11

An "Always On" Approach to Health Care and Public Health Systems: Building Standing Capabilities That Can Respond to Shocks and Emergencies

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ABSTRACT

"Always On" health systems ensure that routine, quality clinical and public health services can address shocks and health emergencies. Such systems should have dual-use functionality, with utility both for routine care and public health, and for outbreaks and emergencies. That is, they consistently provide quality services in routine settings at the same time that they carry out core prevention, preparedness, and response functions. This chapter describes the health benefits, economic benefits, and policy and research opportunities to develop Always On health systems, with a specific focus on three applications: adult vaccination, clinical research, and pathogen surveillance.

INTRODUCTION

The COVID-19 (coronavirus) pandemic demonstrated the importance of preparation for health emergencies. A "stop-start approach" of responding to health crises—which created problems initiating ad hoc research and development, vaccine manufacturing, service delivery, and surveillance activities during the pandemic—serves neither public health nor economic interests. As the risk of health emergencies, including from climate change, increases, health systems need to take a different approach to emergency preparedness, prevention, and response (PPR).

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This chapter proposes an Always On approach to health care and public health systems. The description of these systems as "Always On" means that they consistently provide quality clinical and public health services in routine settings while contributing to PPR for shocks and emergencies. Always On systems have dual-use functionality, with utility both for routine care and public health, and for outbreaks and emergencies. This functionality stands in contrast to a more siloed approach (table 11.1).

Although the COVID-19 pandemic catalyzed new investments in global health security, some countries have already started to scale back and shutter key infrastructure. The Pandemic Fund raised only a fraction of its target, and pandemic PPR now takes lower priority on the international political agenda (Rigby 2023). The pandemic also disrupted health care services, led to backlogs of hospital care, and interfered with routine immunization schedules—leading to the largest decline in childhood vaccination coverage in over 30 years (UNICEF 2022). These disruptions to routine services, such as tuberculosis (TB) programs, led to disproportionately higher numbers of deaths in African countries during the COVID-19 pandemic (Soe-Lin, Bowen, and Hecht 2024). As countries build their usual services back up, they must do so in a way that maximizes emergency PPR capabilities.

Table 11.1 Definitions and Applications of Always On Systems and Dual-Use Functionality

Always On systems	Systems that can consistently provide quality clinical and public health services in routine settings while possessing the ability to respond swiftly to shocks and health emergencies. These routine clinical and public health services should support emergency prevention, preparedness, and response.
Dual-use functionality	Technology and capabilities that can be used for both routine care and public health and during outbreaks and emergencies

Application	**Always On systems**	**Systems where routine services are siloed from emergency prevention, preparedness, and response activities**
Adult vaccination	Standing infrastructure (comparable to childhood EPI services) used to provide routine vaccinations (and preventive injectables) to key population groups and which can also be used to provide vaccines during an emegency/outbreak	Systems that have not strategically integrated adult vaccinations into routine primary care and only deliver adult vaccinations on an ad hoc basis. Therefore, when emergencies and outbreaks occur, there is a requirement for new infrastructure to be stood up to deliver the appropriate vaccinations.
Clinical research	Trial-agnostic infrastructure to conduct well-deigned and ethical clinical research and trials. This infrastructure has linkages with routine clinical care and can be used to conduct research and test medical countermeasures at speed during health emergencies.	Clinical research capabilities that are stood up for specific studies, without clear plans for sustainability or use after the specific study. Often, these capabilities are not maintained after the relevant study or research program is completed. During outbreaks and emergencies, there is not sufficient capacity for research using existing capabilities, so new capabilities need to be stood up.
Pathogen surveillance	Pathogen surveillance systems that leverage, as appropriate, routine clinical diagnostic workflows. As technology develops, these systems will be flexible enough to take a "pathogen-agnostic" approach to surveillance. These systems can also track and monitor the spread of diseases, including novel pathogens, during an outbreak or emergency and results can be shared with relevant stakeholders for emergency response.	A lack of core pathogen surveillance activities, training, and capabilities making the detection of pathogens at the point-of-care level challenging and delaying the Identification, tracking, and response to outbreaks and emergencies.

Source: Original table compiled for this publication.

Note: EPI = Expanded Programme on Immunization.

This chapter argues that taking an Always On health approach that has use cases outside the context of emergencies will have more predictable funding, because it will provide reasons to use, and pay for, well-functioning health systems on a continual basis. Continuous funding for strong health systems is essential to guarantee both routine services and emergency PPR capabilities. Investments should support political leaders and the private sector to justify their investments in Always On systems with more predictable and visible utility, rather than providing only "insurance value" against hypothetical catastrophic events. In particular, political leaders can rationalize investments that improve health status, financial risk protection, and citizen satisfaction with the health system (Seidman and Atun 2016).

An Always On approach has relevance at the global, national, and subnational levels across countries of various income levels. It will help embed emergency response capacity in activities that support universal health coverage. Both academic research and strategic planning documents support the theoretical foundation for Always On capabilities. Examples of these frameworks include the World Health Organization (WHO) model for integrating Health Emergency Preparedness, Response, and Resilience, along with frameworks for Health System Strengthening, Pandemic Preparedness and Response, and universal health coverage (FCDO 2021, particularly figure B; Wenham et al. 2019; WHO 2022a, particularly figure 5). Despite that focus, the literature lacks information on how to operationalize such an approach for specific applications.

This chapter demonstrates the benefits and opportunities of applying an Always On approach to three applications of health care and public health: adult vaccination, clinical research, and pathogen surveillance.[1] These three applications highlight essential benefits for both routine health care and emergency PPR, are rapidly evolving because of recent advances in technology, and can have significant value for a country's life sciences industry (for example, research and development, and manufacturing of vaccines, therapeutics, diagnostics, and devices), which can generate sustained commitment from governments interested in economic growth and the private sector. The following sections provide an overview of each application and describe

- Evidence of population health and economic benefits from taking an Always On approach
- Key policy challenges and opportunities to advance the application
- Ethical considerations.

Subsequent sections discuss the importance of digital technology for supporting Always On systems as well as limitations and future directions.

ADULT VACCINATION

The COVID-19 pandemic not only highlighted inadequate vaccine development, manufacturing, supply chains, and health care delivery systems for adult vaccinations but also showed the far-reaching public health benefits of prioritizing

adult vaccination alongside childhood immunization (Williams et al. 2021). The risk now, however, is that these adult vaccine delivery systems are viewed as relevant only for COVID-19 and that the public and private sectors will fail to maintain them. Building robust and adaptable Always On adult vaccination infrastructure could address both endemic diseases and improve response to outbreaks, an approach consistent with WHO's Immunization Agenda 2030 (Wallace et al. 2022).

