeting was held in February 2024 to further discuss our findings. In March 2024, we assembled a group of trial and modeling experts to discuss the rising costs of clinical trials and their implications for our modeling. In addition, we organized regional consultations in Africa, Asia, and Latin America to better understand regional ecosystem needs. Over 60 additional stakeholders were consulted in this regional consultation process.

本文基于文献综述和 对高收入国家和中低等收入国家的关键信息提供者访谈，目的是明确 (a)可能提高研发效率的研发生态系统转变； (b)产品开发和推进的具体需求。本研究始于一场论证会：2023年8月8-9日. 全球医药研发决策相关的 30 多位高级专家在伦敦参加了为期两天的研讨会，中低收入国家也有充分的代表，我们分享了研究方法并收到了很多反馈。与会者分享了未来二十年研发生态系统可能发生的转变的关键因素产品开发和推进的具体需求。
此次研讨会的目的是确保我们了解研发领域一系列关键因素并在工作中加以考虑。此后在2023年8月至2024年3月间我们对60位关键信息提供者进行了访谈；2024年2月又举行网络会议进一步讨论研究发现。2024年3月我们着急试验和建模专家讨论临床试验与日俱增的成本及其对我们模型的启示。此外，我们还组织了亚洲、非洲拉丁美洲区域咨询会以便更好的了解区域生态系统的需求，60多位利益相关者提供了咨询意见。

This working paper analyzes the R&D ecosystem across six key dimensions:

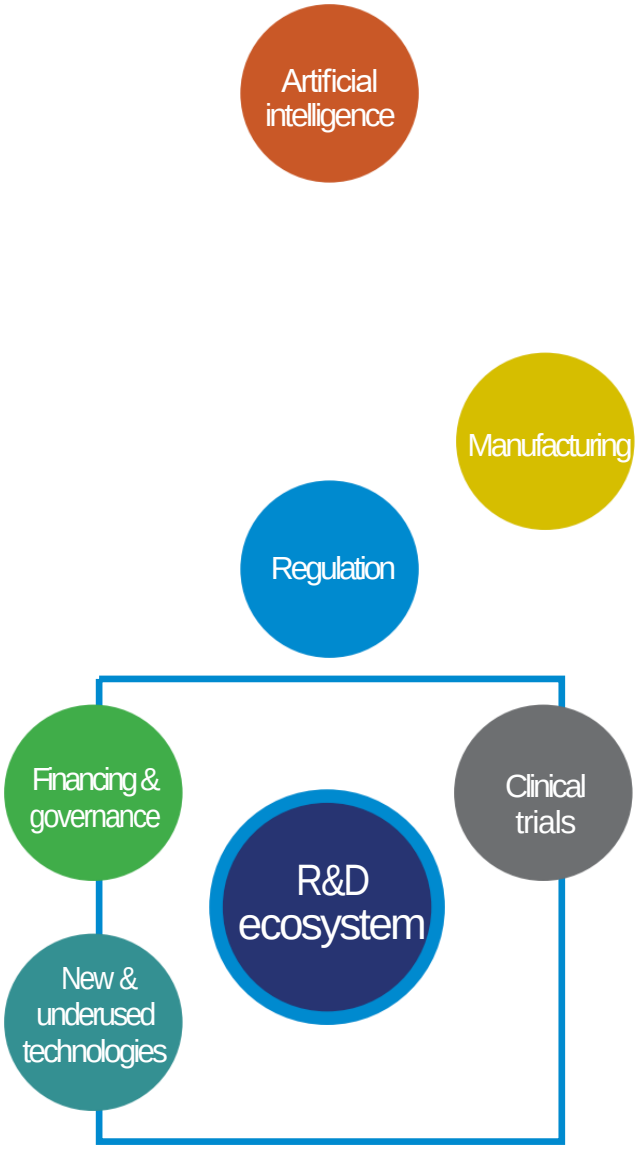
- Artificial intelligence (AI)
- Clinical trials
- Manufacturing
- Regulatory systems
- New and underused health innovations (mRNA-based vaccines/therapeutics; monoclonal antibodies)
- Financing and governance (Figure ES1).

本工作文件从六个关键方面分析了研发生态系统：
- 人工智能 (AI)
- 临床试验
- 生产
- 监管系统
- 新的和未充分利用的健康创新（基于 mRNA 的疫苗/治疗；单克隆抗体）
- 融资和管理（图 ES1）。

We identified these six dimensions through a literature review and initial KIIs. We then validated the dimensions with stakeholders at the London workshop in August 2023. In addition to laying out key shifts for improving the R&D ecosystem, including ways to lower costs, drive efficiencies, and improve product uptake, this working paper helped to inform a second working paper from our group. The second paper models the likely launches, costs, and public health and economic benefits of advancing the current global health R&D pipeline.[1] The results of this modeling also helped to identify and prioritize the highest impact ("game changing") health technologies, which are summarized in the second paper.

通过文献综述和初步的关键信息提供者访谈，我们确定了这六个维度。然后，在 2023 年 8 月的伦敦论证会上我们与利益相关者进行了验证。除了提出改善研发生态系统的关键转变，包括降低成本、推动电子化和提高产品吸收率的方法外，本工作文件还通报了我们小组的第二份工作报告，这第二篇报告以推进当前全球医药研发管线可能促成的产品发布、成本、公共健康和经济效益建模。建模结果还有助于明确最重要的研发项目和优先次序。该模型的结果还有助于确定影响最大（"改变游戏规则"）的健康技术，并对其进行优先排序，详见第二篇报告。

Figure ES1: Six key dimensions of the R&D ecosystem



Limitations of this study

局限

There are at least four key limitations to our study.本研究还存在以下4个局限。

1. First, we did not aim to assess in detail the opportunities and challenges of each of the six dimensions of the ecosystem. Such detailed analyses have previously been published, and we did not attempt to replicate them; instead, our aim was to collect, appraise, and analyze the evidence on potential efficiency gains and key ecosystem changes across multiple key areas, thereby focusing on evidence for major policy questions. Rather than providing a comprehensive assessment, we aimed to take a broader perspective to succinctly discuss key strategic issues and to lay out action points for the future.
首先，我们的目的不是详细评估生态系统六个维度中每个机遇和挑战。此类详细分析以前已经发表过，不再赘述；相反，我们的目的是收集、评估和分析多个关键领域的潜在效率增益和关键生态系统变化的证据，我们的目标不是提供全面的评估，而是从更广阔的视角简明扼要地讨论关键的战略问题，并提出未来的行动方案。

2. Second, the evidence on potential efficiency gains is still nascent. This was expected, given that we aimed to identify new and emerging innovations and trends, and because we are assessing these innovations in the context of LMICs. For example, the evidence of efficiency gains in clinical trials mostly comes from HICs and often from trials on non-communicable diseases (NCDs),and these findings cannot be easily translated to LMICs and to NDs, EIDs, and MH. The evidence on the benefits ofAlthat we discuss in our report often came directly from biotech companies in HICs. However, we always tried to triangulate data from multiple sources and to validate our findings with independent experts.
其次，有关潜在效率收益的证据仍处于萌芽阶段。这是意料之中的，因为我们的目标是确定新的和正在出现的创新和趋势，而且我们是在中低收入国家的背景下评估这些创新，例如，临床试验中疗效提高的证据大多来自高收入国家，且往往来自非传染性疾病 (NCD) 试验，这些发现不容易转化到中低收入国家和被忽视疾病、新发传染病和孕产妇保健研究。我们在报告中讨论的有关人工智能益处的证据通常直接

来自高收入国家的生物技术公司。不过，我们总是试图对来自多个来源的数据进行三角验证，并与独立专家一起验证我们的发现。

3. Third, our paper is by design restricted to NDs, EIDs, and MHand does not include NCDs. Yet the burden of NCDs will continue to grow in LMICs over the next 20 years, a trend that is not captured by our paper. We do believe, though, that many of our findings are also applicable to NCDs – for example, our findings on the value of AI during drug discovery and of synthetic control arms in clinical research, the manufacturing of mRNA-based vaccines through modular facilities, and the need to expand access to mAbs in LMICs.
第三，我们的报告在设计上仅限于ND、EID和MH，并不包括非传染性疾病。然而，未来 20 年里，非传染性疾病的负担将在中低收入国家继续增长，而我们的论文并未涉及这一趋势。不过我们相信，我们的许多发现也适用于非传染性疾病--例如，我们发现人工智能在药物发现过程中的价值和合成控制臂在临床研究中的价值、通过模块化设施制备基于 mRNA 的疫苗，以及在低收入国家扩大 mAbs 获取途径的必要性。

4. Fourth, this report assesses the R&D ecosystem but does not analyze the delivery systems that are essential to ensure access to new health tools. Such systems are beyond of the scope of this report, so we add a major disclaimer: a robust future R&D ecosystem alone is insufficient to improve the health of people living in LMICs. Adequately financed and effective health systems need to be in place to generate demand and deliver new health tools equitably. Other studies and initiatives, such as the Future of Global Health Initiatives (FGHI) process,[9] discuss the reform needs of global delivery systems.

第四，本报告评估了研发生态系统，但没有分析对确保获得新的医疗工具至关重要的交付系统。这些系统超出了本报告的范围，因此我们补充一个重要的免责声明：仅靠未来强大的研发生态系统不足以改善中低收入国家人民的健康，需要建立资金充足且有效的卫生系统，以创造需求并公平地提供新的医疗工具。其他研究和倡议，如“全球健康倡议的未来”（FGHI）进程9 讨论了全球提供系统的改革需求。

Structure of this report
报告结构

This report is organized into six further sections. In Section 2, we present the findings on efficiency gains driven by AI. Next, in Section 3, we analyze how innovations in clinical trial conduct could drive further efficiencies. In Section 4, we discuss the role of manufacturing, and Section 5 focuses on new and underused technologies. Section 6 discusses ways to streamline and accelerate regulatory approval. Section 7 focuses on governance and financing. It also provides a summary of outcomes from the regional consultations. Section 8 summarizes key efficiency gains from R&D ecosystem changes and lays out our key conclusions. Opportunities for efficiencies and ecosystem reform, as well as challenges, gaps, and missed opportunities are discussed across all sections.

本报告分为六个部分。在第 2 节中，我们介绍了人工智能对效率提升的影响。第 3 节分析临床试验行为的创新如何能进一步提高效率。第 4 节讨论了产品生产作用，第 5 节重点讨论了新技术和未充分利用的技术。第 6 节讨论了简化和加快监管审批的方法。第 7 节重点讨论治理和融资问题，还概述了区域磋商的成果。第 8 节总结了从研发生态系统变化中获得的关键效率收益，并提出了我们的主要结论。所有章节都讨论了效率和生态系统改革的机遇，以及挑战、差距和错失的机遇。

SECTION

2

ARTIFICIAL INTELLIGENCE IN GLOBAL HEALTH R&D

人工智能和全球健康研发

ARTIFICIAL INTELLIGENCE IN GLOBAL HEALTH R&D
人工智能和全球健康研发

KEY BENEFITS: 主要益处

Faster discovery & preclinical research at lower cost. AI offers substantial benefits during the discovery and preclinical phase. The standard time for screening, identifying, and validating target molecules is 3-5 years, with costs of up to US$10 million. There are examples of AI tools that have shortened the timeframe to less than 12 months and lowered the costs by a factor of up to 50. AI tools also enable a much more thorough screening of proteins (new target identification) compared with traditional screening approaches. This in turn could lead to improved quality candidates and therefore less attrition during the clinical phase and, eventually, better health technologies.
以更低的成本加快药物发现和临床前研究。人工智能在发现和临床前研究阶段带来了巨大的好处。筛选、确定和验证目标分子的标准时间为3-5 年，成本高达 1 千万美元。有一些人工智能工具将这一时间缩短到了 12 个月以内，并将成本降低了 50 倍。与传统筛选方法相比，人工智能工具还能对蛋白质进行更彻底的筛选（新目标鉴定）。这反过来又能提高候选药物的质量，从而减少临床阶段的损耗，最终带来更好的健康技术。

Valuable role in drug repurposing. AI platforms have identified optimal drug combinations at significantly reduced time and cost, e.g., for COVID-19.
在药物再利用方面发挥宝贵作用。人工智能平台已经确定了最佳药物组合，大大减少了时间和成本，例如 COVID-19。

Prediction of clinical trial success. One AI-based prediction tool was able to predict trial success with 79% accuracy, which has the potential to reduce the costs of the clinical phase.
预测临床试验的成功率。一种基于人工智能的预测工具能够预测试验的成功率，准确率高达 79%，有望降低临床阶段的成本。

KEY CHALLENGES TO BE ADDRESSED:主要挑战

AI tools require substantial data to perform well. While there is substantial data on the use of AI in R&D for NCDs and specific infectious diseases, there is much less data available on the most neglected diseases. In addition, most of the data feeding into AI tools comes from HICs. 人工智能工具需要大量数据才能良好运行。虽然在非传染性疾病和特定传染病的研发中使用人工智能的数据很多，但关于最容易被忽视的疾病的数据却少得多。此外，为人工智能工具提供的数据大多来自高收入国家。

. Critics of AI in global health have warned that AI may deepen existing inequalities between LMICs and HICs. AI tools are owned by Northern entities, while LMICs have limited infuence over the design and use of these tools.

加深全球不平等的可能性。人工智能在全球卫生领域的批评者警告说，人工智能可能会加深中低收入国家与高收入国家之间现有的不平等。人工智能工具归北方实体所有，而中低收入国家对这些工具的设计和使用的影响力有限。

SUGGESTED ECOSYSTEM CHANGES:生态系统改革建议

- **Further leverage the substantial efficiencies of AI in drug discovery and preclinical research**. There is great potential to reduce the timelines and costs of discovery and preclinical research on NDs, EIDs, and MH. R&Dfunders across sectors should leverage this potential and invest in AI-based companies to develop novel and de-risked drug candidates for clinical testing.
- **Expand the use of AIfor epidemic and pandemic preparedness**. Use AI tools to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library.
- **Further assess the potential of AI in clinical research**. Fully leveraging the potential of AI during clinical research will also require the sharing of clinical trial data.
- **Enable LMICs to meaningfully participate in AI-driven R&D and build respective capacity and expertise**. Without such participation, existing inequalities in global health will be widened. Partnerships between AI companies, which are mostly in HICs, and LMIC researchers will be important.
- **Strengthen existing regulatory frameworks for AI in global health.**

--充分利用人工智能在药物发现和临床前研究方面的巨大潜力。在减少 ND、EID 和 MH 的发现和临床前研究的时间和成本方面存在巨大潜力。各部门的研发资助者应利用这一潜力，投资于以基于人工智能的公司，开发用于临床测试的新型低风险候选药物。
--扩大人工智能在流行病和大流行病防备方面的应用。利用人工智能工具预测重点病原体的蛋白质结构，以协调建立疫苗库。
--进一步评估人工智能在临床研究中的潜力。充分发挥人工智能在临床研究中的潜力，还需要共享临床试验数据。
--让中低收入国家能够有意义地参与人工智能驱动的研发，深化能力建设、强化专业知识。否则全球卫生领域现有的不平等现象将会扩大。主要位于高收入国家的人工智能公司与低收入国家研究人员之间的合作将非常重要。
--加强全球卫生领域现有的人工智能监管框架。

2.1 Overview 概述

The long timelines, high attrition rates, and high costs of R&D are impeding the development and delivery of new health technologies. A recent study, for example, estimated that the average R&D cost per drug is US$1.3 billion and the median drug development time ranges from 5.9 to 7.2 years for non-oncology drugs and 13.1 years for oncology drugs.[10] Another study of drug development projects involving 21,143 compounds estimated that the success rate (the proportion that reached the market) was only 5.2% in 2013,down from 11.2% in 2005.[11,12] Nine out often drug molecules usually fail to pass Phase 2 clinical trials and other regulatory approvals.[13]

研发时间长、损耗率高、研发成本高阻碍了新医疗技术的开发和交付。例如，最近的一项研究估计，每种药物的平均研发成本为 13 亿美元，非肿瘤药物研发时间的中位数为 5.9 至 7.2 年，肿瘤药物研发时间的中位数为 13.1 年（10）。另一项对涉及 21 143 种化合物的药物研发项目的研究估计，2013 年的成功率（进入市场的比例）仅为 5.2%，低于 2005 年的 11.2%。通常90%药物分子无法通过第二阶段临床试验或其他监管审批。

AI tools can contribute to drug development across the whole R&D process, including:

人工智能工具可以在整个研发过程中为药物开发做出贡献，包括

Novel target identification	Molecular compound design and optimization
Understanding of target-disease associations	Development of new prognostic and predictive biomarkers
Drug candidateselection	Biometrics data analysis from wearable devices, imaging, precision medicine
Protein structure predictions	Clinical trial design, conduct, and analysis.

Novel target identification新靶点鉴定

Understanding of target-disease associations了解靶点与疾病的关联

Drug candidateselection候选药物选择

Protein structure predictions蛋白质结构预测

Molecular compound design and optimization
分子化合物设计与优化

Development of new prognostic and predictive

biomarkers

开发新的预后和预测性生物标记物

Biometrics data analysis from wearable devices,

imaging, precision medicine

来自可穿戴设备、成像、精准医疗的生物统计

数据分析

Clinical trial design, conduct, and analysis.
临床试验设计、实施和分析。

AI and machine learning are becoming increasingly important to global health R&D, allowing researchers to assess the safety, efficacy, and potential benefits of new drugs. AI has been used as a tool to reduce R&D time and costs. At the same time, AI poses several challenges and ethical considerations that demand careful attention. For example, AI systems collect and analyze vast amounts of personal data, raising concerns about privacy and data security.[14] The use of AI in the development of new health tools also risks increasing existing inequalities in global health.[15,16] In this section, we provide evidence on efficiency gains, gaps, barriers, and future opportunities in the use of AI and machine learning in global health R&D.

人工智能和机器学习对全球健康研发的重要性与日俱增，使研究人员能够评估新药的安全性、有效性和潜在益处。人工智能已被用作减少研发时间和成本的工具。与此同时，人工智能也带来了一些挑战和伦理方面的考虑，需要谨慎对待。例如，人工智能系统会收集和分析大量个人数据，从而引发对隐私和数据安全的担忧[14]。使用人工智能开发新的医疗工具还有可能加剧全球卫生领域现有的不平等[15,16]。
在本节中，我们将提供有关在全球卫生研发中使用人工智能和机器学习的效率收益、差距、障碍和未来机遇的证据。

2.2. Benefits of AI during discovery and preclinical research

人工智能在药物发现和临床前研究中的优势

In section 2.2, we first discuss the potential of AI for improving the discovery phase, during which target identification and drug lead discovery occur, and in preclinical development, when the efficacy of the drug is interrogated in vitro and in vivo and drug toxicity properties are assessed. Then we discuss the role of AI in drug repurposing and the testing of drug-drug combinations.

在第 2.2 节中，我们首先讨论了人工智能在改进药物发现阶段和临床前开发阶段工作方面的潜力，发现阶段主要是确定靶点和发现药物先导物，而临床前开发阶段则是对药物的体外和体内疗效进行质询，并对药物毒性特性进行评估。然后，我们将讨论人工智能在药物再利用和药物组合测试中的作用。

AI is being increasingly used in discovery.AI在药物发现中运用越来越广泛

Optimization of a lead compound to deliver a safe and potent candidate for clinical testing requires parallel optimization of many parameters, including potency, pharmacokinetics, selectivity, and safety. AI tools can now outperform humans in integrating the outputs from predictive models to efficiently "home in" on an optimized candidate drug. In addition, AI tools have the potential to streamline complex drug discovery workfows and optimize decision making. Advances in AI-based compound synthesis prediction tools can also speed up drug discovery by enabling key compounds to be made more efficiently.

Between 2010 and 2021, there was rapid growth in the number of AI companies in the health sector, with an average annual growth rate of 36%. This growth was mostly driven by assets and programs at the discovery and preclinical stage. Jayatunga et al assessed the combined pipeline from 2010-2021 of 20 "AI-native" companies (i.e., AI is central to their drug discovery programs) and found 160 disclosed discovery programs and preclinical assets and 15 assets in clinical development. To put this in perspective, the discovery and pre-clinical pipeline of AI-native companies is about half the size of the pipeline of the top 20 pharmaceutical companies. The researchers were only able to find drug target information for about a quarter of these AI-enabled R&D programs. The targets were mostly well-established target classes, such as kinases and G-protein coupled receptors. Jayatunga et al acknowledge that there is uncertainty in "how many of the AI-enabled preclinical programmes reach the clinical trial stage, and how successful AI-derived assets will be in clinical trials."[17]

要优化先导化合物，为临床测试提供安全、有效的候选化合物，需要同时优化许多参数，包括药效、药代动力学、选择性和安全性。现在，人工智能工具在整合预测模型的输出结果、对优化后的候选药物进行有效"定位"方面的能力已经超越了人类。此外，人工智能工具还有可能简化复杂的药物发现工作流程并优化决策。

基于人工智能的化合物合成预测工具的进步也能加快药物发现的速度，使关键化合物的制造更加高效。

2010 年至 2021 年期间，卫生领域的人工智能公司数量快速增长，年均增长率达 36%。这一增长主要由处于发现和临床前阶段的资产和项目驱动。Jayatunga 等人评估了 20 家 “人工智能原生 ”公司（即人工智能是其药物发现项目的核心）2010-2021 年的综合管线，发现有 160 项已披露的发现项目和临床前资产，以及 15 项处于临床开发阶段的资产。从这个角度来看，人工智能原生公司的发现和临床前管线约占前20家公司管线的一半。研究人员找到的药物靶点信息只是这些人工智能公司找到的约四分之一。

这些靶点大多是成熟的靶点类别，如激酶和G蛋白偶联受体。Jayatunga 等人承认 “有多少人工智能临床前项目进入临床试验阶段，以及人工智能衍生资产在临床试验中的成功率有多高 ”17，这些都存在不确定性。

The COVID-19 pandemic further fueled the use of AI in health R&D. For example, the Google-owned company DeepMind was instrumental in helping virologists understand how SARS-CoV-2 was behaving. Using the AlphaFold AI program predictions, several of the Sars-CoV-2 proteins were mapped out, which were later experimentally confirmed to be accurate. DeepMind also partnered with DNDi to identify new treatments for neglected diseases like sleeping sickness, Chagas disease, and leishmaniasis. DNDi and its research partners found a molecule that can bind to a protein on Trypanosoma cruzi, the parasite that causes Chagas disease, killing the parasite; AlphaFold helped to rapidly predict the shape of the protein, which could help in drug design.[18,19]

Existing evidence indicates that AI offers signifcant efficiency gains.
证据表明AI提供巨大的效率收益

AI tools have successfully supported new target discovery and toxicity prediction. AI-based algorithms have successfully been used to identify new targets for drug development, such as the specific proteins or genetic pathways involved in diseases. In addition, AI-based toxicity predictions could eventually replace in vitro and animal models during the pre-clinical stage. Models can be used as risk-management and prioritization tools by providing early indication of high-risk compounds fagged with significant safety concerns.

COVID-19 大流行进一步推动了人工智能在医药研发领域的应用。例如，谷歌旗下的 DeepMind 公司在帮助病毒学家了解 SARS- CoV-2 的行为方式方面发挥了重要作用。利用 AlphaFold 人工智能程序的预测，绘制出的几种 SARS-CoV-2 蛋白质的图谱经实验证实都是准确的。

DeepMind 还与 DNDi 合作为昏睡病、南美锥虫病和利什曼病等被忽视疾病寻找新的治疗方法。DNDi 及其研究合作伙伴发现了一种分子可以与导致南美锥虫病的寄生虫--南美锥虫上的一种蛋白质结合，从而杀死寄生虫；AlphaFold 帮助快速预测了这种蛋白质的形状、有助于药物设计[18,19]。

人工智能工具已成功支持了新靶点的发现和毒性预测。基于人工智能的算法已成功用于确定药物开发的新靶点，如与疾病相关的特定蛋白质或遗传途径。此外，基于人工智能的毒性预测最终可以取代临床前阶段的体外和动物模型。 模型可用作风险管理和优先排序工具，及早显示具有重大安全性问题的高风险化合物。

The efficacy and toxicity of new drug compounds can be predicted using these approaches, with greater accuracy and efficiency compared to traditional methods. For example, the costs for traditional reverse vaccinology studies can be as high as US$10 million and take up to 3-5 years. Reverse vaccinology involves sequencing the genome of a target pathogen and scanning for genes that may be useful for vaccines, such as those encoding for virulence factors or surface proteins. In addition, traditional approaches do not comprehensively screen all possible proteins. Existing evidence indicates that AI can substantially accelerate the drug discovery process at lower cost, while simultaneously being more comprehensive. Examples of companies that have used AI tools to cut the time and costs needed to identify preclinical candidates are given below:

与传统方法相比，使用这些方法可以更准确、更高效地预测新化合物的有效性和毒性。例如，传统的反向疫苗学研究成本高达 1000 万美元，耗时长达 3-5 年。反向疫苗学包括对目标病原体的基因组进行测序、扫描可能对疫苗有用的基因，如编码毒力因子或表面蛋白的基因。此外，传统方法无法全面筛选所有可能的蛋白质。现有证据表明，人工智能能以更低的成本大大加快药物发现过程，同时也更全面。以下是一些公司利用人工智能工具缩短临床前候选药物鉴定所需的时间和成本的例子：

Aiming to develop a new vaccine for antibiotic-resistant N. gonorrhoeae, the biotechnology company EVAXION used its AI antigen discovery model EDEN (Efficacy Discriminating Educated Network) to screen thousands of proteins of multiple N. gonorrhoeaestrains. The AI prediction phase happened within 24 hours and led to a list of 26 gonococcal proteins that were predicted to be most efficacious. These 26 proteins were tested in mice; these tests showed that EDEN's protective scores correlated positively with the bacterial burden, providing evidence for the predictive potential of EDEN.[20] The protein antigens that gave best protection were used in EVAXION's final N.gonorrhoeae vaccine. EVAXION estimates that the entire costs for the drug discovery

and preclinical phases totaled about €200,000 (~US$215,000), a fraction of the cost of traditional screening studies (see Panel 1).
为了开发抗生素耐药淋球菌的新型疫苗，生物技术公司 EVAXION 利用其人工智能抗原发现模型 EDEN（效能判别教育网络教育网络）筛选了数千种来自多种淋病菌株的数千种蛋白质。人工智能预测阶段在 24 小时内完成，并得出了 26 种淋球菌蛋白质的清单。这 26 种蛋白质在小鼠体内进行了测试；测试结果表明，EDEN 的保护性评分与细菌负担呈正相关，这为 EDEN 的预测潜力提供了证据[20]。
EVAXION 的最终淋球菌疫苗采用了保护效果最好的蛋白抗原。 据 EVAXION 估算，药物发现和临床前阶段的全部成本约为20万欧元（约合21.5万美元），仅为传统筛选研究成本的一小部分（见Panel 1）

Insilico Medicine's GENTRL platform designed a new drug candidate against fibrosis in 21 days and validated it in another 25 days.[21,22,23] The company also reported the development of a preclinical candidate for idiopathic pulmonary fibrosis in under 18 months, which also entered first-in-human studies in 9 months. A second preclinical candidate for kidney fibrosis was developed in 6 months.[17,24]

Exscientia reported that seven programs took less than 18 months from target identification to candidate identification (including for cardiovascular and oncology drug candidates). Exscientia developed five new assets in less than 14 months, compared to the five-year industry benchmark, with cost savings of more than 80% during the discovery phase and of 30% for the entire drug development process).[22,26]

英矽智能的 GENTRL 平台在 21 天内设计出可用于治疗肝纤维化一种新的候选药物，并在 25 天内进行了验证[21,22,23]。该公司还报告了针对特发性肺泡坏死的临床前候选药物的开发情况。
该公司还报告称在不到 18 个月的时间内开发出了治疗特发性肺坏死的临床前候选药物，并在 9 个月内进入首次人体试验阶段。第二个治疗肾脏坏死的临床前候选药物也在 6 个月内开发完成[17,24]

Exscientia 公司报告说，有 7 个项目从确定靶点到确定候选药物（包括心血管和肿瘤）的时间不到 18 个月。Exscientia 在不到 14 个月的时间内开发了五项新资产，在发现阶段节省了 80% 以上的成本，在整个药物开发过程中节省了 30% 的成本。[22,26]。

PANEL 1

EVAXION's AI-Immunology™ Platform: Potential for faster, cheaper, and risk-reduced vaccine development

EVAXION 的人工智能免疫学™ 平台：更快更便宜更少风险的疫苗开发平台

AI platforms are becoming increasingly important for target identification. One example is the AI-powered vaccine development by the biotech company Evaxion Biotech A/S (EVAXION). EVAXION is developing AI models to decode the human immune system and develop new vaccines for cancer, bacterial diseases, and viral infections. For the development of prophylactic vaccines against infectious diseases, EVAXION uses the AI models EDEN™* (B-cell targets) and RAVEN™ (T-cell targets), which comprise EVAXION's AI-Immunology™ platform.[27]

EDEN™ identifies vaccine targets that elicit an antibody response against infectious disease pathogens. As of November 2023, four vaccine candidates for N. gonorrhoeae and S. aureus were in the preclinical stage, with one of them being tested by Afrigen Biologics (Afrigen) in South Africa (see below). EVAXION also uses the AI-Immunology™ platform's AI models PIONEER™ (neoantigens) and ObsERV™ (ERV antigens) for personalized cancer vaccines, including for skin cancer and lung cancer.[28] A vaccine for metastatic melanoma is currently being tested in a small Phase 2 trial (others are in the preclinical phase or Phase 1).

人工智能平台在药物靶点识别方面正变得越来越重要。Evaxion开发的人工智能驱动的疫苗就是例证。EVAXION 正在开发人工智能模型解码人体免疫系统，并开发针对癌症、细菌性疾病和病毒感染的新型疫苗。在开发预防性传染病疫苗方面，EVAXION 使用人工智能模型 EDEN™*（B 细胞靶标）和 RAVEN™（B 细胞靶标）和 RAVEN™（T 细胞靶标），这两个模型构成了 EVAXION 的人工智能-免疫学™ 平台27

EDEN™可识别针对传染病病原体激发抗体反应的疫苗靶点。截至 2023 年 11 月，有四种淋球菌和金黄色葡萄球菌的候选疫苗已进入临床前阶段，其中一种正由南非的 Afrigen Biologics 公司（Afrigen）进行测试（见下文）。EVAXION 还将 AI-Immunology™ 平台的 AI 模型 PIONEER™（新抗原）和 ObsERV™（ERV 抗原）用于个性化癌症疫苗、 包括皮肤癌和肺癌28。转移性黑色素瘤疫苗目前正在进行一项小型 2 期试验（其他疫苗正处于临床前阶段或 1 期试验阶段）。

There is evidence that EVAXION's AI models can rapidly and efectively identify highly and broadly protective vaccine targets, ofering the opportunity for fast-tracking vaccine candidates into clinical testing and increasing the probability of clinical success. A study conducted by the University of Massachusetts and EVAXION showed that EDEN™ has identifed two promising gonococcal antigens, which, when used in combination as a chimeric, have elicited functional bactericidal antibodies in vitro and have shown efficacy in a preclinical mice model.[20] The EDEN-discovered antigens showed high levels of protection in the study. These fndings indicate that EDEN™ can efectively predict protein-specifc antibody-mediated protection and highlight the utility of the EDEN™ model to rapidly identify novel vaccine candidates that have not been considered using more traditional approaches. EVAXION also illustrates how AI companies can partner with LMICs. In September 2023, EVAXION announced a collaboration with Afrigen.[29] The collaboration aims to develop a prophylactic vaccine based on EVAXION's EDEN-discovered gonorrhea targets. Gonorrhea is a sexually transmitted disease that impairs global sexual and reproductive health (SRH). WHO reported 82 million new gonorrhea infections annually worldwide in 2020 with a rise in antibiotic-resistant cases; gonorrhea also increases susceptibility to HIV. The partnership will explore the expression and biological activity of the antigens in mRNA format, ofering an opportunity to further accelerate clinical validation of the EDEN™ model.

有证据表明，EVAXION 的人工智能模型能够快速、有效地识别具有高度广泛保护性的疫苗靶点，为候选疫苗快速进入临床试验提供了机会，并提高了临床成功的概率。马萨诸塞大学和 EVAXION 公司进行的一项研究表明，EDEN™ 已经确定了两种很有前景的淋球菌抗原、 在体外诱导出功能性杀菌抗体，并在临床前小鼠模型中显示出某种功效20。EDEN 发现的抗原显示出高水平的保护作用。

这些结果表明，EDEN™能够有效地预测蛋白质特异性抗体介导的保护作用，并突出了EDEN™模型在快速识别新型候选疫苗方面的实用性，而这些候选疫苗在传统方法中尚未被考虑。

EVAXION 还展示了人工智能公司如何与中低收入国家合作。2023 年 9 月，EVAXION 宣布与 Afrigen 合作29。该合作旨在开发 EVAXION 的 EDEN 发现的淋病靶点预防性疫苗。淋病是一种损害全球性健康和生殖健康 (SRH) 的性传播疾病。世卫组织报告称，到 2020 年，全球每年新增淋病感染病例将达 8200 万例，抗生素耐药病例激增。淋病也会增加对艾滋病毒的易感性。该伙伴关系将探索mRNA 格式抗原的表达和生物活性，为进一步加快 EDEN™ 模型的临床验证提供机会。

*EDEN™ is an AI-driven model trained to identify novel protective antigens for use in vaccines against pathogenic bacteria. The core of EDEN™ is a proprietary machine learning ensemble of artifcial neural networks used to interpret immunologically relevant information in relation to bacterial antigens that confer protection when administered as vaccines. EDEN™ has been trained on EVAXION's curated data set derived from publicly available data (publications and patents) describing protective and non-protective antigens tested in clinical and pre-clinical settings. EVAXION believes EDEN is applicable to virus vaccine development, hence it is being applied in the development of a virus vaccine against cytomegalovirus, EVX-V1.

*EDEN™是一个人工智能模型，经过训练可识别用于病原菌疫苗的新型保护性抗原。EDEN™ 的核心是一个人工神经网络的专有机器学习集合，用于解释与细菌抗原有关的免疫相关信息，这些抗原在作为疫苗接种时可提供保护。EDEN™ 是在 EVAXION 整理的数据集上进行训练的，这个来自公开出版物和专利的数据集描述了在临床和临床前环境中测试过的保护性和非保护性抗原。EVAXION相信EDEN适用于病毒疫苗的开发，因此将其应用于巨细胞病毒病毒疫苗EVX-V1的开发。

AI is also being used for drug repurposing and the identification of effective drug-drug interactions and combinations.

人工智能还可用于药物的再利用以及有效药物相互作用和药物组合的识别

Many companies are using AI for drug repurposing. For example, Healx used machine learning techniques to predict 22.2% synergistic antimalarial combinations from 1,540 combinations.[30,31] In addition, Healx identifed repurposed therapeutics for Fragile X syndrome, a genetic condition that results in learning disabilities. Using AI analytics as the basis of its in-silico Disease-Gene Expression Matching pipeline, it took 15 months from inception to readiness for the clinical trial phase. This project identifed eight potential candidates, which were also validated in mice. Sulindac, a nonsteroidal anti-infammatory drug, and metformin, a hepatic glucose production inhibitor, have been identifed as promising repurposing candidates for Fragile X.[31]

Another important application of AI in drug discovery is the identifcation of drug–drug combinations and their optimal doses.[32] Within two weeks, Exscientia's AI platform identifed remdesivir, ritonavir, and lopinavir as the optimal regimen to inhibit SARS-CoV-2 live virus out of 530,000 drug combinations. The regimen showed a 6.5-fold improvement in efficacy compared to remdesivir alone.[31] Shen et al developed an AI tool to determine the optimal dose of antiretroviral therapy for HIV treatment. The researchers administered a combination oftenofovir and efavirenz to ten patients, and, using an AI tool, they found that the dose

oftenofovir can be reduced by 33% of the starting dose without causing viral relapse.[13,33]

Pantuck et al developed an AI platform called "CURATE.AI" that used the personal data of a patient with prostate cancer to guide optimal combination

chemotherapy dosing.[34]

许多公司正在利用人工智能进行药物再利用。例如，Healx 公司利用机器学习技术从 1,540 种组合中预测出 22.2% 的协同抗疟组合[30,31]。此外，Healx 还发现了针对脆性 X 综合征（一种导致学习障碍的遗传病）的再利用疗法。利用人工智能分析作为其疾病-基因表达匹配管线的基础，从开始到准备进入临床试验阶段用了 15 个月。

进入临床试验阶段。该项目确定了八个潜在候选药物，并在小鼠体内进行了验证。非甾体抗炎药舒林酸和肝糖生成抑制剂二甲双胍已被确定为有希望用于脆性 X 的候选药物。

人工智能在药物发现中的另一个重要应用是确定药物组合及其最佳剂量[32]。

在两周内，Exscientia 的人工智能平台确定了 雷米替韦、利托那韦和洛匹那韦是在 530,000 种药物组合中抑制 SARS-CoV-2 活病毒的最佳方案，与单独使用雷米替韦相比，该方案的疗效提高了 6.5 倍[31]。

Shen 等人开发了一种人工智能工具用于确定抗逆转录病毒疗法的最佳剂量。研究人员对 10 名患者进行了替诺福韦和依非韦伦的联合治疗，替诺福韦的剂量可减少起始剂量的 33%，而不会导致病毒复发[13,33]。

Pantuck 等人开发了一个名为 "CURATE.AI" 的人工智能平台，该平台利用前列腺癌患者的个人数据来指导最佳联合化疗剂量[34]。

Pantuck 等人开发了一个名为 "CURATE.AI" 的人工智能平台，该平台利用前列腺癌患者的个人数据前列腺癌患者的个人数据来指导最佳联合化疗剂量。

2.3 Benefits of AI in clinical research

AI应用于临床研究的优势

The use of AI in clinical trial stages is less advanced compared to the discovery and preclinical stages. Current applications of AI relate to clinical trial design, conduct, and analysis. Several researchers have suggested that using AI tools to inform clinical trial design can reduce the number of trial participants and trial length and speed up clinical development by increasing the probability of trial success and regulatory approval. However, there is limited quantitative data.

与发现和临床前阶段相比，人工智能在临床试验阶段的应用还不够成熟。目前人工智能只应用于临床试验的设计、实施和分析。一些研究人员认为使用人工智能工具为临床试验设计提供信息，可以减少试验参与人数和试验时间，并通过提高试验成功和监管批准的概率来加快临床开发。然而，目前的量化数据还很有限。

1. Prediction of trial success: AI can help to predict the probability of trial success and help design Phase 2 and Phase 3 trials that are more likely to transition to regulatory approval. For example, using its AI tool, the drug discovery company Insilico Medicine can predict the outcome of Phase II to Phase 3 clinical trial success with impressive accuracy. The prediction tool, trained on data from 55,600 unique Phase 2 clinical trials over 7 years, is able to predict trial success probability with 79% accuracy.[35] The clinical trial data comes from ClinicalTrials.gov, a database that includes studies from over 200 countries. Such tools have the potential to save substantial future costs.

预测试验成功： 人工智能可以帮助预测试验成功的概率，并帮助设计更有可能获得监管部门批准的二期和三期试验。例如，药物发现公司药物发现公司 Insilico Medicine 利用其人工智能工具准确预测二期到三期临床试验的成功结果，该预测工具根据 7 年间 55,600 项独特的 二期临床试验数据进行训练，预测试验成功的概率准确率达 79% [35]。临床试验数据来自 包含 200 多个国家研究的数据库ClinicalTrials.gov，这是一个，此类工具有可能为未来节省大量成本。

2. Patient recruitment has been a particularly challenging aspect of clinical trials, with an estimated 80% of trials not meeting enrollment timelines and 30% of Phase 3 trials terminating early due to enrollment challenges.[36] AI can perform automated eligibility analysis, matching potential participants to trials, and simplifying trial searching capabilities. AI tools such as Criteria2Query and Dquest aim to make trial design and recruitment more efficient. Criteria2Query helps to standardize inclusion and exclusion criteria within databases and simplify data collection, whileDquest helps to improve patient recruitment for trials through dynamic processes (it "generates a series of dynamic questions for patients to answer and then filters their options based on the responses"). Dquest can exclude 60% to 80% of trials for which the patient was not eligible.[37]

临床试验中患者招募一直独具挑战性，据估计，80% 的试验无法达到招募时限，30% 的 三 期试验因招募困难而提前终止[36]。

人工智能可以进行自动资格分析，为试验匹配潜在参与者，并简化试验搜索功能。Criteria2Query 和 Dquest 等人工智能工具旨在提高试验设计和招募的效率。Criteria2Query 有助于规范数据库中的入组和排除标准并简化数据收集，而 Dquest 则有助于通过动态流程（"生成一系列动态问题让患者回答，然后根据患者的回答情况来筛选"）改善试验的患者招募工作。Dquest 可以排除 60% 到 80%不合格患者。

3. Predicting patient outcomes in clinical trials can lead to shorter trial duration. Such tools can also predict dropouts and may help to reduce overall sample sizes, leading to cost savings, since fewer participants are needed for the trial. However, quantitative data on the use of AI for predicting trial outcomes is limited and lowering sample sizes involves risk. Thus, more research on the use of AI is needed in the clinical phase and respective safeguards need to be put in place to both protect patients and produce reliable results.

预测临床试验中患者的预后可缩短试验时间。这些工具还能预测放弃情况，并有助于减少总体样本量，因为试验需要的参与者减少从而节约成本。不过，有关使用人工智能预测试验结果的量化数据还很有限，而且降低样本量也存在风险。因此，还需要对人工智能在临床阶段的使用进行更多的研究，并制定相应的保障措施，既要保护患者，又要得出可靠的结果。

4. During the conduct of trials, AI can be used in many ways:
   (i) digital health technologies, including digital biomarkers developed based on AI algorithms, can help to interpret data and transform it into usable insights;
   (ii) analysis and workflow management of medical images using AI can streamline the review and supplement the analysis of medical images; and
   (iii) AI algorithms can support the automated annotation of important markers, which would normally be derived manually by experts.
These are just some examples; however, there is little quantitative data on the potential efficiency gains.

在试验过程中，人工智能可以有多种用途：

(i) 数字健康技术，包括基于人工智能算法开发的数字生物标记，可以帮助解释数据并将其转化为可用的洞察；

(ii) 利用人工智能对医学影像进行分析和工作流程管理，可简化医学影像的审查和补充分析；以及

(iii) 人工智能算法可支持重要标记的自动注释，而这些标记通常需要专家手动得出。这些只是一些例子，但关于潜在效率收益的量化数据还很少。

5. Clinical trial data analysis and approval: AI has been used to:
   (i) determine effect heterogeneity to identify subgroups that showed differing treatment effects, as well as to identify key risk factors and fast-responders in sub-populations;
   (ii) impute missing data and missing study visits;
   (iii) facilitate more comprehensive statistical analysis; and
   (iv) support the automation of data extraction into statistical analysis tools to reduce the need for manual effort and associated human error.
For example, the Highly Efficient Clinical Trials (HECT) simulator is an open-source, browser-based clinical trial simulator for planning adaptive and platform trials. It is a web application written in Rshiny, a package in the statistical software R and Rstudio. It caters to clinical trial investigators who do not have the statistical capacity for trial simulations available in their team.[38]

5 临床试验数据分析与审批： 人工智能已被用于

(i) 确定疗效异质性，以识别显示不同治疗效果的亚组，以及识别亚组中的关键风险因素和快速反应者；

(ii) 补偿缺失数据和缺失的研究访问；

(iii) 促进更全面的统计分析；以及

(iv) 支持将数据自动提取到统计分析工具中，以减少人工操作和相关的人为错误。

例如，高效临床试验（HECT）模拟器是一个基于浏览器的开源临床试验模拟器，用于规划自适应和平台试验。它是一个用 Rshiny 编写的网络应用程序，Rshiny 是统计软件 R 和 Rstudio 中的一个软件包。它适用于团队中不具备试验模拟统计能力的临床试验研究者[38]。

2.4 Use of AI for strengthening pandemic preparedness
利用人工智能加强大流行病防范

Recent advances in AI technology make it possible to quickly and effectively model potential viral vaccine targets, which is important for pandemic preparedness. Efforts are ongoing to leverage AI for the development of vaccines for diseases with pandemic potential. CEPI has funded research to map potential antigenic targets for 10 priority virus families with epidemic or pandemic potential. [39,40] This CEPI-funded research will initially focus on paramyxoviruses and arenaviruses, which include Nipah virus and Lassa virus, respectively. CEPI intends to store AI-derived antigen designs in a "vaccine library" so they can be quickly used to develop vaccine candidates in the event of an outbreak of a novel pathogenic threat. In such an emergency, these antigen designs could be taken "off the shelf," and gene sequences could then be inserted into a rapid-response vaccine platform, such as mRNA, to start production of vaccines for clinical testing.

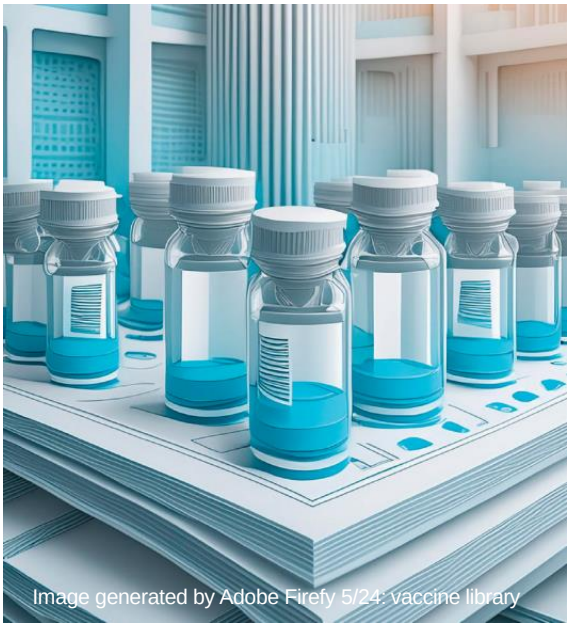


Image generated by Adobe Firefy 5/24: vaccine library

has become even more important in light of a new modeling study by authors from Gingko Bioworks, the Commission on Investing in Health, and the Disease Control Priorities Project showing that the risks of a major pandemic are higher than previously believed.[42] The modeling suggests "that an event having the mortality level of COVID-19 should not be considered a "once in a century" risk, but rather occurring with an annual probability of 2–3 percent (that is, a one in 33–50-year event)."

人工智能技术的最新进展使快速、有效地模拟潜在的病毒疫苗靶点成为可能，这对大流行病的防备非常重要。目前各方正在努力利用人工智为可能的大流行疾病开发疫苗。CEPI 资助了为 10 个具有流行或大流行潜力的重点病毒科绘制潜在抗原靶标图的研究[39,40]。CEPI 资助的这项研究最初将侧重于副黏液病毒（paramyxoviruses）和禽流感病毒（arenaviruses），其中分别包括尼帕病毒（Nipah virus）和拉沙病毒（Lassa virus）。CEPI 打算将AI 衍生的抗原设计储存在 "疫苗库 " 中，以便在出现新致病菌威胁时能迅速用于开发候选疫苗。在这种紧急情况下，可以取用这些抗原设计，将基因序列插入快速反应疫苗平台（如 mRNA）开始生产用于临床试验的疫苗。

建立这样一个资料库将为世界带来先机，因为它将 大大压缩大流行病疫苗的开发时间，有可能将其缩短到 100 天（这一全球目标被称为 "100 天使命"，并得到了七国集团和二十国集团的支持）[41]。鉴于Gingko Bioworks公司、健康投资委员会和疾病预防和控制委员会进行的一项新的模型研究，大流行病的风险比以前认为的要高[42]。 建模表明 "COVID-19 的死亡率水平不应被视为 " 百年一遇"的风险，而是以每年 2-3%的概率发生（即 33-50 年一遇）"。

The creation of such a vaccine library requires inputs from multiple actors. In early 2023, the US National Institute of Allergy and Infectious Diseases, for example, announced US$100 million for similar work on vaccine libraries. However, private actors can also play an important role. For example, DeepMind started to curate protein structure predictions of specific priority pathogens in a much shorter timeframe compared to traditional approaches (which would have needed years).[43] However, DeepMind stopped such curation; experts interviewed for this study called on DeepMind to continue sequencing the proteins of every priority pathogen and to share this knowledge publicly. There are also AI tools that can forecast viral mutations and derive vaccine targets based on these predictions. A tool called EVEscape developed by the Harvard Medical School can estimate the ability of a novel viral variant to escape immunity.[44] A recent study showed that had the EVEscape tool been used at the start of the COVID-19 pandemic, it would have predicted the most frequent mutations and identified the most concerning variants of SARS-CoV-2.[45] The tool also made accurate predictions about other viruses, such as HIV, infuenza, Nipah, and Lassa.

