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VACCINE INSIGHTS

SPOTLIGHT

How close are we to meeting the 100 days target to produce a vaccine?

VACCINE INSIGHTS

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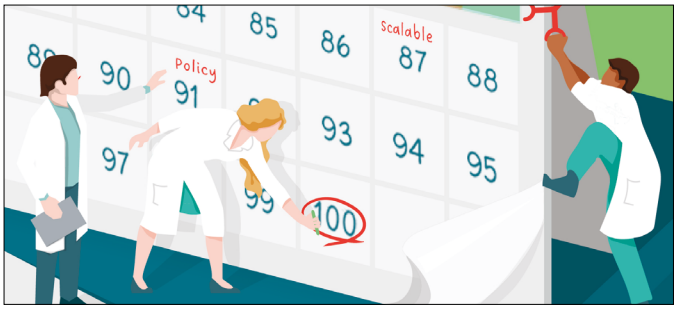

VACCINE INSIGHTS

HOW CLOSE ARE WE TO MEETING THE 100 DAYS TARGET TO PRODUCE A VACCINE?

SPOTLIGHT

REVIEW

Inclusive innovation responses to epidemic challenges: a multi-case study of MERS, Zika and Ebola outbreaks

Jelle J Feddema, Sarah Ward, Riley Terzopoulos, and Linda HM van de Burgwal

The COVID-19 pandemic underscored the need for global preparedness against emerging infectious diseases (EIDs). Inclusive innovation, integrating local actors from affected low- and middle-income countries (LMIC), is critical to effective outbreak response. This study examines inclusivity during MERS, Ebola, and Zika by analysing publications, clinical trials, and patents. Findings show innovation was largely led by high-income countries (HIC): over 80% of publications and 95% of patents were linked to non-affected HIC. LMIC hosted nearly half of clinical trials but contributed minimally to knowledge generation and ownership. Collaboration often excluded LMIC, and HIC provided most funding, concentrating decision-making power. This imbalance undermines global preparedness. Strengthening frameworks like the WHO Treaty and Nagoya Protocol, with adequate resources, is vital to ensure equitable collaboration. Inclusive innovation is essential both ethically and for building sustainable, contextually relevant solutions that enhance global health security and resilience.

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INTRODUCTION

The COVID-19 pandemic highlighted the urgent need for better preparedness for emerging infectious diseases (EIDs). Increasing globalization allows outbreaks to spread rapidly, causing widespread health and socio-economic disruption. Effective responses require coordination with local actors in affected countries, including academics, industry, public health officials, and governments [1,2]. These actors should be involved in research and innovation (R&I), from early stages to clinical testing. However, participation of low-resource countries in the

Global South, where emerging infectious often occur first, remains limited [3,4].

Achieving the active inclusion of local actors is challenging due to numerous factors such as resource constraints, intellectual property issues, and limited access to information and networks [5,6]. Efforts to increase international collaboration, such as the PIP framework, Nagoya Protocol, and WHO's Pandemic Preparedness Treaty, face obstacles around sovereignty, equity, and access, evident by the 2-year failure to finalize the WHO Treaty [7].

Excluding local actors can have severe consequences. Without sufficient knowledge of the local context, countermeasures often fail to address fundamental issues related to their administration and use [1,2]. Opportunities for context-specific solutions, capacity building, and monitoring outbreaks are missed, which undermines global preparedness. Previous outbreaks have demonstrated global preparedness problems arising from excluding local actors from the R&I process and their access to countermeasures. During the 2007 influenza outbreak, Indonesia did not share samples and data with other countries, citing previous experiences when samples were provided but they did not receive access to the subsequent vaccines [8]. Similar reports, driven by comparable concerns, have been noted during the outbreaks of Ebola, Nipah, and even COVID-19 [8–11].

Failure to share pathogen samples can delay interventions and hinder R&I and development of countermeasures, thereby exacerbating the threat of immune-evading variants [12]. During COVID-19, initiatives like COVAX aimed for vaccine equity but faced obstacles such as supply disruptions, vaccine nationalism, and funding shortfalls [13]. These incidents reflect the power imbalances between HIC, who control resources, and low-resource countries, who bear the brunt of the EIDs [14]. Addressing this imbalance is crucial for ensuring equitable global health responses and for facilitating the timely sharing of pathogen samples and data [15].

One way to address this imbalance is through inclusive innovation. Inclusive innovation is essential for integrating marginalized actors into R&I processes and ensuring the equitable sharing of benefits. By focusing on the needs of historically marginalized groups, it addresses inequities and power imbalances and enhances efforts in disease prevention, diagnosis, and treatment [16,17]. The Nagoya Protocol's access and benefit-sharing (ABS) regulation, effective since 2014, supports fair distribution of benefits from genetic resources like pathogens by involving local communities in research and ensuring they receive a share of outcomes such as diagnostics and treatments. This fosters trust, cooperation, and innovation, helping to rectify North-South power imbalances and strengthen global health security [18]. Integrating marginalized actors into EID-related R&I processes makes innovations more relevant and accessible, particularly in low-resource settings. Integration contributes to building capacity, levelling disparities between the North-South actors, and developing sustainable, locally embedded solutions that enhance global preparedness and resilience against future health crises [19].

This study examines inclusive innovation during three outbreaks, MERS, Ebola, and Zika, to identify patterns and gaps in local actor engagement in the R&I process. Understanding these dynamics is essential for improving future responses to EIDs. We study the reflections of inclusive innovation as evidenced in scientific literature, patents, and clinical trial databases, and analyse the timeliness, collaboration, and funding streams in response to the three outbreaks.

Our findings indicate significant geographic imbalances in innovation efforts, with low- and middle-income countries often excluded from ownership of publications, patents, and clinical trials.

Addressing these inequities is essential for future EID preparedness and response.

THEORETICAL DEMARCATION

Inclusive innovation emphasizes integrating marginalized and disenfranchised groups into R&I processes. It ensures equitable sharing of benefits and addresses the needs of typically excluded societal groups [17,19]. This concept is rooted in the broader concept of systems of innovation perspective, which analyses how different actors, institutions, and policies interact to shape technological and scientific development.

At its core, inclusive innovation can be understood along two interrelated dimensions: inclusivity of outcomes and inclusivity of the innovation process itself. Inclusivity in outcomes refers to ensuring that innovation—such as vaccines or diagnostics—are accessible, affordable, and contextually relevant to all populations. Inclusivity in process focuses on empowering local actors by involving them in the design, development, and governance of innovations, thereby enhancing the relevance and sustainability of outcomes and strengthening local innovation capacity [19,20].

This dual lens is particularly relevant for addressing health inequities in global challenges such as EIDs. By focusing on outcomes, inclusive innovation helps direct benefits toward those most in need. Emphasizing inclusive processes, meanwhile, fosters long-term structural change by enabling marginalized actors to shape innovation agendas. Together, these approaches support the development of more equitable, resilient, and context-sensitive innovation systems.

To operationalize the concept of inclusive innovation, we draw on three key dimensions: participation and engagement, collaboration and coordination, and equity and access [17,19,21–25]. *Participation and engagement* emphasize the inclusion of local knowledge and actors across the R&I process. *Collaboration and coordination* refer to partnerships among stakeholders (e.g., including governments, academia, industry, and civil society) to align resources and expertise. *Equity and access* refer to addressing disparities by ensuring that low- and middle-income countries and marginalized communities can both contribute to and benefit from innovation, overcoming barriers like (financial) resource constraints and intellectual property challenges.

In applying these principles to emerging infectious diseases, this study analysed the inclusivity of R&D efforts across various stages, including publications, patents, and clinical trials.

Publications

The geographical distribution and institutional affiliations of authors reveal whether marginalized regions were involved. Mapping collaboration networks shows the diversity of partnerships, with broader networks suggesting a more inclusive approach. Identifying and mapping funding sources provides insight into the equity of funding streams.

Patents

The geographical origins of patent applications indicate regional involvement, with diverse distributions reflecting a more inclusive innovation process. Examining inventor lists shows whether researchers from marginalized countries were involved. Multiple applicants also indicate institutional partnerships.

Clinical trials

The geographical distribution of trials reveals whether LMIC and affected regions were included. Local institution involvement reflects inclusivity, and analysing trial sponsors provides insights into

funding equity and the participation of marginalized countries.

This framework allows us to evaluate the extent to which inclusive innovation principles are integrated into the response to EIDs. By applying this approach, we gain a clearer understanding of how inclusive or exclusive global responses to emerging infectious diseases have been. This evaluation highlights gaps in participation and collaboration, offering valuable insights to guide more equitable and inclusive responses in the future.

MATERIALS & METHODS

This study employs a quantitative research design by analysing scientific literature, patent documents, and clinical trials to assess the extent of inclusive innovation during three recent EID outbreaks: Ebola, Zika, and MERS. Using a multiple case study approach, the research empirically investigates the degree of collaboration and inclusion across low-, middle-, and high-income countries. These cases were selected based on their unique market dynamics, histories of conflict, and anticipated importance for future global health crises, providing valuable insights into innovation inclusivity during health emergencies. A combination of data was gathered to create an overview of the R&I landscape for each outbreak, chosen for their severity and diverse socio-economic impacts. The COVID-19 outbreak was excluded from this analysis due to its ongoing nature at the time of data collection, which could have introduced recency bias and incomplete data. This focus on MERS, Ebola, and Zika ensures consistent historical comparisons and a detailed examination of diverse pathogens.

Data collection and preparation

Scientific publications related to all three outbreaks were collected from the LENS.org scholarly works database [26], with searches conducted on August 10, 2023, based on abstracts and titles (search query details in Table 1 and Supplementary Material). Using the LENS analysis interface, datasets were created and cleaned in Excel, containing information on publication year, authors, institutional locations, funding countries, recipient countries, and institutional and country collaborations. Data on disease burden (annual incidence rates) were retrieved from the Global Burden of Disease Study [27] and supplemented with figures from scientific literature and WHO publications.

Clinical trial data were collected from the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. [28,29]. The searches were conducted on September 26, 2023. The search criteria details are provided in the Annex. Using Excel, datasets were created and cleaned, containing information on trial ID, trial title and description, registration date, trial locations, sponsor locations, and collaborations between organizations involved in the clinical trial. The relevance of clinical trials was assessed by screening the trial titles and descriptions.

Patents were retrieved from Espacenet, a database by the European Patent Office (EPO). Using a search string based on the Cooperative Patent Classification (CPC) code (details in Annex), the search query was designed and quality controlled by an independent patent specialist from the Netherlands Enterprise Agency (RVO). Searches were conducted on March 9, 2023, and the data were pooled and cleaned in Excel. Priority numbers identified patents with the earliest application date for analysis. Exclusion criteria were applied to ensure relevance, with patent titles, abstracts, and descriptions screened accordingly.

Data analysis

To analyse the data and observe correlations, scatter plots and bar charts were generated, comparing the number of

TABLE 1

Degree of collaboration with low-, middle-, and high-income countries in publications, clinical trials, and patents for MERS, Ebola, and Zika.

		Publications (%)	Clinical trials (%)	Patents (%)
MERS	% involving LIC	0.7	0.0	0.0
	% involving MIC	49.5	7.0	36.0
	% involving HIC	90.1	93.3	68.9
EBOLA	% involving LIC	10.8	17.1	0.0
	% involving MIC	50.5	21.7	23.6
	% involving HIC	88.3	78.3	76.4
ZIKA	% involving LIC	1.4	0.0	0.0
	% involving MIC	55.0	40.1	24.2
	% involving HIC	91.1	95.4	81.8

The table summarises the proportion of research outputs involving institutions from different income groups. Across all three outbreaks, collaborations were dominated by HICs, with MICs contributing more modestly and LICs remaining largely excluded. LIC participation was highest during the Ebola outbreak but almost absent in MERS- and Zika-related activities, particularly in patenting.

publications, clinical trials, and patents with the confirmed incidence cases for each outbreak. Y-axes were standardized where possible, though divergent values sometimes prevented this. Additionally, heat maps were created for each outbreak, with colour gradients representing the percentage of publications, clinical trials, patents, or confirmed cases per country.

Collaboration across publications, clinical trials, and patents was assessed by classifying countries as low-, middle-, or high-income based on World Bank standards [30]. The number of collaborations between these categorized countries was visually presented using stacked bar charts. While multiple collaborations per publication or clinical trial were common due to frequent multi-country involvement, no such instances were found for patents, where collaborations per document were singular.

Collaboration and funding networks in scientific publications were mapped using VosViewer. The analysis included determining the number of countries involved, interconnections between them, and the total number of collaborative publications. A minimum link strength of 15 collaborations was set for visualizing connections between countries. However, this threshold was not applied when mapping funding streams, where the top 100 publication funders were visualized.

RESULTS

Correlation between outbreak severity and research outputs: publications, clinical trials, and patents

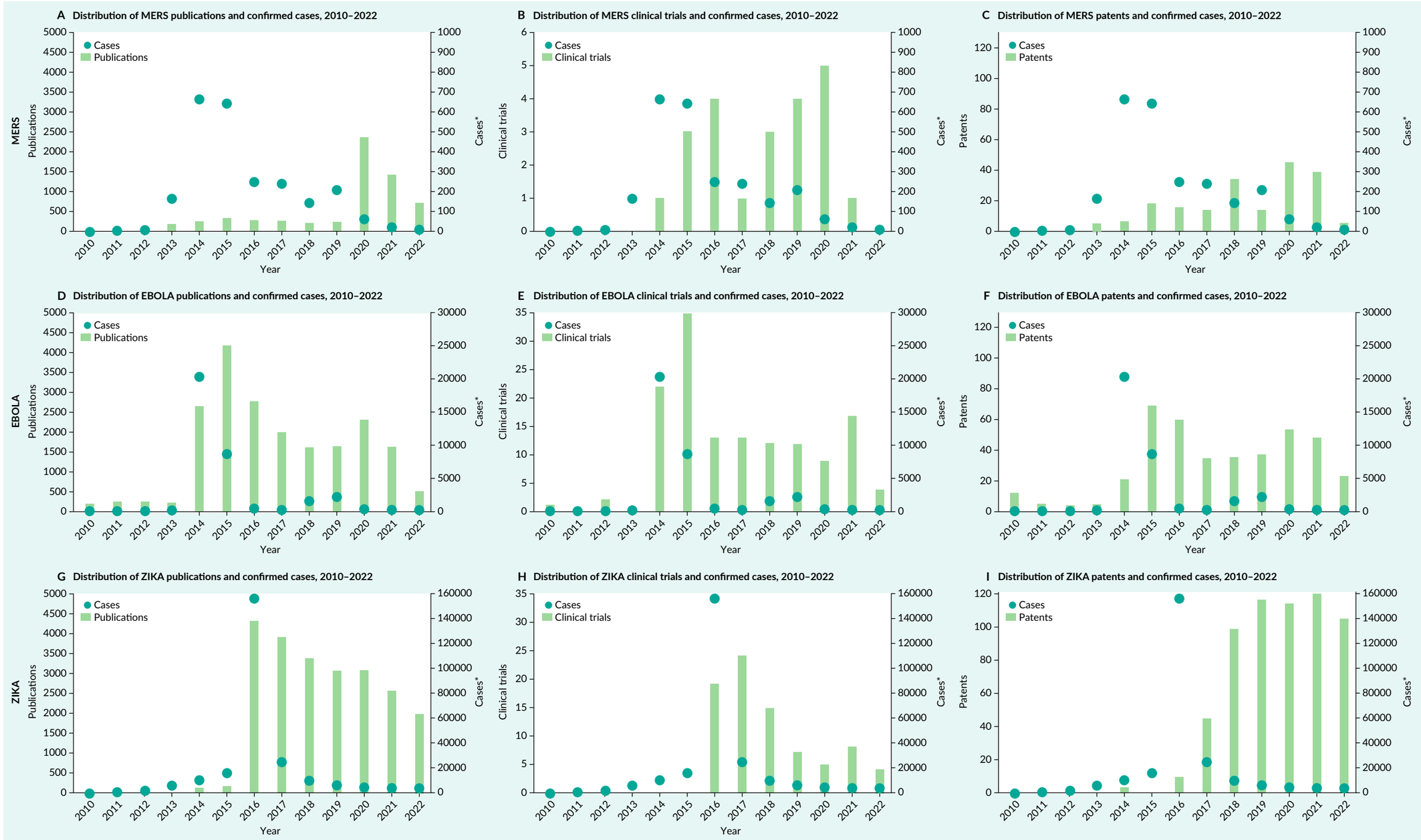
Figure 1 illustrates the relationship between confirmed cases of MERS (2.604), Ebola (34.582), and Zika (152.311) and associated research outputs—publications, clinical trials, and patents.

Publications

For MERS and Ebola (Figure 1A and D), publication output rose with case numbers and declined once outbreaks subsided, more

FIGURE 1

Trends in research and innovation activity compared with outbreak dynamics for MERS, Ebola, and Zika (2010–2022).



Panels (A–I) show annual counts of publications, clinical trials, and patent filings (orange bars) plotted against confirmed cases (blue dots). For MERS and Ebola, research and innovation activity rose and declined largely in parallel with case numbers, indicating a reactive pattern of global attention. In contrast, Zika displays a delayed but sustained increase in publications, trials, and patents, beginning only after the epidemic peak.

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distinctly for Ebola given its scale. Zika (Figure 1G) diverged, showing a delayed surge peaking in 2016 after WHO's emergency declaration. Research interest persisted for Ebola and Zika but declined sharply for MERS, which produced fewer overall publications (5.626 vs. 17.123 for Ebola and 19.644 for Zika). MERS output rose again in 2020, likely reflecting renewed attention during COVID-19.

Clinical trials

Trends in clinical trials (Figure 1B, E, and H) mirrored publication activity. MERS and Ebola trials began as cases rose, whereas Zika trials started years later. Despite Zika's higher case count, only 84 trials were registered (≈1 per 1,800 cases) compared to 22 for MERS (1 per 118) and 143 for Ebola (1 per 242). Clinical development for Ebola, and to a lesser extent Zika, continued even after transmission ceased.

Patents

Patent activity (Figure 1C, F, and I) followed a similar pattern: filings for MERS and Ebola increased with case numbers, with Ebola R&D initiatives already underway before 2014. Zika patents rose only years later but remained high despite falling case numbers, totalling 619 filings versus 336 for Ebola and 205 for MERS. Renewed concern about pandemic preparedness during COVID-19 likely spurred additional patenting activity across all three diseases.

GLOBAL COLLABORATIONS IN PUBLICATIONS, CLINICAL TRIALS, & PATENTS ACROSS OUTBREAKS COLLABORATIONS

Figure 2 and Table 1 illustrate collaboration patterns across publications, clinical trials, and patents. Multiple partnerships within a single publication or trial were counted separately.

Publications

International collaboration in scientific publications was extensive but rarely included LIC. LIC participation was highest during Ebola (11%), compared with only 0.7% for MERS and 1.4% for Zika. MIC were more frequently represented, accounting for about half of collaborations in all three outbreaks. Despite Zika primarily affecting MICs, its share of MIC participation was similar to Ebola and MERS. The Zika outbreak generated exceptionally high collaborative output, 18.492 collaborations from 19.644 publications, compared to Ebola (11.031 of 17.132) and MERS (2.800 of 5.626).

Clinical trials

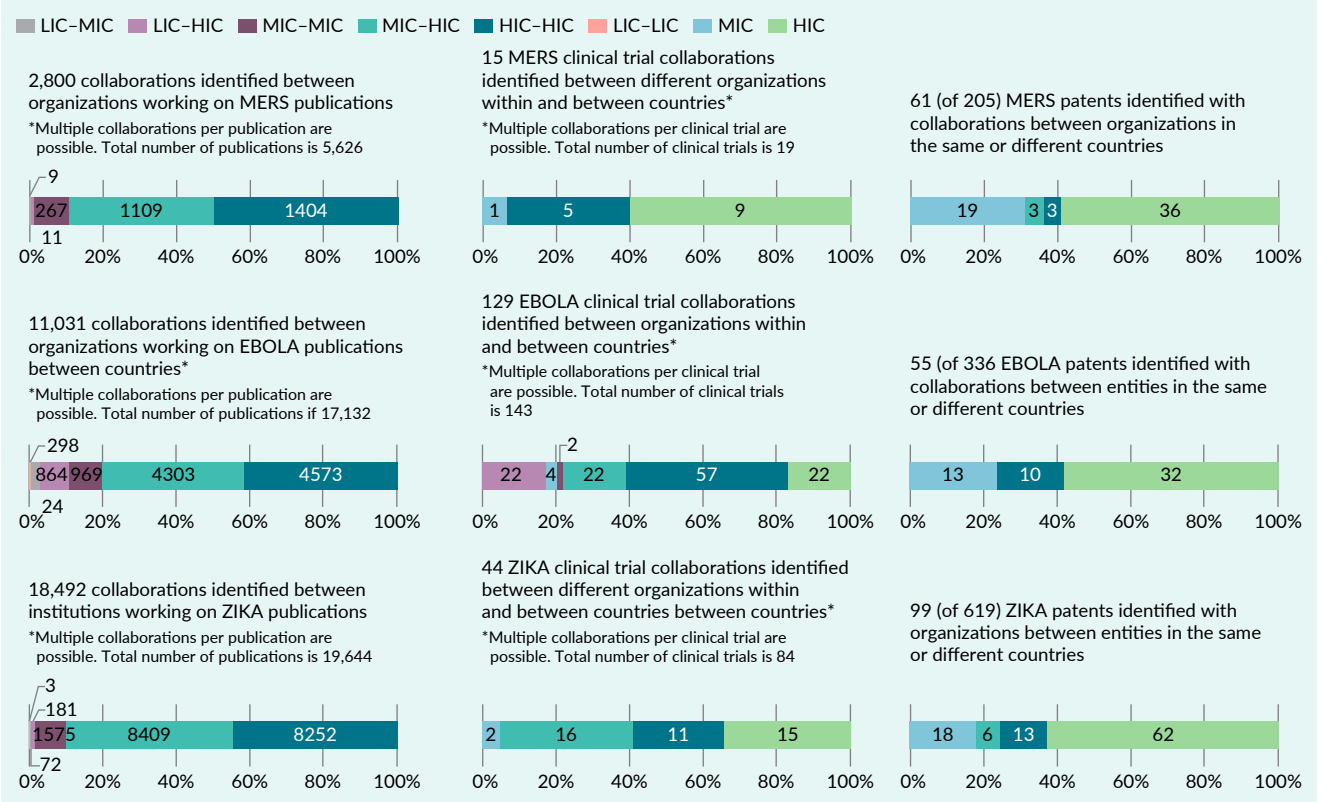
Cross-country collaboration in clinical trials was also substantial, dominated by HIC, which participated in 78.3% (Ebola) to 95.4% (Zika) of collaborative trials. LIC involvement occurred almost exclusively during Ebola, with 22 partnerships between heavily affected LIC and HIC. MERS trials were mainly HIC-led, whereas Ebola and Zika showed greater MIC engagement (21.7% and 40.1%, respectively). Despite strong Zika collaboration in publications, trial partnerships were proportionally higher for Ebola (129 of 143 trials) and MERS (15 of 22) than for Zika (44 of 84).