Critically, the portfolio of vaccines and preventive injectables for both infectious and noncommunicable diseases targeting adults has grown (Alkasir et al. 2022). Strengthening systems that provide routine vaccinations and preventive injectables to adults will be important for maximizing the population health impact of these products. Effectively deploying vaccines in the event of an outbreak will also require Always On adult vaccination systems. The Coalition for Epidemic Preparedness Innovation's 100 Days Mission aims to have vaccines ready for authorization and manufacturing at scale within 100 days of the identification of a pandemic pathogen (CEPI 2022). Despite that commendable target, the world risks having vaccines ready in the event of an outbreak without having the absorption capacity or infrastructure to deliver them, potentially leading to wasted doses similar to the experience of the COVID-19 response (Andersen et al. 2021; Lazarus et al. 2022). For example, in Nigeria, insufficient storage, challenges with health promotion, and accessibility issues resulted in the wastage of over a million doses of COVID-19 vaccines (Musa et al. 2023). Vaccine hesitancy also poses a significant risk to adoption of vaccines. In many countries, the rapid deployment of vaccines during the pandemic led to a missed opportunity to improve long-term service delivery challenges including digital platforms for vaccine tracking, strengthening of the cold chain, implementation of environmentally friendly delivery systems, and the building of public trust (World Bank 2021).

As low- and middle-income countries (LMICs) and the private sector invest in distributed vaccine and biologic manufacturing capacity as a health security measure, keeping manufacturing sites operational and financed will require use cases beyond manufacturing vaccines to respond to outbreaks. Gavi, the Vaccine Alliance, has determined that expanding demand for routine vaccines, both for approved products and those under development that use novel manufacturing platforms, could serve as sustainable business models for novel manufacturing sites (Gavi 2022). Given potentially limited demand for vaccine manufacturing in LMICs, a regionalized vaccine manufacturing approach may help ensure financial sustainability while countering vaccine nationalism. Achieving this expanded demand for vaccines and preventive injectables, including for adults, will require adequate budget, delivery systems, and acceptance of vaccines.

Population Health and Economic Benefits

More than 10 million adult deaths across the globe are attributable to diseases with existing or forthcoming vaccines and preventive injectables (refer to annex 11A). Vaccinating individuals throughout the course of their life improves population-wide immunity for endemic diseases and improves general health within a

population (Privor-Dumm et al. 2021). Vaccination efforts can target the most vulnerable individuals and high-risk groups, for example, by prioritizing the vaccination of health care workers or deploying ring vaccination strategies for those at high risk of disease due to close contact with an infected person (Doherty et al. 2022; Nanni et al. 2017; Swanson et al. 2015).

Importantly, because of the routine nature of select adult vaccinations, such as the seasonal flu vaccine in many countries and potentially COVID-19 or RSV vaccines going forward, adult vaccination systems can provide a point of engagement for individuals to engage with the health care system, often in community and primary care settings, to provide additional preventive services. This delivery infrastructure could bundle the delivery of multiple vaccines and preventive injectables with programs for, among others, high cholesterol, human immunodeficiency virus (HIV), psychiatric conditions, and family planning (Alkasir et al. 2022). These programs could rapidly adapt to incorporate new prevention tools that meet cost-effectiveness and efficacy thresholds (for example, R21/Matrix-M malaria vaccine, potential new TB vaccines, and siRNAs to both PCSK9 and angiotensinogen).

Packaging interventions that have shown cost-effectiveness, and supporting their co-delivery in the context of preventive services at the primary care and community levels, could improve coverage. "Above service delivery" costs (that is, costs to administer health programs not at the points of care) can represent 20–50 percent of all programmatic costs for immunization programs in Africa. Using routine health system capabilities to distribute bundled products would improve the per-unit and per-patient-treated cost of each program. Vaccination programs for working-age adults also minimize absenteeism, promoting a more productive and stable workforce, translating into increased economic output and higher economic resilience in the face of health crises (Quilici, Smith, and Signorelli 2015). (For a summary of cost-effectiveness evidence for specific adult vaccinations, refer to annex 11B.)

Adult vaccination programs also provide significant insurance value in their ability to prevent catastrophic events. Unfortunately classic health economic analyses—which focus only on gains in quality- or disability-adjusted life years and productivity—often miss that insurance value (Lakdawalla et al. 2018). One analysis conducted during the COVID-19 pandemic estimated that an adult vaccination program in the event of another, similar pandemic could save up to US$3.4 trillion in economic losses (Alkasir et al. 2022). However, determining the total value of adult vaccination systems, including insurance value and overall societal benefits, requires further research (Beck et al. 2022).

Policy Challenges and Opportunities

Developing robust and cost-effective Always On adult vaccination systems will require a coordinated effort from multiple sectors. First, policy makers and researchers must consider broader socioeconomic benefits of adult vaccination, including workforce productivity, social value, and health care system resilience to pandemics (Beck et al. 2022). For example, WHO's Seasonal Influenza Vaccines

guide for decision-makers highlights reduced burden of disease, stronger health system, and pandemic preparedness as benefits of such a program (WHO 2020b). Policy makers must also effectively communicate these benefits to the public. Focusing on Always On systems that will have more immediate preventive health benefits against common diseases could help normalize adult vaccination, as done previously for childhood vaccination.

Second, the ability to successfully deliver vaccines relies on patient acceptance and vaccine confidence, which has declined significantly across geographies since the COVID-19 pandemic (UNICEF 2023). Successfully generating demand for adult vaccinations and building sustainable systems that can rapidly pivot to provide vaccinations during outbreaks requires high vaccine confidence and standing systems that can meet demand. For example, the response to the mpox outbreak in the United States in 2022 successfully engaged target populations such as men who have sex with men (World Bank 2021). Unfortunately, supply initially could not meet the demand for vaccines because of insufficient delivery infrastructure, cold chain capacity, vaccine safety systems, and a suitably trained workforce (Dawson and Kates 2023). Encouraging such demand will require engaging with patient acceptance and vaccine confidence—not just during outbreaks but also as part of routine care—with tools such as public education, community engagement, and digital outreach tools.

To remain Always On, health systems will require continuous market access to affordable adult vaccines, particularly in LMICs. Although Gavi has gradually begun to expand its portfolio of vaccines into life course vaccination, most of its products target the under-five population, and Gavi remains rightfully committed to its mission of vaccinating children.[2] As more adult vaccinations and preventive injectables come onto the market, it will be important to ensure market access for target populations without setting prices so low as to jeopardize incentives for pharmaceutical innovation or manufacturing (Gartner 2015). The successful track record of market shaping for essential global health commodities provides a promising template for a similar approach for adult vaccinations. Identified market shaping approaches to support adult vaccinations (and other products, especially for LMICs) include (1) adding adult vaccinations to the WHO Essential Medicines List; (2) harmonizing product registration systems; (3) providing advance market commitments and demand/volume guarantees for manufacturers; (4) subsidizing the cost of manufacturing in LMICs; (5) pooling procurement for adult vaccines, and (6) creating demand among patients for adult vaccines (Berry et al. 2023).