创建这样一个疫苗库需要多方参与。例如，美国国家过敏和传染病研究所在 2023 年初宣布投入 1 亿美元用于类似的疫苗库工作。不过，私人参与者也能发挥重要作用。例如，DeepMind 开始对特定优先病原体的蛋白质结构进行预测，与传统方法（需要数年时间）相比，时间大大缩短[43]。然而，DeepMind 停止了这种预测；本研究采访的专家呼吁 DeepMind 继续对每种优先病原体的蛋白质进行测序，并公开分享这些知识。还有一些人工智能工具可以预测病毒突变，并根据这些预测推导出疫苗目标。哈佛大学医学院开发的一款名为 EVEscape 的工具可以估计新型病毒变种逃避免疫的能力[44]。最近的一项研究表明，如果在 COVID-19 大流行开始时使用 EVEscape 工具，它就能预测出病毒变种逃避免疫的能力。最近的研究表明，如果在 COVID-19 大流行开始时使用 EVEscape 工具，它就能预测出最常见的变异，并识别出最令人担忧的 SARS-CoV-2 变种[45]。该工具还能准确预测其他病毒，如艾滋病毒、流感、尼帕病毒和拉萨病毒。

2.5 Challenges for the use of AI in global health R&D

AI 用于全球健康研发面临的挑战

A recent critique on the use of AI in global health by Jonathan Shaffer and colleagues warned that AI (i) may deepen existing inequalities between LMICs and HICs, (ii) is controlled by large Northern companies, and (iii) is driving a “do more with less” paradigm that could undermine health service delivery for people living in the poorest countries.[16] In a similar vein, Leslie and colleagues asked in a commentary if AI stands for “augmenting inequality.”[15]

Other studies have made similar arguments. For example, Vaisman et al highlighted several concerns with the use of AI for neglected disease R&D, including:

乔纳森-沙伊尔（Jonathan Shaffer）及其同事最近对人工智能在全球卫生领域的应用提出了批评，警告说人工智能（i）可能会加深中低收入国家与高收入国家之间现有的不平等，（ii）被北方的大公司所控制，（iii）正在推动一种 “少花钱多办事 ”的模式，这可能会影响为生活在最贫穷国家的人们提供的卫生服务[16]。同样 Leslie和同事们在一篇评论文章中问到AI是否为 “增强不平等” 两个字的缩写[15]。其他研究也提出了类似的论点。例如，Vaisman 等人强调了将人工智能用于被忽视疾病研发的几个问题，包括

(i) unequal interrelationships between stakeholders (AI research is mostly being conducted in labs located in HICs with limited engagement with scientists and clinicians from endemic low-income settings);

(ii) inadequate informed consent from patients for biologic samples;

(iii) concerns about data security;

(iv) poor accessibility of technology to affected populations;

(v) ensuring that AI-derived diagnostic tools adhere to current and evolving care standards; and

(vi) deciding how to effectively use resources (implementation of AI diagnostics could unintentionally draw vital resources from other programs).[46]

(i) 利益相关者之间的关系不平等（人工智能研究大多在高收入国家的实 验室进行，与来自地方病流行的低收入国家的科学家和临床医生的接触有 限）；

(ii) 病人对生物样本的知情同意不足；

(iii) 对数据安全的担忧

(iv) 受影响人群难以获得技术；

(v) 确保人工智能诊断工具符合当前不断发展的护理标准；以及

(vi) 决定如何有效利用资源（人工智能诊断的实施可能无意中占用其他计划的重要资源）[46]。

The gains of AI for neglected diseases research will only be realized if LMICs are involved in the development and implementation of the technology. The speed with which AI is being developed poses a challenge —LMIC governments and communities must be included now. The key steps need to be determined in a strategic process and should be embedded in broader coordination processes, such as the pandemic treaty and the development of a coordination platform for medical countermeasures (MCMs). At the moment, LMICs and communities do not have a seat at the table to inform the models, so the statistical representations in these models may be less accurate compared to higher-income regions than for regions with better-represented data. If not properly managed, AI tools will do harm by inadvertently reinforcing biases, increasing existing inequalities, and providing misinformation. When AI algorithms are biased or unrepresentative, the resulting predictions may be inaccurate or unfair.[47] African researchers have therefore called for a research agenda on AI grounded in the African context to determine locally relevant strategies for its development and use.[48,49]

只有让低收入与中等收入国家参与到技术的开发与实施中，才能实现人工智能在被忽视疾病研究中的收益。

技术的开发和实施才能实现。人工智能的发展速度带来了挑战--低收入与中等收入国家的政府和社区现在就必须参与进来。

政府和社区现在就必须参与进来。关键步骤需要在战略进程中确定，并应纳入更广泛的协调进程，如大流行病条约和医疗对策（MCMs）协调平台的开发。目前，低收入与中等收入国家和社区在为模型提供信息方面没有发言权，因此这些模型中的统计表示可能不如高收入地区准确

因此，与数据代表性较高的地区相比，这些模型中的统计表示可能不够准确。如果管理不当，人工智能工具会在无意中强化偏见、加剧现有的不平等并提供错误信息，从而造成危害。

47 因此，非洲研究人员呼吁制定一个立足于非洲背景的人工智能研究议程，以确定与当地相关的人工智能发展和使用战略。

There are also questions around data quality, fragmentation of data, and data access. For example, while considerable data has been collected on NCDs in HICs, there is much less data on NDs and EIDs. This limits the use of AI for these disease groups, especially during the clinical phase.

The “black box” nature of ML models is an additional challenge, in which even experts cannot explain how the model arrives at a result and comprehend the biological mechanism behind it.[13] Global standards and oversight for the use of AI in general and for global health specifically are only slowly emerging (see, for example, the efforts by the UK government and the European Union[50,51]).

此外，还存在数据质量、数据分散和数据访问方面的问题。例如在高收入国家收集了大量有关非传染性疾病的数据，但很少有关被忽视疾病和新发传染病的数据，这限制了人工智能在这些疾病群体尤其是在临床阶段中的应用。

ML 模型的 “黑箱 ”性质是另一个挑战，即使是专家也无法解释模型是如何得出结论的，也无法理解模型是如何进行分析的[13]。有关人工智能在一般情况下以及在全球健康领域的使用的全球标准和监督正在慢慢形成（例如，参见英国政府和欧盟的努力[50,51]）。

2.6 Summary and suggested ecosystem changes
小节和生态系统改革建议

While there is clearly a lot of hype about AI in global health, our review has shown that AI technologies can make significant contributions to global health R&D. Substantial efficiency gains can be achieved during the discovery and preclinical phases. Drug candidates can be brought to the clinical phase faster and at much lower cost (Table 1). In addition, AI can provide a much more comprehensive screening compared to traditional approaches, as shown by EVAXION's AI tool, which screened thousands of proteins of multiple N. gonorrhoeae strains within 24 hours. This more comprehensive screening may eventually lead to the development of better, more efficacious tools. AI may also have a positive effect on failure rates during the clinical phases, and the ability to predict clinical trial outcomes may offer substantial cost savings.

人工智能在全球健康领域的应用显然已被炒得天花乱坠，但我们的研究表明，人工智能技术可以为全球卫生研发做出重大贡献。在药物发现和临床前阶段AI可以大大提高效率，候选药物可以更快、以更低的成本进入临床阶段（表 1）。此外，与传统方法相比，人工智能还能提供更全面的筛选，如 EVAXION 的人工智能筛选技术在 24 小时内筛选了多个淋球菌菌株的数千种蛋白质。这种更全面的筛选最终可能会开发出更好、更有效的工具。人工智能还可能对临床阶段的失败率产生积极影响，预测临床试验结果的能力可能会节省大量成本。

Table 1. Cost and time savings of AI in the discovery phase

表1。人工智能在发现阶段节省的成本和时间

	Traditional approaches*	AI-assisted approaches
Costs	US$10 million*	~€200,000 (US$215,000)
Timelines	3-5 years	<1 year

*PAREXEL: Biopharmaceutical R&D Statistical Sourcebook 2018/2019.

PAREXEL: 生物制药研发统计资料 2018/2019

	传统方法*	AI辅助方法
成本	1000万美元	~20万欧元 (21.5万美元)
时间	3-5 年	<1 年

AI also has the potential to play a key role in pandemic preparedness. AI technologies can greatly increase the number of vaccine designs that can be used rapidly to identify the most promising candidates. There are also tools to predict the mutation of viruses.

At the same time, there are important issues to consider. First, AI itself is not the solution to any problem –highly qualified experts are still needed. For example, while AI can provide predictions, the results must still be validated and interpreted by experienced, skilled human researchers. Second, robust regulations and data protection measures are needed to safeguard individuals' privacy, and some experts thus suggest the creation of a global body for AI (similar to the International Atomic Energy Agency). Third, there is an urgent need to strengthen AI expertise and capacity in LMICs, otherwise global inequalities will widen.

人工智能还有可能在防范大流行病方面发挥关键作用。人工智能技术可以大大增加疫苗设计的数量，从而快速确定最有希望的候选疫苗。还有一些工具可以预测病毒的变异。

与此同时，还有一些重要问题需要考虑。首先，人工智能本身并不能解决任何问题--仍然需要高水平的专家。例如，虽然人工智能可以提供预测，但其结果仍必须由经验丰富、技术娴熟的人类研究人员进行验证和解释。第二，需要健全的法规和数据保护措施来保护个人隐私，一些专家建议成立一个全球人工智能机构（类似于国际原子能机构）。第三，迫切需要加强中低收入国家的人工智能专业知识和能力，否则全球不平等将进一步扩大。

Overall, we suggest the following ecosystem changes: 总之，我们建议以下生态系统变革：

1. First, there is substantial potential to further leverage AI for discovery and preclinical research to accelerate the development of new tools for NDs, EIDs, and MH. Funders of global health R&D should leverage the potential of AI and invest in companies that show capability and interest in using their AI tools for neglected disease R&D. This should lead to a much better drug pipeline for these groups of diseases.

2. Second, LMICs need to be enabled to meaningfully participate in AI-driven R&D and build respective capacity and expertise. Without such participation, existing inequalities in global health will be widened. Partnerships between AI companies, most of which are in HICs, and LMIC researchers will be important. The capacity of major regional health agencies, such as Africa CDC, in AI-enhanced R&D needs to be built. These organizations are key when it comes to the development of strategies, data collection and analysis, and policy recommendations.

3. Third,funders should support the expanded use of AI for epidemic and pandemic preparedness. AI tools should be used to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library. Stronger engagement of AI companies, such as DeepMind, should actively be supported.

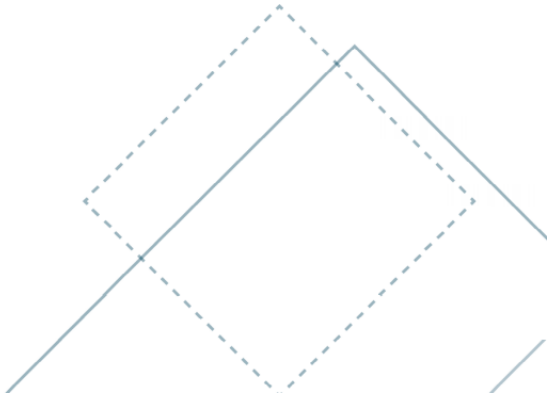
4. Fourth, the potential of AI in clinical research needs further assessment. There is evidence that AI has great potential in the clinical research phases but the current focus is more on drug discovery and preclinical research. For neglected disease R&D in particular, there is the need to build large datasets, which in turn requires stronger data access and data sharing.

首先，进一步利用人工智能进行发现和临床前研究以加速开发治疗ND、EID 和 MH 的新工具具有巨大潜力。全球卫生研发的资助者应利用人工智能的潜力投资于那些有能力、有兴趣将其人工智能工具用于被忽视疾病研发的公司。这将为这些疾病群体带来更好的药物开发渠道。

其次，需要让低收入与中等收入国家能够有意义地参与人工智能驱动的研发，并建设各自的能力和专业知识。如果没有这种参与全球卫生领域现有的不平等将进一步扩大。要加强的人工智能公司（大多数位于高收入国家）与低收入国家的研究人员之间的伙伴关系将非常重要。非洲疾病预防控制中心等主要地区卫生机构在人工智能强化研发方面的能力需要加强。这些机构在制定战略、收集和分析数据以及提出政策建议方面至关重要。

第三，资助者应支持扩大人工智能在流行病和大流行病防备方面的应用。人工智能工具应用于预测重点病原体的蛋白质结构，协调建立疫苗库。应积极支持 DeepMind 等人工智能公司的更多参与。

第四，需要进一步评估人工智能在临床研究中的潜力。有证据表明，人工智能在临床研究阶段具有巨大潜力，但目前的重点更多地放在药物发现和临床前研究上。需要为被忽视疾病的研发建立大型数据集，这反过来又需要加强数据访问和数据共享。



SECTION

3

INNOVATIONS IN CONDUCTING CLINICAL TRIALS

临床试验创新

INNOVATIONS IN CONDUCTING CLINICAL TRIALS
临床试验创新

KEY BENEFITS:主要优势

Decentralized clinical trials (DCTs) using digital health technologies (DHTs) can reduce trial costs, timelines, and the number of patients needed in a trial. Such trials can also improve recruitment and retention of participants.

使用数字医疗技术（DHT）的分散临床试验（DCT）可以降低试验成本、缩短试验时间、减少试验所需患者人数。此类试验还能提高参与者的招募和保留率。

Platform trials can also drive efficiencies in a number of ways. They can shorten trial duration, evaluate more treatments per trial, reduce the number of patients required per trial (by up to 70%), and increase the proportion of programs that accurately recognize an effective treatment.

平台试验还能以多种方式提高效率。它们可以缩短试验持续时间，在每次试验中评估更多的治疗方法，减少每次试验所需的患者人数（最多可减少70%），并提高准确识别有效治疗方法的项目比例。

Real-world data and evidence can lower trial costs. The savings can be US$10 to US$20 million per trial, depending on how much synthetic control arms are used to replace traditional control arms.

真实世界的数据和证据可以降低试验成本。每项试验可节省 1,000 万至 2,000 万美元，这取决于用多少合成对照组来取代传统对照组。

Clinical trial networks can drive efficiencies by using existing sites instead of creating new ones, recruiting patients more quickly and reliably, and reducing the number of patients needed by sharing control groups with other trials. Connecting trial sites, which allows a sponsor to find sites for rapid enrolment, could reduce Phase 2/3 trial costs by 23%. Costs could be reduced by 40-60% by sharing control groups and using control data from previous trials. The ability to rapidly test product candidates during outbreaks relies on the existence of effective and inclusive regional clinical trial networks that are kept active between outbreaks.

临床试验网络可以通过使用现有研究机构而不是新建研究机构来提高效率。

通过与其他试验共享对照组，减少所需的患者人数；通过连接试验场地，申办者可以找到快速招募患者的试验场地，从而将 2/3 期试验的成本降低 23%；通过共享对照组和使用以前试验的对照数据，可将成本降低 40-60%。在疾病爆发期间快速测试候选产品的能力取决于是否存在有效、包容的区域临床试验网络。

KEY CHALLENGES TO BE ADDRESSED主要挑战:

Both trialists and regulatory authorities in LMICs may lack the expertise needed to implement and oversee complex trial designs.

新型试验设计（如平台试验）的复杂性可能会成为低收入和中等收入国家采用这种试验设计的障碍。低收入国家的试验人员和监管机构可能都缺乏实施和监督复杂试验设计所需的专业知识。

Maintaining data quality and privacy can be a challenge in DCTs and DHTs.

在 DCT 和 DHT 中，保持数据质量和隐私可能是一大挑战。

SUGGESTED ECOSYSTEM CHANGES:生态系统改革建议

Research funders and agencies should support sustained, long-term efforts to build clinical trial networks that have the capacity to adopt innovative approaches, building on existing capacities.

研究资助者和机构应支持在现有能力的基础上持续、长期打造有能力采用创新方法的临床试验网络。

Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, IRBs, data safety boards, and regulators to become familiar with these designs. As innovative trial designs become more widespread in LMICs, operational lessons need to be shared so that implementation barriers can be tackled and best practices adopted.

在低资源环境中采用平台试验和其他主方案需要资助机构、机构审查委员会、数据安全委员会和监管机构熟悉这些设计。随着创新性试验设计在中低收入国家越来越普遍，需要分享操作方面的经验教训，以便克服实施障碍并采用最佳实践

3.1 Overview 概述

Clinical trials are essential in showing that a product is safe and effective. However, traditional trial designs are expensive, lengthy, and have low success rates. From 2009-2018, the median capitalized R&D cost for a new drug or biologic agent approved by the US Food and Drug Administration (FDA), including expenditures on failed trials, was US$985 million (in 2018 US dollars) across all phases of development.[10] The clinical development time for innovative new drugs—the period from initiation of first-in-human studies to regulatory marketing—was about 8.3 years on average for FDA-approved drugs between 2010 and 2020.[52] Fewer than 1 in 10,000 innovative therapies achieve FDA approval.[53]

临床试验对于证明产品的安全性和有效性至关重要。然而，传统的试验设计成本高、时间长、成功率低。从2009年到2018年，美国食品药品管理局批准的新药或生物制剂的研发资本化成本中位数为中位数为 9.85 亿美元（按 2018 年美元计算）[10]，其中包括失败试验的支出。创新型新药的临床开发时间--在 2010 年至 2020 年期间，美国食品及药物管理局批准的药物平均开发时间，从开始首次人体研究到监管上市的时间--约为 8.3 年[52]。不到万分之一的创新疗法获得FDA批准[53]。

Nevertheless, recent advances in clinical trial conduct are spurring more efficient trials. The COVID-19 pandemic validated many of these advances—e.g., trial networks were critical to the rapid development of vaccines, while platform trials (e.g., RECOVERY) helped usher in COVID-19 therapies.[54] In this section, we examine these advances to understand their potential for lowering trial costs and timelines, and improving the efficiency and success rate of trials. We exclude the impact of mRNA,AI, and machine learning on trials, as these are discussed elsewhere. There are two important limitations to note about the data on trials. First, most data are from HICs. The burden of NDs, EIDs, and MH falls disproportionately on LMICs,[55] and new products for these conditions should be tested in these high-burden settings, ensuring inclusive and representative selection of trial participants. Yet most trials are conducted in HICs. A study by Coates et al of almost 90,000 trials conducted from 2006-2012 found that 83% were situated in 25 high-income Organization for Economic Co-operation and Development countries, while only 5% were in lower-middle or low-income countries.[55] One promising finding was that by 2012, 19% of Phase 3 trials were in LMICs (up from about 2% in 1999), suggesting that a “global migration of clinical research” is underway, mostly for late stage clinical trials.

尽管如此，最近临床试验取得的进展正在促进更有效的试验。COVID-19 大流行验证了其中的许多进步--例如，试验网络对疫苗的快速开发至关重要，而平台试验（如 RECOVERY）则有助于 COVID-19 疗法的诞生[54]。我们研究了这些进展以了解它们如何降低试验成本和时间表以及提高试验效率和成功率。这一节里我们不讨论其他章节讨论的 mRNA、人工智能和机器学习对试验的影响。关于试验数据，需要关注两个重要的局限性。首先，大多数数据来自高收入国家，ND、EID 和 MH 的负担主要落在中低收入国家和地区[55]，因此针对这些疾病的新产品应在这些高负担地区进行测试，确保试验参与者的选择具有包容性和代表性。然而，大多数试验都是在高收入国家进行的。Coates等人对 2006-2012 年间进行的近 90,000 项试验进行了研究，发现 83% 的试验在 25 个高收入的经合组织国家进行，而只有 5% 的试验在中低收入国家进行[55]。一项令人鼓舞的发现是，到 2012 年，19% 的三期试验在中低收入国家进行（1999 年仅为 2%），这表明 “临床研究的全球迁移 ” 正在进行，其中大部分是后期临床试验。

Second, data on trial parameters (costs, timelines, success rates) comes mostly from trials of product candidates for NCDs and are often pooled from trials of medicines, vaccines, biologics, and other product archetypes. There have been only a few studies that have disaggregated parameters by disease type or product archetype. In one of these disaggregated studies, Moore and colleagues estimated the costs of “pivotal” trials—those that provide key evidence of the benefits of new therapeutic agents (usually phase 3)—and showed the variation in costs by disease type, from US$6 million-US$141 million (Table 2).[56] The most important driver of costs was the number of patients needed to show an effect (which ranged from 4 to 8,442), followed by the number of clinical

Table 2. Cost estimates of clinical trials for therapeutic agents that have received FDA approval by therapeutic area. Data are from 225 pivotal trials that supported the approval of 101 new drugs from 2015-2017

Therapeutic area	Drugs	Median cost (IQR) USD millions
Blood	2	6 (4-8)
Cardiovascular	6	141 (74-183)
Central nervous system	14	42 (16-85)
Dermatology	9	50 (31-77)
Endocrine/metabolism	12	72 (14-144)
Genitourinary	4	23 (12-37)
Gastrointestinal	7	31 (15-63)

site visits (range: 2-166). In another study, Gouglas et al estimated the costs of developing a vaccine against 11 priority EIDs with pandemic potential.[57] Considering the probability of success (i.e., including the costs of the failed candidates), they estimate that the average cost of successfully advancing at least one epidemic infectious disease vaccine from preclinical to the end of phase 2a is US$319 million –US$469 million (the cost from the start of phase 2 to the end of phase 2a is US$84 million–US$112 million). Research by the IQVIA Institute found that clinical trial duration varied by disease area, from 9.7 years (dermatology) to 12.5 years (rare oncology).[58] An important component of this duration is “white space” (the period between trial phases), which, for new drugs, accounts for an average of 43% of the development time (see Annex 3).

其次，有关成本、时间表、成功率的试验参数数据大多来自非传染性疾病候选产品的试验，通常是从药品、疫苗、生物制剂和其他产品类型的试验中汇集而来，只有少数研究按疾病类型或产品原型对参数进行了分类。在其中一项分类研究中，Moore 及其同事估算了 “关键 ”试验（通常是提供了新治疗药物疗效的关键证据的三期试验）的成本，并显示了不同疾病类型的成本差异[56]，从 600 万美元到 1.41 亿美元不等（表 2）。成本的最主要驱动因素是显示疗效所需的患者人数（从 4 人到 8442 人不等）；其次是临床实地考察的次数（2-166）。在另一项研究中，Gouglas 在另一项研究中估算了针对 11 种重点新发流行性传染病开发疫苗的成本[57]。考虑到成功的概率（即包括失败候选者的成本），他们估计成功将一种流行性传染病疫苗从临床前阶段推进到 2a末期的平均成本至少为 3.19 亿美元--即 1.5 亿美元；从 2 期开始到 2a 期结束的成本为 8,400 万美元至 1.12 亿美元）。IQVIA 研究所的研究发现，临床试验持续时间因疾病领域而异，从 9.7 年（皮肤科）到 12.5 年（罕见肿瘤科）不等[58]。新药的 “空白期 ”平均占研发时间的 43%（见附件 3）。

Source: Moore et al, 2020[56]

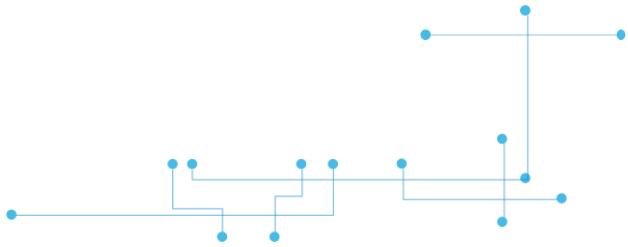


表2。按治疗领域对已获FDA批准的治疗药物进行临床试验的成本估算。数据来自2015-2017年期间支持101种新药批准的225项关键试验

治疗领域	Drugs	Median cost (IQR) USD millions
血液	2	6 (4-8)
心血管	6	141 (74-183)
中枢神经系统	14	42 (16-85)
皮肤科	9	50 (31-77)
内分泌/代谢	12	72 (14-144)
泌尿生殖系统	4	23 (12-37)
胃肠道	7	31 (15-63)

传染病	9	54 (26-102)
肌肉骨骼	2	68 (48-87)
肿瘤学	30	45 (29-72)
眼科	3	36 (34-44)
呼吸科	3	91 (73-110)
总计	101	48 (20-102)

Source: Moore et al, 2020[56]

3.2. Benefits of innovations in trial conduct临床试验创新优势

Advances in clinical trial conduct can be categorized into: 临床试验的进展可分为以下几类

a) 技术创新（如数字化临床试验、开源试验软件、疾病预测）；

b) 创新试验设计（如主方案、人体挑战试验、真实世界证据）；以及

TECHNOLOGICAL INNOVATIONS技术创新

Decentralized clinical trials (DCTs) using digital health technologies (DHTs) 运用数字医疗技术的分散式临床试验

DCTs are those in which some or all activities are conducted at non-traditional sites, such as a laboratory, a participant's home, or a local health center. Such trials usually incorporate DHTs, like wearable devices, telemedicine, and mobile applications. The FDA recently issued guidance on conducting DCTs.[59] The two main advantages of DCTs and DHTs are: (i) streamlining the identification, recruitment, and follow-up of participants, as well as data acquisition; and (ii) making trials more inclusive by reaching more diverse population groups, older people and people with disabilities who find it hard to travel, and patients who are distant from traditional clinical trial sites.[60] Reducing clinical visits is a major advantage, since such visits are costly: Moore et al found that "each additional trial visit added a median of US$2 million (IQR: US$1 million–US$3 million) to the overall estimated trial cost."[56] Durán et al assessed 91 clinical trial protocols across oncology, respiratory, and cardiovascular diseases and found that 74-85% of the studies were amenable to fully remote data collection using clinically validated devices,[61] reducing the number of clinical physical visits by up to 40%. These findings may not, however, be directly applicable beyond NCDs.

分散式临床试验（DCT）是指在实验室、参与者家中或当地卫生中心等非传统场所进行部分或全部活动的试验。这些试验通常包括数字医疗技术（DHT），如可穿戴设备、远程医疗和移动应用。FDA最近发布了实施DCT的指导意见。[59] DCT和DHT的两个主要优点是:(i)简化了参与者的识别、招募和随访，以及数据采集;(ii)通过覆盖更多样化的人群、老年人和出行不便的残疾人以及远离传统临床试验地点的患者，使试验更具包容性[60]，减少费用高昂的门诊随访是一个主要优势。

Moore等人发现 "每增加一次试验就诊，总估计试验费用中位数增加200万美元(IQR: 100万至300万美元)[56]。Durán等人评估了肿瘤学、呼吸系统和心血管疾病的91项临床试验方案，发现74-85%的研究可以使用临床验证的设备完全远程收集数据[61]，减少了高达40%的临床实地就诊次数。然而，这些发现可能并不直接适用于非传染性疾病以外的领域。

Open source trials software 开源试验软件

There have been several studies of the efficiencies associated with DCTs and DHTs (summarized in Annex 3), which have shown the benefits of DCTs and DHTs: reduced costs, a reduction in the number of participants needed, faster timelines, and lower participant drop-out rates. These have mostly been conducted in HICs, and the transferability of the findingsto LMICs remains unclear.

已经有几项与DCT和DHT有关的效率的研究(摘要见附件3)，彰显了DCT和DHT的好处：降低成本、减少所需参与者数量，更快的时间线和更低的参与者退出率。这些研究大多是在高收入国家进行的，研究结果是否适用于中低收入国家尚不清楚。

Disease Forecasting 疾病预告

Advances in clinical trial design and methodologies, such as platform trials (discussed below), have necessitated the use of advanced software to compute possible outcomes of more complex trial designs. Proprietary software, such as FACTS and ADDPLAN, was developed to facilitate these computations,[62,63] but it is expensive and requires experts in the field of biostatistics and mathematics to operate. These barriers prevent clinical researchers with limited resources from adopting contemporary clinical trial designs. To help overcome these barriers, as mentioned earlier in this report, the knowledge integration trial services division of the Bill & Melinda Gates Foundation developed the Highly Efficient Clinical Trials simulator (HECT), an open-source web-based platform built using RShiny , which facilitates platform and adaptive trial simulation.[64] The HECT has been used by trialists together with early stage portfolio planning and "has been used

to examine the likely costs and probabilities of success for a large number of candidate designs under various scenarios for possible target countries."[38] To our knowledge, there is no evidence in the published literature on the efficiency gains of using HECT.

Clinical trials for infectious diseases, including those conducted in response to epidemics, face unique challenges due to seasonal variation or sudden spikes in disease incidence. Furthermore, epidemics and infectious diseases occur across diverse geopolitical zones and disproportionately impact resource-poor settings. These challenges add complexity, time, and costs to infectious disease clinical trials. Forecasting hot spots through improved data gathering and real-time virus tracking can support agile and more efficient clinical trials.[65] For example, Airfinity, a London-based disease surveillance start-up specializing in real-time tracking, prediction, and simulation of population-level disease outcomes, has expertise in identifying and forecasting infectious disease hotspots. The company's COVID-19 tracking data were used by AstraZeneca to estimate the impact of its COVID-19 vaccine and its COVID-19 mAb, Evusheld.[66]

临床试验设计和方法的进步，如平台试验(下文讨论)必须用先进的软件来计算更复杂的试验设计的可能结果。，像FACTS和ADDPLAN这样的专有软件开发方这些计算[62,63]，但价格不菲，而且需要生物统计学和数学领域的专家来操作。这些障碍阻碍了资源有限的临床研究人员采用先进的临床试验设计。本报告前面提到，为解决这个难题，比尔和梅林达·盖茨基金会的知识整合试验服务部开发了高效临床试验模拟器(HECT)，这是一个使用RShiny构建的基于web的开源平台，它促进了平台和自适应试验模拟[64]。HECT已被试验者与早期投资组合规划一起使用，并且“已被用于在可能的目标国家的各种情况下检查大量候选设计的可能成本和成功概率[64]。据我们所知，在已发表的文献中没有证据表明使用HECT可以提高效率。

传染病临床试验，包括为应对流行病而进行的临床试验，由于季节性变化或疾病发病率的突然飙升，临床试验面临着独特的挑战。此外，流行病和传染病发生在不同的地缘政治区域，并对资源匮乏的环境造成严重影响，这些挑战增加了传染病临床试验的复杂性、时间和成本。通过改进数据收集和实时病毒追踪来预测热点地区，从而支持灵活、更高效的临床试验.[65]，例如，Airfnity 是一家总部位于伦敦的疾病监测初创公司，专门从事实时跟踪、预测和模拟人群层面的疾病结果，阿斯利康公司利用该公司的 COVID-19 跟踪数据用于估计其 COVID-19 疫苗和 COVID-19 mAb 思适得（Evusheld） 的影响[66]。

Master protocols, including platform trials

Randomized control trials (RCTs) are widely regarded as the gold standard for establishing effectiveness between health products or interventions and outcomes, but are costly and time consuming and their focus on narrow populations limits generalizability. To address these limitations and drive efficiencies, the past decade has seen the development and use of master protocols, defned by the US National Institutes of Health as "a trial design that tests multiple drugs and/or multiple subpopulations in parallel under a single protocol, without the need to develop new protocols for every trial."[67] The feld of oncology has been at the forefront of using master protocols, but these have also been used for infectious disease trials. There are three key types of master protocols:

随机对照试验（RCT）被广泛认为是确定卫生产品或干预措施与结果之间有效性的黄金标准，但是，随机对照试验成本高、耗时长，而且试验对象范围较窄，限制了试验的普遍性。为了解决这个局限性、提高效率，过去十年"主方案"有了长足的发展和运用。美国国立卫生研究院将主方案定义为 "在单一方案下平行测试多种药物和/或多个亚人群的试验设计，而无需为每种药物和/或每种亚人群制定新的方案"[67]。

肿瘤学领域一直是使用主方案的前沿领域，但这些方案也被用于传染病试验。主方案有三种主要类型：

- Basket trials evaluate the use of a targeted therapy on multiple disease types that share the same underlying genomic abnormality.
- Umbrella trials investigate the effect of multiple targeted therapies on one disease entity that differs by genetic changes in each enrolled patient (i.e. "stratifed by molecular alteration"[68]).
- Platform trials are multi-arm, multistage study designs that compare several intervention groups to one common control group. The landmark COVID-19 RECOVERY trial used a platform trial master protocol; it established that dexamethasone was effective and hydroxychloroquine was ineffective in treating COVID-19. A key beneft of platform trials is that new intervention arms may be added to an ongoing trial. Another example of a platform trial is UNITE4TB, a global clinical trials network, which aims to accelerate the development of new TB drugs by conducting clinical trials using a platform design.[69]

--篮式试验评估一种靶向疗法对具有相同潜在基因组异常的多种疾病类型的治疗效果。

- 伞式试验研究多种靶向疗法对一种疾病实体的影响，这种疾病实体因每个入组患者的基因改变而不同（即 "按分子改变分层"[68]）。

- 平台试验是一种多臂、多阶段研究设计，将多个干预组与一个共同对照组进行比较。具有里程碑意义的 COVID-19 RECOVERY 试验采用了平台试验主方案，该试验确定地塞米松有效，羟氯喹对治疗 COVID-19 无效。平台试验的一个主要优点是可以在正在进行的试验中增加新的干预措施。平台试验的另一个例子是全球临床试验网络UNITE4TB，其目的是通过采用平台设计开展临床试验，加快结核病新药的开发[69]。

Human challenge trials

What kinds of efficiencies do master protocols drive? Saville and Berry conducted a simulation study to assess "the efficiencies of various platform trial designs relative to a traditional two-arm strategy."[70] They found that open adaptive trial platforms, which add new treatments to the treatment arm during the course of the trial to replace ineffective ones, could (i) evaluate more treatments per trial, (ii) reduce the number of patients required per trial, (iii) signifcantly reduce the duration of the trials, and (iv) increase the probability of program success (the percentage of programs that accurately recognize an effective treatment). The authors estimate that an open adaptive trial platform with 10 active treatments could see a "70% reduction in the number of patients and failures compared to the traditional strategy."

Real-world data and evidence

Human challenge trials (HCTs) involve the deliberate infection of healthy, consenting human

study participants with an infectious agent in a controlled environment to better understand the disease biology, host immune response, and effects of drugs, vaccines, or diagnostics. HCTs are receiving increasing attention as they could potentially accelerate product development and reduce costs. There have been HCTs for a range of infections, including RSV, SARS-CoV-2, and schistosomiasis.

主协议推动了哪些方面的效率？Saville 和 Berry 进行了一项模拟研究，以评估 "相对于传统的双臂试验策略，各种平台试验设计的效率 "[70]。

他们发现，开放式适应性试验平台（在试验过程中向治疗组添加新的治疗方法以取代无效治疗方法）[70]。可以（i）在每次试验中评估更多的治疗方法

(ii) 减少每次试验所需的患者人数，(iii) 显著缩短试验持续时间。

(iv) 提高成功率（准确识别出有效治疗方法的项目百分比）。作者估计一个拥有 10 种有效治疗方法的开放式自适应试验平台“与传统策略相比，患者人数和失败案例减少 70%"

Human challenge trials (HCTs) involve the deliberate infection of healthy, consenting human study participants with an infectious agent in a controlled environment to better understand the disease biology, host immune response, and effects of drugs, vaccines, or diagnostics. HCTs are receiving increasing attention as they could potentially accelerate product development and reduce costs. There have been HCTs for a range of infections, including RSV, SARS-CoV-2, and schistosomiasis.

人体挑战性试验（HCT）是指在受控环境中故意让健康的、知情同意的人类研究参与者感染传染性病原体，以更好地了解疾病生物学、宿主免疫反应以及药物、疫苗或诊断方法的影响。HCT正受到越来越多的关注，因为它们有可能加快产品开发并降低成本。目前已有针对一系列感染的 HCT，包括 RSV、SARS-CoV-2 和血吸虫病。

The FDA defnes real-world data (RWD) as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources” and real-world evidence as “the clinical evidence about the usage and potential benefts or risks of a medical product derived from analysis of RWD.”[71] RWD is increasingly being used in clinical trials in a variety of ways, including as synthetic control arms (SCA) – a type of control arm that consists of patient-level data from patients who are not in a clinical trial[72] An analysis by BCG suggests that SCAs could generate around US$10 to US$20 million in savings per trial if 20 to 50% of a clinical trial control arm is replaced, and even greater if completely replaced (see Annex 3).[73]

FDA 将真实世界数据 (RWD) 定义为 "从各种来源常规收集的与患者健康状况和/或提供保健服务有关的数据”；“真实世界证据”定义为从RWD分析中得出的关于医疗产品的使用和潜在益处或风险的临床证据[71]。真实世界数据RWD正越来越多地以各种方式用于临床试验，包括作为合成对照臂（SCA）--一种由非临床试验患者的患者级数据组成的对照臂[72]。BCG 的一项分析表明，如果替换 20%至 50%的临床试验对照臂，SCA 可为每项试验节省约 1,000 万至 2,000 万美元，如果完全替换，节省的费用甚至更高（见附件 3）[73]。

3.3 Benefits of clinical trial networks
临床试验网络的优势

Trial networks are well established in the field of HIV prevention (see case study in Annex 3) as well as other infectious diseases such as tuberculosis (TB) and malaria in LMICs. The HIV Prevention Trials Network has shown several benefits: (i) it has been able to assess a range of different technologies and has expanded to include other diseases, such as TB; (ii) it was able to pivot rapidly to conducting COVID-19 vaccine trials and then Mpox vaccine trials; (iii) there are efficiency gains, such as time savings (using existing sites and capacities, including human resources, is quicker than establishing new ones); and (iv) the network has played a major role in building capacity to conduct trials in LMICs.

A multi-stakeholder working group convened by the Wellcome Trust examined how two types of clinical trial networks could play a critical role in driving efficiencies in the development of new antibiotics.

The first type, which the group calls a Globally Connected Trial Sites System, connects a series of trial sites "so that sponsors can easily come to one if they have a drug they want to test, and can then run the trial as per usual, with each trial having its own individual protocol." This system could potentially reduce the costs of Phase II and Phase III trials by 23%. The second type, a Continuous Master Protocol model, is a "single global network operated by one entity with a single defined protocol"—trials can share control groups and potentially use control data from past trials. This approach could

Connected trial sites could potentially reduce the costs of Phase II and Phase III trials by 23%.

全球连接试验站点能将二期三期试验成本降低23%

Continuous master protocols could reduce costs by 40-60%

连续主方案可将成本降低40-60%

在艾滋病毒预防以及中低收入国家像结核病和疟疾等其他传染病领域已经建立了完善的试验网络(见附件3的案例研究)。艾滋病毒预防试验网络已显示出若干好处:(一)它已能够评估一系列不同的技术，并已扩大到包括结核病等其他疾病;(二)能够迅速转向开展COVID-19疫苗试验，然后是猴痘疫苗试验;(三)效率大大提高，例如节省时间(利用现有场址和能力，包括人力资源，比建立新的场址和能力更快);(四)该网络在中低收入国家开展试验的能力建设方面发挥了重要作用。

一个由惠康基金会召集的多方利益相关者工作组研究了两种类型的临床试验网络如何在提高新抗生素开发效率方面发挥关键作用。第一类被该组织称为"全球连接试验站点系统"，将一系列试验站点连接起来，"这样，如果赞助商有想要测试的药物，他们就可以很容易地照常测试。每个试验都有自己的方案。"该系统可能会降低23%的二期三期试验成本。第二种类型"连续主方案模型"，是"由一个具有单一方案的实体操作的单一全球网络"

试验可以共享对照组和可能会使用过去试验的对照数据，这种方法可以降低成本40-60%。

3.4 Challenges in adopting trial innovations采用试验创新面临的挑战

There are several challenges in adopting trial innovations, especially in LMICs.中低收入国家采用试验创新的挑战如下：

1. DCTs and DHTs can pose challenges for data privacy and authentication, as well as navigating complex data and privacy laws that vary from country to country. The use of remote sensors and wearables raise questions about data reliability and quality.[75]

2. Barriers to adopting novel trial designs, such as platform trials, in LMICs include
   (i) difficulties in implementation due to the complexities of such designs;
   (ii) challenges in securing funders for the complex designs;
   (iii) acceptance and approval by ethics committees and regulatory bodies who may not have the capacity to vet the study protocols; and
   (iv) challenges in statistical analysis due to the scarcity of skilled labor with advanced modelling skills.[76]

1. DCT和DHT可能会给数据隐私和身份验证带来挑战，同时还会影响各国不同的复杂数据和隐私法律。远程传感器和可穿戴设备的使用提出了有关数据可靠性和质量的问题[75]

2. 在中低收入国家采用新试验设计(如平台试验)的障碍包括:
   (i)此类设计的复杂性而难以实施;
   (ii)为复杂设计争取资助机构方面的挑战;
   (iii)伦理委员会和监管机构的接受和批准，他们可能没有能力审查研究方案;以及
   由于缺乏具有先进建模技能的熟练劳动力，统计分析面临挑战[76]

3. Human challenge models face ethical debates and there is limited ethical guidance around their use. There have been questions about the informed consent process, and the risks and benefits of HCTs, particularly to the participants.[77] Furthermore, researchers have also called into question the appropriateness of HCTs in LMICs given the power dynamics, lack of ethical oversight and regulation, and the possibility of inducing participants by offering excessive payments.[78]

人类挑战模型面临伦理争论，关于其使用的伦理指导有限。关于知情同意程序以及HCT的风险和收益，特别是对参与者[77]存在争议；此外，研究人员鉴于权力动态、缺乏道德监督和监管，以及通过提供过高报酬诱导参与者的可能性，在中低收入国家开展hct的适当性也受到质疑[78]

虽然将RWD应用于临床试验可能会显著提高效率，但它并非没有挑战和安全性隐患。特别是与使用合成控制有关的关注。RWD和真实世界的证据可能有潜在的偏见，影响普遍性，以及数据隐私和质量问题[79]。

4. While the application of RWD to clinical trials may offer significant efficiency gains, it is not without its challenges and safety concerns, particularly related to the use of synthetic controls. RWD and real world evidence may have underlying biases affecting generalizability, as well as data privacy and quality issues.[79]

3.5 Summary and suggested ecosystem changes 小节和生态系统改革建议

There are multiple innovations in trial conduct that could potentially drive major efficiencies in R&D for NDs, EIDs, and MH (Table 3). Decentralized trials, master protocols (including platform trials), and trial networks hold particular promise. However, given that many LMICs lack trial capacity and infrastructure even for carrying out traditional two-arm trials, a sea change would be needed to scale up new trial approaches in these settings.

有多种试验行为创新可能提高ND、EID和MH的研发效率(表3)。分散试验、主协议(包括平台试验)和试验网络具有特别的前景。然而，鉴于许多中低收入国家缺乏试验能力和基础设施，即使是进行传统的双臂试验，也需要进行重大变革，以便在这些环境中升级新的试验方法。

1. Research funders and agencies should support sustained, long term efforts to build clinical trial networks that have the capacity to adopt innovative approaches, building on existing capacities. Too often, capacity building efforts are short term, piece meal, and focused on a single trial site, meaning that the human resources and infrastructure can disappear when the trial ends. Building trial networks takes time and sustained funding, but pays large dividends; the HIV Prevention Trials Network, for example, was established 24 years ago. Trial networks have played a critical role in training trialists in LMICs, and would be well placed to help build capacity—including statistical expertise—in platform trials and other innovative approaches.

1.研究资助者和机构应该持续地、长期支持在现有能力的基础上采取创新办法建立临床试验网络。能力建设工作往往是短期的、片面的，集中在一个单一的试验地点，这意味着试验结束时人力资源和基础设施可能会消失。建立试验网络需要时间和持续的资金，但会带来丰厚的回报。例如，艾滋病预防试验网络成立于24年前。试验网络在培训中低收入国家的试验人员方面发挥了关键作用，在平台试验和其他创新方法方面，它将很好地帮助建立包括统计专业知识在内的能力。

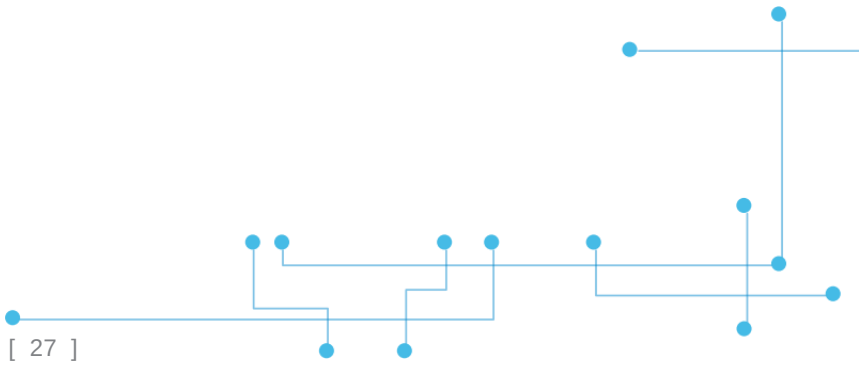
2. Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, IRBs, data safety boards, and regulators to become familiar with these designs. As innovative trial designs become more widespread in LMICs, operational lessons need to be shared so that implementation barriers can be tackled and best practices adopted.

2.在低资源环境中采用平台试验和其他主方案将需要资助机构、机构审查委员会、数据安全委员会和监管机构熟悉这些设计。随着创新试验设计在中低收入国家越来越普遍，需要分享操作经验，以便解决实施障碍并采用最佳做法。

Table 3. Potential efficiency gains from adopting innovative trial approaches
表3. 采用创新试验方法可能提高效率

Innovation	Cost savings
Synthetic control arm	US$10 million -20 million per trial
Rapid enrolment of trial participants through the connection of trial sites	23% (phase 2/3)
Sharing control groups and using control data from previous trials	40-60%

创新	成本节省
综合控制臂	每试验1-2千万美元
通过连接试验地点快速招募试验参与者	23% (2/3期)
共享对照组并使用以前试验的对照数据	40-60%



SECTION

4

ESTABLISHING MANUFACTURING CAPACITY IN LMICs

Section 4
ESTABLISHING MANUFACTURING CAPACITY IN LMICs在中低收入国家打造产能

KEY BENEFITS:主要优点

Innovative modular manufacturing approaches and optimized production processes for mRNA technologies can help to drive production costs down, speed up production, and globalize manufacturing. Container-based modular facilities have a small footprint, so capital costs are much lower compared to traditional manufacturing sites. Optimized production processes for mRNA technologies also have much lower operational costs because of high yields, reduced reagent use, and efficient design. Optimized mRNA production processes using modular, small footprint facilities can save over 60% (more than US$70 million) of the annual cost of goods for the production of 100 million vaccine doses compared to conventional mRNA manufacturing. These savings could lower mRNA vaccine production costs to US$0.5 per dose.

创新的模块化制造方法和优化生产

mRNA技术可以帮助降低生产成本、加快生产速度、实现制造全球化。基于集装箱的模块化设施占地面积小，所以资本成本比传统生产基地的低得多。优化的mRNA技术生产过程也具有更低的运营成本，因为产率高，试剂用量少，以及高效的设计。与传统mRNA生产相比，**使用模块化、占地面积小的优化**mRNA**生产流程生产1亿剂疫苗可节省60%以上(超过7000万美元)的年度货物成本。这些节省可以将mRNA疫苗的生产成本降低到每剂0.5美元。**

An optimized mRNA production offers several other advantages. These include the fexibility to quickly switch from making one vaccine to another, scalable production, and integration of product development with large-scale manufacturing.

Integration enables rapid development and production. The integration of development and production is especially useful during pandemics, supporting a rapid response as defned by CEPI's 100 days mission target.
优化的mRNA生产还提供了其他几个优势。其中包括从一种疫苗快速切换到另一种疫苗的灵活性、可扩展的生产以及产品开发与大规模生产的整合。
集成可以实现快速开发和生产。的积分
集成开发和生产在大流行期间能够快速响应CEPI的 100天任务的号召。

KEY CHALLENGES TO BE ADDRESSED:主要挑战

The full potential of mRNA for LMICs remains untested. While we fnd that modular mRNA sites ofer substantial benefts compared with traditional manufacturing, their full potential for LMICs still needs to be tested over the coming years.

. From this perspective, the strong focus on mRNA manufacturing to the exclusion of other types of manufacturing is a concern.

--mRNA对中低收入国家的全部潜力仍未得到检验。虽然我们发现模块化mRNA位点与传统制造相比有很大的好处，未来几年，它们对中低收入国家的全部潜力仍有待检验。

--中低收入国家目前需要的大多数疫苗都不是**mRNA**疫苗。从这个角度来看，对mRNA制造的强烈关注而排斥其他类型的制造值得关切。

--中低收入国家的可持续制造业需要市场。中低收入国家生产的医疗工具

需要买家，但仍有许多金融、政治和技术挑战亟待解决。建设生产能力还需要与加强监管制度齐头并进。

Sustainable manufacturing in LMICs needs a market. Health tools produced in LMICs need buyers, yet there are still many fnancial, political, and technical challenges to be addressed in this regard. Building production capacity also needs to go hand in hand with the strengthening of regulatory systems.

SUGGESTED ECOSYSTEM CHANGES:生态系统改革建议

1. **Further strengthen efforts to build regional and sub-regional manufacturing capacity.** Building regional manufacturing capacity in a sustainable manner is important to develop tools for MH, EIDs, and NDs. The lack of distributed manufacturing capacity was a substantial barrier in the response to the COVID-19 pandemic. Investments in manufacturing accompanied by regulatory strengthening would have a major public health impact. Through investments in manufacturing, LMICs in the long run would be able to make their own vaccines rather than relying

on external support. While the construction of mRNA-based production sites should continue, diversifed manufacturing is needed to enable production of non-mRNA vaccines in LMICs.

--进一步加强区域和次区域制造业建设能力。以可持续的方式建设区域制造能力

对开发MH、EID和ND工具尤为重要。缺少分布式的制造能力是应对COVID-19大流行的重大障碍。对制造业的投资伴随着加强监管将对公共卫生产生深远的影响。虽然基于mrna的生产基地的建设应继续进行，但需要多样化的生产，以便在中低收入国家生产非mrna疫苗。加强将对公共卫生产生重大影响。通过对制造业的投资，从长远来看，中低收入国家将能够生产自己的疫苗，而不是依赖外部支持。虽然基于mRNA的生产点位的建设应继续进行，但需要多样化的生产，以便在中低收入国家生产非mRNA疫苗。

Donors need to support the creation of manufacturing capacity over the long term. Building such capacity is part of planning for sustainable business models and routine immunization market demand. Gavi recently launched the African Vaccine Manufacturing Accelerator (AVMA), which will provide up to US$1 billion for creating sustainable vaccine production capacity on the continent. Other donors and funding mechanisms need to be willing to subsidize manufacturing from LMIC regions to allow for the creation of sustainable markets. They also need to be willing to provide guarantees that they will purchase from manufacturers in LMICs. They must set clear purchasing targets, following the example of Gavi and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

Donors need to support the creation of manufacturing capacity over the long term. Building such capacity is part of planning for sustainable business models and routine immunization market demand. Gavi recently launched the African Vaccine Manufacturing Accelerator (AVMA), which will provide up to US$1 billion for creating sustainable vaccine production capacity on the continent. Other donors and funding mechanisms need to be willing to subsidize manufacturing from LMIC regions to allow for the creation of sustainable markets. They also need to be willing to provide guarantees that they will purchase from manufacturers in LMICs. They must set clear purchasing targets, following the example of Gavi and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

-捐助者需要长期支持打造生产能力。打造产能是常规免疫市场需求可持续商业模式规划的一部分。全球疫苗免疫联盟Gavi最近启动了非洲疫苗制造加速器(AVMA)，将提供高达10亿美元用于在非洲大陆建立可持续的疫苗生产能力。其他捐助者和筹资机制需要愿意补贴中低收入国家的制造业才能创建可持续的市场。他们还需要愿意保证将从中低收入国家的生产商购买产品、明确采购目标，以全球疫苗免疫联盟和美国总统艾滋病紧急救援计划为榜样。

LMICs should commit to buying products manufactured by LMICs, such as through advanced purchase agreements, to help create sustainable markets. The many benefts of modular production should be leveraged. Modular facilities can be established much faster and at lower costs compared to conventional approaches. Modular mRNA facilities offer specifc benefts: they integrate drug discovery, clinical testing, and manufacturing and are able to develop, test, and produce drug candidates in a rapid, cost-effective manner. This is particularly useful during pandemic outbreaks.

