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VACCINE DEVELOPMENT FOR EMERGING INFECTIOUS DISEASES

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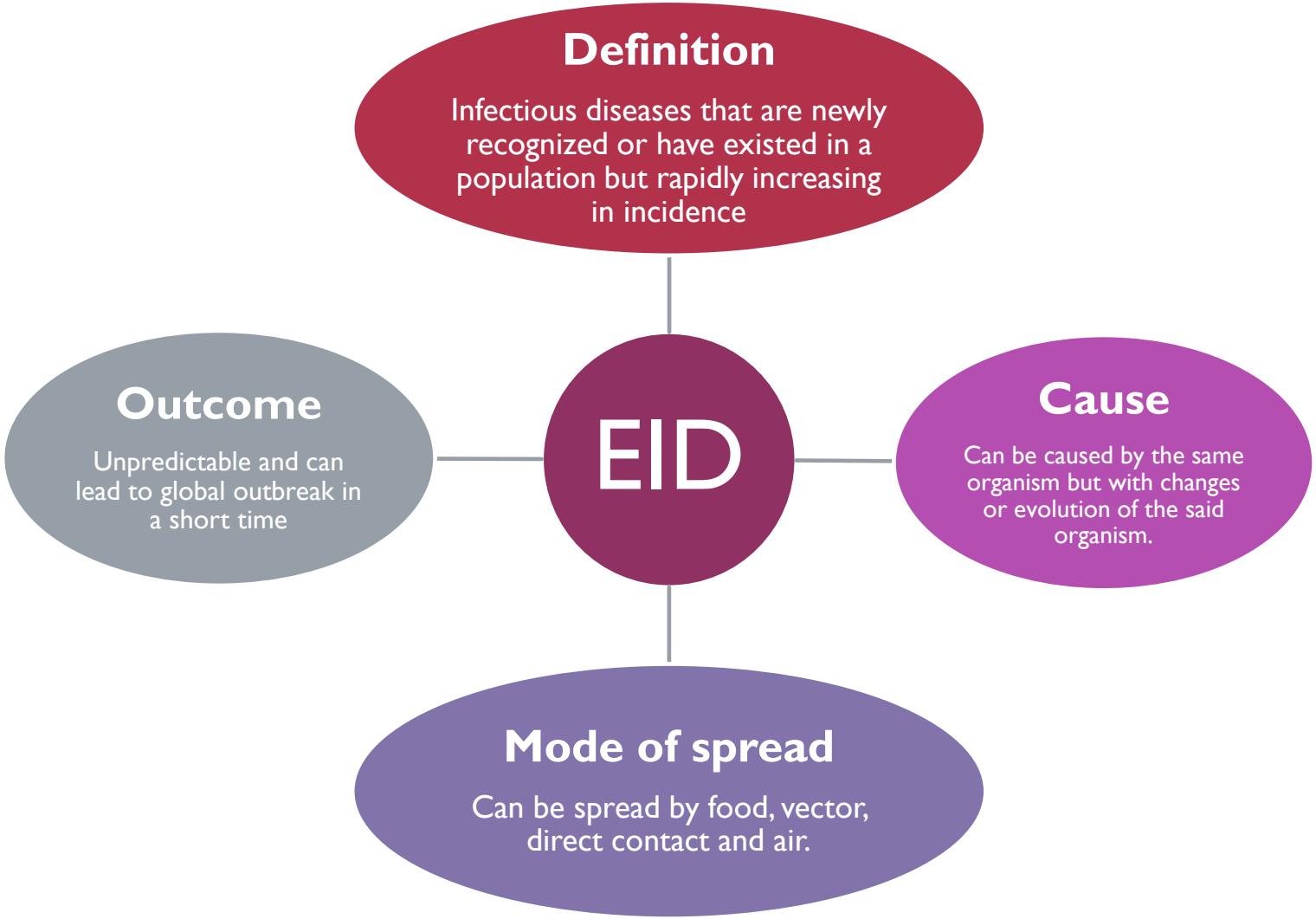
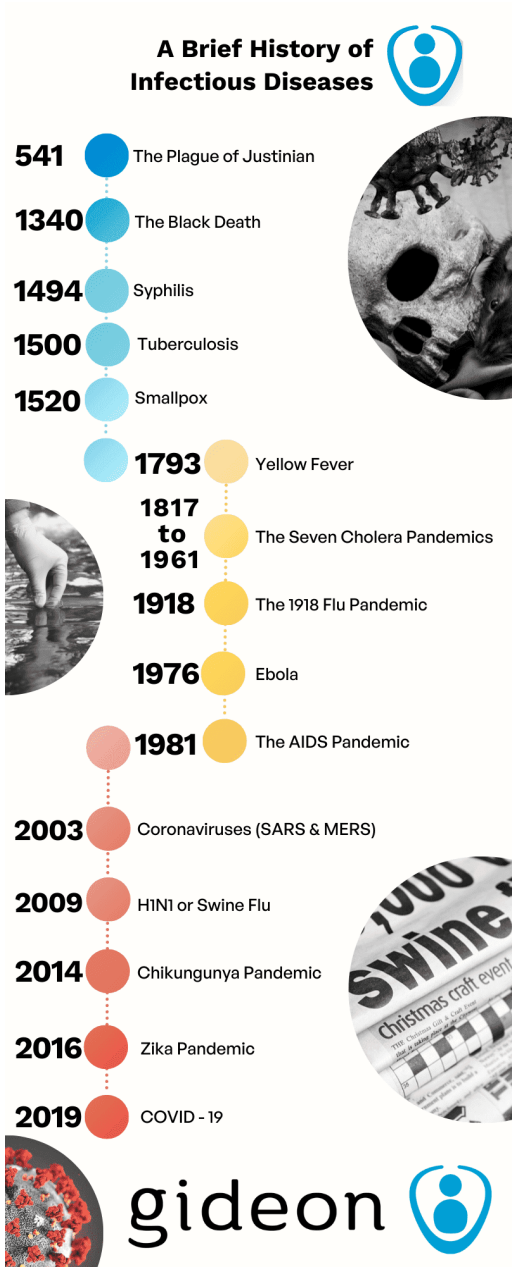
EMERGING INFECTIOUS DISEASE



HISTORY OF EID



EID has been threatening mankind since neolothic revolution (12,000 years ago)

Known ancient EID including Black death, smallpox killed substantial portions of humans ever known.