Last, to ensure the financial sustainability of new manufacturing capacity for vaccines and injectables, that capacity should be used to manufacture vaccines for both routine care and outbreaks. It is unclear whether the level of demand for vaccines could sustain regional vaccine manufacturing, especially in Africa. Although investment decisions should remain the purview of individual countries, companies, and institutional investors, more transparent information about

potential demand and supply for vaccines and manufacturing capacity could inform investment decisions (Berry et al. 2023).

Ethical Considerations

Rollout of adult vaccinations must adhere to principles of harm prevention and fairness (Giubilini 2020). Although the ethical issues concerning dual-use adult vaccination systems for routine care and outbreak prevention do not substantively differ from ethical issues concerning vaccinations more broadly, it is important that the public health community reinforce key ethical considerations and principles as adult vaccines gain importance.

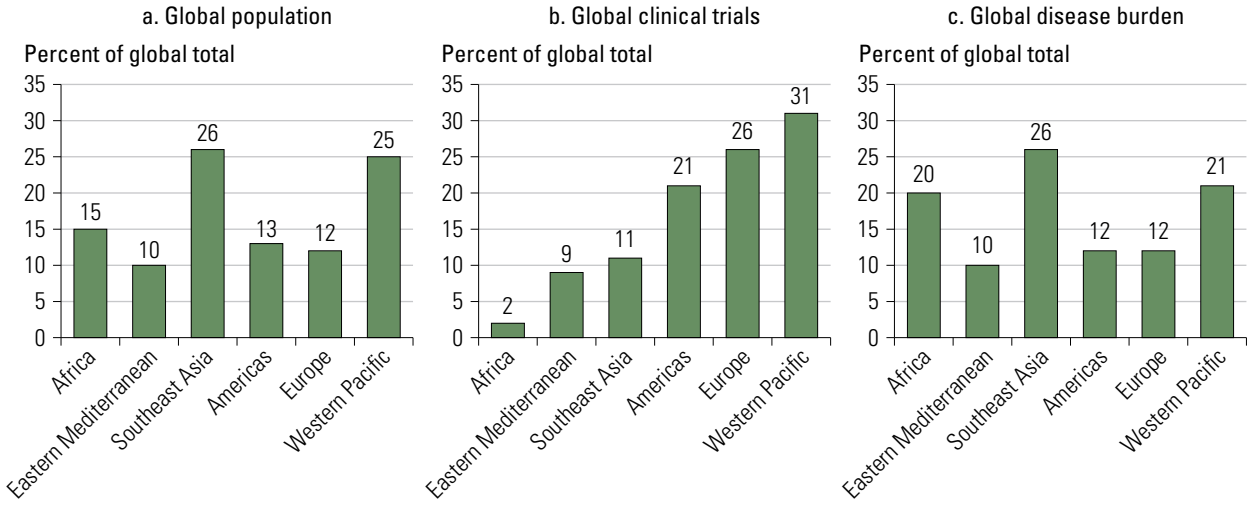
CLINICAL RESEARCH INFRASTRUCTURE

The COVID-19 pandemic not only emphasized the importance of well-designed, randomized clinical trials and new methods to meet public health needs but also highlighted many fundamental issues that exist with the current system (Park et al. 2021). For example, the US Food and Drug Administration found during the pandemic that only 5 percent of 2,895 clinical trial arms were randomized and adequately powered (Bugin and Woodcock 2021). Outside of COVID-19, more than 50 percent of participants annually enter clinical trials with high risk of bias, at a cost of £8 billion (about US$10.35 billion) across 1,659 randomized trials (range: £725 million to £2.1 trillion, or about US$938 million to US$2.7 trillion) (Pirosca et al. 2022). Failure to recruit a sufficient number of patients accounts for one-third of all trial terminations in oncology (Zhang and DuBois 2023).

COVID-19 also demonstrated the power of clinical research infrastructure integrated into routine clinical care. Most notably, the United Kingdom–based RECOVERY trial leveraged such infrastructure to execute the world's largest clinical trial assessing treatment for patients hospitalized with COVID-19, which quickly identified life-saving treatments and those with no effect.[3] Other countries similarly used existing clinical research infrastructure for outbreak response. In Kenya, for example, the established research organization KEMRI led the COVID-19 response for testing (JICA 2021); in South Africa, dedicated HIV and TB research centers pivoted to COVID-19 genomic sequencing and participation in the Oxford-AstraZeneca trial (Nordling 2020).

Clinical research infrastructure, like other essential components of emergency PPR, needs to be Always On and embedded within clinical care. A start-stop approach to clinical research makes it difficult for sites to retain skilled staff and keep equipment operational (Lang et al. 2010). It also leaves sites ill-prepared to rapidly pivot to research during outbreaks and emergencies, a gap that will pose considerable challenges to achieving the Coalition for Epidemic Preparedness Innovation's 100 Days Mission. Africa, in particular, is underrepresented in global clinical research, accounting for approximately 15 percent of the global population and 23 percent of the global burden of disease, but less than 2 percent of all clinical trials globally (figure 11.1).

Figure 11.1 Population, Disease Burden, and Representation in Clinical Trials, by Region



Sources: Original analysis based on Our World in Data, "Global Disease Burden by Region" (https://ourworldindata.org/grapher/disease-burden-by-region); WHO, "Number of Clinical Trials by Year, Country, WHO Region and Income Group (1999–2024)" (https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group); WHO 2023.

Note: Regions refer to World Health Organization (WHO) regions. Global clinical trials data and global disease burden data reflect 2019 statistics. Global population data reflect 2021 statistics.

Recognizing these challenges, the first WHO Clinical Trials Forum called for an "always on, always busy" clinical trials ecosystem with sufficient volume of research to maintain standing infrastructure between emergencies, and to rapidly pivot to research in an outbreak response (Moorthy et al. 2024). Although supporting that goal, this chapter, consistent with recommendations from the International Vaccines Task Force, emphasizes the importance of strengthening an ecosystem for clinical *research*, not just clinical *trials*. Many of the requirements for Always On clinical trial systems can be built into the context of other clinical research, such as epidemiological studies, real-world evidence and registry-based studies, and pharmacovigilance and surveillance (World Bank 2018).

Population Health and Economic Benefits

When embedded within health care services, clinical research capacity enables researchers and policy makers to understand the true burden of disease, interpret outcomes, and analyze the impact of interventions. It also builds capacity to deal with diseases of public health concern, such as endemic infectious disease, and offers research experience to frontline staff. Evidence increasingly shows that the health care centers that prioritize clinical research have lower mortality rates and better patient outcomes (Ozdemir et al. 2015). Unfortunately, as noted earlier, certain geographies, especially in Africa and Southeast Asia, and patient population groups have a longstanding history of underrepresentation in clinical trials.