Patents

Of 1.160 patents identified across the three outbreaks, only 215 involved multiple applicants, and just 35 were cross-country collaborations. None included LICs, even for Ebola, which mainly affected them. Most patent collaborations occurred within HIC or MIC, with cross-country partnerships limited to HIC–HIC or HIC–MIC pairs. Patterns varied slightly by outbreak: Ebola patents showed largely

FIGURE 2

International collaboration patterns in research and innovation during the MERS, Ebola, and Zika outbreaks.



Panels illustrate the proportion of collaborations in publications, clinical trials, and patents among institutions from low- (LIC), middle- (MIC), and high-income countries (HIC). Collaborations were concentrated between HIC and MIC, with minimal involvement of LICs. LIC participation increased slightly during Ebola, reflecting the location of the outbreak, but remained negligible for MERS and Zika. No patent collaborations included LIC-affiliated organisations, underscoring persistent exclusion from intellectual-property-driven research.

domestic MIC collaboration (notably China), Zika involved more diverse partners such as Brazil, Colombia, and Macao, and MERS patents mainly linked HIC (USA, Korea, Canada, the Netherlands, and Germany).

MAPPING GLOBAL COLLABORATION NETWORKS IN SCIENTIFIC PUBLICATIONS DURING MERS, EBOLA, & ZIKA OUTBREAKS

Figure 3 (A–C) maps country collaborations in scientific publications, with node thickness representing publication volume and line thickness collaboration frequency (links <15 omitted for clarity).

For MERS (Figure 3A), 100 countries produced 2.800 collaborative publications across 677 linkages. Among the top 10 organizations, each publication involved 3.1–5.1 partners on average, while major countries such as the USA, China, and India showed more domestic than international collaborations.

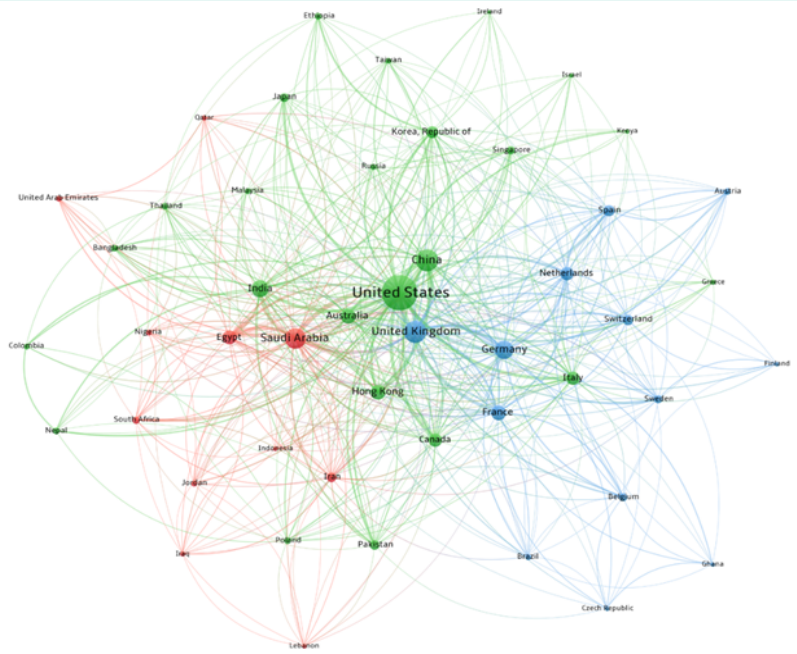
Ebola (Figure 3B) involved 136 countries and 11,013 collaborative publications through 2,303 linkages, more than twice that of MERS. The top 10 organizations averaged 2.9–6.4 partners per publication, but leading countries (USA, UK, Germany) again showed fewer international than domestic collaborations.

Zika (Figure 3C) showed the broadest participation, with a total of 145

FIGURE 3A

Country collaboration network for MERS-related scientific publications.

A



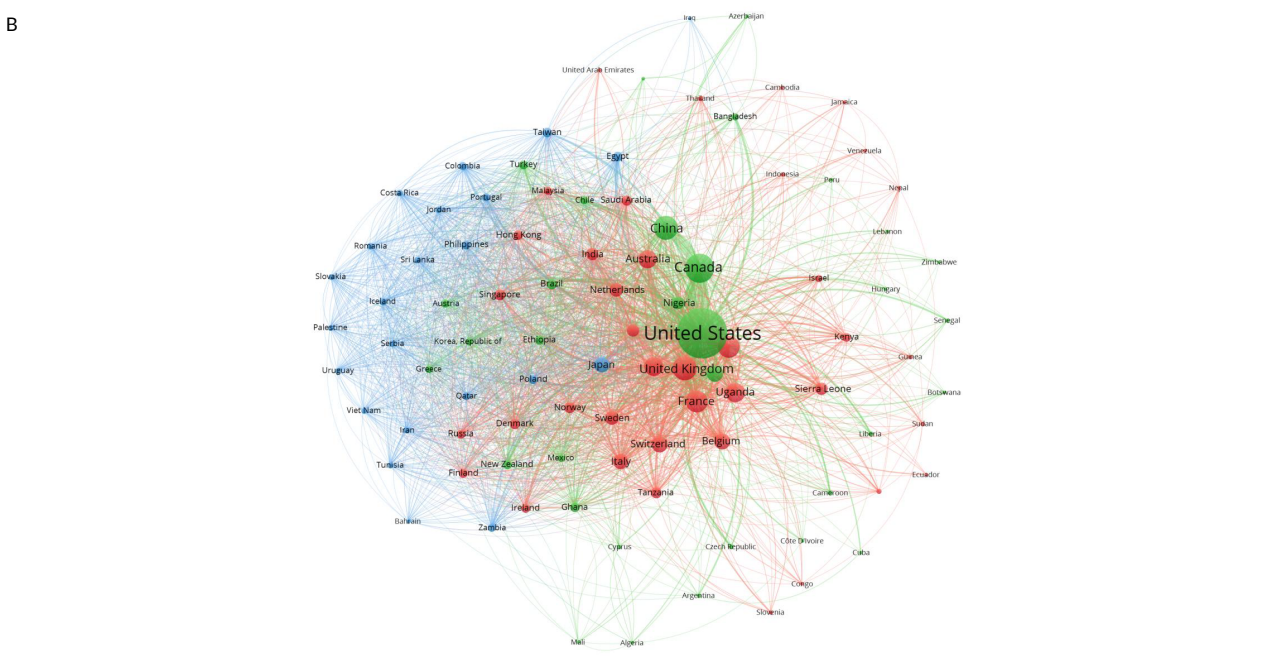
Top 10 collaborating organizations	Number of collaborative publications (total number of publications)	Top 10 collaborating countries	Number of collaborative publications (total number of publications)
University of Hong Kong (HK)	478 (117)	United States	1005 (1386)
National Institutes of Health (US)	428 (130)	China	416 (587)
Chinese Academy of Sciences (CN)	392 (99)	United Kingdom	399 (288)
Centers for Disease Control and Prevention (US)	299 (81)	Saudi Arabia	356 (295)
Johns Hopkins University (US)	293 (57)	Germany	281 (210)
King Saud University (SA)	286 (68)	India	245 (425)
King Abdulaziz University (SA)	252 (68)	France	188 (164)
Alfaisal University (SA)	244 (57)	Australia	182 (142)
University of North Carolina at Chapel Hill (US)	230 (75)	Hong Kong	172 (199)
University of Iowa	188 (55)	Egypt	167 (104)

Node size indicates the volume of publications, and line thickness represents the frequency of collaboration between countries. The visualization reveals that collaboration was primarily concentrated among high-income countries, with the USA, China, and the UK acting as central hubs. Regional clusters emerged around Saudi Arabia and other Middle Eastern countries, but cross-regional collaborations with low- and middle-income countries were limited.

countries and 18.492 collaborative publications across 1.432 linkages. The top 10 organizations averaged 2.4–6.3 partners per publication, and unlike previous outbreaks, all of the top countries had more collaborative than total publications, which indicates extensive international engagement.

FIGURE 3B

Country collaboration network for Ebola-related scientific publications.



Top 10 collaborating organizations	Number of collaborative publications (total number of publications)	Top 10 collaborating countries	Number of collaborative publications (total number of publications)
National Institutes of Health (US)	2741 (794)	United States	4432 (6756)
Harvard University (US)	2160 (403)	Canada	1476 (930)
Centers for Disease Control and Prevention (US)	2113 (639)	China	1023 (816)
World Health Organization (INT)	1921 (359)	United Kingdom	1022 (1764)
French Institute of Health and Medical Research (FR)	1757 (271)	Pakistan	843 (430)
University of Oxford (UK)	1626 (265)	France	833 (696)
Emory University (US)	1423 (273)	Uganda	649 (284)
University of London (UK)	1423 (326)	Germany	644 (744)
Public Health Agency of Canada (CA)	1189 (271)	Australia	580 (485)
United States Army Medical Research Institute of Infectious Diseases (US)	788 (269)	South Africa	467 (299)

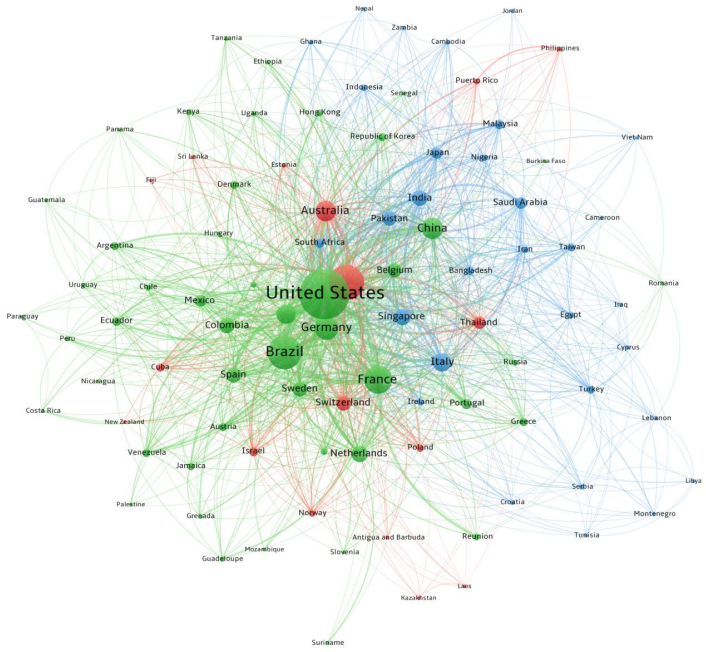
Node size indicates the number of publications, and line thickness reflects collaboration frequency between countries. Ebola research showed the most geographically diverse collaboration network among the three outbreaks, with 136 participating countries and 2,303 unique collaboration linkages. The USA, UK, and France formed major hubs, closely linked to affected West African countries such as Sierra Leone, Liberia, Guinea, and Uganda. This pattern illustrates a surge in cross-regional cooperation during the crisis, though collaborations remained largely driven and funded by high-income countries

Despite greater participation during Zika, Ebola exhibited higher diversity in collaboration, with more unique linkages (2.303 versus 1.432). The VosViewer maps in Figure 3 reflect this, showing denser, more diverse collaboration lines for Ebola.

FIGURE 3C

Country collaboration network for Zika-related scientific publications.

C



Top 10 collaborating organizations	Number of collaborative publications (total number of publications)	Top 10 collaborating countries	Number of collaborative publications (total number of publications)
Oswaldo Cruz Foundation (BR)	2555 (746)	United States	6985 (6582)
Harvard University (US)	1967 (333)	United Kingdom	3450 (1269)
University of São Paulo (BR)	1842 (577)	Brazil	3196 (3111)
French Institute of Health and Medical Research (FR)	1801 (342)	France	2176 (956)
University of Oxford (UK)	1792 (286)	Germany	1566 (540)
Centers for Disease Control and Prevention (US)	1747 (518)	China	1298 (1249)
National Institutes of Health (US)	1562 (337)	Australia	1230 (565)
Emory University (US)	1523 (275)	Canada	1068 (527)
Federal University of Rio de Janeiro (BR)	1338 (390)	Italy	1006 (403)
Pasteur Institute (FR)	826 (351)	Netherlands	742 (215)

Node size represents the number of publications, and line thickness indicates collaboration frequency between countries. Zika research involved 145 countries and 1,432 unique collaboration linkages, showing strong international engagement but lower diversity of connections than Ebola. The USA and Brazil were major hubs, with Brazil emerging as a central middle-income collaborator. Despite extensive global involvement, most collaborations clustered around pre-existing partnerships in high-income and upper-middle-income countries, highlighting persistent structural asymmetries in research participation.

Zika collaborations, though numerous, were likely concentrated within established networks rather than forming new partnerships.

GLOBAL FUNDING NETWORKS & DISTRIBUTION DURING MERS, EBOLA, & ZIKA OUTBREAKS

Figures 4A–C map funding organizations, where node thickness indicates funding frequency and line thickness the strength of funding relationships. Clusters denote groups of organizations that frequently fund one another.

The USA dominated MERS research funding (62.2% of all acknowledgements), led by the NIH, which primarily supported national universities and institutes. Limited funding reached international partners such as the Chinese Academy of Sciences, Fudan University, and the Pasteur Institute. Overall, MERS funding was overwhelmingly concentrated within HIC, with no LIC among the top funders or recipients (tables in Figure 4A).

Funding during Ebola was more diverse but still HIC-driven. The US remained the top contributor (65.3%), while supranational organizations such as the WHO and European initiatives accounted for 14.4% of acknowledged funding (758 publications). Funding streams largely remained domestic: NIH funding mainly supported US institutions, and no LIC organizations appeared among the top 10 recipients. The WHO ranked second overall, while Congo was the only outbreak-affected country among the top recipients, underscoring the global North's dominance in research financing.

Zika funding followed a similar pattern but showed stronger MIC participation. The USA remained the leading funder (57.3%), but Brazil emerged as an important national contributor, ranking second as both funder (15.0%) and recipient country (24.0%). Four Brazilian institutions, led by the Oswaldo Cruz Foundation (8.9%), featured among the top 10 funders and recipients (tables in Figure 4C). Despite Brazil's prominence, most Zika research continued to rely on HIC financing, with the USA and UK far surpassing MIC contributions.

RESEARCH ENGAGEMENT & INNOVATION IN AFFECTED vs NON-AFFECTED COUNTRIES: PUBLICATIONS, CLINICAL TRIALS, & PATENTS

Publications

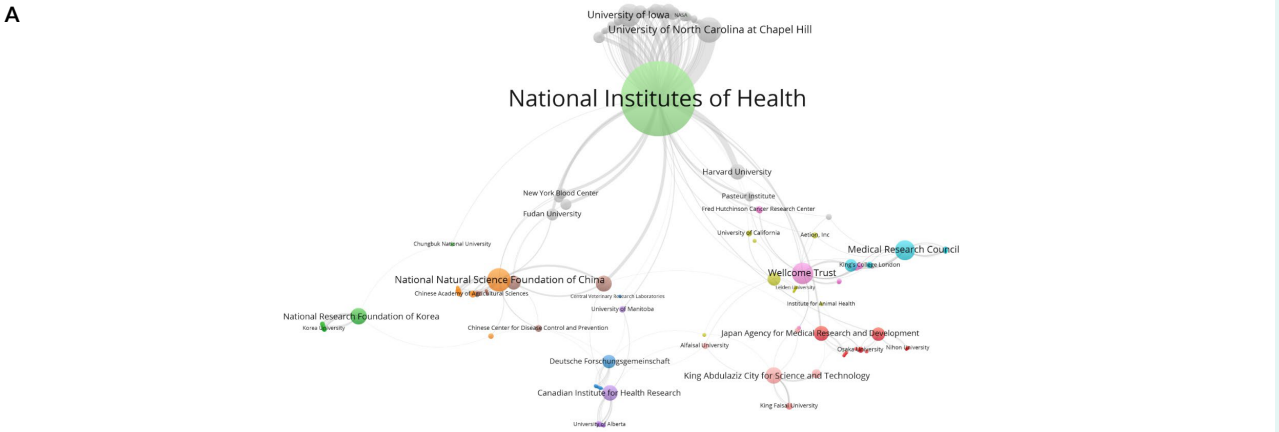
Figure 5A–F shows that publication activity by affected countries was limited across outbreaks. For MERS, Saudi Arabia (84.3% of cases) and South Korea (7.1%) accounted for only 5.0% and 2.9% of publications, respectively. During Ebola, the most affected countries, Sierra Leone (41%), Liberia (31%), Congo (13%), and Guinea (11%), collectively contributed fewer than 2% of publications, with Sierra Leone ranking 20th. Zika showed somewhat higher local engagement: Brazil (39% of cases) produced 14.4% of publications, while India (3%) and El Salvador (<0.1%) contributed marginally. Across all three outbreaks, the USA, China, and the UK dominated publication output regardless of case distribution.

Clinical trials

Affected countries were more active in clinical trials than in publications (Figure 5G–L). For MERS, Saudi Arabia and South Korea conducted 6 and 4 of the 22 total trials, ranking 6th and 8th, respectively. Ebola showed stronger local involvement, with Sierra Leone (24 trials, rank 2), Guinea (14), Liberia (9), and Congo (8) hosting many trials, though local sponsor participation remained limited (e.g., 3 in Sierra Leone, 1 in Congo). For Zika, Brazil conducted 23 of 83 trials, supported by 20 domestic sponsors, ranking second in both. Despite this, non-affected countries, particularly the USA, consistently led in both trial initiation and sponsorship across all outbreaks.

FIGURE 4A

Mapping of funding organizations for MERS-related scientific publications.



Top 10 funding organizations	Number	Top 10 funding countries	Number
National Institute of Health (US)	965	United States	1062
National Natural Science Foundations of China (CN)	109	China	164
Medical Research Council (UK)	41	United Kingdom	98
Wellcome Trust (UK)	38	Supranational	52
National Research Foundation of Korea (KR)	36	Korea	49
National Key Research and Development Program of China (CN)	26	Canada	41
CIHR (CA)	26	Germany	35
Deutsche Forschungsgemeinschaft (DE)	24	Japan	35
US Public Health Service (US)	21	Saudi Arabia	35
King Abdulaziz City for Science and Technology (SA)	19	Brazil	27

Top 10 recipient organizations	Number	Top 10 recipient countries	Number
National Institute of Health (US)	104	United States	751
University or Carolina at Chapel Hill (US)	89	China	85
University of Iowa (US)	73	United Kingdom	79
Chinese Academy of Sciences	38	China	60
Harvard University (US)	34	Saudi Arabia	47
University of Maryland (US)	28	Korea	35
University of Washington (US)	26	Japan	34
University of Pennsylvania (US)	25	Canada	27
University of Texas Medical Branch (US)	25	France	21
University of Oxford (UK)	23	Germany	16

Node size indicates the number of publications funded, and line thickness reflects co-funding frequency. The NIH dominated MERS research funding, forming dense links with US universities and few international partners such as China's NSFC and the Wellcome Trust. Funding was largely concentrated within high-income countries.

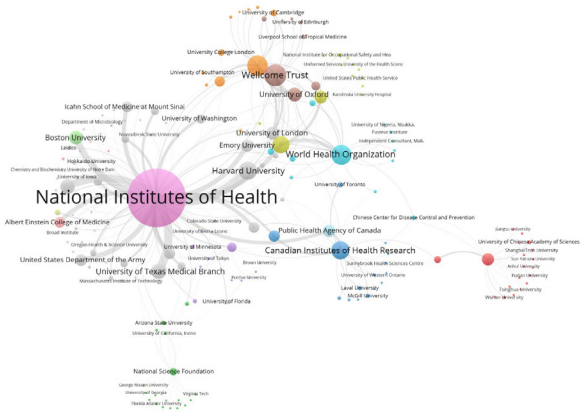
Patents

Patent activity (Figure 5M–R) showed minimal participation from affected countries, with non-affected nations, especially the US and China, dominating applicant and inventor roles. An exception was MERS, where South Korea showed relatively high involvement (89 applicants, 229 inventors out of 202 patents), while Saudi Arabia contributed modestly (6 applicants, 11 inventors). No Ebola patents (336 total; 473 applicants; 1,627 inventors) involved applicants or inventors from the most affected countries; African contributors (11 applicants, 12 inventors) were mainly from non-affected nations. Zika displayed similar patterns: of 619 patents

FIGURE 4B

Mapping of funding organizations for Ebola-related scientific publications.

B



Top 10 funding organizations	Number	Top 10 funding countries	Number
National Institute of Health (US)	2908	United States	3434
World Health Organization (INT)	373	Supranational	758
Wellcome Trust (UK)	298	United Kingdom	374
Medical Research Council (UK)	221	China	182
National Natural Science Foundation of China (CN)	129	Canada	162
Canadian Institute of Health Research (CA)	136	Japan	94
Centers for Disease Control (US)	133	Germany	47
National Institute for Allergy and Infectious Diseases (US)	92	Germany	43
US Public Health Service (US)	57	France	36
National Science Foundation	64	Ireland	31

Top 10 recipient organizations	Number	Top 10 recipient countries	Number
National Institute of Health (US)	652	United States	3713
World Health Organization (INT)	269	United Kingdom	379
Harvard University	267	Canada	276
Centers for Disease Control (US)	252	China	239
University of Texas Medical Branch (US)	200	Germany	112
Scripps Research Institute (US)	180	France	80
University of Oxford (UK)	161	Congo	39
Boston University (US)	159	Japan	26
University of London (UK)	144	Sweden	26
Public Health Agency of Canada (CA)	131	Belgium	20

Node size indicates the number of publications funded, and line thickness shows co-funding frequency. The NIH remained the central global funder, linked with major U.S. and U.K. institutions. The WHO and supranational funders formed secondary clusters, though funding was still concentrated within high-income countries.

(465 applicants, 1,693 inventors), Brazil had 4 applicants and 18 inventors, Colombia 1 of each, and India 3 inventors. Across all outbreaks, patent ownership and inventive activity remained overwhelmingly concentrated in non-affected high-income countries.