The deadliest pandemic ever recorded was during 1918 flu pandemic, killing 50 million people

Cholera

- Global mortality remains high to this day (1.4-4.3 million cases with 21,000-143,000 deaths per year), mostly occurred in Asia and Africa
- Antimicrobial resistance developed

Source: WHO; Hazel, K., *GIDEON*, 2022

HISTORY OF EID

Epidemic/pandemic worldwide with at least 1 million deaths

	Years	Rank*	Epidemics/pandemics	Disease	Causative agent	Death toll	Mode of transmission	Location
Classical era	165–180	8	Antonine Plague	Smallpox or measles	Smallpox virus *(Orthopoxvirus)*	5–10 million	Direct contact	Roman Empire
Middle ages	541–549	3	Plague of Justinian	Bubonic plague	*Yersinia pestis (Enterobacterales)*	15–100 million	Rodents and fleas	North Africa, Europe, and Western Asia
	735–737	14	735–737 Japanese smallpox epidemic	Smallpox	Smallpox virus *(Orthopoxvirus)*	2 million	Direct contact	Japan
	1346–1353	1	Black Death	Bubonic plague	*Yersinia pestis (Enterobacterales)*	75–200 million	Rodents, fleas and humans	Europe, Asia, and North Africa
Early Modern Era	1519–1520	9	1520 Mexico smallpox epidemic	Smallpox	Smallpox virus *(Orthopoxvirus)*	5–8 million	Direct contact	Mexico
	1545–1548	7	Cocoliztli epidemic of 1545–1548	Cocoliztli	Possibly smallpox, *Salmonella typhi and* measles	5–15 million	Direct contact	Mexico
	1576–1580	13	Cocoliztli epidemic of 1576	Cocoliztli		2–2.5 million	Direct contact	Mexico
	1629–1631	18	1629–1631 Italian plague	Bubonic plague		1 million	Rodents, fleas and humans	Italy
	1656–1658	16	Naples Plague	Bubonic plague	*Yersinia pestis (Enterobacterales)*	1.25 million	Rodents, fleas and humans	Southern Italy
Late Modern Era	1772–1773	15	1772–1773 Persian Plague	Bubonic plague		2 million	Rodents, fleas and humans	Persia
	1817–present	17	Cholera pandemic	Cholera	*Vibrio cholerae (Vibrionales)*	1 million+	Aquatic sources	Worldwide
	1855–1960	6	Third plague pandemic	Bubonic plague	*Yersinia pestis (Enterobacterales)*	12–15 million	Rodent and humans	Worldwide
	1918–1920	2	Spanish flu	Influenza A/H1N1	H1N1 Influenza A virus *(Alphainfluenzavirus)*	17–100 million	Aerosol transmission	Worldwide
	1918–1922	10	1918–1922 Russia typhus epidemic	Typhus	*Rickettsia prowazekii (Rickettsiales)*	2–3 million	Lice	Russia
Contemporary era	1957–1958	11	1957–1958 influenza pandemic	Influenza A/H2N2	H2N2 Influenza A virus *(Alphainfluenzavirus)*	1–4 million	Aerosol transmission	Worldwide
	1968–1969	12	Hong Kong flu	Influenza A/H3N2	H3N2 Influenza A virus *(Alphainfluenzavirus)*	1–4 million	Aerosol transmission	Worldwide
	1981–present	4	HIV/AIDS epidemic	HIV/AIDS	HIV *(Lentivirus)*	40 million (as of 2021)	Sexual and blood contact	Worldwide
	2019–present	5	COVID-19 pandemic	COVID-19	SARS-COV-2 *(Betacoronavirus)*	7–34 million (as of Nov 2023)	Droplet transmission	Worldwide