Investments in clinical research also generate strong economic returns for their countries. For example, Ireland, which has invested heavily in building its life

sciences sector, received an average of £1.4 trillion (about US$1.8 trillion) in foreign direct investment in life sciences annually from 2012 to 2022, the second-highest level after the United States (DSIT and DHSC 2023). Research indicates that every dollar invested in clinical trials for infectious diseases in Kenya, South Africa, and India would generate a return of US$21, US$33, and US$67, respectively (Schäferhoff et al. 2022).

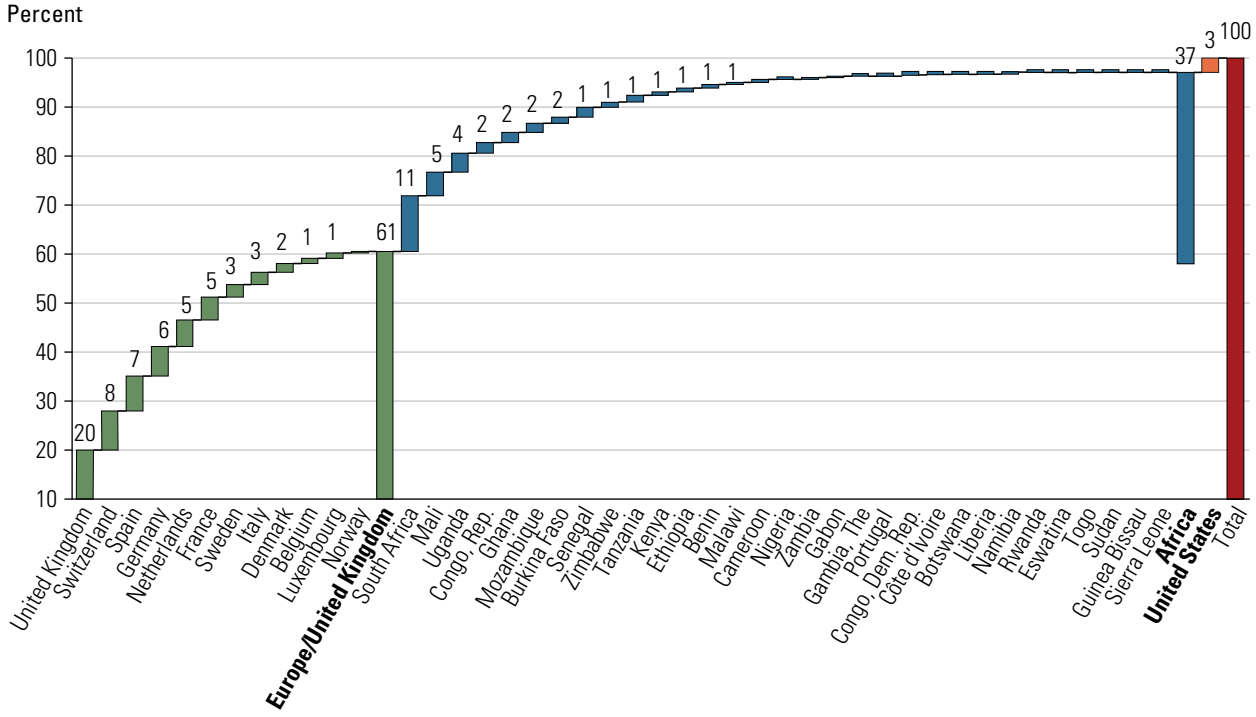
Policy Challenges and Opportunities

An Always On approach to clinical research that can support ongoing work and rapidly pivot to address outbreaks and emergencies needs to have strong links with routine clinical care. The WHO Clinical Trials Forum recommends developing a "clinical trial unit maturity framework," which should specifically include Always On principles and capacity (Moorthy et al. 2024). Building on over a decade of investments in networks for clinical care and research, the European Union is investing in a comprehensive research network known as the European Clinical Research Alliance on Infectious Diseases to use perpetual observational studies and platform trials to keep a "warm base" network of clinical research sites operational (European Commission 2022).

Tremendous progress has been made in increasing donor-driven global health investment targeted at building capacity in LMICs, gradually shifting to more locally driven investment in research and development (Olufadewa, Adesina, and Ayorinde 2021). Expansion of the Africa Centres for Disease Control and Prevention and of the Africa Medicines Agency is helping strengthen regulatory and research capacity on the continent via a regional approach (Makoni 2021). As previously mentioned, however, Africa still hosts a disproportionately low percentage of the world's clinical trials. The current structure of global funding for clinical research perpetuates this disparity, limiting the availability of funding for core research infrastructure. For example, of all research and innovation projects funded by the European & Developing Countries Clinical Trials Partnership—a European Union–led effort "funding clinical research for medical tools to detect, treat and prevent poverty-related infectious diseases in sub-Saharan Africa"[4]—more than 60 percent of funding went to coordinating centers in Europe, the United Kingdom, and the United States (figure 11.2).[5] Although much of this funding may eventually have gone to countries in Africa, structuring funding in this way may have implications for the sustainability and coordination of funds reaching research sites.

Moreover, in a recent survey of more than 2,000 African researchers, participants listed institutional support as one of the primary barriers to clinical research (Lang et al., forthcoming; Wellcome Trust and TGHN 2024). Appropriate legal frameworks and institutional support will help overcome other limitations in clinical research capacity in LMICs, such as those identified by the International Vaccines Task Force: experienced clinical trials teams, appropriate space for trials, biobanking, data management systems, regulatory authority, and appropriate administrative functions (World Bank 2018). Overcoming those challenges will

Figure 11.2 EDCTP2 Funding, by Country



Source: Original analysis based on European & Developing Countries Clinical Trials Partnership, "Public Portal of EDCTP2-Funded Projects" (https://www.edctp.org/edctp2-project-portal/).

Note: Values rounded to nearest whole number. Values not shown for countries less than 0.5 percent. EDCTP2 = European & Developing Countries Clinical Trials Partnership, Second Programme (2014–24).

require government and institutional leadership, and investments in study-agnostic infrastructure (Lang et al. 2010). Those investments and infrastructure should build upon the strength of existing research sites that can integrate with routine care to recruit patients for research. As multiple sites continue to build capacity, a steadier and more predictable pipeline of clinical research funding to African institutions should help ensure sustainability of this infrastructure. Because of the likely insufficient pipeline to support financially sustainable infrastructure in all LMICs, however, regional coordination could help prioritize investments in clinical research capabilities where they are most likely to succeed, namely in countries with strong existing scientific and regulatory capabilities, and strong existing sites can support development of sites in neighboring countries.