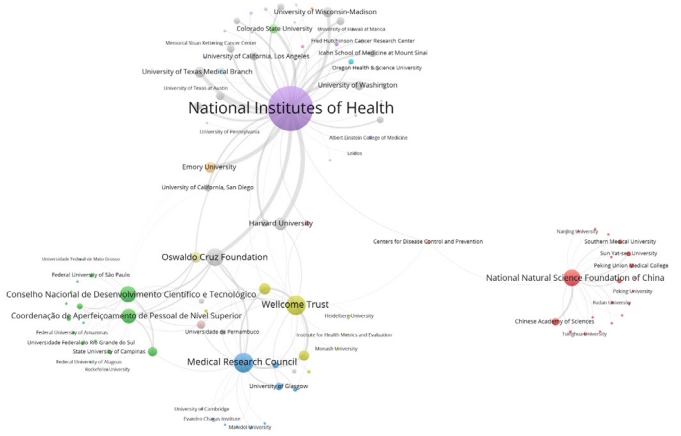
DISCUSSION

Our comparative analysis of MERS, Ebola, and Zika reveals persistent asymmetries in who drives, funds, and benefits from innovation for emerging infectious diseases. Innovation efforts remain geographically divided: affected low- and middle-income countries (LMIC) were often clinical trial hosts but rarely owners of publications or patents. High-income countries (HIC), even those minimally affected, held substantial ownership in publications, patents, and clinical trials, and received by far the largest share of global research funding. Collaborations were most frequent in

FIGURE 4C

Mapping of funding organizations for Zika-related scientific publications.

C



Top 10 funding organizations	Number	Top 10 funding countries	Number
National Institute of Health (US)	3806	United States	4372
National Natural Science Foundation of China (CN)	344	Brazil	1141
Wellcome Trust (UK)	323	United Kingdom	640
Medical Research Council (UK)	278	China	507
Centers for Disease Control (US)	276	Supranational	281
Conselho Nacional de Desenvolvimento Científico e Tecnológico (BR)	274	Canada	112
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (BR)	238	Australia	79
World Health Organization (INT)	131	Singapore	77
Fundação de Amparo à Pesquisa do Estado de São Paulo (BR)	114	Japan	45
Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (BR)	78	Korea	41

Top 10 recipient organizations	Number	Top 10 recipient countries	Number
Oswaldo Cruz Foundation (BR)	365	United States	2274
Harvard University (US)	195	Brazil	990
University of Oxford (UK)	153	United Kingdom	444
Emory University (US)	148	China	323
University of São Paulo (BR)	141	France	41
National Institutes of Health (US)	139	Thailand	13
University of Texas Medical Branch (US)	139	Israel	10
University of London (UK)	136	Australia	8
University of Wisconsin-Madison (US)	116	Germany	7
University of Washington (US)	115	Mexico	7

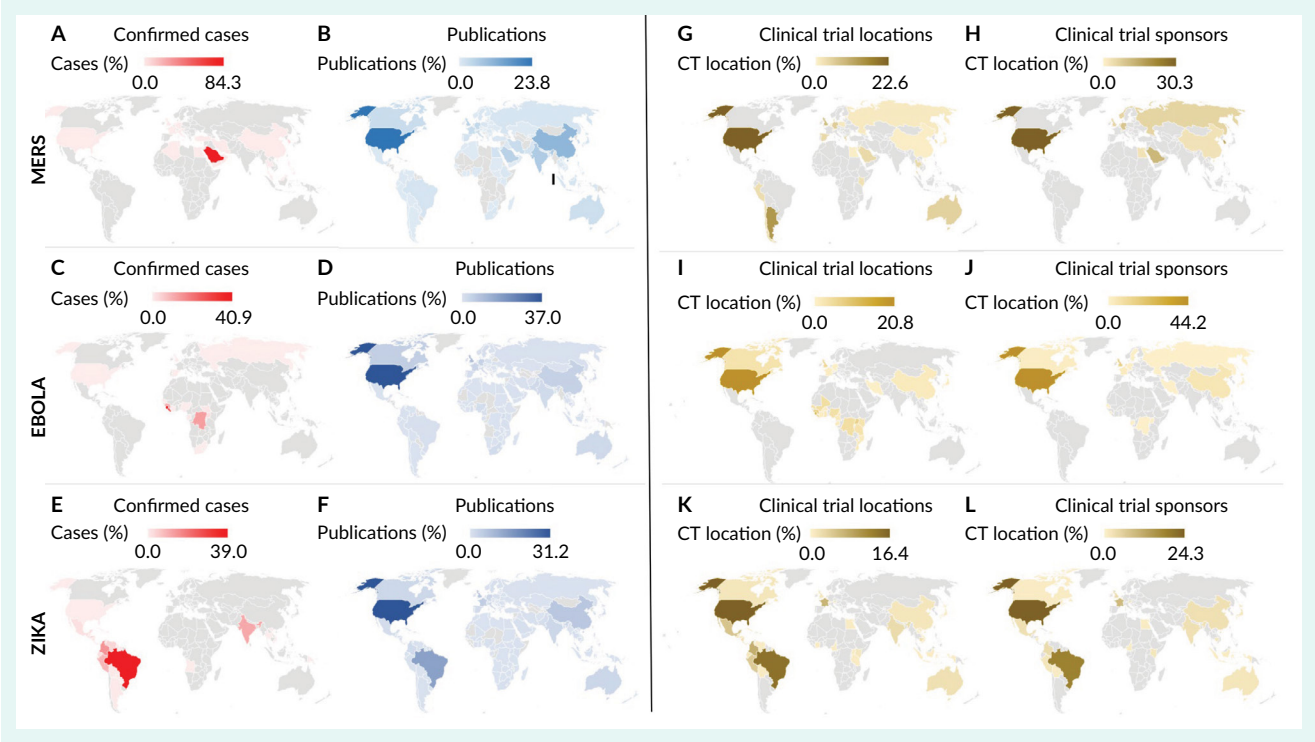
Node size indicates the number of publications funded, and line thickness represents co-funding frequency. The NIH remained the central global funder, while Brazil's Oswaldo Cruz Foundation and national funding agencies emerged as key regional players, reflecting stronger middle-income country participation compared to previous outbreaks.

publications, though rarely involved LIC; patent collaborations across borders were minimal (35 of 1160), with none involving LIC. Funding was highly domestic, concentrated in HIC institutions, underscoring the structural dependence of outbreak-affected regions on external financing.

Across all three outbreaks, over 80% of publications lacked authors from affected countries, and more than 95% of patents were filed by organisations from unaffected ones (<0.2% of confirmed cases). In contrast, affected regions hosted nearly half of clinical trial sites, reflecting functional rather than structural inclusion, where countries contribute data and patients but retain little agency [31]. Patent ownership, unlike publication or trial participation, offers access to intellectual property and financial returns, reinforcing power

FIGURE 5A–L

Mapping the relationship between outbreak case prevalence and participation in scientific outputs.



(A–F) Disparities between case prevalence and publication output for MERS, Ebola, and Zika, with affected countries contributing far fewer publications than non-affected ones. **(G–L)** Clinical trial activity, where affected nations hosted several trials but remained secondary in terms of sponsor involvement.

hierarchies in global research and innovation [32].

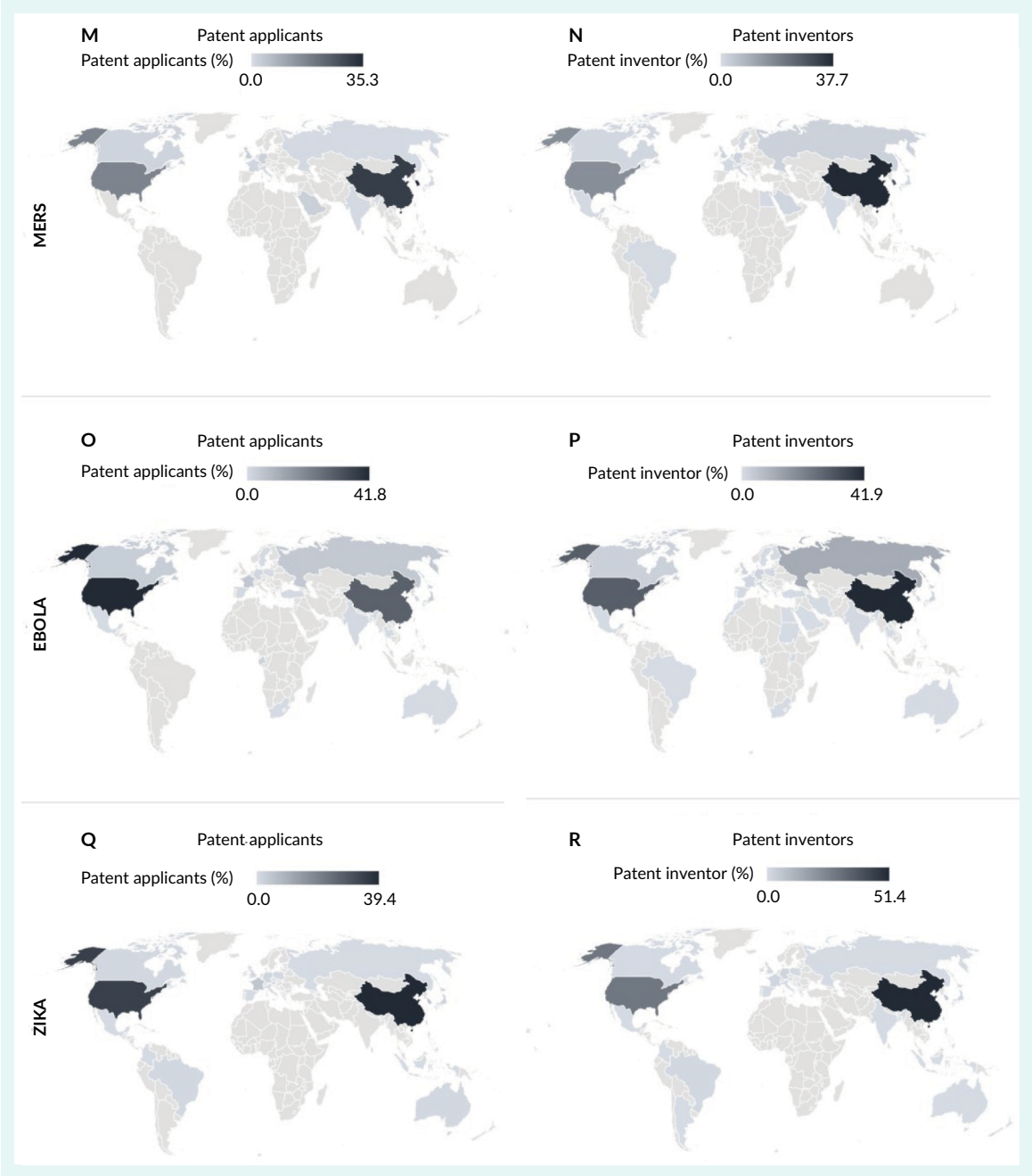
Funding asymmetries further amplify these imbalances. The majority of R&I resources originated from HIC, particularly the USA and the UK. Even in Zika, where Brazil emerged as a notable contributor, its funding share remained modest. As highlighted in previous study, such a concentration shapes priorities and ownership, constraining financial and agenda-setting autonomy in outbreak-affected regions [33]. Co-funding mechanisms between international donors and national science foundations, alongside regional consortia such as the African CDC or ASEAN research networks, could help restore balance and foster shared ownership.

However, funding alone is insufficient without parallel investment in local infrastructure and human capital. Inclusive innovation depends on strong research facilities, skilled professionals, and enabling governance. Strengthening laboratory networks, regulatory systems, and universities, and developing talent through academic partnerships and regional research hubs, can help LMIC evolve from implementers to independent contributors [34]. Without such systemic investments, inclusivity risks remaining a policy ambition rather than an operational reality.

These disparities illustrate the systemic inequality embedded in global R&I. The concentration of benefits and decision-making in HIC maintains institutional hierarchies, a pattern sometimes labelled as helicopter research [35–37]. Barriers such as restrictive IP regimes and uneven resource allocation further marginalise affected-country researchers [32].

FIGURE 5M–R

Mapping the relationship between outbreak case prevalence and participation in scientific outputs.



(M–R) Patent applicant and inventor participation, revealing that non-affected high-income countries dominated innovation ownership, while affected regions played a limited role.

Addressing these inequities requires both structural reforms and targeted incentives to promote reciprocity, trust, and transparency in global partnerships. Global frameworks like the WHO Pandemic Preparedness Treaty are essential to embed these principles and ensure the meaningful participation of affected regions [1,2].

Patterns of collaboration also vary by income group and outbreak context. While

MIC were more involved than LIC, disease location alone did not markedly increase collaboration: partnerships with MICs were similar across Zika (55%), Ebola (50.5%), and MERS (49.5%). Only Ebola showed increased collaboration with LICs (10.4% vs. < 2% for the others). Despite Brazil's legal requirement for local collaboration under the Nagoya Protocol's Mutually Agreed Terms (MAT) [36], Zika patent collaborations were not higher, though more diverse, unlike Ebola, dominated by Chinese partnerships, likely reflecting China's long-standing African engagement [38]. Such patterns show that frameworks like the Nagoya Protocol can encourage but not guarantee equitable collaboration; outcomes depend on local capacity, enforcement, and funding availability [39].

Differences in timing and persistence of innovation responses reveal that scientific mobilisation follows not only epidemiological data but also political attention and perceived global risk [11,40–42]. Zika's surge in research came only after its link to birth defects and PHEIC declaration [39], whereas MERS and Ebola saw faster mobilisation. Initially perceived as mild [43,44], Zika also faced delays in sample and data sharing due to Nagoya Protocol constraints [45,46]. Notably, innovation activity for both Zika and Ebola continued beyond the crises, hinting at a preparedness-oriented approach that extends beyond emergency response.

While COVID-19 is not included here, focusing on MERS, Ebola, and Zika offers a robust historical basis for understanding enduring patterns of imbalance. Nevertheless, the pandemic underscores the relevance of our findings, as similar issues of inequity, ownership, and access remain visible today.

CONCLUSION

Our study highlights deep structural imbalances in global innovation during recent outbreaks. LMIC, despite being epicentres of disease and clinical research, remain underrepresented in scientific and intellectual property ownership, while HIC dominate outputs, patents, and funding. This imbalance limits innovation diversity and contextual relevance, reinforcing the need for equitable collaboration.

The active involvement of affected countries in R&I is both an ethical and practical necessity for achieving resilient, context-specific health solutions. International frameworks such as the WHO Pandemic Preparedness Treaty and the Nagoya Protocol could bridge existing gaps, if implemented with explicit inclusivity goals and backed by resources. Enhancing institutional readiness in LMIC is equally vital: beyond funding, sustainable progress requires foundational scientific capacity and coordination, with health ministries and agencies playing catalytic roles in fostering partnerships and translating investment into innovation.

Operationalising inclusivity demands concrete instruments: benefit-sharing clauses, transparent sample- and data-sharing frameworks, co-funded research hubs, and mobility programmes that enable equitable participation. Governments and global agencies should track and incentivise inclusivity through measurable mechanisms, such as monitoring frameworks, minimum thresholds for local collaboration, and conditional funding for equitable partnerships. Lessons from COVID-19, marked by both unprecedented collaboration and persistent inequality, reinforce the need to embed inclusivity as a core principle of future preparedness efforts.

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AFFILIATIONS

Jelle J Feddema, Sarah Ward, and **Linda HM van de Burgwal,** Athena Institute, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Riley Terzopoulos, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

AUTHORSHIP & CONFLICT OF INTEREST

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VACCINE INSIGHTS

HOW CLOSE ARE WE TO MEETING THE 100 DAYS TARGET TO PRODUCE A VACCINE?

SPOTLIGHT

COMMENTARY

Preparedness to production: a Canadian perspective on building industrial capacity for health emergency readiness

Taylor Caminiti, Aaya Mahdi, Sydney Raduy, Alexandra G Vasiliu, Lynn Berrouard, Fern Bannatyne, and Juan Esteban

This article examines Canada's efforts to rebuild biomanufacturing capacity and industrial readiness for future health emergencies. Specifically, the authors discuss efforts from the federal Innovation, Science and Economic Development (ISED) Portfolio intended to boost domestic vaccine development and manufacturing. The article also outlines the establishment of Health Emergency Readiness Canada in 2024 as a special operating agency tasked with capability mapping, partnership development, and maintenance of protocols to coordinate industrial mobilization during emergencies. Finally, these initiatives are related to international preparedness goals, including CEPI's 100 Days Mission.

Vaccine Insights 2025; 4(9), 373–382 · DOI: 10.18609/vac.2025.052

THE BEGINNINGS

Canada's historical contributions to medical innovation, including the discovery of insulin and the role in developing polio and Ebola vaccines, underscore the nation's scientific leadership in life sciences. Despite this legacy, the COVID-19 pandemic exposed deficits due to a decades-long decline in Canada's domestic biomanufacturing sector: insufficient capacity for large-scale, flexible vaccine production, particularly with emerging technologies such as mRNA, and limited infrastructure for rapid clinical development.

The pandemic underscored the imperative of cultivating a robust domestic life sciences and biomanufacturing sector as integral to national security, including health, social, economic, and political resilience. At the outset of the pandemic, Canada lacked facilities equipped for advanced modalities such as mRNA vaccine production, and had limited capacity to manufacture medical countermeasures (MCMs) at the scale required for public

health needs. Additional systemic challenges included limited coordination of clinical trials, inadequate access to specialized laboratory infrastructure, and insufficient mechanisms to support the translation of research into commercial products.

From a policy and technology perspective, substantial and on-going groundwork must be undertaken well before the emergence of a public health crisis. This includes proactive, strategic investments and partnerships to ensure a continual pipeline of innovative new medicines and other interventions to equip Canada with the assets, experience, and talent to respond to a range of threats. It also includes a commitment to industrial readiness and the capability for rapid mobilization during the onset of the next emergency.

As a response to challenges during the pandemic, the Government of Canada has taken a number of important steps to grow its research, innovation, and industrial capacity in the life sciences—acknowledging the substantial contributions made by the sector, which have further supported Canadians' health and well-being, while simultaneously accelerating technology and economic growth.

This article focuses specifically on efforts that have been driven out of the federal Innovation, Science and Economic Development (ISED) Portfolio over the past 5 years to strengthen internal Government capacity and to drive activities under the authorities of the Minister of Industry to add to existing federal activities, tackling health preparedness through industrial and innovation support measures, partnerships, capabilities mapping, and federal convening powers.

A focus on the life sciences presents a 'win-win' opportunity: Canada's life sciences sector is an economic engine. It is a high-growth sector, with a manufacturing segment that is outpacing other Canadian industrial sectors, and that has one of the highest levels of output per worker in manufacturing. In 2023, the sector accounted for approximately $92 billion in revenues, $16.9 billion in exports, $9.5 billion in manufacturing GDP, and over $3 billion in R&D, and has attracted over $4.8 billion in foreign investment from global pharmaceutical companies since 2017. The sector also contributes to the growth of other high value sectors, for instance through its adoption of and contributions to cross-cutting areas of Canadian scientific and technology leadership, such as artificial intelligence and genomics.

ISED substantially augmented its involvement in this space during the COVID-19 pandemic, when the department, alongside portfolio partners such as the National Research Council of Canada, played a major role in coordinating and growing industrial capabilities to respond to the immediate pandemic threat. ISED led a concerted, whole-of-Government strategy to build longer-term capabilities through the Government's Biomanufacturing and Life Sciences Strategy that was launched in summer 2021. Most recently, the Government has taken steps in recognition of the critical role a strong domestic life sciences sector plays in Canada's broader health security and sovereignty by entrenching these functions permanently within ISED through the creation of a new special operating agency, Health Emergency Readiness Canada (HERC). Through HERC, Canada is embedding health emergency readiness into its broader industrial strategy, creating an end-to-end life sciences ecosystem that can scale rapidly to deliver vaccines, therapeutics, and diagnostics when needed.

Canada's Biomanufacturing and Life Sciences Strategy (BLSS), launched in 2021, pledged an initial $2.2B towards rebuilding Canada's domestic biomanufacturing sector and industrial readiness in response to future pandemics [1,2]. Combined with other pandemic response funding, Government of Canada investments of

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over $2.5 billion through programs such as Canada's Strategic Innovation Fund and the Industrial Research Assistance Program, with an allotted 43 projects, aiming to grow domestic companies and enhance the national ecosystem for biomanufacturing, vaccines, and therapeutics [3]. The Government of Canada also entered into an agreement with Moderna to establish a domestic mRNA manufacturing facility in Québec [4].

In addition to the Government's investments to grow Canada's life sciences sector, funding under the BLSS sought to build complementary strengths in Canada's research and clinical trials systems, supporting an end-to-end pipeline of innovative technologies that are developed and, potentially, manufactured in Canada. In this vein, additional investments under the Strategy include:

- investments in eight high-containment bio-facilities totaling $127 million through the Canada Foundation for Innovation Biosciences Research Infrastructure Fund (BRIF) [5];
- the creation of five Research Hubs at leading academic institutions across the country through the Canada Biomedical Research Fund (CBRF) and BRIF [6];
- nearly $574 million in additional funding committed to 19 projects endorsed by the five hubs, with a focus on innovative technologies, talent development, and research infrastructure [7]; and
- delivery of a $250 million Clinical Trials Fund, which directly supported clinical trials, while also providing funding support for seven clinical trials training platforms and for the creation of a pan-Canadian clinical trials consortium [2].

Collectively, these investments sought to build an end-to-end domestic value chain, targeting activities that would strengthen the domestic research ecosystem, lead to commercialization opportunities, support research to industry collaboration, and build industrial capabilities (including at a globally relevant scale). They are fundamentally transforming Canada's life sciences sector by laying the foundation for a more resilient ecosystem that is better prepared to respond to future health security threats.

An important benefit stemming from activities driven out of the pandemic, specifically under the BLSS and recent creation of HERC, has been the strengthened internal coordination that includes stronger and more expansive federal governance and networks. The partnership between the ISED and Health Portfolios is noteworthy, and this collaboration extends to other relevant federal partners under HERC's governance, including the Department of National Defence and Global Affairs Canada. In this way, Canada's industrial strategy for the life sciences is both fully leveraged and, where appropriate, calibrated to help contribute to the needs of Canadians, including in response to a major health threat. In turn, this collaboration allows for more effective planning and policy deployment, by exploring and leveraging a broader federal toolkit than any one organization could contribute, to support and ensure the sustainability of this critical national sector and asset.

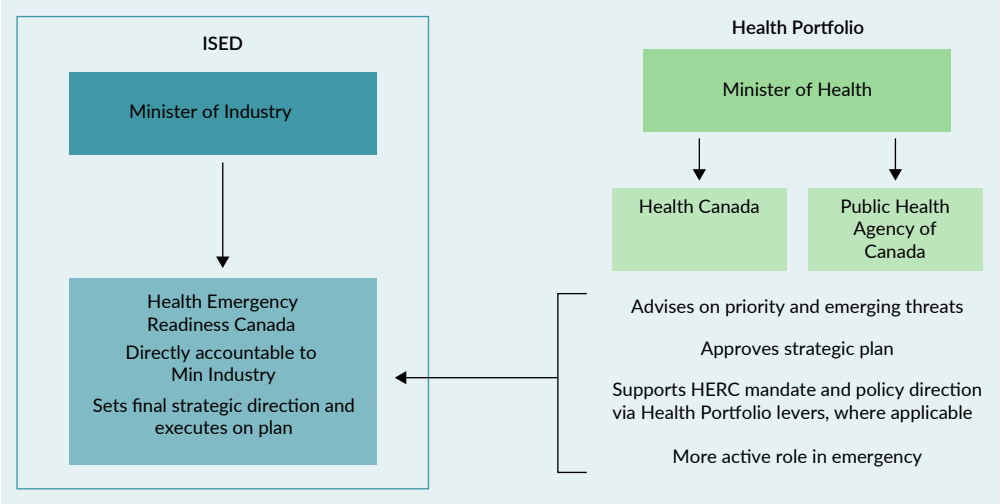
BUILDING PREPAREDNESS

HERC was announced as a new special operating agency in the fall of 2024. Housed within ISED, and in partnership with Health Canada (HC) and the Public Health Agency of Canada (PHAC), HERC consolidates tools and policy centers that were previously dispersed across government departments (Figure 1).