*Rank from the highest death toll

EID IN PANDEMIC

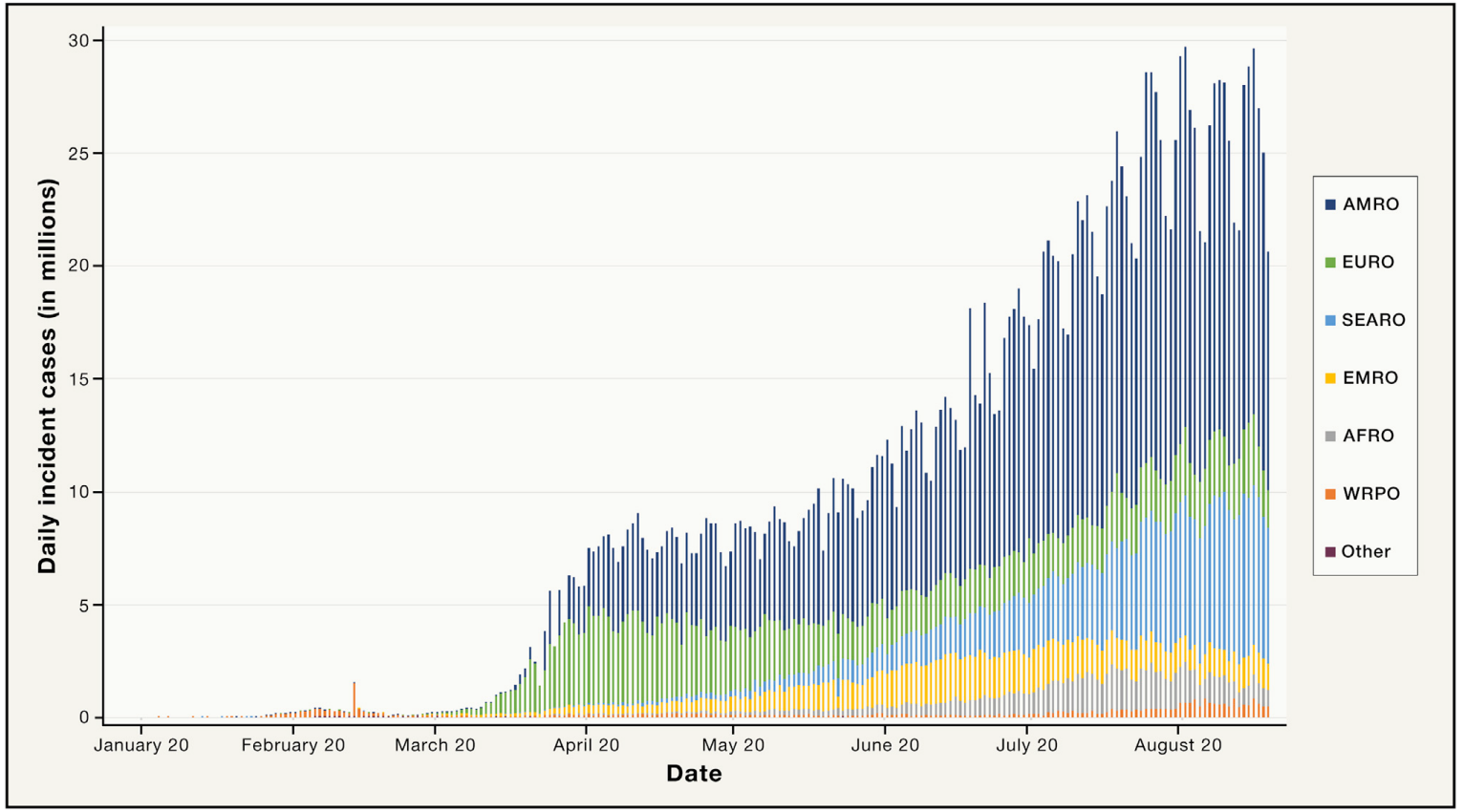


Figure 1. Global Daily Incident Cases of COVID-19 by World Health Organization Region as of August 18, 2020. WRPO, Western Pacific; AFRO, Africa; EMRO, Eastern Mediterranean; SEARO, Southeast Asia; EURO, Europe; AMRO, Americas.

Example of pandemic surge (COVID-19)

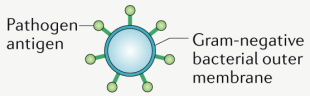
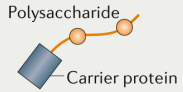
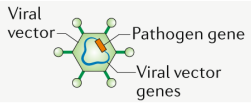
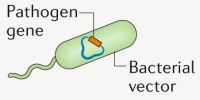
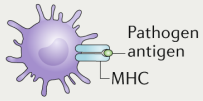
Europe and the Americas

- The pandemic exploded in March 2020, then blunted between March and May 2020, and then began to explode in the Americas and to a lesser extent in Europe in late May.

Generally, since May 2020, the pandemic increased significantly in the SEARO as well as the AFRO regions.

Source: WHO; Morens, D.M. and A.S. Fauci, 2020

VACCINES

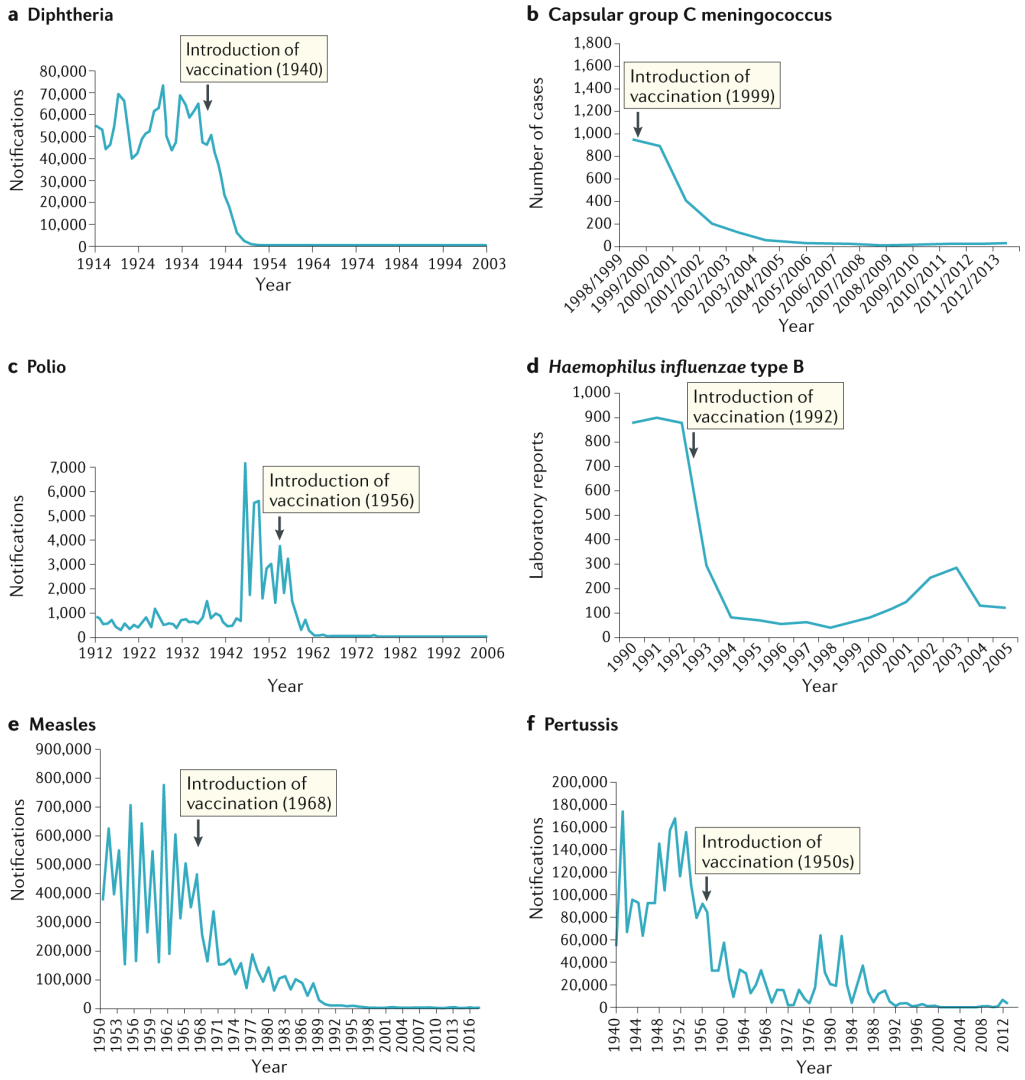
Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

Source: Pollard, AJ. And Bijker, EM., *Nature Reviews Immunology*, 2021.

- Best means to defuse pandemic and epidemic risk in outbreak management
- Faster the vaccine being deployed, faster the outbreak being controlled.

← Different types of vaccines

VACCINE IMPACT ON DISEASES



- Many diseases previously responsible for pediatric deaths eventually diminished.
- WHO estimates that 2-3 million lives are saved per year with implemented immunization programs
- Children mortality decreased globally from 93 deaths/1000 live births to 39 deaths per 1000 live births (1990-2018)

Note: The increase in reports of *H. influenzae* type B in 2001 led to a catch-up vaccination campaign, after which the incidence reduced. For pertussis, a decline in vaccine coverage led to an increase in cases in the late 1970s and 1980s, but disease incidence reduced again after vaccine coverage increased.