中低收入国家应承诺购买中低收入国家生产的产品，例如通过提前采购协议帮助创建可持续市场。应该充分利用模块化生产的诸多好处。与传统方法相比，模块化设施的建立速度更快、成本更低。模块化mRNA设施特别之处在于：整合药物发现、临床测试和制造，能够以快速、经济有效的方式开发、测试和生产候选药物。这在大流行暴发期间特别有用。

4.1 Overview 概述

Multiple high-level national and regional efforts are underway to increase manufacturing capacity in LMICs. The African Union (AU) and Africa Centres for Disease Control and Prevention (Africa CDC), for example, have established the Partnership for African Vaccine Manufacturing (PAVM) to make the African continent self-sufficient in vaccine research, development, manufacturing, regulation, and delivery.[80] The goal of the PAVM is to enable the African vaccine manufacturing industry to develop, produce, and supply at least 60% of the total vaccine doses required in Africa by 2040. PAVM has already launched several projects. In addition, the WHO and its partners have established an mRNA vaccine technology transfer hub in South Africa that will work with an extensive network of LMIC-based technology recipients to build mRNA vaccine production, quality control, and regulation capacity across LMICs.[81,82] LMICs in Latin America, Europe, and Southeast Asia have also started collaborations with other countries to increase vaccine manufacturing capacity in their respective regions.[83,84] While the initial emphasis of these efforts was on stronger vaccine production capacity, the ambition has become broader and now includes advancing production of vaccines, diagnostics, and therapeutics.[85]

中低收入国家有正在进行的多个高级别国家和区域产能项目。例如，非洲联盟(非盟)和非洲疾病控制和预防中心建立了非洲疫苗制造伙伴关系(PAVM)，以使非洲大陆在疫苗研究、开发、制造、监管和交付能自给自足[80]。该计划的目标是使非洲疫苗制造业能够开发、生产和供应到2040年非洲所需的疫苗总剂量的至少60%的疫苗。PAVM已经启动几个项目。此外，世卫组织及其合作伙伴在南非还建立了一个mRNA疫苗技术转让中心，该中心将与基于中低收入国家的技术接受者的广泛网络合作，在中低收入国家建立mRNA疫苗生产、质量控制和监管能力[81,82]。拉丁美洲、欧洲和东南亚的82个中低收入国家也开始与其他国家合作[83,84]，以提高各自区域的疫苗生产能力。虽然这些努力最初的重点是加强疫苗生产能力，但目标已变得更广泛，现在包括促进疫苗、诊断和治疗的生产。[85]

In this section, we summarize the current evidence on the costs and timelines for manufacturing global health products (Section 4.2). We then analyze how efficiency gains—such as reduced production costs and accelerated production processes—could be achieved through optimized mRNA production and modular manufacturing processes (Section 4.3). Finally, we assess key challenges in strengthening LMIC production capacity (Section 4.4).

在本节中，我们总结了目前关于制造全球健康产品的成本和时间表的证据(第4.2节)。然后我们分析如何提高效率——比如降低生产成本和加速生产生产工艺-可以通过优化mRNA生产和模块化制造工艺来实现(第4.3节)。最后，我们评估关键加强中低收入国家生产能力的挑战(第4.4节)。

> The goal of the PAVM is to enable the African vaccine manufacturing industry to develop, produce, and supply at least 60% of the total vaccine doses required in Africa by 2040.
>
> PAVM计划的目标是使非洲疫苗制造业能够开发、生产和供应到2040年非洲所需疫苗总数的至少60%剂量。

4.2 Traditional manufacturing approaches: costs and timeframes
传统的生产方法:成本和时间框架

Studies show diferent price tags for building manufacturing capacity. In our own study, conducted by CPIGH at Duke University and Open Consultants, on late-stage clinical trials and manufacturing from the perspective of three middle-income countries (MICs), we estimated that US$250 million would be needed to strengthen production capacity in each of the three MICs (India, Kenya, and South Africa). We assumed that this amount would be sufficient to establish six manufacturing sites, three each for vaccines and therapeutics, which can collectively produce 90 million vaccine doses and 90 million drug doses per year.[4]

研究显示，生产能力建设的造价各不相同。在我们自己的研究中，杜克大学和Open Consultant的CPIGH进行的CPIGH从三个中等收入国家的角度对后期临床试验和生产进行了研究，我们估计需要2.5亿美元来加强三个中等收入国家(印度、肯尼亚和南非)的生产能力。我们假定这个金额足以建立6个生产基地：疫苗和治疗剂生产基地各3个，每年可生产9 000万剂疫苗和9 000万剂药物。[4]

In 2022, members of our research team also supported a study on vaccine security in the Association of Southeast Asian Nations (ASEAN).[86] The study was commissioned by the World Bank and included a substantial collection of primary data on the costs of health R&D and manufacturing. One-time construction costs and annual operating costs for vaccine manufacturing were based on data shared by World Bank partners and ASEAN countries. The study estimated that the capital costs of a fully integrated vaccine production site amount to US$225-US$275 million, while the costs offll and fnish sites are substantially lower (US$72 million). Table 4 summarizes the evidence on the costs for establishing manufacturing capacity in LMICs.

2022年，我们的研究团队成员还支持了一项关于东盟疫苗安全的研究[86]，这项研究是由世界银行委托进行的，其中包括大量的关于卫生研发和制造成本的原始数据。疫苗生产成本一次性建设费用和年度运营费用来自世界银行合作伙伴和东盟国家共享的数据。这项研究据估计，一个完全一体化的疫苗生产地的资本成本为2.25亿至2.75亿美元，而灌装生产地的成本则低得多(7200万美元)。表4总结了关于在中低收入国家建立制造能力的成本的证据。

Table 4. Cost estimates for conventional vaccine manufacturing

Source of cost estimate	Cost savings
UNIDO, 2017[87]	Fully integratedfacility: 30m doses/yr; US$105-220m Fill-fnish only: 30m doses/yr; US$46-98m
Boyd, 2020[88]	Annual operating costs range from US$58.7m in Copenhagen, Denmark, to US$14.0m in Bangalore, India
African Vaccine Manufacturing Initiative; WHO; UNIDO 2017[89]	Building a manufacturing facility (20 million doses/yr) can cost US$60m-US$130m, depending on technology and formulation. Capital expenditure accounts for over 60% of all costs (can be rationalized through economies of scale and scope)

Grootendorst etal, 2022[90]	"… commercial-scale facility costs are in the order of US$500 million to US$1 billion. Specifcally, Plotkin et al (2017) estimate that the cost of a whole virus vaccine plant is between US$50 to US$500 million per antigen depending on the complexity of design, automation, segregation, utilities, and contamination controls, and as much as US$700 million for multiple vaccines. Sanof's new egg-based whole virus plant at its Connaught campus is expected to cost C$925 million [Canadian dollars] to construct and certify (Sanof Canada 2021). Lonza's vaccine and biologics contract facility in Switzerland cost US$715 million (Kansteiner 2021). Novartis' cell-based infuenza vaccine plant (…) cost US$1 billion."
Plotkin et al, 2017[91]	Provides overview on major cost drivers and options to reduce costs
Open Consultants/ World Bank	30 million doses: • Construction cost for fully integrated manufacturing site (traditional): US$225m • Construction cost for fully integrated manufacturing site (mRNA): US$275m • Construction cost for fll and fnish manufacturing site: US$72m

表4. 传统疫苗生产的成本估算

成本估算来源	成本节省
UNIDO, 2017[87]	完全集成的设施:3000万剂/年; 灌装:每年3000万剂;46 - 98 m美元
Boyd, 2020[88]	每年的运营成本从丹麦哥本哈根的5870万美元到印度班加罗尔的1400万美元不等
African Vaccine Manufacturing Initiative; WHO; UNIDO 2017[89]	根据技术和配方的不同，建造一个生产设施(2000万剂/年)可能需要6000万至1.3亿美元。资本支出占所有成本的60%以上(可以通过规模经济和范围经济来合理化)
Grootendorst etal, 2022[90]	"……商业规模的设施费用约为5亿至10亿美元。具体而言，Plotkin等人(2017)估计，根据设计、自动化、分离、公用事业和污染控制的复杂性，整个病毒疫苗厂的成本在每个抗原5000万至5亿美元之间，而多种疫苗的成本高达7亿美元。Sanof在康诺特校区新建的以鸡蛋为基础的全病毒工厂预计将耗资9.25亿加元(加元)来建造和认证(Sanof Canada 2021)。龙沙在瑞士的疫苗和生物制品合同设施耗资7.15亿美元(Kansteiner 2021)。诺华的细胞流感疫苗工厂(……)耗资10亿美元。"
Plotkin et al, 2017[91]	概述了主要的成本驱动因素和降低成本的方法
Open Consultants/ 世界银行	3000万剂: ·完全集成生产基地(传统)的建设成本:2.25亿美元 ·完全集成生产基地(mRNA)的建设成本:2.75亿美元 ·整个生产基地的建设成本:7200万美元

Abbreviations: m = million; yrs = years

4.3 Efficiencies from optimized mRNA production processes and modular manufacturing approaches
优化的mRNA生产效率流程和模块化制造方法

Modular manufacturing is not a new approach, but it has received renewed attention due to the emergence of mRNA vaccine manufacturing, which lends itself to smaller footprint facilities. However, a modular site with a smaller footprint does not mean that the annual production volume is necessarily lower. For example, one pharmaceutical company built a modular facility for seasonal infuenza plus a contingency for pandemics. The capital costs for this particular facility were about US$20 million, with an annual dose output of 25-50 million doses. Another modular site for infuenza vaccines was built in an existing building at a cost of just US$5 million. This facility was able to produce 25 million doses per year. In comparison, a different company created a site in North Carolina for about US$1 billion for 50 doses – twice the capacity, but 50 times the costs. Another example is the creation of a modular manufacturing site in Senegal. The facility, which is supposed to be operational by the end of 2024, will be based on 10 modules made in Sweden. It will be able to produce 200 million doses of COVID-19 vaccines in the frst year, and up to 300 million doses from year two onwards if needed (the original plan was that it could even develop 1 billion doses a year). There are already major partnerships that aim to build modular mRNA production capacity. In August 2021, BioNTech agreed to set up vaccine production capabilities in Africa together with the kENUP Foundation, President Paul Kagame of Rwanda, President Macky Sall of Senegal, and President Ursula von der Leyen of the European Commission.

模块化制造并不是一种新方法，但由于mRNA疫苗生产的出现，因为模块化制造可以减少设施的占地面积重新受到了关注。然而，一占地面积小并不意味着年产量更低。例如，一制药公司为季节性流感建立了模块化设施，并为流行病建立了应急设施，这特别设施需要资本成本

约为2 000万美元，年剂量产量为2 500万至5 000万剂。另一个流感疫苗的模块化站点是在现有建筑物中建造的，成本仅为500万美元。该设施每年能够生产2500万剂疫苗。相比之下，另一家公司在北卡罗来纳州建立了一个基地，耗资约10亿美元，生产50剂疫苗——产能是前者的两倍，但成本却是后者的50倍。另一个例子是在塞内加尔建立一个模块化制造基地。该设施将基于瑞典的10个模块，预计将于2024年底投入运营，第一年产能为2亿剂COVID-19疫苗，需要的话从第二年开始最多可生产3亿剂，（最初的计划是每年甚至可以生产10亿剂）。目前已经有主要的合作伙伴关系旨在建立模块化mRNA的生产能力。2021年8月，BioNTech同意与kENUP基金会、卢旺达总统保罗·卡加梅(Paul Kagame)、塞内加尔总统麦基·萨尔(Macky Sall)和欧盟委员会主席乌尔苏拉·冯德莱恩(Ursula von der Leyen)共同在非洲建立疫苗生产能力。

The decision was guided by the African Union (AU), Africa CDC, and the African Medical Agency (under formation). In June 2022, BioNTech started to build its frst manufacturing facility in Kigali, Rwanda, to support the production of mRNA vaccines in Africa. In December 2023, the Kigali production site was inaugurated and it is expected to be operational with the manufacturing of mRNA-based vaccine batches required for process validation in 2025. The site can manufacture up to 50 million doses per year of a product and has an RNA process similar to that of the Pfzer-BioNTech COVID-19 vaccine. BioNTech itself has invested US$150 million in the construction of the production site.[92] The company plans to also establish sites in Senegal and South Africa.[93] BioNTech has developed a container-based plug & play approach with modular design, standardized equipment, and software components. The container-based production sites are called “BioNTainers” and are supposed to be fully self-sufficient and capable of manufacturing a range of mRNA-based vaccines, which could include the COVID-19 vaccine, BioNTech’s investigational vaccine candidates for malaria and TB, and possibly cancer vaccines if developed and approved by regulatory authorities.[94]

The Kigali plant will also feature power and water supply infrastructure, quality control labs, quality assurance set-up, warehousing, and cold and frozen storage. The facility’s initial production capacity is expected to be 50 million doses a year. Manufacturing in the BioNTainers can begin from 12 to 18 months post-installation. Local qualifcation runs will also be carried out before the start of production to ensure vaccine production is compliant with Good Manufacturing Practice (GMP) and to train local employees. More of these partnerships will be needed.

该决定是在非洲联盟、非洲疾病预防控制中心和正在组建中的非洲医疗机构的指导下作出的。2022年6月BioNTech开始在卢旺达基加利建立第一家制造工厂，以支持在非洲生产mRNA疫苗。2023年12月，基加利生产基地落成，预计在2025年生产工艺验证所需的mRNA疫苗批次。该工厂每年可生产多达5000万剂的产品，其RNA工艺类似辉瑞BioNTech COVID-19疫苗。BioNTech公司在生产基地的建设上投资了1.5亿美元[92]。该公司还计划在塞内加尔和南非建立工厂[93]。BioNTech已经开发了一种基于集装箱的即插即用方法，采用模块

化设计、标准化设备和软件组件。这种基于集装箱的生产基地被称为“BioNTainers”，预计完全自给自足且有能力制造一系列基于mRNA疫苗，其中可能包括BioNTech的研究疫苗COVID-19疫苗、疟疾和结核病的候选疫苗，如果得到管理当局的开发和批准，可能还包括癌症疫苗[94]。

基加利工厂还将配备电力和供水基础设施、质量控制实验室、质量保证设施、仓储以及冷库和冷冻库。该设施的初始生产能力预计为每年5000万剂。BioNTainer的生产可以在安装后的12到18个月开始。在开始生产之前，还将进行当地资格检查，以确保疫苗生产符合良好生产规范(GMP)，并培训当地员工。我们需要更多这样的伙伴关系。

There are also companies that offer modular platforms. Quantoom is a key example—its modular facility offers substantial savings in terms of costs of goods sold (Panel 2).

也有公司提供模块化平台。Quantoom就是一个关键的例子——它的模块化设施能大大节省主营业务成本 (板块2)。

PANEL 2 Quantoom's modular mRNA manufacturing approach Quantoom的模块化mRNA制造方法

Quantoom Biosciences is part of Univercells, a global life science company founded in 2013.[95] Quantoom aims to remove the barriers to making mRNA-based vaccines and therapeutics from sequence up to mass production.[96] mRNA-based manufacturing involves multiple barriers, such as complicated workfows (including the challenge to scale volumes from R&D to commercial production), highly specialized infrastructures, supply chain challenges, and complex operations that are prone to error and delay. The lack of tailored equipment and processes can result in delays and is also a major cost driver, which in turn affects the product price and is a key barrier to global access. To enable efficient end-to-end production of mRNA-based products, Quantoom introduced its Nfnity™ production platform, which consists of three technologies: Nplify™ for DNA production, Ntensify™ for RNA production, and Ncapsulate™ for lipid nanoparticle formulation.[97]

Here we discuss Ntensify™, an automatized mRNA production system that supports the entire drug development process from discovery to commercial production. With a small footprint, Ntensify™ is based on a construct-agnostic mRNA process that aims to drive high yields, minimize reagent use, and eliminate the need for resource-intensive scale-up.[98] These three elements should result in a much more efficient production. At the same time, Ntensify™ only requires a space as compact as a shipping container, and this small footprint contributes to cost savings and capital expenditure reduction while enhancing reproducibility. There are three Ntensify™ models. The mini is for drug discovery and preclinical research. It enables researchers to test multiple similar mRNA constructs in parallel. The midi is for clinical research and commercial production; it can make up to 15 million doses per year. The maxi, which will come to market in 2024, is for larger volumes, making up to 100 million doses per year, ideal for pandemic readiness.

Univercells是一家成立于2013年的全球生命科学公司[95] ，Quantoom Biosciences是Univercells的一部分。Quantoom的目标是消除mRNA疫苗和从序列到治疗方法大规模生产的壁垒[96]。mRNA生产有很多挑战，例如复杂的工作流程(包括从研发到规模商业生产的挑战)、高度专业化的基础设施、供应链挑战以及容易出错和延迟的复杂操作等。缺乏量身定制的设备和流程可能导致延迟，也是主要的成本驱动因素，进而影响产品价格和全球准入。为了高效地端到端生产mRNA的产品，Quantoom推出了其Nfnity™生产平台，该平台由三种技术组成:Nplify™用于DNA生产，enhance™用于RNA生产，Ncapsulate™用于脂质纳米颗粒配方[97]。

在这里，我们讨论的是一种自动化的mRNA生产系统，它支持从发现到商业生产的整个药物开发过程。占地面积小，Ntensify™基于一个结构无关的mRNA工艺，旨在提高产量，最大限度地减少试剂的使用，无需资源密集型扩容[98]，[这]三个要素使生产更高效。同时，intentify™只需要一个像集装箱大小空间，有助于节省成本和减少资本支出，同时提高可重复性。Ntensify™有三种型号。mini型用于药物发现和临床前研究，研究人员能够并行测试多个相似的mRNA结构。Midi型用于临床研究和商业化生产，每年可生产多达1500万剂。Maxi型将于2024年上市，产量更大，每年可达1亿剂，这是为大流行做好准备的理想选择。

Quantoom itself has estimated the savings resulting from Ntensify™. So, while these are self-reported estimates, Quantoom gave us a solid introduction to the underlying cost model. We also consulted external production experts to validate that Quantoom's approach can lead to efficiencies; these independent experts told us that Quantoom's self-reported cost estimates are realistic.

Quantoom自己估计了使用Ntensify™带来的节省。虽然这些都是内部估算，Quantoom向我们详细介绍了基础成本模型的。我们也咨询了外部生产专家以验证Quantoom的方法可以提高效率。这些独立专家告诉我们，Quantoom自己报告的成本估算是现实的。

Time savings: Ntensify™ can reduce the timeline for mRNA-based vaccine production to just three months, aligning with CEPI's 100 days mission for expedited vaccine development. Ntensify™ also makes it possible to quickly ramp up volumes, a crucial feature during pandemics. [99]

Reduced cost of goods (CoGs): Conventional drug development entails annual CoGs of about US$2.3 million, while adopting Ntensify™ reduces this cost to only US$0.7 million (US$1.6 million savings). Immediate access to Ntensify™'s optimized process adds an extra US$2.3 million savings during drug discovery. [98] For commercial vaccine production, Quantoom estimates that Ntensify™ can reduce annual CoGs from US$307 million (conventional production) to US$129 million (savings of US$178 million) .[100] Quantoom estimates that Ntensify™, for the annual production of 100 million doses of mRNA vaccines (50 µg/dose), saves 61% (or US$74 million) of the annual CoGs compared to conventional manufacturing (Ntensify: US$47 million; conventional: US$122 million). [101] At a scale of 100 million doses, 10% of the total annual CoGs of Ntensify is attributed to capital expenditures (equipment and facility), and 90% to operational expenditures (consumables and labor), of which 83% is allocated to reagents mixes.

Lower price per dose: Lowering production costs will have a positive impact on product prices. A company representative reported that the company has met a Bill & Melinda Gates Foundation-specifed target of US$0.5 per vaccine dose (of this US$0.5, 50% is for DNA and mRNA production, and 50% for the formulation). [102]

节省时间：Ntensify™可将mRNA疫苗生产时间缩短至仅3个月，符合CEPI加快疫苗开发的“100天使命”。Ntensify™还使快速增加产量成为可能，这是大流行期间的一项关键功能[99]。

降低运营成本：传统药物开发每年的成本约为230万美元，而采用Ntensify™[9]将这一成本降至70万美元(节省160万美元)立即使用Ntensify™的优化流程可在药物发现过程中额外节省230万美元. [98]。对于商业化疫苗生产，Quantoom估计，Ntensify™可将年度CoGs从3.07亿美元(传统生产)减少到1.29亿美元(节省1.78亿美元) .[100]。 Quantoom估计，与传统生产相比，每年生产1亿剂mRNA疫苗(50微克/剂)的Ntensify™可节省61%(或7400万美元)的年度CoGs (Ntensify™ 4700万美元;常规:1.22亿美元)。101在1亿剂规模下，总年度成本的10%是资本支出(设备和设施)，90%是运营支出(消耗品和劳动力)，其中83%是试剂混合物成本。

降低每剂价格：降低生产成本将对产品价格产生积极影响。一名公司代表报告说，该公司已达到比尔和梅林达·盖茨基金会指定的每剂疫苗0.5美元的目标(其中0.5美元50%用于生产DNA和mRNA, 50%用于配方) [102]。

Quantoom's technologies have been adopted by Bio-Manguinhos (Brazil), Institut Pasteur (Dakar), and Afrigen (South Africa), among others, demonstrating the relevance for LMICs.

Quantoom的技术已被巴西Bio-Manguinhos、达喀尔巴斯德研究所和南非Afrigen等机构采用，证明了其与中低收入国家的相关性。

4.4 Challenges for the strengthening of LMIC production capacity
加强中低收入国家生产能力的挑战

There are multiple challenges for strengthening LMIC production capacity.

加强中低收入国家产能面临多重挑战。

1. First, modular platforms and optimized product processes need to be tested further over the coming years. However, modular approaches are not new, so the risk of failure appears to be low.

2. Second, KIs highlighted that supply chain issues are a huge challenge.[103] The production of RNA requires the supply of more than 100 reagents or inputs, and 10-15 of these are very expensive and heavily controlled. Due to supply chain issues, producers face problems in accessing the needed reagents and ingredients. In addition, the patent holders for the various production inputs are mostly in HICs, which contributes to existing equity gaps. Addressing this issue requires stronger sharing of IP, licensing agreements, and technology transfer.

3. 1. 首先，模块化平台和优化的产品流程需要在未来几年进一步测试。然而，模块化方法并不新鲜，因此失败的风险似乎很低
2. 其次，关键信息提供者强调供应链问题是一个巨大的挑战[103]RNA的生产需要提供100多种试剂或输入物，其中10-15种非常昂贵且受到严格控制。由于供应链问题，生产商在获取所需试剂和成分方面面临问题。此外，各种生产投入的专利持有人大多在高收入国家，这势必加大现有的公平差距。解决这一问题需要更强有力的知识产权共享、许可协议和技术转让。

RNA的生产需要提供100多种试剂或输入物，其中10-15种非常昂贵且受到严格控制。大约一半的体外诊断市场被四家公司占据。

The production of RNA requires the supply of more than 100 reagents or inputs, and 10-15 of these are very expensive and heavily controlled.

Around half of the market for in-vitro diagnostics is accounted for by just four companies.

Third, the lack of regional manufacturing capacity was apparent during the COVID-19 pandemic. While there is a lot of discussion and some action on globalizing mRNA production, obstacles remain. For example, the mRNA hubs supported by WHO face the problem of no demand. A recent study by Africa CDC, CHAI and PATH emphasized that uncertain demand is a major challenge and that the creation of vaccine production capacity in other countries (China, India) has been supported by government-backed demand commitments. [104] According to a recent media report, Moderna decided to pause building an mRNA vaccine factory in Kenya due to a lack of demand. [105]

第三，COVID-19大流行期间，区域生产能力明显不足。虽然有很多mRNA生产全球化讨论和一些行动，但各种矛盾依然存在。例如，世卫组织支持的mRNA枢纽面临有供无求的问题。非洲疾病预防控制中心、CHAI 和 PATH最近的一项研究强调，需求不确定是一项重大挑战，在其他国家(中国印度)建立疫苗生产能力得到了政府支持，疫苗的需求有保证[104]。根据最近的媒体报道，由于缺乏需求，Moderna决定暂停在肯尼亚建设mRNA疫苗工厂。

Initially, the price of vaccines from countries with large existing production capacity, especially India, will be lower compared to newly established facilities. In cases where the global prices of vaccines are lower, global funders need to be willing to pay higher prices, or middle- and high-income countries in the subregions could collectively offer cross-subsidies to the poorest countries. Over the long run, such subsidies will help to establish a strong regional ecosystem for the production of health tools, with substantial medium-term health, economic, and societal benefits. In 2023, Gavi made important adjustments to its procurement policy to allow for procurement from vaccine producers in LMIC regions.
Gavi also launched the African Vaccine Manufacturing Accelerator (AVMA), which can provide up to US$1 billion for creating sustainable vaccine production capacity on the continent. PEPFAR committed to procure 15 million HIV tests produced by African manufacturers in 2025 at an estimated cost of US$20 million. For antiretroviral drugs, PEPFAR aims to work alongside other partners to shift at least two million clients on first-line antiretroviral treatments to use African-made products by 2030. [106,107] Other global health financing mechanisms, such as the Global Fund, should also set concrete procurement targets and consider subsidizing manufacturing from LMIC regions to support the creation of sustainable markets.

最初，来自现有产能大的国家，特别是印度的疫苗价格将低于新建立的设施。在全球疫苗价格较低的情况下，全球资助者需要愿意支付较高的价格，或者次区域的中高收入国家可以集体向最贫穷国家提供交叉补贴。从长期来看，这种补贴将有助于为医疗工具的生产建立一个强大的区域生态系统，具有可观的中期健康、经济和社会效益。2023年，全球疫苗和免疫联盟对其采购政策进行了重要调整，以便从中低收入国家区域的疫苗生产商采购。全球疫苗免疫联盟Gavi还启动了非洲疫苗制造加速器(AVMA)，该加速器可提供高达10亿美元的资金，用于在非洲大陆建立可持续的疫苗生产能力。总统防治艾滋病紧急救援计划承诺在2025年采购非洲制造商生产的1500万件总值2000万美元艾滋病毒检测试剂。在抗逆转录病毒药物方面，总统防治艾滋病紧急救援计划的目标是与其他伙伴合作，到2030年使至少200万接受一线抗逆转录病毒治疗的患者改用非洲生产的药物[106,107]。其他全球卫生筹资机制，如全球基金，也应制定具体的采购目标，并考虑补贴中低收入国家区域的医疗制造业以支持建立可持续市场。

4. Fourth, there are specific challenges around the manufacturing of diagnostics. Diagnostics experts highlighted the lack of production capacity for diagnostics in LMICs—FIND has recently been shining a light on this barrier.[108] KIs argued that the market for diagnostics is dominated by just a few major players. The Lancet Commission on Diagnostics showed that HICs also dominate the global supply of diagnostics: around half of the market for in-vitro diagnostics is accounted for by just four companies from the US and Europe, and three-quarters of the market for medical imaging is accounted for by just four companies from the US, Europe, and Japan.[109] These market failures contribute to high prices of, and inequitable access to, diagnostics.[110] LMICs cannot afford them: PATH estimates that 47% of the global population has little to no access to diagnostics. As such, the market needs to be diversified by creating more production capacity in LMICs. Key enablers include tech transfer, public-private partnerships, and technical support.

第四，诊断产品的生产面临着特殊的挑战。诊断专家强调，中低收入国家缺乏诊断生产能力，FIND最近揭示了这一问题[108]关键信息提供者认为，诊断市场仅由少数几家主要公司主导。《柳叶刀》诊断委员会显示，高收入国家还主导着全球诊断产品的供应：体外诊断产品市场的一半左右由来自美国和欧洲的四家公司；医学成像产品市场的四分之三由来自美国、欧洲和日本的四家公司占据[109]。这些市场的失败导致了诊断产品的高价格和不公平获取低[110]中低收入国家负担不起。PATH估计，全球47%的人口很少或根本无法获得诊断。因此，市场需要实现多元化、中低收入国家应开创更多产能。关键促成因素包括技术转让、公私伙伴关系和技术支持。

In addition to financial investments in R&D and manufacturing, targeted policy actions are required, for example through stronger regional regulatory harmonization and focused human resource development. As highlighted in a recent blog by the Center for Global Development, any effort to increase vaccine manufacturing capacity in LMICs needs to also consider the fact that many regulatory systems lack the required capacity (see Section 6 for details).[111] In addition, building sustainable production capacity also requires more technology transfer and technical support.
除了对研发和制造业进行财政投资外，还需要采取有针对性的政策行动，例如，通过加强区域监管协调和重点人力资源开发。正如全球发展中心最近在一篇博客中所强调的那样，任何提高中低收入国家疫苗生产能力的努力都要关注这个事实，许多监管系统缺乏所需的能力(详见第6节)[111]此外，建设可持续的生产能力还需要更多的技术转让和技术支持。

4.5 Summary and suggested ecosystem changes 小节和生态系统改革建议

Optimized mRNA production processes and modular manufacturing approaches offer multiple benefits over traditional manufacturing. We have summarized the cost and time savings in Table 5 and 6.

优化的mRNA生产流程和模块化制造方法比传统制造具有多种优势。我们在表5和表6中总结了节省的成本和时间。

Table 5. CoGs: conventional mRNA production and efficiencies through optimized mRNA production

表5. 主营业务成本：传统mRNA生产和优化mRNA生产和效率

	Conventional mRNA manufacturing	Optimized mRNA production process
CoGs (drug development)	US$2.3 million	US$0.7 million
Annual CoGs (production of 100 million doses)	US$122 million	US$47 million
Vaccine development timeline	20 months during COVID-19	3 months (ambition)

	传统mRNA 生产	优化 mRNA 生产process
业务成本(药物开发)	US$2.3 million	US$0.7 million
总业务成本 (生产1亿剂)	US$122 million	US$47 million
疫苗开发时间	COVID-19期间 20个月	3个月（目标）

ng and modular facilities (example: seasonal influenza vaccine)
性流感疫苗)

	Conventional manufacturing	Modular mRNA facilities
Construction of production site	Up to US$1 billon	US$5-50 million
Construction timelines	Several years	~1 year

	常规生产	模块化 mRNA 设施
生产点位建设	Up to US$1 billon	US$5-50 million
建设时间	几年	~1 年

We recommend the following ecosystem changes:生态系统改革建议

1. Further strengthen efforts to build regional and sub-regional manufacturing capacity. Building regional manufacturing capacity in a sustainable manner is important to develop tools for MH, EIDs, and NDs. The lack of distributed manufacturing capacity was a substantial barrier in the response to the COVID-19 pandemic. Investments in manufacturing accompanied by regulatory strengthening would have a substantial public health impact. Through investments in manufacturing, LMICs in the long run would be able to make their own vaccines rather than relying on external support.

进一步加强区域和次区域制造能力建设。
以可持续方式打造区域产能对于开发MH、EID和ND工具非常重要。缺乏分布式制造
能力是应对COVID-19大流行的重大障碍。伴随着制造业的投资
加强监管将对公共卫生产生重大影响。从长远来看，通过对制造业的投资，中低收入国家
将能够制造自己的疫苗，而不是依赖外部支持。

2. Donors need to support the creation of manufacturing capacity over the long term. Building such capacity needs to be part of planning for sustainable business models and routine immunization market demand. In 2023, Gavi made important adjustments to its procurement policy to allow for procurement from vaccines produced in LMIC regions. All donors need to be willing to subsidize manufacturing from LMIC regions to allow for the creation of sustainable markets, and donors should guarantee that they will buy products from manufacturers in LMICs. Setting clear purchasing targets and commitments, as Gaviand PEPFAR did, will be important to promote action and to track progress.

捐助者需要长期支持制造能力的建立。打造中低收入国家产能必须有可持续商业模式规划和常规免疫市场需求。2023年，全球疫苗免疫联盟调整其采购政策，以便采购中低收入国家区域生产的疫苗。所有捐赠者都需要愿意为中低收入国家的制造业提供补贴，以创造可持续的市场，捐助国也应该保证会从中低收入国家的制造商购买产品。像全球疫苗免疫联盟和总统防治艾滋病紧急救援计划那样制定明确的采购目标和承诺对于促进行动和跟踪进展至关重要。

3. Leverage the multiple benefits of optimized mRNA production and modular facilities. Modular facilities can be established much faster and at lower costs compared to conventional manufacturing approaches. In addition, optimized mRNA production processes promise huge benefits because they integrate drug discovery, clinical testing, and manufacturing and can develop, test, and produce drug candidates in a speedy and cost-effective manner (Panel 2).

充分利用优化的mRNA生产和模块化设施的多重优势。

与传统制造方法相比，建立模块化设施速度更快，成本更低。此外，优化的mRNA生产过程巨大的好处是整合了药物发现、临床测试和生产，可以快速、经济地开发、测试和生产候选药物(板块2)。

SECTION 5

SECTION

5

SECTION

5

NEW AND UNDERUSED HEALTH INNOVATIONS: mRNA-BASED TECHNOLOGIES AND MONOCLONAL ANTIBODIES

未被充分利用的健康创新：基于 mRNA 的技术和单克隆抗体

NEW AND UNDERUSED HEALTH INNOVATIONS: mRNA-BASED TECHNOLOGIES AND MONOCLONAL ANTIBODIES

未被充分利用的健康创新：基于mRNA 的技术和单克隆抗体

KEY BENEFITS: 主要优点：

mRNA platforms are suited for speed and are highly versatile, which are major advantages, especially during pandemics. Compared with conventional manufacturing of vaccines and therapeutics, the mRNA production process is simpler with fewer steps so production yields are less variable, production is much faster, and facilities can be smaller There are now multiple attempts to build regional self-sufficiency in mRNA manufacturing capacity.

mRNA平台具有研发速度快、通用性高两大主要优点，在大流行期间其优势更加显著。相较于传统的疫苗生产方式和治疗方法，mRNA的生产过程更加简单：生产步骤更少，因此产量变化较小，生产速度更快，生产设备体积更小。现在人们已多次尝试实现mRNA生产能力的区域性自给自足。

Monoclonal antibodies (mAbs) have come of age in clinical medicine, and more than 100 monoclonal antibody products have been licensed over the past 30 years to treat, prevent, and cure NCDs. However, only seven mAbs were licensed for infectious diseases. Availability and affordability are two of the biggest barriers impeding global access.

单克隆抗体(mAbs)在临床医学上应用已经成熟。过去的30年中，超过100种单克隆抗体产品已获批用于治疗、预防和治愈非传染性疾病。然而，仅有7种单克隆抗体获批用于传染性疾病。可及性和可负担性是目前影响其全球使用的两个最大障碍。

KEY CHALLENGES TO BE ADDRESSED: 尚未解决的关键挑战：

The chances of developing mRNA vaccines against some pathogens are low, e.g., against bacteria and parasites with complicated structures that can evade the immune system. Nevertheless, mRNA candidates for critical NDs, such as TB and malaria, are in the clinical phase of development (or at least in the preclinical stage, e.g., HIV).

对部分病原体（如结构复杂、可逃避免疫系统攻击的细菌和寄生虫）而言，研发其专用的mRNA疫苗可能性很低。然而，用于关键被忽视疾病(如结核病和疟疾)的mRNA候选疫苗正处于临床开发阶段(或至少处于临床前阶段，如艾滋病毒)。

While mAbs have substantial potential, there is too little R&D on mAbs that target NDs, EIDs, and MH. The production of mAbs is complex and costly.

尽管单克隆抗体具有巨大的潜力，针对被忽视疾病、新发传染病和孕产妇保健的单克隆抗体的研发仍然不足。单克隆抗体的生产复杂且成本高昂。

SUGGESTED ECOSYSTEM CHANGES: 生态系统变革建议

针对mRNA：

mRNA platforms have signifcant comparative advantages over more traditional technologies.
加大对研发用于被忽视疾病、新发传染病和孕产妇保健的mRNA技术的投资。
mRNA平台相较于传统技术而言具有显著的比较优势。

It is critical for LMICs to be able to produce their own mRNA technologies. The global health community needs to further strengthen its ongoing support to strengthen mRNA production capacity in LMICs.
对于中低收入国家来说，开发自己的mRNA技术是至关重要的。全球卫生界需要加大对提高中低收入国家mRNA生产能力的一贯支持。

A lipid needs to be available without the IP constraints.

取消脂质使用的知识产权保护。

针对mAbs：

加大对研发用于被忽视疾病、新发传染病和孕产妇保健的单克隆抗体的投资。

寻求新生产方法，降低成本。实现这一目标的方法之一是在探讨mRNA生产能力时，考虑到中低收入国家的单克隆抗体生产能力。

虽然研发单克隆抗体的融资环境目前严重受限，但我们仍有机会进行大规模推广试点。人们错失了新冠肺炎这一良机。尽管印度已经批准了两种基于单克隆抗体的产品用于狂犬病暴露后预防(一种是单一的人类单克隆抗体，另一种是含两种小鼠单克隆抗体的鸡尾酒混合物)，目前尚未有在中低收入国家大规模推广单克隆抗体的案例。通过抗逆转录病毒疗法，我们有可能以相对较快的方式开发昂贵的药物，并使其成本迅速降低。RSV单克隆抗体可能会改变游戏规则：它是一种正处于研发阶段的低成本单克隆抗体，可能会成为使全球社区团结一致的产品。
同时，我们需要进一步评估低中收入国家使用单克隆抗体的情况。公平起见，我们需要大力推动在中低收入国家研发、生产和使用单克隆抗体，并找出在不同环境下药效和药品性价比的证据。

For mAbs:

- **There needs to be more investments in R&D on mAbs that target NDs, EIDs, and MH.**
- **New approaches are needed to bring down production costs**. One way to do this is to link discussions of manufacturing capacity for mRNA to mAb production in LMICs.
- **While the financial environment for mAbs is currently severely constrained, there is the opportunity to pilot their wide-scale introduction**. COVID-19 was a missed opportunity to do so. There is as yet no example of scaled up mAbs in LMICs, although India has licensed two mAbs-based products for post-exposure prophylaxis against rabies (one is a single human mAb, the other is a cocktail of two mice mAbs). We saw with antiretroviral therapies that it is possible to introduce expensive drugs in a relatively fast manner and see costs fall quickly. RSV mAbs could be a game changer—a low-cost mAb is believed to be under development—and could serve as a product for the global community to rally around.
- **In parallel, the case for using mAbs in LMICs needs to be further assessed**. From an equity perspective, there needs to be a strong push for developing, producing, and using mAbs in LMICs and for generating evidence on effectiveness and cost effectiveness in different settings.

5.1 mRNA platform mRNA平台

OVERVIEW 概述

Platform technologies can be defined as "an underlying technology or process that can be adapted for use in product development for more than one product or disease area."[112] Such platforms can be used to develop vaccines, biologics, drugs, and diagnostics, as well as the adjuvants and immunomodulators that are used to improve vaccine efficacy. COVID-19 validated two platform technologies for vaccines that had been based on decades of prior research. The first was the mRNA platform, used by Moderna and Pfizer-BioNTech to develop their COVID-19 vaccines, and the second was the viral vector platform, used by Oxford University/AstraZeneca and Johnson & Johnson in developing their COVID-19 vaccines. R&D funding for these technologies increased significantly from 2015, especially due to the COVID-19 pandemic. There has been a steady rise in annual funding for platform technologies for NDs, EIDs, and MH, reaching a record high of US$358 million in 2022.[113] There was a sharp jump from 2015 to 2016 (up US$71 million, 37%), after the WHO's addition of "Disease X" (an unknown pathogen) to the Blueprint list (Figure 2). During the COVID-19 pandemic, platform technologies benefited not just from large amounts of funding but also streamlined regulatory approval.[114]

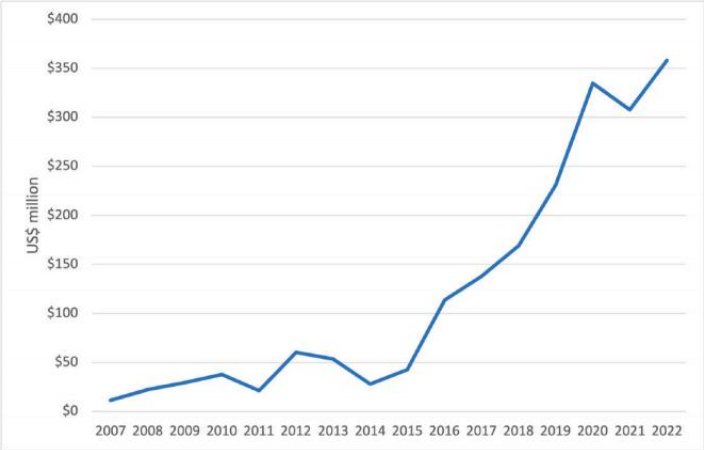
Of the range of available platform technologies, KIs argued that mRNA is garnering the most attention given its potential applications for a range of diseases – including NDs, EIDs, and certain cancers.

平台技术指"一种可用于针对多个产品或疾病的产品开发基础技术或过程。[112]此类平台可用于开发疫苗、生物制剂、药物和诊断，也可用于开发提高疫苗效力的佐剂和免疫调节剂。新冠肺炎验证了两种基于数十年来已有研究的疫苗研发平台技术。第一种是mRNA平台，莫德纳和辉瑞公司均使用该平台研发COVID-19疫苗；第二种是病毒载体平台，牛津大学/阿斯利康和强生公司使用该平台研发COVID-19疫苗。由于新冠肺炎的暴发，这两种平台技术的研发资金自2015年以来显著增加。每年用于被忽视疾病、新发传染病和孕产妇保健的平台技术的资金也稳步增长，于2022年达到创纪录的3.58亿美元。[113]在世卫组织将"X疾病"(一种未知病原体)列入流行病研发蓝图后(图2)，平台技术的研发资金在2015年至2016年间出现了大幅增长(增加7100万美元，占37%)。受益于新冠肺炎疫情，平台技术不仅获得了大量的研发资金，其监管审批流程也得到了简化。[114]

在一系列可用的平台技术中，主要信息提供者认为mRNA平台所获关注度最高，因其可能应用于一系列疾病之中，如被忽视疾病、新发传染病和某些癌症。

Figure 2. R&D funding for platform technologies for neglected diseases over time

图2.用于被忽视疾病的平台技术历年所获研发资金



POTENTIAL OF mRNA PLATFORMS mRNA平台的潜力

The development of safe, effective COVID-19 vaccines in under a year was a powerful validation of the mRNA platform. It has "sparked optimism that a vaccine revolution is under way,"[114] potentially leading to vaccines for NDs, EIDs, and cancers. There are five major advantages of the mRNA platform.

用时不到一年即研发出安全有效的COVID-19疫苗有力验证了mRNA平台技术。它"使人们感到乐观，认为当下正是一场疫苗革命"，[114]针对被忽视疾病、新发传染病和癌症的疫苗有可能被研制出来。mRNA平台有五个主要优点。

Speed
开发速度快

First, mRNA is suited for speed.[114] The rapid production of vaccine candidates using mRNA technology can accelerate candidate identification and optimization, especially if preclinical models are available, as well as initiation of early phase clinical studies.[115] It took Moderna just 42 days to produce the first batches of its COVID-19 vaccine (mRNA-1273). This was revolutionary because most previous vaccines were developed using established platforms, e.g., whole inactivated virus (polio vaccine) or live attenuated virus (yellow fever vaccine). In the past, with traditional methods (cell-based, egg-based, or recombinant vaccine manufacturing), at best it would take 18 months to two years. And if large volumes of vaccines need to be made in a very short time period for a new pathogen, mRNA is at this stage the only available option.
首先，mRNA的生产速度快。[114]使用mRNA技术快速生产候选疫苗可以加速候选株的鉴定和优化，如果有临床前期模型和早期临床研究可用则更是如此。[115]莫德纳仅用42天就生产出了第一批产品COVID-19疫苗(mRNA-1273)。这是革命性的研发，因为此前的大多数疫苗都是利用既定平台研发，例如全灭活病毒(脊髓灰质炎疫苗)或减毒活病毒(黄热病疫苗)。过去，使用传统方法(细胞培植、鸡蛋培植或基因重组制备)开发疫苗最长需要18个月到两年的时间。如果需要在很短的时间内为一种新的病原体生产大量疫苗，mRNA是目前唯一可用的选择。

Versatility
高度通用性

A second attractive feature of platform technologies is their versatility: developers can use existing mRNA platforms for multiple pathogens rather than creating new ones. This is much faster and cheaper than previous processes, i.e., the development of new platforms from scratch. There is no need to develop toxicity studies, which are expensive and take a minimum of seven months, because the platform is already validated. As mentioned by one KI, "you only change the immunogen, the FDA either says no toxicity study is needed or you do a modified one that is much quicker…..the dream is that we have a 'plug and play' platform, i.e., agnostic to the pathogen – you just plugin the new pathogen and it produces vaccine."
平台技术的第二个引人瞩目的特点是其高度通用型:研发人员可以使用现有的mRNA平台来处理多种病原体，而无需创建新的平台。这比以前的流程(即从头开始开发新平台)要快得多，成本也更低。由于该平台已经经过验证，因此无需进行毒性研究，而毒性研究既昂贵又需要至少7个月的时间。正如一位主要信息提供者说道，"你只需改变免疫原，食品药品监督管理局（FDA）要么说不需要毒性研究，要么做一个修改后生产速度更快的平台.....我们梦想有一个'即插即用'的平台，也就是说，在病原体尚不可知的情况下，你只要导入新的病原体，它就会生产疫苗。"

Faster Production
生产速度更快

Third, as we discussed in the manufacturing section, mRNA technology is promising because "the production process is simpler with fewer steps so production yields are less variable, production is much faster, and facilities can be smaller,"[115] compared with the traditional cell-based, egg-based, or recombinant vaccine manufacturing. Costs to establish a manufacturing plant are lower. "Product-independent manufacturing also makes multi-production facilities feasible to operate because a single facility can be leveraged for rapid sequential small-scale production of vaccines against several pathogens."[116] This is a key advantage for EIDs and NDs.
第三，正如我们在生产一章中所探讨过的，mRNA技术前景良好。因为与传统的细胞培植、鸡蛋培植或基因重组疫苗制备相比，mRNA"mRNA的生产过程更加简单：生产步骤更少，因此产量变化较小，生产速度更快，生产设备体积更小。"。[115]建立疫苗制造工厂的成本也会更低。"产品独立生产也使多用途生产设施可用，因为单个设备就可用于快速、连续、小规模生产针对特定几种病原体的疫苗。[116]这是对研发治疗新发传染病和被忽视疾病疫苗而言的一个关键优势。

主动性
Proactivity

Fourth, platform technologies can be proactive rather than reactive to a pathogen—they have been successfully applied to a previously unknown pathogen.
第四，平台技术可以主动而非被动地检测病原体，该技术已经成功地应用于一种此前未知的病原体。

Overcoming delivery challenges

Fifth, there is also hope that mRNA vaccines could help overcome delivery challenges for NDs, EIDS, and MH by being thermostable, single dose, or delivered nasally, though this will require intensified R&D.

克服递送挑战

第五，mRNA疫苗也有希望通过具备耐热性、单剂量或经鼻给药等方法来克服被忽视疾病、新发传染病和孕产妇保健的递送挑战，而这需要我们加强研发。

The reasons why mRNA-based vaccine development for NDs has not been successful to date include:

迄今为止，用于被忽视疾病的mRNA疫苗开发未能取得成功的原因如下:

1. Low scientific feasibility given that many PRND pathogens "are bacterial or parasitic with complicated structures, or lifecycles, rendering it difficult to identify the protective antigen(s) to be included in the vaccine."[117]

   由于许多PRND病原体"是具有复杂结构或生命周期的细菌或寄生虫，因此难以确定疫苗中需含有的保护性抗原"[117]，因此科学可行性较低。

2. An uncertain regulatory pathway.

   监管路径不明确。

3. Lack of clarity about which groups and which geographies would benefit most from a vaccine. Some of these challenges are true for EIDs, except that the priority EIDs are all viruses.

   尚不清楚从疫苗中受益最多的群体和地区。这些挑战中的一部分对新发传染病来说都是真实存在的，但优先新发传染病的病原体都是病毒。

4. For NDs and EIDs, there are scientific challenges with mRNA vaccines, e.g. the need for ultra-cold chain, lack of data in young children, waning immunity, shortages of raw materials, IP barriers, and the need to identify the antigen.

   对于被忽视疾病和新发传染病，使用mRNA疫苗存在科学方面的挑战，例如使用超冷链运输、缺乏幼儿接种疫苗的相关数据、接种后导致免疫力下降、原材料短缺、知识产权壁垒以及抗原识别需要。

5. The biggest barrier for mRNA vaccine production is the lipids—they are the most complex part and are the part most constrained by IP.

   mRNA疫苗生产的最大障碍是脂质，因为脂质是最复杂的部分，也是最受知识产权限制的部分。

Advances are now being made in mRNA platform approaches that could address some of the challenges. For example, the Duke Human Vaccine Institute (DHVI) has developed a "straightforward, scalable, reproducible production and purification platform that provides mRNA with the quality, purity, and safety profile required for clinical trial use."[118] DHVI is now developing mRNA vaccines against HIV and also against infuenza (the infuenza vaccine under development, funded by the NIH Collaborative Infuenza Vaccine Innovation Centers [CIVICS] program, involves a cocktail of 10 strains).

