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A Review of the Development of Vaccines for Newly Developing Infectious Illnesses

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ABSTRACT

The emergence and rapid spread of newly developing infectious illnesses, exemplified by the coronavirus disease 2019 (COVID-19) pandemic, has highlighted the critical need for efficient vaccine development and deployment strategies. Historical and recent outbreaks, including dengue, cholera, typhoid, Ebola, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), demonstrate the persistent global vulnerability to emerging pathogens, exacerbated by urbanization, globalization, and inadequate public health infrastructures. Vaccine development faces numerous challenges, from virus surveillance and pharmacovigilance to ensuring equitable access, especially in low- and middle-income countries. Traditional vaccine development pathways, often spanning 5-10 years, are inadequate during pandemics, necessitating rapid-response platforms like mRNA and DNA technologies. The unprecedented speed of COVID-19 vaccine development, achieving initial efficacy trials within 300 days, reflects the success of collaborative global efforts, advanced platforms, and funding mechanisms such as CEPI and COVAX. Despite these advancements, hurdles remain in regulatory harmonization, manufacturing scalability, supply chain logistics, and vaccine acceptance. Lessons learned from COVID-19 emphasize the importance of flexible vaccine platforms, proactive investment in research and infrastructure, and global coordination to mitigate future pandemics. Vaccine-induced herd immunity, non-inferiority trials against approved vaccines, and considerations of equitable distribution are essential for comprehensive public health benefits. Standardizing labelling, tracking vaccine safety, and implementing no-fault compensation mechanisms are pivotal in fostering public trust. Ultimately, an integrated approach involving scientists, regulators, health authorities, and funders is imperative to streamline vaccine development and ensure timely and fair access in the face of evolving infectious threats.

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Introduction

Throughout history, infectious viral illnesses have posed a hazard to humankind due to their frequent emergence and re-emergence. The emergence and spread of animal viruses as existential human threats have been accelerated by a number of interconnected and synergistic factors, such as demographic trends and high-density urbanization, modernization that favours high mobility of people by all modes of transportation, large gatherings, altered human behaviours, environmental changes with modification of ecosystems, and inadequate global public health mechanisms. When the "Spanish flu" struck in 1918, there

were an estimated 1.8 billion people on the planet. By 2050, it is expected to have grown by more than 25% from the current population of 7.8 billion in 2020 to 9.9 billion (https://www.worldometers.info). With over 100 million cases and over 2 million fatalities, the best chance for pandemic control now appears to lie in the addition of a vaccine or vaccines to current countermeasures [1][2][3].

The coronavirus disease 2019 (COVID-19) pandemic was caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which spread throughout the world in less than six months and had a high death rate among the elderly and people with related co-morbidities. The global economy has been seriously impacted by the outbreak. The only control methods available, other from lockdowns, have been a number of restrictive and ineffective mitigation strategies, including mask wearing, self-distancing, travel limitations, and avoiding crowds. With over 100 million cases and over 2 million fatalities, the best chance for pandemic control now appears to lie in the addition of a vaccine or vaccines to current countermeasures [4][5].

New and resurfacing viral illnesses

Traveling the world and becoming more interdependent has made controlling these infectious diseases more difficult, even with advancements in countermeasures (diagnostics, treatments, and vaccines). Human health and international stability are at risk from emerging infectious diseases (EIDs) [6][7]. A perspective on the emergence and features of coronavirus epidemics, with a focus on the SARS-CoV-2 pandemic, can be gained by reviewing developing pandemic diseases throughout history [8][9].

A short list of emerging viral infectious diseases that occurred between 1900 and 2020 is included in Table 1 to demonstrate the ongoing susceptibility of populations to new and re-emerging infections, as well as the potential for these diseases to quickly develop into catastrophic outbreaks and pandemics.

The four dengue virus strains (DENV1–4) are already co-circulating in the majority of dengue endemic locations, making dengue a growing global public health concern. Dengue infections and sickness have been steadily increasing due to a combination of factors such as population growth, the expansion of locations that are conducive to Aedes mosquito species, and the ease of travel. Dengue is widespread in over 100 nations worldwide. Up to 400 million people contract dengue every year. About 100 million individuals are infected, and 22,000 of them pass away from severe dengue [10][11][12].