Ethical Considerations

All research should conform to globally accepted ethical principles and national laws. Establishing Always On clinical research in LMICs raises specific ethical concerns, particularly in LMICs where research frequently involves vulnerable populations and can have severe outcomes or mortality as endpoints (Lang et al. 2010). Substantial gaps exist between where drugs approved by the US Food and Drug Administration are tested and where they ultimately become available to patients, raising concerns about the equitable distribution of research benefits and

market access (Miller et al. 2021). Finally, as more research becomes digitized, research sponsors will have to ensure that they have appropriate privacy and security safeguards in place to protect patient data.

PATHOGEN SURVEILLANCE

The COVID-19 pandemic reinforced the importance of pathogen surveillance systems to provide near real-time information for the detection, tracking, and management of public health events (Ling-Hu et al. 2022; WHO 2022b). Unfortunately, it also revealed significant disparities in countries' abilities to conduct pathogen surveillance, including genomic surveillance, because of varying levels of prepandemic infrastructure, training, and capabilities (Inzaule et al. 2021; refer also to table 11.2 for an overview of relevant surveillance terminology). These issues included data quality, delays in reporting, and an inability to link surveillance data to individual cases (Price et al. 2023).

An Always On system leverages routine diagnosis to support pathogen surveillance when possible, rather than operating in a parallel system. At its most basic level, it involves provider reporting of notifiable conditions, including infectious diseases and cancers, to public health agencies.[6] As diagnostic technologies continue to progress, they have the ability to improve clinical management of patients, reduce oversubscribing of unnecessary antibiotics (potentially helping slow antimicrobial resistance), and contribute data to pathogen programs surveillance (Salami et al. 2020).

In particular, next generation sequencing, which can clearly define pathogen relationships and rapidly identify genetic and functional associations, can support both pathogen surveillance and day-to-day management of certain diseases (Rantsiou et al. 2018; WHO 2022b). The introduction of more affordable genomic sequencing tools and the subsequent decentralization of national platforms have begun to expand countries' surveillance capacities, with the potential to enable sequencing to take place in diverse and remote settings (Price et al. 2023). As clinical applications of genomic sequencing expand—namely, to test drug susceptibility of infectious diseases—the resulting clinical-grade genomic data could also contribute to broader public health surveillance and inform treatments for infectious diseases and cancers (Marquart, Chen, and Prasad 2018).

Table 11.2 Pathogen Surveillance Definitions

Pathogen surveillance term	Definition
Next generation sequencing	Technology able to identify nucleic acid sequence data (DNA and RNA) rapidly and cost-effectively
Whole genome sequencing	Technique used to establish the full genetic makeup of an organism
Metagenomic sequencing	Untargeted approach to genomic sequencing directly from an environmental or clinical sample used to identify all present organisms

Sources: Gardy and Loman 2018; Rantsiou et al. 2018.

Investments in genomic infrastructure during the COVID-19 pandemic could be leveraged and pivoted toward more pathogen-agnostic approaches. Metagenomic sequencing involves the reading of all genetic material from a sample, permitting the unbiased detection of both known and unknown pathogens. The technique makes it possible to detect novel pathogen spread early, potentially enabling timely containment of outbreaks and effective suppression of transmission. For example, Liberia successfully used metagenomic capabilities while managing an unexpected outbreak of meningococcal disease in 2017. The country quickly identified the sequence type, linked to a hypervirulent strain with unusual presentation and a high fatality rate (Bozio et al. 2018). Clinical metagenomic sequencing could also aid diagnosis for certain patients with polymicrobial or difficult-to-identify infections (Chiu and Miller 2019).

Population Health and Economic Benefits

Always On real-time reporting of certain notifiable conditions diagnosed in the clinic to public health agencies will support effective outbreak investigation and response. Building from this approach, genomics data that are routinely collected in clinical care can and should feed into larger data sets that will make it easier to identify novel pathogens or variants of concern, and help understand the spread of a disease within a population (Gardy and Loman 2018). The United Kingdom demonstrated the utility of such a system when it began integrating genomic testing into the routine clinical diagnosis of selected diseases to support outbreak response for gastrointestinal illnesses in 2012 (Grant et al. 2018). In 2022, the United Kingdom's routine sequencing of all presumptive salmonella cases led to the identification of a salmonella disease cluster in children. The quick sharing of genomic data with neighboring countries, which linked to chocolate products originating from a factory in Belgium, led to a comprehensive outbreak response, including product recall to prevent further transmission (UKHSA 2022).

Pathogen surveillance infrastructure, including genomic sequencing, can be flexible enough to support response to outbreaks from multiple pathogens. The Democratic Republic of Congo built up genomic sequencing capacity and infrastructure during the 2018 Ebola outbreak and then maintained the system, allowing a rapid response to the COVID-19 pandemic. It provided COVID-19 surveillance support to surrounding countries and was one of the first countries to share sequencing data on a public database in March 2020, two weeks after its first case was reported. The Democratic Republic of Congo's infrastructure has also been able to pivot to support several other public health emergencies such as malaria, mpox, and polio, emphasizing the flexibility and utility of pathogen-agnostic surveillance (WHO 2022c). Similarly, countries with strong diagnostic infrastructure for TB, such as GeneXpert, could pivot and use their equipment to concurrently test for COVID-19 and other respiratory pathogens—as both Guinea and Nigeria have done successfully (Soe-Lin, Bowen, and Hecht 2024).

These examples show the potential for genomic sequencing infrastructure beyond the borders of a single country, with regional coordination of both equipment and human resources potentially strengthening surveillance capabilities. Regional efforts like the Africa Centres for Disease Control and Prevention's Integrated Genomic Surveillance and Data Sharing Platform, and Integrated Genomic Surveillance for Outbreak Detection show the promise of this approach (Africa CDC 2024). However, regional coordination would also require robust regulatory frameworks for sample sharing and protection of personal health information.

The cost-effectiveness and economic value of pathogen surveillance requires further research, particularly because the total costs of outbreaks and pandemics are difficult to estimate and vary widely (de Vries et al. 2021; Herida, Dervaux, and Desenclos 2016). Additionally, accounting for positive externalities of surveillance systems in cost-effectiveness analyses, and understanding best approaches for implementing novel technologies, will be important to leverage investments in clinical diagnostic infrastructure, especially for applications in LMICs (Price et al. 2023).

Sharma et al. (2023) estimate the costs of metagenomics to detect a novel respiratory pathogen as part of routine surveillance for patients with influenza-like illness across emergency departments in the United States. They estimate that, with 30 percent population coverage, their modeled metagenomic surveillance system has a 95 percent chance of detecting a novel respiratory pathogen with COVID-19 characteristics after approximately 10 emergency department presentations. Despite the considerable costs of implementing such a system (between US$400 million and US$800 million annually for the United States, compared to an annual budget for the US Centers for Disease Control and Prevention's Advanced Molecular Detection program of only US$35 million), it could significantly reduce the expected losses from pandemics.[7]

The application of these genomic systems and their cost-effectiveness needs to be better understood in LMICs. Efforts to reduce the cost of genomic tests through negotiations with manufacturers and multiplexing will play an important role in making this technology more accessible (Marais, Hardie, and Brink 2022). LMICs could adapt and build on existing infectious disease genomic infrastructure to start metagenomic surveillance, and scale coverage as technology and affordability improve.

