FROM THE ANALYST'S COUCH

The mRNA vaccine development landscape for infectious diseases

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The Pfizer/BioNTech and Moderna mRNA vaccines were authorized for emergency use less than one year after the emergence of COVID-19, demonstrating the incredible development speed of the mRNA platform technology. However, while the versatility of the mRNA platform could allow for worldwide development of new vaccines, constraints including restricted intellectual property (IP), high cost of goods, raw material bottlenecks and lack of trained staff limit access to mRNA vaccines in low- and middle-income countries (LMICs).

Here, we provide a perspective on the global state of mRNA vaccine development for infectious diseases, and the manufacturing capabilities needed to enable vaccine access to combat ongoing/future pandemic and epidemic threats.

mRNA vaccine development landscape

Vaccine developers. At present, around 90 lead developers of mRNA vaccines have been identified in a global landscape evaluation (see Supplementary information for details on data analysis). These lead developers have 137 mRNA vaccine candidates in the pipeline; 76% in preclinical/exploratory and 24% in clinical development (Supplementary Table 1). However, this is rapidly changing.

As shown in FIG. 1a, the majority of mRNA vaccine development is being led by biopharma companies based in Asia and Oceania or North America.

Often, mRNA vaccine development is accomplished through a consortium of many participants from different sectors, illustrating the complexity of IP rights and access to technical knowledge. Shortly after the emergence of COVID-19, some partnerships were established between pharmaceutical companies and members of the Developing Countries Vaccine Manufacturers Network, allowing a pathway for technology transfer to companies that produce vaccines in LMICs.

mRNA platform diversity. Two major technical considerations for mRNA vaccine development are the mRNA construct format that encodes the immunogen and the delivery vehicle that facilitates cellular entry and expression. Specific similarities and differences between mRNA platforms are beyond the scope of this article; however, high-level trends in approaches being taken by the lead developers are illustrated in FIG. 1b. Modified nucleosides included in the two licensed mRNA COVID-19 vaccines are highly utilised in other development programmes. There is a similar number of self-amplifying RNAs in development, but their promise of greater potency has yet to be demonstrated in clinical trials. Finally, fewer non-modified nucleoside formats are in development. Their promise of greater potency has been hindered by a small tolerability window, and by data from CureVac's recent phase III trial of their unmodified vaccine candidate for COVID-19 that showed efficacy levels apparently lower than modified nucleoside vaccines.

With regards to delivery vehicles, >50% of mRNA vaccines in development use lipid nanoparticle (LNP) formulations (FIG. 1b), which were clinically validated by small interfering RNA (siRNA) therapeutics.

The IP landscape regarding LNP formulations is complicated and the supply chain for some components can be limited. Moreover, alternative delivery vehicles such as cationic nanoemulsions, lipidoids and polymers are rapidly advancing into the clinic. Developers claim advantages in stability, potency, immunogenicity and valency with new formulations, but this has yet to be proven.

For prophylactic vaccines, safety, tolerability and immunogenicity are factors that will probably lead to further product advancement. As >1 billion doses have already been administered, modified nucleoside mRNAs formulated in LNPs are most likely to be used in the foreseeable future for rapid responses to emerging epidemic or pandemic threats.

Pathogen targets. SARS-CoV-2 is the primary target for most lead vaccine developers (>80%), while ~14% are moving forward with other lead vaccine candidates and 6% did not disclose their pipeline. A similar trend is seen in the targets of vaccines that have reached clinical trials (FIG. 1c).

Unfortunately, vaccine developers have little commercial incentive to pursue programmes against many existing epidemic pathogen threats, and <10% have initiated vaccine programmes against WHO and CEPI priority pathogens (excluding SARS-CoV-2). Influenza vaccines, which do have commercial potential, make up the second most frequent pathogen target for development after SARS-CoV-2. mRNA vaccines against bacterial and parasitic targets are in early preclinical studies.

Manufacturing footprint. Regional vaccine manufacturing and distribution sites can prevent barriers to vaccine access created by national and economic interests. The majority of mRNA manufacturing sites are located or announced in North America, Europe, and Asia and Oceania (>15 each) (FIG. 1d). Africa and Latin America also joined the race and recently announced mRNA manufacturing sites (>3), suggesting a growing interest in these regions. Before the COVID-19 pandemic, commercialization of mRNA vaccines was focused on high-cost personalized cancer vaccines, and prophylactic vaccine development was slow and limited. With the demonstration of large-scale manufacturing of mRNA vaccines during the COVID-19 pandemic, the creation of local manufacturing capabilities holds promise for more equitable access to COVID-19 and other vaccines.

The WHO has sought to facilitate mRNA vaccine technology hubs in developing countries (for example, the South African consortium to establish the first COVID-19 mRNA vaccine technology transfer hub in Africa). This ambitious initiative is described as a training centre for mRNA