Numerous vaccinations have been created. Twenty nations have licensed Sanofi Pasteur's Dengvaxia, a dengue vaccine based on the yellow fever 17D backbone, but acceptance has been slow. An international review of the vaccine performance profile, new WHO recommendations for use, and controversy in the Philippines involving the government, regulatory bodies, Sanofi Pasteur, clinicians who test and administer the vaccine, and parents of vaccinated children were all prompted by a safety signal in dengue-seronegative vaccine recipients [13][14]. Since 1817, there have been seven worldwide pandemics of cholera, which are caused by pathogenic strains of Vibrio cholerae. Notably, the seventh pandemic began in 1961 [15]. Chloramphenicol, furazolidone, trimethoprim-sulfamethoxazole, nalidixic acid, tetracycline, and fluoroquinolones are only a few of the helpful antibiotics that have caused antimicrobial resistance throughout Asia and Africa over time. Numerous vaccines have been created and approved by the WHO; these make up a worldwide stockpile backed by Gavi that may be quickly distributed during epidemics [16].

The Gram-negative bacterium Salmonella enterica subsp. enterica serovar Typhi (S. Typhi) is the cause of the serious illness known as typhoid fever. The prevalence of S. Typhi strains that are resistant to antibiotics has increased. In Sindh, Pakistan, a unique extensively drug-resistant (XDR) S. Typhi clone was first observed to arise and spread on a broad scale. Since then, reports of its dissemination have been made in India, Bangladesh, Nepal, the Philippines, and Iraq [17][18][19][20]. By lowering the number of typhoid fever cases requiring antibiotic treatment, the effective development of enhanced typhoid vaccines (conjugation of the Vi polysaccharide with a carrier protein) with enhanced immunogenicity and efficacy, including in children under the age of two, will aid in the control of typhoid, particularly in XDR areas [21][22].

A paradigm for developing vaccines against newly emerging infectious illnesses

Over the past 20 years, our understanding of newly developing infectious illnesses has changed. Even though there were only a few deaths and infections during the 2002 SARS-CoV outbreak, its high mortality and transmissibility caused major disruptions around the world. As the development of vaccines began, the epidemic came to an end. Since wet markets were shut down and civet transmission to people stopped, the disease has not resurfaced. As a result, research on SARS-CoV vaccines was discontinued, and funding was reduced. In a phase 1 clinical trial, only a DNA vaccine and a complete inactivated vaccine were examined [23][24]. A vaccination for an infectious agent takes five to ten years to create using a conventional research and development pathway. When a new disease emerges during an epidemic, this

Table 1: Emerging Viral Infectious Diseases Occurred Between 1900 And 2020

Year	Name	Deaths	Comments
1918	'Spanish influenza'	50 million -100 million	1918: H1N1, 1957–1958 (H2N2), 1968 (H3N2). 2009 (H1N1)
1931	Rift Valley Fever	Overall CFR < 1%; ~50% for hemorrhagic fever	Contact with mosquito-borne diseases blood or organs of infected animals
1937	West Nile fever	CFR ~5%	Mosquito-borne, global outbreaks 1999–2010 in USA
1969	Acute hemorrhagic conjunctivitis	Rare	First identified in 1969; pandemic in 1981; frequent outbreaks worldwide
1976–2020	Ebola hemorrhagic fever	>15,000; CFR 75%	Primarily identified in 1976; outbreak (2013–2016) in West Africa, (2018) in Democratic Republic of Congo
1981	HIV/AIDS	~37 million	Ongoing pandemic
1996	Avian flu	CFR > 60%	H5N1 and H7N9 viruses from poultry; several outbreaks worldwide; last outbreak in China in 2018
1999	Nipah fever	<1,000	Outbreaks in Malaysia, Singapore, Bangladesh and India
2002	SARS	813; CFR ~ 10%	Contained and did not become a pandemic
2009	H1N1; H7N9 'swine flu'	284,000;	Pandemic
2012	MERS	935; CFR 34.4%	Outbreak (2012–2019), Eastern countries
2015	Zika	Unknown	Mosquito-borne
2019–2022	COVID-19 (SARS-CoV-2)	>2.3 million; CFR 2–10%; high in elderly and those having comorbid conditions	Pandemic: human to human, animal-to-animal, animal-to-human

CFR, case-fatality rate.

strategy is ill-suited to meet the demands. The 2014 Ebola outbreak, which claimed 11,325 lives and lasted more than 24 months, was lengthy enough to allow for the creation and testing of Ebola vaccines, with one vaccine (among several) demonstrating efficacy near the conclusion of the outbreak [25][26].

