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REVIEW

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# Overcoming barriers to medical countermeasures: Strengthening global biosecurity

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**ABSTRACT**

The COVID-19 pandemic revealed global disparities in accessing medical countermeasures, as high-income countries prioritised their own interests while disregarding low- and middle-income countries. Despite global efforts to ensure an equitable pandemic response, these initiatives largely failed to achieve their objectives for LMICs due to systemic inequalities. This review critically examines these disparities, identifying that excessive stockpiling by HICs, fragmented international coordination, inadequate research and manufacturing capacity, restricted access to emergency research funding, intellectual property constraints, unequal participation in clinical trials, and inadequate regulatory harmonisation collectively hinder LMICs ability to respond effectively. By analysing diverse case scenarios and global response strategies, all plausible key shortcomings that contributed to the failure of coordinated pandemic preparedness were highlighted. Based on these insights, actionable strategies are proposed to address these gaps in LMICs so as to ensure affordability, accessibility, and equitable distribution of vaccines, diagnostics, and biotherapeutics in future public health emergencies, strengthening global biosecurity.

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## Introduction

Medical countermeasures (MCMs) are medicines and medical supplies that are used for diagnosing, preventing, and treating diseases related to chemical, biological, radiological, or nuclear (CBRN) threats or naturally occurring emerging infectious diseases.[1–3] These include vaccines, blood products, antibodies, antimicrobials, antivirals, diagnostic kits, and personal protective equipment (PPE), which play a pivotal role in reducing mortality during public health emergencies.[1–3] The coronavirus disease 2019 (COVID-19) pandemic has undisputedly become one of the most significant medical catastrophes in human history.[4] Since the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, nearly 209 million people have been diagnosed[4], resulting in over 6.8 million deaths.[5] The pandemic's impact has driven extensive efforts to develop treatment strategies.[4] During the early stages of the Wuhan-alpha wave of SARS-CoV-2, medicines like lopinavir/ritonavir, convalescent plasma, remdesivir, and monoclonal antibodies (mAbs) were used. Therapies like sotrovimab and molnupiravir, as well as anti-inflammatory drugs like tocilizumab, anakinra, baricitinib, and sarilumab, were made available during the Delta wave. As the Omicron variant emerged, newer treatments like tixagevimab/cilgavimab and PF-07321332/ritonavir were deployed to address variant-specific challenges.[6] The COVID-19 pandemic has accelerated the research and development (R&D) of MCMs at an unprecedented pace, with the rapid implementation of pharmaceutical interventions (PIs) such as vaccines, diagnostics and biotherapeutics, and non-pharmaceutical interventions (NPIs), including personal protective, environmental (N95 masks, gloves, face shields and hand hygiene), environmental (disinfection and ventilation) and community measures (social distancing and travel ban) implemented worldwide.[7–9] However, the pandemic revealed that the existing framework for the development, manufacturing, allocation, and distribution of these MCMs favoured high-income countries (HICs), leaving low- and middle-income countries (LMICs) underserved.[9,10] This is evidenced by the gap of over 100 days between the initial COVID-19 vaccination in low-income countries (LICs) and HICs,[11] as depicted in Figure 1. This illustrates the necessity for a global, robust, integrated, and end-to-end platform that can facilitate quick and equitable access to MCMs with a resilient healthcare system for pandemic prevention, preparedness, and response (PPPR)[20–22] Multiple forums, viz., the World Health Assembly, the Group of Twenty (G20), the Group of Seven (G7), etc., have deliberated on plausible solutions to enhance access to MCMs, and it is vital to ensure that these efforts are complementary and converging toward a shared goal.[20] Rapid and equitable access to MCMs is critical for mitigating the

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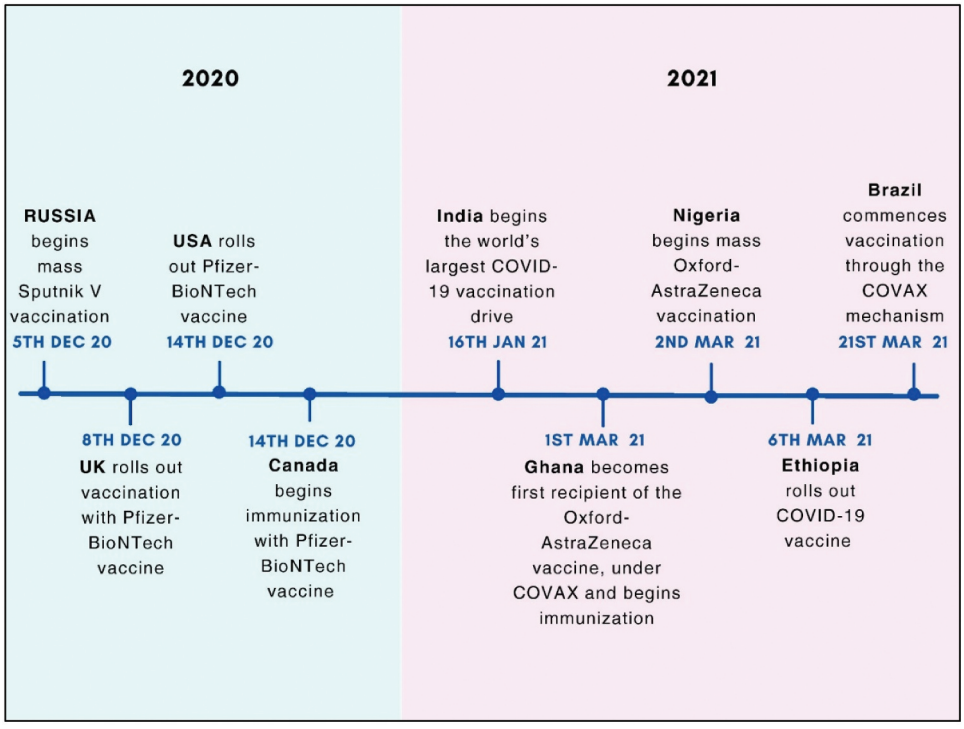