Figure: The impact of vaccination on selected diseases in the UK. The introduction of vaccination against infectious diseases such as diphtheria (part a), capsular group C meningococcus (part b), polio (part c), *Haemophilus influenzae* type B (part d), measles (part e) and pertussis (part f) led to a marked decrease in their incidence.

Source: Pollard, AJ. And Bijker, EM., *Nature Reviews Immunology*, 2021. Adapted from the Green Book, information for public health professionals on immunisation, Public Health England, contains public sector information licensed under the Open Government Licence v3.0.

COVID-19 VACCINE IMPACT

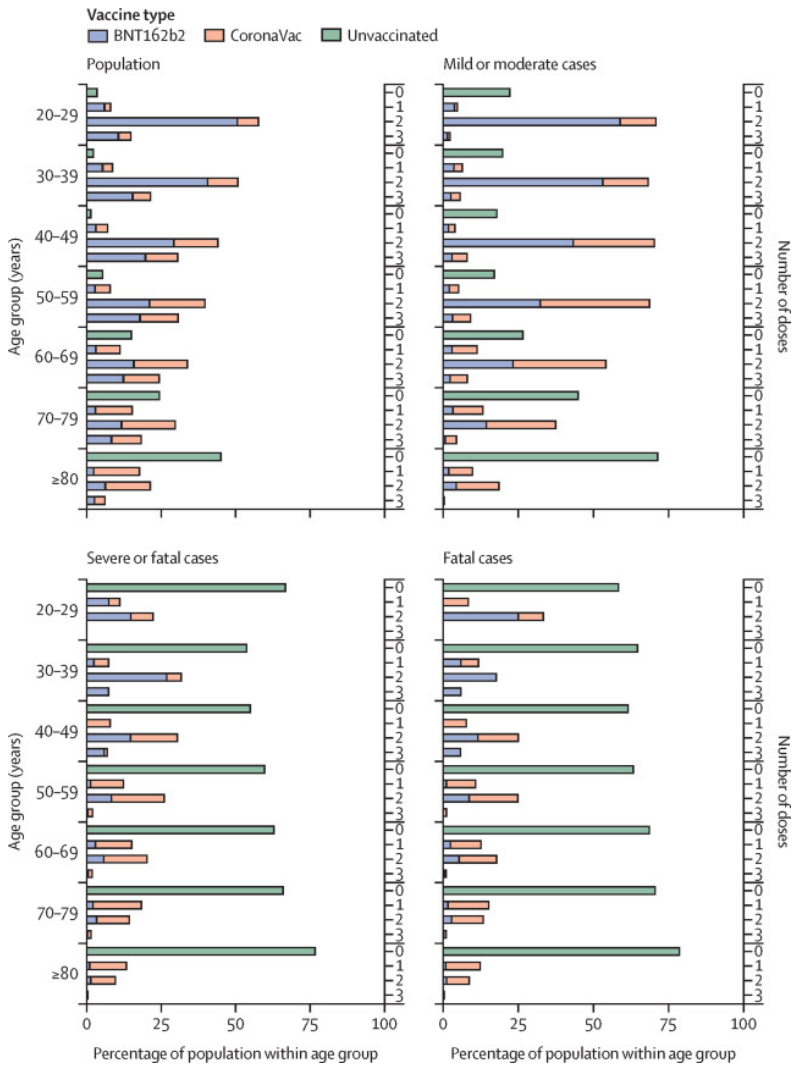


Figure: Vaccine status, age group, and vaccine type

Source: McMenamin, M.E., et al.,, *Lancet Infectious Diseases*, 2022.

- Previous SARS-COV-2 infection in England has shown to reduce fatality due to delta or omicron by:
  - ~ half (hazard ratio 0·47 [95% CI 0·32–0·68]) in vaccinated individuals
  - ~ five times (0·18 [0·06–0·57]) in unvaccinated individuals
- This was further proven that HK individuals without vaccine dosage were prevalent in severe fatal cases