The COVID-19 pandemic is noteworthy since the entire research and development process was completed in less than 300 days, from the initial sequencing of the SARS-CoV-2 virus to the preliminary evaluations of vaccine efficacy trials. WHO called for accelerating the development and assessment of potential vaccines in mid-2014 due to growing worries of uncontrolled transmission during the Western African Ebola outbreak that lasted from 2013 to 2016 [27].

In order to prepare for "disease X," CEPI also made investments in cutting-edge rapid response platforms, like mRNA and DNA technology, which could go from sequencing to clinical trials in a matter of weeks as opposed to months or years. These platforms proved helpful when COVID-19 was deemed a global health emergency in January 2020 and a pandemic in March 2020 [18][19][20][21][27].

A number of vaccine development initiatives have been funded by CEPI, including those of Moderna, Inovio, Oxford-AstraZeneca, and Novavax. By reducing financial risk for vaccine inventors, upfront funding enabled these organizations to simultaneously create scaled production methods and move vaccine concepts to clinical trials [22].

Platforms for vaccinations and vaccines against newly developing infectious illnesses

Vaccines are the most reliable way to reduce the danger of pandemics and epidemics and are the cornerstone of managing infectious disease outbreaks. An outbreak can be contained more quickly the sooner a vaccination is made available [23][24]. The typical vaccine development cycle is not appropriate for the demands of explosive pandemics.

However, new vaccination platform technologies could shorten that cycle and enable the faster development, testing, and production of many vaccines as in Table 2 [25][26]. Using mRNA technology, two COVID-19 vaccines were created (Pfizer–BioNTech and Moderna). Both vaccines have demonstrated good efficacy and safety, and they currently have conditional marketing clearance from the European Medicines Agency (EMA) and Emergency use authorization (EUA) from the US Food and Drug Administration (FDA) [27][28].

No DNA vaccine has received approval for use in humans, despite the fact that a number of them are licensed for use in veterinary applications and that they have demonstrated safety and immunogenicity in human clinical studies. For the same pathogen, recombinant proteins can have a wide range of designs (subunits, virus-like particles, etc.) [29].

They are frequently made using adjuvants, but their development timeframes are longer. Hepatitis B and human papillomavirus vaccines based on virus-like particles are safe, highly immunogenic, effective, and simple to produce in large quantities. Additionally, the technology is simply transferable. Each pathogen has its own live attenuated vaccines (e.g., SARS-CoV-2, polio, cholera) or whole inactivated pathogens (e.g., SARS-CoV-2, polio). These vaccines may also need to be manufactured at biosafety level 3 depending on the pathogen (at least for COVID-19 and polio), which could restrict the ability to transfer knowledge to increase global manufacturing capacity.

Speed of development, ease of manufacturing and scaling up, ease of logistics (administration, storage conditions, and presentation), technology transfer to other manufacturers to guarantee global supply, and pricing of goods are additional equally significant factors. Lastly, regulatory bodies only authorize vaccinations, not platforms. Every vaccination is unique [30][31][32][33].

As part of the COVID-19 vaccine response, efforts are being made to standardize vaccine labelling so that different countries and regions can use them interchangeably, date of production instead of expiration so that shelf life can be tracked, three-dimensional bar coding to allow for the updating of critical information, standard indemnity and liability language that would allow agreement with all manufacturers, a no-fault compensation mechanism for serious adverse events related to vaccine administration, and regulatory harmonization. These measures are crucial and must be optimized for future outbreaks.

The route to EUA, certification, and beyond

Large pharmaceutical or biotechnology firms have carried out effectiveness trials in nations or areas with the highest SARS-CoV-2 incidence rates, with assistance from organizations like CEPI or initiatives like Operation Warp Speed. The same organizations have also pledged funds for risky large-scale manufacturing. It is unclear if vaccine candidates not included in the initial round of testing and approvals will be able to advance to EUA and licensure based only on the outcomes of randomized clinical efficacy trials with clinical endpoints, given that there are currently over 60 vaccine candidates in clinical trials and an additional 170 in preclinical development (WHO COVID-19 vaccine landscape). Ethics committees and regulators may determine that additional approvals will require non-inferiority clinical studies against comparator vaccines with established clinical efficacy [34].

The population-level protective impact of vaccines may be understated by randomized controlled trials. This would happen if the COVID-19 vaccine not only directly protects people but also lowers the spread of the virus from person to person, protecting unprotected people and improving protection for vaccinated people who come into touch with vaccinated people. Trials that are individually randomized and studies that do not account for the geographic distribution of persons in the population will miss vaccine-induced herd protection, which may be essential to a vaccine's public health benefit [35].