**Figure 1.** Timeline of COVID-19 vaccine rollout: HICs & LMICs.[12–19]

risks of future pandemics, given the prolonged timelines required to develop and deploy these MCMs so as to identify and combat disease transmission.[23] In this article, we analysed various barriers encountered during the COVID-19 pandemic causing MCM inaccessibility, the impact of governance policy framework and mitigation plans, and the contribution of global organisations toward PPPR, and suggested practical strategies to be implemented to enhance biosecurity as part of future public health emergency response.

## Method

This article is based on a literature review and desk research. A systematic search was conducted using Google, Google Scholar, PubMed Central, Web of Science, and preprint servers such as bioRxiv to retrieve relevant articles, reports, policy papers, and other relevant documents. We reviewed institutional websites such as the Africa Centres for Disease Control and Prevention (Africa CDC), Program for Appropriate Technology in Health (PATH), the World Health Organization (WHO), the Pan American Health Organization (PAHO), the United Nations International Children's Emergency Fund (UNICEF), and the Coalition for Epidemic Preparedness Innovations (CEPI) to gather related report insights. The review prioritised publications in English that focused on MCMs, including diagnostics, vaccines, and biotherapeutics, and detailed insights into financial, logistic and supply chain, research and development (R&D), intellectual property (IP), regulatory, and other socio-economic barriers specific to LMICs. We used an iterative search process while writing the manuscript to ensure the inclusion of all case scenarios with a focused approach to fully evaluate the challenges associated with MCMs accessibility and suggest plausible solutions that could be put into action for future pandemics.

## Inequity in access to medical countermeasures: case scenarios

### *Limited supply of vaccines, diagnostics, and biotherapeutics*

#### *Vaccines*

The limited presence of R&D facilities and manufacturing capacity in a few countries has impacted the timely deployment of MCMs, particularly LMICs.[9] This is mainly due to a lack of incentives to repurpose or expand the existing manufacturing capacity, a shortage of experienced and well-trained staff, limited procurement resources, and insufficient technical expertise.[24,25] Ali et al. emphasised that access can be further limited by factors such as travel time and cost, the challenges of balancing healthcare and work-seeking, safety concerns where there is political instability, vaccine hesitancy, and lack of awareness of immunisation services.[26] The US Pharmacopeia (USP) reported that 99% of vaccines are imported across Africa, and many countries are reliant on donations or donor-driven initiatives.[27] Reza et al. discovered internal distribution barriers faced by LMICs during the COVID-19 pandemic, primarily due to inadequate cold chain systems and storage facilities for vaccines.[28] For instance, the United Nations Children's Fund (UNICEF), through the COVID-19 Vaccines Global Access (COVAX) initiative, delivered 26 ultra-low temperature freezers to Bangladesh and 3 to Ukraine, enabling the storage and distribution of Pfizer

COVID-19 vaccines.[29,30] A joint statement by WHO and UNICEF in 2014 revealed that 20% of health facilities lack cold chain equipment, 14% had non-functional cold chain equipment, 41% had equipment that performed poorly, 23% had outdated cold chain technologies, and only 2% had a functional cold chain with optimal technology.[31]

### Diagnostics

LMICs face barriers along the diagnostic value chain, which reduces their effectiveness and efficiency.[32,33] The 2022 PATH report highlights nine major market failures that act as the significant barriers to diagnostic supply security in LMICs. These include limited investments, insufficient workforce, deterring regulations, inefficient purchasing and procurement, operational inefficiencies, inadequate infrastructure and technology, high costs, low trust, and inadequate government and policy support.[34] These challenges are mainly responsible for the global inequity in access to diagnostic testing, with approximately 47% of the world's population lacking proper diagnostic services. The situation is even more severe in LMICs, where only 19% of patients have access to adequate diagnostics, further exacerbating health disparities.[34] Even the 2021 Lancet Commission on Diagnostics reported that limited local R&D, manufacturing, and distribution of diagnostics are major contributors to the lack of affordability in LMICs.[34,35] For instance, the shortage of ribonucleic acid (RNA) extraction kits and quantitative reverse transcription-polymerase chain reaction (qRT-PCR) materials and machines hampered the accurate identification of virus carriers, as demonstrated by Alcántara et al.[36]

### Biotherapeutics

The accessibility of biotherapeutics, such as recombinant proteins and monoclonal antibodies (mAbs), in LMICs is impeded by several factors, such as health infrastructure limitations, high production, import, and distribution costs, as well as significant barriers to the market entry of biosimilars.[37–39] For instance, Moore and Gray emphasised that inadequate production capacity for COVID-19 mAbs acts as a major hurdle for African nations, depriving vulnerable populations of access to essential treatments.[25] Similarly, Gieber et al. substantiated that LMICs have licensed far fewer mAbs than high-income countries (HICs), limiting their ability to fully benefit from these advanced therapies.[40] For instance, only a small fraction of the mAbs authorised in the United States and European Union are approved for use in LMICs. By late 2022, six mAbs had been licensed for the treatment of COVID-19 in the United States and Europe, but only a few were available in LMICs.[40] According to a 2020 report by Wellcome and the International AIDS Vaccine Initiative (IAVI), only 20% of global mAb sales occurred outside the United States, Europe, and Canada.[37,41] Africa, which accounts for 17% of the global population, represented just 1% of mAb sales.[37,42] Introducing biosimilars represents a viable avenue for enhancing access to mAbs in LMICs.[40] However, some LMICs lack clear biosimilar guidelines, due to which developers are hesitant to enter these markets.[40]