目前，mRNA平台方法不断取得新进展，可以用于解决一部分挑战。例如，杜克大学人类疫苗研究所(DHVI)开发了一种"简单、可扩展、可重复的生产和纯化平台，为临床试验提供其所需质量、纯度和安全性的mRNA。"DHVI目前正在研发针对HIV和流感的mRNA疫苗(正在研发的流感疫苗共包括10种不同菌株的鸡尾酒，由美国国立卫生研究院合作流感疫苗创新中心(CIVICS)项目资助)。

Another innovation is the ferritin nanoparticle delivery system, which DHVI is using in developing HIV and COVID-19 mRNA vaccines. This system allows researchers to further decorate the mRNA platform with other immunogens – this could, for example, result in a combined vaccine for infuenza, COVID-19 and RSV. A combination vaccine would be especially useful in LMIC settings, because only one shot would be needed for three diseases.
另一项创新是铁蛋白纳米颗粒递送系统，DHVI正在使用该系统研发HIV和COVID-19 mRNA疫苗。例如，该系统允许研究人员用其他免疫原进一步修改mRNA平台，可以得到同时对流感、COVID-19和RSV有效的联合疫苗。联合疫苗在中低收入国家尤其有用，因为注射一针疫苗可对三种疾病同时有效。

In this context, there are potential interlinkages between the technological advances that we discuss in our paper. First, one concern with the development of combined mRNA vaccines for respiratory diseases, using the ferritin nanoparticle delivery system, is that adverse reactions might be intense. In this context, AI could help to predict which combinations give the most severe reactions. Second, DHVI has ordered Quantoom's technology for making RNA (specifically, the midi). Third, for COVID-19 boosters, there could be a scenario akin to what happens with infuenza vaccines: the WHO decides which strain is needed each year in the Northern hemisphere and the Southern hemisphere, and then companies make it. Similarly, the WHO could state which COVID-19 booster is needed, and mRNA manufacturing plants around the world would make the vaccine (provided they have the ingredients).
在此背景下，我们在本报告中所讨论的技术进步之间有潜在的相互联系。首先，使用铁蛋白纳米颗粒递送系统研发用于呼吸道疾病的联合mRNA疫苗的一个担忧是不良反应可能会很强烈。在这种情况下，人工智能可以帮助预测哪种组合会产生最严重的不良反应。其次，DHVI购买了Quantoom公司用于制造RNA(特别是三种Ntensify™模型的mini型)的技术。第三，COVID-19疫苗加强针可能会面临与流感疫苗相似的情况:由世界卫生组织决定每年北半球和南半球需要哪种毒株，然后交由公司制造疫苗。同样，世卫组织也可以说明需要哪种COVID-19加强针，再由世界各地的mRNA制造工厂生产疫苗(只要他们有原料)。

SUGGESTED ECOSYSTEM CHANGES 生态系统变革建议

1. First, there should be increased investment in mRNA technologies for NDs, EIDs, and MH because mRNA platforms have significant comparative advantages over more traditional technologies. mRNA-based technologies for HIV, TB, and malaria are in the current R&D pipeline and could be powerful tools against the three diseases. LMICs also need to be enabled to produce their own mRNA technologies. This is a critical step.

   首先，由于mRNA平台与传统技术相比具有显著的比较优势，因此应增加对NDs, EIDs, 和MH mRNA技术的投资。针对艾滋病毒、结核病和疟疾的基于mRNA的技术目前正在研发管线中，可能成为对抗这三种疾病的有力工具。中低收入国家还需要有开发自有mRNA生产技术的能力。这是关键的一步。

2. Second, IP barriers need to be addressed. mRNA production requires many different inputs and the IP holders come almost exclusively from HICs; there is an urgent need for IP sharing and tech transfer programs. For example, a lipid needs to be available without the IP constraints, otherwise equity gaps will likely persist.

   第二，破除知识产权壁垒。mRNA的生产需要许多多方投入，而知识产权持有者几乎完全来自高收入国家，因此当下迫切需要知识产权共享和技术转让项目。例如，脂质需要在没有知识产权限制的情况下可用，否则公平差距可能会持续存在。

3. Third, at the same time, we acknowledge that there is low scientific feasibility for developing mRNA vaccines against certain bacteria and parasites with complicated structures that represent a substantial share of the disease burden in LMICs. Developing such vaccines is a key priority for these countries, so a diversified investment approach is needed. R&Dfunders need to invest in more traditional technologies, not just in mRNA.
   第三，与此同时，我们承认开发针对某些结构复杂的细菌和寄生虫的mRNA疫苗的科学可行性很低，但中低收入国家的相当一部分疾病是由这些细菌和寄生虫所引发的。采取多样化的投资方法开发这类疫苗是此类国家的一个关键优先事项。疫苗研发的资助方需要更多投资传统技术，而不仅仅是mRNA技术。

5.1 Monoclonal antibodies 单克隆抗体

OVERVIEW概述

mAbs are a large and growing segment of the pharmaceutical market

and they are also the largest class of biologic products in development.[119] More than 100 mAb products have been licensed over the past 30 years and they are transforming the way doctors treat, prevent, and even cure many diseases, especially NCDs, including certain cancers and autoimmune disorders. These mAb products are often more effective than previous therapies, easier to deliver, and better tolerated by patients.[120] In addition, in tackling infections, mAbs can have "dual use," i.e., they provide passive immunity and have a therapeutic effect in those already infected.[121]

单克隆抗体是医药市场中一个庞大且不断增长的部分，也是还在开发中最大的一类生物制品。[119]过去的30年里，已有100多种单抗产品获得许可。它们正在改变医生治疗、预防甚至治愈许多疾病的方式，尤其是非传染性疾病，如某些癌症和自身免疫性疾病。相较于之前的治疗方法，这些单抗产品通常更有效力，更易递送，并且患者的耐受性更好。[120]此外，在治疗感染时，单克隆抗体有"双重用途"：它们既可以提供被动免疫，也可以治疗已经感染的患者。[121]

There are mAbs in the clinical pipeline for selected EIDs and NDs. mAbs that target SARS-CoV-2 showed a reduction in viral load[122,123,124] and, in the US, COVID-19 mAbs were the first COVID-19-specific product to receive emergency use authorization (in November, 2020). However, laboratory studies found that the activity of anti-SARS-CoV-2 mAbs against specific variants and subvariants varied greatly. The NIH concluded that these products are not expected to be effective in treatment or prevention of COVID-19 in areas where the circulating variants and subvariants are resistant to mAbs.[125] Nevertheless, there is significant ongoing research on COVID-19 mAbs, including on broadly neutralizing antibodies for prophylactic and therapeutic use.[126]

目前已有针对特定新发传染病和被忽视疾病的单克隆抗体进入临床研发阶段。对SARS-CoV-2使用单克隆抗体可使得病毒载量减少[122,123,124]，在美国，COVID-19单克隆抗体是第一个获得紧急使用授权的COVID-19特异性产品(2020年11月)。然而，实验室研究发现，抗SARS-CoV-2单克隆抗体对特定变体和亚变体的活性差异很大。美国国立卫生研究院的研究结论是，在循环变体和亚变体对单克隆抗体耐药的地区[125]，这些产品预计不会有效治疗或预防COVID-19。尽管如此，目前仍有大量关于COVID-19单克隆抗体的研究，包括用于预防和治疗的广泛中和抗体。[126]

Broadly neutralizing mAbs (i.e., against whole viral families) are also of great interest for other viruses, as well as for malaria—a broadly neutralizing

Since broadly neutralizing antiviral mAbs can be developed, manufactured, and stockpiled in advance, they could serve as a real-time intervention upon detection of a pathogen of concern while complementing vaccines.

由于广泛中和的抗病毒单克隆抗体可以预先开发、制造和储存，它们可以在检测到所关注的病原体时作为实时干预，同时补充疫苗。

malaria mAb would be of particular value in pregnancy.[127] A preventive malaria mAb (CIS43LS) is in the pipeline, with Phase 1 and 2 trials showing promising results.[128] There are also mAbs for Ebola virus, showing therapeutic benefts.[129,130] However, a recent study raised some concerns about the risk of reinfection or reactivation of the virus in patients previously treated with Ebola mAbs, pointing to the need for additional research.[131]

广泛中和的单克隆抗体(即针对整个病毒家族的单克隆抗体)对其他病毒和疟疾也有很大的兴趣——广泛中和的疟疾单克隆抗体在孕期有特别的价值。[127]预防性疟疾单抗(CIS43LS)正在研发管线中，第一和第二期试验结果良好。目前也有针对埃博拉病毒的单克隆抗体，且已经显现出治疗效果。[129,130]然而，最近的一项研究则对此表示担忧，因为先前接受埃博拉单克隆抗体治疗的患者可能面临再次感染或病毒被再次激活的风险，这一点还需要进一步研究。

As highlighted by Gupta et al,[121] mAbs can potentially address critical needs in a pandemic – either to complement vaccines or because they have characteristics that are not being met by vaccines. They can:

正如Gupta等人所强调的那样，[121]单克隆抗体可能解决一场大流行中的关键需求：要么是可以补充疫苗，要么是因为它们具有疫苗无法满足的特性。单克隆抗体可以:

Provide primary prophylaxis while waiting for vaccines to be developed.

在等待疫苗研发的同时提供一级预防。

Provide immediate protection during the time it takes for an individual to mount a response after vaccination; this could help in a ring vaccine response ("pre- and post-exposure mAb prophylaxis could help to quell an outbreak at its nascent stage"[121]).

在接种疫苗后产生免疫应答所需时间内立即提供保护;这有助于环形疫苗免疫应答("暴露前和暴露后单克隆抗体预防有助于在暴发初期平息疫情"[121])。

Provide passive immunity to patients who do not mount an adequate immune response to vaccines or who are vaccine hesitant.

为对疫苗免疫应答不足或对接种疫苗犹豫不决的患者提供被动免疫。

Reduce transmission by reducing viral load ("treatment as prevention").

通过减少病毒载量来减少疾病传播("治疗即预防")。

Potentially be stockpiled. Gupta et al argue that since "broadly neutralizing antiviral mAbs can be developed, manufactured, and stockpiled in advance, they could serve as a real-time intervention upon detection of a pathogen of concern while complementing vaccines."[121]

具备存储可能性。Gupta等人认为，由于"广泛中和的抗病毒单克隆抗体可以预先开发、制造和储存，它们可以作为一种实时干预措施，在检测到所关注的病原体时补充疫苗。[121]

CHALLENGES挑战

We identifed four challenges with mAbs.

我们发现单克隆抗体面临四个挑战。

1. Access. First, access to mAbs is severely limited in many countries – 80% of sales are in the U.S., Canada, and Europe, while 85% of the world's population live in LMICs. One factor, which the global community has largely neglected thus far, is the high costs (Panel 3). In low-income countries, very few mAbs are even registered, and those that are registered in middle-income countries are often not covered by the public health systems, impeding access due to high costs. Unless action is taken now, the access gap will further widen because mAbs constitute an increasingly large portion of the pharmaceutical pipeline. The biggest barriers to access are affordability and availability, including registration and inclusion on national medicine lists. Currently, the global ecosystem also lacks an international "buyer" for monoclonal products, which makes it difficult to shape markets and negotiate prices that are affordable to LMICs. So, even if a mAb became available for malaria, it is unclear who would buy it as no single organization is leading on this.
可及性不足。首先，许多国家在获得单克隆抗体方面受到严重限制——单克隆抗体80%的销售在美国、加拿大和欧洲，而世界上85%的人口生活在中低收入国家。截至目前，国际社会在很大程度上还忽视了高成本这一因素(第3小节)。在低收入国家，甚至很少有单克隆抗体注册；而那些在中等收入国家注册的单克隆抗体往往不在公共卫生系统的覆盖范围内，成本高，可及性低。随着单克隆抗体在药品研发管线中所占的比例越来越大，倘若我们现在不采取行动，单克隆抗体的可得性差距将进一步扩大。获得单克隆抗体的最大障碍是可负担性和可用性，包括注册和列入国家药物清单。目前，全球生态系统还缺乏单克隆产品的国际"买家"，这十分影响市场环境，使中低收入国家更加难于通过谈判获得负担得起的价格。所以，即使预防疟疾的单克隆抗体目前可用，我们也不清楚谁会购买，因为还没有一个组织在这方面处于领先地位。

2. Insufficient R&D. Second, the development of mAbs for infectious diseases has been limited, partially due to their high production costs and limited duration of protection. Only seven currently licensed mAbs are for infectious diseases despite their potential for treating and preventing infectious diseases that disproportionately impact LMICs as well as emerging pathogens with pandemic potential. The insufficient R&D for infectious disease mAbs reflects a lack of commercial incentives to invest in R&D for mAbs in LMIC settings. For those mAbs that are available for infectious diseases, access and availability issues largely prevent their use in LMICs (Panel 3).
研发不足。第二，针对传染病的单克隆抗体开发受到限制，部分原因是其制备成本高，对人体的保护时长有限。目前，只有7种针对传染病的单克隆抗体获得许可。它们具有预防和治疗传染病以及具有大流行可能的新病原体的潜力，但这些传染病对中低收入国家的影响程度不同。针对传染病的单克隆抗体研发不足反映出中低收入国家缺乏投资研发单克隆抗体的商业动机。对于那些可用于治疗传染病的单克隆抗体，可及性和可得性低在很大程度上阻碍了它们在中低收入国家的使用(第3小节)。

3. Lack of trials in LMICs. Third, only 12% of clinical trials for mAbs are conducted in LMICs. The scientific community remains concerned that large and complex trials for mAbs cannot be successfully conducted in low-resource settings. However, the Antibody Mediated Prevention study, which evaluated an innovative mAb for HIV prevention, was successfully conducted in seven countries in Sub-Saharan Africa, providing proof-of-concept for the feasibility of conducting complex trials.[132] Furthermore, it has proven more difficult to gain regulatory approval for biosimilars compared to small-molecule generics, mainly due to the requirement for comparative clinical trials and the limited experience of LMIC regulators with the review of mAbs dossiers. As highlighted in Section 6 of this report, more collaborative regulatory approaches are needed across countries.
缺乏在中低收入国家的试验。第三，只有12%的单克隆抗体临床试验在中低收入国家进行。科学界仍然担心在资源匮乏的条件下无法成功开展复杂、大规模的单克隆抗体试验，然而7个撒哈拉以南非洲国家成功开展了抗体介导预防研究。该研究评估了一种用于预防艾滋病毒的新单克隆抗体，为开展复杂试验的可行性提供了概念验证。此外，事实证明，与小分子仿制药相比，生物仿制药更难获得监管部门的批准，这主要是因为后者需要进行比较临床试验，且中低收入国家监管体系在审评单克隆抗体卷宗方面的经验有限。正如本报告第6章所强调的，各国需要采取更具协作性的监管方法。

4. Lack of target product profiles (TPPs) and preferred product characteristics (PPCs). Fourth, there are only a few TPPs or PPCs for mAbs for LMICs. TPPs and PPCs are released by WHO and lay out product attributes with a focus on LMICs. The lack of TPPs and PPCs for mAbs to guide product development by industry is a major roadblock. Developing such TPPs and PPCs would be an important step for accelerating and expanding access of new mAb tools.[133]
缺乏目标产品概况(TPPs)和首选产品特性(PPCs)。第四，中低收入国家所用的单克隆抗体只有少数目标产品概况或首选产品特性。目标产品概况和首选产品特性由世卫组织推出，要求列出产品属性，重点关注中低收入国家。当下的主要障碍是缺少单克隆抗体的目标产品概况和首选产品特性来指导本行业的产品开发。制定目标产品概况和首选产品特性将会是加速和扩大新单抗工具可及性的重要一步。

Overall there are multiple challenges – as one KI said, “even if I had a billion doses of a mAb for a specifc disease in an LMIC, there is no buyer, there is no regulatory pathway, there is nothing….manufacturing, implementation, regulatory, procurement—who is going to do it? Companies aren’t going to do it. There’s no one-stop shop.” However, there are also many opportunities to improve the landscape for mAbs, such as new manufacturing techniques, conducting trials in LMICs (rather than in HICs), and the creation of TPPs.
总体而言，我们面临多重挑战。正如一位主要信息提供者所说的，“即使我有10亿剂用于中低收入国家特定疾病的单克隆抗体我也没有买家，还没有监管路径，什么都没有....制造、实施、监管、采购，谁来负责?公司是不会这么做的。现在也没有一站式服务。”然而，改善单克隆抗体的前景还有许多机会，例如开发新的制造技术，在中低收入国家(而非高收入国家)开展试验，以及制定目标产品概况。

PANEL 3 mAbsfor respiratory syncytial virus 呼吸道合胞病毒单克隆抗体

Respiratory syncytial virus (RSV) can infect people of all ages, but young infants have the highest incidence of severe disease. RSV has been estimated to globally cause 33 million acute lower respiratory tract infections in young children annually, with 3.2 million severe cases requiring hospitalization, and 118,000 deaths. Although RSV is a global disease (e.g., it is the leading cause of hospitalization for children under one year old in the U.S.), 99% of global deaths and 88% of hospital admissions occur in LMICs. In 2023, a new monoclonal antibody for RSV (nirsevimab, made by AstraZeneca/Sanofi) was introduced. It was given an FDA Fast Track designation, a process designed to expedite drugs to treat serious conditions and fill unmet needs. Compared to a previous registered mAb for RSV (Synagis), nirsevimab is longer lasting (a single dose will shield infants for the whole RSV season), and it costs much less (US$400-500[134] in the U.S. and between US$300-900 in European countries) compared to Synagis.[135,136] Nirsevimab is effective at preventing RSV in young infants, providing around 75% protection against severe RSV disease and hospitalization.[137,138]

呼吸道合胞病毒(RSV)可感染所有年龄段的人群，但婴幼儿的重症发病率最高。据估计，RSV每年在全球造成3300万幼儿患急性下呼吸道感染，其中有320万重症病例需要住院治疗，11.8万死亡病例。虽然RSV是一种全球性疾病(例如，RSV是导致美国1岁以下儿童住院的首要原因)，但该病全球99%的死亡病例和88%的住院病例都出现在中低收入国家。2023年，一种新的RSV单克隆抗体(由阿斯利康/赛诺菲生产的Nirsevimab)问世，并获得了FDA的快速通道认证，其旨在促进治疗严重疾病和解决未满足医疗需求的药物的开发。与之前注册的RSV单抗(Synagis)相比[135,136]，Nirsevimab的保护期更长(单剂即可在整个RSV流行季保护婴儿)，成本也要低得多(美国为400-500美元[134]，欧洲国家为300-900美元)。Nirsevimab可有效预防婴幼儿感染RSV，对重症和住院病例的保护可达75%。

Nirsevimab illustrates an important point – it is an effective tool against a disease that causes a lot of harm globally, but especially in LMICs. For example, its use in HICs could reduce hospitalizations by 50%, preventing hundreds of thousands of children becoming severely sick and reducing pressure on healthcare systems.[139] However, for the time being, the monoclonal will not be available at scale in LMICs. Given the high costs and the reluctance of the producing companies to introduce tiered pricing for LMICs, LMICs cannot afford to purchase the monoclonal RSV product.

Nirsevimab还证明了重要的一点，即它可以有效对抗一种在全球、尤其是在中低收入国家造成严重危害的疾病。例如，在高收入国家使用Nirsevimab可以减少50%的住院率，防止数十万儿童病患发展为重症病例，并减轻卫生保健系统的压力。然而，目前该单克隆抗体还无法在中低收入国家投入大规模使用。其成本高，生产公司不愿为中低收入国家引入分层定价机制，这使得中低收入国家无力购买单克隆RSV产品。

The TPP states that “the mAb price should be similar to other new vaccines for feasibility of use in LMIC settings” and that the price “should be acceptable to Gavi investment case for use in Gavi-eligible countries.” However, the reality is that price is a barrier to global access. One key determinant of the high price is the fact that mAbs can be even more expensive to produce than vaccines. Antibody production is difficult, requiring multiple steps, particularly their downstream isolation and their purification, making it harder to produce larger batches. Still, for real progress in global health outcomes, these new breakthrough technologies need to benefit everyone. Several published articles have argued that there are ways to lower manufacturing costs.140, 141, 142 For example, in a paper on key considerations for global use of RSV mAbs, Sparrow and colleagues say:

目标产品概况指出，“单克隆抗体的价格应与其他新疫苗差不多，以便中低收入国家使用”，且其价格“应当是全球疫苗免疫联盟投资案例所能接受的，以便联盟国家使用”。然而现实情况是，价格阻碍了单克隆抗体的全球市场准入。单克隆抗体价格高昂的一个关键决定性因素是其制备成本甚至可能高于疫苗本身。单克隆抗体的生产有一定难度，步骤多，特别是下游分离和纯化两个步骤，使得大批量生产变得更加困难。然而要想取得全球卫生健康成果的真正进步，这些新的突破性技术需要惠及所有人。已发表的几篇文章认为，一些方法可以降低制备成本。[144,141,142]例如，在一篇关于全球使用RSV单克隆抗体的关键考虑因素的论文中，Sparrow及其同事认为:

> “However, given the small dose of mAb required to protect young infants against RSV and given new manufacturing technologies, the cost of preventive RSV mAbs could be relatively low, potentially enabling them to be marketed in a price range similar to the price points of newer vaccines in use in LMICs. Based on projections, for a 50 mg dose of mAb, the cost of goods could be less than US$5 per dose.”[141]

“考虑到保护婴幼儿免受RSV感染所需的单克隆抗体剂量小，且我们有了新的生产技术，预防性RSV单克隆抗体的成本可能会相对较低，这也有可能使其以与中低收入国家使用的新疫苗差不多的价格范围上市。根据预测，50毫克剂量的单克隆抗体成本可能每剂不到5美元。”[141]

Going forward, the potential to reduce production costs needs to be assessed. Recent improvements in antibody optimization, and advancements in manufacturing technologies and packaging and delivery, have the potential to lower mAb production costs. For example, one of the leading mAb manufacturers based in China has “a continuous bioprocess system integrated with single-use bioreactors that is predicted to reduce mAb manufacturing costs from $95–$200 per gram to less than $15 per gram, or $3 for an average 200 mg dose of most mAbs.”[119] And while local mAb production in LMICs remains untested, the manufacturing of mAbs in LMICs must be put on the agenda, e.g., in the context of discussions about the creation of mRNA hubs. Studies of the cost-effectiveness of the use of mAbs in LMICs are needed, as well as post-introduction surveillance in early introducing countries to further assess the case for using mAbs in LMICs.

展望未来，我们需要评估降低制备成本的可能性。近期在抗体优化方面的改进以及制备技术、包装和交付方面的进步，都有可能降低单克隆抗体的制备成本。例如，中国一家领先的单克隆抗体生产商拥有“一个与一次性生物反应器集成的连续生物工艺系统，预计可将单克隆抗体的制备成本从每克95–200美元降低到每克不到15美元，或将平均规格为200毫克剂量的大多数单克隆抗体的制备成本降到3美元。[119]”虽然在中低收入国家本土制备单克隆抗体仍未开展试验，但这一事项必须提上议程，例如在讨论创建mRNA中心时。我们需要研究中低收入国家使用单克隆抗体的成本效益，并在早期投入使用的国家开展使用监测，以进一步评估在中低收入国家使用单克隆抗体的情况。

5.3 Summary and suggested ecosystem changes 总结和生态系统变革建议

IAVI and Wellcome put out a call to action to expand access to mAbs, highlighting the need to develop effective new solutions for increased global access to mAbs.[119] These two institutions highlight four immediate actions:

国际艾滋病疫苗行动组织（IAVI）和伦敦惠康（Wellcome）呼吁各方采取行动，扩大单克隆抗体的可及性，并强调我们需要找到新的有效的解决方案，以增大单克隆抗体的全球可及性[119]。这两个机构着重指出了四项应立即采取的行动:

(i) increase advocacy and awareness around the need to make mAbs more widely accessible;

加强宣传，提高人们对更易获得单克隆抗体必要性的认识;

(ii) develop expanded policy and regulatory pathways to increase availability of mAbs;

扩大政策和监管路径，增加单克隆抗体的可用性;

(iii) invest in and apply new technologies to lower development costs; and

投资和应用新技术以降低开发成本;并且

(iv) establish alternative business models to enable innovative market approaches that promote global access.

In addition to these broad steps, we suggest additional concrete steps to boost the development and use of mAbs in LMICs within the next 10-20 years:

建立新的商业模式，以实现促进全球准入的创新市场方法，促进全球准入。除了这些宽泛的举措外，我们还建议在未来10-20年内采取其他具体方法，促进中低收入国家单克隆抗体的开发和使用:

1. There needs to be more investment in R&D on mAbs for NDs, EIDs, and MH. While there is substantial potential, current R&D efforts do not sufficiently target infectious diseases.

   加大治疗被忽视疾病、新发传染病和孕产妇保健的单克隆抗体的研发投资。尽管潜力巨大，目前针对传染性疾病的研发工作依然不足。

2. There needs to be investment in manufacturing capacity for mAbs in LMICs, including through mRNA. More attention has to be given to ways to bring production costs down.

   对中低收入国家单克隆抗体的制备能力进行投资，包括对mRNA单抗制备法进行投资。必须更加注意降低制备成本的方法。

3. There is no example of scaled up mAbs in LMICs, although India has licensed two mAbs-based products for post-exposure prophylaxis against rabies. Yet we saw with antiretroviral therapies that it is possible to introduce expensive drugs in a relatively fast manner and see costs fall quickly. While the financial environment is severely constrained, there is an opportunity to pilot the wide-scale introduction of monoclonals as a scale up project (COVID-19 was a missed opportunity to do so). The RSV monoclonal could be a game changer and could serve as a product for the global community to rally around. This will require funding and negotiations with industry, and it would also require a decision about who is going to invest in the product and procure it on behalf of countries. There is no appetite for new global mechanisms, so it would either be an existing global mechanism or potentially different regional mechanisms coordinated at global level.
   尽管印度已经批准了两种基于单克隆抗体的产品用于狂犬病暴露后预防，但在中低收入国家还没有大规模使用单克隆抗体的例子。然而通过抗逆转录病毒疗法，我们有可能以相对较快的速度研制出昂贵的药物，并使成本迅速下降。虽然研发单克隆抗体的融资环境目前严重受限，但我们仍有机会进行大规模推广试点。人们错失了新冠肺炎大流行这一良机。RSV单克隆可能会改变游戏规则，并可能成为使全球社区团结一致的产品。这就需要资金支持和行业谈判，还需要决定由谁来投资该产品并代表各国采购。人们没有兴趣建立新的全球机制，因此，要么沿用现有的全球机制，要么是在全球层面将很可能不同的区域机制协调一致。

4. In parallel, the case for using mAbs in LMICs needs to be further assessed. From an equity perspective, there needs to be a strong push for developing, producing, and using mAbs in LMICs. However, under the current financially constrained environment, there needs to be more evidence to guide development, production, and use in different settings, including cost-effectiveness studies and post-introduction surveillance.

   与此同时，我们需要进一步评估在中低收入国家使用单克隆抗体的情况。公平起见，我们需要大力推动中低收入国家开发、制备和使用单克隆抗体。然而，在目前资金吃紧的情况下，我们需要有更多证据来指导不同环境中单克隆抗体的开发、制备和使用，包括成本效益研究和投入使用后的监测。

For pandemic preparedness more specifcally, we agree with Gupta et al that it would be possible to have "a stockpile of broad-spectrum predeveloped mAbs capable of targeting emerging pathogens that have a high barrier to resistance, are rapidly deployable, and can be administered in multiple settings to halt outbreaks through prophylaxis and treatment."[121] In other words, an arsenal of pandemic preparedness mAbs targeting priority pathogens could be created. Having such an arsenal ready would require seven things:

就具体的大流行预防而言，我们同意Gupta等人的观点，即我们有可能拥有"广谱预先开发的单克隆抗体储备，能够针对具有高抗性屏障的新出现病原体快速部署，并且可以在多种环境中使用，通过预防和治疗来阻止疫情暴发。"[121]换句话说，我们可以创建针对重点病原体的大流行预备性单克隆抗体库。我们需要以下7样武器:

Identifying the pathogenic targets
确定致病靶点

Establishing TPPs
制定目标产品概况

Creating sustainable markets, e.g., advanced market commitments
创建可持续的市场，例如制定预先市场承诺机制

Defining and harmonizing regulatory pathways
制定和协调监管路径

Building global trial networks
建立全球试验网络

Producing a ready-to-use supply and scalable manufacturing process
生产即用型供应和可扩展的制造工艺

Manufacturing sites able to produce non-pandemic Abs between outbreaks.
有能够在两次疫情暴发之间制备非大流行抗体的生产地点。

6

REGULATION
监管

KEY BENEFITS OF RELIANCE AND ACCELERATED APPROVAL:

信赖和加速审批的主要优势：

There is evidence that subregional regulatory initiatives have contributed to regulatory harmonization and reliance. Mechanisms such as the use of reference agencies and joint reviews have significantly shortened registration timelines. Substantial progress towards regulatory harmonization has been made in Africa. However, there is potential to further deepen the collaboration between national regulatory authorities (NRAs). For example, many LMICs still lack legislation for the use of reference agencies and organizational policies and standard operating procedures that guide how to apply reliance. Strong leadership is needed to drive the institutional transformation required to optimize reliance.

有证据表明，次区域监管倡议增进了监管协调和信赖。使用推荐审理部门和联合审查等机制极大缩短了注册用时。非洲在监管协调方面取得了重大进展。然而，我们仍有可能进一步深化国家监管体系(NRAs)之间的合作。例如，许多中低收入国家仍然缺乏使用推荐审理部门和组织政策的相关立法，缺乏指导如何使用监管信赖的组织政策和标准作业程序。这需要强有力的领导来推动提升监管信赖所需要的制度转型。

The COVID-19 pandemic contributed to more efficient regulatory processes. For example, in Europe, rapid scientific advice and review was reduced from 40-70 days to 20 days.

新冠肺炎疫情提高了监管流程的效率。例如，在欧洲，快速科学咨询和审查从40-70天减少到20天。

KEY CHALLENGES TO BE ADDRESSED: 尚未解决的关键挑战：

There is still a substantial gap in market authorization of health products between LMICs and HICs. One study estimated that there is lag of 4 to 7 years between first submission for regulatory approval, which is usually to a regulator in a HIC, and final approval in Sub-Saharan Africa (SSA). The study found that WHO's prequalification processes and NRAs often repeated assessments of quality, safety, and efficacy already performed by stringent regulatory authorities (SRAs) and that manufacturers did not prioritize market access in LMICs, slowing down access. While additional reviews may not have been needed, they are usually conducted out of good intent (e.g., to ensure availability of sufficient safety data for local contexts).

在保健产品的市场授权方面，中低收入国家和高收入国家之间仍存在很大差距。一项研究曾估算，从首次提交监管批准(通常是向高收入国家的监管机构提交)到撒哈拉以南非洲(SSA)国家的最终批准之间存在4至7年的滞后。研究发现，世卫组织预认证流程和国家监管体系经常重复严格监管机构(SRAs)已经进行过的质量、安全性和疗效评估，而且制造商也不会优先考虑进入中低收入国家市场，这使得其获得产品的进度被迫放缓。虽然有时可能不需要额外的审查，但通常出于良好的意图(例如，确保为当地提供足够的安全数据)，仍然会进行额外审查。

. Furthermore, of the 14 African countries where vaccine manufacturing projects have been announced, only two have regulatory systems operating at the level required for WHO vaccine prequalification. Without stronger regulatory systems, these countries will not be eligible for support from Gavi's African Vaccine Manufacturing Accelerator (WHO prequalification is a requirement for participation in this mechanism).

在全球范围内，只有57个国家监管体系(30%)有能力履行核心监管职能。其中，只有5个在非洲。此外，在已宣布疫苗生产项目的14个非洲国家中，只有两个国家的监管体系达到了世卫组织疫苗资格预审所需的水平。如果没有更强有力的监管体系，这些国家将没有资格获得全球疫苗免疫联盟非洲疫苗制造加速器(AVMA)的支持(世卫组织资格预审是参与该机制的一项要求)。

SUGGESTED ECOSYSTEM CHANGES: 生态系统变革建议：

Harmonization and reliance are key strategies to accelerate market registration and access to new drugs and vaccines. They remain underused mechanisms.

监管协调和信赖是加速市场注册和获得新药品和新疫苗的关键战略。这些机制仍未得到充分利用。

In parallel, capacity gaps need to be gradually and strategically addressed. LMICs should assess their current regulatory systems using existing WHO tools and allocate

与此同时，我们需要逐步、战略性地解决能力差距。中低收入国家应利用世卫组织现有工具评估其现行监管体系，并为其分配更多资金。高收入国家应向非洲药品管理局等国家和区域监管机构提供技术和融资支持，以确保这些机构能够有效地履行核心监管职能。高收入国家监管体系与中低收入国家监管体系之间建立伙伴关系（如孪生或联合评估）对于监管能力建设和提高效率也至关重要。近年来，许多国家间已经建立了这类伙伴关系。

more funding to these systems. HICs should provide technical and financial support

虽然目前世卫组织资格预审认证仍有必要，但应该有更大的灵活性。世卫组织预认证是在监管体系非常薄弱时使用的，但这种情况已经在一定程度上发生了变化，需要灵活性。各国和全球采购机构(如联合国儿童基金会)应越来越多地接受世卫组织所列机构和/或过渡性机构的审查，作为世卫组织预认证的替代方案。

to national and regional regulatory agencies, such as the African Medicines Agency, to ensure that these agencies can efectively perform core regulatory functions. Partnerships between regulatory authorities of HICs and those in LMICs, such as twinning or joint assessments, will also be critical to build capacity and achieve efficiency gains. Several of these types of partnerships were launched in recent years.

Any efforts to strengthen vaccine manufacturing capacity need to be accompanied by investments in regulatory systems. To be eligible for WHO prequalifcation for vaccine manufacturing, maturity levels 3 or 4 are currently still a requirement.

任何提高疫苗生产能力的努力都离不开对监管体系的投资。目前，世卫组织疫苗生产资格预认证仍要求国家疫苗监管体系成熟度达到3级或4级。

While the WHO PQ system is currently still needed, there should be more fexibilities. WHO PQ was introduced at a time when regulatory systems were very weak, but this has changed to a certain degree, and fexibilities are needed.

6.1 Overview概述

Efective regulatory systems assure the quality, safety, and efficacy of medical products. In contrast, poor regulatory systems are often a major barrier to providing safe, efective health tools. Globally, only 57 countries (about 30%) have regulatory systems at maturity level 3 or 4 as measured by the WHO Global Benchmarking Tool (GBT).[143] The WHO introduced this tool to assess and benchmark NRAs, promote coordination and good regulatory practices, improve the efectiveness of regulatory strengthening activities, and facilitate harmonization. GBT level 3 refers to stable, well-functioning and integrated regulatory systems, while level 4 refers to advanced systems (see Annex 4 for GBT defnitions). Countries with GBT levels 3 or 4 can become a WHO-listed authority (WLA), which "designates regulatory authorities that may be considered as a reference point by WHO and other regulatory authorities for reaching their own decisions in approving medical products" (see Panel 4 for further details).[144,145] Most LMICs have maturity levels 1 or 2—weak systems that are only considered as functional when they rely on prior work by other regulators. As of October 2023, only fve NRAs in Africa—Egypt, Ghana, Nigeria, South Africa, and Tanzania—had attained maturity level 3.[146]

有效的监管体系能够确保医疗产品的质量、安全性和有效性。相反，不良的监管体系往往是提供安全有效的健康工具的主要障碍。根据世卫组织全球基准工具(GBT)的衡量，全球只有57个国家(约30%)的监管体系达到成熟度3级(ML3)或4级(ML4)。[143]世卫组织采用这一工具以评估和衡量国家监管体系，促进监管合作和良好的监管实践，提高监管加强活动的有效性，并促进监管协调。GBT3级指稳定、功能完善且完整的监管体系，而GBT4级是指具备先进水平的监管体系(GBT定义见附录4)。GBT等级为3级或4级的国家可获批成为世卫组织列名机构(WLA)，"指定的监管机构可被世卫组织及其他监管机构视为在批准药品方面做出自己决定的参考点"(详情见第4小节)。[144,145]大多数中低收入国家的监管体系成熟度为1级或2级，它们的监管体系只有在依赖于其他监管体系的前期工作时，才被认为可发挥其功能。截至2023年10月，非洲只有埃及、加纳、尼日利亚、南非和坦桑尼亚这5个国家的国家监管体系达到了成熟度3级。[146]

PANEL 4 WHO-listed authorities (WLA)

This panel provides the WHO defnitions of WLAs and transitional WLAs. The WLA replaces the SRA defnition (the defnition of an SRA, frst published by the Global Fund in 2008, was based on membership in the International Conference [now Council] of Harmonization before October 2015). We still use "SRA" if studies that we cite used the term.

A **WHO-listed authority (WLA)** is defned as "a regulatory authority (RA) or a regional regulatory system (RRS) that complies with all the relevant indicators and requirements specifed by WHO for regulatory capability as defned by an established benchmarking and performance evaluation process. A regulatory authority provides the framework that supports the WHO recommended regulatory functions. This is the authority and affiliated institutions that are responsible for regulatory oversight of medical products in a given country or region and in charge of assuring the quality, safety and efficacy of medical products as well as ensuring the relevance and accuracy of product information."

To be designated as a WLA, "a regulatory authority should undergo i) a formal assessment with the WHO-Global Benchmarking Tool (GBT) to demonstrate adequate maturity (ML3 as entry point) and ii) a performance evaluation (PE) process that complements the results against international standards and best practices. Some transitional arrangements are in place for previously designated stringent regulatory authorities and regulatory authorities which had been previously assessed by WHO. RAs that have reached a high-level regulatory capability and performance (WLA) maybe used as a reference and to be relied on by other authorities, to avoid duplicating activities, foster better use of human and economic resources, [and] increase oversight of the pharmaceutical products along the whole supply chain…."

A transitional WLA (tWLA) is an RA "previously included in the WHO Interim list of regulatory authorities (published by WHO from 2019 to 2022), which compiled all RAs already recognized by WHO that work at an acceptable level of regulatory performance before the introduction of the WLA concept. A transitional WLA is not a WLA, in that it still needs to undergo the performance evaluation process and demonstrate compliance with the requirements to be designated as a WLA. The transitional list will be valid until 31 March 2027. During this time, tWLAs are expected to apply for being subject to the performance evaluation (PE) to be able to transition either to the permanent WLA list or the list of RAs operating at ML3/4."

For further details, see WHO Listed Authorities. March 1, 2024. https://www.who.int/news-room/questions-and-answers/item/who-listed-authorities

第4节 世卫组织列名机构

本小节给出了世界卫生组织对世卫组织列名机构（WLA）和过渡性世卫组织列名机构（tWLA）的定义。WLA取代了SRA的定义(全球抗击艾滋病、结核病和疟疾基金于2008年首次发布的SRA定义，是基于2015年10月前人用药品注册技术规定国际协调会[现在为"理事会"]的成员资格)。如果本报告所引用的研究中使用了WLA这一术语，本报告依然使用SRA来指代。

世卫组织列名机构(WLA)的指"符合世卫组织规定的所有相关指标和要求的监管机构(RA)或区域监管体系(RRS)，这些指标和要求由已有的基准和效能评估过程定义。监管机构提供框架，支持世卫组织建议履行的监管职能。监管机构及其附属机构共同负责在特定国家或地区监管医疗产品，负责确保医疗产品的质量、安全性和有效性，并确保产品信息的相关性和准确性。"

若想成为世卫组织列名机构，监管机构需要：1.经过GBT官方评估，并证明自身有足够的成熟度（ML3级是门槛）2. 符合国际标准和最佳规范。对于以前指定的严格监管机构和世卫组织以前评估过的监管机构，世卫组织已经制定了一些过渡性安排举措。具备高水平监管能力和效能(WLA)的监管机构可能被其他机构用作参考和信赖，以避免重复监管，更好地利用人力和经济资源，[并]加强对整个供应链上药品的监管...."

过渡性世卫组织列名机构(tWLA)是此前被列入世卫组织监管机构临时清单(世卫组织于2019年至2022年发布)的监管机构，该清单汇编了世卫组织列名机构出现之前，世卫组织已经认可的具备可接受的监管效能水平的所有监管机构。过渡性世卫组织列名机构并非世卫组织列名机构，因为它仍需经过效能评估流程，证明其符合被指定为世卫组织列名机构的各项要求。过渡性世卫组织列名机构名单有效期至2027年3月31日。在这段时间内，过渡性世卫组织列名机构需要申请效能评估，以便能够过被列入永久清单，或ML3/4级监管机构名单。"

更多细节请参见世卫组织列名机构。2024年3月1日。https://www.who.int/ news-room/questions-and-answers/item/who-listed-authorities

In addition to NRAs, there is a complex system of global, regional, and subregional regulatory agencies and initiatives. At the global level, WHO supports the introduction of safe new health tools in LMICs through the Certifcate of Pharmaceutical Product (CPP). One recent regional initiative is the African Medicines Agency (AMA), established as a legal entity in November, 2021. By January, 2024, 27 countries had ratifed the AMA treaty. The agency was established to improve regulatory capacity, provide technical support to countries with limited regulatory expertise, strengthen governance in pharmacovigilance, and oversee clinical trials. AMA is still at a nascent stage, but is set to take on an important future role for the African continent.[147]

In this section, we summarize the evidence on existing regulatory challenges, such as the time lag in access to new health tools between HICs and LMICs (Section 6.2). We then analyze how regulatory processes could be accelerated (Section 6.3). Finally, we make suggestions on how the regulatory ecosystem could be strengthened (Section 6.4).

除了国家监管体系之外，还有一个由全球、区域和次区域监管机构和倡议组成的复杂系统。在全球层面，世卫组织通过颁发药品证书(CPP)的方式支持在中低收入国家采用安全的新健康工具。最近发起的一项区域性倡议是成立非洲药品管理局(AMA)，该机构于2021年11月作为一个法律实体成立。到2024年1月，已有27个国家签署了AMA条约。设立该机构的目的是为了提高监管能力，向监管专业知识有限的国家提供技术支持，加强药物警戒治理，并监管临床试验。非洲药品管理局仍处于初创阶段，但在未来将为非洲大陆发挥重要作用。[147]

在本节中，我们总结了现有监管挑战的例证，如高收入国家和中低收入国家在获得新健康工具方面的时间差(第6.2节)。然后，我们分析了如何加快监管审批(第6.3节)。最后，我们就如何完善监管生态系统给出了建议(第6.4节)。

6.2 The gap between HICs and LMICs in market authorization of global health products高收入国家与低收入国家在全球保健产品市场授权方面的差距

In 2022, the Centre for Innovation in Regulatory Science assessed new active substance approvals by six HIC regulatory agencies: the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Devices Agency, Health Canada, Swissmedic and the Australian Therapeutic Goods Administration. The study found that approval timelines are fast, with small differences between the agencies. In 2021, the median approval time ranged from 245 days (FDA) to 428 days (EMA).[148] The approval times refect the fact that HICs largely adhere to a uniform set of scientifc and technical standards, as a result of their membership in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[149]
2022年，英国监管科学创新中心（CIRS）评估了六个高收入国家监管体系对新活性物质的审批，包括欧洲药品管理局(EMA)、美国食品药品管理局(FDA)、日本药品和医疗器械管理局、加拿大卫生部、瑞士药品管理局和澳大利亚药品管理局。研究发现，这些机构的审批速度快，用时相近。2021年，中位批准时间从245天(FDA)到428天(EMA)不等。[148]这反映出高收入国家在很大程度上是遵守一套统一的科学和技术标准的，因为它们都是ICH的成员。

Three key studies have collected evidence on registration timelines in LMICs, pointing to substantial lags in product approval between HICs and LMICs. First, Ahonkhai and colleagues focused on vaccines and drugs eligible for WHO PQ.[150] Based on data for 2009-2012, they estimated that there was a lag of up to 4 to 7 years between the time medicines and vaccines were submitted for regulatory approval, which was usually in a HIC, and its registration in the last of the 20 SSA countries included in their analysis. Ahonkhai et al identifed four main factors for these delays:
有三项关键研究收集了中低收入国家的注册时间表作为证据，指出高收入国家和中低收入国家之间的产品审批有很大的时间差。首先，Ahonkhai及其同事重点关注符合世卫组织预认证[150]要求的疫苗和药物。根据2009-2012年的数据，他们估计，从药物和疫苗提交监管机构批准(通常是在高收入国家)到其所分析的20个撒哈拉以南非洲国家中的最后一个国家注册完成，存在长达4至7年的滞后。Ahonkhai等人认为造成延误的四个主要因素如下:

1. SRA-approved vaccines took a median of 16 months to complete the WHO PQ process. Many review activities were repeated as part of the process, despite previously being conducted by an SRA. Manufacturers also contributed to the delay due to their slow response to WHO questions. PQ time for drugs was much faster (4 months) because review activities were not repeated.

   严格监管机构审查通过的疫苗平均需要16个月才能完成世卫组织预认证流程，该流程又重复进行了一些审查。制造商对世卫组织问题的迟缓回应也造成了延误。如果没有重复审查行为，药物的预认证流程要快得多(仅需4个月)。

2. Generics from emerging markets required a median of 27 months to complete the PQ process. The standards for the registration of generics in emerging markets (e.g., China, India) were often less stringent than ICH standards required by WHO PQ. Thus, "additional time was often required for manufacturers from those countries to raise the standards of their submissions to meet the PQ requirements."
新兴市场国家的仿制药平均需要27个月才能完成预认证流程。新兴市场国家(如中国、印度)的仿制药注册标准往往不如世卫组织预认证的ICH标准严格。因此，"这些国家的制造商通常需要额外花时间来提高他们提交审查时的标准，以满足预认证的要求。"

3. NRAs often repeated assessments already performed by SRAs or PQ. As a result, products first registered by an SRA or PQ process took an additional 1–2 years to receive NRA approval in SSA.

国家监管体系经常重复严格监管机构或世卫组织预认证已经完成的评估。因此，已经完成严格监管机构审查或世卫组织预认证流程注册的产品需要额外花费1-2年才能在撒哈拉以南非洲获得国家监管体系的批准。

4. Submissions by manufacturers in SSA countries were usually spread over several years – one key reason was that producers did not prioritize registration due to limited commercial incentives.

撒哈拉以南非洲国家的制造商通常在几年内分散提交申请，其中的一个关键原因是商业激励有限，制造商不会优先考虑注册。

Second, Miller et al assessed approval timelines of 34 new drugs approved by the FDA in 2012 and 2014 in selected HICs and upper- and lower-middle income countries.[151] Approvals were faster in HICs (median [IQR], 8 [0-11] months) than in upper-middle-income countries (median [IQR], 11 [5-29] months) and lower-middle-income countries (median [IQR], 17 [11-27] months) after FDA approval.

第二，Miller等人评估了2012年和2014年美国食品药品管理局（FDA）批准的34种新药在选定的高收入国家、中高收入国家、中低收入国家的审批时间表。[151]FDA批准后，高收入国家(中位数[IQR]，8[0-11]个月)的审批速度快于中高收入国家(中位数[IQR]，11[5-29]个月)和中低收入国家(中位数[IQR]，17[11-27]个月)。

Third, Sithole et al analyzed approval times for mainly generics in six African countries (Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe) in 2019 and 2020.[152] These countries are members of the Southern African Development Community Medicines Regulatory Harmonization (SADC-MRH) initiative, and more specifcally, of the ZAZIBONA Collaborative Procedure for Medicines Registration, through which the participating NRAs jointly assess medicinal product dossiers.[153] In the study by Sithole et al, approval times signifcantly varied across the six countries, with a range of 5-30 months.[154]

第三，Sithole等人主要分析了2019年和2020年6个非洲国家(莫桑比克、纳米比亚、南非、坦桑尼亚、赞比亚和津巴布韦)仿制药的审批周期。[152]这些国家是南部非洲发展共同体药品监管协调(SADC-MRH)倡议的成员，更具体地说，是ZAZIBONA药品注册合作程序的成员，成员国的国家监管体系通过该程序联合评估产品卷宗。[153]在Sithole等人的研究中，六个国家的审批周期相差很大，为5-30个月。[154]

6.3 Potential for efficiencies: strategies to accelerate regulatory approval 提高效率的潜力：加快监管审批的战略

Which regulatory reforms contribute to accelerating the introduction of new quality-assured and effective health tools in LMICs? We focus on three major categories:

(i) regulatory harmonization and reliance;

(ii) strengthening regional and national regulatory capacity; and

(iii) regulatory reforms induced by the COVID-19 pandemic.

哪些监管改革有助于中低收入国家加快采用新的、有质量保证和有效的健康工具呢?我们关注以下三个主要方面:

(i)监管协调和信赖;

(ii)加强区域和国家监管能力;

(iii) 新冠肺炎疫情引发的监管改革。

REGULATORY HARMONIZATION AND RELIANCE监管协调和信赖

Regulatory harmonization refers to a process in which regulatory authorities align technical requirements for the development and marketing of pharmaceutical products.[155] The harmonization of technical requirements and standards for health product regulation enables work sharing between agencies, including joint reviews of marketing authorization applications, joint inspections of manufacturing sites, and the increased use of reliance in health product regulation. Harmonization has been pursued for many years through international and regional initiatives, and it can also be an important step on the way to regulatory convergence as provided by the ICH standards.
监管协调是指监管机构在药品开发和销售阶段协调技术要求的过程。[155]统一保健产品监管的技术要求和标准能够使各机构之间共享工作成果，包括联合审查销售许可申请、联合检查生产场所，以及在保健产品监管中更多地使用监管信赖。监管协调已通过国际和区域倡议实现了多年，它也可以成为ICH标准打造的监管趋同道路上的重要一步。

In the past decade, subregional regulatory initiatives, which are linked to regional economic communities (RECs), contributed to regulatory harmonization. In 2009, the African Medicines Regulatory Harmonization (AMRH) initiative under the leadership of the AUDA-NEPAD (African Union Development Agency-NEPAD) was launched to encourage harmonization of regulatory requirements, strengthen regulatory capacity, and accelerate access to medicines. AMRH is a platform to support health product regulation in RECs, and evidence indicates that it has contributed to faster product registration. Sithole and colleagues showed that ZAZIBONA members were able to shorten approval times because they relied on reference agencies and used verification and abridged review models for the assessment of applications for registration rather than full reviews.[152] An earlier study found that the ZAZIBONA initiative was able to reduce the median timeline from dossier submissions to national market authorization to less than one year.[156] Other studies found that the AMRH helped to shorten registration timelines from 2-7 years to less than one year in the East African Community (EAC).[157,158] PATH also conducted a modeling study to estimate the potential health impact of regulatory harmonization in selected EAC and SADC countries.[159] The model estimated that launching two medicines two years earlier through harmonization—heat-stable carbetocin for postpartum hemorrhage and amoxicillin dispersible tablets for childhood pneumonia—could save about 23,000 lives compared to a non-harmonized scenario.
在过去十年中，与区域经济共同体相联系的次区域监管倡议促进了监管协调的发展。2009年，非洲联盟开发署（ZAZIBONA）领导启动了非洲药品监管协调(AMRH)倡议，鼓励统一监管要求，提高监管能力，加快药品获取。AMRH是一个支持区域经济共同体保健产品监管的平台，证据表明，它有助于加快产品注册流程。Sithole及其同事的研究还表明，ZAZIBONA成员国能够缩短药品获批时间，因为他们依靠推荐审理部门，并

使用核查和精简审查模式来评估注册申请，而非全面审查。一项更早期的研究发现，ZAZIBONA能够将从提交卷宗到获得国家市场授权的中位时间缩短至不到1年。其他研究表明，AMRH有助于将东非共同体(EAC)国家的药品注册时间从2-7年缩短至不到1年。[157] 适宜卫生科技组织(PATH)还开展了一项模型研究，以估计在选定的EAC国家和SADC国家实行监管协调对健康的潜在影响。结果表明，与监管不协调的情况相比，两年前通过监管协调推出的两种药物，即用于产后出血的热稳定卡贝菌素和用于儿童肺炎的阿莫西林分散片，可以挽救约2.3万人的生命。

These studies show that harmonization and reliance mechanisms, such as the use of reference agencies and joint reviews, can accelerate market authorization by limiting duplicative assessments. Reliance is an emerging trend to make regulatory processes more efficient; it is recommended by WHO[160,161], and is seen as a key concept by the private sector.[162] KIs from both the public and private sectors emphasized the positive experiences of regional harmonization initiatives, such as AMRH. At the same time, they highlighted the untapped potential to deepen harmonization. For example, they emphasized the lack of legislation for reliance in countries that also do not have capacity to fulfill the range of regulatory functions. They mentioned that the implementation of reliance is often done poorly. These KIs thus recommended stronger collaboration between WLAs/tWLAs and NRAs using the concept of reference agencies. In this context, there are also studies that question the continuing importance of the WHO CPP. Sithole et al found that five of the six countries analyzed require the WHO CPP. The authors recommended that countries should review the need for the CPP where there is capacity to conduct full reviews.[152] A study by Rodier et al showed that 16 out of 18 NRAs require CPP approval (the authors also question the need for the CPP in all of these countries).[163] Another challenge highlighted by our KIs is the poor coordination between regulatory agencies and ethics committees, leading to delays for product registration and also for clinical trial approval.

