The KIDS RESEARCH INSTITUTE AUSTRALIA

DISCOVER · PREVENT · CURE

Vaccines: research to implementation

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Clinical Microbiologist | PathWest Laboratory Medicine WA

Quiz

What phase of clinical trials involves testing a new vaccine in a small group of people for the first time?

- Phase I
- Phase II
- Phase III
- Phase IIV

Who must approve the safety and efficacy of a vaccine, ahead of consideration for public or private use?

- TGA
- ATAGI
- PBAC
- Commonwealth Dept of Health

Learning objectives

To understand:

- Vaccine development and trial pipeline: bench to licensure
- Purpose and characteristics of vaccine trials: phase I to III
- Pathway from licensure to policy: Australia and internationally

To provide real-world examples using meningococcal vaccines

- Conjugate meningococcal vaccine (4vMenCV)
- Recomb. multicomponent meningococcal B vaccine (MenB-MC)

The pipeline to a vaccine

Vaccine Design

Choice of antigen
Choice of platform

Preclinical testing

Safety, Immunogenicity
+/- Efficacy
in animal models

Clinical testing

Phase I
Phase II
Phase IV

Licensure

Regulation; Use

Phase IV

Phase I

Safety
Tens of participants

Phase II

Identify optimal formulation, doses and schedules
Safety
Hundreds of participants