### Stockpiling and vaccine hoarding

In alignment with the WHO recommendations, the majority of the developed countries maintain significant stockpiles of medical supplies, including vaccines, antiviral drugs, gloves, gowns, masks, and syringes, to prepare for public health emergencies.[43] However, stockpiling by HICs often limits the availability of these supplies in LMICs.[44–46] Boro and Stoll, Kavanagh et al. Ondoa et al. and Peeling et al. all evidenced that HICs significantly outspent LMICs to secure access to personal protective equipment (PPE), ventilators, vaccines, diagnostics, and biotherapeutics.[47–50] Furthermore, Tatar et al. and Kunyenje et al. emphasised that HICs were widely criticised for stockpiling COVID-19 vaccines, reserving additional doses for booster shots by early 2022, even as some low-income countries (LICs) struggled to administer a single dose to significant portions of their populations.[51,52] Previous pandemics have observed similar patterns of inequity. For instance, during the 2009 h1N1 pandemic, HICs prioritised purchasing and stockpiling vaccines, leaving limited donations to LMICs despite interventions by the WHO and the United Nations.[53] This disparity was further evident during the monkeypox outbreak, where HICs, such as the United States, secured Imvanex vaccine stockpiles from a sole manufacturer for their population, neglecting the urgent needs of endemic regions.[54]

The Center for Global Development (CGD) 2022 report mentioned that HICs signed advance purchase agreements (APAs) for COVID-19 vaccines as early as May 2020, middle-income countries (MICs) finalised contracts three months later, and LICs followed five months thereafter.[23] Gonsalves et al. and Holzer et al. reported that HICs hoarded vaccines far beyond their population needs through the APA mechanism. For instance, by November 2020, HICs had already secured 51% of the 7.48 billion doses of COVID-19 vaccines projected to be produced by 13 manufacturers, with 80% of Pfizer's vaccines purchased by the United States, the United Kingdom, the European Union, and Japan, as corroborated by So, Woo, Saksena, Yamey, and Amaya and De Lombaerde.[55–58] Canada too procured enough doses to vaccinate its citizens 10 times over, while the United Kingdom pre-ordered at least 400 million doses, sufficient for ≥5 doses per citizen.[56,59,60] Tagoe et al. Burgess et al. and Figueroa et al. further emphasised that the lack of transparency in vaccine pricing across countries and manufacturers significantly deepened inequities.[49–51] For instance, the European Union in 2021 paid $3.50 per dose for the Oxford-AstraZeneca vaccine, while South Africa paid $5.25 per dose and Uganda $7 per dose.[61] This disparity left many LMICs unable to procure sufficient vaccines for their populations, underscoring the urgent need for equitable pricing and transparent procurement processes.[62–64]

### Disparities in emergency health research funding

Emergency care research continues to face substantial funding and resource limitations in LMICs.[65] For instance, Aluisio et al. reported that between 2012 and 2016, major research funders supported only 115 projects in Africa, 4 in South

America, and 13 in Asia, compared to 1411 projects in North America.[65] Stewart et al. further emphasised that this disparity between the burden of emergency health needs in LMICs and the lack of corresponding clinical research support underscores the urgent need for increased and equitable funding to bridge these gaps.[66]

### Vaccine acceptance and hesitancy

Vaccine acceptance and reluctance continue to pose a considerable problem, particularly among rural, semi-urban, slum-dwelling, elderly, and less-educated demographics; however, research indicates inconsistent outcomes in LMICs compared to HICs.[63,67,68] A study by Arce et al. across 10 LMICs indicated that citizens in these countries are more inclined to accept COVID-19 vaccines, with an average of 80.3% as compared to the USA with a coverage of 64.6% or Russia with 30.4%.[69] Similarly, Abedin et al. investigated vaccine acceptability in Bangladesh, where 74.6% of the 3646 participants expressed willingness to accept a free, safe, and effective vaccine, while 46.5% were willing to pay a nominal fee for vaccination.[67]

### Unequal representation in clinical trials and research

Conducting clinical trials in LMICs is fraught with numerous challenges with ethical, organisational, cultural, and infrastructural for researchers, pharmaceutical companies, sponsors, and regulatory authorities, as evidenced by Jalali et al.[70] Further, Mohajel, Arashkia, and Alemayehu et al. noted additional obstacles, including lack of focus on clinical research within medical curricula, insufficient funding, poor-quality data, and inadequate clinical research training.[71,72] The low representation of LMICs in global clinical trials exacerbates these challenges. Park et al. reported that LMICs were inadequately represented in clinical trials for COVID-19 technologies, with the majority being conducted in the EU, the UK, and North America, while only a few trials took place in Africa, South and Southeast Asia, and Central and South America.[73] For instance, the recommendation of dexamethasone for severe or critically ill COVID-19 patients requiring supplementary oxygen was based on evidence from clinical trials conducted in HICs and later extrapolated to LMIC settings.[74] During the initial phase of the WHO's flagship solidarity trial in March 2020, only two African countries participated, with the trial expanding to eight additional African countries by late 2022[40].