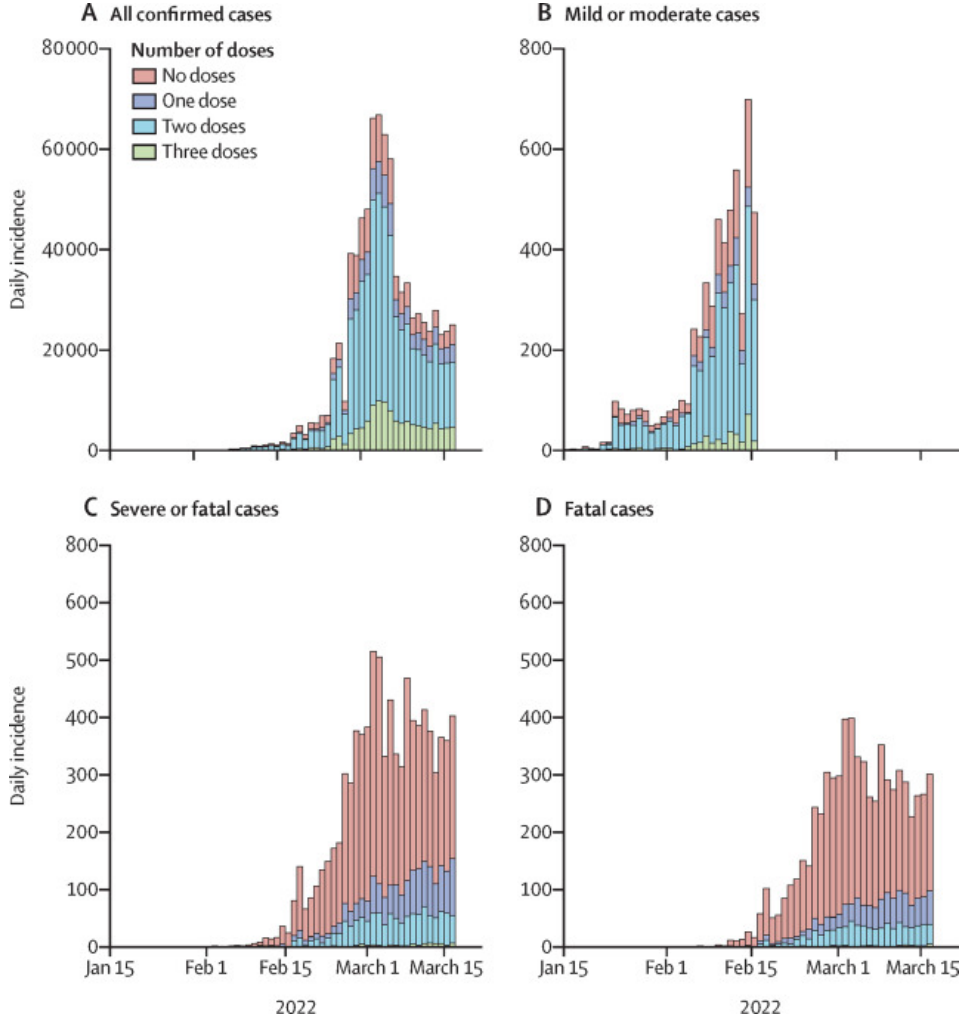


Figure: Daily incidence of cases and deaths by vaccination status. (A) All confirmed COVID-19 cases. (B) Mild or moderate cases in the early part of the fifth wave before Feb 15, 2022. (C) Severe or fatal cases. (D) Deaths throughout the fifth wave in Hong Kong. Severe disease was defined as having ever been listed as serious or critical during hospitalisation for COVID-19 or having a fatal outcome within 28 days of positive test. Vaccination status was categorised according to the number of doses received plus a 14-day lag for all doses, to allow for the immune response to vaccination. Mild cases were only included up until Feb 15, 2022, to account for change in admission criteria.

VACCINE DEVELOPMENT

Traditional vaccine development pipeline

1 - 5 years

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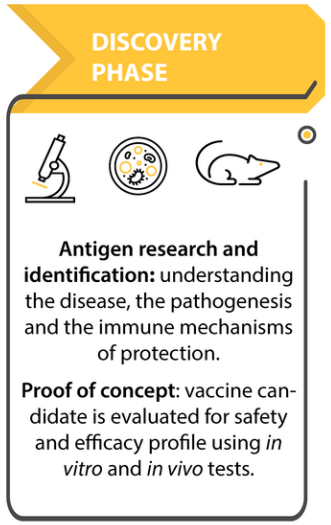


Identification of correlates of protection in clinical trials

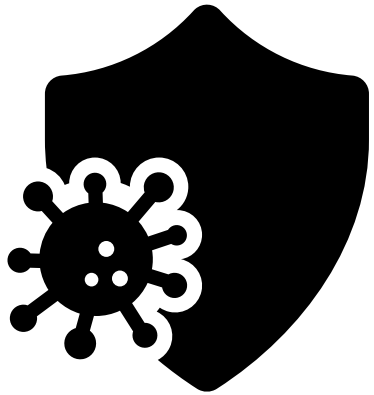
- E.g. Total igG antibodies level correlates in mechanism but the mechanism or protection against pneumococci in the body is not directly measured if correlates of protection is not identified.

- to identify
  - collect large-scale serum from post-vaccinated individuals (who develop or do not develop disease)
  - Estimate by extrapolating from seroepidemiological studies in vaccinated population and relate the data to disease incidence in a population

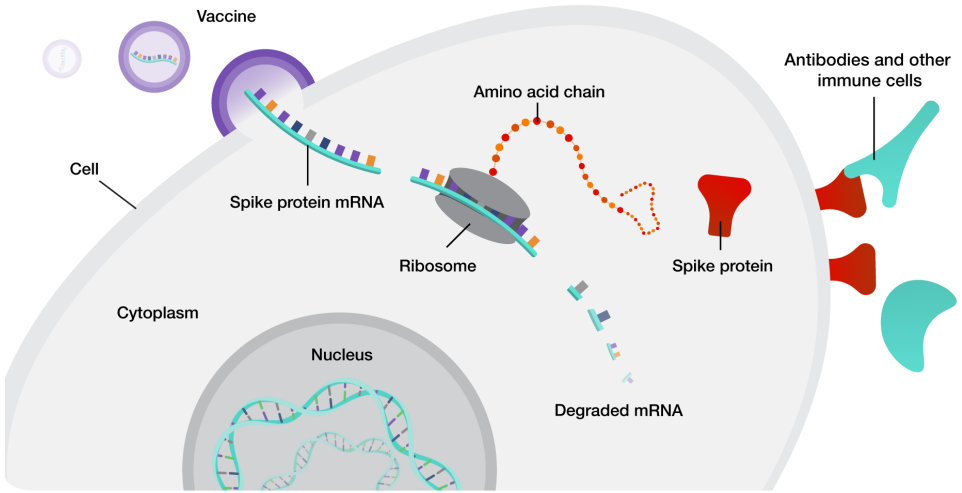
Source: Bactivax, https://www.bactivax.eu/blog/the-process-of-designing-and-testing-a-vaccine. The figure was redrawn based on infographics from Vaccines Europe, Vaccine Development: From Preclinical Studies to Phase 1/2 Clinical Trials chapter (Springer, 2019, DOI) and SARS-CoV-2 Vaccines in Development (Nature volume 586, pages516–527(2020).

VACCINE DEVELOPMENT

- Traditional R&D pipeline – from 5 and up to 20 years
  - Not suited for EID during epidemic/pandemic
- In the past, the fastest was for mumps in 1960s – 4 years
- Ebola – 2 years
- COVID-19 – managed to develop and test under 300 days.



REASONS OF RAPID COVID-19 VACCINE DEVELOPMENT



Previous years of research on related viruses

Thanks to many continuous research on coronaviruses

Due to the devastating effect of those lethal and infectious viruses, motivated the R&D on vaccine development

COVID-19 epidemic → sequencing of SARS-CoV-2 in Jan 2020 → COVID-19 vaccine develop

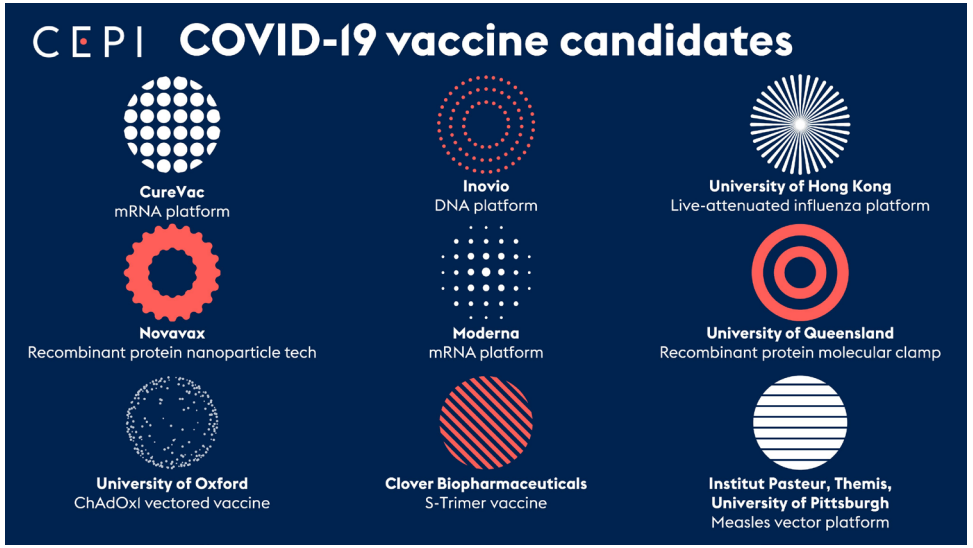
Nucleic acid vaccine technology

Nucleic acid vaccine studied since 25 years ago (DNA vaccine, 25 years; RNA vaccine, 10-15 years) and technology was ready when COVID-19 epidemic occurred