Phase III

Safety and efficacy
Thousands of participants

Human Challenge Models

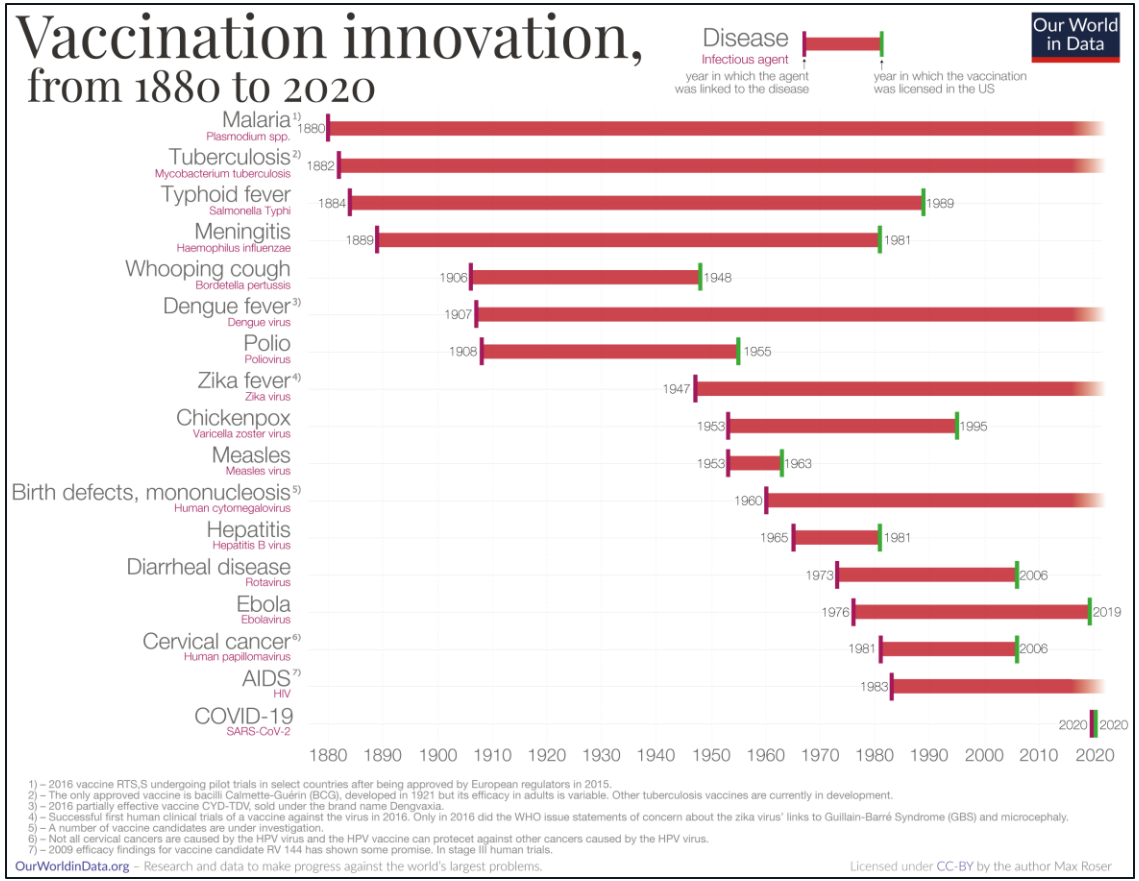
Phase Ia
Single Ascending Dose

Phase Ib
Multiple Different Doses

Phase IIa
Data about optimal dose

Phase IIb
How a vaccine works at a given dose

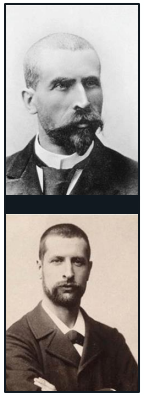
The pipeline to a vaccine



Vaccine design: Choice of the target

1821 Clinical syndrome named by Pierre Bretonneau

1883 Bacteria isolated by Edwin Klebs



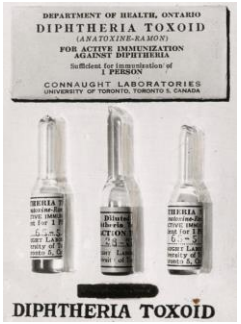
1888 Roux and Yersin discover toxin

1890 Antisera against toxin generated by Behring and Shibasaburo

Diphtheria antisera generated – serum therapy became the treatment of choice

1913 Behring develops diphtheria toxin–antitoxin (AT)

1921 Park rolls out diphtheria campaign using diphtheria AT



1923 Gaston Ramon discovers way to inactivate toxin, creating a toxoid. Product effective but immunogenicity not as great as diphtheria AT. Gaston goes on to identify Al as an adjuvant

1927

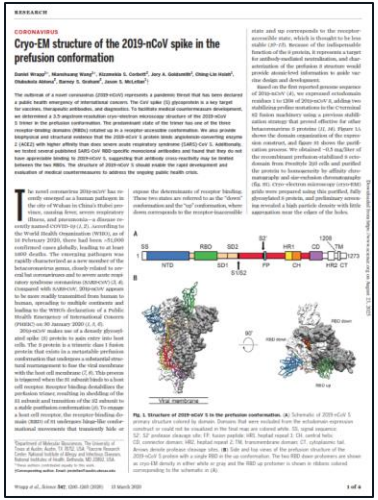
Vaccine design: Choice of the target


Article

A new coronavirus associated with human respiratory disease in China

Novel coronavirus isolated

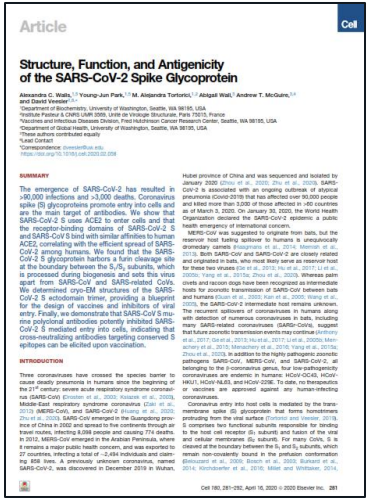
Public release of the SARS-CoV2 sequence 10th January 2020


RESEARCH

CORONAVIRUS

Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Structure of the spike protein first published: 10th February 2020


Article

Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein

Function / antigenicity of spike protein reported : 9th March 2020


Article

Structural basis of receptor recognition by SARS-CoV-2

Crystal structure of receptor binding domain of the spike protein reported: 30th March 2020