### Restrictive impact of intellectual property rights

The restricted access to essential medical products during the COVID-19 pandemic was predominantly driven by intellectual property (IP) rights, encompassing patents, trademarks, copyrights, and trade secrets.[47] Pharmaceutical firms in HICs, which developed many COVID-19 vaccines, retained control over IP rights, preventing LMICs from independently manufacturing or acquiring these vaccines.[47,75] The Médecins Sans Frontières (MSF) report emphasised that this dependency compels LMICs to rely heavily on donations and imports, which are often insufficient to meet the demands of their populations.[75,76] The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, which safeguards the patent system, has also been a significant factor in exacerbating the market imbalance for vaccine development.[47] For instance, India and South Africa proposed a TRIPS waiver to temporarily suspend patent protection for COVID-19 medical products until the pandemic end.[47,75] However, this proposal faced strong opposition from HICs, who argued that intellectual property (IP) was not a barrier and cited LMICs' limited production capacity as a concern.[47,75] Kohler et al. further reported that critics feared that the waiver could undermine the global IP framework, while proponents emphasised the importance of technology transfer and knowledge sharing to support LMIC manufacturers.[77] Extensive patent protection also delays the market entry of generic drugs, a proven mechanism for sustainably reducing medicine prices.[78] For instance, the Médecins Sans Frontières (MSF) report highlighted the application of Pfizer for at least one primary patent on nirmatrelvir in several countries, including low- and middle-income countries (LMICs) such as Cuba, Russia, and Peru. This could potentially block the production and supply of generic versions until the year 2041 in countries where the patent is granted.[76]

### Inadequate regulatory expertise

The pandemic has exposed vulnerabilities in regulatory frameworks globally, acting as a stress test for drug regulators.[40] Regulatory authorities in LMICs face significant limitations in capacity and resources, hindering their ability to perform core regulatory functions.[79] The United States Agency for International Development (USAID) report titled *Strengthening Regulatory Systems to Improve Medical Product Quality in Low- and Middle-Income Countries* revealed that at least 30% of regulatory authorities worldwide operate with limited capacity, a figure that exceeds 90% in Africa.[79] This is further illustrated by Mukherjee and Goodman, who noted that only 26% of WHO Member States have functioning National Regulatory Authorities (NRAs), with just seven from LMICs namely Egypt, Ghana, India, Indonesia, Nigeria, Tanzania, and Vietnam, achieving Maturity Level 3 (ML3).[80]

In LMICs, inadequate regulatory expertise creates barriers to accessing quality health products and allows substandard COVID-19 products to enter their markets.[47] Gieber et al. highlighted the challenges faced by India's Central Drugs Standard Control Organization (CDSCO) in its handling of Itolizumab for COVID-19 treatment.[40] Despite being evaluated in a small cohort of 30 patients, the regulator granted Emergency Use Authorization (EUA) based on these results. Concerns over the trial design, the selection of the Subject Expert Committee (SEC), and regulatory processes led to the COVID-19 taskforce rejecting Itolizumab from the national treatment protocol, highlighting misalignment and a lack of trust between government offices.[40] The author also stated that many LMICs also lack defined local regulations for developing and testing new mAbs, resulting in additional layers of approvals and significant delays in timely authorisation.[40] Pharmacovigilance systems in LMICs are also underdeveloped

or entirely absent, in stark contrast to the robust frameworks in HICs.[81] Barry et al. revealed that during 2017–2018, less than 1% of health facilities in Ethiopia, Kenya, and Tanzania reported suspected Individual Case Safety Reports (ICSRs) to national pharmacovigilance systems.[82]

## Discussion

### Boosting local production

Strengthening local production capacity is essential for making LMICs self-reliant to reduce import dependency, mitigate supply inconsistencies, and ensure the availability of safe, affordable, and high-quality vaccines, diagnostics, and biotherapeutics.[83,84] Local manufacturing also reduces the dependence on donor programmes and helps in creating a resilient vaccine supply chain.[27] For instance, a) construction of a cutting-edge manufacturing facility in Kigali, Rwanda, by BioNTech in June 2022, to support the production of messenger ribonucleic acid (mRNA) vaccines for people residing in member states of the African Union[85,86] and b) Moderna entering into a Memorandum of Understanding (MoU) with the government of the Republic of Kenya for establishing an mRNA vaccine manufacturing facility in the country to produce up to 500 million vaccine doses annually for the African continent.[87] Expanding local or regional manufacturing capacity is a feasible option to enhance access to mAbs.[38] Although most mAbs are manufactured in Europe and North America, facilities are also expanding in Asia and South America.[38] Given the high requirement for capital investment, LMIC manufacturers can adopt different stage-wise approaches for the production of vaccines and biotherapeutics with the most WHO-recommended model, such as forward, backward, or hybrid integration models, as shown in Figure 2.