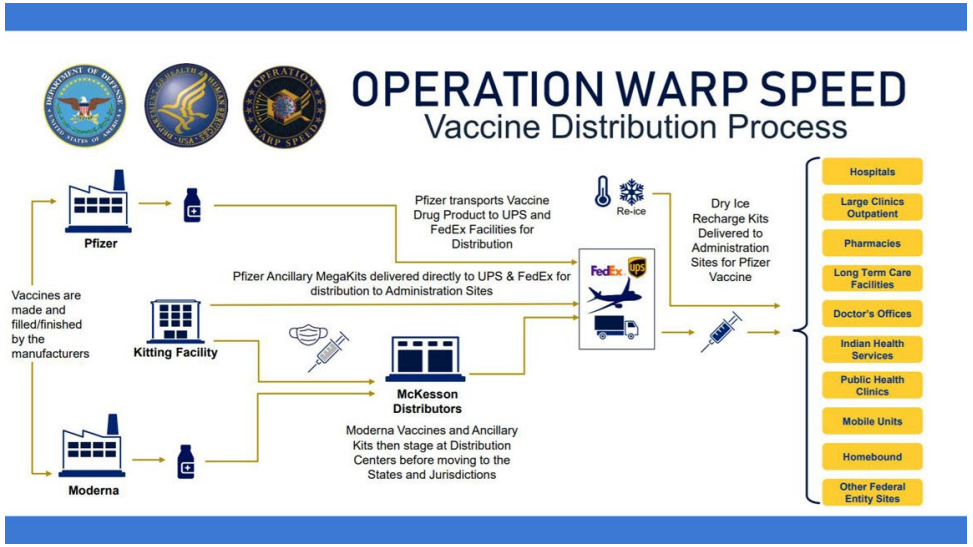
Coat the genetic material in pre-fusion state to stabilize spike protein product

Source: National Human Genome Research Institute, Understanding COVID-19 mRNA Vaccines.

REASONS OF RAPID COVID-19 VACCINE DEVELOPMENT



Source: CEPI



Source: U.S. Department of Health and Human Services

Regulators moving quickly on safety evaluation and approval of use

Coalition for Epidemic Preparedness Innovations (CEPI) was developed for public health emergencies (launched in 2017) - a non-profit organization dedicated to timely develop vaccine during pandemic

Target on viruses having epidemic potential (e.g. MERS, Ebola, Zika)

To push candidate vaccines through phase 2

To prepare vaccine stocks for usage/testing during epidemic

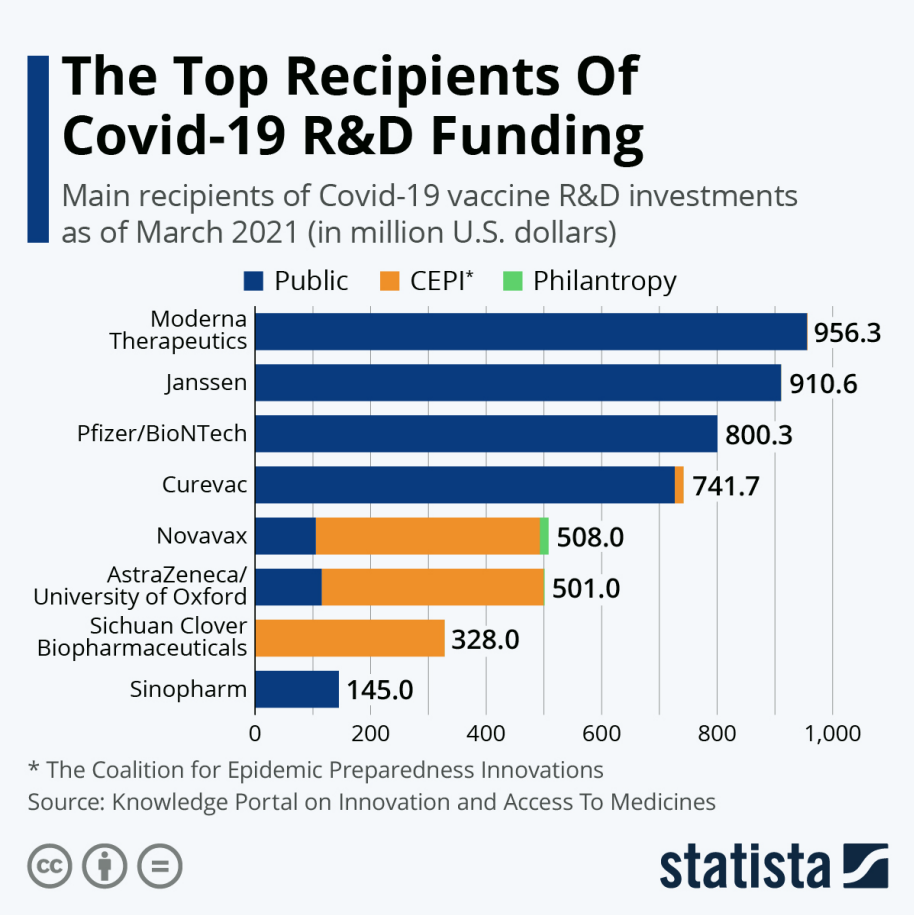
Rapid manufacturing

Simplicity of mRNA vaccine technology

Years of research and having a "template"

Operation Warp Speed (2020 launched) to increase manufacturing speed and scale for public use in short time

REASONS OF RAPID COVID-19 VACCINE DEVELOPMENT



Enormous funding on firms to run multiple trials in parallel

Large sums given to vaccine firms by public sponsors and private philanthropists

E.g. USD 10 billion by US government with the "US Operation Warp Speed vaccine programme" stimulus package