Policy Challenges and Opportunities

Sustaining pathogen surveillance systems and adapting to novel technologies will face several challenges. Historically, policy makers have undervalued the importance of pathogen surveillance systems because the benefits of such systems are hidden in insurance value (that is, the avoidance of catastrophic events and costs), which would go unnoticed until the system fails. Undervaluing leads to limited political engagement and financial commitment from governments

to maintain systems outside of outbreak contexts (Ling-Hu et al. 2022; WHO 2022b). In LMICs, reliance on external grant-based funding for time- and priority-restricted pathogen surveillance activities can lead to duplication and tends to ignore local disease priorities (Mfuh, Abanda, and Titanji 2023). Researchers and policy makers should better assess the economic case for pathogen surveillance and invest appropriately.

Surveillance systems, including workflows between clinical diagnosis and reporting, are often fragmented, and infrastructure and capacity vary between and within countries, particularly but not only in LMICs (Bentley and Lo 2021). Data collection needs to be interoperable and standardized, with the appropriate governance frameworks in place to allow for the sharing of data nationally, regionally, and globally (Nicholls et al. 2021).

Metagenomics as an emerging approach will be especially important with its broad application to health, but the high cost of the technology may restrict widespread adoption (Chiu and Miller 2019). Governments should invest in and incentivize the development of novel technologies that would reduce the cost and increase the speed of pathogen surveillance, including using metagenomic approaches.

Last, global data sharing platforms must have the appropriate legal and regulatory mechanisms to ensure integrity and transparency, and to guarantee that scientists receive appropriate credit for their work (Lenharo 2023).

Ethical Considerations

Pathogen surveillance systems that collect individual patient data need to adhere to ethical data sharing principles when analyzing and exchanging information (Crook and Fingerhut 2022). Secure data sharing is of particular importance when dealing with sensitive disease conditions and vulnerable populations. International data sharing should avoid unintended negative consequences such as border closures or trade restrictions, as experienced by South Africa after sharing SARS-CoV-2 Omicron data (Gardy and Loman 2018; Joi 2022). Governing bodies such as WHO should implement incentives to share data, which would encourage countries to collaborate and would prevent withholding of crucial data, as witnessed during the avian influenza A (H5N1) outbreak in 2006, when Indonesia withheld virus information because of controversy around the development of vaccines without consent or assurances for access (Fidler 2008).

DIGITAL OPPORTUNITIES

Achieving Always On systems, including for the three applications described in this chapter, will require implementation of appropriate digital systems. Given the overlapping and mutually reinforcing value of health data and digital

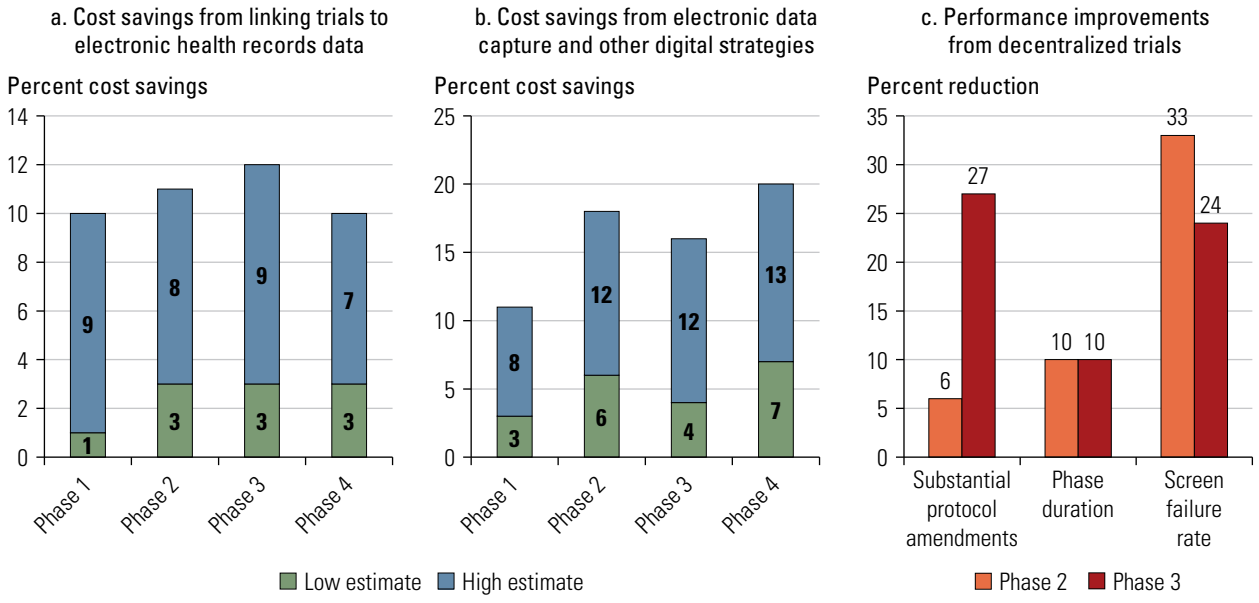
technology, countries should strive to adopt integrated enterprise architecture for Always On systems. That approach is consistent with recommendations from WHO and policy proposals at the Group of Twenty (Seidman et al. 2023; WHO 2020a).

For adult vaccinations, digital tools can offer an integrated ecosystem to optimize vaccination campaigns, including electronic immunization registries, appointment registration, patient communication, clinical trial enrollment, integration of diagnostics and labs data, clinical decision support, population targeting, collection of real-world evidence, and supply chain monitoring (Alkasir et al. 2023).[8]

For clinical research, digital solutions—including linking trial data to electronic health records, electronic data capture, and decentralized trials—can yield 3–13 percent cost savings for a given trial (Sertkaya et al. 2014) (refer to figure 11.3). Digital health has particularly large potential to drive cost savings in health systems in Africa, using digital solutions including virtual interactions, paperless data, workflow automation, decision intelligence systems, patient self-care, and patient self-service. Digital decentralized clinical trials can strengthen community engagement using a digital approach and can enhance equity (McKinsey & Company 2023).

Pathogen surveillance, including for genomics data, requires a well-defined minimum set of data and the ability to electronically report cases (Crook

Figure 11.3 Cost Saving and Performance Improvements due to Digital Technologies



Sources: Sertkaya et al. 2014; Tufts Center for the Study of Drug Development 2022.