### Forward integration

Forward integration entails a sequential approach, wherein manufacturers systematically advance from laboratory and/or pilot-scale to full-scale commercial production and supply.[88] This strategy provides manufacturers with enhanced control over pricing, the ability to respond rapidly to fluctuations in demand, and opportunities to differentiate their products through improved services during distribution. This enables value addition, ensures robust quality control, and creates higher barriers to customer switching, thereby fostering market competitiveness.[88] However, this requires significant capital investment, a long timeline for product commercialisation due to clinical trials, and a rigorous regulatory approval process. For instance, COVAXIN®, developed by Bharat Biotech in collaboration with the Indian Council of Medical Research – National Institute of Virology (ICMR -NIV), has shown strong immunogenicity and efficacy in preclinical trials. It entered accelerated Phase I/II human trials in July 2020 and Phase III in November 2020. On November 3, 2021, WHO granted an Emergency Use Listing (EUL). This development exemplifies forward integration, as Bharat Biotech progressed from research to manufacturing and distribution.[89]

### Backward integration

Backward integration involves local partners initiating activities such as distribution and secondary packaging, gradually acquiring the expertise necessary for more advanced processes, including fill-finish, formulation, and eventually drug substance manufacturing. This approach facilitates swift project execution, faster revenue generation, harmonising navigation of regulatory hurdles, and incremental learning with low risks. However, it often comes with constraints imposed by technology transfer agreements, limited operational autonomy, and dependency on suppliers, which may lead to temporary disruptions.[88] For instance, the South African government previously paid $13.45 per dose for Pfizer's Prevnar 13 pneumonia vaccine. In 2015, the Biovac Institute (47% government-owned) partnered with Pfizer to locally produce the Prevnar 13. Through this backward integration model, Pfizer transferred technology to Biovac, enabling local formulation and fill-finish production starting in 2021.[90]

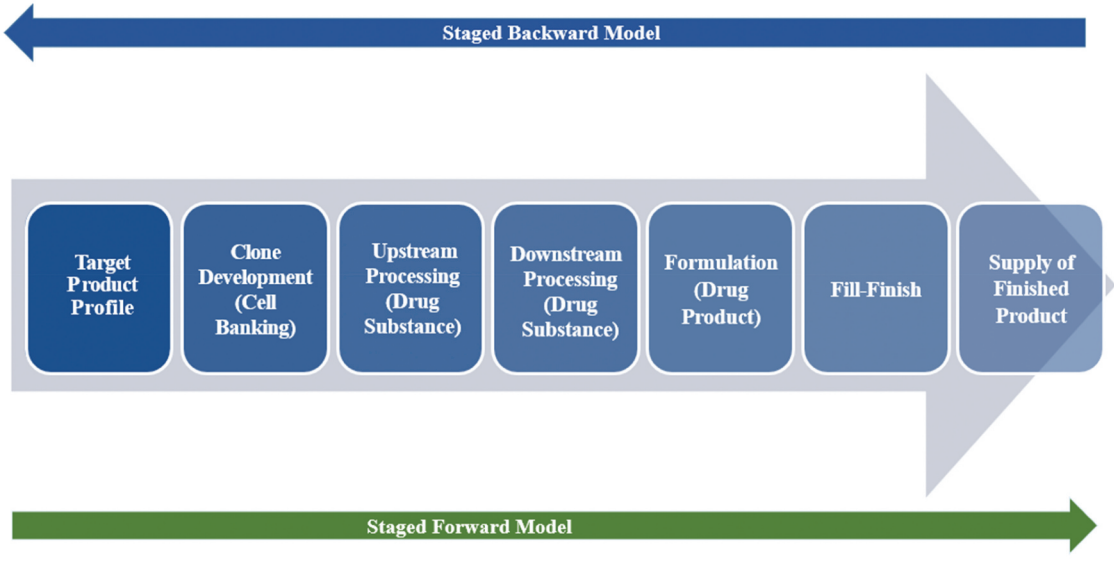


Figure 2. Forward and backward manufacturing model.

### Hybrid integration

The hybrid integration model offers distinct advantages by combining forward and backward processes. This method starts the formulation and fill-finish processes at the same time, which speeds up time to market while also laying the groundwork for full-cycle vaccine production through strong research and development. The hybrid model not only meets immediate needs by making it easier to get locally made vaccines and biotherapeutics, but it also encourages long-term independence and sustainability in vaccine production. The selection of an appropriate integration model depends on factors such as available capital, time-to-market requirements, market conditions, and industry-specific demand.

In selecting any suitable indigenous vaccine manufacturing model, countries should carefully evaluate factors such as the annual volume requirements dictated by their National Immunisation Programs (NIP), Expanded Immunisation Programs (EPI), population size and birth cohort, potential for export, the maturity level of their National Regulatory Authority (NRA), and the scale of financing required. Strengthening manufacturing capabilities in LMICs requires robust financing from national governments, international funding agencies, venture capitalists (VCs), and other stakeholders.[91]

### Increasing financial investment

As we anticipate future pandemics, ensuring adequate investments in health systems for PPPR is crucial.[11] Financial support from national governments, supranational entities, development finance institutions, and private philanthropies can be directed toward LMICs.[91–93] For instance, during COVID-19, the World Bank launched the Pandemic Fund in September 2022 to support LMICs.[94] Similarly, Gavi committed USD 500 million to the First Response Fund, ensuring immediate vaccine deployment in future pandemics.[95] In Africa, the African Development Bank pledged USD 3 billion over the next decade to enhance local vaccine manufacturing, aligning with the African Union's goal of producing 60% of vaccines locally by the year 2040.[96] Also, Afreximbank is providing financial backing to small- and medium-sized manufacturers, supporting facility upgrades, capacity building, and the production of high-quality medical supplies to reduce import dependency.[97] However, loan disbursement through international financial agencies is often complex and time-consuming, delaying urgent healthcare infrastructure upgrades. To address this, social investors, including national governments, development finance institutions (e.g., the World Bank, the Asian Development Bank, and the African Development Bank), and private philanthropies, can leverage financial instruments such as production subsidies, capacity subsidies, concessional loans, and volume guarantees to stimulate investment in underfunded yet essential products.[11] Similar mechanisms can be applied to diagnostics, where market uncertainty deters investment. For instance, MedAccess entered a volume guarantee agreement with SD Biosensor to increase the adoption of glucose-6-phosphate dehydrogenase (G6PD) tests in LMICs, facilitating better access to critical diagnostics.[34] Drawing lessons from global financing initiatives such as the Pandemic Emergency Financing Facility (PEF) and the Pandemic Fund, as well as regional African initiatives like the Africa Medical Supplies Platform (AMSP), the Africa Vaccine Acquisition Trust (AVAT), and the transition of the COVID-19 Response Fund into the African Epidemics Fund (AEF), there is a need to develop many such innovative financing mechanisms by the policy-makers and the global health communities.[11]