Novel pneumonia cluster first reported

SARS-CoV-2 named 11th February 2020

WHO declares COVID-19 a pandemic

December 2019

January 2020

February 2020

March 2020

April 2020

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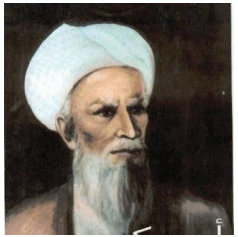
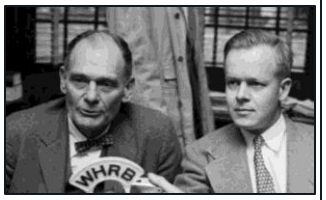
Vaccine design: Choice of the platform

	Technology	Example pathogens
Protein	Purified antigen protein	Influenza, Diphtheria, Pertussis, Tetanus, Anthrax, COVID-19, RSV
	Protein-VLP (virus like particles)	Varicella, HPV, Hepatitis B, Malaria
Carbohydrate	Capsid Carbohydrate	Pneumococcal
	Carbohydrate-protein conjugate	Pneumococcal, Hib, Meningococcal vaccines
Cell	Live attenuated bacterial pathogen	Typhoid (BCG), Cholera
	Inactivated bacteria	Typhoid
Viral	Live attenuated viral pathogen	Measles, Mumps, Rubella, Smallpox, Yellow Fever, Varicella, influenza, Rotavirus, Dengue
	Inactivated pathogen	Polio, Rabies, Influenza, JEV, COVID-19
	Recombinant viral vector, non replicating	COVID-19
	Recombinant viral vector, replicating	Ebola
Nucelic acid	mRNA	COVID-19, influenza, RSV

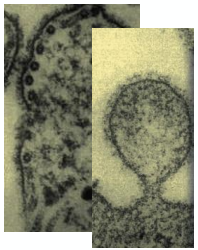
Vaccine design: Choice of platform



First clinical description attributed to Abu Bakr al-Razi



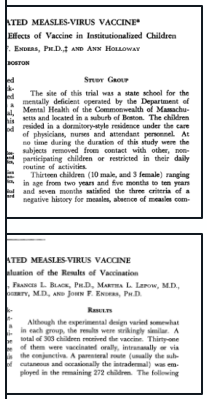
John Enders and Thomas Peebes isolated measles from 13yo boy: David Edmonston



Serial passage through human kidney cells, human amnion cells, embryonated hens' eggs, and finally chick embryo cell cultures

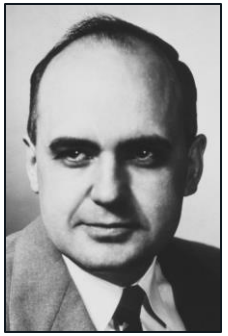
Potency Measurement of Inactivated Measles Vaccines

Measles Vaccine Clinical trials



Measles vaccine (Edmonston-B strain) licensed for use

Adjuvanted formalin inactivated vaccine licensed for use



Edmonston-B strain further attenuated by Maurice Hilleman to reduce reactogenicity (Edmonston-Enders strain)