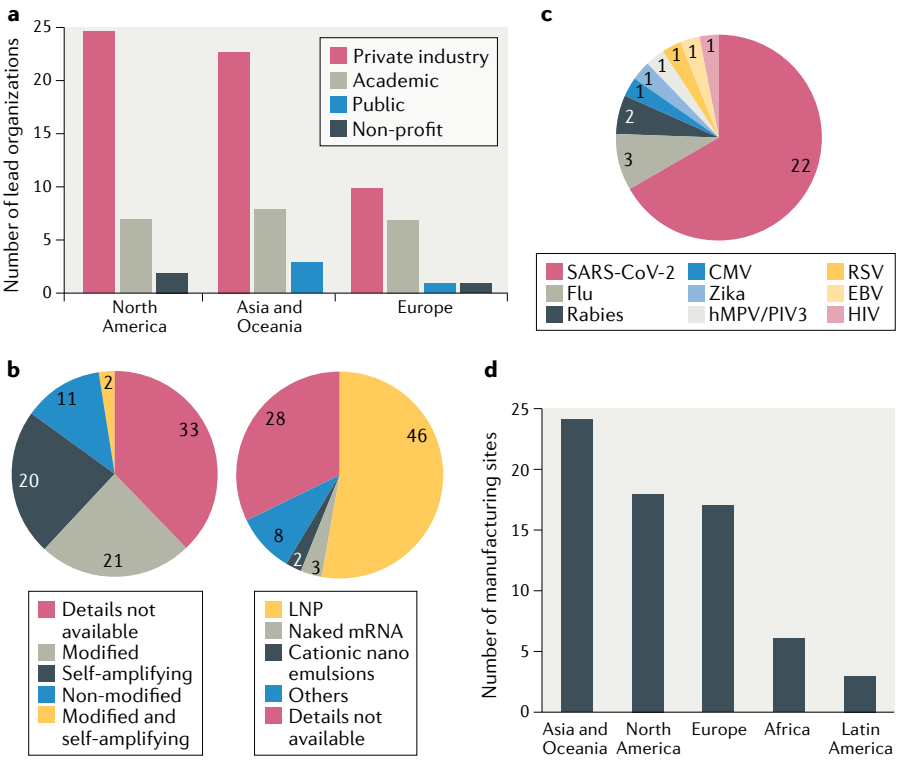

Fig. 1 | **The mRNA vaccine development landscape. a** | Lead developers by geographic area, sector and maturity. **b** | Lead developers by mRNA technology format and delivery vehicle. **c** | Targets of mRNA vaccines in clinical development. **d** | mRNA vaccine manufacturing footprints. LNP, lipid nanoparticle. Data sourced 4 February 2022. See Supplementary information for details.

vaccine manufacturing. Similarly, the Pan American Health Organization (PAHO) has selected centres in Argentina and Brazil to develop COVID-19 mRNA vaccines, and private companies including Moderna and BioNTech have announced their intention to build manufacturing capacity in Africa with sizeable investments.

A major bottleneck is the supply of raw materials and access to critical ingredients, including plasmid DNA templates, deoxynucleotide triphosphates and in-vitro-transcription, capping and DNA digestion enzymes. Limited capacity worldwide is driving increased costs for these raw materials, negatively affecting the rollout of approved COVID-19 mRNA vaccines. The COVAX Marketplace has been created to address shortages in raw materials and consumables by anonymously linking suppliers that have excess reagents with vaccine developers/manufacturers in need of critical supplies.

Challenges. For next-generation mRNA vaccines to have impact, several challenges should be considered (Supplementary Box 1). With regard to the targeted disease, multivalency has yet to be established across strains and other pathogens. Clinical questions include reactogenicity and its implications for risk–benefit profiles outside of a pandemic setting, immunogenicity (pathogens other than SARS-CoV-2 may need a greater cellular response) and durability of protective immunity. For delivery, intramuscular administration requires skilled personnel, and products with stability at 4 °C or ambient temperature in liquid formulation are currently not available. Cost-effective and sustainable manufacturing methods are also lacking. Most of the clinical-stage pipeline of vaccines is owned by entities in North America and Europe, and there is uncertain freedom to operate in various countries owing to IP restrictions. Some entities are also based in LMICs and face problems related to limited access to regulated facilities for clinical trial grade material production.

Outlook

The COVID-19 pandemic has accelerated the development of mRNA vaccine technology platforms. With the demonstrated clinical efficacy of the mRNA-based Pfizer/BioNTech and Moderna vaccines, there is promise for the use of such technology in the prevention and control of future epidemics and pandemics. The rapid response potential of mRNA vaccine platforms, both in terms of construct generation against novel pathogens and scale-up using cell-free manufacturing systems, make them highly suitable for epidemic/pandemic response. Multivalent approaches, which many mRNA developers are actively investigating, along with systematic immunogen design approaches, could expand the breadth of protection. Furthermore, the substantial increase in experience with selected mRNA technologies, including nucleoside-modified mRNA formulated with LNPs, could help facilitate regulatory pathways using these mRNA platforms for future pathogen targets in outbreak situations. Thus, mRNA vaccine platforms are ideally suited to support the ambition to respond to future epidemics/pandemics within 100 days.

While rapid response potential is a critical feature of mRNA platforms, the COVID-19 pandemic has demonstrated the need for equitable access to have maximum impact. Improvements in storage and stability, production costs, and wider geographic distribution of research, development and manufacturing are required for mRNA technology to ensure a more effective global response to future epidemics or pandemics. Progress in these areas is likely given the current private and public interest and investment in mRNA technologies. Efforts to diversify and distribute global research, development and manufacturing capabilities are increasing to try to address some of these global disparities. Although many technological and non-technological challenges remain, mRNA-based vaccines will certainly play a crucial role in the future.

CEPI has laid out an ambitious US$3.5 billion plan to tackle future epidemics and pandemics, and is committed to strengthening, accelerating and expanding the ability of vaccine technology platforms such as mRNA to support this strategy. A new funding opportunity for the development of RNA vaccine platform technologies and vaccine library development against emerging and select endemic infectious diseases has been recently announced.

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Competing interests

CEPI is a funder of different vaccine platforms, including mRNA.

Supplementary information

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