Note: Phases 1–3 refer to clinical drug development phases, and phase 4 refers to postmarket studies.

and Fingerhut 2022). For the data to be actionable, they must be collated in a standardized manner regardless of the surveillance platforms and techniques used to gather the information, with common vocabularies and harmonized processes throughout (Nicholls et al. 2021; WHO 2022b). Interoperability of data sets enables successful harmonization for the analysis and sharing of the metadata at local, national, and global levels. Only with adequate digital systems can researchers and health systems appropriately share data while maintaining privacy and security of personal health information. Various researchers have identified case studies of successful digital applications in global health.[9]

LIMITATIONS AND FUTURE DIRECTIONS

Always On presents a novel approach that will require practical considerations for implementation. The three applications presented in this chapter share two limitations—resource allocation and political economy.

All countries, particularly LMICs, face resource constraints and limited fiscal space for publicly funded health service delivery and public health. Even high-income countries such as the United States face challenges related to stop-start funding cycles for public health (Bipartisan Policy Center 2021). Cross-sectional analyses have found capability gaps in LMICs for all three of the applications described in this chapter: vaccine deployment, clinical research, and genomic-informed pathogen surveillance (Inzaule et al. 2021; World Bank 2018, 2021).

Despite meaningful and evidence-based means to improve fiscal space for health—including economic growth, budget reprioritization, and efficiency improvements—countries will nonetheless continue to face budget shortfalls for health care. Further, there will always be opportunity costs for public sector investments, and it is difficult, if not impossible, to measure allocative efficiency while considering the insurance value of health systems investments. Often, political priorities, rather than efficiency arguments, drive decisions about resource allocation, financial and otherwise (Seidman and Atun 2016).

Although COVID-19 focused attention on the importance of health systems, and helped justify investments in them, securing additional funding for emergency PPR beyond the pandemic will require elevating other health issues (Fox and Reich 2015). Always On systems with dual-use capabilities will address barriers and allow citizens to benefit outside of emergency contexts, ensuring that the value of investments are maximized to address multiple health problems without requiring a political opening for investment via an outbreak or emergency.

Testing the hypothesis that an Always On approach can help overcome some of the resource allocation and political economy barriers to investing in health systems will require much additional research, implementation science, and country examples. To address these barriers, this chapter proposes the following:

- **Adult vaccination.** Studying the cost-effectiveness of a new delivery models including the "bundling" of vaccines
- **Clinical research.** Investigation into the economic and political benefits of investing in clinical research capabilities to increase funding for research
- **Pathogen surveillance.** Use of implementation science and economic analysis to establish the best pathways to integrate new surveillance technologies into clinical and public health workflows.

Additional implementation considerations cut across all three applications. Although a full treatment of these considerations is beyond the scope of this chapter, researchers and practitioners should consider planning, monitoring, and evaluation with a focus on how Always On systems and dual-use functionality differ from traditional health systems strengthening. They could consider the following relevant questions, among others:

- How should the implementation of functionalities be phased?
- How can available financing be leveraged, and what cost savings are incurred by taking an Always On approach?
- What is the comparative cost-effectiveness of Always On approaches?
- How should capacity building be sequenced to ensure talent and institutions have the full set of capabilities for dual-use functionality?
- How can we ensure that Always On approaches are integrated into existing or novel global health frameworks and with global multilateral organizations, such as the Coalition for Epidemic Preparedness Innovation, Gavi, and WHO?

CONCLUSION

As we reflect on lessons learned during the COVID-19 pandemic, we must take advantage of the opportunities that event has provided the globe. This chapter has described important health, economic, and political aspects of building Always On health care and public health systems. Always On systems have dual-use functionality; they incorporate emergency and pandemic preparedness into routine health care and public health activities. However, much work remains to define the details of Always On systems, including for applications not described in this chapter (such as climate-resilient health care delivery); to test the best way to implement these systems; and to scale this approach.

ANNEX 11A. ADULT DEATHS ATTRIBUTABLE TO DISEASES OR RISK FACTORS WITH ADULT VACCINATIONS AND PREVENTIVE INJECTABLES

Status of vaccine or preventive injectable	Disease	Deaths (thousands)	Year	Notes	Source
Approved product	Pneumococcal pneumonia	889 (515–1,316)	2019	Assumes 50 percent (29–74 percent) of 1.78 million deaths attributable to lower-respiratory tract infections attributable to pneumococcal pneumonia.	GBD 2016 Lower Respiratory Infections Collaborators 2018
	Influenza	At least 260 (187–333)	2002–11 (average)	Includes only deaths among population ages 65 and older. Total annual deaths estimated at 389,000 (239,980–518,230).	Paget et al. 2019
	Cervical cancer	280	2019		
	COVID-19[a]	—		Age-stratified number of deaths due to COVID-19 not available. Approximately 1.3 million deaths due to COVID-19 in 2022.	IHME[b]
	High LDL cholesterol	4,400	2019		
	Ebola[a]	3	2019		
	Herpes zoster	7.8	2019		
	Dengue	25	2019		
	Meningitis	101	2019		
	Respiratory syncytial virus	57 (41–78)	2019	Assumes 3.2 percent (2.3–4.4 percent) of 1.78 million deaths attributable to lower-respiratory tract infections attributable to pneumococcal pneumonia.	GBD 2016 Lower Respiratory Infections Collaborators 2018
In clinical development	Tuberculosis	1,309	2019	Includes HIV/AIDS-related deaths caused by tuberculosis.	
	Malaria	247	2019		
	ETEC and Shigella	276	2015	Includes all deaths in individuals over five years of age.	Anderson et al. 2019
	Group B streptococcus	147	2015	Stillbirths and infant deaths.	Seale et al. 2017
	Cholera	—		Age-stratified number of deaths due to cholera not available. Approximately 117,167 deaths due to cholera in 2019.	Ilic and Ilic 2023
	Leishmaniasis	2.4	2019		
	Schistomosiasis	11.1	2019		
	Typhoid	44	2019		
	Salmonella infections	15	2019		
	HIV	594	2019	Excludes tuberculosis-related deaths to avoid double-counting. Includes maternal deaths aggravated by HIV/AIDS.	
	Parathyphoid	11	2019		
	Chikungunya	—		Age-stratified number of deaths due to chikungunya not available.	

table continues next page

Status of vaccine or preventive injectable	Disease	Deaths (thousands)	Year	Notes	Source
In clinical development	Zika[a]	Limited number of deaths	2019		
	MERS[a]	Limited number of deaths	2022		WHO Regional Office for the Eastern Mediterranean 2022
	Hepatitis C	541	2019		
	Rheumatic fever	300	2019		
	Lassa fever[a]	—		Age-stratified number of deaths due to Lassa fever not available. About 5,000 deaths due to Lassa fever occur annually.	US Centers for Disease Control and Prevention[c]

Source: All statistics for deaths come from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease database ("GBD Results," https://vizhub.healthdata.org/gbd-results/) and include deaths for individuals aged 15 and older, unless otherwise specified in the notes and references.