9th Cent

1954

1960

1963

1960

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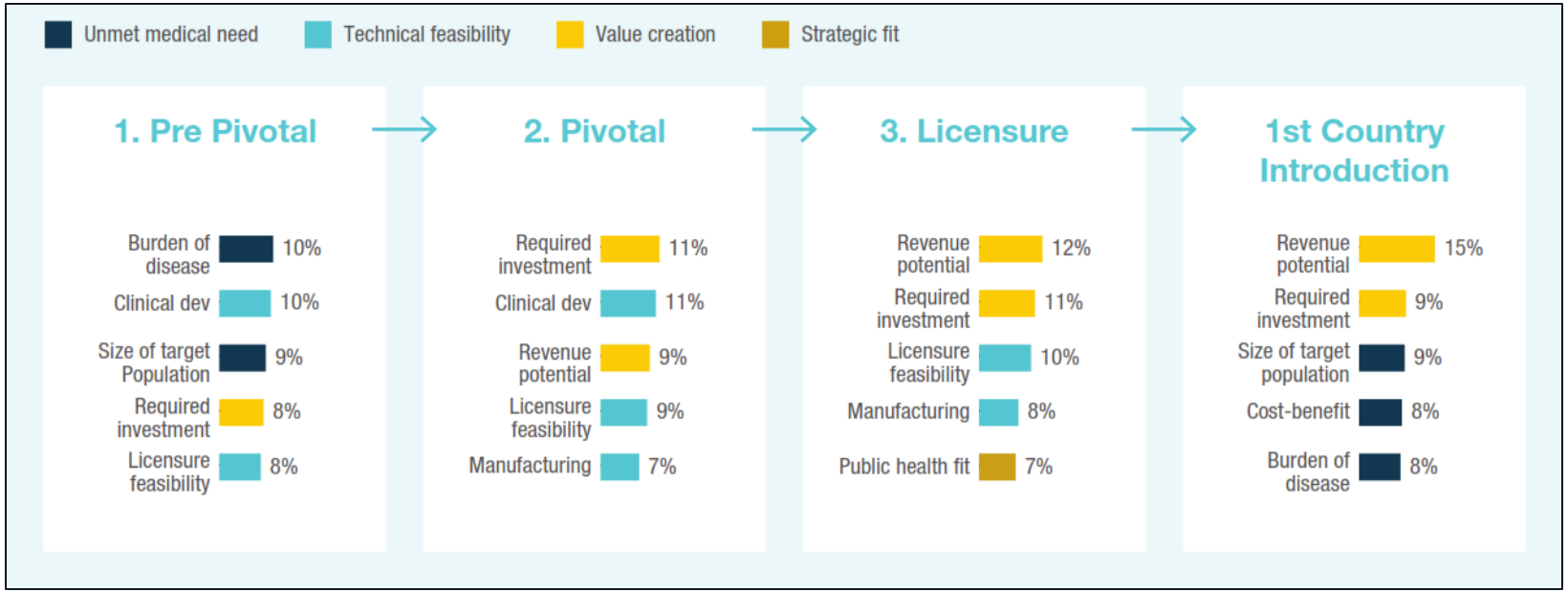
Choice of platform: some strategic choices

Technology	Attraction	Regulatory challenges
Whole virus – live attenuated or inactivated virus	Easy to prepare Can induced long-term immunity	**Hard to scale up and manufacture consistently** **Safety concerns for live viruses** Vaccines using inactivated viruses may be less efficacious
Protein subunit and VLP vaccines	Non-infectious Widely established	**Can be expensive and complex to manufacture** Low efficacy without boosters and/or adjuvants
Viral vector vaccines	High cellular and antibody immune responses	**Hard to scale up** Rare but serious safety concerns **Pre-existing immunity to vector can limit efficacy**
Nucleic acid (mRNA and DNA)	Rapid to design and manufacturer	**Stability – needs low temperature storage** mRNA reactogenicity and potential AEs Potential safety signal with DNA

Investment decision – health need, commercial viability

Major factors influencing vaccine developers considerations



A vaccine ecosystem equipped to meet the challenges of future infectious disease|Wellcome

Pre-clinical testing

A series of key laboratory and animal studies conducted before a candidate is tested in humans – designed to evaluate

- Immune response generated by the vaccine candidate
- Safety profile in vitro and in vivo
- Optimal dosage and delivery methods
- Any potential side effects and adverse reactions