LMICs must prioritise substantial investments in R&D to develop or enhance products tailored to local needs,[98] considering factors such as pathogen prevalence, affordability, healthcare infrastructure, and population-specific requirements. Investments in high-tech ventilators and medical technologies can improve crisis preparedness by enabling timely and effective care, particularly when new treatments are unavailable. A study analysing mechanical ventilator availability across nine countries found that nations with higher ventilator capacity (26.76 per 100,000 people) had a lower fatality rate (1.44%) compared to those with fewer ventilators (10.38 per 100,000 people) and a higher fatality rate (2.46%) as of December 2020.[99] The COVID-19 pandemic underscored the importance of robust critical care systems, comprehensive public health strategies, and global collaboration. Moving forward, initiatives similar to the Access to COVID-19 Tools Accelerator (ACT-A) should prioritise coordinated R&D efforts, contingent funding from Day Zero of the next pandemic, strong regional representation in governance structures, and enhanced technology transfer.[11]

### Promoting clinical trials and research

Strengthening the clinical research framework is also critical to bolstering the local manufacturing ecosystem, as it will allow LMICs to quickly test and deploy MCMs during health emergencies. Governments need to implement changes that can reduce approval timelines and accelerate regulatory processes to attract more funding for clinical trials.[100] LMICs should actively participate in global randomised clinical trials (RCTs), as this will improve infrastructure, strengthen clinical trial regulations, establish new collaborations, and provide clinical research experience and expertise for investigators lacking mentorship training.[101] The European & Developing Countries Clinical Trials Partnership (EDCTP), a public-public partnership (PPP) between European countries and sub-Saharan Africa, enhances the capacity of sub-Saharan African countries to conduct clinical trials by investing in new research infrastructure and developing the next generation of African researchers.[102,103] It also strengthens the regulatory and legal frameworks with respect to clinical research in these countries.[103] The Oxford University Clinical Research Unit (OUCRU) is a renowned clinical and public health research institution based in Vietnam, with additional sites in Indonesia and Nepal. Its efforts are focused on strengthening the clinical research capacity in LMICs.[104]

### Facilitating technology access through intellectual property rights

LMICs should strengthen their legal capacities for understanding, navigating, and using the legal and regulatory routes available internationally for protecting their rights.[98] Global

countermeasures platforms like the ACT-A should explicitly support LMICs for the adoption of IP waivers at the regional, national, and international levels and the full adoption, use, and protection of TRIPS flexibilities, including compulsory and government use licenses.[89] Companies should be incentivised to enter into voluntary licenses and tech transfer agreements with organisations like the Medicines Patent Pool (MPP) and the COVID-19 Technology Access Pool (C-TAP).[105] Voluntary licenses represent a promising approach to enhancing access to mAbs and biosimilars in LMICs.[38]

### Strengthening national regulatory agency

The governments in LMICs must prioritise investments in bolstering national regulatory systems.[106] However, this may vary considerably due to the requirement of enormous funding as well as other priorities.[80] To tackle this issue, the establishment of regional regulatory systems can help in getting access to quality medical products in a specified geography. For example, the Caribbean Regulatory System (CRS) serves as the regulatory body for 15 countries forming the Caribbean Community (CARICOM).[80] LMICs can also engage with the WHO's capacity-building initiatives and technical assistance so that the NRAs upgrade to a maturity level that enables a stable and well-functioning system.[106] For regulatory authorities in LMICs with insufficient financial or human resources to carry out regulatory functions, various approaches, such as harmonisation, collaboration with other regulatory authorities, etc., can help in building capacity and improving regulatory efficiencies.[79] Harmonisation promotes the alignment of regulatory standards across multiple countries, thereby facilitating greater efficiency in key regulatory functions.[79] The establishment of the African Medicines Regulatory Harmonization (AMRH) initiative has played a significant role in addressing regulatory capacity limitations across Africa and streamlining challenges related to dossier submissions.[107] Similarly, countries in Latin America have entered into cooperation agreements and Memoranda of Understanding (MoUs) with inter-regional partners and well-established regulatory agencies, such as Swissmedic and the European Medicines Agency (EMA).[40]