HERC serves as the federal focal point for the development and execution of the Government's industrial policy for the life

FIGURE 1

HERC collaborative structure.



sciences. This includes work to protect Canada's economic and health security through policy measures and supports for innovation, R&D, and industrial capacity (including biomanufacturing), which can be leveraged to respond to a range of health threats. Similarly, HERC's dual mandate to grow the biomanufacturing and life sciences sector while strengthening Canada's health security through increased industrial capacity, places it in a position to make strategic long-term investments that ensure ecosystem sustainability. For instance, HERC's mandate extends into the area of dual-use technologies; HERC is focused on building domestic capabilities and partnerships that can support Canada's response to a public health emergency with implications for civilian or military populations. As part of this work, HERC maintains a wide range of relationships with the domestic life sciences industry, and with international counterparts, including its direct equivalents in jurisdictions such as the United Kingdom and the European Union [8,9]. HERC also leads the development and maintenance of emergency protocols to coordinate and mobilize Canada's industrial response to health emergency threats [10].

Collaboration with the Health Portfolio is essential in achieving HERC objectives. While PHAC and the broader Health Portfolio, including HC and the Canadian Institutes of Health Research (CIHR), have longstanding roles in detecting, assessing epidemiological risk, and responding to outbreaks and health security threats, HERC expands this assessment capability by adding an industrial readiness lens. PHAC and HC continue their critical roles in core aspects of emergency management, such as public health surveillance, epidemiological risk assessment, regulation of medical products, and ensuring supply of medical countermeasures in collaboration with provinces and territories.

HERC complements these functions by focusing on industry and ecosystem intelligence, partnership development, and sectoral support, layering information about domestic industrial capabilities and trends, emerging technologies, and supply chain vulnerabilities onto traditional health threat assessment. This integrated approach helps provide a more comprehensive understanding of both health security risks and Canada's operational capacity

and sectoral opportunities to mount an effective response.

Canada's health emergency preparedness will also be strengthened by building a skilled, talented, and diverse workforce through training programs and advancing university research. For example, the Government of Canada, through its regional development agencies, has contributed to the expansion of the Canadian Alliance for Skills and Training in the Life Sciences and its network of facilities in Charlottetown, Montreal, and Vancouver to provide training in good manufacturing and good laboratory practices. The establishment of the five Research Hubs and subsequent contributions to their research infrastructure through the CBRF-BRIF funding program are intended to give researchers the resources needed to help translate their biomedical research into products.

HERC's efforts are further supported by the suite of tools the Government of Canada has introduced since COVID-19 to bolster preparedness for emerging health threats. For example, the establishment of the Centre for Research on Pandemic Preparedness and Health Emergencies (CRPPHE), housed within CIHR. The CRPPHE aims to ensure Canada has an emergency-ready health research system to support health emergency preparedness, prevention, response, and recovery [11]. Close collaboration among PHAC, HC, HERC, CRPPHE, and other partners strengthens Canada's readiness to deliver timely and effective responses to future health emergencies by ensuring both scientific and industrial preparedness are integrated into Canada's approach.

HERC is focused on building and sustaining strategic partnerships with industry, research, academia, governments, and international bodies, with emphasis on collaborative innovation for current and emerging health threats. During inter-pandemic periods, HERC will focus on strategic efforts spanning research, clinical development, translational activities, commercialization, manufacturing, and procurement, concentrating on R&D services, industry development, and MCM manufacturing support. During emergencies, HERC intends to leverage pre-established domestic capabilities and capacities, alongside domestic and multi-lateral partnerships to rapidly coordinate an industrial response. Established and ongoing coordination and collaboration will in turn, further advance HERC's participation in key global health initiatives, contributing to MCM readiness not just in Canada but also abroad.

Due to the sector's inherently high-risk nature, support to industry, research, and associated ecosystem components should prioritize innovative life science initiatives and the enhancement of Canada's industrial capabilities. This includes accepting calculated risks with respect to support for R&D undertakings; developing leading-edge technology platforms and capabilities; strengthening domestic supply chains; accelerating the commercialization of novel technologies; and fostering the growth of companies positioned to improve Canada's access to critical health assets. Ensuring sustained support for the sector will foster an innovative and competitive ecosystem that helps ensure access to vaccines, drugs, therapies, and diagnostic tools required to respond to modern health security threats. An integrated approach to building and maintaining life sciences capabilities will enhance resilience against future health crises and will also attract investment.

Part of HERC's mandate is to address high-priority threats to health security that have the potential to cause large-scale harm to Canadians. Due to significant technological crossovers, MCM development for epidemic and pandemic infectious diseases may yield advances applicable to other health domains. For example, investments in monoclonal antibody therapeutics for viral diseases may translate to advances in

oncology. Likewise, many of these investments and technological platforms have dual-use applications, supporting not only public health responses to naturally occurring outbreaks but also enhancing Canada's capacity to respond to intentional biological threats or bioterrorism. As a result, advancements in R&D, manufacturing, and ecosystem readiness serve both civilian health security needs and broader biodefence objectives.

Growing domestic production strengthens Canada's health and national security, supports innovations across both defence and life sciences ecosystems, and protects Canada's sovereignty by building resilient supply chains for MCMs. HERC recognizes that building capacity in research, companies, and technologies is critical to maintaining an agile response framework that can rapidly pivot to address new, unforeseen threats, whether naturally occurring or intentional by origin.

ESTABLISHING A STATE OF READINESS

Given the unique characteristics of the biomanufacturing and life sciences industry, consistent, continuous, and sustained effort is required to maintain sectoral growth and enable a rapid response to a health threat or an emergency, once declared. Establishing readiness through policies and technology frameworks in advance of an emerging threat is essential for effective prevention, as well as enabling a timely response.

To achieve an optimal state of readiness, HERC is developing evidence-based guidelines for rapidly mobilizing and deploying domestic research and industrial assets in the event of a health emergency, as well as to ensure HERC's actions are coordinated with other Government of Canada departments and international partners. These protocols will detail emergency readiness operations and plans for mobilizing an industrial response, with activities escalating as the threat level intensifies. By consolidating research and industry intelligence, HERC will develop a comprehensive understanding of industry, academia, and other key stakeholders' activities, assets, and capabilities across the ecosystem. This enhanced situational awareness will enable HERC to identify critical gaps and opportunities in Canada's ability to prepare for and respond to high-priority health security threats.

During the COVID-19 pandemic, the Government of Canada relied heavily on the COVID-19 Vaccine Task Force to guide critical MCM initiatives. Building on this experience, the Council of Expert Advisors was established during the pandemic as a standing external advisory body. The Council has provided multidisciplinary guidance on life sciences and MCM activities during peacetime and can be leveraged to support rapid, coordinated responses in future emergencies. Moving forward, HERC intends to maintain access to such advisory expertise to ensure proactive readiness and evidence-based decision-making across both interpandemic and emergency contexts.

INTERNATIONAL COLLABORATION

Pandemics do not respect geopolitical borders and no one country is entirely self-sufficient in preparing for, and responding to, health emergencies. At the same time, pharmaceutical, medical device, and other life science supply chains are highly integrated globally, and it is important to coordinate with trusted partners to ensure continuity and security of supply. Recognizing that domestic MCM readiness cannot be achieved in isolation, international collaboration and strategic partnerships are vital. Canada continues to navigate a rapidly evolving global economic and security landscape alongside likeminded nations. In this respect,

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Canada must use inter-pandemic periods to secure supply chain agreements, build research collaborations, and link domestic manufacturing with global partners. To support an effective industrial response against cross-border threats, HERC collaborates with international partners to bolster Canada's existing industrial capabilities. With a focus on strengthening global medical product supply chains and expanding research, innovation, and development opportunities, the aim is to leverage global partnerships to enable a timely industrial response.

Maintaining dialogues with international partners helps Canada address domestic supply chain gaps, and positions Canadian industry within global supply chains. Current geopolitical and fiscal pressures underscore the vulnerabilities of overreliance on a single trading partner, especially amid growing global fiscal restraints. Disruptions in supply chains and evolving trading dynamics can introduce substantial price volatilities, threatening the timely delivery of essential health services and access to MCMs during public health emergencies. International partnerships are critical to build a strong, self-sustaining Canadian biomanufacturing sector and mitigate risks from trade barriers and protectionism.

HERC is diligently prioritizing pre-emergency engagement with global partners, including participating in international MCM R&D networks, coordinating talent mobility, and aligning Canadian capacity with multinational preparedness strategies, to ensure MCM readiness before Day 1. This alignment is essential to strategically direct federal supports, reduce duplication, and enhance understanding of the highest-impact approaches across key areas such as: viral families and pathogens; critical medicines and security of supply; MCM manufacturing technologies; R&D; clinical trials and regulatory approval processes; and end-to-end pharmaceutical supply chains.

Canada maintains an ongoing biomanufacturing Memorandum of Collaboration with the United Kingdom to support pandemic preparedness and innovation and recently signed an Administrative Arrangement with the European Commission's Health Emergency Preparedness and Response Authority (HERA) to collaborate on medical countermeasure commercialization and pandemic preparedness [9,12]. Together, these collaborations aim to combat and contain pandemics, epidemics, and serious cross-border health threats by cooperating on advancing MCMs for infectious disease emergency preparedness and response.

100 DAYS MISSION

To date, the Government of Canada continues to support global preparedness efforts such as the 100 Days Mission (100DM). Led and founded by CEPI, the 100DM aims to support advancements and acceleration of R&D for MCMs that can be rapidly deployed in the face of the next pandemic [13]. The overarching concept is to equip the world with the ability to respond to the next health threat or 'Disease X' within 100 days of initial detection of a pandemic pathogen [14,15]. With this in mind, since CEPI's 100DM creation back in June 2021, the world has experienced vast and disruptive changes across society, ranging from incredible advances in technology, to new emerging and re-emerging communicable diseases, and unexpected economic uncertainty and upheaval. As such, now more than ever, is it imperative that Canada and the world's leaders join forces to effectively prepare, invest and collaborate in order to quickly address the next global health emergency.

Reflective of its active involvement, Canada has the unique opportunity to play a leadership role and contribute to CEPI's 100DM by chairing the 100DM Steering Group, composed of select G7 scientific

advisors. HERC's newly established mandate and mission also correlate strongly with the 100DM's objectives and key priorities focused on strengthening scientific and industrial innovation for R&D of critical MCMs [16]. In the same way, HERC also seeks to leverage collaboration with its aligned stakeholders including governments, academia, industry and its international counterparts towards advancing global public health preparedness and readiness, a core facet underpinning the 100DM. For instance, HERC continues to work closely with the five multidisciplinary research hubs, which are implementing projects that are bolstering the Canadian life sciences and biomanufacturing ecosystem, which will, in turn help accelerate ongoing efforts to achieve the goals of the 100DM [17,18].

Nonetheless, there is an ongoing need for attentive coordination, collaboration, and strategic initiatives to support continued progress across CEPI's 100DM priorities, building on what is currently being achieved in the life sciences and biomanufacturing landscape. Working towards this, HERC is building out domestic capabilities with the strategic vision of contributing to a rapid response, and advancing technologies that support the goals of speed, flexibility, and pivotability.

WHAT COMES NEXT?

To ensure Canada is equipped to respond to future high-impact health threats, ongoing efforts must be directed, through mechanisms such as HERC, to establish leading-edge domestic capacity and capabilities that can be leveraged as part of Canadian and global response to an emergency well before Day 0. By proactively investing in research, infrastructure, skills and talent development, and leveraging strong coordination with industry, HERC can foster sustainable ecosystem growth across the sector. A robust ecosystem, supported by strategic and forward-looking policies and plans that enable rapid mobilization and scale-up, will enhance Canada's ability to respond effectively to future health threats. Furthermore, to assess the impact of federal investments in biomanufacturing and life sciences, HERC has developed a comprehensive framework with indicators that measure sector growth and sustainability, collaboration across the ecosystem, expanded industrial capacity and improved health emergency readiness. In parallel, Canada must also continue to pursue collaborative partnerships with like-minded allies to address domestic gaps, strengthen supply chain resilience, and foster innovation across the sector. By supporting the translation of emerging technologies from R&D through to commercialization and maintaining alignment with public health priorities across government and industry, Canada can secure enhanced national health security and greater preparedness for future health emergencies.

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AFFILIATIONS

Taylor Caminiti, **Aaya Mahdi**, **Sydney Raduy**, **Alexandra G Vasiliu**, **Lynn Berrouard**, **Fern Bannatyne**, and **Juan Esteban**, Health Emergency Readiness Canada, Innovation, Science and Economic Development Canada, Government of Canada

AUTHORSHIP & CONFLICT OF INTEREST

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HOW CLOSE ARE WE TO MEETING THE 100 DAYS TARGET TO PRODUCE A VACCINE?

SPOTLIGHT

A career in containment: insights from the epicenter of WHO's COVID-19 response

INTERVIEW

"Many governments have announced cuts to health spending, with funding reallocated to defense. I believe that this is short-sighted because health **is** defense."

Thanks to WHO's daily televised press briefings, Maria Van Kerkhove (Acting Director of the Department of Epidemic and Pandemic Preparedness and Prevention and COVID-19 Technical Lead, WHO) became one of the most recognizable scientists of the COVID-19 era. Speaking with Charlotte Barker (Editor, *Vaccine Insights*), she reflects on the pressures of communicating in real time during an unfolding emergency. She describes WHO's strategy for building stronger surveillance systems for high-risk pathogens and explains why health security must remain a priority as geopolitical tensions rise and global attention drifts.

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Q What was your route into your current role?

MVK I always loved science and, as early as high school, I became fascinated with infectious diseases. I studied Biology at Cornell University, and fell in love with the idea of working in outbreak investigation and emergency

"[...]With so many concurrent threats and a high degree of misinformation and mistrust in science, it's becoming harder and harder to prevent and respond to outbreaks."

response. I earned a master's degree in Epidemiology at Stanford University and a PhD from the London School of Hygiene & Tropical Medicine, and have worked as an epidemiologist ever since.

I'm sorry to say that I really didn't know about WHO growing up. I didn't need to - I grew up in upstate New York, with very few infectious threats and good health care. But as soon as I learned about WHO, I was desperate to work there. I believe deeply in what the organization has been set up to do.

The first role I had at WHO was as a consultant during the 2009 influenza pandemic, coordinating a mathematical modeling network to support the response. I wanted to listen and learn and absorb how WHO works with the world to make sense of the natural messiness of an outbreak. How does WHO understand what is going on? How does WHO work with governments? How can WHO offer actionable, evidence-based, implementable advice, even in the heat of an outbreak? It was the most incredible way to learn about outbreak control. And I'm still learning every single day.

After two years heading the Outbreak Investigation Task Force at Institut Pasteur, I returned to WHO as the MERS-CoV technical lead, responsible for prevention control programs, developing evidence-based guidance, and strengthening outbreak investigation using a One Health approach.

This is not an easy field to work in, but it is absolutely fascinating. With so many concurrent threats and a high degree of misinformation and mistrust in science, it's becoming harder and harder to prevent and respond to outbreaks. But I feel very lucky to love what I do.

Q Can you talk us through your current roles at WHO and your key priorities?

MVK When COVID-19 was first identified and declared a public health emergency, my expertise in MERS-CoV led to my joining the incident management team as the Health Operations and Technical Lead for this event. This involves directing the various technical elements of the response—including laboratory detection, clinical management, infection prevention and control, and the animal-human interface—to allow WHO to issue regular and reliable guidance. I still hold that role, and also became Unit Head for emerging diseases and zoonoses in 2020.

For the past 2 years I have been the Acting Director of the Department of Epidemic and Pandemic Management. My responsibilities in that role include managing a team working on respiratory pathogens (influenza, coronaviruses, RSV), arboviruses, and high-impact epidemics and high-threat pathogens, from COVID-19 to Ebola to mpox to cholera.

I also manage an interim medical countermeasures network, which is working across WHO to advance R&D and ensure medical countermeasures are available to countries based on equity and need, in line with the WHO Pandemic Agreement Member States adopted in May 2025.

The last area under my responsibility is laboratory biosafety, biosecurity, and emerging threat diagnostics. It's a large portfolio and I work with amazing people at WHO and beyond.

Q How do you stay calm and resilient in the face of a major crisis like COVID-19 and communicate effectively to the world in a rapidly changing situation?

MVK I am surrounded by extraordinary people at WHO, both here in Geneva and in our regional and country offices, and we all support each other. We each know what our role is in a crisis and work together effectively. During COVID, I had never seen such solidarity before with such strong leadership from Dr Mike Ryan, our Executive Director of the Health Emergencies Program and Dr Tedros Adhanom Ghebreyesus, the Director-General of WHO. My job was to make sure everybody knew what they were doing and had the equipment and support to do it.

Another aspect of my role was communicating the latest information through many different channels including live televised press conferences, although this was not something I ever thought I would be doing.

Sitting next to the Director General and Executive Director of WHO at press conferences was the privilege of a lifetime, and a massive responsibility. I'm only now realizing the weight of it all, when I meet people around the world and they say, "I know you—you were in my living room every day during the pandemic!"

As well as the public, health officials tell me they watched our press conferences every day to help shape their countries' responses to the pandemic.

Usually, the advice is to tailor your communication to your audience. But in this case the audience was the entire world. I remember thinking "I'm talking to a journalist. But I'm also talking to my grandmother, a family doctor, a scared child, and a top virologist."

Participating in press conferences was not my main role during the pandemic, it was an opportunity to answer a few questions at the end of each day. We had to think on our feet, consolidate the knowledge we had, be clear about what we knew (at the time), what we did not know, what we—as a global community—were doing to find the answers to these questions, and what that meant for people, communities, leaders, and nations. We needed to explain complex concepts in terms that a wide range of people could understand. That is a skillset I did not know I had until then!

Q Keeping in mind lessons from COVID-19, how is WHO enhancing global genomic surveillance and data sharing protocols to detect and respond to emerging pathogens?

MVK An important element in pandemic prevention is strengthening the global laboratory networks we rely on for earlier detection and identification of pathogens. That requires ensuring that there are pathways for the right biological sample reaching the right lab, with the appropriate analytical approach. We are developing shared terms of reference for communication across global and regional laboratory networks working with pathogens with epidemic and pandemic potential. We have

well established networks for flu and coronaviruses, and we're working with countries and partners to strengthen networks for more high-threat pathogens.

What is incredible is that because of COVID and other global threats like polio and measles, there are strong labs located all around the world. No longer are low-income countries required to send samples to high-income countries for sequencing—as of 2022, 163 out of 194 member states had sequencing capacity in-country. We are working to support labs to maintain these capacities, and to ensure strong laboratory biosafety and biosecurity.

We are also working to strengthen public databases for sharing pathogen genome data. Existing databases do great work and support better understanding of circulating pathogens, but, of course, all have areas that can be improved.

Q How does your work contribute to achieving the 100-day target from recognition of a threat to vaccine authorization?

MVK There is incredible work happening on the 100-day mission at WHO, CEPI, and elsewhere. In my role, the question I am most concerned with is what we need to have in place before day zero so that we can hit the ground running.

My area of work is largely around early detection and sharing of pathogen materials. For flu, we do this very well because we have the Global Influenza Surveillance and Response System (GISRS). We have more than 150 labs in 134 countries sharing samples that allow us to make recommendations for seasonal flu vaccine composition and spot emerging threats.

We don't have that system for all pathogens, which is why the Pathogen Access and Benefit Sharing (PABS) system that Member States are negotiating as part of the Pandemic Agreement is so critical. I have been impressed with the rigor and enthusiasm Member States are bringing to their ongoing negotiations.

Q What are the most impactful aspects of the WHO Pandemic Agreement, and what are the next steps towards operationalizing them?

MVK Firstly, I'm excited about the simple fact that it exists—that Member States came together to agree and adopt the Pandemic Agreement! Of course, the language is not perfect and there will be challenges in implementation but, at a time when many countries are becoming more insular, the Pandemic Agreement represents a collective commitment to do better, and that is a massive step forward. When member states adopted the Agreement with no objections at the World Health Assembly in May 2025, I was moved to tears.

The COVID-19 pandemic affected every single one of us—every family, every community, every nation. It not only took the lives of so many, but changed the futures of countless others. COVID caused trillions of dollars in economic damage. There were an estimated 1.6 billion kids out of school at one point. So it confounds me to see the world trying to forget the impact it had—and is still having. The Pandemic Agreement is an important step toward better epidemic and pandemic prevention and response to future pandemics, which we know will happen again.

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I am also very proud of the Member States for negotiating a Pandemic Agreement that is comprehensive, covering everything from supply chains to addressing the root causes of spillover events and epidemics using a One Health approach.

Q Several months on from the US government announcing withdrawal from WHO and cuts to global health funding, what are your current thoughts on the impact these changes will have for global pandemic preparedness?

MVK We cannot sugarcoat it—these policy changes have already had a substantial impact on global health security.

The loss of US funding has been substantial, but it's not just the US. Many governments have announced cuts to health spending, with funding reallocated to defense. I believe that this is short-sighted because health **is** defense. With COVID-19, we saw a pathogen shut down the world, kill millions, and cost trillions, and new threats continue to emerge. There is this notion that there is 'peace time' in our field—but just because there aren't outbreaks in your communities right now, it doesn't mean that there are not outbreaks happening all over the world. It's a very challenging and some may say scary time right now in global health.

That said, I'm hopeful we'll find a way through. There are many inspiring people dedicated to this field. Whether we have a job tomorrow or not, we are in this fight for life and we will do everything we can to keep the world safe.

BIOGRAPHY

Maria Van Kerkhove is the Acting Director of the Department of Epidemic and Pandemic Management at WHO. She has played a pivotal role in global health, notably as COVID-19 Technical Lead and as global Incident Manager during the 2024 mpox outbreak, declared a Public Health Emergency of International Concern. With over 20 years of experience in infectious disease epidemiology, Dr Van Kerkhove is known for her expertise in emerging diseases such as Ebola, Zika, MERS, and avian influenza. She is widely recognized for her leadership, diplomacy, and ability to translate complex science into clear, actionable public health guidance. Her work focuses on the human-animal interface in disease transmission, driving policies that improve pandemic preparedness and response. Through science-based leadership, she has shaped global health strategies and supported coordinated international responses to major health emergencies.