Note: ETEC = Enterotoxigenic Escherichia coli; HIV/AIDS = human immunodeficiency virus and acquired immune deficiency syndrome; LDL = low-density lipoprotein; MERS = Middle East respiratory syndrome; — = not available.

a. Indicates World Health Organization (WHO) priority diseases that have epidemic potential or the unavailability of sufficient medical countermeasures; refer to WHO, "Prioritizing Diseases for Research and Development in Emergency Contexts" (accessed August 29, 2023). https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts.

b. IHME, "COVID-19 Projections" (accessed August 29, 2023), https://covid19.healthdata.org/global?view=cumulative-deaths&tab=trend.

c. US Centers for Disease Control and Prevention, "About Lassa Fever," https://www.cdc.gov/lassa-fever/about/index.html.

ANNEX 11B. SUMMARY OF COST-EFFECTIVENESS RESEARCH FOR SELECT ADULT VACCINES

Table 11B.1 Approved Vaccines

Disease	Geography	Main outcome metric	Findings and source
Influenza	Multiple LMICs	Systematic review	"Influenza vaccination provided value for money for elderly, infants, adults and children with high-risk conditions. Vaccination was cost-effective and cost-saving for COPD patients and elderly above 65 years from model-based evaluations, but conclusions from RCTs on elderly varied" (Ott et al. 2013).
Pneumococcal pneumonia	Multiple LMICs, primarily South America	Systematic review	"Compared with no vaccination, either PPSV23 or PCV13 was economically favorable, highly cost-effective, and in many cases, cost-saving for older adults" (Shao and Stoecker 2020).
Pertussis (one component of DTaP vaccine)	Bangladesh, Brazil, and Nigeria	Cost per DALY	"Maternal aP immunization would be cost-effective in Brazil, a middle-income country, under the base-case assumptions, but would be very expensive at infant vaccination coverage in and above the threshold range necessary to eliminate the disease (90–95%). Scenarios representing low-income countries showed that maternal aP immunization could be cost-saving in countries with low infant coverage, such as Nigeria, but very expensive in countries, such as Bangladesh, with high infant coverage" (Kim et al. 2021).
Herpes zoster	HICs only	Systematic review	"A majority of studies of ZVL found it to be cost-efective compared with no vaccine using the authors' chosen willingness-to-pay thresholds" (Chiyaka et al. 2019). The high prices observed in HICs mean that these findings are likely not generalizable to LMICs.
HPV	Multiple HICs and LMICs	Mean cost per FIG	Cost-effectiveness of the HPV vaccine is widely accepted, and various service delivery strategies can reduce the cost per FIG (Akumbom et al. 2022).
RSV	Gavi-eligible countries	Effectiveness and cost-effectiveness of maternal vaccination	"Maternal vaccination would prevent 1.2 million cases [95% PI 0.6–1.9 million], 104 thousand hospital admissions [95% PI 19–309 thousand], and 3 thousand deaths [95% PI 1–11 thousand] in those countries. It can avert 98 thousand discounted DALYs [95% PI 16–308 thousand] and 186 million USD [95% PI 144–206 million]. The mAb strategy would prevent more cases and avert more discounted DALYs and treatment costs). However, the mAb strategy would also result in higher discounted net costs compared to the maternal strategy due to the assumed higher intervention costs (6 USD vs. 3 USD)" (Li et al. 2020).

Source: Original table for this report compiled using the sources cited in the table.

Note: COPD = chronic obstructive pulmonary disease; DALY = disability-adjusted life year; FIG = fully immunized girl; HIC = high-income country; HIV = human immunodeficiency virus; HPV = human papillomavirus; LMICs = low- and middle-income countries; RCT = randomized controlled trial; RSV = Respiratory syncytial virus.

Table 11B.2 Vaccines Currently under Development

Disease	Country studies	Main outcome metric	Findings and sources
HIV	LMICs	Cost per QALY	An HIV/AIDS vaccine would need to cost below US$20–US$40 per regimen, depending on scale-up and other scenarios (Harmon et al. 2016).
Group B streptococcus	37 countries in Sub-Saharan Africa	Cost per DALY for maternal vaccination	"Maternal GBS immunization could be a cost-effective intervention in low-income sub-Saharan Africa, with cost-effectiveness ratios similar to other recently introduced vaccines. The vaccination cost at which introduction is cost-effective depends on disease incidence and vaccine efficacy" (Russell et al. 2017).
Tuberculosis	LMICs	DALY	Depending on the efficacy of the vaccine, a tuberculosis vaccine "targeted at adolescents/adults could be cost-effective at $4, $9, and $20 per dose in low-, lower-middle–, and upper-middle– income countries, respectively" (Knight et al. 2014).

Source: Original table for this report compiled using the sources cited in the table.

Note: DALY = disability-adjusted life year; GBS = Group B streptococcus; HIV/AIDS = human immunodeficiency virus and acquired immune deficiency syndrome; LMICs = low- and middle-income countries; QALY = quality-adjusted life year.

NOTES

1. Refer also to the Tony Blair Institute for Global Change's "Global Health Security Consortium" web page, https://institute.global/tags/global-health-security-consortium.
2. Gavi, "Vaccine Investment Strategy 2024" (accessed August 24, 2023), https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy-2024.
3. UK Research and Innovation, "The RECOVERY Trial" (accessed October 8, 2023), https://www.ukri.org/who-we-are/how-we-are-doing/research-outcomes-and-impact/mrc/recovery-trial-identifies-covid-19-treatments/.
4. From the European & Developing Countries Clinical Trials Partnership's home page, https://www.edctp.org.
5. European & Developing Countries Clinical Trials Partnership, "Public Portal of EDCTP2-Funded Projects" (accessed August 24, 2023), https://www.edctp.org/edctp2-project-portal/.
6. Refer to US Centers for Disease Control and Prevention, "Elecronic Case Reporting (eCR)," https://www.cdc.gov/ecr/php/about/?CDC_AAref_Val=https://www.cdc.gov/ecr/what-is-ecr.html.
7. US Centers for Disease Control and Prevention, "National Investment Maps" (accessed August 24, 2023), https://www.cdc.gov/advanced-molecular-detection/php/investments/maps.html?CDC_AAref_Val=https://www.cdc.gov/amd/investments/maps.html.
8. For additional sources, refer to Gavi, "Gavi Digital Health Information Strategy Technical Brief Series," https://www.gavi.org/programmes-impact/our-impact/evaluation-studies/gavi-digital-health-information-strategy-technical-brief-series.
9. For one set of case studies on best practices in digital health applications, refer to Exemplars in Global Health, "Digital Health Tools," https://www.exemplars.health/emerging-topics/epidemic-preparedness-and-response/digital-health-tools.

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