### Implementing robust policy framework

Lessons from various effective measures implemented during the COVID-19 pandemic can be considered for incorporation into a policy framework for LMICs to enhance crisis preparedness and response. One critical aspect is implementing effective contact tracing systems, as demonstrated by Italy's early health policies during the first wave of the COVID-19 pandemic (February–July 2020). Also, a case study from Veneto and Piedmont shows that timely testing and a well-coordinated epidemiological taskforce reduced deaths and minimised health impacts in the absence of vaccines and antiviral drugs.[108] To detect, prevent, and control unknown pathogens, such as disease X, China's strategic framework, aligned with the WHO's prioritisation methodology, offers a systematic approach. This model, which includes identifying potential pathogens, screening, prioritising, finalising selections, and generating an R&D Blueprint, can be adopted by LMICs at the national level to accelerate early development and manufacturing of pharmacological interventions and ensure the strategic stockpiling of targeted MCMs to prevent their resource wastage.[109] For evaluating LMICs performance in countering future pandemic threats, having a framework model to assess its preparedness (p) and resilience (r) is essential. For instance, a study on nine European nations found that no country had high preparedness, but those with smaller populations, better governance, and higher healthcare expenditures managed crises more effectively.[110] During early-phase crisis management, especially for unknown pathogens, technological exaptation plays a key role. For instance, the repurposing of drugs like remdesivir (antiviral) and tocilizumab (anti-rheumatoid arthritis drug) during COVID-19 demonstrated their effectiveness. Such an approach enables the modification of existing resources to address emerging challenges, offering valuable insights for policymakers directing innovation efforts.[111] LMICs should plan effective vaccine rollout policies. For instance, an analysis of 192 countries (March–May 2021) found that 80 doses per 100 inhabitants significantly reduced cases and fatalities. Early intensive vaccination campaigns required fewer doses (~47 per 100 inhabitants) to curb infections effectively, highlighting the need for strategic early vaccine distribution to minimise public health and socioeconomic impacts.[112] The policymakers should consider the role of PIs & NPIs, as they played a significant role in controlling the COVID-19 pandemic. For instance, a study across 175 countries found that cancelling public events, restricting private gatherings, and closing schools and workplaces effectively reduced infections. However, internal movement restrictions and public transport bans had no measurable effects, while international travel bans provided only short-term benefits. These findings highlight the need for evidence-based policy design for future pandemics.[113] Integrating environmental and sustainable policies is essential for mitigating future pandemics. For instance, studies suggest that air pollution, particularly in high-moisture, low-wind -speed, fog-prone areas, accelerated COVID-19 transmission by enhancing airborne viral infectivity rather than direct human-to-human contact.[114] By integrating policies on early detection, vaccine rollout strategies, effective PIs and NPIs, and environmental sustainability measures, governments and global health organisations can develop a more resilient and adaptive pandemic preparedness framework as summarised in Table 1.

The following table outlines the discussion summary of actionable measures and collaborative approaches essential for enhancing the development and distribution of medical countermeasures (MCMs) in resource-limited settings, especially in LMICs.

In order to address all the key challenges discussed and those beyond the current scope of the review, a collaborative framework needs to be implemented through public-private partnerships (PPPs) from early discovery to accelerated development and deployment of MCMs, particularly in resource-limited settings. PPPs will ensure rapid scale-up, reduce import dependency, and bolster the healthcare system resilience. As illustrated in Figure 3, coordinated contributions from various stakeholders are vital to accelerate rapid development, foster a new innovation platform wherein the academic institutions

**Table 1.** Key actionable measures to strengthen medical countermeasures ecosystems in LMICs.

| Actionable Measures | Mechanism | Key Initiatives |
|---|---|---|
| Boosting local production | Focus on domestic manufacturing adopting hybrid, forward, and backward integration models depending on volume and value to enhance local capacity and to reduce import dependency. | BioNTech in Rwanda to support mRNA vaccine manufacturing; Moderna entering into a MoU with Republic of Kenya for mRNA vaccine manufacturing; Pfizer tech transfer agreement with Biovac for Prevenar 13 pneumonia vaccine manufacturing. |
| Increasing financial investment | Mobilising financial support from national governments, supranational entities, development finance institutions, and private philanthropies to strengthen pandemic prevention, preparedness, and response (PPPR); Leveraging financial instruments like subsidies, concessional loans, and volume guarantees to drive investments in critical health infrastructure, R&D, and local manufacturing. | World Bank's Pandemic Fund (2022) to support LMICs; Gavi's USD 500M First Response Fund and African Development Bank's USD 3B pledge for local vaccine manufacturing in LMICs; Afreximbank's support for SMEs in facility upgrades and capacity building; MedAccess' volume guarantee with SD Biosensor for G6PD diagnostics; innovative financing iniatives such as AMSP, AVAT, and AEF to support LMICs. |
| Promoting clinical trials and research. | Strengthen clinical trial frameworks in LMICs with inclusivity of all age group and participation in global randomized clinical trials. | EDCTP partnership between Europe and sub-Saharan Africa; OUCRU in Vietnam, Indonesia, and Nepal. |
| Facilitating technology access through IPRs | TRIPS flexibilities and IP waivers to incentivise voluntary licenses and tech transfer agreements so as to enhance access to MCMs | TRIPS flexibilities; voluntary licenses with MPP and C-TAP. |
| Strengthening national regulatory authorities | Invest in national and regional regulatory systems in collaboration with WHO initiatives to strengthen framework and accelerate approval timelines. | CRS for CARICOM; AMRH in Africa; Harmonisation efforts in Latin America with EMA and Swissmedic. |
| Implementing robust policy framework | Strengthening pandemic preparedness through contact tracing, epidemiological task forces, stockpiling medical countermeasures, and early vaccine rollout; Integrating environmental policies to mitigate transmission risks as part of PPPR strategies. | Italy's contact tracing (Veneto & Piedmont); China's R&D Blueprint for Disease X; Drug repurposing (remdesivir, tocilizumab); Strategic vaccine distribution (80 doses per 100); Effective PIs and NPIs (school/workplace closures, event restrictions); Environmental policies to curb air pollution-linked transmission of diseases. |

Abbreviations: MCMs: Medical Countermeasures; PPPs: Public-Private Partnerships; LMICs: Low- and Middle-Income Countries; TRIPS: Trade-Related Aspects of Intellectual Property Rights; MPP: Medicines Patent Pool; C-TAP: COVID-19 Technology Access Pool; EDCTP: European & Developing Countries Clinical Trials Partnership; OUCRU: Oxford University Clinical Research Unit; CRS: Caribbean Regulatory System, and AMRH: African Medicines Regulatory Harmonization; EMA: European Medicines Agency; AMSP: Africa Medical Supplies Platform; AVAT: Africa Vaccine Acquisition Trust; AEF: African Epidemics Fund; G6PD: glucose-6 phosphate dehydrogenase; CARICOM: Caribbean Community; IPRs: Intellectual Property Rights.