Maria Van Kerkhove PhD, Acting Director, Department of Epidemic and Pandemic Management Health Emergency Preparedness and Response Programme, WHO, Geneva, Switzerland

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VACCINE INSIGHTS

HOW CLOSE ARE WE TO MEETING THE 100 DAYS TARGET TO PRODUCE A VACCINE?

SPOTLIGHT

COMMENTARY

Preparing for the 100 days mission: end-to-end transformation for emerging infectious disease preparedness

Hamilton Bennett and Alan Embry

The '100 Days Mission' aims to enable initial deployment of safe, effective vaccines within approximately 100 days of identifying a novel threat. Delivering that consistently requires more than faster science: it demands an end-to-end transformation spanning pre-Day 0 research, platform-level regulatory pathways, warm-base manufacturing, and flexible push–pull financing. We outline a practical continuum to get there: (1) sustained foundational R&D organized around prototype pathogens and standardized assays; (2) vaccine libraries advanced to Phase 1/2 with validated immune readouts and clear licensure paths; (3) regulatory convergence through platform master files, pre-approved master protocols, and global reliance/work-sharing; (4) distributed, warm-base manufacturing exercised via 'drills'; and (5) financing that blends catalytic push funding with advance-purchase pull incentives and pooled procurement. Case studies from COVID-19, Mpox, and the 2022 Sudan ebolavirus outbreak illustrate both successes and failure modes. We argue that aligning these components turns extraordinary, crisis-only performance into routine capability, and makes 100-day vaccines a repeatable public-health standard rather than a one-off feat.

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INTRODUCTION

Outbreaks repeatedly exposed systemic weaknesses in how the world develops, regulates, and finances vaccines. While extraordinary efforts during COVID-19 produced vaccines at record speed, those results relied on unprecedented emergency measures that are unsustainable in the long term. The 100 Days Mission aims to ensure that vaccines can be ready within 100 days of a new pathogen's emergence [1]. Achieving this consistently requires a shift: from piecemeal fixes to an end-to-end

transformation of the vaccine ecosystem. While significant scientific progress enables faster development and manufacturing of new vaccines, without regulatory and market reforms those advances will remain fragile, potentially risking our readiness to protect people at risk in the event of an outbreak of a novel pathogen.

MAPPING THE THREAT SPACE: THE ROLE OF FOUNDATIONAL RESEARCH

True pandemic preparedness begins well before the emergence of a novel pathogen in humans. The first imperative is to deeply understand the viral 'threat space' through sustained basic and translational research. Foundational research includes virology, immunology, and host-pathogen interactions, but also the creation of standardized immunological assays, animal models, and challenge systems. These tools, when developed in advance, allow rapid evaluation of vaccines during an emergency. This is not optional; without a baseline of knowledge, the ambition of producing a vaccine within 100 days is impossible. Beginning in 2015, the World Health Organization's (WHO) R&D Blueprint has served as a call to action to build 'outbreak-ready' data sets for key pathogens with epidemic potential, including Ebola, Marburg, Crimean-Congo hemorrhagic fever, Lassa fever, Nipah, MERS, Rift Valley and a placeholder for 'Disease X' [2].

More recently, National Institute of Allergy and Infectious Diseases (NIAID) led the field to reframe their research from individual pathogens to prototype pathogens within prioritized viral families [3], and the WHO followed with the creation of the family-based Collaborative Open Research Consortia (CORC). Expanding our perspective from pathogens to viral families serves as both a warning and a roadmap: recognizing the breadth of the potential threat space, while defining where science must invest now to enable rapid responses when outbreaks occur. By advancing vaccines for selected representatives of high-threat viral families, the field generates insights that can be leveraged across related threats.

For example, decades of coronavirus research on SARS and MERS meant that by 2020, scientists already knew the spike protein was the critical antigenic target, and could rapidly adapt preclinical assays and models to the newly emergent SARS-CoV-2 [4]. This prior work shaved months off the COVID-19 response and ultimately saved lives.

In response to the 2022 public health emergency of international concern (PHEIC) of Mpox, foundational research on poxvirus disease was leveraged to develop Moderna's mRNA-based Mpox vaccine. Preclinical and clinical data on the DNA-based 4pox vaccine targeting Smallpox informed the composition of an mRNA-based Mpox vaccine; access to animal challenge models and immuno assays through our collaborations with the United States Army Medical Research Institute of Infectious Diseases and National Institute of Health allowed us to generate a robust preclinical dataset rapidly. Nearly 20 years after the initial studies, the foundational research continues to drive vaccine innovation [5,6].

To continue this work at scale, in 2022 Moderna launched mRNA Access, a global public health initiative to accelerate innovation for emerging and neglected infectious diseases. Through the program, external partners can leverage Moderna's mRNA platform to design, synthesize, and test vaccine candidates, and use those candidates to inform assay and model development. With over 30 partnering institutions—including CEPI-funded teams using AI-technology to accelerate antigen design and evaluation—the program is building a pipeline of discovery and preclinical assets for the prioritized viral families and beyond, generating important early proof of concept data.

Mapping the threat space through sustained investment in basic science is the essential first step of the end-to-end continuum. Organizing pre-Day 0 work around prototype pathogens within prioritized viral families enables standardized immunologic assays, reproducible animal/challenge models, and early identification of surrogate markers of protection. By strengthening the evidentiary base across viral families, we create the conditions under which every subsequent step—regulatory review, manufacturing, financing—becomes faster, less expensive, and more reliable.

VACCINE LIBRARIES & THEIR ROLE IN A CONTINUUM TO COMMERCIAL.

A vaccine library is more than a collection of preclinical constructs stored in freezers; it is a dynamic portfolio of candidates strategically advanced towards clinical, regulatory and commercial deployment. To achieve this vision, vaccine libraries must transition deliberately from preclinical exploration, through clinical evidence, to commercial readiness.

Several lessons from recent outbreaks illustrate the promise and pitfalls of this approach. During the 2022 Sudan Ebola outbreak, vaccine candidates existed in Phase 1 but were not fill-finished or trial-ready until the outbreak had waned, demonstrating that partially advanced products are not sufficient [7]. Conversely, the 2022 Mpox outbreak was mitigated by the availability of a stockpiled smallpox vaccine, which had been carried through to licensure, showing the value of preparedness that extends beyond early trials [8]. The lesson: evidence and operational readiness must be in place before Day 0.

For the 100 Days Mission, vaccine libraries must be curated to cover viral families with pandemic potential. For each candidate we should have a fundamental understanding of immunologic mechanisms of protection, the asset should be developed through Phase 1 or 2 with validated immune assays, and we should establish a clear regulatory path to licensure.

Preclinical and Phase 1 clinical programs are crucial because they generate datasets on potential immune markers of protection. These markers—such as neutralizing antibody titers or T cell responses—provide early signals of whether a vaccine is likely to be protective. Over time, such data help establish surrogates of protection that regulators can use to evaluate vaccines in the absence of large-scale efficacy trials. This evidence becomes central in risk–benefit assessments, especially when a product may need to be deployed during an outbreak. By demonstrating consistent immune signatures across multiple pathogens on a common platform, developers and regulators together can build the scientific justification for accelerated licensure and emergency use.

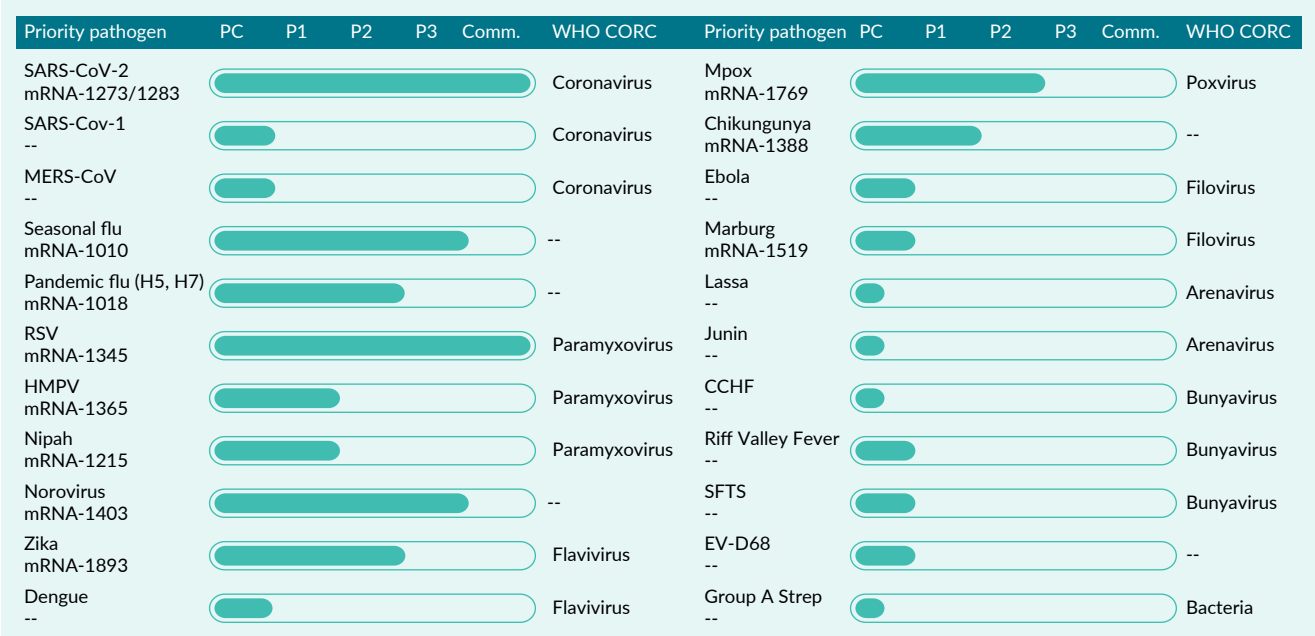
The concept of generating Phase 1 data on prototype vaccines is not new, researchers like those at the Oxford Vaccine Group have been prolific in the field. Moderna's opportunity lies in executing this work on a platform that has supported over 50 clinical-stage vaccine candidates and achieved global licensure for three infectious disease vaccines. The scope of regulatory engagement across this platform is likely unprecedented.

Moderna's health security portfolio—including Zika, Nipah, Mpox, and Chikungunya candidates—demonstrates how industry can align its pipeline to advance these objectives (Figure 1).

Through our mRNA Access and Global Health Portfolio programs, Moderna and our collaborators are actively testing key assumptions from the discovery phase. For example, our Nipah candidate—developed with NIAID's Vaccine Research

FIGURE 1

Moderna Global Health: phase-appropriate advancement across WHO priority families (illustrative).



Center—has demonstrated preclinical efficacy and immunogenicity and is now in a Phase 1 trial to evaluate surrogate markers of protection [9]. This comprehensive dataset can inform regulatory pathways for rapid authorization in the event of a Nipah, Nipah-X, or related Henipavirus outbreak. This same model is now being applied across additional priority virus families.

This raises a strategic question: if the licensed Ebola vaccines had been developed using programmable platforms such as mRNA, would we have been able to authorize countermeasures for Sudan or Marburg strains with greater speed? A viral family-based approach—supported by cross-pathogen data and harmonized platform performance—should aim to make the answer unequivocally 'yes.'

Aligning WHO's 2025 prioritization of ten viral families through its CORCs, Moderna has generated clinical data in four of these families to date, with preclinical data covering four more.

Ultimately, the objective is to provide robust evidence so as to establish regulatory confidence in platform technologies as adaptable, validated backbones rather than as bespoke solutions requiring *de novo* evaluation. Realizing this vision will likely depend on advancing one or more exemplar programs through full licensure, either via traditional efficacy trials or through accelerated pathways supported by robust surrogate endpoints and confirmatory post-marketing data.

REGULATORY CONVERGENCE & INNOVATION

Establishing such a precedent for other viral families will take time and careful alignment between developers and regulators; but once in place, it would fundamentally reshape the vaccine development paradigm. Preparedness would no longer be an exception to the norm; it would become embedded in a system designed for continuity, agility, and scalability across a broad range of emerging threats.

Three enablers turn regulation from bottleneck to accelerator:

1. Platform master files capturing core CMC, nonclinical, and class-wide safety so antigen swaps become streamlined;

2. Pre-approved master protocols for priority families (adaptive/platform designs; standardized endpoints; correlate-driven success criteria) that activate on Day 0; and

3. Global reliance/work-sharing wherein a single emergency dossier is reviewed collaboratively and recognized across agencies, supported by secure data sharing and inspection mutuality.

Innovation must first begin with clinical trial design. Pre-approved, adaptive master protocols for priority pathogens could allow immediate activation of studies when outbreaks arise. These protocols could enable comparisons across multiple vaccine candidates, employ standardized endpoints, and incorporate immune correlates of protection identified in earlier trials. Rather than designing a bespoke study from scratch during an emergency, the global community would have vetted protocols ready to implement [10].

Following on the exemplar vaccines mentioned above, once licensed, these initial products can serve as the foundational evidence base for subsequent candidates developed using the same platform architecture, analogous to the model employed for seasonal strain updates in influenza or SARS-CoV-2. Consider pandemic influenza: today, each subtype (H5, H7, H9, etc.) requires a largely independent regulatory package, even though the antigen, delivery mechanism, and manufacturing process are nearly identical. A streamlined approach could allow a single dossier to cover multiple subtypes, with variant-specific inserts reviewed as amendments rather than wholly new submissions. This type of family-level authorization would save months and millions of dollars while ensuring that the evidence across the influenza platform is aggregated and leveraged [11]. Taking this further, aggregating safety and efficacy data across a family of vaccines—such as filoviruses—would create a richer evidence base while reducing unnecessary duplication. This would also enable more efficient risk–benefit assessments when a new outbreak occurs [12,13].

Finally, regulators can embrace greater reliance and work-sharing mechanisms. A global emergency dossier submitted to multiple agencies at once, with review responsibilities distributed across regulatory networks, would minimize duplication and accelerate global access. The EMA, FDA, and WHO already collaborate informally; formalizing distributed review processes that extend beyond a limited few health authorities would make regulatory innovation a permanent feature of preparedness [14,15]. Operationally, agencies should pre-agree minimum Day 100 evidence packages (e.g., first-in-human safety, rigorous animal protection or human correlates, and Phase 2 immunogenicity), enable rolling submissions, and publish templates for distributed review (e.g., chemistry by Agency A, clinical by Agency B) with joint conclusions to accelerate authorizations. This will require deliberate investment in regulatory capability building: equipping agencies with the expertise, tools, and resources to conduct high-quality, timely reviews while safeguarding the confidentiality of proprietary industry submissions.

Taken together, these innovations point to a vision where regulation is not a bottleneck but an enabler of preparedness. The exemplar case mentioned in Section 2—where a regulator approves a vaccine primarily based on platform-level data and pathogen-specific immunogenicity—would send a powerful signal. It would demonstrate that regulators can safeguard safety and efficacy while unlocking the speed and sustainability required for the 100 Days Mission.

MANUFACTURING: FROM SCALE-UP TO DISTRIBUTED READINESS

Manufacturing readiness is the bridge between scientific breakthroughs and real-world impact. Even if vaccines are designed and approved in record time, they are of little use without the ability to produce and deliver them at scale. The COVID-19 experience highlighted both the possibilities and the limitations of our current system: unprecedented global output was achieved, but only through extraordinary measures and inequitable distribution [16].

Warm-base manufacturing—facilities producing routine/seasonal products on shared platforms—keeps supply chains active, staff trained, and assays harmonized so a pivot is operationally trivial. Annual SARS-CoV-2 strain updates function as de-facto manufacturing drills: recurring tech transfer, release testing, and scale-up within ~100 days of strain selection. Replicating this discipline across geographies and platforms (mRNA, vectors, proteins) is key.

The future must be different. Rather than reactive, piecemeal investments in response to access and equity crises, we need manufacturing systems that are embedded in sustainable, commercially viable pipelines. The concept of warm-basing is central to this vision. When a platform technology—such as mRNA—supports a portfolio of licensed commercial products, it brings with it an end-to-end supply chain, a trained workforce, and an active manufacturing base. This ecosystem can be redirected quickly toward a novel threat, scaling rapidly to meet the needs of a declared PHEIC or pandemic [17]. Because the platform is already producing other products, the infrastructure remains in use and ready.

The challenge is that such systems must be built and tested well in advance of Day 0. Conducting 'manufacturing drills' with mock candidates or variant vaccines ensures that technology transfer is smooth, assays are standardized, and facilities can pivot without delay. In a sense, the annual strain updates for COVID-19 vaccines have become this 'manufacturing drill': for each of the last 4 years, Moderna and Pfizer have released approved, updated COVID-19 vaccine into immunization channels within 100 days of the strain recommendation of the FDA advisory committee. This shows that where there is existing manufacturing capacity, and a reliable regulatory process, the promise of a 100-day vaccine is achievable.

Distributed manufacturing is often discussed in the context of equity: building new facilities in regions that were last in line during COVID-19. While well-intentioned, reactive approaches that establish stand-alone facilities disconnected from routine vaccine markets are unlikely to be sustainable. Idle plants are costly, and demand surges cannot be anticipated with enough precision to keep them viable. Instead, distributed manufacturing should be built into existing, continuously operating networks [18]. Facilities producing routine or seasonal vaccines on a shared platform can remain 'warm' and pivot when necessary.

Examples of this are beginning to emerge. Moderna's facilities in Canada, the UK, and Australia are structured to serve both domestic needs for seasonal respiratory vaccines and create global surge capacity for pandemic response. BioNTech's modular manufacturing units locate clinical scale production in Rwanda to support near-by clinical trials. And the WHO's mRNA Technology Transfer Hub contributes to an ecosystem that is building skills and local suppliers [2, 19]. These initiatives illustrate how warm-base manufacturing can take different forms to address different weakness in the supply chain. They have the ability to reinforce each other, provided they are connected to real, ongoing markets.

In short, the goal is not simply to add more factories, but to ensure that platform-based pipelines underpin manufacturing capacity. This way, supply chains are active, workers are trained, and production lines are humming long before a crisis hits. When the next outbreak occurs, the question will not be whether vaccines can be made—it will be how quickly facilities can redirect capacity to deliver them. That is the standard of readiness required for the 100 Days Mission.

FINANCING THE TRANSITION: FLEXIBLE PUSH & PULL MECHANISMS

Even if science, regulation, and manufacturing capacity are optimized, vaccines will not reach those who need them without financing models that align incentives and reduce risk. The COVID-19 pandemic revealed both the power and fragility of our current financial architecture. Mechanisms like COVAX aggregated demand and delivered over a billion doses, but their reactive nature led to inefficiencies, unspent funds, and surplus doses that arrived too late to meet peak demand [20].

To support the 100 Days Mission, financing must become proactive, flexible, and hybrid in design. Push funding—upfront investment in R&D and platform technologies—remains essential to de-risk discovery and early-stage development. CEPI's initial investments in Lassa, Nipah, and MERS vaccines exemplify how catalytic grants can move candidates into Phase 1 and 2 trials, creating the data that informs regulatory science [21]. Moderna, Pfizer, and BioNTech have all benefited from such early public investments, whether through BARDA, CEPI, or Horizon Europe.

Pull incentives are equally vital. Advance Market Commitments (AMCs), tiered pricing structures, and pooled procurement arrangements provide the demand signals industry needs to invest in scaling production. The pneumococcal AMC led by Gavi demonstrated how a credible buyer pool can unlock industry participation. During COVID-19, Operation Warp Speed and donor-backed commitments to COVAX provided the assurance that billions of doses would find a market, enabling manufacturers to scale at unprecedented speed [15].

The next step is to blend push and pull more seamlessly. Flexible facilities like the World Bank's Pandemic Fund could serve as vehicles to rapidly disburse funds to procurement mechanisms at the first signs of a promising candidate. Contracts should be designed with adaptive clauses—allowing adjustments in volume, variant specifications, or delivery timing. This would reduce the risk of oversupply while maintaining strong incentives for manufacturers to pre-invest [22].

Tiered pricing will continue to play a role, with higher-income markets cross-subsidizing access in lower-income countries. Moderna, for example, offered its COVID-19 vaccine to Gavi at its lowest global price, signaling a willingness to support equitable access. Ensuring such commitments are pre-negotiated and built into financing frameworks will make access less dependent on ad hoc negotiations.

Financing innovation also needs to consider sustainability. As regulatory innovation lowers the cost and time of vaccine development, and as manufacturing warm-bases spread costs across portfolios, the overall financial burden of preparedness decreases. This opens the possibility that AMCs for vaccines targeting emerging infectious diseases alone might suffice to keep manufacturers engaged, even without extraordinary donor subsidies. In such a scenario, the market would be self-correcting: preparedness vaccines would be commercially viable because the development and production costs are shared across a platform's wider portfolio.

Finally, financing must anticipate demand not only at the global level but

also within communities, underwriting delivery infrastructure and risk communication so early supply converts to uptake. Strong delivery infrastructure and public confidence are critical to ensuring that vaccines are used effectively once they exist. Investments in routine immunization programs, cold chains, and risk communication strategies pay dividends in pandemic response [12].

In short, financing must evolve from a reactive scramble to a standing system of push–pull mechanisms that share risk, create predictable demand, and ensure equity. Only then will the science and manufacturing advances outlined in previous sections translate into real protection for populations when the next outbreak occurs.

CONCLUSION

The vision of the 100 Days Mission is compelling because it forces us to think beyond incremental fixes and toward structural transformation. As scientists specializing in emerging infectious disease, we have experienced firsthand how outbreaks repeatedly reveal weaknesses across the continuum—from research to regulation, manufacturing, and financing. Our perspective in this commentary is not that of seasoned policymakers or financiers, but of vaccine developers who recognize that science alone is insufficient unless embedded in an ecosystem that can translate discoveries into rapid, equitable access.

The evidence is clear: investing in foundational research creates the prototypes, assays, and immune correlates that accelerate the regulatory process. Advancing vaccine candidates through Phase 1 and 2 trials builds a cumulative dataset that can serve as the backbone for platform-level regulatory science. Regulators who embrace platform master files, adaptive trial protocols, and reliance mechanisms will reduce costs and timelines while maintaining safety and efficacy. Warm-base manufacturing linked to commercially viable pipelines demonstrates that capacity can be sustained and redirected at need. Financing models that blend push and pull incentives offer industry the confidence to invest in preparedness without requiring perpetual crisis-driven subsidies. And vaccine libraries that progress deliberately toward licensure provide the bridge between early science and ready-to-deploy public health tools.

Taken together, these elements describe not a series of disconnected interventions, but an end-to-end continuum. This continuum makes preparedness sustainable, because each step reinforces the next: basic science informs regulatory science; regulatory clarity drives manufacturing investment; manufacturing efficiency lowers costs; and financing ensures equity and access. When aligned, these elements can transform the way the world responds to outbreaks.