The risk of speed in the EUA and licensing approval process

Traditionally, the country's national regulatory body, like the US FDA, or a centralized process through the EMA approves vaccines. The manufacturing company can submit a dossier for WHO prequalification after being granted licensure by a strict or operational national regulatory body in the nation of manufacture. WHO prequalification was not necessary for first use of SARS-CoV-2 vaccines for COVAX, nevertheless, if they had been granted WHO EUL. The WHO, the European Commission (EC), and France announced the Access to COVID-19 Tools Accelerator in April 2020, with COVAX as one of its three pillars. UNICEF (United Nations International Children's Emergency Fund), the biggest buyer of vaccines for Gavi, the Vaccine Alliance, is able to acquire vaccines that have been granted WHO EUL [36].

Manufacturing: How to produce more quickly

A number of companies have licensed or contracted the production of COVID-19 vaccines to other manufacturers, including Chinese Sinovac with Butantan (Brazil) and BioFarma (Indonesia); Moderna with Lonza (Switzerland); Johnson & Johnson with Biological E (India); and AstraZeneca and Novavax with the Serum Institute (India) and SK Bioscience (Korea). It was hoped that the license and contract manufacturing agreements would enable the

Table 2: Different vaccine platforms for viral infectious diseases

Vaccine	Developed for	Shortcomings and advantages
Live attenuated	Influenza; yellow fever; poliomyelitis	Biosafety level 3 manufacturing plant for handling dangerous viruses
Whole inactivated	Influenza; poliomyelitis; COVID-19	Biosafety level 3 manufacturing plant for dangerous viruses; needs adjuvant; HPB regimens possible
DNA		Poorly immunogenic; electroporation requires device; difficult use for rollout; HPB regimens possible
mRNA	COVID-19	Rapidly adaptable to new emerging viruses; HPB regimens possible; ultracold chain currently unpractical for large-scale use in resource-limited settings
Recombinant vectors		
Ad5		Preexisting immunity to Ad5
ChAd3		Cell-line-produced; adaptable construct to emerging virus in 5–6 months; HPB regimens possible
ChAdOx1	COVID-19	
Ad26	COVID-19	
Live attenuated		
MVA	Ebola	MERS
VSV	Ebola	COVID-19[a]; Lassa fever;
Measles		MERS; Lassa fever;
		COVID-19[a]
Protein based		
Virus-like particle	COVID-19	emerging viruses; likely needs adjuvant
Monomer; dimer	COVID-19;	HPB regimens possible
trimer	Influenza; MERS;	
Molecular clamp	COVID-19	

production of enough vaccine doses to give at-risk communities around the world fair access. The necessity for quick proof of concept took precedence over the optimization of more pragmatic aspects of vaccine application, supply, and dosing due to the pandemic's constraints and the need for quicker COVID-19 vaccine development. Both VSV-EBO Ebola vaccine and COVID-19 mRNA vaccine require ultra-cold chain storage [37].

Ensure that everyone has equal access to vaccinations and treatments

The goal of 2030 Agenda for Sustainable Development was to ensure that no one was left behind, especially in low-income nations. By the end of 2021, COVAX hoped to supply participating nations with at least 2 billion doses of the WHO-approved vaccine, or around 20% of each nation's vaccination requirements. The majority of the vaccine would be distributed to 92 LMICs via an AMC organized by Gavi. COVAX recently reported that it secured agreements for enough doses to reach the 2030 target, and it now looks like the USA will participate [38].

Concluding thoughts

Future vaccines against new infectious illnesses and pandemic pathogens must be developed using the lessons learned from the COVID-19 pandemic. Vigilance, surveillance, and readiness for vaccine development and implementation are necessary due to the ongoing threat of emerging pathogens. These cross-cutting activities must be executed flawlessly by epidemiologists, scientists, developers, human and veterinary health authorities, regulators, and funders. Stakeholders in global health have gained knowledge about the effective development of vaccines, but they still have a lot to learn about producing and utilizing them with appropriate consideration for access and fairness.

Authors' contributions

ICMJE criteria	Details	Author(s)
1. Substantial contributions	Conception, OR	1,6
	Design of the work, OR	2,4,5
	Data acquisition, analysis, or interpretation	3
2. Drafting or reviewing	Draft the work, OR	1,2,6
	Review critically for important intellectual content	3,4,5
3. Final approval	Approve the version to be published	1,2,3,4,5,6
4. Accountable	Agree to be accountable for all aspects of the work	1,2,3,4,5,6

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Declarations

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Competing interests
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