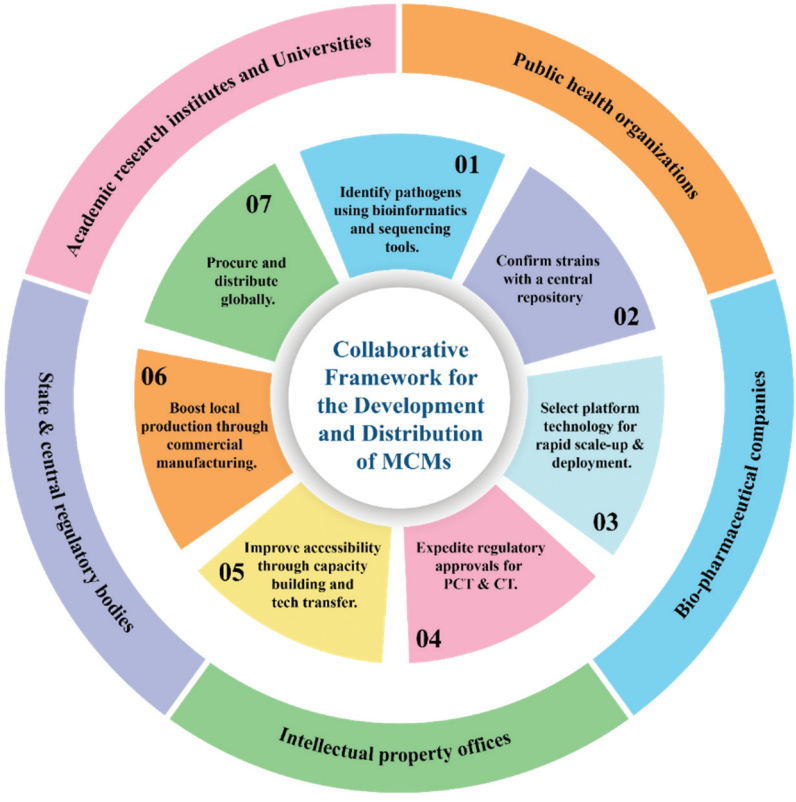


**Figure 3.** Collaborative framework for development and equitable distribution of medical countermeasures (MCMs).

play a key role in early-stage research taking the technology to proof-of-concept (PoC) stage; public health organisations to guide priority-setting and global health needs; biopharmaceutical companies to drive platform technology development and manufacturing; intellectual property offices to facilitate technology transfer and ensure equitable access; and regulatory agencies to expedite approvals and maintain safety standards. These coordinated efforts will help in capacity building, rapid development, scale-up and distribution of MCMs across LMICs.

## Conclusion

The COVID-19 pandemic highlighted global disparities in healthcare equity, revealing major gaps in governance, healthcare infrastructure, global investment for fundraising, clinical trials, intellectual property, regulatory, and supply chain. Hence, there is an urgent need to address these multifaceted challenges. Addressing these gaps requires integrated, evidence-based strategies to strengthen PPPR. Key priorities include strengthening local manufacturing capacity to reduce import dependency, harmonising multicentric clinical trials for diverse population inclusion, and strengthening National Regulatory Authorities (NRAs) by advancing their maturity levels through robust regulatory frameworks. Additionally, facilitating technology transfers via public-private partnerships (PPPs) and securing financial support from national governments, international organisations, development finance institutions, and philanthropic entities are essential to advancing R&D and accelerating market access for innovative healthcare products. Furthermore, policy initiatives must build public trust, address socio-political barriers such as vaccine hesitancy, and promote inclusive, cohesive PPPR strategies. Public health organisations, policymakers, and decision-makers must prioritise equitable access mechanisms while investing in capacity-building initiatives. Achieving global health equity demands international collaboration, structural reforms, and proactive interventions that transform systemic gaps into sustainable, long-term solutions, fostering a resilient and inclusive global health ecosystem.

Note: As this review relies on secondary data, limiting the scope of primary evidence and detailed region-specific or country-specific nuances. Hence, findings, focused on COVID-19, may not fully generalize to other health crises and lack quantitative or meta-analytic approaches for stronger statistical insights. While actionable recommendations are provided, feasibility assessments remain beyond the manuscript's scope. Additionally, the evolving nature of global health policies may require periodic updates to maintain relevance.

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## Author contributions

Conceptualization, K.S., S.S., S.M.S., S.A.K., P.S., S.K., A.K., A.C., S.P., S. A.; writing - original draft preparation, K.S., S.S., S.M.S., S.A.K., P.S., S.K., A.K., A.C., S.P., S.A.; writing - review and editing, K.S., S.S., S.A.; supervision S.A. All authors have read and agreed to the published version of the manuscript.

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