COVID-19 showed us what is possible under extraordinary circumstances; our task is to institutionalize that performance in peacetime. The lesson is not to wait for crisis conditions to mobilize. It is to build now, in peacetime, the structures that will allow extraordinary results to become routine. If bold partnerships can demonstrate the power of regulatory innovation, if governments and industry commit to warm-base manufacturing and flexible financing, if vaccine libraries transition from concept to licensed products, then the 100 Days Mission will move from aspiration to reality.

The next pandemic threat is inevitable. The question is whether the world will meet it with fragmented, reactive measures, or with a system deliberately designed for speed, equity, and sustainability. The choice is ours. Ultimately, the success of the 100 Days Mission will depend not only on scientific and operational readiness, but on public confidence in the systems delivering those vaccines, requiring transparent communication, early engagement with

communities, and sustained investment in trust as a core element of preparedness. End-to-end transformation is not only possible—it is essential if we are to deliver on the promise of protecting the world within 100 days.

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AFFILIATIONS

Hamilton Bennett EMBA, Exective Director, Global Health Security, Moderna, Cambridge, MA, USA

Alan Embry PhD, Exective Director, Influenza Program lead, Moderna, MD, USA

AUTHORSHIP & CONFLICT OF INTEREST

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VACCINE INSIGHTS

HOW CLOSE ARE WE TO MEETING THE 100 DAYS TARGET TO PRODUCE A VACCINE?

SPOTLIGHT

Keystones of regulatory preparedness in pandemic vaccine development

Isabelle Bekeredjian-Ding

VIEWPOINT

"Pandemic preparedness is a disparate mixture of resilience and agility, enabling crisis responsiveness."

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COVID-19 vaccines were an unexpected challenge to the regulatory world. They were based on new technologies and there was great urgency to achieve licensure. This 'crisis mode' revealed the weaknesses and strengths of the system. Nevertheless, concerted efforts and funding enabled the development of new vaccines at unprecedented speed [1].

From a regulatory perspective, the basic principles of the licensure path for COVID-19 vaccines were not new; there was prior experience with rolling reviews and seamless transitioning of clinical trials. Important success factors were high motivation of regulators and regulatory affairs teams in the private sector, frequent communication between regulators and developers, the attempt to harmonize regulatory decision making on global level, and the efforts made to communicate regulatory decisions to the public. The pandemic demonstrated the functionality of the system within its framework but

"The basic idea is to secure expertise, networks, protocols, and infrastructure for a quick response independent of the pathogen."

attempts to go beyond the existing regulatory guidance were limited. This reflects the nature of the regulatory domain, which primarily secures the safety of the citizens.

Uncertainty is probably the most relevant roadblock in preparing for a new pandemic. It delivers an argument not to act, considering the multiple unknowns we might encounter. In this context vaccine platform technologies together with the 'Disease X' concept provide a viable solution to the overwhelming number of potential threats [2]. The basic idea is to secure expertise, networks, protocols, and infrastructure for a quick response independent of the pathogen. In the aftermath of the pandemic, uptake of the lessons learned led to the implementation of new organizations and infrastructure. Governments supported pathogen-agnostic capacity building in epidemiology, diagnostics, vaccine development, clinical trial networks, and manufacturing. In particular, the implementation of digital tools and artificial intelligence promoted by public funding was unsurpassed. However, since sustainability was not at the core of the funding programs, we still need to understand whether the transformative potential of these measures was sufficient to install an improved level of preparedness and reactivity for a future pandemic.

Pandemic preparedness is a disparate mixture of resilience and agility, enabling crisis responsiveness. In the regulatory domain this obvious contradiction raises questions about the capability to adapt and go beyond the state-of-the-art defined before the crisis. What benchmarks need to be retained and what is disposable? And why should we adhere to benchmarks for routine approvals that would not be held in a crisis? Acknowledging that preservation of trust is core to any regulatory procedure and that regulators must prioritize the safety and efficacy of vaccine products, it becomes evident that the principles underlying regulatory decision making need to be safeguarded along with the ethical considerations [3].

The conclusion is that regulatory reactiveness in a crisis highly depends on the preparative measures taken before the crisis. Thus, anticipation of regulatory requirements is key to pandemic preparedness and a long-term task. There are at least four major aspects of implementation of regulatory preparedness:

PREPARING PRODUCT DEVELOPMENT

A multitude of preparative measures have been proposed that could speed up pandemic vaccine development in a crisis. Implementation includes warm base concepts for clinical trial and production sites and preapproval of clinical trial protocols and master files for manufacturing of platform technology-based vaccines [4–9].

ACCELERATING VACCINE DEVELOPMENT

The inclusion of extra building blocks in vaccine development with predictive value for clinical trial outcomes. These can range from cell and tissue models for functional testing of protective immune responses in preclinical and clinical development to developmental decision making in human challenge trials [10,11]. This approach could be extended to innovative trial designs or concepts prioritizing phase four

studies in infections with high transmissibility, high lethality, and insufficient physical protection measures.

ENABLING REGULATORY DECISION-MAKING

Lack of data is the biggest blockade to regulatory decision making. It is therefore proposed to systematically analyze the knowledge gaps that regulators encounter in a crisis. Pandemic preparedness could be interpreted as the requirement to install data collection and analysis in anticipation of regulatory decisions in a crisis. This requires regulatory research concepts that exploit ongoing vaccine developments to generate data sets with predictive value for pandemic vaccine development.

EXPERT TRAINING

One of the challenges encountered in the COVID-19 pandemic was the lack of experts at all stages of vaccine development, manufacturing and regulatory. It is advisable to maintain expertise through education and training programs in interpandemic periods. There is, of course, no one-size-fits-all solution. Nevertheless, existing training programs and university courses could contribute to filling this gap.

This article proposes four keystones for pandemic preparedness in the regulatory field. For reasons of public trust, the regulatory framework is hard to adapt in emergency situations, so it is even more important to implement anticipatory approaches to regulatory issues that arise in a crisis. Since the most difficult issue to cope with is lack of data to support regulatory decision-making, there is an urgent need to generate data that permit conclusions on safety and efficacy of future pandemic vaccine products. This preparedness objective reaches beyond the warm base concepts and protocols for vaccine development and manufacturing and respects the need to avoid ad hoc regulatory decisions on highly innovative but immature vaccine developments.

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BIOGRAPHY

Isabelle Bekeredjian-Ding is a physician specialized in medical microbiology and immunology with an executive MBA degree from Mannheim/ESSEC Business Schools. She attended medical school in Heidelberg, Padova and Mt Sinai, New York. After graduation and her doctorate in immunology she worked at the Großhadern Hospital in Munich, at the Baylor Institute for Immunology Research in Dallas and in Clinical Pharmacology at the University of Munich. In 2005, she moved to Heidelberg as Research Group Leader at the Department for Infectious Diseases; in 2012, she joined the Institute of Medical Microbiology, Immunology and Parasitology in Bonn as Deputy Medical Director. From 2015–2023 she was head of the Division of Microbiology at the Paul-Ehrlich-Institut. She was responsible for approval of clinical trials, marketing authorizations for vaccines and the microbiological safety aspects of biomedicines and served in many offices including the EMA CHMP Vaccines Working Party and pandemic Task Force, Chair of the subgroup on infectious pathogens of the German Blood working group and chaired the Scientific Committee of the Innovative Medicines Initiative (IMI2) from 2017–2021. In the pandemic, she became Founding Director of the Center for Pandemic Vaccines and Therapeutics (ZEPAI), a unit responsible for procurement, demand forecast, storage and distribution of COVID-19 vaccines as well as pandemic preparedness contracts with vaccine manufacturers (2021–2023). Since 2024, she is full Professor and Chair of Medical Microbiology at Marburg University where she focusses her research on host-pathogen interaction, vaccine development and pandemic preparedness. Bekeredjian-Ding is a co-founder of the EU Vaccines Hub (Pillar 4 lead), an EU-funded program for end-to-end development program for pandemic vaccines (EU4Health GA #101202831) and a member of the German Center for Infectious Disease Research (DZIF).

Isabelle Bekeredjian-Ding MD, EMBA, Professor, Institute for Medical Microbiology and Hospital Hygiene, Marburg University and Regulatory Intelligence Unit, Karl-von-Frisch-Str. 14, 35043 Marburg, Germany

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VACCINE INSIGHTS

VACCINE CLINICAL UPDATE

COMMENTARY

The new era of vaccines: scientific challenges and their regulatory needs

Lucia Gabriele, Christopher Mann, Leo Van der Pol, David Morrow, Lauranne Duquenne, Annemarie Rosan Kreeftmeijer-Vegter, and Giovanni Migliaccio

The COVID-19 pandemic has confirmed that vaccines for infectious diseases have made the greatest contribution to global health of any intervention. On the other hand, it was not long ago that vaccines for cancer were just a dream for the future, whereas now they represent a viable option for active immunotherapy. Vaccines for the prevention of infectious diseases are referred to as traditional vaccines or prophylactic or preventive vaccines because they intend to directly prevent pathologies, whereas cancer vaccines are mainly therapeutic vaccines because they are used to treat cancer after it has already appeared. From the scientific point of view, both infectious and cancer vaccines aim to harness the immune system as part of the mechanism of action to achieve the therapeutic effect. Although for a long time the development of efficacious vaccines has relied on the better-known models of the immune response to infections, the recent breakthrough in cancer immunotherapy has disclosed the great advantage of sharing knowledge of host immunity to design novel vaccines. In addition, the recent remarkable technological advancements are now fostering a rapid evolution of the therapeutic potential of vaccinations. This new and vivid scientific landscape inevitably calls for a more suitable regulatory environment to promote the advancement in vaccines for infectious, degenerative and cancer diseases. Therefore, it has become urgent to clarify ambiguities in vaccinology, to absorb most meaningful scientific achievements in the processes for navigating the regulatory maze to bridge scientific challenges and regulatory needs.

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INTRODUCTION

The WHO defines vaccines as "biological preparations that improve immunity to a particular disease" underlying the fact that the immune system is the most important player determining the response to vaccines. Historically, the term vaccine has

been associated with infectious diseases, with prophylactic or preventive vaccines designed to prevent or reduce the severity of infection. These vaccines have been remarkably successful, saving millions of lives annually [1], and eradicating or drastically reducing diseases such as smallpox, polio, and measles. Although prophylactic vaccines are among the most effective tools for combatting infectious diseases, with efficacy rates exceeding 90% for illnesses like polio or measles, and over 75% for malaria and TB, efficacy among many old and emerging infectious diseases including Marburg virus disease, Lassa or Zika fever, continues to pose major global health challenges. In contrast to prophylactic vaccines, therapeutic vaccines are designed to treat established diseases, particularly cancer, by stimulating an immune response against malignant cells. Despite decades of research, the development of effective therapeutic cancer vaccines has proven exceptionally challenging. Early successes were largely limited to cancers associated with infectious agents: for example, the FDA-approved hepatitis B and HPV vaccines prevent liver and cervical cancers, respectively [2]. More recently, therapeutic cancer vaccines targeting non-viral cancers have been developed [3,4], including Sipuleucel-T (Provenge®) for metastatic prostate cancer and Talimogene laherparepvec (T-VEC®) for unresectable metastatic melanoma. These approaches illustrate the potential of immunotherapy but also highlight the complexity of translating preclinical success into clinically effective treatments.

A critical barrier to the development and adoption of cancer vaccines is regulatory complexity. Unlike traditional vaccines, therapeutic cancer vaccines face unclear regulatory definitions, extensive preclinical and clinical requirements, and stringent approval pathways that differ across regions. Regulatory challenges include establishing robust endpoints for efficacy, navigating combination therapy approvals, and demonstrating long-term safety in heterogeneous patient populations. These hurdles often delay clinical translation, increase costs, and limit patient access, even for vaccines with promising preclinical data.

The COVID-19 pandemic has revolutionized the vaccine field and demonstrated that accelerated regulatory pathways can dramatically shorten vaccine development timelines [5]. Applying these lessons to cancer vaccines requires aligning innovative therapeutic strategies with evolving regulatory frameworks to ensure safety, efficacy, and accessibility.

This review aims to clarify the key concepts in vaccinology needed to integrate emerging expertise from infectious diseases and cancer research with current regulatory processes. It highlights critical barriers in regulatory and clinical translation and discusses strategies to accelerate the development and advancement of these promising immunotherapies.

THE NEED TO CLARIFY REGULATORY AMBIGUITIES IN THE DEFINITION OF 'VACCINE'

The Oxford Dictionary reports that the noun vaccine originates from the late 18th century and derived from the Latin word 'vaccinus' , meaning 'of the cow' (vacca), referring to the early 'vaccine' use of dried cowpox virus lesions to protect against smallpox. In 1799, Edward Jenner used material from bovine scabs of ulcers caused by cowpox virus, also known as vaccinia virus, to inoculate children for the first time. However, the use of vaccinia scabs for immunization had been reported earlier by Lady Montague, wife of the English Ambassador to the Ottoman Empire [6], suggesting that the practice may have been imported from the Far East. Therefore, the first vaccines were based on inactivating the whole infective agent to reduce virulence, whereas modern vaccine

development often relies on recombinant viral material to obtain antigens capable of eliciting a targeted immune response. Nowadays, a vaccine is defined as a medicinal product whose mode of action consists of priming the adaptive immune system to recognize antigens expressed by a pathogen and protect the individual from the associated disease, consistent with definitions provided by EU [7] and FDA [8].

DIFFERENCE BETWEEN A 'CONVENTIONAL VACCINE' AND A 'CANCER VACCINE'

'Classical' prophylactic vaccines are usually intended to prevent the development of a disease in response to infection by priming the immune system to a rapid immune response. An important consideration (and frequent misconception, especially with SARS-CoV-2) is that vaccines do not always prevent infection but aim to control disease severity. Conventional vaccines are preventive, inducing adaptive immune response and long-term memory in healthy individuals to protect against future infections. Cancer vaccines, in contrast, are therapeutic, designed to stimulate the immune system against existing tumors, by targeting malignant cells. Searching for 'cancer vaccine' in PubMed from 2014 will retrieve more than 3,000 results. The term is catchy and clearly indicates the scope of these products, which leverage the individual's own immune system to fight cancer [9]. Tumors evade immune surveillance, requiring cancer vaccines to overcome mechanisms of immune suppression and escape [10]. These mechanistic differences between conventional and cancer vaccines shape their clinical development and regulatory pathways, with cancer vaccines specifically evaluated for inducing anti-tumor responses in patients, often alongside immune checkpoint inhibitors. Understanding these distinctions clarifies the unique positioning and challenges of cancer vaccines in immunotherapy.

For EU regulators, the term 'cancer vaccine' can be misleading because, by definition, vaccines are medicinal products intended to prevent infectious diseases, and cancer itself is not an infection. However, in some cases, cancer can result from previous or persistent infections—such as HPV, which may lead to cervical cancer. In these situations, medicinal products aimed at preventing cancer are classified as prophylactic vaccines, since their primary goal is to prevent the infectious agent rather than directly treat or target the cancer that may later develop. Conversely, the EU Regulation 1394/2007 clearly states that Advanced Therapy Medicinal Products (ATMPs) cannot be defined as vaccines if used for the treatment of non-infective diseases. The EMA defines immunotherapies as medicines that stimulate the immune system to kill the cancer cells [11]. Therefore, many innovative products such as tumor-specific T-lymphocytes, tumor-infiltrating lymphocytes, or CAR-T cells have been licensed as ATMPs rather than as vaccines [12]. Therefore, cancer vaccines are considered ATMPs and fall under the ATMP regulatory framework. In this review, the terms 'cancer vaccines' and 'ATMPs' are used interchangeably.

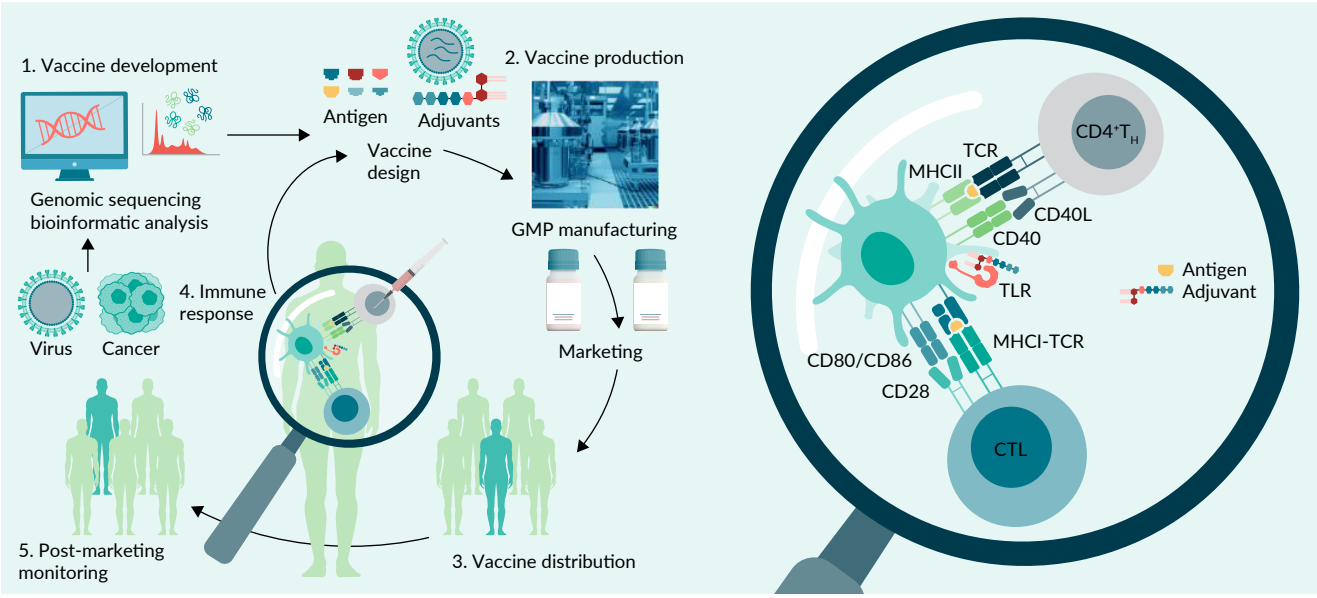
From a technological perspective, the advent of mRNA-based vaccines for active immunization against COVID-19 and their documented efficacy have generated considerable interest in mRNA-based therapeutics. Both Pfizer-BioNTech and Moderna leveraged previous experience developing mRNA cancer vaccines to accelerate the initial COVID-19 vaccine development. This has now come full circle, positioning mRNA technology as a key platform for producing vaccines against cancer [13]. mRNA technology allows for the rapid and precise design of vaccines by instructing cells to produce specific antigens that elicit targeted immune responses. In conventional vaccines, these pathogen-derived antigens are often well-characterized

and train the immune system to establish long-term protection against future infections. By contrast, cancer vaccines rely on tumor-specific antigens, frequently unique to an individual tumor, to activate immunity against existing cancers, highlighting their therapeutic rather than preventive role. Importantly, unlike conventional vaccines, cancer vaccines are often administered in combination with or as adjuncts to other therapies, such as immune checkpoint inhibitors (e.g., anti-PD-1 or anti-PD-L1). Current vaccine or ATMP regulations should be strengthened to address these considerations, supporting a regulatory framework tailored to the unique nature of cancer vaccines.

Both conventional vaccines and ATMPs require a clear description of identity and potency. Identity testing confirms that the correct active ingredient is present in the final product and refers to its composition, whereas potency is a measure of biological activity, informing the treatment dose and directly linking to therapeutic or prophylactic efficacy. For ATMPs such as vector–based vaccines, delineating identity and potency can be complex due to the highly composite molecular structure and antigenic properties of these biological products [14–16]. This complexity is further increased for cell-based ATMPs, such as dendritic cell (DC)–based vaccines, which exhibit high intrinsic variability due to factors such as lineage, differentiation stage, *in vitro* derivation, patient origin, and autologous or allogeneic status. Therefore, pre-defined variance in certain parameters should be accepted in the identity characterization of ATMPs. These factors should

FIGURE 1

Schematic overview of the vaccine development process.



(1) Vaccine development: genomic sequencing and bioinformatic analyses identify antigens for infectious vaccines or tumor-specific neoantigens for cancer vaccines. Infectious vaccine antigens are typically derived from pathogens, whereas cancer vaccines target tumor-associated or patient-specific neoantigens. Adjuvants may be selected differently depending on whether the vaccine is prophylactic or therapeutic. (2) Vaccine production: identified antigens and adjuvants are formulated and manufactured under GMP conditions for both infectious (e.g., COVID-19) and cancer vaccines. (3) Vaccine distribution: vaccines are distributed to target populations, with infectious vaccines administered to healthy individuals and cancer vaccines to patients with established tumors. (4) Immune response: vaccines elicit antigen-specific immune responses; conventional vaccines stimulate long-term protective immunity, whereas cancer vaccines activate cytotoxic T lymphocytes to recognize and attack tumor cells. (5) Post-marketing monitoring: ongoing safety and efficacy monitoring occurs for both vaccine types. Differences in antigen selection, adjuvant use, and patient population reflect the distinct preventive versus therapeutic purposes of infectious and cancer vaccines.

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also be considered when defining potency, for which potency assays must be developed in accordance with product-specific EU regulatory guidance [17–20].

VACCINE INNOVATION BRIDGING SCIENTIFIC CHALLENGES

The novel immune concepts to bring into vaccine development

A fundamental grasp of certain pivotal mechanisms that drive the immune response is essential for expediting every stage of the vaccine development process, whether targeted at infectious agents or cancer (Figure 1).

The induction of specific adaptive immune response by vaccination is the key step for both eliciting long-lasting host resistance to infection or for eradicating cancer. The activation of both B and T cell arms of adaptive immunity is dependent on innate response. Over the past few years, the innate-adaptive immune paradigm has gained deeper knowledge, becoming a new source to improve vaccines. Successful vaccines activate innate immunity, and specifically DCs, which drive the generation of antigen-specific naive B and T cells, producing long-lived plasma cells, primary antibodies and memory B and T cells. This process, mostly achieved with the first vaccine immunization, generates resting trained innate cells, displaying memory-like features characterized by enhanced innate effector response upon restimulation able to strengthen the secondary effector and memory adaptive response, upon the vaccine boost dose [21]. Notably, both innate and adaptive immunity to vaccination are mediated by the activation of cellular signals governed by IFN type I (IFN-I) [22]. On the other hand, several intrinsic host factors, such as sex and age, may affect individual immune responses to vaccines.