这些研究均表明，监管协调和信赖机制（如使用推荐审理部门和联合审查等），能够限制重复评估，加速市场授权。监管信赖是一种新兴趋势，可以提高监管流程的效率;世卫组织推荐该机制[160,161]，私营部门也将其视为一个关键概念。[162]来自公共和私营部门的主要信息提供者都强调区域监管协调倡议（如AMRH）的积极实践。与此同时，他们还强调释放深度监管协调的潜力。例如，他们和特别指出那些没有能力履行各种监管职能的国家，也缺乏监管信赖立法。他们还提到，监管信赖的实施往往较差。因此，这些主要信息提供者都建议使用推荐审理部门这一概念，加强WLAs/tWLAs与国家监管体系之间的合作。在此背景下，也有研究质疑持续使用世卫组织药品证书的重要性。Sithole等人发现，他们所分析的6个国家中有5个需要世卫组织药品证书。文章作者建议有能力进行全面审查的国家评估世卫组织药品证书的必要性。[152]Rodier等人所研究的18个国家监管体系中也有16个需要世卫组织药品证书批准(该文章作者还质疑是否所有这些国家都需要一张药品证书)。[163]我们的主要信息提供者所强调的另一个挑战是监管机构和伦理委员会之间协调不力，迫使产品注册和临床试验批准延迟。

Overall, while there are still substantial gaps and barriers to rapid and effective regulation in LMICs, especially in SSA, the evidence indicates that African harmonization initiatives have contributed to regulatory efficiencies. Similar harmonization initiatives have emerged across other regions, such as the Pan American Network for Drug Regulatory Harmonisation and the South-East Asia Regulatory Network.[164] These provide important entry points to further deepen regulatory harmonization and reliance.

总体而言，尽管中低收入国家，特别是撒哈拉以南非洲国家，在快速有效监管方面仍存在巨大差距和障碍，但证据表明，非洲的监管协调组织有助于提高监管效率。其他区域也出现了类似的组织，例如泛美药品监管协调网络和东南亚监管网络[164]这些组织为进一步深化监管协调和监管信赖提供了重要的切入点。

STRENGTHENING REGIONAL AND NATIONAL REGULATORY CAPACITY提高区域和国家监管能力

While harmonization and reliance mechanisms appear to be successful strategies to bring efficiencies to regulatory processes, NRAs need further strengthening. LMICs need to fund their own NRAs and use the GBT process, which offers an important opportunity to measure and strengthen regulatory capacity.

However, creating this capacity takes time and resources. For example, it took Nigeria four years to reach GBT maturity level 3 for medicines and vaccines (importation only, without production). Countries like Bangladesh and Rwanda, which underwent their frst GBT assessments in 2016 and 2018, respectively, have still not achieved maturity level 3. Going forward, it will be important that WLAs and tWLAs from HICs provide more support to NRAs in LMICs. In Africa, countries with NRAs operating at ML3 should also collaborate with other countries. For example, Tanzania, which has an ML3 NRA, supports Rwanda's NRA.[165] Regional initiatives, such as the AMA, require more support from donors to ensure that the agency can effectively perform core regulatory functions. KIs emphasized that the AMA needs to play a key future role for the continent, including to allow for better access to complex drug therapies.

KIs argued that there are at least four major challenges that need to be addressed. First, there is a lack of expertise and human resources in the regulatory system. Second, NRAs may engage in too many unnecessary activities, e.g., the testing of a huge number of batches. Third, there is a challenge to enforcement – the interests of the wider government may confict with the work of the NRA, undermining efforts that are needed to ensure safety and quality. It is a GBT requirement that NRAs can function independently. Fourth, another issue that is not fully under the control of the NRA relates to pharmacovigilance – the required post-introduction data need to come from the health system (hospitals, primary health care centers, etc.) and underreporting can affect a country's regulatory performance as measured by the GBT. This data collection is not entirely outside the control of NRAs—they can work with other health system actors to improve reporting and they can mandate market authorization holders to collect and report evidence. Nevertheless, the collection of sufficient quality data also relies on the ability of the wider health system.

虽然监管协调和信赖机制似乎是提高监管流程效率的成功战略，国家监管体系能力也需要进一步提升。中低收入国家需要为自己的国家监管体系提供资金支持并使用GBT评估，这是一个衡量和加强监管能力的重要契机。

然而，打造这种能力也需要时间和资源。例如，尼日利亚就用了四年时间才达到药品和疫苗的GBT成熟度3级(仅进口，不生产)。孟加拉国和卢旺达等国分别在2016年和2018年进行了首次GBT评估，但仍未达到成熟度3级。展望未来，重要的是来自高收入国家的WLA和tWLA应当为中低收入国家的国家监管体系提供更多支持。在非洲，拥有3级成熟度国家监管体系的国家也应与其他国家合作。例如，坦桑尼亚的国家监管体系成熟度为3级，就可以支持卢旺达的国家监管体系。[165].区域协调组织，如AMA，需要赞助方提供更多支持，以确保该机构能够有效地履行核心监管职能。他强调，在未来，AMA需要在非洲大陆发挥关键作用，包括使复杂的药物治疗更易为人们所获。

主要信息提供者认为至少还有四个核心挑战需要解决。第一，监管体系缺乏专业知识和人力资源。第二，国家监管体系可能开展了太多不必要的审查活动，例如，对大量批次进行测试。第三，执法方面存在挑战，更大范围政府的利益可能与国家监管体系的工作发生冲突，削弱了其为确保药品安全和质量所做出的努力。国家监管体系能够独立运作是GBT的要求。第四，另一个不完全受国家药品监管机构控制的问题与药物警戒有关。药品投入使用所需的数据需要来自卫生系统(医院初级卫生保健中心等)，漏报可能影响一个国家按GBT衡量的监管效能。这种数据收集并非完全不受国家监管体系的控制它们可以与其他卫生系统行为主体合作，优化汇报，并可以要求市场授权持有人收集和报告证据。然而，收集足够的高质量数据也依赖于更广泛的卫生系统的能力。

LMICs need to invest more in their NRAs and use their Global Benchmarking Tool (GBT) to measure and strengthen their regulatory capacity.

中低收入国家需要加大对其国家监管体系的投资，并使用其全球基准工具(GBT)来衡量和提升其监管能力。

The literature also highlights the need to strengthen regional and national regulatory capacity. As pointed out by Greenhoe and Guzman, there is a specifc need to build regulatory capacity in those countries that aim to establish vaccine manufacturing capacity: “Of the 14 African countries where manufacturing projects have been announced, only two—Egypt and South Africa—have NRAs operating at ML3 for producing vaccines.”[111] In vaccine manufacturing countries, strong NRAs will be needed to assure product quality and efficacy.[166] NRAs at ML3 or 4 are needed to qualify for WHO prequalifcation, and many countries legally require WHO PQ before the introduction of new vaccines. UNICEF, as the procurement agent for Gavi, also requires WHO PQ, as does the Global Fund. The WHO PQ process was introduced to support the Expanded Program on Immunization, i.e., at a time when regulatory systems were very weak across most LMICs. To a certain extent, this has changed. Today, there are more SRAs and, since the introduction of the GBT, about 10 countries have achieved ML3. While the WHO PQ system is currently still needed, there should be more fexibilities. Countries and global procurement agencies (e.g., UNICEF) should increasingly accept reviews from SRAs as an alternative to WHO PQ, which itself can be complicated and lengthy. Any initiative that aims to increase vaccine manufacturing capacity in LMICs should include a strategy for the strengthening of regulatory capacity through technical and fnancial assistance. Vaccine production plans need to go hand in hand with NRA strengthening. For example, Rwanda aims to produce mRNA vaccines in the near future, but it is still at ML2 and does not qualify for WHO PQ. However, Rwanda is currently also bolstering its NRA and may become a good example of developing both capacities together.

这些文献还强调了加强区域和国家监管能力的必要性。正如Greenhoe和Guzman所指出的，在那些旨在建立疫苗生产能力的国家，特别需要建立监管能力：“在宣布了生产项目的14个非洲国家中，只有埃及和南非两个国家的国家监管体系在生产疫苗方面享有成熟度3级。疫苗生产国需要强有力的国家监管体系来确保药品质量和药效。只有达到成熟度3级或4级的国家监管体系才能获得世卫组织预认证，许多国家在法律上要求在开发新疫苗之前开展世卫组织的预认证。联合国儿童基金会作为全球疫苗和免疫联盟的采购代理，也需要世卫组织的预认证，Global Fund也是如此。世卫组织预认证流程是为了支持扩大免疫规划而使用的，即大多数中低收入国家监管体系非常薄弱的时候。在某种程度上，这种情况已经改变。如今，严格监管机构的数量增加，自使用GBT以来，约有10个国家的国家监管体系达到了成熟度3级。虽然目前全球仍然需要世卫组织预认证，但本报告认为应有更多的灵活选择。各国和全球采购机构(例如，联合国儿童基金会)可以更多地接受严格监管机构的审查，以替代世卫组织预认证流程，后者可能非常复杂和冗长。任何旨在提高中低收入国家疫苗生产能力的倡议都应包括一项通过技术和财政援助加强监管能力的战略。疫苗生产计划需要与提升国家监管体系能力齐头并进。例如，卢旺达的目标是在不久的将来生产信使RNA疫苗，但该国国家监管体系仍处于成熟度2级阶段，不满足世卫组织的预认证要求。然而，卢旺达目前也在增强其国家监管体系的能力，并可能成为同时增强国家监管体系并获得世卫组织预认证的一个很好的例证。

DIAGNOSTICS诊断

LMICs, and particularly LICs, are less likely to have functional regulatory systems for medical devices, the category under which pathology and laboratory medicine diagnostics and diagnostic imaging devices fall. This impedes the ability of LMICs to conduct pre-market evaluation, ensure quality and safety, and perform post-marketing controls. In addition, diagnostics have their own unique approvals process, which can be complex. For example, the European Union Medical Device Regulation led to a backlog of medical devices that required approval.[167] Some regulatory bodies lack capacity (WHO PQ), while others do not cover diagnostics (EMA). There is also no organization working to convene and synergize efforts around diagnostics regulation globally. At the regional level, the African Medical Device Forum brings together experts in collaboration with Africa CDC to address the issue. Like vaccines and therapeutics, diagnostics also need common, cloud-based platforms for sharing master files and data.
中低收入国家，特别是低收入国家，在监管医疗器械方面不太可能有功能完善的监管体系，而医疗器械涵盖病理、实验室医学诊断和诊断成像设备等范畴。这阻碍了中低收入国家进行上市前评估、确保质量和安全以及实施上市后监管的能力。此外，诊断有自己独特的审批流程，可能很复杂。例如，《欧洲联盟医疗器械条例》会使需要审批的医疗器械积压。一些监管机构缺乏能力(WHO PQ)，而另一些监管机构(EMA)则不负责诊断审批。目前也没有任何一个组织致力于召集和协同力量完善全球诊断法规。在区域层面，非洲医疗器械论坛汇集了许多专家，与非洲疾病预防控制中心合作解决这一问题。与疫苗和治疗方法一样，诊断也需要基于云技术的通用平台来共享主文件和数据。

LESSONS FROM COVID-19 COVID-19给我们的启示

The COVID-19 pandemic led to the introduction of a range of regulatory agilities that aimed to accelerate development and authorization of COVID-19 control tools. For example, measures adopted by the EMA for the development, authorization, and monitoring of COVID-19 treatments and vaccines included:
新冠肺炎疫情中，我们采用了一系列监管措施，旨在加快控制疫情所需工具的开发和授权。例如，EMA针对新冠肺炎治疗及其疫苗开发、授权和监测采取的措施包括:

- **Rapid scientifc advice and review**: review time was reduced from 40-70 days to 20 days.

  快速的科学建议和审查:审查时间从40-70天减少到20天。
- **Rolling reviews**: an ad hoc process for continuous assessment of data for highly promising products.

  滚动审查:指持续评估极有前景的产品的数据的特别过程。
- **Accelerated marketing authorization and temporary exemptions** to expedite access to COVID-19 products.

  加快上市许可和临时豁免，加快获取COVID-19产品。
- **PRIority MEdicines scheme (PRIME)**, which was used to enhance R&D for COVID-19 treatments and vaccines.

  实施优先药品计划(PRIME)，用于加强COVID-19的治疗和疫苗研发。
- **Remote source data verifcation** for monitoring of trials.

  实现用于试验监测的远程源数据验证。

The COVID-19 pandemic also increased regional harmonization. For example, the African Union (AU) launched the African Union-Smart Safety Surveillance (AU-3S).[168] African NRAs used the AU-3S to quickly implement or enhance ongoing safety surveillance protocols and activities for COVID-19 vaccines. Chong et al reviewed progress in regulatory convergence in the Asia-Pacific region during COVID-19 across four areas of best practice.[169] As described further below (see Section 7.3.2), their study concluded that convergence efforts accelerated medical product availability. Geraci et al provide an industry perspective: “Standard regulatory frameworks during normal times can be enhanced by leveraging digitalization, further simplifying and harmonizing requirements, and using reliance mechanisms which can help to increase efficiency in regulatory decision-making regarding medicinal products.” KIs interviewed for this study argued that many of the regulatory innovations triggered by COVID-19 are no longer in use and that it would be valuable to assess which ones should be retained. The African Vaccine Regulatory Forum (AVAREF), for example, was used for accelerated authorization of vaccines by Africa countries following the WHO Emergency Use Listing Procedure. This platform is still in place and run by WHO AFRO. It is very likely that digitalization is one of the advances that should become routine worldwide.

新冠肺炎疫情也加强了区域协调。例如，非洲联盟(AU)启动了非洲联盟智能安全监视系统(AU-3S)。[168]非洲国家国家监管体系利用AU-3S快速实施或加强正在进行的COVID-19疫苗安全监测方案和活动。Chong等人回顾了新冠肺炎疫情期间亚太地区在四个最佳实践领域监管趋同方面取得的进展，下文将进一步说明(见第7.3.2节)，结论表明，监管趋同加速了医疗产品的供应。Geraci等人则提供了一个行业视角:“要加强正常时期的标准监管框架，可通过数字化、进一步简化和协调要求以及使用有助于提高药品监管决策效率的依赖机制等方法。”接受本研究采访的主要信息提供者认为，部分由新冠肺炎疫情带来的许多监管创新举措已不再使用，而评估哪些举措应该保留将十分有价值。例如，非洲疫苗监管论坛(AVAREF)可以加速非洲国家按照世卫组织紧急使用清单程序批准疫苗。该平台仍然存在，并由世卫组织非洲办事处(WHO AFRO)管理。数字化很有可能成为世界范围内的常规进步之一。

6.4 Summary and suggested ecosystem changes总结和生态系统变革建议

Strong regulatory systems are key to accelerating the introduction of new health tools in LMICs, and they are also a critical determinant to successfully expanding regional manufacturing capabilities. In this section, we have shown that approval times in LMICs can be significantly reduced through regional harmonization and reliance mechanisms. If these strategies were to be applied more rigorously, market authorization of—and thus access to—new health tools could happen on a similar timeline as in HICs. We suggest three broad ecosystem changes:
强有力的监管体系是在中低收入国家加速采用新健康工具的关键，也是成功扩大区域生产能力的关键决定因素。在本节中，我们已经阐明，区域协调和信赖机制大大缩短了中低收入国家的审批用时。如果这些战略得到更严格的应用，新健康工具的市场授权与获取可能会和高收入国家审批用时相近。我们建议对生态系统进行以下三方面的变革:

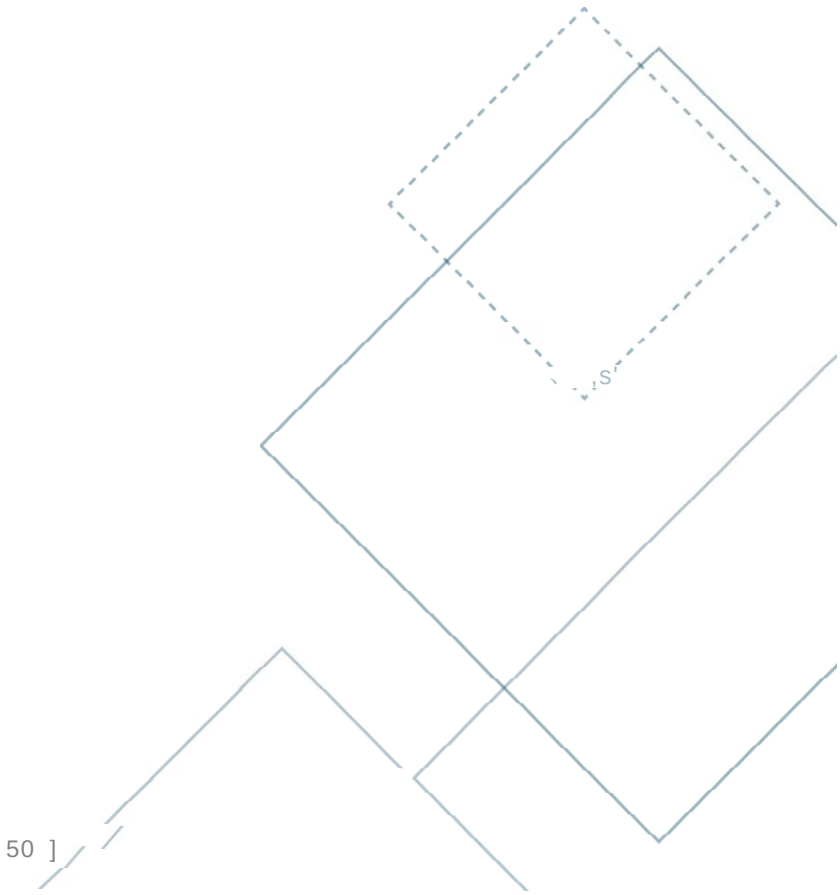
1. Harmonization and reliance. Existing evidence indicates that regulatory harmonization and reliance are key means to achieve regulatory efficiencies. Some African RECs have made great progress in this regard and other initiatives should learn from their examples. Rather than duplicating existing reviews, reliance mechanisms, such as the use of reference agencies, should be expanded and become standard operating procedure – for both NRAs and WHO PQ. CPP continues to be highly important for many countries, as, for example, shown by Rodier etal (in their study, 16 out of 18 NRAs require CPP approval).
促进监管协调和信赖。现有证据表明，监管协调和信赖是确保监管效率的关键手段。一些非洲区域经济共同体在这方面取得了较大进展，其他组织应向它们学习。与其重复现有的审查，不如扩大诸如使用推荐审理部门之类的监管信赖机制，并使之成为国家监管体系和世卫组织预认证的标准操作程序。药品证书对许多国家仍然非常重要，例如，Rodier等人的研究表明，18个国家监管体系中有16个需要药品证书批准)。

2. Strengthening regulatory capacity in LMICs. While regional harmonization and reliance are important, regulatory capacity in LMICs needs to be strengthened. Global health donors should provide support to regulatory hubs, such as AMA, which can serve as WLAs/tWLAs and promote cooperation and mutual recognition of regulatory decisions. WLAs/tWLAs should partner with LMIC counterparts to conduct joint inspections, twinned regulatory reviews, and other capacity-building activities.

提升中低收入国家的监管能力。虽然区域监管协调和信赖很重要，中低收入国家的监管能力更需要加强。全球卫生捐助方应向AMA等监管中心提供支持，这些中心可作为WLAs/tWLAs，推动监管决定的合作与互认。WLAs/tWLAs应与中低收入国家的同行合作，开展联合检查、联合监管审查和其他能力建设活动。

3. Strengthening NRAs is also important for countries that are currently building manufacturing capacity. As highlighted by Greenhoe and Guzman, WHO PQ is the only regulatory pathway for Gavi support through AVMA.[111] However, vaccine manufacturers can only apply to WHO PQ if the country of the manufacturer has a regulatory authority that has reached at least ML3. Going forward, it will be critical, say the authors, to establish "alternative, viable regulatory pathways." These alternatives may include WHO-listed authorities or capacities within regional or sub-regional mechanisms, such as AMA. Currently, some of these mechanisms lack sufficient regulatory capacity, so it will be important to strengthen them and to recognize them as future regulatory pathways. Gavi should be open to alternative regulatory pathways, such as formal collaborations between African NRAs and WLAs/tWLAs. Such pairing arrangements could address the short-term capacity issues and contribute to the capacity building of selected African NRAs. An example of such a strategy is a European Commission-funded project that supports Rwanda's FDA.[170]

增强国家监管体系能力对目前正在建设制造能力的国家也很重要。正如Greenhoe和Guzman所强调的，世卫组织预认证是通过AVMA支持Gavi的唯一监管途径。[111]然而，疫苗制造商只有在其所在国家的监管机构达到至成熟度3级时，才能申请世卫组织预认证。文章作者认为，展望未来，建立"可替代的、可行的监管路径"举足轻重的。这些替代办法可能包括WLA或区域或次区域机制内的能力，如AMA。目前，其中一些机制监管能力不足。因此，加强这些机制并将其视为未来的监管路径将非常重要。全球疫苗免疫联盟应该对其他监管路径持开放态度，例如非洲国家监管体系与WLAs/tWLAs之间的正式合作。这种组合安排可以解决短期能力问题，并有助于某些非洲国家自治机构的能力建设。这种战略的例子之一是欧洲委员会资助的一个项目，该项目为卢旺达食品药品监督管理局提供支持。[170]



7

FINANCING AND GOVERNANCE融资和治理

FINANCING AND GOVERNANCE融资和治理

KEY BENEFITS:主要优势：

Financing innovations have played an important role in supporting R&D. Financial instruments, such as priority review vouchers (PRVs) and volume guarantees, have played an important market shaping role for neglected disease R&D and access to new health tools.

融资创新在支持研发方面发挥了重要作用。优先审查凭证(PRVs)和数量担保等金融工具在被忽视疾病的研发和获得新健康工具方面深刻塑造着市场。

Regional governance mechanisms are becoming increasingly important. While the COVID-19 pandemic showed that the world's response was too centralized, it also led to the emergence and strengthening of regional R&D governance initiatives.

区域治理机制日益重要。新冠肺炎疫情暴露出全球应对措施过于集中的问题，也促使区域研发治理倡议的出现和加强。

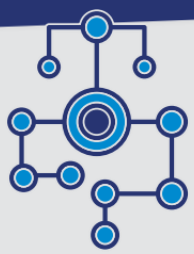
KEY CHALLENGES TO BE ADDRESSED:尚未解决的核心挑战：

There is too little funding for R&D for NDs, EIDs, and MH. R&D funding for NDs peaked at US$4.6 billion in 2018 but has been on a downward trend since then (to US$3.9 billion in 2022). Funding for EIDs R&D has substantially increased, but the increase was mostly due to the COVID-19 pandemic. While funding for SRH R&Dgrew from 2018 to 2021 (totaling US$593 million[7] in 2021), only a small share of this funding was for MH tools and the share declined over time. Funding from industry only accounts for a small share of funding for R&D for NDs, EIDs, and MH, and while there has been a recent increase in domestic LMIC funding for such R&D, the absolute amount remains very small.

用于NDs, EIDs, and MH的研发资金远远不足。被忽视疾病所获得的研发资金在2018年达到46亿美元的峰值，但此后一直呈下降趋势(2022年降至39亿美元)。新发传染病的研发资金则大幅增加，但主要是因为新冠肺炎疫情。虽然用于性健康和生殖健康的研发资金自2018年至2021年有所增长(2021年总计5.93亿美元)，但这些资金中只有一小部分用于孕产妇保健产品，且这一比例随着时间的推移而下降。行业内捐助的资金只占NDs, EIDs, and MH研发资金的一小部分。尽管最近中低收入国家国内对此类研发的资金有所增加，但绝对额度仍然很小。

The 100 days mission is under-funded. Despite the substantial benefits of health innovations, there remain substantial funding gaps for NDs, EIDs, and MH. This gap became apparent in CEPI's 2022 replenishment. Even after the worst pandemic in a century, donors did not provide the US$3.5 billion requested by CEPI for its "100 days mission".

“百日使命”倡议资金不足。尽管卫生创新带来了巨大的好处，但NDs, EIDs, 和MH仍存在巨大的资金缺口。这一缺口在防疫创新联盟(CEPI) 2022年的增资中表现得很明显。即使一个世纪以来最严重的大流行结束之后，捐助者也没有提供CEPI要求的35亿美元，用于其“百日使命”倡议。



SUGGESTED ECOSYSTEM CHANGES: 生态系统变革建议：

Financing 融资

- **A priority review voucher (PRV) should be created in Europe, hosted by the European Medicines Agency**. An EU voucher would provide an additional incentive of US$100million-US$200 million, which investors say would be a meaningful stimulus.
  在欧洲创建优先审查凭证(PRV)，由欧洲药品管理局主管。该审查凭证将提供1至2亿美元的额外激励，投资者认为这十分有意义。

- **Volume guarantees should remain a key mechanism to promote access to new health tools**. There needs to be new thinking on how to best expand the use of these guarantees while managing associated risks (overreliance on such guarantees can create a moral hazard).
  数量担保仍应是促进获得新的健康工具的关键机制。对于如何最好地扩大这些担保的使用，同时管理相关风险(过度依赖此类担保可能会产生道德风险)，我们需要作出新的思考。

Rather than only targeting individual research projects, such as clinical trials, R&D funders also need to invest in the underlying research system. A system-wide approach would include investments in clinical trial infrastructure, capacities for drug discovery and preclinical research, and local manufacturing.
研发资助者不应该只针对个别研究项目，如临床试验开展投资，还需要投资于基础研究系统。全系统方法将包括对临床试验基础设施、药物发现和临床前研究能力以及当地生产的投资。

LMIC governments need to increase their own funding for health R&D. This will be important to advance product development for NDs, EIDs, and MH.

中低收入国家政府需要增加自己的卫生研发资金。这对于推进NDs、EIDs和MH的产品开发非常重要。

通过加强区域优先事项设置，并为临床试验、监管系统和产品制造创建区域和次区域中心，将改善总体研发生态系统。治疗方面的协调差距尤其大。

Governance/priority setting:

The overarching R&D ecosystem would be improved by stronger regional priority

7.1 Trends in R&D financing for NDs, EIDs, and MH and the respective pipelines被忽视疾病、新发传染病和孕产妇保健的研发融资趋势以及各自的研发管线

In this section, we analyze funding trends for product development for NDs, EIDs, and MH and review the candidate products that are in the pipeline, using data from Policy Cures Research.
本节我们将分析针对NDs, EIDs和MH的产品开发融资趋势，并使用政策治疗研究所的数据回顾正在研发中的候选产品。

NDs: R&D FUNDING AND PIPELINE被忽视疾病：研发融资和研发管线

Funding

融资

Annual funding for PRND R&D increased from US$3.7 billion in 2013 to US$4.6 billion in 2018, then fell to US$4.4 billion in 2021 (Figure 3).[171] In 2022, funding dropped by another 10% compared to the previous year, down to US$3.9 billion, the lowest level since 2016. However, this large fall is accounted in part by global infation eroding the real value of R&Dfunding.[172]

PRND研发的年度资金从2013年的37亿美元增加到2018年的46亿美元，2021年下降到44亿美元(图3)。[171]2022年，资金比上一年又减少了10%，降至39亿美元，为2016年以来的最低水平。然而，这种大幅下降的部分原因是全球通货膨胀侵蚀了研发资金的实际价值。

Funding for HIV R&D accounted for 34.4% of this funding, totaling US$1.6 billion in 2022. TB and malaria accounted for 17.9% and 15.4%, respectively, which means that HIV, TB, and malaria received more than two-thirds (67.6%) of R&D funding for NDs in 2022.

用于HIV研发的资金占总额的34.4%，2022年总计16亿美元。结核病和疟疾分别占17.9%和15.4%，这意味着艾滋病毒、结核病和疟疾在2022年获得了新药研发经费的三分之二以上(67.6%)。

Between 2007 and 2022, two-thirds (66.5%) of R&D funding for NDs came from public sources; the US National Institutes of Health was the largest public funder (46.2% of all funding). While the data, which are collected through an annual survey, may underestimate funding from LMIC sources, there is very little investment in R&D on NDs by LMICs. Philanthropy accounted for 20.6% of all funding between 2007 and 2022, with most of the philanthropic funding coming from the Bill & Melinda Gates Foundation (18.0% of all funding). Industry only accounted for 12.9% of all funding (Figure 3).
2007年至2022年间，三分之二(66.5%)的被忽视疾病研发资金为公共资助;美国国立卫生研究院是最大的公共资助者(资助额占总资金的46.2%)。虽然通过年度调查收集的数据可能低估了中低收入国家

的资金资助，但中低收入国家在被忽视疾病研发方面的投资的确很少。2007年至2022年间，慈善事业资助占总资金的20.6%，其中大部分慈善资金来自比尔及梅林达·盖茨基金会(占总资金的18.0%)。行业内资助只占总资金的12.9%(图3)。

In summary, funding for R&D on NDs:总而言之，针对被忽视疾病的研发资金：

(i) has declined since 2018 and further dropped in 2022,

自2018年以来有所下跌，2022年进一步下跌，

(ii) remains heavily focused on HIV, TB, and malaria,

主要用于艾滋病病毒、结核病和疟疾，

(iii) relies on a few public and philanthropic donors,

依赖于极小部分的公共和慈善资助，

(iv) receives limited funding from industry, and

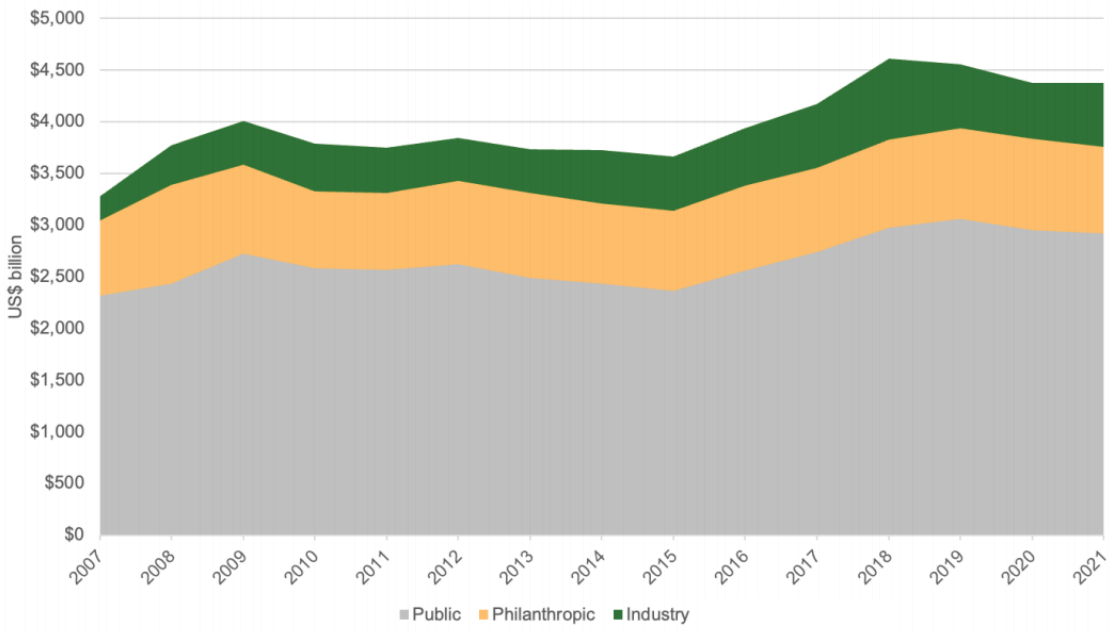
接收到的行业内资助有限，且

(v) involves very low levels of investment from LMICs.

中低收入国家投资水平极低。

Figure 3. Funding for R&D on NDs by funder type

图3。
按资助方类型划分的
被忽视疾病的研发资金来源



Pipeline

管线

New cutting-edge solutions are on the horizon. According to Policy Cures Research, the innovation pipeline to tackle neglected diseases has grown by 27% since 2019.[8] Two malaria vaccines were launched in 2021 and in 2023.Three TB vaccines candidates have now entered late-stage trials: (i) M72, a fusion protein of two M. tuberculosis antigens administered with a potent adjuvant; (ii) VPM 1002, a next-generation, genetically modifed BCG vaccine, and (iii) MTBVAC, an M. tuberculosis strain attenuated via two genetic mutations. Still, many key products are missing and the pipeline is totally empty for others. For example, the pipeline lacks preclinical and clinical vaccine candidates for cryptosporidiosis, multiple helminth infection, sleeping sickness, and strongyloidiasis as well as drug candidates for hookworm, lymphatic flariasis, multiple Salmonella infections, non-typhoidalS. enterica, scabies, strongyloidiasis, and tapeworm.

新的尖端解决方案即将问世。根据政策治疗研究所的数据，自2019年以来，应对被忽视疾病的创新管线增长了27%。[8] 2021年和2023年研制出了两种疟疾疫苗。三种结核候选疫苗现已进入后期试验阶段:(i) M72，两种结核分枝杆菌抗原的融合蛋白与免疫佐剂一起注入体内，进行免疫增强;(ii) VPM 1002，下一代转基因卡介苗以及(iii) MTBVAC，一种通过两种基因突变减毒的结核分枝杆菌菌株。尽管如此，许多关键产品仍然缺失，其他产品的供应管线也完全空白。例如，该管线缺乏用于隐孢子虫病、多发性蠕虫感染、昏睡病和圆线虫病的临床前和临床候选疫苗，以及用于钩虫、淋巴丝虫病、多发性沙门氏菌感染、非伤寒肠链球菌、疥疮、圆线虫病和绦虫的候选药物。

EIDs: R&D FUNDING AD PIPELINE新发传染病：研发融资和研发管线

In 2019, R&Dfunders provided US$1.5 billion for R&D on EIDs. Due to the COVID-19 pandemic, funding for R&D on EIDs increased substantially to US$7.6 billion and US$7.7 billion in 2020 and 2021, respectively. In 2022, funding dropped to US$5.8 billion. **These trends highlight four challenges**.

2019年，资助者为新发传染病的研发捐赠了15亿美元。由于新冠肺炎疫情，新发传染病的研发资金大幅增加，分别在2020年和2021年达到76亿美元和77亿美元。2022年，该资金减少至58亿美元。这些趋势突出了四大挑战。

1. First, funding for COVID-19 R&D drove the increase in EID R&D funding. Of the US$21.1 billion for EID R&D, 81% (US$17.0 billion) was for coronaviral diseases, and R&D for many other EIDs remains under-funded.[173]

   第一，新冠肺炎研发资金带动了新发传染病研发资金的增加。在用于新发传染病研发的211亿美元中，81%(170亿美元)用于冠状病毒疾病，而许多其他新发传染病的研发资金仍然不足。

2. Second, funding for vaccines is about twice as high as funding for diagnostics and therapeutics (US$2.7 billion for vaccines vs. US$1.4 billion for diagnostics and therapeutics in 2022).

第二，用于疫苗的资金大约是用于诊断和治疗的资金的两倍(2022年用于疫苗的资金为27亿美元，用于诊断和治疗的资金为14亿美元)。

3. Third, EID funding is highly reactive. The world has not yet adopted a preparedness approach and the drop in funding in 2022 maybe considered as a good proxy that we are already in a phase of neglect.

第三，新发传染病资金的反应性很强。全世界尚未采取备灾方法。2022年的资金下降可能被认为是一个很好的标志，这表明我们已经处于忽视阶段。

4. Fourth, funding is overly reliant on the US government, with 66.5% of all EID R&Dfunding in 2022 coming from US agencies. This lack of diversify puts sustainable funding at risk.

第四，资金过度依赖美国政府。2022年新发传染病研发总资金的66.5%来自美国机构。资金来源多样性不足使可持续融资面临风险。

Only COVID-19 and Ebola (the Zaire and ebolavirus species) have a full set of approved drugs, vaccines, and diagnostics, and these are not available to patients in all countries who need them. Diagnostics are only approved for Crimean-Congo haemorrhagic fever, Rift Valley Fever, Lassa and Zika, none of which have been approved in endemic countries. Other priority pathogens have no approved MCMs at all.[174,175] When it comes to candidates that have reached the clinical trial phase, the reactive nature of R&D means that pathogens that have caused recent outbreaks (and are thus perceived as a greater threat) have a more mature pipeline (the pipelines for COVID-19, Ebola, and Zika are mature). However, with the exception of COVID-19, all vaccines and therapeutic candidates are in phase 1. Even the preclinical pipeline is empty for many of the Blueprint diseases, which highlights the need to invest in preclinical research using AI.

只有新冠肺炎和埃博拉病毒(扎伊尔病毒和埃博拉病毒)拥有全套审批通过的药物、疫苗和诊断方法，但并非所有国家的患者都能获得这些药物、疫苗和诊断方法。诊断方法只被批准用于克里米亚-刚果出血热、裂谷热、拉沙和寨卡病毒，这些疾病在其流行国家都没有获得审批。其他重点病原体根本没有获审批的医疗对策（MCMs）。[174,175] 对于已进入临床试验阶段的候选药物，研发的反应性意味着导致最近暴发的病原体(因此被认为是更大的威胁)拥有更成熟的管线(新冠肺炎、埃博拉和寨卡病毒的管道已经成熟)。然而，除新冠肺炎外，所有疫苗和候选治疗方案均处于1期试验阶段。就连许多蓝图疾病的临床前研究渠道都是空白的，这凸显了投资使用人工智能进行临床前研究的必要性。

MATERNAL HEALTH: R&D FUNDING AND PIPELINE 孕产妇保健：研发融资与研发管线

In 2021, total funding for SRH R&D was US$593.7 million.[176] In the same year, R&D funding for sexually transmitted infections, excluding HIV, hepatitis B, and potentially sexually transmissible infections (e.g., hepatitis C andZika virus), totaled $146.3 million. In addition, US$142.5 million was spent on R&D for human papillomavirus (HPV) and HPV-related cancers, US$93.0 million on platform technologies, US$49.9 million on multipurpose prevention technologies, and US$23.6 million on other R&D areas (including core funding).
2021年，用于SRH的科研资金总额为5.937亿美元[176]。同年，不包括艾滋病毒、乙型肝炎和潜在的性传播感染(如丙型肝炎和寨卡病毒)，性传播感染的研发资金总计为1.463亿美元。此外，用于人类乳头瘤病毒(HPV)和HPV相关癌症的研发支出为1.425亿美元，用于平台技术的研发支出为9300万美元，用于多用途预防技术的研发支出为4990万美元，用于其他研发领域的研发支出为2360万美元(包括核心资金)。

Only a small share of R&D funding was allocated to maternal health. R&D funding for preeclampsia and eclampsia (PE&E) totaled US$20.7 million in 2021, though it saw a 25% reduction in funding from 2020 to 2021. Between 2018 and 2021, US$101 million was spent on PE&E, with basic research consistently accounting for about 60% of spending. Funding for postpartum hemorrhage (PPH) has fallen since 2018, with a 56% reduction between 2020 and 2021. The total spending on R&D for PPH between 2018 and 2021 was US$16.0 million, with US$0.9 million spent in 2021. While SRH funding overall has been on the rise, increasing by about 50% since 2018, funding for maternal health R&Dfell by 15% since 2018. This disparity in R&D investment refects a focus on HIC markets, where the burden of maternal health challenges is lower than in LMICs.
只有一小部分研发资金用于孕产妇保健。2021年，用于子痫前期和子痫(PE&E)的研发资金总计2070万美元，但从2020年到2021年，该资金减少了25%。2018年至2021年期间，在PE&E方面的支出为1.01亿美元，基础研究一直占支出的60%左右。自2018年以来，产后出血(PPH)的研发资金有所削减，2020年至2021年期间减少了56%。2018年至2021年，PPH的研发总支出为1600万美元，2021年为90万美元。虽然SRH的总研发资金一直在增加（自2018年以来增加了约50%），但孕产妇保健的研发资金自2018年以来下降了15%。研发资金方面的这种差异反映了对高收入国家市场的重视，这些市场在孕产妇保健方面所面临的挑战负担低于中低收入国家。

The 2022 Access to Medicine Index, which tracks the engagement of the 20 largest pharmaceutical companies, found that “five diseases and conditions are not addressed at all by any R&D project. Conditions related to maternal health are especially underrepresented, with just four projects split between maternal hemorrhage and maternal sepsis.”[177,178]
PPH is the leading cause of maternal deaths. Currently, treatment for this condition requires intravenous or intramuscular administration of oxytocin by a skilled healthcare worker. A new formulation is needed that is both heat stable and can be easily and quickly administered as an alternative. Companies covered by the Access to Medicine Index have no R&D projects to address this need. Another key gap in R&D for maternal health is for diagnostics for preeclampsia. None of the companies covered by the index have projects addressing this gap.[179] A Policy Cures Research report on R&D for SRH confirms that there are substantial gaps for pre-eclampsia, PPH, and sexually transmitted infections particularly hepatitis B, herpes simplex virus type 2, chlamydia, gonorrhea, syphilis, human T-cell lymphotropic virus type 1 (HTLV-1) and HIV/AIDS. There are other major R&D gaps for women’s health that we do not discuss here, including for HPV-related cervical cancer.
2022年药品可及性指数(Access to Medicine Index) 追踪了最大的20家制药公司的参与情况，发现“有五种疾病和病症尚未被任何一个研发项目解决。与孕产妇保健有关的疾病尤其缺乏代表性，只有4个项目分别攻克产妇出血和产妇败血症。”[177,178]。产后出血是产妇死亡的主要原因。目前，治疗这种病症需要由熟练的卫生保健工作者静脉注射或肌肉注射催产素。该催产素需要更换新的配方，这种配方应既具备热稳定性，又可以轻松快速地作为替代品被注射进产妇体内。药品可及性指数上榜公司没有研发项目来满足这一需求。孕产妇保健研发方面的另一个关键差距是子痫前期诊断。该指数所涉及的公司也都没有解决这一差距的研发项目。政策治疗研究所关于SRH研发的报告证实，在子痫前期、产后出血和性传播感染，特别是乙型肝炎、单纯疱疹

病毒2型、衣原体、淋病、梅毒、人类t细胞嗜淋巴病毒1型(HTLV-1)和艾滋病毒/艾滋病方面存在很大差距。在妇女保健方面还有其他我们未在此讨论的较大的研发差距，如HPV相关的子宫颈癌。

R&D FUNDING GAPS 研发融资差距

In previous studies, we tried to estimate funding gaps for R&D on NDs. Using the 2019 PRND R&D pipeline, in 2020 we published a study that suggested that that there was an annual product development funding gap of up to US$2.6 billion.[6] We also estimated that the total annual resource needs for late-stage trials of product candidates for NDs were US$1.72 billion, while only about US$700 million was being spent on Phase 3 trials. As such, we argued that there was an annual funding gap of at least US$1.0 billion specifically for late-stage clinical trials.[180] Our new modeling paper led by Ogbuoji provides an updated R&D funding gap analysis for NDs. It also assesses the R&D funding gap for EIDs and MH.[1] Many reports have identified the need for new for funding for PPR and more specifically for R&D for EIDs in the wake of the COVID-19 pandemic. CEPI called for US$3.5 billion for its "100 days mission," which is part of CEPI's five-year (2022–2026) pandemic plan. While the 100 days mission has been endorsed by the G7, G20, and other governments, the global community failed to provide the requested funding to essentially break the cycle of panic and neglect—the replenishment fell short of the target (only US$1.5 billion was raised at the pledging event).[181,182] From an R&D perspective, CEPI plays a key role for PPR. However, breaking the cycle requires support for other rapid response technologies, including diagnostics. FIND estimates that it needs US$80-100 million for its 100 days mission diagnostics framework. The Pandemic Fund, which will likely not invest in R&D, has also only secured about US$2 billion so far and thus it is falling far short of the ambitious target of US$10.5 billion in international financing per year indicated as the required level by the G20 High-Level Independent Panel.[184,185]

在前人研究中，我们试图估计被忽视疾病的研发资金缺口。依据2019年的PRND研发管线，我们在2020年发表了一项研究，该研究表明每年的药品开发资金缺口高达26亿美元。[6]我们还估计每年用于被忽视疾病候选产品后期试验的总资金需求为17.2亿美元，而用于第三阶段试验的资金仅为7亿美元左右。因此，我们认为专门用于后期临床试验的年度资金缺口至少为10亿美元。[180]由Ogbuoy主持撰写的新模型研究文章为被忽视疾病提供了最新的研发资金差距分析。报告还对新发传染病和孕产妇保健的研发资金缺口进行了评估。[1]许多报告都指出，在新冠肺炎疫情之后，需要为大流行病的准备和应对(PPR)，特别是新发传染病的研发提供新的融资。CEPI呼吁为其"百天使命"筹集35亿美元，这是CEPI五年(2022-2026)大流行计划的一部分。虽然"百天使命"得到了七国集团、二十国集团和其他国家政府的支持，但国际社会未能向其提供所需资金，从根本上打破恐慌和忽视的循环。补充资金也未能达到目标(在认贷活动上仅筹集了15亿美元)。[181182]从研发角度看，CEPI在PPR研发中发挥着关键作用。然而，打破这一循环需要支持其他快速反应技术，包括诊断技术。创新诊断基金会(FIND)估计其"百天使命"诊断框架需要8000万至1亿美元资金支持。大流行病基金很可能不会投资于研发，并且迄今只获得了约20亿美元的资金支持，因此远远达不到二十国集团高级别独立小组提出的每年获得105亿美元国际融资的宏伟目标[184,185]

7.2 Evidence on resource mobilization mechanisms for R&D on NDs, EIDs, and MH
ND、EID和MH研发资源调动机制证据

The large, rapid rise in funding to develop COVID-19 tools showed how quickly HICs can mobilize significant amounts of funding for new health tools when their own populations are affected by global health threats. The pandemic also showed the potential of the global pharmaceutical industry in the development of new tools. Within just 326 days, the first safe and effective vaccines were being rolled out to begin to reduce cases of severe disease and COVID-19 death rates. However, we have not seen a similar level of engagement when it comes to R&D for diseases of poverty. Indeed, as indicated by the Access to Medicine Index, there is limited progress in the NDs pipeline of companies.[178] Most ND candidates get stuck in early R&D stages (preclinical; Phase 1) and do not progress into more advanced clinical stages, which account for the lion's share of the costs (Annex 3). In this section, we discuss mechanisms to mobilize additional funding for ND research.

用于COVID-19工具研发的资金大幅快速增长，表明当本国人口受到全球健康威胁影响时，高收入国家可以迅速为新的健康工具筹集大量资金。这次大流行还彰显了全球制药行业在开发新健康工具方面的潜力。在短短326天内，首批安全有效的疫苗就投入了使用，新冠肺炎重症病例和死亡率开始减少。然而，我们尚未看到贫困所致疾病的研发有类似参与度。事实上，正如药品可及性指数所显示的，各公司在被忽视疾病研发管线的进展有限。[178]大多数被忽视疾病的候选产品都停留在早期研发阶段(临床前;1期试验)，并且不会进入更高级的临床阶段，这占了成本的大部分(附录3)。在本节中，我们讨论了为被忽视疾病研究筹集额外资金的机制。

INCENTIVIZING INDUSTRY ENGAGEMENT: PRIORITY REVIEW VOUCHERS (PRVs) AS AN R&D INCENTIVE

In 2007, the US Congress and the FDA introduced the "Tropical Disease Priority Review Voucher Programme to encourage product development (therapeutics and vaccines) for neglected diseases."[186] Voucher eligibility was expanded to rare pediatric diseases and for MCMs in public health emergencies in 2012 and 2016, respectively. PRVs are a pull incentive to reward developers of a new health product for an eligible neglected or rare disease with a tradeable voucher that grants priority review of a second product candidate. The US voucher entitles the developer to regulatory review in six months rather than the standard ten months. In addition, two drugs receive priority review: the drug winning a voucher for an eligible neglected or rare pediatric disease, and the drug using a voucher for another indication (e.g., a blockbuster drug for the US market). The potential for additional revenue from marketing a blockbuster drug four months sooner is an incentive for companies to develop drugs for neglected diseases. In addition, the developer can sell the voucher—a small company may win a voucher for developing a drug for a neglected disease and sell the voucher to a large company for use on a commercial disease. As such, PRVs can help to incentivize the development of new health tools for neglected diseases, while they may also accelerate the approval of potential blockbuster therapies in the US.