Firms could gamble on starting large-scale testing and manufacturing

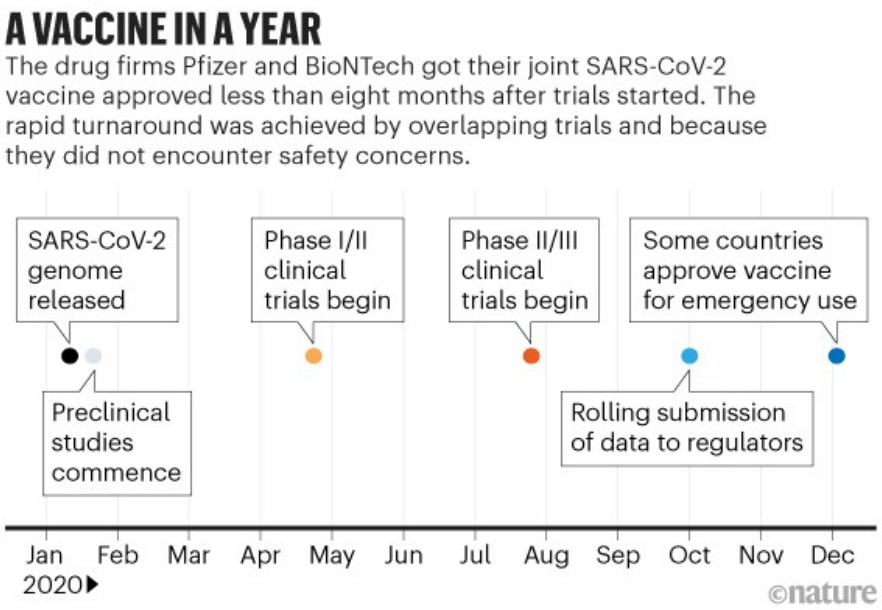
This didn't happen with Ebola (2014-2016) – due to global inflation

Large-scale spread helps in efficacy trials

Globally prevalent helps firms understand infection quickly and comprehensively

Disease outbreaks that are prevalent in an area but not in another area can affect the evaluation (e.g. MERS)

VACCINE DEVELOPMENT FOR COVID-19 PANDEMIC



Sources: BioNTech/Pfizer; Nature analysis

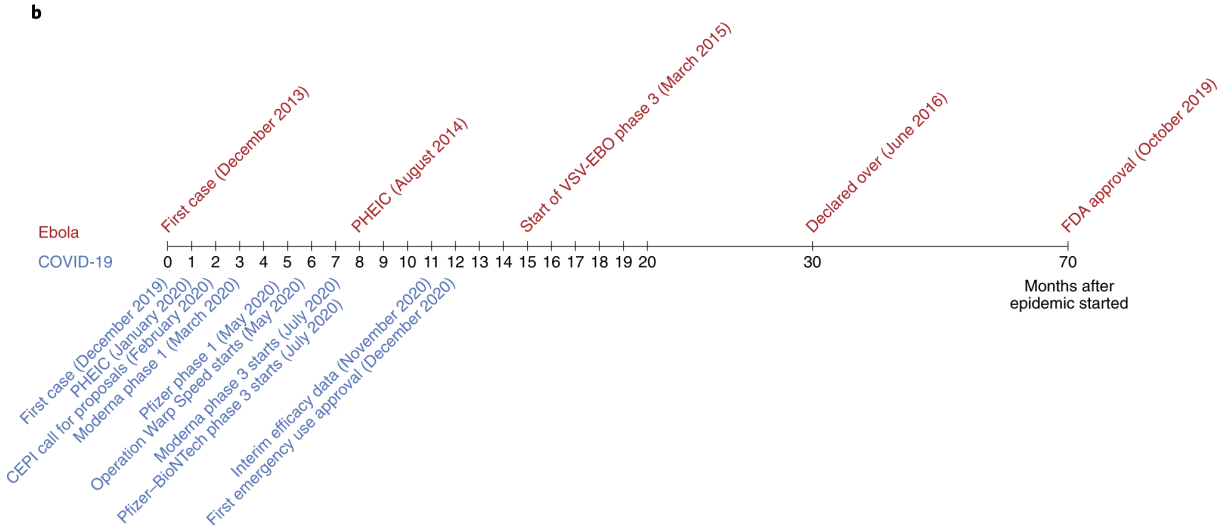


Figure: b, Vaccine development timelines for COVID-19 versus Ebola in the context of particular events during the respective outbreaks. PHEIC, public health emergency of international concern.

Source: Excler, J.-L., et al., *Nature Medicine*, 2021.

- When covid-19 epidemic first hit, PHEIC raised alert, CEPI calls for proposal on developing vaccine
- Firms start to produce few batches of newly developed vaccines for trial within 1-3 months
- Operation Warp Speed then commence to produce large scale of vaccine and distribute for phase 3 trials (this step skipped phase 2)
- Once collecting efficacy and safety data from the trials after 4 months, the next month then approved with EUA (emergency use approval)
- With collaborative efforts of previous years of research, new technology, help from government and WHO and large-scale spread, the vaccine was able to be approved within a year

LIMITATIONS IN RAPID VACCINE DEVELOPMENT

Higher cost per dose of mRNA vaccine technology compared to other vaccines

- E.g. Adenovirus-vectored vaccine – USD2 while mRNA vaccine – USD20
- Burden to low- to middle-income countries
- Storage conditions (ultracold chain) - Less accessible to countries with lesser resources

Unpredictability of the disease

- How long the outbreak will last is unpredictable – worthwhile to proceed?
- Ways to cope – implement master protocol or collaboration across locations and teams

Long-term effect of mRNA vaccine technology

- Long-term monitoring on latent side effects

Post-vaccination symptoms

- Require prolonged monitoring for side effects

Limited resources in vaccine development

- Vaccines for dangerous pathogens require manufacturing plant with high biosafety level
- Supply unable to meet demands during pandemic
  - Global immunization requires multiple companies and manufacturers to meet high demands of vaccine