In terms of sex differences, induction of toll-like receptor (TLR) and IFN-I pathways are greater in females than in males [23]. A positive regulatory feedback loop exists between 17β-estradiol-estrogen receptor-α (E2–ERα) and IFN-I signal in regulating the development and function of some DC populations. In particular, the activity of plasmacytoid DCs, which represent the central DC subset responsible for robust IFN-α production upon viral infection or vaccination, is under the control of TLR7, whose X chromosome-linked gene is regulated by E2–Erα [24]. Therefore, timing, and strong activation of innate immune response occurs more frequently in females, with the possibility to strengthen trained immunity to ensure a long-lasting state of activation of innate cells via epigenetic modifications and a prompter functional response upon reencountering antigen [21]. More vigorous adaptive immune responses are also observed in females than males. In addition, females usually develop higher antibody responses following vaccination against many viral infections such as influenza, HBV, yellow fever, smallpox, rabies, and HSV [25]. For T cell response, while males exhibit higher CD8+ and Treg cell counts associated with Th1 dominance, females have higher CD4+ T cell frequency combined with an increased CD4+/CD8+ T cell ratio, denoting Th2 prevalence. Therefore, females experience more robust T cell activation during infection and males may have weakened CD8+ T cell function in an androgen receptor androgen receptor-dependent manner [26]. In the light of all this, it is worth emphasizing that several genes directly and indirectly regulating B and T cell function are located on the X chromosome and may escape the dosage-compensation inactivation mechanism [27]. Importantly, these mechanistic and immunological differences are supported by clinical and epidemiological evidence showing sex-specific variations in vaccine efficacy, immune response magnitude, and immune-related adverse events (irAEs). For instance,

females often develop higher antibody titers and more robust cellular responses to vaccines and immunotherapies, whereas they may also experience irAEs at higher rates than males. These observations highlight the need to consider sex as a critical factor in vaccine design, immunotherapy trials, and risk assessment for adverse events [28,29].

The variability in immune responses is also shaped by age, as both development and aging influence immune function. Early infants develop very short-lived immune responses to vaccines, likely due to the interference of maternal antibodies and the immaturity of their immune systems. In contrast, older children mount stronger and more durable immune responses as their lymphoid tissues and immune cell populations mature, allowing for more effective T and B-cell activation and memory formation [25]. For instance, BCG vaccination elicits stronger protection in children than in adults, which has been attributed to the early establishment of trained immunity and the greater plasticity of the developing immune system [30]. Epidemiological studies further support these age-dependent differences, showing higher vaccine efficacy and lower incidence of infectious diseases in older children compared to infants [31].

With aging, immune function gradually declines, a process known as immunosenescence, while chronic low-grade inflammation, or inflammaging, increases. Immune changes in older adults are highly heterogenous due to lifelong exposure to pathogens, environmental stressors, and other harmful stimuli, yet some traits consistently differ between sexes. These age-related alterations reduce vaccine responsiveness, resulting in weaker antibody production, impaired T cell function, and diminished long-term protection [32]. Elderly females typically experience a slower decline in T and B-cell functions with higher IL-10 production, which helps limit inflammaging, whereas older males show greater chronic inflammation due to persistence of high monocyte activity and inflammation [33]. Consequently, most vaccines provide limited protection in the elderly, despite general immune response in females. Therefore, incorporating the full spectrum of sex- and age-dependent immune factors is crucial for developing vaccines that provide robust and long-lasting immunity.

These concepts emphasize the need to adopt different strategies for obtaining a successful vaccination, defined as an efficacious and balanced immune response in the specific target population. For example, rethinking the best doses as well as the immunization schedules of vaccines across the course of life could maximize the protective effects while limiting adverse events. For example, since adult females typically have stronger immune responses, they could potentially benefit from lower doses of vaccines. Likewise, designing a next generation of vaccines adjuvanted with substances able to target additional signals of the immune system could overcome the unresponsiveness of elderly people. Therefore, fostering better knowledge of individual mechanisms paves the way for safer and more efficacious vaccines in the future.

Exploitation of vaccine-induced immunity by adjuvants

Adjuvants are one of the most crucial components of vaccine formulations, strengthening the immune response to vaccination in terms of magnitude and durability. Despite the intense effort of the research community, to date only six different adjuvants have been licensed by the regulatory authorities to be incorporated into authorized vaccines in many parts of the world. The revolution in the field has come from the recent deeper understanding of the fine mechanisms regulating

the immune response, and in particular innate immunity, providing new avenues for developing novel adjuvants with the potential to generate superior immunity ensuring safety while limiting toxicity.

Adjuvants can be classified as immunostimulants and delivery systems [34]. Immunostimulants function as agonists of TLRs, cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING), c-type lectin receptors (CLRs) and other pattern recognition receptors (PRRs), and include agents such as cytokine, monophosphoryl lipid A (MPL) and CpG. By triggering these signals, adjuvants target innate immune cells promoting the activation of antigen presenting cells (APCs), such as DCs, via stimulation of intracellular pathways that reinforce MHC-dependent antigen presentation and cytokine production. Thus, these signals operate synergically to both induce antigen-specific T cell activation and support antibody class switching in B-cells amplifying the antibody response [35]. Ideally, a vaccine formulation which contains the appropriate antigen, per se poorly immunogenic, and a suitable immunostimulant has the potential to properly stimulate a specific and efficacious immune response. One example of an authorized product with this kind of adjuvant is Heplisav B which consists of hepatitis B surface antigen (HBsAg) adjuvanted with CpG 1018. An important consideration for the historical development of hepatitis B vaccines was also the recognition that, in addition to adjuvants, the self-assembly of HBsAg into larger particles was important for potency [36].

Delivery systems include polymer-based systems, such as aluminum salts and poly(-lactide-co-glycolide) (PLGA), as well as lipid-based systems, such as lipid nanoparticles. Antigens absorbed onto aluminum salts are the most commonly used delivery systems for commercially approved vaccines including Engerix B (purified recombinant hepatitis B surface antigen that contains aluminum oxide) and HBVaxPro (HBsAg adsorbed on amorphous aluminum hydroxyphosphate sulphate), amongst others. Delivery systems are designed to increase antigen uptake and presentation by DCs in order to promote stronger antigen-specific adaptive immunity. Specifically, delivery systems modulate the release of antigens by several processes including the extension of their bioavailability via cargo protection, the targeting of APC-specific receptors, the enhancement of cargo trafficking to lymph nodes, and the increase of antigen cross-presentation. Therefore, delivery systems enhance vaccine targeting of innate immune cells, reinforcing their capability to promote robust cellular and humoral responses [37]. In addition, there are the so-called 'adjuvant systems' that consist of the combination of immunostimulants and delivery systems. One example is AS04, which is composed of MPL absorbed onto aluminum hydroxide and is a component of the approved vaccine Cervarix (HPV type 16 and type 18 L1 proteins).

In this complex landscape, given that the main goal of any adjuvant is to enhance the innate immune functions in order to stimulate efficacious and long-lasting antigen-specific adaptive immune responses, it is crucial to advance vaccine formulations, selecting suitable adjuvant to be combined with specific antigens. Therefore, to maximize vaccine design, key issues relating to the features of the vaccine-induced immunity need to be considered. For example, the time-dependent difference of action between antigens and adjuvant at the site of immune reaction may raise the constraint on the specific vaccine formulation for modulating antigen release, or the immunogenic potency of a particular antigen may require the use of a specific adjuvant. Overall, the number of approved adjuvants is still limited, although some experimental adjuvants are still being tested in trials. Since adjuvants are intimately linked to

vaccine manufacturing and quality, there is often limited data comparing similar vaccines adjuvanted differently such that comparative mechanism, safety, and efficacy are often lacking [38].

From the regulatory point of view, the exploitation of these research topics is extremely challenging since adjuvants are not licensed on their own but as a component of a specific vaccine. Consequently, preclinical testing for evaluating the safety and potency profile of adjuvants needs to be tailored to the specific product on a case-by-case basis. Particularly important are toxicology studies aimed at confirming that adjuvants do not adversely alter the safety or potency of the vaccine by inducing unwanted events such as hyper-inflammation and excessive cytokine production causing reactogenicity with break of immune self-tolerance [39]. Nowadays, the gained technological and scientific knowledge in the field of vaccines has broken new ground for using novel adjuvants rather than classical adjuvants to develop more potent vaccine formulations for infectious and cancer diseases. However, expediting the development of new adjuvants from the initial hypothesis to the regulatory process for clinical use demands robust mechanistic insights into the targeted immune response.

HOW TO NAVIGATE THE REGULATORY MAZE IN VACCINE DEVELOPMENT

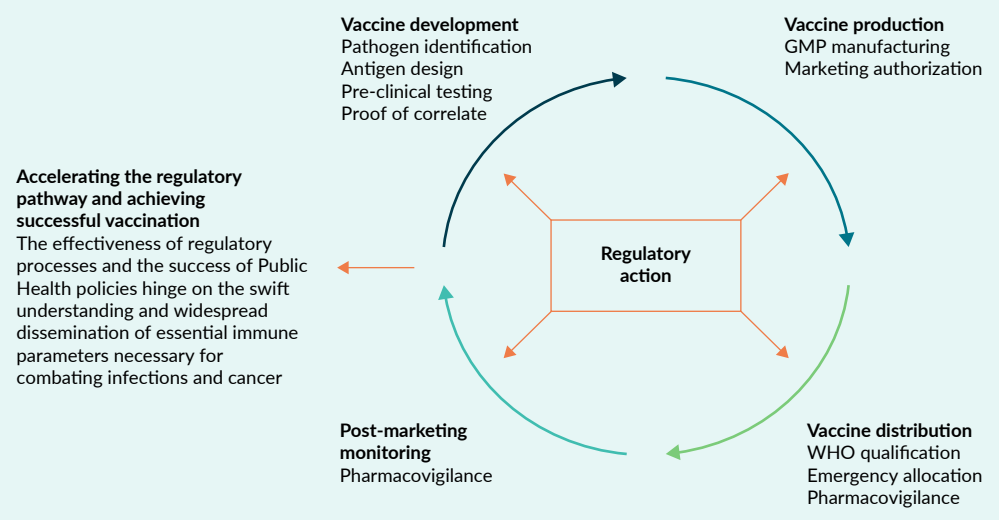
Ensuring a timely alignment between the regulatory process and each phase of vaccine development is critical for generating an effective product. This ensures a balance between scientific effort and economic commitment, facilitating an effective vaccine for administration to diverse groups of individuals, both in routine circumstances and during pandemics (Figure 2).

The regulatory pathway to develop a novel vaccine was well described and historically well-trodden until a new generation of vaccines based on the use of RNA to encode the desired antigens directly within the recipient cells won the race for the prophylaxis of COVID-19. A new set of guidelines will now be critical to deal with the technical specifications of this new class of products [40]. However, the development path remains unchanged, as a vaccine is considered a medicinal product and as such is covered by the relevant legislations and guidelines specifically designed for the development of medicinal products. In particular, it requires a marketing authorization to be commercialized. The European marketing authorization is released by the European Commission on recommendations from the EMA while in USA it is covered by the FDA. In both cases, the process leading to the marketing authorization of vaccines for infectious diseases is focused on establishing a positive risk/benefit ratio and demonstrating non-inferiority compared to existing treatments. The efficacy of a vaccine is clinically tested by treating a healthy population that could be exposed to the infective pathogen and then comparing the rate and severity of disease between treated and untreated subjects.

In fact, prophylactic vaccines do not prevent infection itself but rather the pathology resulting from the infection. To design the most effective development plan for a new vaccine, various information is required, as set out in the guidelines provided by EMA [41]. Several crucial factors to be considered include the nature of the infective agent, its epidemiology, potential carriers, and the mode of transmission. Similarly, critical parameters like the frequency and intensity of epidemics, pinpointing the target population for vaccination, understanding their environment, and planning the logistics for distribution and administration, play a significant role in shaping of the development approach. In addition, economic issues as well as cost and reimbursement

FIGURE 2

Summary of the regulatory process in vaccine development.



The figure illustrates regulatory actions across key stages, from early research through clinical development to marketing authorization, showing how scientific and economic considerations are coordinated. It covers both infectious disease vaccines, typically administered to healthy populations for prophylaxis, and therapeutic cancer vaccines, which are given to patients with established disease. Notably, differences in trial design, efficacy evaluation, and risk/benefit assessment between these two vaccine types exist, emphasizing the need for tailored regulatory strategies for cancer vaccines.

policies are factors to be considered before initiating vaccine development.

When translating these principles to cancer vaccines, several fundamental differences arise. Unlike prophylactic vaccines, therapeutic cancer vaccines are administered to patients with established disease, meaning the clinical objectives focus on disease regression, control, or improved survival rather than prevention. Consequently, efficacy evaluation, risk/benefit assessment, and trial design are substantially more complex. Patient heterogeneity, tumor microenvironment, prior therapies, and disease stage can all affect outcomes and must be carefully considered in regulatory submissions. These challenges highlight the need for tailored guidelines for therapeutic cancer vaccines that differ from those used for infectious disease vaccines, including the design of adaptive clinical trials, incorporation of surrogate endpoints, and integration of biomarker-based patient selection.

As of January 2025, the new EU Health Technology Assessment Regulation (HTAR) 2021/2282 became applicable to marketing authorization applications for new cancer medicines or ATMPs. The new HTAR rules will also be extended to orphan medicines in January 2028. This has immediate implications for cancer vaccines, as early-stage clinical development for such products, even for experimental therapies, should now also consider developing data to support future HTA interactions. Tailored regulatory strategies that address the unique challenges of therapeutic cancer vaccines are increasingly necessary to ensure both timely approval and alignment with health technology assessments.

Development of prophylactic vaccines

The developmental pipeline of a prophylactic vaccine, particularly for emerging infectious diseases, is inherently complex,

starting with the identification of the pathogen. From identifying a new disease to collecting biological samples and isolating the agent, a chain of events needs to take place. First, transporting samples to specialized laboratories is possible but requires that the collection process supports the preservation of the integrity of the infectious agent, implying recognition of the uniqueness of the condition. Subsequently, the identification of new pathogens must be exceptionally precise, resulting in distinct outcomes. In this context, the introduction of cheap DNA/RNA sequencing technologies can facilitate rapid identification, though they are currently accessible primarily in advanced economies. Once the genome of the agent is identified, *in silico* technologies can be applied to identify structural components of the antigen, pinpoint potential targets for inhibition, and assist in design of the vaccine. This method is considerably faster than the traditional approach, which requires cultivating the infective agent in a suitable host, either *in vitro* or *in vivo*, followed by purification and characterization. A requirement for this fast approach is to have predictive assays in place that can effectively reflect major vaccine efficacy (correlate of protection) and indicate potential safety issues (e.g., excessive inflammation) or immune evasion effects. This usually requires a solid understanding of the pathogen, the disease, and its immune evasion strategies. Once the vaccine is formulated with the addition of an adjuvant and excipients, where applicable, considerations regarding the target, logistic constrains, and economic factors will guide the definition of the desired final characteristic of the product. Therefore, a suitable manufacturing process can be planned and executed, and the initial batch can undergo *in vitro* testing for purity and suitability. Depending on the characteristics of the disease, an appropriate *in vivo* animal model is selected, and a proof of principle for efficacy is obtained.

In the clinical development of vaccines for infectious diseases, obtaining authorization to conduct clinical trials with a large number of healthy volunteers is crucial, and requires providing preclinical data that assess the safety of the product and a proof of principle, demonstrating its ability to elicit an immune response and offer protection in an adequate animal model. The authorization to treat healthy individuals with a new vaccine is released by the national competent authorities based on the evaluation of the risk/benefit ratio. The quality and safety data are also required to assess a new vaccine and to define the initial dosage for the first in human clinical trial. Nevertheless, for non-endemic pathogens, such clinical trials need an epidemic scenario, as observed for example in SARS coronavirus in 2003, H1N1 in 2009, MERS in 2015, and notably the global health emergency of SARS-CoV-2 in 2019. In each of these instances, central to the required clinical data are i) the backward pathway for establishing quality and safety requirements and ii) the identification of an appropriate correlate of protection.

Development of therapeutic vaccines for cancer

The mode of action of a therapeutic vaccine is still based on the immune recognition of a target based on anomalous antigen expression, including tumor-associated antigens and tumor-specific antigens. Cancer cells evade immune clearing through multiple mechanisms, such as downregulation of MHC molecules, expression of immune checkpoint inhibitors (e.g., PD-L1), and recruitment of immunosuppressive cells, which collectively dampen anti-tumor immunity. To overcome these barriers, cancer vaccines may employ autologous cells, engineered components, or synthetic constructs designed to enhance immune activation. AI tools are increasingly being used to design synthetic immunogens or

receptors and to predict immune responses, potentially streamlining vaccine development and informing alternative nonclinical models [42]. However, the validation of AI-driven designs and their regulatory acceptance remain areas of active investigation. Despite these innovations, therapeutic cancer vaccines must comply with established medicinal product regulations. At the time of marketing authorization, they require clear definitions of identity (precise characterization of the active components), potency (ability to elicit the intended immune response), and mode of action (mechanistic basis for the therapeutic effect), ensuring safety, reproducibility, and efficacy in patients. The identity of cell-based medicinal products is addressed in the EMA Guideline On Human Cell-Based Medicinal Products [43]. Due to the complexity of cell populations, it is defined through a combination of biomarkers, biological functions, capacities, and the specific manufacturing process. Potency is often challenging to assess *in vitro* and may require validated surrogate biomarkers for timely assessment. A common approach in cancer immunotherapy is to use autologous cells equipped with a recombinant antigen receptor to directly eliminate target cancer cells, such as in CAR-T therapies. These genetically modified autologous cells are considered gene therapies and must follow the Guideline On Quality, Non-Clinical And Clinical Aspects Of Medicinal Products Containing Genetically Modified Cells [44] where applicable.

Preclinical and clinical study requirements are further detailed in the Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials [45]. Unlike prophylactic vaccines, clinical development for therapeutic cancer vaccines involves patients rather than healthy volunteers, with the primary endpoints focusing on survival or complete remission and often requiring prolonged follow-up to confirm durable responses and non-recurrence.

Importantly, therapeutic cancer vaccines require special consideration during marketing development due to their unique characteristics. They are typically patient-specific, administered in hospital settings, and demand stringent storage and logistic conditions because of their short shelf-life and sensitivity to environmental factors. Their cost per unit is substantially higher than conventional vaccine and they are associated with an increased risk of complication for patients. Additional challenges in cancer vaccine design involve the need to overcome immune tolerance while minimizing the risk of autoimmunity. As scientific knowledge advances, greater personalization of vaccine design may become possible, targeting novel antigens and potentially pushing the limits of predicted immunogenicity and mechanism of action. Potential risks, such as autoimmunity or other irAEs, should be carefully evaluated based on experience from related products, highlighting the importance of collaboration to advance the field and ensure patient safety.

CONCLUSION

The COVID-19 pandemic has shown that vaccine development can be significantly accelerated when regulatory processes are streamlined and coordinated with scientific innovation. A central lesson is the importance of understanding the immune mechanisms underlying vaccine responses, particularly in specific target populations, to guide the design of next-generation vaccines. This requires precise definitions of vaccines, the knowledge of their mode of action, and the rational use of advanced adjuvants to optimize immune responses. Despite these advances, substantial uncertainties remain, including the challenges of navigating complex regulatory frameworks

and addressing emerging societal factors such as vaccine hesitancy, global migration, and the impacts of climate change. To overcome these challenges, early and continuous dialogue among all stakeholders, including regulators, developers, manufacturers, and policymakers, is essential. Structured collaboration and effective communication platforms can bridge scientific, regulatory, and societal considerations, ensuring that vaccines are developed efficiently, safely, and equitably. In summary, the actionable takeaway is that future vaccine development must integrate scientific innovation, regulatory preparedness, and societal awareness into a coordinated framework. This approach will enable rapid, safe, and effective responses to both emerging infectious diseases and the growing field of therapeutic vaccines, ensuring public health needs are met proactively and efficiently.

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AFFILIATIONS

David Morrow, **Lauranne Duquenne**, and **Giovanni Migliaccio**, EATRIS (European infrastructure for translational medicine), Amsterdam, the Netherlands; **Lucia Gabriele**, Istituto Superiore di Sanità, Italy; **Christopher Mann**, Asphalion, Barcelona, Spain; **Leo A Van der Pol**, Intravacc, Bilthoven, the Netherlands

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VACCINE INSIGHTS

VACCINE CLINICAL UPDATE

In the making: lessons from 50 years in vaccine development

Jerry Sadoff

PROFILE

"Each step forward depends not only on innovation, but on the discipline to test and question what we think we already know."

Over a career spanning five decades, Jerry Sadoff has helped shape some of the most significant advances in modern vaccinology, playing a key role in bringing no less than 14 licensed vaccines to market. Here, he reflects on the projects that shaped his approach to vaccine innovation and the principles that have guided his work: the balance between risk and responsibility, the importance of ethical clarity in scientific decision-making, and the persistence needed to turn long-held hypotheses into clinical reality.

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EARLY LESSONS: RISK, REWARD, & ETHICAL INNOVATION

At Merck, I led the clinical development of a rotavirus vaccine in collaboration with the Children's Hospital of Philadelphia between 2003 and 2006, when the vaccine was ultimately licensed. Rotavirus is an important cause of hospitalizations and deaths in young children, especially in low- and middle-income settings, so we knew a vaccine would have a huge impact.

At the time, another company had licensed the first vaccine but withdrew it after a rare safety signal, intussusception (a form of bowel obstruction caused by telescoping of one segment of the intestine into another), was detected at a rate of roughly one in ten thousand cases. The withdrawal prompted a re-examination of publicly available data, which showed that cases were restricted to infants who were first vaccinated at 3–4 months, with no cases in infants who received their first dose at 2 months.

Physiologically, this finding made sense: intestinal motility remains immature in 2-month-old infants, making the bowel less likely to intussuscept. Drawing on that reasoning, I proposed that earlier immunization, prior to the development of normal peristaltic organization, could reduce the risk of intussusception.

When we sought to test the hypothesis, new challenges emerged. To demonstrate that our vaccine did not increase the incidence of intussusception compared with placebo, our statisticians calculated that a sample size exceeding 300,000 participants would be required—a number unfeasible for any sponsor.

In consultation with our chief statisticians, Joe Hayes and Ivan Chan, we used modeling to determine if the trial size could be reduced without compromising the statistical validity or safety of the study. For ethical reasons I had previously designed a sequential safety monitoring boundary—a running comparison of intussusception events between vaccine and placebo groups. Should the difference ever cross a p-value threshold of 0.05, enrollment would stop immediately to prevent further exposure. By modeling the fact that we could never cross that line to complete the trial we demonstrated that a sample size of approximately 60,000–70,000 participants would provide sufficient data for evaluation. The trial subsequently progressed without any indication of imbalance in safety outcomes between vaccine and placebo groups. The resulting data ultimately supported regulatory approval.

This outcome reinforced a broader principle. Ethical decisions in science are not just moral choices; they are operational strategies that stand the test of time. Acting ethically may not always appear to be the most expedient option, but it leads to stronger, more sustainable outcomes over time. To me, ethics represents a method, one refined through history, for doing things in a way that consistently proves best in the long run. In this case, adhering to ethical principles did more than satisfy conscience; it provided a method for making the work feasible thereby making licensure of the vaccine possible.