2007年，美国国会和美国食品药品管理局推出了"热带病优先审查凭证计划"，以激励针对被忽视疾病的产品开发(治疗药物和疫苗)[186]。在2012年和2016年，PRVs分别将儿童罕见病和突发公共卫生事件中的医疗对策纳入计划之中。PRV是一种拉动激励，用于奖励计划中被忽视或罕见疾病的新保健产品的研发人员，并给予其可交易的优先审查凭证，以优先审查第二种候选产品。美国的优先审查凭证允许开发商在6个月内接受监管审查，标准审查周期为10个月。此外，两类药物可获得优先审查资格：一类是获得了计划内被忽视疾病或儿科罕见病优先审查凭证的药物，另一类是可使用审查凭证用于另一种适应症的药物(如美国市场的重磅药物)。提前4个月销售重磅药物可能带来额外收入，这将激励公司开发治疗被忽视疾病的药物。此外，开发商可以出售优先审查凭证，如小公司可能会因为研发被忽视疾病的药物而获得优先审查凭证，并将其出售给大公司，用于治疗商业期望值很高的疾病。因此，PRVs可以帮助激励针对被忽视疾病的新健康工具的开发，同时它也可能加速美国审批可能的治疗药物。

自2007年以来，FDA已颁发了60多个优先审查凭证。每张凭证的售价约为1亿美元。

What do we know about the effectiveness of PRVs, as of March 2024? Research on the US voucher program points to four benefits. First, more than 60 vouchers have been awarded since 2007, roughly four per year, which indicates that the prospect of accelerated marketing of a commercially viable product draws industry interest.[186] Second, vouchers were sold for about US$100 million

More than 60 priority

each, showing that the financial incentive is also substantial.[187,188] Third, the US voucher has yielded multiple concrete benefits. It contributed to the development of a drug for river blindness, provided commercial incentives for continuation of a new TB drug, and helped enable patient access to a Chagas drug through the sale of a voucher. Fourth, the accelerated regulatory pathway itself may contribute to faster access to the drug and as such may have a positive public health impact.[189] In addition, there is no evidence from the US voucher program that the accelerated regulatory pathway negatively impacted on the quality of product.

截至2024年3月，我们对PRVs的有效性了解多少呢?相关研究表明，美国优先审查凭证有四个好处。第一，自2007年以来，美国已经以大约每年4张的速度颁发了共60多张优先审查凭证，这表明加快推广对商业期望值很高的药品引起了业界的兴趣。第二，每张优先审查凭证的售价约为1亿美元，可见其金融激励也相当可观。[187,188]第三，优先审查凭证有许多切实好处。它促进了一种治疗河盲症的药物的研发，为继续使用一种新的结核病药物提供了商业激励，并通过出售优先审查凭证帮助患者获得一种治疗南美锥虫病的药物。第四，加速监管路径本身可能促进药物快速研发上市，这将对公共卫生产生积极影响。此外，来自美国优先审查凭证计划的证据表明，加速监管路径不会对产品质量造成负面影响。

Nevertheless, the true incentive effect of the US voucher remains debated. First, a report by the US Government Accountability Office (GAO) from 2020 questioned whether the voucher has rewarded research that would have been conducted anyway even without the voucher. It concluded that existing studies found little effect of the PRV on drug development, but it also reported that "all seven drug sponsors GAO spoke with stated that PRVs were a factor in drug development decisions—six sponsors said they were one of a number of factors, while one sponsor said they were pivotal in its development of a drug."[190,191] Second, the amount that vouchers are selling for (about US$100 million) is less than the overall drug development costs.[192] Some investors thus indicated that US$100 million is no longer sufficient as an incentive – if that is correct, the voucher might be most useful to pull through drugs that have already started development.

然而，美国优先审查凭证的实际激励效果仍存在争议。首先，美国政府问责局(GAO)于2020年的发布了一份报告，质疑优先审查凭证是否激励了那些即便没有优先审查凭证也会开展的研究。报告总结道，现有研究发现PRV对药物研发的影响很小，且"与GAO谈判的7位药品试验委托者都表示PRV是影响药品开发决策的因素之一，6位药品试验委托者表示它只是众多因素之一，而有1位药品试验委托者说它们在药物研发中是重要的。[190, 191]"第二，优先审查凭证的售价(约1亿美元)低于药物研发总成本。[192]因此，一些投资者指出，1亿美元作为奖励已经不够了。如果事实的确如此，那么优先审查凭证可能对已经开始研发的药物最有用。

We agree with David Ridley at Duke University, one of the researchers who proposed the creation of the PRV in 2006, that the PRV should be introduced in Europe, hosted by the European Medicines Agency (EMA).[187,193] An EU voucher would provide an incentive of US$100 to US$200 million, so the combined value of the US and EU vouchers would be in the range of US$200 to US$300 million, which investors say would be a meaningful stimulus. In addition, Ridley and colleagues argue that an EU voucher could cut regulatory times by six months.
我们认同杜克大学David Ridley的观点。Ridley是2006年提出创建PRV的研究人员之一，且他认为欧洲应该引入PRV，由欧洲药品管理局(EMA)主持。[187,193]欧盟优先审查凭证将提供1至2亿美元的激励，所以美国和欧盟优先审查凭证计划总价值将在2至3亿美元之间，投资者认为这一激励十分有意义。Ridley及其同事还认为，欧盟优先审查凭证可以将审查周期缩短6个月。

An EU voucher program should involve the obligation for developers to provide detailed access plans. In addition, the voucher program should have stringent eligibility criteria to ensure that the focus is on NDs and to reward research that would not have been conducted without the stimulus. Finally, the program should be embedded in a larger strategy for stimulating research rather than being a standalone solution. An EU voucher should be integrated with the PRIority MEdicines scheme (PRIME) and the EUM4all programme, a coordinated mechanism between EMA, the WHO, and national regulators, providing a scientifc opinion on high priority human medicines for use outside the EU.
欧盟优先审查凭证计划应明确药品开发商的义务，要求其提供详细使用计划。此外，该计划应该有严格的发放标准，以确保激励重点依然是被忽视疾病，并奖励那些没有资金激励就无法开展的研究。最后，该计划应该被嵌入到一个更大的战略之中，而非是作为独立解决方案来刺激各项研究。欧盟优先审查凭证计划应该与优先药品计划(PRIME)和EUM4all程序整合在一起，形成EMA、世卫组织和国家监管体系之间的协调机制，为欧盟以外使用的高优先级人用药物提供科学建议。

VOLUME GUARANTEES TO INCENTIVIZE MANUFACTURING AND LOWERING PRICES数量担保激励生产，降低价格

In the past, volume guarantees played an important role in creating sufficient incentive to manufacture health products. There are many successful examples of volume guarantees in global health. For vaccines, one example is a volume guarantee in 2012 for the production of the pentavalent vaccine by an Indian producer, which led to substantial cost savings for Gavi.[194] For HIV, a volume guarantee to two manufacturers allowed the transition to a newer combination of HIV therapies in 2016/17 (from tenofovir, lamivudine, and efavirenz [TLE] to tenofovir, lamivudine, and dolutegravir [TLD]). Millions of people had access to this new drug combination due to the price reduction generated by volume guarantees.[195,196,197] For malaria, a four-year volume guarantee for innovative bed nets that combine pyrethroid and chlorfenapyr insecticides led to a reduction in price by two-ffths.[198] More recently, there were also volume guarantees for COVID-19 vaccines and therapeutics.[199]

过去，数量担保创造了足够多的激励，在生产保健品方面发挥了重要作用。在全球卫生领域有许多数量担保的成功例证。就疫苗而言，2012年，一家印度生产商生产的五价疫苗获得了数量担保，为Gavi极大节省了成本。[194]就艾滋病毒而言，向两家制造商提供数量担保能够使其在2016/17年过渡到新的艾滋病毒治疗组合(从替诺福韦、拉米夫定和依非韦伦[TLE]过渡到替诺福韦、拉米夫定和多鲁替韦[TLD])。数量担保使药品价格降低，数百万人能够获得这种新的药物组合。[195 196 197]在疟疾方面，结合了拟除虫菊酯类杀虫剂和杀虫腈杀虫剂的新型蚊帐获得了为期四年的数量担保，使其价格降低了五分之二。最近，也有COVID-19疫苗和治疗药物也获得了数量担保。[199]

Volume guarantees should remain a key mechanism to promote access to new health tools. There needs to be thinking on how to best expand the use of these guarantees while managing associated risks. For example, there is a risk of overreliance on such guarantees and creating a moral hazard.[198]
数量担保仍应是推动获得新健康工具的关键机制。我们需要考虑在管理相关风险的同时如何最大化这些担保的使用。例如过度依赖数量担保可能会面临道德风险。

DOMESTIC FINANCING FOR R&D BY MIDDLE-INCOME COUNTRIES中等收入国家研发的国内融资情况

Domestic funding for R&D on NDs, EIDs, and MH from LMIC governments remains highly limited according to the data from G-FINDER.[173] Many countries will not have the capacity to increase these investments over the short-term. For example, low-income countries accounted for only 0.24% of global health expenditures, despite having 8% of the world's population, according to the WHO's 2023 Global Health Expenditure Report.[200] Middle-income countries face additional challenges, such as slowing economic growth, high infation, and increased debt servicing obligations, as recently highlighted by the latest report of the Lancet Commission on Tuberculosis.[201]
G-FINDER[173]的数据显示，中低收入国家政府对NDs, EIDs, and MH研发的国内融资仍然非常有限。[173]许多国家在短期内没有能力增加这些投资。例如，世卫组织《2023年全球卫生支出报告》指出，低收入国家的人口占世

界人口的8%，但仅使用了全球卫生支出的0.24%。这也与《柳叶刀》结核病委员会最近发布的报告所强调的一致，中等收入国家面临着更多挑战，如经济增长放缓、高通胀和偿债义务增加。

Still, increased domestic investment in R&D platforms, regulatory systems, and manufacturing by middle-income countries is critical to advancing the R&D ecosystem. Existing evidence indicates that these investments pay of. For example, an upcoming study on the vaccine security and self-reliance initiative of the Association of Southeast Asian Nations (ASEAN) fnds that coordinated investments at the regional level could avert up to 61.5 million disability-adjusted life years (DALYs) and 1.9 million deaths in ASEAN by 2040, with economic returns outweighing investments by a factor of 35.[86] This modeling was based on fve NDs and an additional outbreak scenario, simulating an outbreak of a magnitude similar to the COVID-19 pandemic in the 10 ASEAN countries. ASEAN can also serve as an interesting example because the 10 member countries have diferent income levels. Countries with higher income levels can take a leading role in upgrading the existing ecosystem, considering their investments as a contribution to a regional public good.

Coordinated investments at the regional level could avert up to 61.5 million disability-adjusted life years (DALYs) and 1.9 million deaths in ASEAN by 2040, with economic returns outweighing investments by a factor of 35.

中等收入国家增加对研发平台、监管体系和医药制造行业的国内投资对于变革研发生态系统至关重要。现有证据表明，这些投资已经产生了回报。例如，一项即将发布的针对东盟疫苗安全和自力更生倡议的研究发现，到2040年，区域一级的协调投资可避免东盟国家多达6150万的伤残调整生命年(DALYs)和190万人死亡，经济回报比投资高出35倍[86]。该模型基于五种被忽视疾病和一种疫情暴发情景，模拟了在东盟十国暴发与新冠肺炎规模相似的疫情。东盟也是一个有趣的例子，因为其10个成员国的收入水平不同。收入水平较高的国家可以在升级现有生态系统方面发挥主导作用，将其投资视为对区域公共产品的贡献。

到2040年，区域一级的协调投资避免东盟国家多达6150万的伤残调整生命年(DALYs)和190万人死亡，经济回报是投资的35倍。

AFFORDABILITY REQUIREMENTS/IP WAIVERSk可负担性要求/知识产权豁免

In a recent analysis paper in the BMJ, Suleman and colleagues acknowledge the contributions of push and pull mechanisms and pooled funding approaches, but argue that these mechanisms are in themselves insufficient to ensure fair pricing.[202] They argue that governments and other R&Dfunders should insist on binding affordability requirements as a condition of all R&D to ensure fair pricing of medicines.

在最近发表于《英国医学杂志》的一篇分析论文中，Suleman及其同事认可推拉机制和募资方法的贡献，但认为这些机制本身不足以确保公平定价。[202]他们认为，政府和其他研发出资者应该坚持将具有约束力的可负担性要求作为所有研发的一个条件，以确保药品的公平定价。

HOW R&D FUNDING SHOULD FLOW – THE NEED TO INVEST IN FUNDAMENTAL R&D SYSTEMS研发资金应该如何流动——投资基础研发系统的需要

LMIC representatives interviewed for this study emphasized the need to move away from funding individual research projects, such as clinical trials, to invest in the underlying research system. A system-wide approach would include investments in clinical trial infrastructure, capacities for drug discovery and preclinical research, and local manufacturing. LMIC interviewees emphasized that fragmented project-by-project funding has heavy transaction costs and is both unpredictable and unsustainable.

参与这项研究访谈的中低收入国家代表强调，出资者有必要从资助个人研究项目(如临床试验)转向投资于基础研究体系。全系统方法包括投资临床试验基础设施、药物发现和临床前研究能力以及本地生产。低收入和中等收入国家的受访者强调，分散的项目融资交易成本沉重，既不可预测又不可持续。

In addition, ownership of LMICs in research projects is often limited. LMIC representatives highlighted the need to sustainably strengthen the underlying R&D system through the provision of long-term funding, which will enable countries to conduct their own R&D in the future. Indeed, a recent analysis of grant investments by 10 of the world's largest international funders of health research shows signifcantdifferences in resource allocation across countries. Adam and colleagues note that: "In 2020,out of grants totaling US$ 37 billion, low-income countries (LICs) received only 0.2% (US$ 85 million). Lower-middle-income countries (LMICs) and upper-middle-income countries (UMICs) received each 0.5% (US$ 188 million US$ 193 million, respectively).[203]

此外，中低收入国家在研究项目中所肩负的责任往往是有限的。来自中低收入国家的代表强调，我们需要通过提供长期资助来可持续地加强基础研发体系，这将使各国能够在未来开展自己的研发。事实上，世界上最大的10个国际卫生研究资助者最近对赠款投资的分析表明，各国的资源分配存在显著差异。Adam及其同事指出:"2020年的赠款总额为370亿美元，其中，低收入国家仅获得0.2%(8500万美元)，中低收入国家(LMICs)和中高收入国家(UMICs)各获得0.5%(分别为1.88亿美元和1.93亿美元)。[203]

7.3 Governance 治理

7.3.1 Global coordination efforts 全球协调工作

For PPR, the evaluation of the Access to COVID-19 Tools Accelerator (ACT-A) found that the ACT-A agencies working on R&D did not sufficiently coordinate their R&D efforts across and to some extent within the pillars. The evaluation recommended enhanced coordination through three permanent MCM structures for each product type, withdefned leads for diagnostics, therapeutics, and vaccines. In addition, it recommended that a joint platform should be established to coordinate the work across the three product areas. The discussion has been taken forward – led by WHO, there is now discussion on an interim coordination mechanism to enhance collaboration for timely and equitable access to MCMs against pandemic threats.

对PPR，一项对加速抗新冠肺炎手段使用权(ACT-A)的评估发现，从事研发工作的ACT-A机构未能充分协调其跨支柱的研发工作，并在一定程度上在支柱内协调其研发工作。评估建议加强对每种产品类型的三个永久性MCM结构的协调，并对诊断、治疗和疫苗给予明确的指导。此外，它建议建立一个联合平台，以协调三个产品领域的工作。在世卫组织的领导下，讨论取得了进展，目前正在讨论建立一个临时协调机制，以加强合作，及时和公平地获得抗流行病威胁的MCM。

While the ongoing discussion on the interim MCM platform is critical, it does not cover the coordination for other global health R&D needs. As highlighted elsewhere,[180] LMICs must be included in R&D prioritization processes, including

prioritization across product types and diseases/conditions. Our KIs indicated that TPPs and PPCs are useful, but these are often outdated. In addition, evidence indicates that the actual candidates in the pipeline do not align sufficiently with the TPPs. This mismatch also highlights the need for better health R&D data sharing, particularly on R&D investments and capacity, to enable better coordination and informed decisions. The Global Observatory on Health R&D may be able to support this effort by serving as a platform to track and analyze relevant health R&D data and document progress in key indicators over time.

虽然当下关于临时MCM平台的讨论至关重要，但它不包括协调其他全球卫生研发需求。正如其他研究[180]所强调的那样，[180]中低收入国家必须被纳入到研发优先排序过程，包括跨产品类型和疾病/病症的优先排序。我们的主要信息提供者表示，目标产品概况和首选产品特性是有用的，但它们往往是过时的。此外，有证据表明，管线中的实际候选产品与目标产品概况并不完全一致。这种不匹配还突出表明，我们需要更好地共享卫生研发数据，特别是关于研发投资和能力的数据，以实现更好的协调和知情决策。世卫组织全球卫生研发观察站可以作为一个平台，跟踪和分析相关的卫生研发数据，并记录关键指标的进展情况，从而支持这一工作。

7.3.2 Regional R&D ecosystems 区域研发生态系统

We conducted three regional consultation processes in Africa, Asia, and Latin America to better understand the key needs of the three regional R&D ecosystems. The aim of these consultations was to throw a spotlight on major themes across the regions. More details on the regional R&D ecosystem can be found in Annex 5.

我们在非洲、亚洲和拉丁美洲开展了三个区域磋商进程，以更好地了解这三个区域研发生态系统的关键需求。这些协商的目的是使人们关注各区域的主要主题。更多关于区域研发生态系统的细节见附录5。

THE NEED FOR PRIORITIZATION AND COORDINATION AT REGIONAL LEVEL区域协调和优先排序的必要性

Coordination and prioritization at regional level need to play an increasingly important role, feeding into global coordination. For example, Africa CDC has recently published its first list of priority pathogens, including a risk ranking and analysis of areas such as risk trajectory, epidemic potential, disease severity, and preparedness.[204] At the same time, African stakeholders who we interviewed reported that there is a need for stronger structured processes to determine regional health R&D priorities. These stakeholders also recommended that regional R&D coordination and priority setting should build on national R&D priorities.

区域层面的协调和优先排序需要发挥更加重要的作用，并融入全球协调。例如，非洲疾病预防控制中心最近公布了第一份重点病原体清单，其中包括风险排名和对风险轨迹、流行潜力、疾病严重程度和预防等领域的分析。[204]与此同时，接受我们采访的非洲利益攸关方称，有必要加强结构化进程，以确定区域卫生研发重点。他们还建议，区域研发协调和优先事项的确定应以国家研发优先事项为基础。

For Asia, KIs emphasized that countries are characterized by significant political, economic, cultural, and health-related differences, which makes R&D coordination very complex. Still, the KIs argued that stronger regional R&D coordination would be useful and called for regular analysis of the R&D pipeline. Such analysis, they said, should include technology assessments, feasibility studies, eliciting expert opinions, understanding changes in patient demand, and other indicators. They also argued that AI tools should be used to predict product pipeline developments and to eventually ensure the development of needed technologies over the next two decades. Latin American stakeholders pointed to several significant coordination challenges, including political tensions between countries.

主要信息提供者强调，亚洲各国政治、经济、文化和卫生差异大，这使得研发协调非常复杂。尽管如此，主要信息提供者认为，加强区域研发协调将是有益的。他们还呼吁定期分析研发管线，包括技术评估、可行性研究、征求专家意见、了解患者需求的变化以及其他指标。他们还指出，人工智能工具应该用于预测产品管线的发展，并最终用于确保未来20年所需技术的发展。拉丁美洲利益攸关方指出了几个重大的协调挑战，如国家间的政治紧张局势。

KIs believed that Latin American countries even failed to collaborate during the COVID-19 pandemic due to diverging political views. Latin American KIs also considered existing R&D capacity as limited and were concerned about a lack of R&D culture among policymakers.

主要信息提供者认为，即便是在新冠肺炎疫情期间，拉美国家也因为政治观点分歧而未能合作。拉丁美洲的主要信息提供者还认为现有的研发能力有限，并且担心决策者中缺乏研发思维。

THE NEED FOR REGULATORY HARMONIZATION AND CAPACITY BUILDING监管协调与能力建设的必要性

In Section 5, we described the urgent need to further strengthen African regulatory systems and to support regional regulatory harmonization initiatives on the continent. In Latin America, KIs described important steps towards strengthened and harmonized regulatory systems, highlighting the useful role of the Pan American Health Organization (PAHO) in this process. However, stakeholders also mentioned that PAHO needs to show even stronger leadership and support to foster harmonization and stronger NRAs. For example, only about a quarter of the 35 PAHO member states have established comprehensive legal bases and organizational frameworks for regulation (see Annex 5 for details). Countries are considered as “overprotective,” which often results in duplicative processes, according to our KIs. Countries also tend to “hyperregulate” rather than trying to optimize existing processes. Some KIs mentioned that governments at times threaten the autonomy and independence of NRAs. One major recommendation for Latin America was stronger collaborations with international regulatory initiatives, such as ICH, to further improve regional and national systems.

For Asia, KIs argued that the region has seen progress in terms of regulatory harmonization, which is also indicated in a study by Chonget al.[169] The study found that from 2008-2020, there was a 14% increase in the number of APEC (Asia-Pacific Economic Cooperation[205]) members’ regulatory authorities sharing GMP certificates and a 28% increase in the number of regulatory authorities accepting multisite licenses. However, the

在第5章中，我们提到了了进一步加强非洲监管体系和支持非洲大陆区域监管协调倡议的迫切需要。在拉丁美洲，主要信息提供者描述了加强和协调监管体系的重要举措，强调了泛美卫生组织在这一进程中的有益作用。然而，利益攸关方还提到，PAHO需要拿出更强有力的领导和支持力度，推动打造协调和更强大的国家监管机构。例如，PAHO的35个成员国中只有大约四分之一建立了全面的法律基础和组织框架(详见附录5)。我们的主要信息提供者也认为一些国家的“过度保护”往往导致重复审查。各国也倾向于“过度监管”，而非试图优化现有流程。一些主要信息提供者提到，政府有时会威胁到国家监管机构的自主权和独立性。对拉丁美洲的一项主要建议是加强与国际管制倡议(如ICH的合作)，以进一步改善区域和国家体系。

capacities of NRAs vary widely across Asian countries. In addition, the KIs reported that regulatory agencies have difficulties keeping pace with rapidly evolving global clinical guidelines and statistical designs. KIs recommended that Asian NRAs should learn from European and American countries to improve regulators' understanding, professional ability, and knowledge
of specific products and technology fields. In addition, governments should adopt a more innovation-friendly approach rather than focus only on constraints and
restrictions. Chong et al recommend that APEC should pilot a regional reliance program, including a mechanism that coordinates multiple regulators to jointly reach
regulatory decisions.[169]

Only about a quarter of the 35 PAHO member states have established comprehensive legal bases and organizational frameworks for regulation.

对于亚洲，主要信息提供者认为该地区在监管协调方面取得了一定进展，Chong等人的一项研究也证实了这一点。[169]该研究发现，从2008年到2020年，亚太经合组织(APEC)[205]成员国共享GMP证书的监管机构数量增加了14%，接受多站点许可证的监管机构数量增加了28%。然而，亚洲各国国家注册机构的能力差别很大。此外，主要信息提供者称，监管机构难以跟上快速发展的全球临床指南和数据统计设计的步伐。主要信息提供者建议亚洲的国家监管机构向欧美国家学习，以提高监管机构对特定产品和技术领域的理解，提升专业能力，学习专业知识。此外，政府应采取更有利于创新的方式，而非只注重约束和限制。Chong等人建议，亚太经合组织应试行一项区域信赖计划，其中应包括一个协调多个监管机构共同达成监管决策的机制。[169]

在PAHO的35个成员国中，只有大约四分之一的国家建立了全面的法律基础和监管组织框架。

THE NEED TO STRENGTHEN REGIONAL MANUFACTURING CAPACITY提升区域生产能力的必要性

As highlighted in Section 4 above, there are multiple coordinated eforts on the way to strengthen manufacturing capacity and expertise in Africa. The African Union has taken a strong leadership role and, with Africa CDC and AMA, there are also strong technical regional leads. While many hurdles still need to be overcome, building up manufacturing capacity for all product types is of critical importance to the region. For Asia, KIs pointed to the signifcantdiferences between Asian countries in terms of manufacturing capacity. While China and India have comparatively strong capacity, manufacturing capabilities of many other Asian countries is much more limited or even non-existent. For example, certain ASEAN countries (Indonesia, Thailand, and Vietnam) have strengthened their vaccine manufacturing capacity, including for COVID-19 vaccines, through fll and fnish arrangements, a signifcant asset for building regional vaccine security. However, despite these growing manufacturing capacities, the existing ASEAN vaccine production is far from meeting the demand of ASEAN for their routine immunization programs and emergency response.[86] Consulted KIs pointed to the need for much more international cooperation and tech transfer agreements.
正如上文第4章所强调的，我们已经共同努力提升非洲的生产能力和补充专业知识。非洲联盟发挥了强有力的领导作用，非洲疾病预防控制中心和非洲医药协会也给予了本区域强有力的技术指导。尽管仍有许多障碍需要克服，但打造全品类生产能力对该地区至关重要。主要信息提供者指出，亚洲国家在制造能力方面存在显著差异。虽然中国和印度的产能相对较强，但许多其他亚洲国家的制造能力要有限得多，甚至根本没有。例如，部分东盟国家(印度尼西亚、泰国和越南)通过全面和完整的安排加强了疫苗生产能力，包括COVID-19疫苗的生产能力，这是建立区域疫苗安全的重要资产。[86].然而，尽管制造能力不断提高，现有的东盟疫苗生产远远不能满足东盟常规免疫规划和应急反应的需求。一位接受咨询的主要信息提供者指出，我们需要更多的国际合作和技术转让协议。

Experts from Latin America argued during the consultations that the region remains strongly reliant on Western producers, which became apparent during the COVID-19 pandemic. The supply of essential materials poses a signifcant challenge, with supply shortages and sustainability of reagents being considered as major concerns, among others. KIs encouraged greater local production of supplies, reagents, and key health technologies. They argued for government subsidies, partnerships with private companies, and investments in local manufacturing to ensure sufficient capacity to produce key health technologies. Such a shift will also require training local scientists and other personnel to strengthen the region's self-sufficiency. Finally, KIs in Latin America recommended greater regional collaboration to share resources and knowledge, and collectively negotiate better access to health technologies.
来自拉丁美洲的专家在咨询中指出，该地区仍然严重依赖西方生产商，这在新冠肺炎疫情期间表现得尤为明显。基本材料的供应是一大严峻挑战，除此之外，原材料供应短缺和试剂可持续性也是主要问题。主要信息提供者鼓励更多地在当地生产原材料、试剂，研发核心卫生技术。他们提出政府应当采取给予补贴，与私营公司建立伙伴关系，投资当地制造业等方式确保有足够的能力开发关键卫生技术。这种转变还需要培训当地科学家和其他人员，以增强该地区的自给自足能力。最后，拉丁美洲的非政府组织建议加强区域合作，分享资源和知识，开展集体谈判，以更好地获得卫生技术。

THE NEED FOR EQUITABLE AND SUSTAINABLE FINANCING

African KIs emphasized the need to move away from funding individual research projects towards investment in the underlying research system. They also argued that more domestic funding for health R&D is needed. African governments, they said, should inject a much larger proportion of domestic funds into R&D value chains and ecosystems, including into capacity building. Improving the R&D ecosystem in Africa will require human capacity development, including in innovation and manufacturing relevant to the continent, so that all the necessary human resources are in place along the whole value chain.
非洲的主要信息提供者强调，我们需要从资助单个研究项目转向投资基础研究体系。他们还认为，各国应向健康研发提供更多的国内资金。他们说，非洲各国政府应该为研发价值链、研发生态系、研发能力建设统注入更大比例的国内资金。改善非洲的研发生态系统需要提升人员能力，包括与非洲大陆相关的创新和制造业，以便在整个价值链上配备所有必要的人力资源。拉丁美洲利益攸关方认为，研发资金明显缺乏，拉丁美洲国家的健康研发投资大大落后于其他区域。因此，他们还强调需要更多的国内研发资金。

Latin American stakeholders argued that there is a notable lack of funding for R&D, and that health R&D investments by Latin American countries signifcantly lag behind other regions. Thus, they also highlighted the need for more domestic R&Dfunding.

For Asia, KIs argued that the obstacles faced in healthcare innovation are multifaceted. Industry representatives highlighted that costs of new medicines might be too high for those who need them. At the same time, the costs for R&D are also high and increasing. Complex regulatory environments and high costs for certifcation exacerbate these issues, according to industry KIs. The mismatch between technology standards across borders and difficulties in obtaining rare samples further complicate the economic viability of health products.

Stakeholders recommended increasing domestic government funding to ensure that new products are afordable. From an industry perspective, the solutions include developing a more fexible research environment, encouraging innovation, and establishing partnerships supporting start-ups and established technologies.

主要信息提供者认为，亚洲的医疗保健创新面临多重障碍。行业代表强调，新药的成本对于那些需要它们的患者来说可能太高了。此外，研发成本也很高，而且还在不断增加。业内人士表示，复杂的监管环境和高昂的认证成本加剧了这些问题。跨国技术标准的不匹配和获取稀有样品的困难进一步使保健产品的经济可行性复杂化。利益相关者建议增加国内政府资助，以确保人们负担得起新药。从行业视角来看，解决方案还包括发展更灵活的研究环境，鼓励创新，建立支持初创企业和成熟技术的伙伴关系。

THE NEED FOR SUSTAINABLE CLINICAL TRIAL HUBS
建立可持续的临床试验中心的必要性

Long-term, sustainable clinical trial networks and hubs have played a critical role in trials of many candidate products for NDs and EIDs, including for HIV, COVID-19, and Mpox. For example, the HIV Prevention Trials Network (HPTN) conducts trials of biomedical HIV prevention approaches across 69 study sites in 14 countries, including countries in Latin America (Argentina, Brazil, Peru), SSA (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe) and Asia (Thailand, Vietnam). These kinds of networks have many advantages over establishing single, unconnected trial sites. Networks or hubs can test many

Networks or hubs can test many different types of health technologies and pivot quickly between diseases when needed (the HPTN pivoted to conduct COVID-19 vaccine trials and then again to conduct Mpox trials).

长期、可持续的临床试验网络和中心在艾滋病毒、新冠肺炎和麻疹在内的许多被忽视疾病和新发传染病候选药品试验中发挥了关键作用。例如，艾滋病毒预防试验网络(HPTN)在14个国家的69个研究地开展艾滋病毒生物医学预防方法的试验，这些国家包括拉丁美洲(阿根廷、巴西、秘鲁)、撒哈拉以南非洲(博茨瓦纳、斯威士兰、肯尼亚、马拉维、南非、乌干达、赞比亚、津巴布韦)和亚洲(泰国、越南)的国家。这些类型的网络与单一的、不相连的试验站点相比有许多优点。

临床试验网络或中心可以测试多种不同类型的卫生技术，必要时可在不同疾病之间快速切换(HPTN切换到进行COVID-19疫苗试验，然后再次切换到进行Mpox试验)。

different types of health technologies. They can pivot quickly between diseases when needed (the HPTN pivoted to conduct COVID-19 vaccine trials and then again to conduct Mpox trials). They drive multiple efficiencies by, for example, coordinating trials across the network, pooling data ,and sharing knowledge, such as on recruitment strategies for trials. For all these reasons, there would be great value in all regions developing strong, coordinated hubs for clinical trials.
临床试验网络和中心可以测试许多不同类型的卫生技术。必要时，他们在疾病之间快速切换(HPTN切换到进行COVID-19疫苗试验，然后再次切换到进行Mpox试验)。他们可以通过协调整个网络的试验、汇集数据和共享知识(如被试招募策略)来提高多倍效率。所有这些优势都使得在所有地区发展强大、协调的临床试验中心具有巨大的价值。

With respect to better coordination, Africa CDC and AUDA-NEPAD convened experts in May 2023 to discuss concrete solutions for strengthening the impact and efficiency of the African clinical trials ecosystem, with the goal of accelerating access to new lifesaving technologies in line with public health priorities. The experts agreed that a coordination mechanism was needed to enable increased efficiency and impact and recommended that this mechanism be housed at Africa CDC and managed in partnership with AUDA-NEPAD, WHO AFRO, and AVAREF.[206] This is a critical step given that most clinical trials are being conducted in HICs (studies show that between 2007 and 2018, 38% of infectious disease trials took place in North America and only 10% in Africa[7]).
在加强协调方面，非洲疾病预防控制中心和非洲发展新伙伴关系（AUDA-NEPAD）于2023年5月召集专家，讨论提升非洲临床试验生态系统的影响力和效率的具体解决办法，目标是根据公共卫生优先事项加速获得新的救生技术。专家们一致认为，我们需要建立一个协调机制，以提高影响力和效率。专家们还建议将该机制设在非洲疾病预防控制中心，并与非洲发展新伙伴关系AUDA-NEPAD、WHO AFRO和AVAREF [206]合作管理。考虑到大多数临床试验都是在高收入国家进行的，这是关键的一步(研究表明，2007年至2018年期间，38%的传染病试验在北美进行，只有10%在非洲进行)。

Conducting clinical trials in Latin America presents both challenges and opportunities. A signifcant challenge is the lack of needed infrastructure, such as trained medical staff and the certifed centers necessary for conducting clinical trials. The regulatory processes also pose signifcant challenges, with countries like Mexico, despite having substantial infrastructure, facing many barriers due to these processes. There is a tendency among many countries to duplicate efforts, leading to inefficiencies, instead of optimizing existing processes. Despite these challenges, there is a signifcant opportunity for optimization of the regulatory framework and capacities of the region, which would facilitate an environment conducive to clinical research. There are bright spots, with Argentina serving as a hub for clinical trials and Brazil standing out for the volume of its clinical trials. These regional hubs represent key opportunities for growth and development in the feld of clinical research. Asian stakeholders pointed to the difficulties in conducting clinical trials across different ethnic groups. They also requested more government support, such as reducing or exempting clinical trial fees to lower R&D costs.
在拉丁美洲开展临床试验既有挑战，也有机遇。一项重大挑战是拉丁美洲缺乏必要的基础设施，例如训练有素的医务人员和进行临床试验所需的认证中心。监管流程也带来了重大挑战，像墨西哥这样的国家，尽管拥有大量的基础设施，但由于这些程序，面临着许多障碍。许多国家都有重复努力的趋势，导致效率低下，而不是优化现有程序。尽管存在这些挑战，但该地区的监管框架和能力仍有很大的优化机会，这将促进有利于临床研究的环境。也有亮点，阿根廷是临床试验的中心，巴西因其临床试验的数量而脱颖而出。这些区域中心代表了临床研究领域增长和发展的关键机会。亚洲利益相关者指出，在不同种族群体中进行临床试验存在困难。他们还要求政府提供更多支持，例如减少或免除临床试验费用，以降低研发成本。

SUMMARY OF REGIONAL CONSULTATIONS 区域协商总结

In summary, stakeholders see the need to strengthen regional R&D systems, including regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing (Table 7). These regional platforms could play an important role for each region and need to be meaningfully integrated into global structures to ensure that regional priorities are refected.
总之，利益相关者认为有必要加强区域研发系统，该系统包括区域优先事项设置和创建区域和次区域临床试验、监管体系和产品制造中心(表7)。这些区域平台可以为每个地区发挥重要作用，需要有意义地整合到全球结构中，以确保反映区域优先事项。

Table 7. Strengthening regional systems to drive R&D and improve access to new tools
表7 增强区域体系建设，促进研发，提高新保健用品可及性。

Action points	Outcomes

Adopt a portfolio approach at regional level	• Decentralized decision-making, feeding into global priority setting (e.g., MCM platform) • Regional level priority-setting
Build regional capacity	• Pool of clinical trial sites • Sub-regional production linked to free-trade zones • Harmonized regulation to accelerate registration of new tools
Ensure access and equity through global public goods	• New tools with strong global public goods element (supply, pricing, licensing) • Industry buy-in through incentivizes • LMIC government commitment to invest in R&D, NRAs, and local production
Strengthen delivery systems	• Stronger regional procurement • Regional technical support

具体行动	成果
在区域层面采用组合方法	•分散决策，纳入全球优先级设置(例如，MCM平台) •区域层面确定优先事项
建设区域能力	•汇集临床试验地点 •在自由贸易区开展次区域生产 •协调法规，加快新工具的注册
通过全球公共产品确保获取和公平	•具有强大全球公共产品元素的新工具(供应、定价、许可) •通过激励机制获得行业认同 •中低收入国家政府政府承诺投资研发、国家监管体系和本地生产
加强运输系统	•更强的区域采购 •区域技术支持

SECTION

8

CONCLUSIONS: TOWARDS A REFORMED R&D ECOSYSTEM

总结：改革研发生态环境

In this study, we examined key shifts and innovations across six major domains of the R&D ecosystem for NDs, EIDs, and MH. We found that there is great potential for accelerating R&D, lowering R&D and production costs, and shortening market approval timelines. Below, we highlight ten key practices to make the product development ecosystem more efficient, effective, and equitable:

本研究探讨了被忽视疾病、新发传染病和孕产妇保健研发生态系统的六个主要领域的关键转变和创新。研究发现，这些领域在加速研发、降低研发和生产成本以及缩短市场审批时间方面具有巨大潜力。接下来，我们将重点介绍使产品开发生态系统更加高效、有效和公平的十个关键举措:

1. **Scale-up adoption of AI for product development for NDs, EIDs and MH.**

AI has great potential in the discovery and preclinical phases. There are examples of AI tools that have shortened discovery timeframes to less than one year and lowered the costs by a factor of up to 50. There is also an urgent need to expand the use of AI for epidemic and pandemic preparedness: AI should be used to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library. While the evidence on the benefits of AI in clinical trials is less strong, it indicates that AI can also play an important role during the clinical stages. In clinical evaluations, AI tools can predict the probability of trial success and help design Phase 2 and Phase 3 trials that are more likely to transition to regulatory approval. AI tools can also help with patient recruitment, the prediction of patient outcomes, and clinical trial data analysis and approval. However, if AI is rolled out inequitably, it could augment inequalities between LMICs and HICs. African researchers have therefore called for a research agenda on AI grounded in the African context to determine locally relevant strategies for its development and use.

2. **Leverage the efficiencies from innovative clinical trial designs.**

DCTs using DHTs can reduce trial costs, timelines, and the number of patients needed in a trial. Platform trials can shorten trial duration, evaluate more treatments per trial, reduce the number of patients required per trial (by up to 70%), and increase the proportion of programs that accurately recognize an effective treatment. Synthetic control arms can lower trial costs. The savings can be US$10 million to US$20 million per trial, depending on how much synthetic control arms are used to replace traditional control arms.

3. **Unlock the efficiency potential of clinical trial networks.**

Clinical trial networks can drive efficiencies by using existing sites instead of creating new ones, recruiting patients more quickly and reliably, and reducing the number of patients needed by sharing control groups with other trials. Connecting trial sites, which allows a sponsor to fnd sites for rapid enrolment, could reduce Phase 2/3 trial costs by 23%. Costs could be reduced by 40-60% by sharing control groups and using control data from previous trials. Furthermore, the ability to rapidly test product candidates during outbreaks relies on the existence of effective and inclusive regional clinical trial networks that are kept active between outbreaks.

4. **Scale-up quality-assured, low-cost manufacturing across regions.**

Optimized mRNA production processes can save over 60% (about US$70 million) of the annual cost of goods for the production of 100 million vaccine doses compared to conventional mRNA manufacturing. While mRNA technologies offer signifcant potential, diversifed vaccine manufacturing is needed to also enable production of existing licensed products (routine non-mRNA vaccines) across regions, including Africa. Modular production facilities have also been used in the past to lower production costs of non-mRNA-based vaccines. Production capacity for drugs and diagnostics also needs to be strengthened. To build more sustainable, resilient, and equitable future markets, frm purchasing commitments from funders are a key requirement.

5. **Strengthen regional regulatory harmonization and reliance models.** 加强区域监管协调和信赖模型

Regulatory harmonization through stronger national regulatory agencies and the use of reliance mechanisms can accelerate market authorization by limiting duplicative assessments.

加强国家监管体系的监管协调和监管信赖依赖机制，限制重复评估，加速市场授权。

Leverage the potential of mRNA platforms for NDs, EIDs and MH. 释放mRNA平台技术在治疗被忽视疾病、新发传染病和

6. 孕产妇保健方面的潜力

mRNA platforms have signifcant comparative advantages over more traditional technologies, including their versatility and the ability to rapidly develop new tools.

mRNA平台技术具有多功能属性，能够快速开发新医药产品，与更传统的技术相比具有显著的相对优势。

7. **Scale-up investments in R&D on mAbs that target NDs, EIDs, and MH.**

Developing mAbs for EIDs, for example, would offer many benefts. In addition, the global inequity in access to existing mAbs needs to be addressed. RSV mAbs could be a game changer—a low-cost RSV mAb is believed to be under development—and could serve as a product for the global community to rally around. COVID-19 was a missed opportunity to do so.

增加对新发传染病单克隆抗体研发的投资

例如，研发针对新发传染病的单克隆抗体将带来许多好处。此外，我们需要解决在获取现有单克隆抗体方面的全球不平等问题。RSV单克隆抗体可能会改变游戏规则，一种低成本的RSV单克隆抗体正在研发之中，未来可能成为使全球社区团结一致的产品。我们错失了新冠肺炎这一机会。

8. **Introduce a PRV in Europe to help incentivize industry investment. 在欧洲使用优先审查凭证，激励行业投资。**

An EU voucher would provide an additional incentive of US$100 million to US$ 200 million, which investors say would be a meaningful stimulus.

欧盟优先审查凭证将提供1至2亿美元的额外激励。投资者认为这一激励十分有意义。

9. **Rather than only targeting individual research projects, such as clinical trials, R&Dfunders also need to invest in the underlying research system. 研发资助方不应只投资个别研究项目，如临床试验，还需要投资基础研究体系。**

A system-wide approach would include investments in clinical trial infrastructure, capacities for drug discovery and preclinical research, and local manufacturing. LMIC governments need to increase their own funding for health R&D. This will be important to advance product development for NDs, EIDs, and MH.

全系统方法包括投资临床试验基础设施、药物发现和临床前研究能力以及本地生产。中低收入国家政府需要增加自己的卫生研发资金。这对于推进被忽视疾病、新发传染病和孕产妇保健产品开发非常重要。

10. **Strengthen regional R&D ecosystems. 增强区域研发生态系统**

The overarching R&D ecosystem would be improved by stronger regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing. Regional coordination on priority products is critical to ensure that R&D investments are driven by LMIC priorities. Global prioritization also needs to be strengthened—the coordination gap is especially large for therapeutics.
加强区域优先事项设置，为临床试验、监管体系和产品制造建立区域和次区域中心，将改善总体研发生态系统。优先产品的区域协调对于确保研发投资由中低收入国家优先事项驱动至关重要。全球优先次序也需要加强——治疗方面的协调差距尤其大。

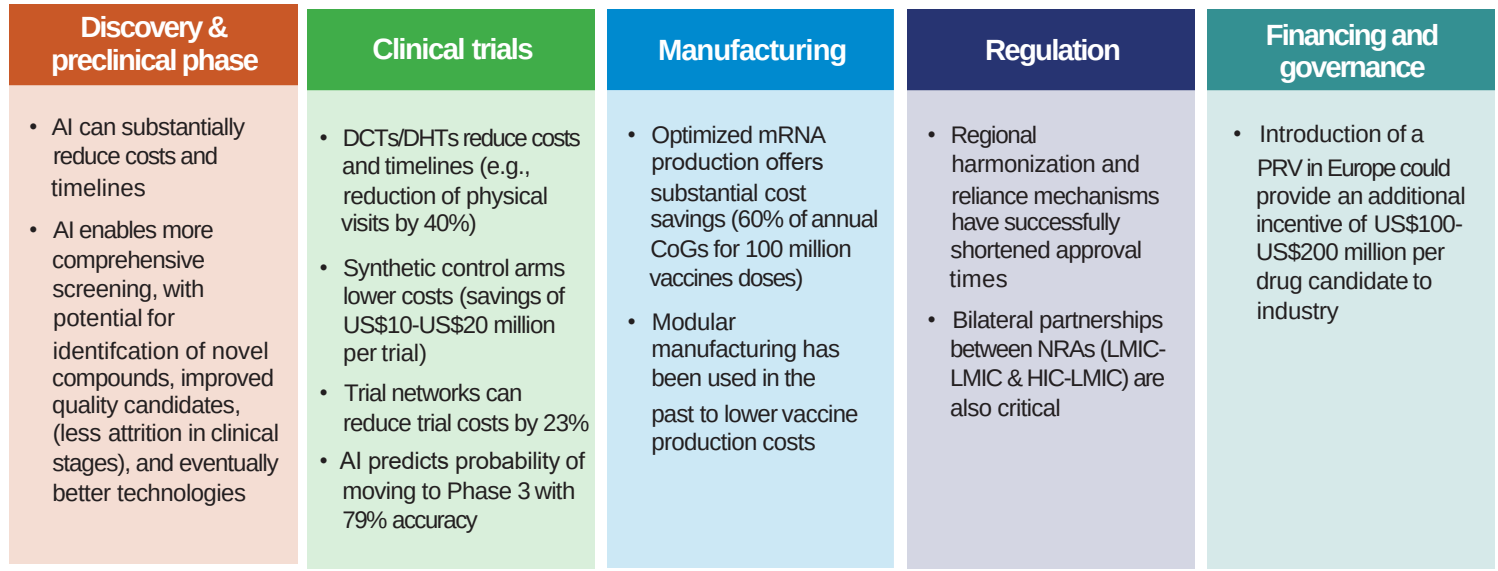
Figure 4 summarizes the efficiency gains resulting from the innovations and improvements in the R&D ecosystem identifed in our study. In addition, we believe that investments in R&D for LMICs should be driven by the priorities that they set themselves. The shifts identifed above must link to these priorities if we are to move in the direction of equity. These shifts in R&D must be accompanied by increased ownership by LMICs and increased investments from LMIC governments, as well as from the private sector and industry players.
本研究发现，研发生态系统的创新和改进将带来效率的提升（总结见图4）。此外，我们认为，对中低收入国家的研发投资应由它们自己确定的优先事项来驱动。如果我们要朝着公平的方向前进，上述转变必须与这些优先事项联系起来。这些研发方面的转变必须伴随着中低收入国家肩负更多责任以及中低收入国家政府以及私营部门和行业参与者的投资增加。

Our report's fndings have been an important input into the upcoming third report of the Lancet Commission on Investing in Health ("CIH 3.0"), Global Health 2050, which will be launched at the World Health Summit in Berlin in October 2024 (several of us are CIH Commissioners).[207] The CIH 3.0 report examines the feasibility of all countries halving their probability of premature death (defned as death before the age of 70 years) by 2050, with an interim target of reducing this probability by 30% by 2035. Global Health 2050 points to the critical importance of developing new health technologies for NDs, EIDs, and MH in reaching these 2035 and 2050 milestones.
本报告的研究发现是《柳叶刀》健康投资委员会("CIH 3.0")即将发布的第三份报告《全球健康2050》的重要组成，该报告将于2024年10月在柏林举行的世界卫生首脑会议上发布(我们中有几位是CIH专员)[207]CIH3.0报告审查了所

7. Scale-up investments in R&D on mAbs that target NDs, EIDs, and MH.

有国家到2050年将其人口过早死亡(指70岁之前死亡)概率减半的可行性，并设定了到2035年将这一概率降低30%的中期目标。《2050年全球卫生》指出，为实现2035年和2050年这些里程碑，研发针对被忽视疾病、新发传染病和孕产妇保健的新卫生技术至关重要。

Figure 4. Key efficiency gains from shifts in the R&D ecosystem



Defnitions of neglected diseases, emerging infectious diseases, and maternal health

被忽视疾病、新发传染病和孕产妇保健的定义

Neglected diseases*

- Bacterial pneumonia & meningitis
- Buruli ulcer
- Cryptococcal meningitis
- Dengue
- Diarrheal diseases
- Helminth infections
- Hepatitis B
- Hepatitis C
- Histoplasmosis
- HIV/AIDS
- Kinetoplastid diseases
- Leprosy
- Leptospirosis
- Malaria
- Mycetoma
- Rheumatic fever
- Salmonella infections
- Scabies
- Snakebite envenoming
- Trachoma
- Tuberculosis
- Yaws

Note: The G-FINDER defnition refers to diseases and products, i.e., not all product areas are included for all diseases in the G-FINDER scope (for more details, see the "G-FINDER Neglected Disease R&D Scope"*).