High mutation/adaptability rate of the pathogen

- RNA viruses have higher mutation rate

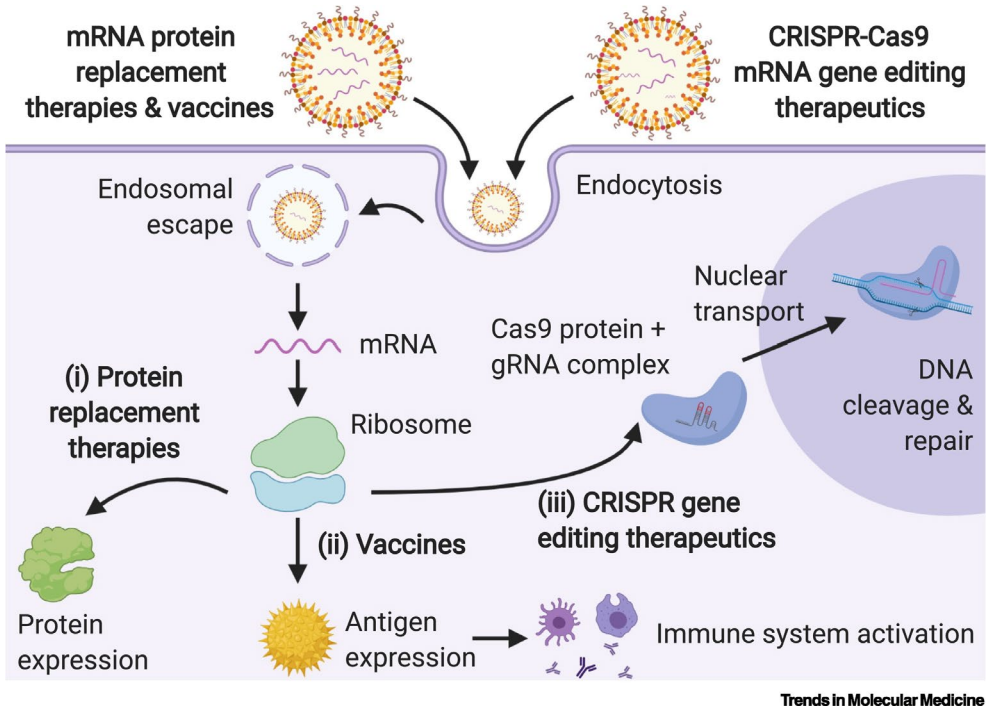
Vaccine platform	Other specifications	Developed for	Under development or stopped[a] for	Shortcomings and advantages
Live attenuated		Influenza; yellow fever; poliomyelitis	COVID-19; RVF (veterinary and human use) Lassa fever; chikungunya	Biosafety level 3 manufacturing plant for handling dangerous viruses
Whole inactivated	With or without adjuvant	Influenza; poliomyelitis; COVID-19	SARS[a]; Zika; RVF (veterinary use); chikungunya	Biosafety level 3 manufacturing plant for dangerous viruses; needs adjuvant; HPB regimens possible
DNA	Electroporation; adjuvant		SARS[a]; MERS; Zika; Lassa fever; COVID-19	Poorly immunogenic; electroporation requires device; difficult use for rollout; HPB regimens possible
mRNA		COVID-19	Lassa fever; disease X	Rapidly adaptable to new emerging viruses; HPB regimens possible; ultracold chain currently unpractical for large-scale use in resource-limited settings
Recombinant vectors				
Nonreplicating				
Ad5			COVID-19	Preexisting immunity to Ad5
ChAd3			Ebola	Cell-line-produced; adaptable construct to emerging virus in 5–6 months; HPB regimens possible
ChAdOx1		COVID-19	MERS; RVF; Lassa fever; Nipah; Zika; chikungunya	
Ad26		Ebola; COVID-19		
Live attenuated				
MVA		Ebola	MERS	
VSV		Ebola	COVID-19[a]; Lassa fever; Nipah	
Measles			MERS; Lassa fever; Nipah; chikungunya; COVID-19[a]	
Protein based				Requires more time to adapt to new emerging viruses; likely needs adjuvant; HPB regimens possible
Virus-like particle	With adjuvant	COVID-19	COVID-19	
Monomer; dimer; trimer	With adjuvant		COVID-19; RFV; Nipah	
Molecular clamp	With adjuvant		Influenza; MERS; COVID-19[a]	

[a]Vaccine development stopped.

Limited resources

Source: Excler, J.-L., et al., *Nature Medicine*, 2021.

FUTURE ASPECT IN VACCINE DEVELOPMENT FOR EID



- CRISPR
  - Using CRISPR genome editing technology to delete virulence factors and input antigens into a vectored virus to generate recombinant vaccine vectors
  - Atasoy developed NHEJ-CRISPR/Cas9 (non-homologous end-joining, NHEJ) & Cre–Lox-mediated genome-editing to delete virulence factors and insert antigens into infectious laryngotracheitis virus simultaneously (Atasoy et. Al., *Vaccines*, 2019.)
  - Chang, P. et. al. even developed a selective vaccine,where CRISPR/Cas9 was combined with erythrocyte binding to generate recombinant HVT-H7HA vaccine for Turkey herpesvirus H7N9 strain. (Chang, et. al., *Vaccines*, 2019)

FUTURE ASPECT IN VACCINE DEVELOPMENT FOR EID

- Epidemic/pandemic forecast modelling
  - Predict how the epidemic take shape – for pandemic-related decision making
  - Reliability is unclear
  - Currently, a study on evaluating forecasting modelling from different teams within a geographical location (https://covid19forecasthub.org/)
  - Ensemble all of them for COVID-19 forecasting but differences were huge so the accuracy is diminished in prediction
  - However, their ensemble could not predict the sudden surge phase of COVID-19 incidence, hence not accurate enough
  - But plausible after fine tuning the flaws (in the model and have a "gold standard" model.

Source: Lopez, VK, et. al., *medRxiv*, 2023

FUTURE ASPECT IN VACCINE DEVELOPMENT FOR EID

- Machine learning on vaccine development strategy
  - Rapid Assessment of Platform Technologies to Expedite Response (RAPTER) project (under development)
  - Using machine learning and AI to perform literary search on how to build effective vaccines against emerging pathogens
  - Aim to produce new effective vaccine with reduced time and cost
  - To find best strategy for specific pathogen from different strategies documented and to maximize values of immune response from the host
  - Once the tool is built, research institutes will corroborate experimentally for validation

Source: Pacific Northwest National Laboratory, https://www.pnnl.gov/news-media/guiding-vaccine-development-machine-learning

TAKE HOME MESSAGE

- Epidemiology and surveillance on pathogens for monitoring/discovering strains are crucial
- Continuous research on the causative agent/products (e.g. surface antigens, spike proteins) of pathogens to prepare for "rainy days"
- Forecasting EID modelling and vaccine design from machine learning are potential approaches in rapid vaccine development
- Collaborative efforts with generous funding from public and private sectors help vaccine development quickly to cope epidemic/pandemic

THANK YOU!

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