RETHINKING PROTECTION: THE PANDEMIC YEARS

When I led clinical development of the Johnson & Johnson (J&J) COVID-19 vaccine, two findings stood out and have continued to shape how I think about pandemic readiness.

During enrollment, it was not feasible to determine recent prior infection by history alone, as many infections were asymptomatic and waiting for results of the N-ELISA test for previous infection would slow enrollment down. To address this, at the time of enrollment but after the participants were immunized we ran an ELISA on all participants to retrospectively identify serologic evidence consistent with recent exposure and stratified the analysis accordingly. The trial enrolled approximately 40,000 individuals. When we compared non-immunized placebo participants with serologic evidence of recent asymptomatic infection to seronegative participants in the placebo arm, those with prior infection showed around 90% protection against COVID-19. All participants with serologic evidence of infection had been asymptomatic by self-report, indicating

the protective effect of recent subclinical exposure. Among participants who were seropositive for prior asymptomatic infection and received the vaccine, protection rose to approximately 98%. In a period of active public debate about natural immunity, these data provided an important perspective: recent asymptomatic infection conferred substantial immunity on its own, and prior infection combined with vaccination yielded the highest levels of protection.

The COVID-19 vaccine trials also offered us an opportunity to learn more about the role of cellular immunity. For decades, many in the field believed that T cell responses were critical to immune protection, and yet this had never been demonstrated prospectively in a large, randomized trial. The limitation was largely operational. In studies enrolling tens of thousands of participants, it is not feasible to collect and process sufficient blood samples to isolate and analyze viable cells at multiple timepoints. As a result, while epidemiologic, animal, and small-scale human studies suggested a link between T cell immunity and protection, direct clinical evidence remained elusive. This constraint also explains why most vaccine constructs historically emphasized antibody responses rather than cellular ones.

To enable evaluation of T cell responses to the SARS-CoV-2 spike protein in J & J's trial, blood samples were collected at day 0 and day 28 and preserved for subsequent mRNA sequencing, allowing later assessment of transcriptional and immunologic signatures associated with vaccination.

After completion of the primary efficacy analysis, collaboration with an external group enabled the application of an artificial intelligence–driven method to identify antigen-specific T cell receptor (TCR) responses. The model had been trained on mRNA datasets from over 1,000 early-pandemic cases to recognize TCR patterns associated with responses to the SARS-CoV-2 spike antigen. Applying this algorithm to trial samples enabled quantitative assessment of vaccine-induced T cell activation.

Using this approach, a closely matched subset of approximately 300 vaccinated participants was analyzed, including 28 independently adjudicated cases of severe COVID-19. Comparison of vaccinated individuals who became infected with those who did not become infected revealed no significant difference in T cell signal with respect to infection incidence.

However, when analysis focused on severe outcomes, a clear association emerged: participants who mounted a vaccine-induced T cell response were protected from severe disease ($p=0.004$). Neutralizing antibodies contributed significantly to protection, but the addition of a vaccine-induced T cell response produced an additive effect that further reduced risk. These findings underscore that effective vaccines should aim to elicit both strong neutralizing antibody and T cell responses to achieve durable protection against severe outcomes.

Beyond the randomized trial setting, colleagues in South Africa vaccinated approximately 80,000 healthcare workers with the Ad26-based vaccine used in our Phase 3 study. Protection against hospitalization was observed and remained stable even as circulating variants evolved. When the predominant strain shifted to one associated with markedly lower neutralizing antibody titers, protection from hospitalization in this cohort did not diminish. During subsequent Omicron waves, neutralizing antibody levels were low in most individuals, yet protection against severe outcomes was largely preserved.

These findings provided real-world confirmation of what the immunological analyses suggested: protection from hospitalization and severe disease was maintained even as neutralizing activity declined, indicating a durable contribution from vaccine-induced cellular immunity. The results also illustrated a broader principle. T cell epitopes are typically located in viral proteins

that are functionally constrained and therefore less prone to mutation. Vaccines that elicit responses to such conserved regions can provide cross-reactive protection, blunting the impact of new variants or divergent pathogens while more specific vaccines are developed. In practical terms, this cellular immunity helps reduce severe disease and hospitalizations during that interval, buying time until strain-matched vaccines become available.

The implications extend beyond COVID-19. Stratifying efficacy analyses by prior infection status can clarify the respective roles of natural and vaccine-induced immunity. Incorporating T cell measurements into large clinical trials is now feasible when sampling and analytic methods such as TCR profiling are built into the design. Most importantly, future vaccine platforms should include antigens that generate both potent neutralizing antibodies and broad, conserved T cell responses to sustain protection against severe disease across variants and related emerging pathogens.

Comparing the rotavirus program 25 years ago to the COVID-19 program more recently, I recognize the same guiding principle at work. Progress in vaccinology often depends on revisiting earlier ideas with the benefit of new tools and evidence. Many of us long believed that cellular immunity played a crucial role in protection from infection but lacked the technology to confirm it. When analytical methods finally made it possible to test that hypothesis, the data validated what experience had long suggested, and, in doing so, reaffirmed how persistence, collaboration, and technological progress continue to drive advances in vaccine science.

TOWARD UNIVERSALITY: THE NEXT FRONTIER IN VACCINE DESIGN

When I was at J & J, our team pursued the development of a universal influenza vaccine, an effort that built on earlier work at Crucell. The Crucell scientists had identified monoclonal antibodies that bound to conserved epitopes in the stem region of hemagglutinin (HA), common to all influenza subtypes. The idea was straightforward in concept but technically demanding: if we could design a vaccine that elicited antibodies to these stem epitopes, rather than the highly variable head, we could achieve broad and durable protection across strains.

The head of the HA protein mediates binding to the sialic acid receptor on host cells, while the stem facilitates entry of the viral nucleic acid into the cytoplasm. As the stem performs an essential structural function, it is far more evolutionarily constrained than the head and therefore represents a stable target for vaccine design. Our approach was to remove the immunodominant head region to focus the immune response on the stem, allowing for the induction of cross-reactive antibodies.

Despite the strong rationale, one major obstacle soon became clear: there was no straightforward regulatory path to licensure. The accepted correlate of protection for influenza vaccines is the hemagglutination inhibition (HAI) assay, which measures antibodies that block receptor binding. Stem-directed antibodies block nucleic acid entry into the cell rather than receptor binding and therefore do not yield a positive HAI result. Since annual influenza vaccine updates are licensed on the basis of HAI titers against WHO-recommended 'guidance strains' rather than full efficacy trials, a stem-only vaccine did not fit within existing regulatory frameworks without huge clinical efficacy trials. For that reason, we began to explore complementary approaches that could induce broadly neutralizing HAI antibodies as well.

By that time, J & J had decided to exit the vaccines field. Having worked closely with a company called Centivax, which had demonstrated a strategy for inducing broad

HAI activity against diverse influenza strains in animals, I joined them as Chief Medical Officer. Their approach challenged conventional vaccine design by applying the idea that reducing individual antigen immunogenicity could, paradoxically, enhance recognition of shared epitopes. By combining many antigenically distinct HA molecules, each present at a dose too low to elicit a strong strain-specific response, the vaccine shifts the immune focus toward epitopes that are shared among them.

In principle, the immunological reasoning is simple arithmetic. When an individual is immunized with, for example, ten H1N1 and ten H3N2 variants spanning more than a century of viral evolution, most epitopes vary among strains, but a few remain invariant because they are essential for viral function. At very low antigen doses, B-cells recognizing these variable epitopes receive only a single stimulation event, whereas B-cells recognizing conserved epitopes encounter them repeatedly across variants. The cumulative signal favors expansion of B-cells targeting the conserved regions—the ones the virus cannot easily mutate. In practice, the vaccine includes 22 mRNA components: ten encoding H1N1 HAs, ten encoding H3N2 HAs, one encoding influenza B HA at standard dose, and one construct incorporating selected T cell epitopes derived from four internal viral proteins conserved across nearly all influenza isolates. The epitopes were selected for presentation by the most common human leukocyte antigen alleles. Each has also been associated with cytotoxic T cell responses in prior studies.

In animal models, this multivalent formulation has induced both broad HAI activity and cross-neutralization against diverse strains, including H5N1, together with strong cellular immune responses. If these results translate to humans, such a vaccine could prime populations against future pandemic strains, reducing severe disease and hospitalizations while strain-specific vaccines are still in development. Clinical evaluation is now underway, beginning with a dose-escalation study planned in Australia, followed by studies in the United Kingdom, United States, and the Netherlands.

Encouraged by these findings, we have begun exploring whether the same logic could be applied to other highly variable pathogens such as malaria. For the first time in decades, it feels as though we may be closing in on a general solution to the problem of pathogen variability and evasion mechanisms. By designing vaccines that selectively emphasize what the virus cannot change, we stand a real chance of moving from reactive vaccine updates to durable, broad-spectrum protection.

FROM INSIGHT TO IMPACT: TRANSLATING IMMUNOLOGY INTO PRACTICE

The success of any vaccine ultimately depends on how well preclinical findings translate into human efficacy. The universal influenza program is no exception. Beyond safety, our objective is to demonstrate that the immune responses elicited by this vaccine are at least comparable to those induced by current seasonal formulations, and, critically, that they extend protection to strains that have diverged substantially from those used in annual strain guidance. In regulatory terms, that requires showing non-inferiority against matched strains and superiority against drifted ones. Together, those data would establish that the vaccine not only meets existing standards but also addresses a clear medical need.

Advances in structural biology have made this goal more attainable. Across multiple viral families, class I fusion proteins, such as influenza HA, the coronavirus spike, and the RSV F protein are intrinsically unstable. Their trimeric structures dissociate readily, reducing the proportion

"Over the years, I've learned that scientific progress is rarely linear. It moves through cycles of discovery, uncertainty, and renewal[...]"

of properly folded, immunogenic antigen in conventional vaccine preparations. By stabilizing these trimers and anchoring them in a membrane-bound form, we can markedly enhance immune recognition. In mouse studies, the combination of trimer stabilization and membrane presentation increased HAI titers roughly 15-fold relative to the native soluble protein. This effect appears to result from prolonged surface expression on antigen-presenting cells, which extends interaction with T follicular helper cells and promotes improved B-cell affinity maturation, a process that mirrors natural infection while offering greater stability.

These findings exemplify how cross-pathogen insights accelerate innovation. Knowledge gained from prefusion stabilization in COVID-19 and RSV now directly informs influenza vaccine design, and the same structural principles are likely to improve immunogenicity and durability across diverse viral targets.

Equally important are the people behind these advances. None of these achievements stem from a single scientist; they reflect the collective creativity, persistence, and technical excellence of multidisciplinary teams. I have been fortunate to work alongside such colleagues throughout my career. The satisfaction lies not only in the vaccines themselves, but in the collective effort that brings them into being.

REFLECTIONS ON COMMUNICATION, TRUST, & INTEGRITY IN VACCINE DEVELOPMENT

Looking back over a career in vaccines, the most satisfying part is seeing a scientific idea validated and translated into real-world impact. Few experiences compare to seeing a hypothesis confirmed and turned into something that saves lives. Still, a vaccine that reaches no-one, protects no-one. Development is only part of the story; communication and public trust complete it.

In recent years, the scientific community has faced challenges not only in developing vaccines but also in communicating about them effectively. During the pandemic, for example, the urgency of the moment sometimes led to oversimplified public messages. Simplification has its place, but it can sow confusion when recommendations evolve. A more transparent message might have been: 'we do not yet know if this will work, but evidence from similar infections suggests it might, and we will test it.' People are capable of understanding that kind of nuance, and when we tell the truth, including its uncertainties, we safeguard the credibility of science itself.

Over the years, I've learned that scientific progress is rarely linear. It moves through cycles of discovery, uncertainty, and renewal; ideas once set aside return with new technologies or stronger evidence. In vaccine development, those cycles unfold in real time, often under intense ethical and public scrutiny. Each step forward depends not only on innovation, but on the discipline to test and question what we think we already know.

Credibility, I believe, is as important as discovery. Without it, even the best science loses its power to serve society. That means acknowledging what we do not know, updating our conclusions when new data emerge, and resisting the temptation to treat provisional knowledge as dogma. Science progresses through challenge: questioning accepted truths while respecting the evidence we have.

My wife likes to say about me that: "Jerry knows a lot about vaccines, and nothing about anything else." She's probably right. But after decades in this field, what I do think I know is that boldness only matters when it's guided by ethics, and discovery only endures when it earns trust.

BIOGRAPHY

Jerry Sadoff is an Internal Medicine Infectious Diseases trained physician and researcher, with over 50 years of experience in vaccine development. Over the course of his career at Walter Reed, Merck Inc, Aeras Global TB Vaccine Foundation, Crucell Inc, and Janssen Infectious Diseases and Vaccines (Johnson & Johnson) he has overseen or played a key role in the approval of 14 vaccines, including vaccines against Hepatitis A (VAQTA); Cholera (Dukoral), Haemophilus, (Liquid Pedvax); Varicella, (Varivax II®); Measles, Mumps, Rubella and Varicella combination (ProQuad®); Zoster, (Zostavax™); Rotavirus (Rotateq®); Human Papilloma Virus, Gardasil®; Hexavalent combination of HepB, Hib. IPV, DPT (Hexavac); Malaria (GSK, RTS,S/AS01); Ebola, (Zabdeno®+Mvabea®) and Covid-19, (Jcovden). He is currently the Chief Medical Officer at Centivax Inc. where he is leading the clinical development of a universal influenza vaccine Centi-flu 01 and a vaccine to prevent Alzheimer's disease.

Jerry Sadoff MD, Chief Medical Officer, Centivax Inc., South San Francisco, CA, US

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VACCINE INSIGHTS

INDUSTRY INSIGHTS · NOVEMBER 2025

Multiomics, mucosal immunity, and mRNA vaccine benefits

Charlotte Barker

Charlotte has over 20 years of experience as a science writer and editor. As Commissioning Editor of *Vaccine Insights*, she works with leading scientists to produce content covering all aspects of vaccine R&D and manufacturing. For this month's Industry Insights, Charlotte shares the news that has caught her attention—from promising results with intranasal formulations to the immune-boosting properties of mRNA vaccines.

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DISCOVERY AND IMMUNOLOGY

Multiomics reveals molecular mechanisms behind weakened vaccine responses in older adults [1]

Tracking 96 healthy young and older adults over 2 years, researchers at the Allen Institute used single-cell RNA sequencing, proteomics, and spectral flow cytometry to show that specific, nonlinear age-related changes in T cells contribute to weaker vaccine responses in older adults. These findings were supported by the Human Immune Health Atlas, mapping 71 immune cell types and over 16 million cells from adults aged 25 to 90+.

FORMULATION AND DELIVERY

Novel LNP with 100-fold lower dose of influenza mRNA vaccine in mice [2]

MIT scientists reported that a new LNP platform, based on degradable cyclic amino ionizable lipids, enabled dosing of an mRNA influenza vaccine at a 100-fold lower dose than a conventional ionizable lipid.

Intranasal pertussis vaccine generates strong local T cell immunity in mice [3]

Researchers at Trinity College Dublin reported preclinical results for a novel intranasal pertussis vaccine formulated using antibiotic-inactivated Bordetella pertussis [3]. In mice, administration of the vaccine via aerosol or intranasal routes conferred a high level of protection, outperforming both current acellular and historic whole-cell vaccines.

Intranasal recombinant H5N1 vaccine induces mucosal and systemic immunity in adults [4]

A Phase 1 randomized, placebo-controlled trial evaluated NanoVax's intranasal recombinant H5N1 influenza vaccine in 40 adults aged 18–45 years. Participants received low, medium, or high doses of the adjuvanted clade 2.1 rH5 vaccine, an unadjuvanted dose, or placebo, followed by an intramuscular H5 booster 6 months later. The adjuvanted intranasal vaccine elicited higher IgG and IgA antibody levels, increased memory immune cells, and improved neutralizing activity compared with unadjuvanted or placebo groups.

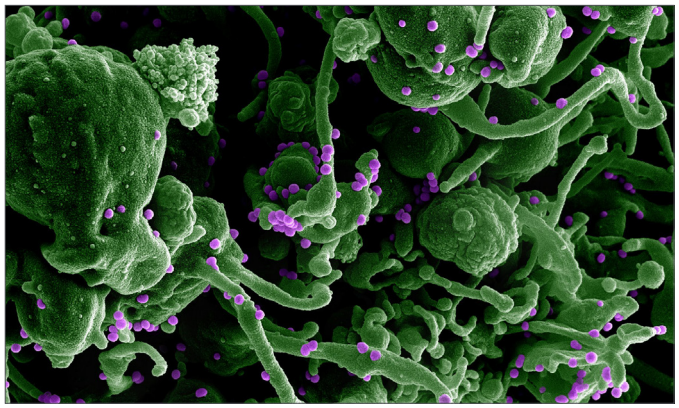
5-methylcytidine modulates innate immunity in self-amplifying RNA vaccines [5]

VLP Therapeutics, Boston University, and NIH researchers reported that incorporating modified base 5-methylcytidine (5mC) into replicon-based saRNA COVID-19 vaccines reduced excessive innate immune activation via suppressing type I interferon production by plasmacytoid dendritic cells, while maintaining strong adaptive responses.

CLINICAL TRIALS

IAVI's rVSVΔG-LASV-GPC Lassa vaccine safe and immunogenic in Phase 1 trial [6]

A first-in-human Phase 1 trial of IAVI's rVSV vector-based Lassa virus vaccine candidate demonstrated an acceptable safety profile and robust, durable immune responses after a single dose. The study enrolled 114 adults in the US and Liberia, who received one of four dose levels or placebo and were followed for 12 months. Humoral and cellular responses were robust across all dose levels, with antibodies cross-reactive to multiple Lassa virus lineages. No vaccine-related serious adverse events were observed.



Better protection but more reactogenicity in Phase 3 trial of Moderna's mRNA influenza vaccine [7]

A randomized trial of more than 18,000 adults aged 18–64 years compared a modified mRNA influenza vaccine with a licensed inactivated vaccine during the 2022–2023 season. The mRNA vaccine reduced laboratory-confirmed influenza by

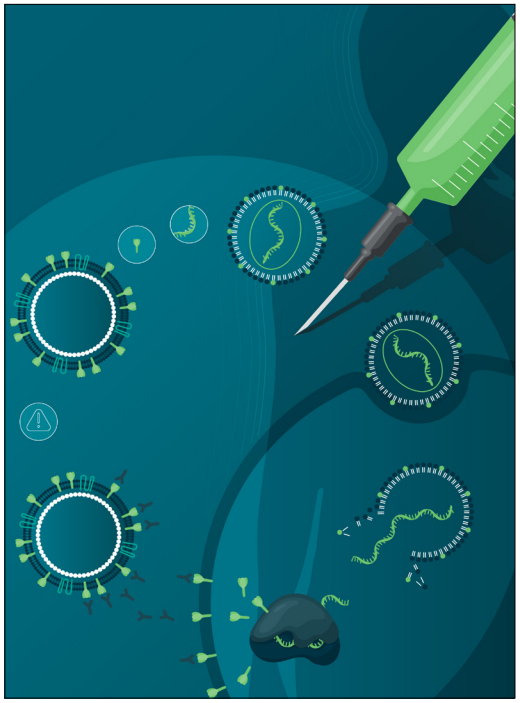
60–67%, versus 44–54% for the traditional vaccine. However, local and systemic reactions were more frequent. Serious adverse events were rare and comparable between groups, with no myocarditis cases observed at 6 months follow up.

Greater risk of cardiac complications in children after COVID-19 infection than vaccination [8]

A retrospective cohort study of nearly 14 million children aged under 18 in England assessed short- and long-term risks of rare cardiovascular and inflammatory complications following COVID-19 infection or BNT162b2 vaccination. Over 6 months, infection was associated with 2.24 additional myocarditis or pericarditis cases per 100,000, compared with 0.85 after vaccination.

RTS,S/AS01E malaria vaccine maintains effectiveness in real-world use [9]

A Phase 4 surveillance study across Ghana, Malawi, and Kenya found that the RTS,S/AS01E malaria vaccine demonstrated real-world effectiveness consistent with clinical trial results. Researchers followed 45,000 children under 5 for 1 year after completion of the three-dose primary schedule. Adjusted incidence rate ratios showed a



30% reduction in malaria and a 58% reduction in severe malaria among vaccinated children.

New human challenge models for hMPV, RSV B, and SARS-CoV-2 Omicron BA.5 [10]

hVIVO reported data from several newly developed human challenge models at the World Vaccine Congress Europe. The company presented findings from its contemporary-strain hMPV model, its SARS-CoV-2 Omicron BA.5 model, and its first RSV B challenge model.

THERAPEUTIC VACCINES

COVID-19 mRNA vaccination linked to longer survival in cancer immunotherapy patients [11]

In a retrospective analysis, researchers from the University of Florida and the University of Texas MD Anderson Cancer Center reported that receiving a COVID-19 mRNA vaccine within 100 days of initiating immune checkpoint inhibitor therapy for advanced non-small cell lung cancer or metastatic melanoma was associated with significantly improved survival. The researchers hope to confirm the findings in a prospective, randomized trial.

Intranasal nanogel HPV vaccine shows therapeutic activity against cervical cancer in preclinical models [12]

Researchers at Chiba University developed a cationic nanogel–based intranasal therapeutic vaccine targeting the HPV16 E7 oncoprotein and demonstrated antitumor activity in mice and macaques. In mice, intranasal vaccination slowed tumor growth and induced strong E7-specific CD4+ and CD8+ T cell responses in cervicovaginal tissue. In macaques, four intranasal doses administered via a human-compatible spray device elicited robust and sustained cervical mucosal immunity, including persistent E7-specific cytotoxic T cells.

MANUFACTURING INNOVATION

CSL Seqirus supports local production of cell-based influenza vaccines in Saudi Arabia [13]

CSL Seqirus entered a collaboration with the Saudi Ministry of Health to supply seasonal and pandemic cell-based influenza vaccines and to support the establishment of local manufacturing capacity. Working with Vaccine Industrial Company, Seqirus will help set up production at a facility in Sudair City and assist in building pre-pandemic vaccine stockpiles for high-risk groups, alongside an advance purchase agreement for broader pandemic immunization.

MARKET TRENDS

Moderna secures $1.5B loan and outlines strategy amid declining vaccine revenue [14]

Moderna announced it has obtained a $1.5 billion, 5-year loan facility from Ares Management Credit Funds as it restructures its pipeline and aims to break even by 2028. The company reported continued revenue declines in a post-pandemic market after limited market uptake of its RSV vaccine and disappointing clinical trial results for its CMV program. The company's 3-year strategy targets up to 10% revenue growth in 2026, driven by upcoming seasonal vaccines for norovirus, influenza, and a combined flu/COVID candidate.

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