Emerging infectious diseases**

- COVID-19
- Crimean-Congo hemorrhagic fever, Rift Valley fever, and other bunyaviral diseases
- Chikungunya
- Ebola, Marburg, and other floviral diseases
- Lassa fever and other arenaviral hemorrhagic fevers
- MERS, SARS & multiple coronaviruses
- Mpox
- Nipah and other henipaviral diseases
- Zika
- Disease X

Maternal health***

- Preterm labor/birth
- Preeclampsia/eclampsia
- Intrauterine growth restriction
- Postpartum hemorrhage
- Intrapartum fetal distress
- Maternal enteric microbiome/environmental enteric dysfunction
- Maternal iron defciency anemia

被忽视疾病*

- 细菌性肺炎和脑膜炎
- 布鲁里溃疡
- 隐球菌脑膜炎
- 登革热
- 腹泻病
- 寄生虫感染
- 乙型肝炎

•丙型肝炎
•组织胞浆菌病
•艾滋病毒/艾滋病
•着丝质体疾病
•麻风
•钩端螺旋体病
•疟疾
•足分支菌病
•风湿热
•沙门氏菌感染
•疥疮
•毒蛇咬伤
•沙眼
•肺结核
•雅司病
注:G-FINDER的定义是指疾病和产品，也就是说，不是所有的产品领域都包括在G-FINDER范围内的所有疾病(更多详细信息，请参见“G-FINDER被忽视疾病研发范围”*)。

新发传染病**

•COVID-19
•克里米亚-刚果出血热、裂谷热、
以及其他布尼亚病毒疾病
•基孔肯雅热
•埃博拉病毒、马尔堡病毒和其他病毒性疾病
•拉沙热和其他沙粒病毒性出血热
•MERS、SARS和多种冠状病毒
•Mpox
•尼帕病毒和其他亨尼帕病毒疾病

孕产妇健康* * *

·早产/分娩
·子痫前期和子痫
·宫内生长受限
·产后出血
·产时胎儿窘迫
·母体肠道微生物组/环境
肠功能障碍

*https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2023/05/05211731/G-FINDER_ND_RD_scope.pdf
** https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2024/04/08192259/G-FINDER_EID_RD_scope.pdf
***https://www.policycuresresearch.org/maternal-health-pipeline/

ANNEX 2
附录 2

Portfolio to Impact (P2I) modeling tool

项目组合影响(P2I)建模工具

Table A2. Assumptions for the product pipeline development model

表A2。对产品管线开发模型的假设

	Cost per phase每期成本 (US$ million)				每期时长Length of phase (years)				Probability of success成功率 (%)			
Archetype 原型	**Pre-clinical 临床前**	**Phase 1**	**Phase 2**	**Phase 3**	**Pre-clinical 临床前**	**Phase 1**	**Phase 2**	**Phase 3**	**Pre-clinical 临床前**	**Phase 1**	**Phase 2**	**Phase 3**
Vaccine-simple 疫苗-简单	$6.66	$2.25	$13.22	$111.10	3.36	1.57	2.23	2.33	41.0%	68.4%	45.9%	70.8%
Vaccine-complex 疫苗-复杂	$16.63	$2.47	$13.88	$133.32	3.33	1.97	3.71	3.50	41.0%	50.0%	21.6%	63.6%
NCE-simple 简单NCE	$5.00	$2.21	$5.81	$32.82	2.49	1.80	3.38	3.18	65.0%	59.7%	38.8%	69.1%
NCE-Innovative 创新NCE	$7.50	$4.83	$6.10	$34.46	2.70	1.81	3.35	3.10	60.0%	51.9%	28.4%	57.8%
NCE-complex 复杂NCE	$10.00	$7.44	$6.39	$36.10	2.87	1.93	3.51	2.80	55.0%	57.2%	19.7%	40.3%
Drug repurpose-simple 简单药物再利用	$-	$-	$5.81	$17.61	0.00	0.00	2.14	2.14	100.0%	100.0%	45.7%	68.1%
Drug repurpose-complex 复杂药物再利用	$5.00	$2.21	$5.81	$17.61	2.33	1.63	2.14	2.14	75.0%	58.5%	45.7%	68.1%
Biologic-simple 生物 简单	$10.79	$2.41	$7.53	$54.12	3.29	1.62	2.47	2.10	75.0%	66.2%	44.3%	70.9%
Biologic-complex 生物 复杂	$21.59	$7.65	$8.28	$59.53	3.24	1.49	4.16	3.38	77.0%	69.6%	32.2%	62.5%
Diagnostic, assay Development诊断分析开发	$3.00	$2.00	$3.50	$-	1.00	1.25	1.33	0.00	50.0%	100.0%	100.0%	100.0%

Diagnostic, simple platform development诊断 简单平台开发	$-	$100.00	$3.50	$-	0.00	2.50	2.00	0.00	100.0%	75.0%	100.0%	100.0%

Source: Terry RF, Yamey G, Miyazaki-Krause R, et al. Funding global health product R&D: the Portfolio-To-Impact Model (P2I), a new tool for modelling the impact of different research portfolios. Gates Open Res 2018;2:24

ANNEX 3
附录 3

Clinical trials临床试验

Table A3.1. Examples of studies of the efficiencies associated with decentralized clinical trials and digital health technologies

Type of efficiency	Study details	Magnitude of benefit	Innovations studied
Cost reduction	DAPA-MI trial (Sweden, UK): evaluated use of dapaglifozin in patients with myocardial infarction incorporating digital approaches; compared costs with those of DAPA-HF (a similar study that did not use digital approaches)[1]	• 60% reduction in no. of patient study visits • 43% reduction in total cost per patient from US$ 22,698 in traditional approach to US$12,826 using DCT/DHT • US$25 million in savings	• Digital clinical platform for patients and sites • AI cardiovascular event detection platform • Digital patient registries
	Eastern Research Group study: modeled the effect of different DCT/DHT innovations, using data on >27,000 trials for over 1400 indications[2]	**Innovations most likely to reduce costs were:** • use of lower cost facilities or at-home testing: up to 17% reduction in phase III trial costs • mobile technologies for data capture: up to 12% reduction • electronic health records (EHRs) to recruit patients and capture data: up to 9% reduction • simplifed clinical trial protocols (up to 8% reduction)	• Use of lower cost, non-traditional sites (e.g., local clinics and pharmacies) • At-home testing • Mobile tech • EHRs • Simplifed trial protocols
Fewer participants needed, reduced costs, shorter timeline	CRESCENDO trial: is using digital technologies to evaluate a new drug (AZD4831) for chronic obstructive pulmonary disease (COPD)[1]	• Required no. of participants was reduced from an estimated 604 (for a traditional trial) to 288 • 32% reduction in costs (the number of in-person visits is halved) • 15% reduction in trial duration	• Digital primary and secondary endpoints • Smart spirometer (home-based) • Digital clinical platform • AI
Shorter timelines, improved patient recruitment, lower drop-out rates	IQVIA analysis of DCTs: analysis of 12 DCTs for 3 therapeutic areas—neurology, infectious diseases, dermatology; 17% Phase 1, 25% Phase 2, 58% Phase 3[3]	• 49% reduction in the time taken from fnalizing the protocol to enrolling the 1st patient [1st patient in, FPI] (in oncology, the average time from protocol submission to enrolling the 1st patient is 33 weeks[4]) • 78% reduction in time taken from enrolling the 1st patient [FPI] to enrolling the last patient [last patient in, LPI] • In a phase III DCT for infectious diseases, involving over 23,000 patients, there was an 86% reduction in fnal protocol to FPI and a 94% reduction in FPIto LPI timelines—with huge fnancial and time implications • 39% reduction in "screen failure rate" (the proportion of patients screened as eligible to be in a trial who do not enroll) • 15% lower dropout rates—probably related to lower time and travel burden for the participants	• Hybrid trials that combined "site visits with technology-enabled data collection and home-based services"[3]
	IQVIA analysis of phase 2 or 3 remote, virtual, or decentralized (RVD) trials: the highest number of trials in the analysis were from infectious diseases, vaccines, immunology and neurology	• Despite higher average complexity, the cohort of RVD trials "completed just over 20% faster than non-RVD trials"[5]	

表A3.1 与分散临床试验和数字卫生技术相关的效率研究实例

效率	研究细节	优点	研究创新点
减少成本	DAPA-MI试验(瑞典、英国): 评价达格列净在合并心肌梗死患者中的应用 数字的方法;与DAPA-HF(一个类似的没有使用数字方法的研究)的成本进行比较	• 患者研究访视次数减少60% ·每位患者的总成本降低43%，从传统方法的22,698美元降至使用DCT/DHT的12,826美元 ·节省2500万美元	• 病患和点位数字临床平台的 ·AI心血管事件检测平台 ·患者登记数字化
	Eastern Research Group的研究:使用超过1400个适应症的超过27000个试验的数据，对不同DCT/DHT创新的效果进行了建模[2]	**最有可能降低成本的创新是:** **·使用成本更低的设备或在家测试:三期试验成本降低17%** **·用于数据捕获的移动技术:最多减少12%** **·用于招募患者和获取数据的电子健康记录(EHRs):最多减少9%** **·简化临床试验方案(最多减少8%)**	•使用成本较低，非传统地点(如当地诊所和药房) ·在家测试 ·移动技术 ·电子医疗纪录 ·简化试验方案
更少的参与者需要，降低成本，更短时间	CRESCENDO试验:正在使用数字技术 评估一种治疗慢性阻塞性肺疾病(COPD)[1]的新药AZD4831	• 所需的参与者人数从估计的604人(传统试验)减少到288人 ·成本降低32%(亲自就诊次数减半) ·减少15%的试验时间	•数字主要和次要端点 ·智能肺活量计(家庭)·数字临床平台 ·人工智能
更短的时间，改善患者招募;更低的退出率	DCT的IQVIA分析：对3个治疗领域的12个DCT进行分析 神经病学、传染病、皮肤病;一期17%; 二期25%，三期58%[3]	• 从提交方案到第1名患者入组所需的时间减少了49% [FPI](在肿瘤学中，从方案提交到入组第1名患者的平均时间为33周[4]) ·从入组第一名患者(FPI)到入组最后一名患者(LPI)的时间缩短了78% ·在传染病的第三期DCT中， 在超过23,000名患者中，最终方案到FPI减少了86%，FPI到LPI时间减少了94%，这对财务和时间都有巨大的影响 · “筛查失败率”降低39%(筛查为符合试验条件但未入组的患者比例) ·降低15%的退出率——可能与参与者时间和旅行负担减少有关	• 混合试验将“实地考察与技术支持的数据收集和居家服务相结合[3]”
	2期或3期远程、虚拟或分散(RVD)试验的IQVIA分析:最高分析中的试验数量来自传染病、疫苗、免疫学和神经学	•尽管平均复杂性更高，但RVD试验队列的完成速度比非RVD试验快20%以上[5]	

Case study 案例分析

The HPTN, established in 1999, is a powerful example of a sustained international trials collaboration that partners with academia, industry, and philanthropy to conduct trials of biomedical HIV prevention approaches across 69 study sites in 14 countries. In addition to the U.S., the 13 other countries are in LatinAmerica (Argentina, Brazil, Peru), sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe) and Asia (Thailand, Vietnam). The network is remarkable in five key ways:

HPTN成立于1999年，是持续国际试验合作的有力范例，HPTN与学术界、工业界和慈善机构合作在14个国家的69个研究地点开展艾滋病毒生物医学预防方法的试验。除美国外，其他13个国家分别位于拉丁美洲(阿根廷、巴西、秘鲁)、撒哈拉以南非洲(博茨瓦纳、斯威士兰、肯尼亚、马拉维、南非、乌干达、赞比亚、津巴布韦)和亚洲(泰国、越南)。该网络展现出五大突出优点：

Multiple technology types
多种技术类型

The HPTN conducts trials of different types of HIV prevention technologies: HIV vaccines in partnership with the HIV Vaccines Trial Network (HVTN); pre-exposure prophylaxis (antiretrovirals, broadly neutralizing antibodies); and multipurpose prevention technologies, which are designed to simultaneously prevent HIV and pregnancy, STIs, or opioid dependence.

HPTN对不同类型的艾滋病毒预防技术进行试验：与世界卫生组织合作艾滋病毒疫苗试验网络；暴露前预防(抗逆转录病毒药物、广泛中和抗体);以及多用途预防技术，这些技术旨在同时预防艾滋病毒和怀孕、性传播感染或阿片类药物依赖。

Pivoting rapidly to other emerging infections
迅速转向其他新发感染

As long-running established platforms, the HPTN and HVTN could pivot quickly to conduct COVID-19 vaccine trials. They joined the COVID-19 Prevention Network (CoVPN), along with the Infectious Diseases Clinical Research Consortium (IDCRC) and the AIDS Clinical Trials Group (ACTG). "By bringing together multiple networks," say CoVPN authors in a recent paper, "CoVPN was able to draw on existing clinical and laboratory infrastructure, community partnerships, and research expertise to quickly pivot clinical trial sites to conduct COVID-19 vaccine trials as soon as the investigational products were ready for phase 3 testing."[6] The HPTN/HVTN pivoted rapidly again to run Mpox vaccine trials.

作为长期运行的成熟平台，HPTN和HVTN可以迅速转向进行COVID-19疫苗试验。他们加入了COVID-19预防网络(CoVPN)，以及传染病临床研究国际艾滋病协会(IDCRC)和艾滋病临床试验组(ACTG)。"通过汇集多个网络，"CoVPN的作者在最近的一篇论文中说，"CoVPN能够利用现有的临床和实验室基础设施、社区伙伴关系和研究专业知识，一旦研究产品准备好进行第三阶段测试，就迅速转向临床试验地点进行COVID-19疫苗试验[6]。HPTN/HVTN再次迅速转向开展麻疹疫苗试验。

Efficiency gains
效率增益

The rapid launch of the CoVPN showed that trial networks can drive several efficiencies. There were time savings, since existing trial sites, infrastructure, laboratories, human resources (including analytics expertise), and community outreach mechanisms could be used—saving time that would have been spent establishing new sites and hiring and training staff. Using the HPVN for COVID-19 vaccine trials meant that a network of clinician investigators was already in place. Lawrence Corey, HPVN Principal Investigator, says that these clinicians "could discriminate between mild and serious disease, follow people sequentially, do pulse oximetry, and draw bloods for correlates of protection."[7] Time was also saved by using rapid, simplified budgeting and payment to trial sites. Another efficiency was generated by pooling data. The CoVPN used data generated by multiple existing platforms (HPTN, HVTN, IDCRC, ACTG) across the US, Latin America, and sub-Saharan Africa, involving 136,382 trial participants. Data from these multiple trials and platforms were shared and analyzed. The CoVPN authors argue that this cross-platform approach "led to harmonization of data collection across trials and the ability to analyze data from all studies, a novel approach that will continue to yield answers to pressing questions and help guide public health policy."[6] Trials networks also share knowledge, such as on recruitment strategies for trials.

CoVPN的快速发布表明，试验网络可以提高多重效率。节省时间，由于可以使用现有的试验站点、基础设施、实验室、人力资源(包括分析专家)和社区扩展机制，从而节省了建立新站点以及雇用和培训员工所花费的时间。在COVID-19疫苗试验中使用HPVN意味着临床研究人员网络已经到位。HPVN首席研究员Lawrence Corey说，这些临床医生"可以区分轻度和严重的疾病，要按顺序进行随访，做脉搏血氧测定，并抽血进行相关保护[7]。

Potential to be used to study additional PRNDs
有可能用于研究更多的国别规划

Capacity building
能力建设

通过使用快速、简化的预算付款方式也节省了时间。另一个效率是通过数据整合产生的。CoVPN使用了美国、拉丁美洲和撒哈拉以南非洲多个现有平台(HPTN、HVTN、IDCRC、ACTG)交叉生成的数据，涉及136,382名试验参与者，这些试验和平台的数据被共享和分析。CoVPN的作者认为，这种跨平台方法"导致了统一各试验的数据收集和分析所有研究数据的

能力，这是一种新颖的方法，将继续为紧迫问题提供答案，并有助于指导公共卫生政策。试验网络也共享知识，例如试验的招聘策略。

development of a tuberculosis vaccine.

利用艾滋病毒监测网络、艾滋病行动小组和国际孕产妇、儿科、青少年艾滋病临床试验网络来促进结核病疫苗的研制。

The HVTN, the ACTG, and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network have been leveraged to facilitate the

The CoVPN runs international scholarship programs. One of these is a scientific leadership development program that is providing support to promising junior clinical investigators who maybe in a position in 5-10 years to be a clinical trials site leader.

CoVPN运营着国际奖学金项目。其中之一是科学领导力发展项目，为有前途的初级临床研究人员提供支持他们可能在5-10年内成为临床试验现场负责人。

1 IQVIA Institute. Global Trends in R&D, 2023.Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf

2 LauerMS, Gordon D, Wei G, Pearson G. Efficient design of clinical trials and epidemiological research: is it possible? Nat Rev Cardiol. 2017 Aug;14(8):493–501.

3 IQVIA Institute. DCTs Deliver Big ROI. 2022.Available from: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/dcts-deliver-big-roi.pdf

4 Byatt L, Deutsch K, Dayao ZR. Improving start-up times in oncology clinical trials: An ASCO quality improvement project. JCO. 2018 Oct 20;36(30_suppl):297–297.

5 IQVIA Institute. Global Trends in R&D, 2023.Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf

6 Mena Lora AJ, et al. Rapid Development of an Integrated Network Infrastructure to Conduct Phase 3 COVID-19 Vaccine Trials. JAMA Network Open 2023;6(1):e2251974, at https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2800703

7 From HVTN to CoVPN: the importance of vaccine trial networks [Internet]. BioInsights. [cited 2023 Nov 18]. Available from: https://www.insights.bio/vaccine-insights/journal/article/2926/From-HVTN-to-CoVPN-the-importance-of-vaccine-trial-networks

ANNEX 4
附录 4

WHO Global Benchmarking Tool (GBT) Performance Maturity Levels
世卫组织全球基准工具(GBT)绩效成熟度水平

WHO GBT Performance Maturity Levels				
ISO 9004	1	2	3	4
	No formal approach	**Reactive approach**	**Stable formal system aproach**	**Continual improvement emphasized**
	Some elements of regulatory system exist	Evolving national regulatory system that partially performs essential regulatory functions	Stable, well-functioning and integrated regulatory system	Regulatory system operating at advanced level of performance and continuous improvement
	Can be considered as functional if rely on other regulators for some specifc functions		**Target of WHA Resolution 67.20**	**Advanced/reference Regulatory Authorities**

世卫组织全球基准工具(GBT)绩效成熟度水平

ISO 9004	1	2	3	4
	无形式方法	反应式方法	稳定形式系统方法	强调持续改进

	存在监管系统的一些元素	执行部分重要监管职能的国家监管体系	稳定、运作良好的 监管体系	监管体系运行表现处于先进水平并不断改进
	Can be considered as functional if rely on other regulators for some specifc functions 某些功能如果依赖其他监管者可被认定为functional		**世界卫生大会第67.20号决议目标**	**先进/参考监管机构**

Source: Figure from BroojerdiAK, Sillo HB, Dehaghi ROA, et al. The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage. Front Med (Lausanne) 2020;7:457.

ANNEX 5
附录 5

5.1. LatinAmerica: key regional shifts needed in the regional R&D ecosystem
拉丁美洲:区域研发生态系统所需的关键区域转变

The regional assessment involved consultations with stakeholders from 10 countries (Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay). It also included consultations with representatives from two major regional organizations: the Pan American Health Organization (PAHO) and the Latin American Federation of the Pharmaceutical Industry (FIFARMA). Consultations were conducted with policymakers and technical experts from government, public sector institutions (e.g., ministries of health, national institutes of health), national regulatory authorities (NRAs), industry, academia, multilateral institutions, and civil society.

区域评估涉及与来自10个国家(阿根廷、玻利维亚、巴西、哥伦比亚、哥斯达黎加、厄瓜多尔、墨西哥、巴拿马、秘鲁和乌拉圭)的利益攸关方进行磋商；还包括咨询两个主要区域组织的代表:泛美卫生组织和拉丁美洲制药业联合会；以及咨询来自政府、公共部门机构(如卫生部、国家卫生研究所)、国家监管机构、工业界、学术界、多边机构和民间社会的决策者和技术专家。

THE CLINICAL TRIAL ECOSYSTEM IN LATIN AMERICA 拉丁美洲的临床试验生态系统

Conducting clinical trials in Latin America presents both challenges and opportunities. A significant challenge is the lack of critical infrastructure for conducting trials, such as trained medical staff and certified centers. However, even when there is substantial infrastructure, such as in Mexico, inefficient regulatory processes create barriers to conducting trials (see below). Despite these challenges, there are some bright spots, with Argentina serving as a hub for clinical trials and Brazil standing out for the volume of its trials. These regional hubs represent key opportunities for growth and development in the field of clinical research.

在拉丁美洲开展临床试验既有挑战，也有机遇。一项重大挑战是缺乏进行试验的关键基础设施，例如训练有素的医务人员和认证中心。然而，即使有大量的基础设施，例如在墨西哥，低效的管理程序也会对试验带来壁垒(见下文)。尽管存在这些挑战，但也有一些亮点，阿根廷是临床试验的中心，巴西因其试验数量而脱颖而出。这些区域中心代表了临床研究领域增长和发展的关键机会。

REGULATORY SYSTEMS IN LATIN AMERICA 拉丁美洲的监管体系

There is wide variation in how well NRAs function. Around one fifth of the 35 PAHO countries have limited legal and organizational regulatory structure. About one quarter have established comprehensive legal bases and organizational frameworks for regulation (including Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and the US). PAHO is in the process of transitioning to the Global Benchmarking Tool (GBT) to assess NRAs. However, no NRA in Latin America has been fully assessed with this tool yet—only self-assessments have been conducted. The introduction of the GBT is expected to be very beneficial in benchmarking, harmonizing, and strengthening regulatory systems.
国家监管机构的功能有很大的差异。泛美卫生组织35个国家中约有五分之一的国家的法律和药物组织监管结构有限。大约四分之一的国家已经建立了全面的监管法律基础和组织框架(包括阿根廷、巴西、加拿大、智利、哥伦比亚、古巴、墨西哥和美国)。泛美卫生组织正在过渡到全球基准工具(GBT)来评估国家监管机构。然而在拉丁美洲，没有一个国家的监管机构得到了充分的评估，而只是进行了自我评估。预计GBT的引入将在制定基准、协调和加强监管体系方面非常有益。

Over the last decade, there have been a number of regional efforts to improve regulation, including efforts to adopt a more uniform approach to regulation across different jurisdictions and greater use of reliance. For example, thanks to the North American Free Trade Agreement, there is now reliance between the NRAs of the US, Canada, and Mexico. In terms of harmonization and international convergence, organizations like the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have incorporated NRAs from middle-income countries. This has facilitated the strengthening of regulatory systems. Currently, Brazil and Mexico are Latin American members of the ICH, with Colombia and Argentina participating as observers.

在过去十年中，改善监管有若干区域性努力，包括在不同司法管辖区采取更统一的监管方法和更多地使用监管依赖。例如，由于《北美自由贸易协定》的签署，美国、加拿大和墨西哥的国家注册机构之间现在存在监管依赖。在协调和国际趋同方面，

人用药品技术要求国际协调理事会 (ICH)等组织纳入了中等收入国家的国家监管机构，促进了监管制度的加强。目前，巴西和墨西哥是ICH的拉丁美洲成员，哥伦比亚和阿根廷作为观察员参加。

However, despite these improvements, there are still gaps in the regulation of medicines. These include:

(i) the use of self-assessments, which are not as comprehensive or objective as a full assessment using the GBT;

(ii) resource limitations and a lack of political will and sustainable plans;

(iii) dependence on the administration in power, which often leads to a reset with each new government;

(iv) nationalism or protectionism in some nations, often under the guise of respecting national sovereignty;

(v) the use of physical documentation for administrative processes, instead of using electronic methods; and

(vi) poor preparation for assessing and registering new types of medicines, such as monoclonal antibodies and mRNA-based technologies.

然而，尽管取得了这些进展，在药品监管方面仍然存在差距。这些包括:

(i) 自我评估不如使用GBT的全面评估那样全面或客观；

(ii) 资源有限，缺乏政治意愿和可持续计划;

(iii) 对执政政府的依赖，往往导致政府更迭后任务重置；

(iv) 某些国家的民族主义或保护主义，往往打着尊重国家主权的幌子;

(v)在行政程序中使用纸质文件，而不是使用电子方法;和

(vi)评估和注册新类型药物(如单克隆抗体和mRNA的技术)的准备不足。

In addition to adopting the GBT, key informants (KIs) made several recommendations to improve regulatory systems:

- **Expedite the review of tools**. The COVID-19 pandemic necessitated expedited review of tools such as vaccines, which were found to be efective post-pandemic; this shows the value of expedited review processes.
- **Maintain data quality and ethics**.
- **Adopt faster trials processes**. KIs stressed the need for faster evaluation models with shorter clinical trial phases that can be evaluated simultaneously.
- **Create multidisciplinary groups**. The pandemic underscored the need for multidisciplinary groups, including social scientists such as anthropologists, to understand cultural diferences and improve community communication.
- **Adapt to urgent situations**. COVID-19 pushed regulatory authorities to adapt to urgent situations and speed up their processes.
- **Establish better communication channel**s. KIs emphasized the importance of continuous communication between regulators and those being regulated.

除了采用GBT外，关键信息提供者（KI）还提出了几项改善监管制度的建议：

- 加快对工具的审查。COVID-19大流行需要加快对疫苗等工具的审查，这些工具在大流行后被发现是有效的，凸显了加速审查过程的价值。
- 维护数据质量和道德规范。
- 采用更快的试验流程。关键信息提供者强调需要更快的评估模型和可以同时进行评估更短的临床试验阶段。
- 创建多学科小组。大流行病强调了包括人类学家等社会科学家在内的多学科团体需要了解文化差异并改善社区沟通。
- 适应紧急情况。COVID-19促使监管部门适应紧急情况并加快流程。
- 建立更好的沟通渠道。KI强调了监管机构与被监管机构之间持续沟通的重要性

MANUFACTURING OF HEALTH PRODUCTS IN LATIN AMERICA 拉丁美洲健康产品的生产

Latin America faces signifcant hurdles in manufacturing health tools, including a lack of incentives and support, making it challenging to foster innovation and production. The COVID-19 pandemic highlighted the region's dependency on the Global North for health products and its vulnerability in times of global health crises. Other challenges include shortages of supplies, sustainability of reagents, and maintenance of equipment.

Strengthening local and regional production of supplies, reagents, and key health technologies could be achieved through government subsidies, partnerships with private companies, and investment in local manufacturing facilities and in training and capacity building.

拉丁美洲在制造医疗工具方面面临重大挑战：缺乏激励措施和支持，难以促进创新和生产。新冠疫情大流行凸显了该地区对全球北方的医疗产品的依赖和在全球卫生危机时期的脆弱性。其他挑战包括供应短缺、试剂的可持续性和设备的维护。

应该加强地方和区域试剂和关键医疗技术的供应，通过政府补贴、与私营公司合作、投资当地生产设施、培训和能力建设。

R&D GOVERNANCE IN LATINAMERICA 拉丁美洲的研发治理

The governance of the R&D ecosystem faces signifcant barriers, gaps, and challenges. At the heart of these issues is poor health systems, which are often characterized by defcits in infrastructure, logistics, and funding for R&D, and high levels of corruption leading to the misuse of resources. Another challenge is the gap between research and policy—there is a pressing need to develop communication channels or strategies to translate research results into public health policies. The knowledge of and capacity for research among health and regulatory authorities is often lacking. There is also a noticeable lack of R&D culture among health authorities and decision-makers, which can stife innovation and slow down the development of new health technologies.

研发生态系统的治理面临着重大的障碍、差距和挑战。这些问题的核心是医疗卫生系统薄弱，基础设施、物流和研发资金不足，腐败严重导致资源滥用。另一个挑战是研究与政策之间的差距——迫切需要发展沟通渠道或战略，将研究成果转化为公共卫生政策。医疗机构和监管机构往往缺乏研究知识和能力，医疗管理机构和决策者也明显缺乏研发文化，这可能会阻碍创新和发展、减缓新医疗技术的发展。

Our study highlighted the importance of adopting intersectoral, interdisciplinary approaches to improve the R&D governance ecosystem, such as improving coordination between institutions and fostering greater regional collaboration to facilitate the sharing of resources, knowledge, and best practices.

我们的研究强调了采用跨部门、跨学科的方法来改善研发治理生态环境的重要性，例如改善机构之间的协调，促进更大的区域合作，以促进资源、知识和最佳实践的共享。

R&D FINANCING IN LATINAMERICA 拉丁美洲的研发融资

One of the primary obstacles to product development in the region is the lack of sufficient funding for R&D, including for pre-clinical research and clinical trials. Often, research is conducted more for the beneft of the researcher rather than out of necessity, and the research agenda is heavily infuenced by the availability of funding.

In terms of R&D investment, Latin America signifcantly lags behind other regions. While countries like the United States, Japan, Korea, and the European Union allocate 2-3% of their gross domestic product (GDP) to R&D, Latin America only dedicated 0.65% of its GDP to R&D in 2020, the most recent year for which data are available.[1] The lack of R&D fnancing leads to a lack of specialized training and capacity building opportunities within the R&D feldand a lack of institutional capacity.

Nevertheless, there are new players emerging within academic circles and the private sector who are beginning to make their mark on the R&D landscape. A new report on “Health Innovation and Technology in Latin America and the Caribbean,” by the Inter-American Development Bank, maps out these emerging actors,[2] which include fnance organizations and philanthropies.

该地区产品开发的主要障碍之一是缺乏足够的研发资金，包括用于临床前研究和临床试验的资金。通常，研究更多是为了研究人员的利益，而不是出于必要性，研究议程受到资金可用性的严重影响。

在研发投资方面，拉丁美洲明显落后于其他地区。而像美国、日本、韩国和欧盟等国家将其国内生产总值(GDP)的2-3%用于研发，拉丁美洲在2020年仅将其国内生产总值(GDP)的0.65%用于研发，这是最近可获得数据的年份。[1]缺乏研发资金导致研发领域缺乏专业培训和能力建设机会，也导致机构缺乏行动力。

然而，学术界和私营部门中出现了一些新的参与者，他们开始在研发领域崭露头角。美洲开发银行(Inter-American Development Bank)一份关于“拉丁美洲和加勒比地区卫生创新和技术”的新报告列出了这些新兴行动派[2]，其中包括金融组织和慈善机构。

1. https://data.worldbank.org/indicator/GB.XPD.RSDV.GD.ZS?locations=XJ.
2. IDB. Health Innovation and Technology in LatinAmerica and the Caribbean. April 2024. https://publications.iadb.org/en/health-innovation-technology-latin-america-caribbean

5.2. Africa: key regional shifts needed in the regional R&D ecosystem

非洲:区域研发生态系统需要的关键区域转变

The regional assessment involved interviews with key stakeholders in the R&D ecosystem in Africa to identify priorities for ecosystem changes. These key informants included heads and key personnel in science, regulatory, funding, and manufacturing organizations, as well as conveners of innovators in Africa. They included representatives of the South African Health Products Regulatory Authority, AfricaBio (an independent non-proft stakeholders' association that represents Africa's biotechnology sector), the Drugs for Neglected Diseases Initiative, Institut Pasteur de Dakar, the Science for Africa Foundation, Amref Health Innovations, the African Union COVID-19 Commission, Africa CDC, and Ghana's Food and Drugs Authority.

区域评估包括与非洲研发生态系统的主要利益相关者进行访谈，以确定生态系统变化的优先事项。这些关键信息提供者的包括科学、监管、资助和行政部门、制造业组织的负责人和关键人员以及非洲创新机构者的召集人。他们包括来自南非健康产品监管局、AfricaBio(一个代表非洲生物技术部门的独立非营利性利益攸关方协会)、被忽视疾病药物行动、达喀尔巴斯德研究所、非洲科学基金会、Amref医疗创新、非洲联盟COVID-19委员会、非洲疾病预防控制中心和加纳食品和药物管理局。

THE CLINICAL TRIAL ECOSYSTEM IN AFRICA

Clinical trials that test medicines, vaccines, and diagnostics for high-burden neglected diseases, emerging infectious diseases, and maternal health conditions in countries in Africa need to be conducted in those countries themselves. These trials, say Toto and colleagues "can beneft from local healthcare knowledge and are better able to address context-specifc questions that would then lead to more effective interventions."[1] Yet, less than 10% of all clinical trials are conducted in Africa.[2] Trials in Africa are hindered by a range of barriers. For example, a qualitative study investigating barriers to conducting trials in Ethiopia found "limited funding allocation, weak regulatory and administrative systems, few learning opportunities, limited human and material capacity and poor incentives for conducting research."[3]

非洲国家的高负担被忽视疾病、新发传染病测试药物、孕产妇健康测试和诊断方法的临床试验需要在这些国家本身进行。Toto和同事们说，这些试验"可以从当地的医疗保健知识中获益，并且能够更好地解决当地人民的问题，从而导致更有效的干预。"然而，不到10%的临床试验是在非洲进行的[2]。非洲的临床试验受到一系列问题的阻碍。例如，一项有关在埃塞俄比亚进行试验的障碍的定性研究发现"资金分配有限、监管和行政系统薄弱、学习机会很少、人力和物质能力有限、开展研究的激励措施不足"[3]。

In May 2023, the Africa Centres for Disease Control and Prevention (Africa CDC) and the African Union Development Agency (AUDA-NEPAD) held a convening to examine the state of the clinical trial ecosystem in SSA and identify ways to strengthen its impact and efficiency.[4] Participants agreed that the current trials ecosystem is "not equipped to effectively manage a global health product pipeline that is expected to grow in both complexity and size." Recommendations arising from the convening included:

2023年5月，非洲疾病控制和预防中心和非洲联盟发展机构召开会议检查撒哈拉以南非洲临床试验生态系统的状态，并确定加强其影响和效率的方法[4]与会者一致认为，目前的试验生态系统"不具备有效管理预计在复杂性和规模上都将增长的全球健康产品管线的能力"。会议提出的建议包括:

- **Urgently improving coordination of trials**, including through the sharing and reporting of information, data, processes, and tools.
- **Establishing a new coordination mechanism** housed at Africa CDC and managed in partnership with AUDA-NEPAD, the African Vaccine Regulatory Forum (AVAREF), and the WHO Regional Office for Africa. Its mandate would be "evaluation of the pipeline of clinical trials in line with African public health and research priorities, aligning on fnancing needs and mechanisms, building cohesive capacity strengthening partnerships, and driving evaluation of the impact of these changes on the clinical trial ecosystem."[4]
- **Strengthening the clinical trials workforce**.

通过共享和报告信息、数据、程序和工具尽快改善试验的协调;

•在非洲疾控中心建立一个新的协调机制，由非洲发展新伙伴关系、非洲疫苗管理论坛和世卫组织非洲区域办事处合作管理，任务是"根据非洲公共卫生和研究优先事项，对正在进行的临床试验进行评估资助需求和机制，建立有凝聚力的能力建设伙伴关系，并推动对这些变化对临床试验生态系统影响的评估

*加强临床试验队伍建设。

THE REGULATORY SYSTEM IN AFRICA

Regulatory bodies in Africa have been working on three priorities: (i) the African Medicines Regulatory Harmonization (ARMH) initiative, which was "launched to accelerate access to quality, safe, effective medical products by optimizing the regulatory environment on the continent"[5] ; (ii) strengthening regulators, and (iii) setting up the African Medicines Agency (AMA). The ARMH process resulted in a pilot of a continent-wide review mechanism, with an information technology platform hosted by the South African Health Products Regulatory Authority (SAPHRA); capacity building is a large component of the process.

非洲的监管机构一直致力于三个优先事项:(i)非洲药品监管协调(ARMH)倡议，旨在通过优化非洲大陆的监管环境，快速获得优质、安全、有效的医疗产品[5]； (ii)加强监管机构，(iii)建立非洲药品管理局(AMA)。ARMH进程促成了一个全非洲审查机制的试点，其信息技术平台由南非卫生产品监管局托管；能力建设是这一进程的重要组成部分。

The strengthening of regulators is focused on the process of getting accreditation for advanced levels of maturity e.g., transitioning from maturity level (ML) 2 to ML 3, and putting in place interventions in partnership with global health actors to achieve the necessary progression. Progress has also been seen in setting up the AMA, with at least 26 countries now subscribed; the Africa Union is in the process of appointing a governing Board and a Director General. These interventions are taking place at three levels of governance: the continent level, with the Africa Union and associated entities; the regional level, such as through the Economic Community of West African States (ECOWAS) and the Southern African Development Community (SADC); and the national level to accommodate national priorities and needs.

Barriers to strengthening regulatory bodies include lack of human capacity, weak systems and processes, and inadequate fnancial resources. Since government funding is limited for most regulators, and no additional strategic investments have been made, nearly all countries depend on donor funding to fnance interventions to strengthen their regulatory bodies. Regulators attempt to maintain their independence and reduce potential conficts of interest by not taking funds from industry, since regulators review industry's submissions. Currently, there is no explicit disease prioritization pathway to help understand national priorities and priority products in South Africa, and the same problem likely

applies in most African countries. Finally, African regulators are confronted with the major challenge of navigating the WHO pre-qualification process to unlock local manufacturing, which is considered too slow and expensive for local manufacturers. It is hoped that current interventions, with the support of the WHO, can assist in resolving the bottlenecks at continental, regional and national levels.

加强监管机构的重点是获得高级成熟度认证的过程，例如，从成熟度级别(ML) 2过渡到ML 3，并与全球卫生部门合作实施干预措施以达到必要的进步。在建立非洲药品管理局方面也取得了进展，目前至少有26个国家加入了该组织；非洲联盟正在任命理事会和总干事。这些干预措施在三个治理层面进行：非洲大陆层面、非洲联盟和相关机实体；区域层面，例如通过西非国家经济共同体(西非经共体)和南部非洲发展共同体(南共体)；在国家层面，以适应国家的优先事项和需要。

加强监管机构还存在以下困难：人员能力不足、系统和程序薄弱以及缺乏财政资源。由于政府对大多数监管机构的资助有限，而且没有额外的资金投入，几乎所有国家都依靠捐赠资金为干预措施提供资金，以加强其监管机构。因为监管机构会审查行业提交的文件，所以监管机构试图通过不从行业获取资金来保持其独立性，并减少潜在的利益冲突。目前，没有明确的疾病优先排序途径来帮助了解南非的国家优先事项和优先产品，同样的问题可能适用于大多数非洲国家。最后，非洲监管机构面临的挑战是通过世卫组织资格预审程序才能启动当地生产，这对当地制造商来说过于缓慢和昂贵。希望在世卫组织的支持下，目前的干预措施能够帮助解决非洲大陆、区域和国家各级的瓶颈问题。

MANUFACTURING OF HEALTH PRODUCTS IN AFRICA 在非洲生产医疗产品

Key informants (KIs) argued that the main priority is to achieve “end-to-end” manufacturing, implying the whole value chain of manufacturing from laboratory to shelf. One of the major gaps that the KIs identified is production of active pharmaceutical ingredients (APIs)—Africa needs the capacity to produce these. The mRNA platform may be a game-changer in that it would not require APIs; however, the cold chain infrastructure required for mRNA is also a potential barrier.

Around a dozen countries in Africa are considered to have the capacity to build or strengthen their manufacturing capability, considering both public and private sector resources. Stakeholders propose that manufacturing platforms and product pipelines should not be duplicated. Instead, unique and focused manufacturing can happen in different regions of Africa, and these products can then be made available to the rest of the continent, provided barriers to distribution and procurement can be overcome.

关键信息提供者(KI)认为，首要任务是实现“端到端”制造，这意味着从实验室到货架的整个制造价值链。KI确定的主要差距之一是活性药物成分的生产——非洲需要具备生产这些成分的能力。mRNA平台可能会改变游戏规则，因为它不需要API；然而，mRNA所需的冷链基础设施也是一个潜在的挑战。

考虑到公共和私营部门的资源，非洲大约有十几个国家被认为有能力建立或加强其制造业能力。利益相关者建议不要重复建造生产平台和产品管线。相反，在非洲的不同地区可以进行独特和集中的生产，如果能够克服分销和采购方面的障碍，这些产品就可以提供给非洲大陆的其他地区。

Africa will need to have access to intellectual property (IP) to manufacture health products. Open science and innovation will be crucial. The patent pool and other IP owners could become partners to support the development of the R&D ecosystem in Africa. Part of the scholarship on the continent could be to track and trace IPs that are no longer under protection, and learn how to repurpose products and innovations that may have previously failed in light of new technologies. The ecosystem in Africa will require a much stronger cold chain if tools such as mRNA and monoclonal antibodies are going to be used. The temperatures in Africa can be very high, and tools that require storage levels at -70 degrees Celsius can make operations very difficult.

非洲将需要获得制造医疗产品的知识产权。开放的科学和创新将至关重要。专利池和其他知识产权所有者可以成为支持非洲研发生态系统发展的合作伙伴。在非洲大陆，奖学金的一部分可能是跟踪和追踪不再受保护的知识产权，并学习如何重新利用以前可能因新技术而失败的产品和创新。如果要使用mRNA和单克隆抗体等工具，非洲的生态系统将需要一个更强大的冷链。非洲的气温可能非常高，需要在零下70摄氏度储存的工具会使操作变得非常困难。

R&D GOVERNANCE IN AFRICA 非洲的研发治理

Stakeholders in Africa reported a lack of cohesive and structured processes to determine priorities for health R&D product development. At best, stakeholders have been able to reach some consensus on priority diseases, but these priorities are also adopted as a reaction to crises and tend to vary depending on the interests of conveners and participants

of such proceedings. As a result, there is no reputable platform currently known to facilitate such proceedings for SSA, particularly when one considers the need for a forward-looking perspective to planning.

KIs said that there is a range of infectious diseases, including emerging infections, and non-communicable diseases that are high priority for R&D. Products need to be developed in preparation for future pandemics. KIs argued that efforts in SSA in the wake of the COVID-19 pandemic to build biomanufacturing capability in preparation for future pandemics have been a positive outcome of the pandemic era. However, much work is still needed in mapping pathogens that constitute an outbreak threat.

非洲的利益攸关方报告说，确定医疗研发产品开发的优先事项亟需连贯和有组织的程序，最好利益攸关方能够就重点疾病达成一些共识，但这些优先事项也被当做危机应对、往往因此类程序的召集人和参与者的利益而异。因此，目前需要知名平台促进撒哈拉以南非洲SSA的此类程序，特别是当人们考虑到需要前瞻性的规划时。

关键信息提供者（KI）说有一系列传染病，包括新出现的传染病和非传染性疾病，是研发的高度优先事项。为未来的大流行做准备需要开发产品。KI认为，疫病大流行时代的积极成果是SSA为应对未来大流行病积极打造产能。然而，在绘制构成爆发威胁的病原体图谱方面仍需要做大量工作。

Stakeholders made it clear that conversations about health product prioritization in Africa will be have to be held both at national and regional levels before these are collated at the continent level. It also seems the actions or operations will also unfold much more smoothly if implemented at a regional level and national level. Therefore, focused discussions with ECOWAS, SADC and the West African Health Organization (WAHO) in Western Africa may bear fruit, perhaps together with groups in Northern and Central Africa.

At a continent level, a large role is played by the African Union; most representatives at this level are country presidents. However, much of the leadership in health is led by ministers of health, including leadership of biomanufacturing and product development. KIs pointed out the anomaly of having such ministers leading these conversations when their focus is generally only health services—they are rarely involved in manufacturing, science innovation, or the research enterprise. Stakeholders pointed out that in the countries in Africa that are leading in health product development, Egypt, Rwanda, and South Africa, their presidents—Kagame, El Sisi, and Ramaphosa—are the ones personally coordinating efforts around health innovation.

利益攸关方明确表示，必须先在国家和区域两级就非洲卫生产品的优先次序进行讨论，然后才能在整个大陆层面对这些问题进行整理。如果能在区域层面和国家层面执行，那么所有行动也会更加顺利地展开。因此，与西非经共体、南部非洲发展共同体和西非卫生组织在西非进行重点讨论可能会取得成果，也许还可以与北部和中部非洲的团体一起进行讨论。
在非洲大陆层面，非洲联盟发挥了很大的作用，这个层面的大多数代表是国家总统。然而，卫生领域的大部分领导是由卫生部长领导的，包括生物制造和产品开发的领导。KI指出，让这样的部长主导这些对话是不合适的，重点通常只关注医疗服务——他们很少涉及制造业、科学创新或研究机构。利益攸关方指出，在卫生产品开发方面处于领先地位的非洲国家，埃及、卢旺达和南非的总统——卡加梅、塞西和拉马福萨——都是亲自协调卫生创新方面的典范。

R&D FINANCING IN AFRICA 非洲研发融资

KIs said that R&D is currently mostly funded by international agencies and funders, with very little injection of funds from African governments. Countries that already have significant funding from their governments are the ones ahead in terms of manufacturing capabilities. Therefore, a clear shift is needed: African governments should inject a much larger proportion of public funds into R&D value chains and ecosystems. Funding is needed for capacity building, including human capacity development.

KI说，目前研发主要由国际机构和资助者资助，非洲政府的资金注入很少。那些已经从政府获得大量资金的国家在制造能力方面处于领先地位。因此，需要一个明确的转变：非洲各国政府应该提高公共资金投入研发价值链和生态系统的比例。能力建设需要资金，包括人力能力发展。

1. Toto N, Douglas E,GmeinerM, et al. Conducting clinical trials in sub-Saharan Africa: challenges and lessons learned from the Malawi Cryptosporidium study. Trials 2020;21:680

2. Singh N. Benefits of conducting clinical trials in developing countries like India. Pharmaceutical Regulatory Affairs. 2018;7(2):1–2.

3. Franzen SRP, Chandler C, Enquselassie F, et al. Understanding the investigators: a qualitative study investigating the barriers and enablers to the implementation of local investigator-initiated clinical trials in Ethiopia. BMJ Open 2013;3: e003616.

4. Africa CDC, AU-NEPAD. Optimizing efficiency and impact in the African clinical trials ecosystem. Meeting report. May 2023. https://africacdc.org/download/meeting-report-optimizing-efficiency-and-impact-in-the-african-clinical-trials-ecosystem/

5. Ndomondo-SigondaM, Azatyan S, Doerr P, et al. Best practices in the African Medicines Regulatory Harmonization initiative: Perspectives of regulators and medicines manufacturers. PLOS Glob Public Health 2023;3:e0001651.

5.3. Asia Pacific region: key regional shifts needed in the regional R&D ecosystem

亚太地区：区域研发生态系统所需的关键区域转变

INTRODUCTION 引言

The regional assessment involved consultations with 30 interviewees from a wide range of sectors. About half were from leading pharmaceutical and biotech companies, including major domestic and multinational firms in China and across the Asia Pacific region (APR). Interviewees were also from governmental agencies, such as China's National Medical Products Administration (the country's national regulatory agency), and from national level specialized organizations, such as the Chinese Center for Disease Control and Prevention (which reports to the cabinet-level National Health Commission).

Other stakeholders represented international, regional, and Chinese domestic not-for-profit organizations, industrial associations, and public institutions—including APACMed (the Asia Pacific Medical Technology Association, based in Singapore); the Chinese Preventive Medicine Association; the Global Health Drug Discovery Institute; and the China Chamber of Commerce for Import and Export of Medicines and Health Products. Finally, we interviewed infectious disease experts from hospitals in the Philippines and scholars from think tanks and universities in the region, including key informants in India and South Korea.

该区域评估涉及与来自各行各业的30名受访者进行磋商。大约有一半是来自领先的制药和生物技术公司，包括中国和亚太地区的主要国内和跨国公司。受访者还有来自政府机构，如中国国家药品监督管理局以及国家级专业组织

比如中国疾病预防控制中心(隶属于国家卫生健康委员会)。

其他利益相关者代表国际、地区和中国国内的非营利组织、行业协会和公共机构，包括APACMed(总部位于新加坡的亚太医疗技术协会)、中华预防医学会、全球卫生药物发现研究所、中国医药保健品进出口商会。最后，我们采访了菲律宾医院的传染病专家以及该地区智库和大学的学者，包括印度和韩国的关键信息提供者。

THE CLINICAL TRIAL ECOSYSTEM IN THE ASIA PACIFIC REGION 亚太地区临床试验生态系统

In recent decades, there has been a sharp rise in the number of trials conducted in the APR. For example, a study by Ali et al found a 7-fold increase in the annual number of registered clinical trials in Asia between 2008 and 2017.[1] This rise was driven in particular by sharp increases in Japan, China, Republic of Korea, and India.

The APR has substantial clinical trial capacity for infectious diseases, but it is concentrated in a few countries.[2] For example, Postigo analyzed all vaccine clinical trials as of March 2022, and found that just under one quarter (24.1%)

were conducted in the APR.[3] China was in the lead—responsible for a fifth of all vaccine trials in the APR and about 1 in 20 vaccine trials worldwide. The other countries where trials were concentrated were Australia, Japan, Republic of Korea, and Thailand. The increase in vaccine trials in more recent years might be related to the COVID-19 pandemic.

Given the benefits of trial networks, there have been several initiatives to establish such networks for infectious diseases at national and regional level. Examples include:

近几十年来，在亚洲进行的试验数量急剧增加。例如，Ali等人的一项研究发现，2008年至2017年期间，亚洲每年注册的临床试验数量增加了7倍。这一增长尤其受到日本、中国、韩国和印度的急剧增长的推动.[1]。

亚太地区具有相当大的传染病临床试验能力，但主要集中在少数几个国家.[2] 例如，Postigo分析了截至2022年3月的所有疫苗临床试验，发现只有不到四分之一(24.1%)在亚太地区国家进行。[3] 中国处于领先地位，负责亚太地区所有疫苗试验的五分之一，以及全世界约二十分之一的疫苗试验。其他试验集中在澳大利亚、日本、韩国和泰国。近年来疫苗试验的增加可能与COVID-19大流行有关。

鉴于试验网络的好处，国家和区域层面已经采取了若干举措打造这种传染病网络。例如：

- **The Indian Clinical Trial and Education Network (INTENT)**, launched by the Indian Council of Medical Research. INTENT is a "pan-India network of clinical trial sites, with the overarching goal of providing evidence-based, robust, and culturally sensitive solutions to priority health problems of the country through conduct of large multicenter clinical trials."[4]
- **The Asian Infectious Diseases Clinical Trials Network (ADVANCEID)**, a network of over 30 hospitals across Asia that collaborate on clinical trials for infectious diseases.
- **The Southeast Asia Infuenza Clinical Research Network**, which includes Indonesia, Thailand, and Vietnam.

由印度医学研究理事会发起的印度临床试验和教育网络(INTENT)。
INTENT是一个"泛印度临床试验站点网络，其总体目标是通过开展大型多中心临床试验，为该国优先卫生问题提供循证有效和文化敏感的解决方案。
•亚洲传染病临床试验网络(ADVANCEID)，这是一个由亚洲30多家医院组成的网络，在传染病临床试验方面进行合作。
•东南亚流感临床研究网络，包括印度尼西亚、泰国和越南。

- **The Asian Health and Welfare Initiative (AHWIN)**, created by the Japanese government in 2019, which has "promoted establishing a clinical research network to improve the infrastructure and development capacity of clinical research in Asia."[5]The network, called ARISE—the ARO (academic research organizations) Alliance for Association of Southeast Asian Nations (ASEAN) & East Asia—promotes regional clinical trials in Indonesia, the Philippines, Vietnam, and Thailand.
  日本政府于2019年提出的亚洲健康与福利倡议(AHWIN)，旨在“推动建立临床研究网络，以提高亚洲临床研究的基础设施和开发能力[5]。该网络被称为ARISE(东南亚国家联盟(东盟)和东亚联盟学术研究组织），促进印度尼西亚、菲律宾、越南和泰国的区域临床试验。

THE REGULATORY SYSTEM IN ASIA 亚洲的监管体系

While the regulatory landscape is diverse and heterogeneous in the APR, there is a general trend towards regulatory harmonization and convergence.[6] Japan, a founding regulatory member of the ICH, has played a leading role in this trend. China, Republic of Korea, Singapore, and the region of Taiwan are also ICH members; India and Malaysia are observers. The main regional harmonization initiative is ASEAN, founded in 1967, which now has 10 member states—its goals include "facilitating reorganization and harmonization within the member countries."[6] The association's Consultative Committee for Standards Quality and its Product Working Group on Pharmaceuticals take the lead in developing harmonization schemes across ASEAN member states.

National regulatory authorities (NRAs) in China, India, Indonesia, Thailand, and Vietnam are operating at maturity level (ML) 3.[7] The Republic of Korea and Singapore are operating at ML4 (Singapore was the first WHO member state to achieve ML4).

虽然亚太地区的监管格局多种多样、各不相同，但总体趋势是监管协调和趋同[6]。日本作为人用药品技术要求国际协调理事会（ICH）的创始监管成员发挥了主导作用。中国、韩国、新加坡也是ICH成员，印度和马来西亚是观察员。主要的区域协调倡议是成立于1967年的东盟，目前有10个成员国，其目标包括“促进成员国内部的重组和协调”[6]。协会的标准质量咨询委员会及其药品产品工作组在制定跨东盟成员国的协调方案方面发挥领导作用。

中国、印度、印度尼西亚、泰国和越南的国家监管机构正在以成熟水平(ML3)运行[7].韩国和新加坡正在以成熟水平(ML4)运行(新加坡是世卫组织第一个达到这一水平的会员国)。

MANUFACTURING OF HEALTH PRODUCTS IN ASIA 亚洲卫生产品的生产

Establishing vaccine security and self-sufficiency is of particular importance to Southeast Asia. Countries in the region are dependent on imports not only for COVID-19 vaccines, but also to a large extent for national immunization programs. Moreover, Southeast Asia has long been recognized as a hotspot for emerging infectious diseases.[8] Increasing vaccine development, manufacturing, and regulation capacity in the region as well as efforts to boost health system strengthening is therefore essential to ensuring that countries can sustain their immunization programs and respond effectively and efficientlyto future outbreaks and pandemics.[9] To achieve this goal, ASEAN established the ASEAN Vaccine Security and Self-Reliance (AVSSR) initiative.

建立疫苗安全和自给自足对东南亚特别重要。该地区各国不仅在COVID-19疫苗而且免疫接种项目在很大程度上方面也依赖进口此外，东南亚长期以来一直被认为是新兴传染病的热点地区[8]加强该地区疫苗开发、制造和监管能力，并努力加强卫生系统至关重要，这样才能确保各国能够维持其免疫规划，并有效和高效地应对未来的疫情和大流行[9]。为了实现这一目标，东盟成立了东盟疫苗安全和自立(AVSSR)倡议。

R&D GOVERNANCE IN ASIA 亚洲研发治理

Investment case modeling conducted by Open Consultants for the World Bank in 2023 showed that a coordinated investment approach in ASEAN countries would have many benefits.[9] Through investments in trial sites and manufacturing capacity for both traditional vaccine technologies and new mRNA vaccine technologies, ASEAN countries would be enabled to leverage their own research, product development, and manufacturing capacity rather than relying on external support. Investments in trial sites and manufacturing will be useful for a much broader range of infectious and non-communicable diseases, as well as for the development and production of other medical countermeasures such as therapeutics and diagnostics. Investments in local manufacturing will also produce new jobs thereby generating additional economic growth. Improved regulatory capacity will have an impact on the quality of locally produced medicines. In addition, vaccinations have multiple other socioeconomic benefits and they also have benefits throughout health systems.

Open Consultants为世界银行制作的2023年投资案例建模显示：在东盟国家进行统筹投资将有许多好处[9]。通过投资试验场地、传统疫苗技术和新的mRNA疫苗技术的制造能力，东盟国家将能够利用自己的研究、产品开发和制造能力，而不是依赖外部支持。对试验场和生产的投资将有助于更广泛的传染病和非传染性疾病，以及治疗和诊断等

其他医疗对策的制定和生产。对当地制造业的投资也将创造新的就业机会，从而推动额外的经济增长。监管能力的提高将对当地生产药物的质量产生影响。此外，疫苗接种还具有多种其他社会经济效益，并可惠及整个卫生系统。

However, NGOs and governments face a number of obstacles, including insufficient policy support, asymmetric information, limited awareness, and limited global health practice experience, particularly in China. Poor alignment between research institutions and businesses, alongside weak monitoring and early warning capabilities, also hinder the effective response to health emergencies. Despite strong political will for international cooperation, substantial action is lacking, and international assistance struggles to ensure health equity.
然而，非政府组织和政府面临着一些困难，包括政策支持不足、信息不对称、有限的认识和有限的全球卫生实践经验，中国也不例外。研究机构和企业之间的不协调，以及监测和预警能力薄弱，也阻碍了对突发卫生事件的有效应对。尽管国际合作的政治意愿很强，但缺乏实质性行动，国际援助难以确保卫生公平。

R&D FINANCING IN ASIA 亚洲研发融资

From an economic perspective, the obstacles faced in healthcare innovation and delivery in the APR are multifaceted. Financial challenges such as unaffordability, high R&D investment with low returns, and significant funding gaps impede progress. A lengthy R&D cycle, complex regulatory environments, and high costs for certifications like WHO prequalification exacerbate these issues. Additionally, market-related challenges like unclear demand, access barriers, and the high incidence of diseases in poor areas create a challenging landscape for new developments to gain traction. The mismatch between technology standards across borders and difficulties in obtaining rare samples further complicate the economic viability of health products.
从经济角度来看，亚太地区在医疗创新和服务方面面临的障碍是多方面的：资金方面的挑战，如负担不起、研发投资高但回报低、资金缺口大等都阻碍了进一步发展。漫长的研发周期、复杂的监管环境以及世卫组织等认证的高成本资格预审加剧了这些问题。此外，与市场有关的挑战，如需求不明确、市场准入壁垒和贫困地区的高发病率也为进一步发展带来挑战。跨国技术标准的不一致和进一步获取稀有样品的困难使卫生产品的经济可行性复杂化。

Medically, the industry grapples with inadequate and ineffective vaccines, disparities in expert levels, and limited drug certification fields. High skill requirements for medical trainers, cultural constraints limiting technology applications, and fuctuating disease stages demanding varied treatments present substantial hurdles. Moreover, the lack of consensus on medical product regulations and neglect of certain diseases highlight systemic issues in global healthcare. The medical community also contends with the need for more targeted investment, particularly in overlooked conditions like non-tuberculous mycobacterial diseases. The pharmaceutical sector faces its own challenges, including disparities in international standards and limited communication with global counterparts, which hinders China's ability to export domestically developed drugs. Technological deficiencies in curing diseases like HIV/AIDS and the infancy of vaccine development refect the sector's innovation struggles. Additionally, Chinese regulatory agencies face the complex task of aligning with rapidly evolving global clinical guidelines and continuously optimizing products post-market release.
在医学上，该行业面临着疫苗不足和疫苗效能低、专家水平差异以及药物认证领域有限等问题。对医疗培训人员的高技能要求、限制技术应用的文化限制以及需要不同治疗方法的不同疾病阶段构成了重大障碍。此外，医疗产品法规缺乏共识和被忽视的某些疾病凸显了全球医疗保健的系统性问题。医学界还认为有必要进行更有针对性的投资，特别是在非结核分枝杆菌病等被忽视的疾病方面。制药业面临着自身的挑战，包括国际标准的差异和与全球同行的有限沟通，这阻碍了中国出口自主研发药物的能力。在治疗艾滋病等疾病方面的技术缺陷和疫苗开发的初级阶段反映了杨业在创新方面的困境。此外，中国监管机构面临着与快速发展的全球临床指南保持一致并不断优化产品的复杂任务。

A range of solutions has been proposed to address the obstacles identified across economic, medical, pharmaceutical, NGO, and government sectors. Economically, the focus is on improving affordability and funding accessibility. This includes increasing health financing inputs, better policy formulation to enhance foreign aid, and creating information exchange platforms integrating academia, business, and government. There is a call for synchronization of foreign personnel training and fostering specialization and interdisciplinary collaboration. Capacity building is one of the most important tasks to fulfil, including specialized training for professionals in companies and for staff in drug regulatory administration. Given the diversity of countries in the region, a tailored approached must be adopted in a country-specific context, especially for low-resource countries. The World Health Organization has formulated its policies to promote local production with the focus on capacity building, which can be leveraged. Therefore, one or two regional training centers are needed.
要解决经济、医疗、制药、非政府组织和政府部门明确的困难，已经提出了一系列解决办法，在经济上，重点是提高可负担性和融资可及性。这包括增加卫生融资投入，更好地制定政策以加强对外援助，以及创建整合学术界、商界和政府的信息交流平台。呼吁同时进行外部人员培训、促进专业化和跨学科合作。能力建设是最重要任务之一，包括对公司专业人员和药品监督管理人员进行专门培训。鉴于本区域各国的多样性，必须根据各国的具体情况采取有针对性的办法，特别是对资源匮乏的国家。世界卫生组织制定了促进当地生产的政策，重点是能力建设。因此，需要一个或两个区域培训中心。

From a pharmaceutical perspective, the solutions include developing a more fexible research environment, encouraging innovation, and establishing partnerships supporting start-ups and established technologies. The survey advocates for a government-led effort in manufacturing and distribution, ensuring equitable access to products and technologies.

NGOs and governments play a crucial role in implementing the proposed solutions. They are advised to increase funding, focus on disease management, and facilitate communication among stakeholders. Solutions such as boosting international aid and adopting the public-private partnership model are suggested to aid in R&D and ensure the equitable distribution of technologies. By taking these steps, NGOs and governments can significantly contribute to the improvement of healthcare accessibility and affordability. In academia, recommendations are made to engage in dialogue with various stakeholders, such as regional entities, governments and professional institutions, promote the application of technologies through field interventions, and leverage public health projects to apply products and technologies more widely. Technology transfer needs to be promoted and patent pools can be created to meet the growing demand for the large-scale supply of badly needed products in the region. Moreover, market-shaping strategies are also needed to galvanize companies into R&D and production.
从制药的角度来看，解决方案包括发展更灵活的研究环境、鼓励创新以及建立支持初创企业和成熟技术的伙伴关系。该调查倡导政府主导制造和分销，确保公平获得产品和技术。
非政府组织和政府在实施拟议的解决方案方面发挥着关键作用。建议增加资金，注重疾病管理，并促进利益攸关方之间的沟通。建议通过增加国际援助和采用公私伙伴关系模式来帮助研发并确保技术的公平分配。通过采取这些步骤，非政府组织和政府可以为改善医疗保健的可及性和可负担性作出重大贡献。

在学术界，建议与各利益攸关方，如区域实体、政府和专业机构进行对话，通过实地干预措施促进技术的应用，并利用公共卫生项目更广泛地应用产品和技术。要促进技术转让，并且可以创建专利池来满足该地区不断增长的大规模急需产品的需求。此外，还需要市场塑造战略来激励企业投入研发和生产。

1 AliS, EgunsolaO, Bbar ZUD, Hasan SS. Clinical trials in Asia: A World Health Organization database study. Perspect Clin Res 2019;10: 121-124.

2 Yamey G, McDade KK, Mao W, Osakwe E. Financing research and development for new vaccines in Asia-Pacific developing countries. ESCAP Working Paper, 2022. https://artnet.unescap.org/publications/working-papers/financing-research-and-development-new-vaccines-asia-pacific-developing

3 Postigo A. Reseach and development in vaccines in the Asia-Pacific: state of play and the potential. ESCAP Working Paper, 2022

4 SabuST, Venkatraman S, Cherian JJ, et al. A review of clinical trials registered in India from 2008 to 2022 to describe the first-in-human trials. Perspect Clin Res 2024;15: 18-23.

5 Sonoda M, Urbiztondo MRU, Siburian MD, et al. Boosting multiregional clinical trials (MRCT) in Asia through the establishment of the Japan-led network for clinical research, the ARO alliance for ASEAN & East Asia (ARISE). Glob Health Med 2022;4: 247–249.

6 Han F, Weiss K. Regulatory trends in drug development in Asia Pacific. Ther Innov Regul Sci 2019;53:497-51.

7 https://www.who.int/publications/m/item/list-of-nras-operating-at-ml3-and-ml4

8 Morand S, Jittapalapong S, Suputtamongkol Y, et al. Infectious diseases and their outbreaks in Asia-Pacific: biodiversity and its regulation loss matter. PloS ONE 2014;9:e90032.

9 Mutasa R,Gandham R, Newmarch G, et al. ASEAN regional vaccine manufacturing and development. The World Bank Group. April 18, 2023. Chapter 5 includes the investment case prepared by Open Consultants. https://shorturl.at/tGJN6

REFERENCES参考文献

1. OgbuojiO. et al. Health and economic benefits of improving efficiencies in product development for neglected diseases, emerging infectious diseases, and maternal health, May 21, 2024. https://centerforpolicyimpact.org/wp-content/uploads/sites/18/2024/05/reforming-research-and-development-ecosystem.pdf
2. World Health Organization. Global immunization efforts have saved at least 154 million lives over the past 50 years. April 24, 2024.https://www.who.int/news/item/24-04-2024-global-immunization-efforts-have-saved-at-least-154-million-lives-over-the-past-50-years
3. Jamison DT, Murphy SM, Sandbu ME. Why has under-5 mortality decreased at such different rates in different countries?J Health Econ 48:16-25.
4. Schäferhoff M, Zimmerman A, Diab MM, et al. Investing in late-stage clinical trials and manufacturing of product candidates for five major infectious diseases: a modelling study of the benefits and costs of investment in three middle-income countries. Lancet Glob Health 2022;10:E1045-E1052.
5. Zimmerman A, Diab MM, Schäferhoff M, et al. Investing in a global pooled-funding mechanism for late-stage clinical trials of poverty-related and neglected diseases: an economic evaluation. BMJ Global Health 2023;8: e011842.
6. Bandara S, Chapman N, Chowdhary Vetal. Analysis of the health product pipeline for poverty-related and neglected diseases using the Portfolio-to-Impact (P2I) modeling tool. F1000Res 2020; 9:416.
7. Wellcome Trust. Towards a reformed research and development ecosystem for infectious disease. May 30, 2023. https://wellcome.org/reports/towards-reformed-research-and-development-ecosystem-infectious-disease
8. Policy Cures Research. The impact of global health R&D: the high return of investing in R&D for neglected diseases. Forthcoming.
9. Future of Global Health Initiatives. https://futureofghis.org/about/
10. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA 2020;323:844–853.
11. Wong CH, Siah KW, LoAW. Estimation of clinical trial success rates and related parameters. Biostatistics 2019; 20:273–86.
12. Another study found that the proportion of all drug development programs that lead to approval is 13.8%: KolluriS, Lin J, Liu R, et al. Machine learning and artificial intelligence in pharmaceutical research and development: a review. AAPS J 2022;24:19.
13. Gupta R, Srivastava D, SahuM, et al. Artificialintelligence to deep learning: machine intelligence approach for drug discovery. MolDivers 2021;25:1315–60.
14. Vaisman A, Linder N, Lundin J, et al. Artificial intelligence, diagnostic imaging and neglected tropical diseases: ethical implications. Bull World Health Organ 2020;98:288–9.
15. Leslie D, MazumderA, Peppin A, et al. Does 'AI' stand for augmenting inequality in the era of COVID-19 healthcare? BMJ 2021;372:n304.
16. Shaffer J, AlenichevA, Faure MC. The Gates Foundation's new AI initiative: attempting to leapfrog global health inequalities? BMJ Glob Health 2023;8:e013874.
17. Jayatunga MKP, Xie W, Ruder L, et al. AI in small-molecule drug discovery: a coming wave? Nat Rev Drug Discov 2022;21:175–6.
18. Nast C. DeepMind wants to use itsAIto cure neglected diseases. Wired UK. June 23, 2021. https://www.wired.co.uk/article/deepmind-alphafold-protein-diseases
19. DNDi. Harnessing AI and new technologies to meet neglected patients' needs. https://dndi.org/about/annual-reports/annual-report-2021/harnessing-ai-and-new-technologies-to-meet-neglected-patients-needs/
20. GulatiS, MattssonAH, Schussek S, et al 2023. Preclinical efficacy of a cell division protein candidate gonococcal vaccine identified by artificialintelligence. mBio 2023;14:e0250023.
21. GENTRL stands for Generative Tensorial Reinforcement Learning.
22. Deloitte. Intelligent drug discovery. Powered by AI. November 6, 2019. https://www2.deloitte.com/content/dam/Deloitte/ch/Documents/life-sciences-health-care/deloitte-ch-en-intelligent-drug-discovery.pdf
23. ZhavoronkovA, Ivanenkov YA, Aliper A, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nat Biotechnol 2019;37:1038–1040.
24. Insilico. New Milestone in Kidney Fibrosis. 2021. https://insilico.com/blog/pcc_kidney
25. Savage N. Tapping into the drug discovery potential of AI. Nature. News feature. May 27, 2021. https://www.nature.com/articles/d43747-021-00045-7
26. Exscientia. 2021 Annual report and Financial Statements. https://s28.q4cdn.com/460399462/files/doc_financials/2021/ar/2021-UK-Annual-Report.pdf
27. RAVEN™ is an AI model for uncovering unique cross-protective T-cell antigens, which can boost vaccine efficacy and response time. See: Persson G, Restori KH, Emdrup JH, et al. DNA immunization within silico predicted T-cell epitopes protects against lethal SARS-CoV-2 infection in K18-hACE2 mice. Front Immunol 2023;14:1166546.
28. Evaxion Biotech. Pipeline. https://www.evaxion-biotech.com/pipeline
29. Evaxion Biotech. Evaxion partners with pharmaceutical company Afrigen Biologics. September 20, 2023. https://investors.evaxion-biotech.com/news-releases/news-release-details/evaxion-partners-pharmaceutical-company-afrigen-biologics
30. Mason DJ, Eastman RT, Lewis RP, et al. Using machine learning to predict synergistic antimalarial compound combinations with novel structures. Front Pharmacol 2018;9:1096.
31. Rashid MBMA. Artificial intelligence effecting a paradigm shift in drug development. SLAS Technol 2021;26:3–15.
32. Ianco-González A, CabezónA, Seco-González A, et al. The role of AI in drug discovery: challenges, opportunities, and strategies. Pharmaceuticals (Basel) 2023;18;16:891.
33. See also: ShenY, LiuT, Chen J, et al. Harnessing artificial intelligence to optimize long term maintenance dosing for antiretroviral naive adults with HIV 1 infection. Adv Therap 2020;3:1900114.
34. Pantuck AJ, Lee D, Kee T, et al. Modulating BET bromodomain inhibitor ZEN 3694 and enzalutamide combination dosing in a metastatic prostate cancer patient using CURATE.AI, an artificial intelligence platform. Adv Therap 2018;1:1800104.
35. Aliper A, Kudrin R, Polykovskiy, et al. Prediction of clinical trials outcomes based on target choice and clinical trial design with multi-modal artificialintelligence. Clin PharmacolTher 2023;114:972-980.

36. KolluriS, Lin J, Liu R, et al. Machine learning and artificial intelligence in pharmaceutical research and development: a review. AAPS J 2022; 24:19.
37. Cramer G. Forward thinking for the integration of AI into clinical trials. ACRP. June 20, 2023. https://www.acrpnet.org/2023/06/forward-thinking-for-the-integration-of-ai-into-clinical-trials/
38. Thorlund K, GolchiS, Haggstrom J, et al. Highly Efficient Clinical Trials Simulator (HECT): Software application for planning and simulating platform adaptive trials. Gates Open Res; 2019;3:780.
39. CEPI. Machine vs nature: new machine learning platform to accelerate vaccine development against new viral threats. June 5, 2023. https://cepi.net/news_cepi/machine-vs-nature-new-machine-learning-platform-to-accelerate-vaccine-development-against-new-viral-threats/
40. CEPI. Using AI to speedup vaccine development against Disease X. July 18, 2023. https://cepi.net/news_cepi/using-ai-to-speed-up-vaccine-development-against-disease-x/
41. CEPI. Delivering pandemic vaccines in 100 days. What will it take? 2022. https://static.cepi.net/downloads/2024-02/CEPI-100-Days-Report-Digital-Version_29-11-22.pdf
42. Madhav NK, Oppenheim B, Stephenson N, et al. Estimated future mortality from pathogens of epidemic and pandemic potential. November 4, 2023. https://www.cgdev.org/sites/default/files/estimated-future-mortality-pathogens-epidemic-and-pandemic-potential.pdf
43. UK Government. 100 days mission: first implementation report. December 7, 2021.https://www.gov.uk/government/publications/100-days-mission-first-implementation-report/100-days-mission-first-implementation-report-html
44. Caruso C. An AI tool that can help forecast viral variants. October 11, 2023. https://hms.harvard.edu/news/ai-tool-can-help-forecast-viral-outbreaks.
45. Thadani NN, Gurev S, Notin P, et al. Learning from prepandemic data to forecast viral escape. Nature 2023;622: 818–825.
46. Vaisman A, Linder N, Lundin J, et al. Artificial intelligence, diagnostic imaging and neglected tropical diseases: ethical implications. Bull World Health Organ 2020;98:288–9.
47. Blanco-González A, CabezónA, Seco-González A, et al. The role of AI in drug discovery: challenges, opportunities, and strategies. Pharmaceuticals (Basel) 2023;16:891.
48. Adams, R., Alayande, A., Brey, Z. et al. A new research agenda for African generative AI. Nat Hum Behav 2023;7: 1839–1841.
49. HoodaY, Saha S. Code sharing and artificial intelligence can help decolonise public health modelling. BMJ 2024; 384:q27.
50. UK Government. AI regulation: a pro-innovation approach (white paper). August 3, 2023. https://www.gov.uk/government/publications/ai-regulation-a-pro-innovation-approach/white-paper
51. European Parliament. Artificial intelligence in healthcare. Applications, risks, and ethical and societal impacts. June 2022.https://www.europarl.europa.eu/RegData/etudes/STUD/2022/729512/EPRS_STU(2022)729512_EN.pdf
52. Brown DG, Wobst HJ, Kapoor A, et al. Clinical development times for innovative drugs. Nat Rev Drug Discov 2022;21:793–4.
53. Ramsey BW, Nepom GT, LonialS. Academic, foundation, and industry collaboration in finding new therapies. N EnglJ Med 2017;376:1762–9.
54. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N EnglJ Med 2021; 384:693-704.
55. Coates MM, EzzatiM, Aguilar GR, et al. Burden of disease among the world's poorest billion people: An expert-informed secondary analysis of Global Burden of Disease estimates. PLoS One 2021;16:e0253073.
56. Moore TJ, Heyward J, Anderson G, et al. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. BMJ Open 2020;10:e038863.
57. Gouglas D, LeTT, Henderson K, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimization study. Lancet Glob Health 2018;6:e1386-e1396
58. Iqvia Institute. November 16, 2023. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf
59. U.S. Food and Drug Administration. FDA takes additional steps to advance decentralized clinical trials. May 2, 2023. https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials
60. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. NPJ Digit Med 2020;3:101
61. Durán CO, Bonam M, Björk E, et al. Implementation of digital health technology in clinical trials: the 6R framework. Nat Med 2023;29:2693-2697.
62. Berry Consultants. FACTS. Fixed and Adaptive Clinical Trials Simulator. https://www.berryconsultants.com/wp-content/uploads/2014/09/FACTS-Overview.pdf
63. Berry Consultants. ADDPLAN. https://www.berryconsultants.com/software/addplan/
64. HECT – Highly Efficient Clinical Trial simulator.https://mtek.shinyapps.io/hect/
65. Sigfrid L, Maskell K, Bannister PG, et al. Addressing challenges for clinical research responses to emerging epidemics and pandemics: a scoping review. BMC Med 2020;18:190.
66. Financial Times. Airfinity gives decision makers big picture on health. November 14, 2023. https://www.ft.com/content/f7b3f9ff-b57a-4fcd-8dd7-83301b1908b9
67. National Center for Advancing Translational Sciences. Master protocol. https://toolkit.ncats.nih.gov/glossary/master-protocol/
68. SubbiahV. The next generation of evidence-based medicine. Nat Med 2023;29:49–58.
69. UNITE4TB. UNITE4TB concept. https://www.unite4tb.org/about/unite4tb-concept
70. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. ClinTrials 2016;13:358–66.
71. U.S. Food and Drug Administration. Real-world evidence. February 5, 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
72. Medidata. Synthetic control arm® in clinical trials. 2021. https://www.medidata.com/wp-content/uploads/2021/09/SCA-Whitepaper.pdf
73. BCG Global. Transforming clinical trials with real-world evidence. February 17, 2021. https://www.bcg.com/publications/2021/synthetic-control-arms-changing-clinical-trials
74. Wellcome Trust. Clinical trial networks for antibiotic development. 2016. https://www.wellcome.org/sites/default/files/clinical-trial-networks-for-antibiotic-development-wellcome-oct16.pdf
75. Oracle. Top 5 challenges in decentralized clinical trials. https://www.oracle.com/a/ocom/docs/industries/life-sciences/ls-top-5-challenges-decentralized-clinical-trials-wp.pdf

76. BhandariN, Upadhyay RP, Chowdhury R, et al. Challenges of adopting new trial designs in LMICs. Lancet Glob Health 2021;9:e575–6.
77. SekharA, Kang G. Human challenge trials in vaccine development. Semin Immunol 2020;50:101429.
78. Kaewkungwal J, Adams P, Sattabongkot J, et al. Conducting human challenge studies in LMICs: A survey of researchers and ethics committee members in Thailand. PLoS One 2019;14:e0223619
79. McKinsey & Company. Real-world data quality: What are the opportunities and challenges? https://www.mckinsey.com/industries/life-sciences/our-insights/real-world-data-quality-what-are-the-opportunities-and-challenge
80. Africa CDC. African Union and Africa CDC launches Partnerships for African Vacccine Manufacturing (PAVM), framework to achieve it and signs 2 MoUs. April 16, 2021. https://africacdc.org/news-item/african-union-and-africa-cdc-launches-partnerships-for-african-vaccine-manufacturing-pavm-framework-to-achieve-it-and-signs-2-mous/
81. World Health Organization. The mRNA vaccine technology transfer hub. https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub
82. World Health Organization. Recipients of mRNA technology from the WHO mRNA technology transfer hub. https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub/recipients-of-mrna-technology-from-the-who-mrna-technology-transfer-hub
83. Zeng W, Bajnauth D, Jarawan E, et al. Strengthening pandemic preparedness: Build the vaccine manufacturing capacity in low- and middle-income countries. Public Health Pract (Oxf) 2022;4:100326.
84. ASEAN. ASEAN leaders' declaration on ASEAN vaccine security and self-reliance (AVSSR). November 2, 2019. https://asean.org/asean-leaders-declaration-on-asean-vaccine-security-and-self-reliance-avssr/
85. Africa Centres for Disease Control and Prevention. USP and Africa CDC launch MOU to advance regional manufacturing and strengthen regulatory and laboratory systems in Africa. June 30, 2023.https://africacdc.org/news-item/usp-and-africa-cdc-launch-mou-to-advance-regional-manufacturing-and-strengthen-regulatory-and-laboratory-systems-in-africa/
86. Mutasa R,Gandham R, Newmarch G, et al. ASEAN regional vaccine manufacturing and development. The World Bank Group. April 18, 2023. https://shorturl.at/tGJN6
87. UNIDO, WHO. Establishing manufacturing capabilities for human vaccines (white paper). 2017. https://www.unido.org/sites/default/files/files/2017-12/Establishing-Manufacturing-Capabilities-for-Human-Vaccines-ebook.pdf
88. Boyd, John H. Biomanufacturing cost in cities around the globe. Genet Eng Biotechn N 2020;40:58-60.
89. African Vaccine Manufacturing Initiative, WHO, UNIDO. Vaccine Manufacturing and procurement in Africa. An analytical assessment of vaccine manufacturing capacity and procurement mechanisms for establishing sustainable vaccine manufacturing capacity in Africa. 2017. https://www.avmi-africa.org/wp-content/uploads/2017/09/VMPA-Study-e-book.pdf
90. Grootendorst P, Moradpour J, SchunkM, et al. Home remedies: how should Canada acquire vaccines for the next pandemic? May 2022. https://www.cdhowe.org/sites/default/files/2022-05/Commentary_622.pdf. Grootendorstetal cite the following articles: Sanofi Canada. Vaccines. https://www.sanofi.ca/en/products-and-resources/vaccines; Sanofi Canada. Sanofi to build new manufacturing facility in Toronto to strengthen domestic pandemic preparedness and increase global supply of high-dose infuenza vaccine. March 31, 2021. https://www.sanofi.com/en/media-room/press-releases/2021/2021-03-31-14-05-00-2202566; Pharmaceutical Technology. Novartis vaccine manufacturing facility, North Carolina. March 21, 2013. https://www.pharmaceutical-technology.com/projects/novartis-vaccine/?cf-view; Kansteiner F. Lonza plots $935M in capacity upgrades in Europe and U.S., plans to add 550jobs over next 3 years. Fierce Pharma. May 6 2021. https://www.fiercepharma.com/manufacturing/lonza-plots-nearly-1b-mammalian-capacity-upgrade-switzerland-and-new-hampshire-adding
91. Plotkin S, Robinson J, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing–an overview. Vaccine 2017;35:4064–71.
92. BioNTechSE. BioNTech achieves milestone: mRNA-based vaccine manufacturing. December 18, 2023. https://investors.biontech.de/news-releases/news-release-details/biontech-achieves-milestone-mrna-based-vaccine-manufacturing-0.
93. Pharmaceutical Technology. BioNTech mRNA vaccine manufacturing facility, Rwanda. April 24, 2024. https://www.pharmaceutical-technology.com/projects/biontech-mrna-facility-rwanda/?cf-view
94. Africanews. BioNTech mobile mRNA vaccine labs reach Rwanda. March 14, 2023. https://www.africanews.com/2023/03/14/biontech-mobile-mrna-vaccine-labs-reach-rwanda/
95. Univercells. Who we are. https://www.univercells.com/who-we-are
96. Quantoom Biosciences. https://quantoom.com/
97. Quantoom Biosciences. mRNA production reinvented. April, 2023. https://quantoom.com/wp-content/uploads/2023/04/Quantoom-Biosciences_Non-Confidential_2023-04.pdf
98. Quantoom Biosciences. A new paradigm in mRNA bioprocessing. How Ntensify reshapes affordability and reduces time-to-market. White paper. https://content.quantoom.com/white-paper-tco
99. Coalition for Epidemic Preparedness Innovations. CEPI 2.0 and 100 days mission. https://cepi.net/cepi-20-and-100-days-mission
100. Key informant interview with Quantoom representatives. Of the US$178 million in savings, US$51 million will be realized during the commercial launch (assuming a volume of 15 million vaccine doses), US$52 million during production ramp up (already at 100 million doses scale with Ntensify solution), and US$74 million during final scale production (100 million doses). Ntensify offers immediate capacity to produce at final scale production. CoGs includes CAPEX depreciation.
101. Key informant interview with Quantoom representatives. Most of the savings result from the optimized process and an optimized reagents concentration. Note that the saving is US$74 million due to rounding.
102. Key informant interview with Quantoom representatives. See also: Rybicki EP. First WHO/MPP mRNA technology transfer programme meeting. Lancet Microbe 2023;4:e564-e566.
103. King ML. How manufacturing won or lost the COVID-19 vaccine race. Vaccine 2024;42:1004–1012.
104. Africa CDC. Current and planned vaccine manufacturing in Africa: results from a joint assessment by Africa CDC, CHAI, and PATH. October 3, 2023. https://africacdc.org/download/current-and-planned-vaccine-manufacturing-in-africa-results-from-a-joint-assessment-by-africa-cdc-chai-and-path/
105. Paun C. Moderna pauses plans to build vaccine plant in Kenya. Politico Pro. April 11, 2024. https://subscriber.politicopro.com/article/2024/04/moderna-pauses-plans-to-build-vaccine-plant-in-kenya-00151773.
106. U.S. Department of State. PEPFAR sets bold manufacturing targets for Africa. December 13, 2022. https://www.state.gov/pepfar-sets-bold-manufacturing-targets-for-africa/
107. Global Fund. PEPFAR and Unitaid collaboration paves way to accelerate approval of African-manufactured HIV rapid tests. August 8, 2023. https://unitaid.org/news-blog/global-fund-pepfar-and-unitaid-collaboration-paves-way-to-accelerate-approval-of-african-manufactured-hiv-rapid-tests/#en

108. Sarin S. G20 presidency: fostering global collaboration to accelerate regional manufacturing for diagnostics. August 17, 2023. https://www.finddx.org/publications-and-statements/opinion-piece/g20-presidency-fostering-global-collaboration-to-accelerate-regional-manufacturing-for-diagnostics/

109. Fleming KA, Horton S, Wilson M, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet 2021;398:1997–2050.

110. PATH. Market failures and opportunities for increasing access to diagnostics In low- and middle-income countries. 2022. https://media.path.org/documents/Dx_MarketFailures_Report_2022_v1b.pdf

111. Greenhoe S, Guzman J. The role of regulation in advancing African vaccine manufacturing: policy options for Gavi. Center for Global Development. November 29, 2023. https://www.cgdev.org/blog/role-regulation-advancing-african-vaccine-manufacturing-policy-options-gavi

112. Policy Cures Research. A decade of R&D funding for platform technologies. 2022. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2022/06/30024039/2022-Snapshot-Platform-Technology.pdf

113. Policy Cures Research. G-FINDER Database. 2024. https://gfinderdata.policycuresresearch.org/

114. Yamey G. Developing vaccines for neglected and emerging infectious diseases. BMJ; 2021;372:n373.

115. Hodgson J. The pandemic pipeline. Nat Biotechnol 2020;38:523–32.

116. Sparrow E, Hasso-Agopsowicz M, Kaslow DC, et al. Leveraging mRNA Platform Technology to Accelerate Development of Vaccines for Some Emerging and Neglected Tropical Diseases Through Local Vaccine Production. Front. Trop. Dis 2022; 3:844039.

117. National Institute of Allergy and Infectious Diseases. Strategic plan for COVID-19 research—2021 update. 2021. https://www.niaid.nih.gov/sites/default/files/NIAID-COVID-19-Strategic-Plan-2021.pdf

118. Whitley J, Zwolinski C, Denis C, et al. Development of mRNA manufacturing for vaccines and therapeutics: mRNA platform requirements and development of a scalable production process to support early phase clinical trials. Transl Res 2022;242:38-55.

119. Wellcome Trust, IAVI. Expanding access to monoclonal antibody-based products: a global call to action. 2020. https://wellcome.org/sites/default/files/expanding-access-to-monoclonal-antibody-based-products.pdf

120. Liu J. The history of monoclonal antibody development – Progress, remaining challenges and future innovations. Ann Med Surg (Lond) 2014;3: 113-116.

121. Gupta R, Purcell LA, Corti D, et al. Pandemic preparedness strategies must go beyond vaccines. Sci Transl Med 2023;15:eadd3055.

122. Gottlieb RL, NirulaA, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19. JAMA 2021;325: 632-644.

123. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N EnglJ Med 2021;384:238-251.

124. Taylor PC, Adams AC, Hufford MM, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol 2021;21:382–393.

125. National Institutes of Health. Anti-SARS-CoV-2 monoclonal antibodies. February 29, 2024. https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/anti-sars-cov-2-monoclonal-antibodies/.

126. Zhou D, Ren J, Fry EE, et al. Broadly neutralizing antibodies against COVID-19. Curr Opin Virol 2023;61:101332.

127. Aleshnick M, Florez-Cuadros M, MartinsonT, et al. Monoclonal antibodies for malaria prevention. MolTher 2022;30:1810-1821.

128. GruellH, VanshyllaK, Tober-Lau P, et al. Safety and efficacy of a monoclonal antibody against malaria in Mali. N EnglJ Med; 2022;387:1833-1842.

129. Gaudinski MR, Coates EE, Novik L, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. Lancet 2019;393:889-898.

130. Rijal P, Donnellan FR. A review of broadly protective monoclonal antibodies to treat Ebola virus disease. CurrOpin Virol 2023;61:101339.

131. Nkuba-NdayseA, Dilue-KetiA, Tovar-Sanchez T, et al. Effect of anti-Ebola virus monoclonal antibodies on endogenous antibody production in survivors of Ebola virus disease in the Democratic Republic of the Congo: an observational cohort study. Lancet 2023;24:3,266-274.

132. Corey L, Gilbert PB, Juraska M, et al. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. N. Engl. J. Med. 2021;384:1003–1014.

133. Gieber L, Muturi-KioiV, Malhotra S, et al. Clinical and regulatory challenges and opportunities for monoclonal antibodies in low- and middle-income countries: lessons from COVID-19 and beyond. PharmaceutMed 2023;37:203-214.

134. Jones JM, Fleming-Dutra K, Prill MM. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices—United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:920-925.

135. European Medicines Agency. First RSV vaccine to protect infants 6 months of age and older adults. July 21, 2023. https://www.ema.europa.eu/en/news/first-rsv-vaccine-protect-infants-6-months-age-and-older-adults

136. U.S. Food and Drug Administration. FDA approves first respiratory syncytial virus (RSV) vaccine). May 3, 2023.https://www.fda.gov/news-events/press-announcements/fda-approves-first-respiratory-syncytial-virus-rsv-vaccine

137. Sharfstein J. Two new RSV products to protect infants. November 13, 2023. https://publichealth.jhu.edu/2023/two-new-rsv-products-to-protect-infants

138. Centers for Disease Control and Prevention. Healthcare providers: RSV prevention information. September 28, 2023. https://www.cdc.gov/vaccines/vpd/rsv/hcp/child.html

139. KiefferA, Beuvelet M, Sardesai A, et al. Expected impact of universal immunization with nirsevimab against RSV-related outcomes and costs among all US infants in their first RSV season: a static model. J Infect Dis 2022; 226(Suppl 2):S282-S292.

140. Karron RA. Preventing respiratory syncytial virus (RSV) disease in children. Science 2021;372:686–687.

141. Sparrow E, Adetifa I, Chaiyakunapruk N, et al. WHO preferred product characteristics for monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) in infants—key considerations for global use. Vaccine 2022;40:3506-3510.

142. World Health Organization. WHO preferred product characteristics for respiratory syncytial virus (RSV) vaccines. January 1, 2017. https://www.who.int/publications/i/item/WHO-IVB-17.11

143. Azatyan S. Strengthening the regulation of health products through networking, cooperation, and harmonization. Technical briefing seminar on medicines and health products, May 8-12, 2023. https://shorturl.at/xIY19

144. World Health Organization. Saudi Arabia regulatory system becomes third to reach WHO maturity level 4. October 30, 2023. https://www.who.int/news/item/30-10-2023-saudi-arabia-regulatory-system-becomes-third-to-reach-who-maturity-level-4

145. World Health Organization. WHO Listed Authority (WLA). A framework for evaluating and publicly designating regulatory authorities as WHO Listed Authorities (WLAs). https://www.who.int/initiatives/who-listed-authority-reg-authorities

146. World Health Organization. List of National Regulatory Authorities (NRAs) operating at maturity level 3 (ML3) and maturity level 4 (ML4) (as benchmarked against WHO Global Benchmarking Tool (GBT)). As of October, 2023. https://cdn.who.int/media/docs/default-source/medicines/regulatory-systems/wla/list-of-nras-operating-at-ml3-and-ml4.v2.pdf?sfvrsn=ee93064f_14&download=true

147. Nkubito BM, GeyselsY. The African Medicines Agency: impacts on the continent's clinical trials regulation. Applied Clinical Trials. June 20, 2023. https://shorturl.at/jEFPX

148. Sharpe DJ. Shorter timelines, evolving strategies: four key trends in regulatory approvals of new medicines. Clarivate. August 2, 2022. https://clarivate.com/blog/shorter-timelines-evolving-strategies-four-key-trends-in-regulatory-approvals-of-new-medicines/

149. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. https://www.ich.org/

150. Ahonkhai V, Martins SF, PortetA, 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 2016;16;11:e0166515.

151. Miller JE, Mello MM, Wallach JD, et al. Evaluation of drug trials in high-, middle-, and low-income countries and local commercial availability of newly approved drugs. JAMA Netw Open 2021;4:e217075

152. Sithole T, MahlanguG, Capote V, et al. Evaluation of the review models and approval timelines of countries participating in the Southern African Development Community: Alignment and strategies for moving forward. Front Med 2021;8:742200.

153. Tanzania Medicines and Medical Devices Authority. The ZAZIBONA collaborative medicines registration procedure. https://www.tmda.go.tz/pages/the-zazibona-collaborative-medicines-registration-procedure

154. Compared to the review of new drugs (as assessed in the study by Miller et al – reference 151), the regulatory process for generics (assessed by Sithole et al – reference 12) should take less time and resources, i.e., the ZAZIBONA timelines should have been comparatively shorter.

155. U.S. Food and Drug Administration. International regulatory harmonization. March 26, 2020. https://www.fda.gov/drugs/cder-international-program/international-regulatory-harmonization

156. Ndomondo-SigondaM, MiotJ, Naidoo S, et al. Harmonization of medical products regulation: a key factor for improving regulatory capacity in the East African Community. BMC Public Health 2021; 21:187.

157. MwangiJM. Towards African medicines regulatory harmonization: the case of the East African Community. Pharm Policy Law 2016;18:91–8.

158. Schofield I. Janssen pilot speeds up African approvals as harmonization project expands. February 6, 2017.http://pink.citeline.com/PS119980/Janssen-Pilot-Speeds-Up-African-Approvals-As-Harmonization-Project-Expands

159. PATH. Making the case: How regulatory harmonisation can save lives in Africa. December 2018. https://www.path.org/resources/making-case-how-regulatory-harmonisation-can-save-lives-africa/

160. Liberti L. Globally applicable facilitated regulatory pathways to improve equitable access to medicines. 2017. Utrecht University Repository. http://dspace.library.uu.nl/handle/1874/353474

161. Ndomondo-Sigonda M, Azatyan S, Doerr P, et al. Best practices in the African Medicines Regulatory Harmonization initiative: Perspectives of regulators and medicines manufacturers. PLOS Glob Public Health 2023; 26:3(4):e0001651.

162. BolislisWR, de Lucia ML, Dolz F, et al. Regulatory Agilities in the Time of COVID-19: Overview, Trends, and Opportunities. ClinTher 2021;43:124e139.

163. Rodier C, Bujar M, McAuslane N, et al. Use of the Certificate for Pharmaceutical Products (CPP) in 18 maturing pharmaceutical markets: comparing agency guidelines with company practice. Ther Innov Reg Sci. 2020:1–11.

164. Wellcome Trust. Strengthening regulatory systems in LMICs. 2022. https://cms.wellcome.org/sites/default/files/2022-07/strengthening-regulatory-systems-in-low-and-middle-income-countries-improving-the-sustainability-of-the-vaccine-innovation-ecosystem-in-africa.pdf

165. Rwanda Food and Drug Authority. Cooperation in the regulation of medical products. August 2021. https://rwandafda.prod.risa.rw/news-details/agreement-mou-was-signed-between-rwanda-and-tanzania-governments-for-collaboration-between-the-nras-of-the-2-countries-rwanda-fda-and-tmda

166. Guzman J, PrashantY. To increase vaccine manufacturing in LMICs, we also need to strengthen regulatory capacity. Center for Global Development. May 25, 2021. https://www.cgdev.org/blog/increased-vaccine-manufacturing-lmics-we-also-need-strengthen-regulatory-capacity

167. Kearny B, McDermott O. The challenges for manufacturers of the increased clinical evaluation in the European Medical Device Regulations: A Quantitative Study. Ther Innov Regul Sci 2023; 57(4): 783–796. See also: VDE Health. The EU Medical Device Regulation (MDR): What is changing. February 29, 2024. https://www.vde.com/topics-en/health/consulting/the-eu-medical-device-regulation-mdr-what-changes

168. African Union Development Agency-NEPAD. African Union Smart Safety Surveillance (AU-3S). https://www.nepad.org/microsite/african-union-smart-safety-surveillance-au-3s

169. Chong SSF, Kim M, LimoliM, et al. Measuring progress of regulatory convergence and cooperation among Asia-Pacific Economic Cooperation (APEC) member economies in the context of the COVID-19 pandemic. Ther Innov Regul Sci. 2021;55:786-798.

170. European Commission. Strengthening Rwanda Food and Drug Authority's regulatory functions related to medicinal products including vaccine. https://international-partnerships.ec.europa.eu/news-and-events/stories/lessons-and-successes-rwanda-food-and-drug-authority-and-team-europe-twinning-project_en

171. Policy Cures Research. Neglected disease research and development: The higher costs of lower funding. 2023 Neglected Disease G-FINDER report. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2024/01/08035109/2023-Neglected-Disease-G-FINDER-report.pdf

172. Policy Cures Research calculated that "in the absence of any infation, global funding would have fallen by only 3.0%". See reference 171.

173. Policy Cures Research. G-FINDER Database. https://gfinderdata.policycuresresearch.org/

174. International Pandemic Preparedness Secretariat, Policy Cures Research. 100 days mission scorecard: Today's data to inform tomorrow's preparedness. January 2022. https://d7npznmd5zvwd.cloudfront.net/prod/uploads/2024/01/100-Days-Mission-Scorecard-Report.pdf

175. International Pandemic Preparedness Secretariat. 100 days mission: Therapeutics roadmap. January 2024. https://d7npznmd5zvwd.cloudfront.net/prod/uploads/2024/01/100-Days-Mission-Therapeutics-Roadmap.pdf

176. Policy Cures Research. Sexual and reproductive health research and development: Beyond spill-overs. 2023. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2023/10/04050842/2023-SRH-G-FINDER.pdf

177. Access to Medicine Foundation. 2022 Access to Medicine Index. Special report: Women's health and SRHR. November 25, 2022. https://accesstomedicinefoundation.org/resource/what-is-the-role-of-r-and-d-in-addressing-srhr-needs-in-low-and-middle-income-countries

178. Access to Medicine Foundation. 2022 Access to Medicine Index. November 15, 2022. //accesstomedicinefoundation.org/resource/2022-access-to-medicine-index

179. Merck for Mothers, Ferring Pharmaceuticals and WHO collaborated to support the advancement ofFerring's proprietary and investigational heat-stable carbetocin for the prevention of postpartum haemorrhage, which is better suited to use in LMICs as it can be stored and transported at much higher temperatures than oxytocin; however, it still needs to be administered intramuscularly.

180. Yamey G, Schäferhoff M, Moran M, et al. Developing an aggregator mechanism for late-stage clinical trials of neglected disease product candidates. The Center for Policy Impact in Global Health. Duke Global Working Paper Series 23. October 2020. k/our-publications/developing-an-aggrega-

181. CEPI. Global community comes together in support of 100 days mission and pledges over $1.5 Billion for CEPI's pandemic-busting plan. March 8, 2022. https://cepi.net/ andemic-busting-plan/

182. Schäferhoff M, Chodavadia P, Martinez S, et al. International funding for global common goods for health: an analysis using the Creditor Reporting System and G-FIND- ER databases. Health Syst Reform 2019;5:350-365.

183. International Pandemic Preparedness Secretariat, FIND. Embedding diagnostic best practice to improve pandemic preparedness: An independent report from the Inter- national Pandemic Preparedness Secretariat and FIND. 2023. -Report_2023.pdf

184. Xu M, Benn C, Reid-Henry S, Brown T, Zhou S, Yang J, Chen Y, Wang Z. Rethinking international financing for health to better respond to future pandemics. BMJ Glob Health 2023;8(11):e012988.

185. World Health Organization, World Bank. Analysis of pandemic preparedness and response (PPR) architecture, financing needs, gaps and mechanisms. 2022.

186. Ridley DB. Priority review vouchers. Durham (NC): Duke University Fuqua School of Business. ttps://sites.fuqua.

187. Ridley DB, Lasanta AM, Storer Jones F, et al. European priority review vouchers for neglected disease product development. BMJ Glob Health 2024;9:e013686

188. Valneva. Valneva gibt Verkauf seines Priority Review Vouchers für $103 Mio bekannt. February 5, 2024. le-of-

189. Ridley DB, Ganapathy P, Kettler HE. US tropical disease priority review vouchers: Lessons in promoting drug development and access. Health Aff 2021; 40(8).

190. U.S. Government Accountability Office. Drug development: FDA's priority review voucher programs (GAO-20-251). January 31, 2020. 251

191. Aerts C, Barrenho E, Miraldo M et al. The impact of the priority review voucher on research and development for tropical diseases. PharmaceutMed 2022;36(3):189-197.

192. Ridley DB. Priorities for the Priority Review Voucher. Am J Trop Med Hyg 2017; 96:14–15.

193. Ridley DB, Sánchez AC. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. Lancet 2010;376:922-7.

194. Bank D. Guaranteed Impact. Stanford Social Innovation Review. Supplement. 2016.

195. Reuters: Africa to get state-of-art HIV drugs for $75 a year. September 21, 2017.

196. Clinton Health Access Initiative. New high-quality antiretroviral therapy launched in South Africa and Kenya, available in 90 low- and middle-income countries at re- duced price. September 21, 2017.

197. ReliefWeb. Bill & Melinda Gates Foundation commits $120 million to accelerate access to COVID-19 drug, lower prices for developing countries. October 19, 2021.

198. Yadav P. How the pandemic changed the future of work. Financial Times. October 15, 2023.

199. The Global Fund. Global partnership to make available 120 million affordable, quality COVID-19 rapid tests. October 20, 2023.

200. World Health Organization. Global Health Expenditure Report 2023.

201. Reid M, AgbassiYJP, Arinaminpathy N, et al. Scientific advances and the end of tuberculosis: a report from the Lancet Commission on Tuberculosis. Lancet 2023;402:10411, 1473-1498.

202. Suleman F, Low M, MoonS, Morgan SG. New business models for research and development with affordability requirements are needed to achieve fair pricing of medi- cines. BMJ2020;368:10–2.

203. Adam T, RalaidovyAH, Ross AL, et al. Tracking global resources and capacity for health research: time to reassess strategies and investment decisions. Health Res Policy Syst 2023;21:93.

204. Africa CDC. (2023). Risk ranking and prioritization of epidemic-prone diseases. February 26, 2023.

205. In addition to Asian countries, APEC also includes several countries from North and LatinAmerica and the Pacific.

206. Africa CDC. Meeting report: optimizing efficiency and impact in the African clinical trials ecosystem. November 8, 2023.

207. Summers LH, Jamison DT, et al. Global health 2050: challenges and opportunities in the post-COVID world. Lancet, 2024. Forthcoming.

Gavin Yamey, Director Trent Hall, Room 113 310 Trent Drive
Durham 27710
Twitter: @gyamey
centerforpolicyimpact.org

OPEN CONSULTANTS

Marco Schäferhoff, PhD Managing Director
Jägerstr. 54/55
10117 Berlin, Germany +49(0)17681037928
mschaeferhoff@openconsultants.org openconsultants.org
linkedin.com/company/open-consultants