Animal models are a critical component to pre-clinical testing

Pre-clinical testing

Species	Advantages	Disadvantages
Mouse / Rat	**Low cost**; easy to handle; short breeding cycles Genetically well defined; reagents/assays ++ Immune system well characterised; **Hemochorial placentation (transfer of IgG subclasses);** **Well-defined transgenic strains (e.g. knockouts);**	Small size; **Limited access to mucosal surfaces / immune compartments**; manipulation of neonates very difficult; short life span
Rabbit	Moderate costs; good serum donors; longer life span; hemochorial placentation	Larger infrastructure requirements to house large numbers, fewer reagents available
Ferrit	Moderate costs; outbred species; **Excellent model for respiratory viral infections;** Greater access to mucosal compartments	Small size, difficult to handle, require specific training and infrastructure
Pig	Moderate costs; ready access to mucosal surfaces Outbred species; similar physiology to humans; Access to fetal tissue; easy mucosal vaccine delivery	Requires dedicated facilities and training; rapid growth; host to endogenous retroviruses
Sheep, Cattle	**Ready access to mucosal surfaces** **Epitheliochorial placenta (no transfer of Ab)** Access to fetal tissue; easy mucosal vaccine delivery Mucosal immunity at birth; Long neonatal period	**Moderate to high cost;** Requires dedicated facilities and training; long breeding cycle
Non-human primate	**Physiology very similar to humans**; easy access to mucosal surfaces and many immune compartments; Immune functions well defined; hemochoiral placentation	**Very high cost**; Requires dedicated facilities training; Long breeding cycle; immune system develops post partum

Kiros TG et al, Importance of animal models in the development of vaccines

Pre-clinical testing

There is no guarantee that results from animal models will be observed when a vaccine is used in humans

Increasing use of alternatives:

- In vitro experiments using cell cultures models, tissue organoids or 3D tissue models
- In silico and analytical techniques to predict immune responses and suggested adjuvants

Clinical trials

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Phase IIa
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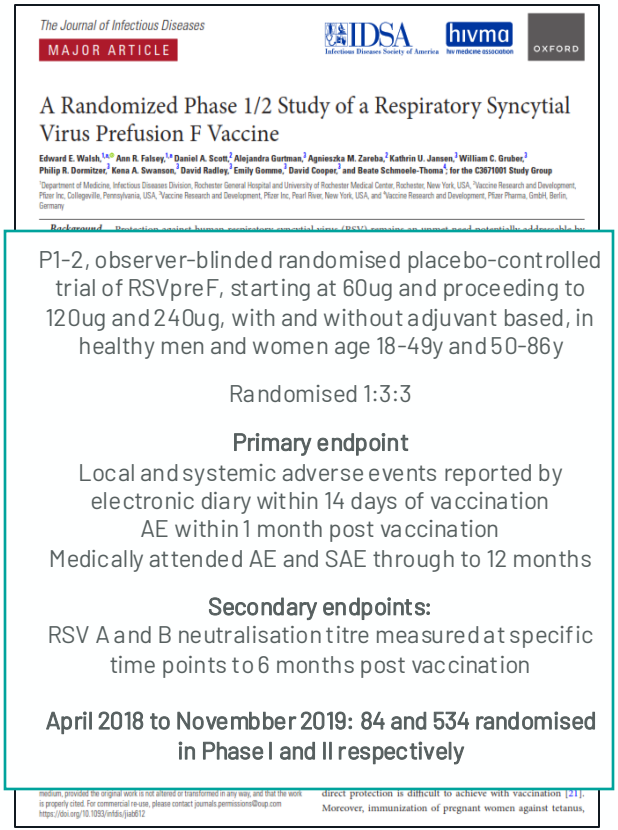
Clinical trials



The Journal of Infectious Diseases

MAJOR ARTICLE

A Randomized Phase 1/2 Study of a Respiratory Syncytial Virus Prefusion F Vaccine

P1-2, observer-blinded randomised placebo-controlled trial of RSVpreF, starting at 60ug and proceeding to 120ug and 240ug, with and without adjuvant based, in healthy men and women age 18-49y and 50-86y

Randomised 1:3:3

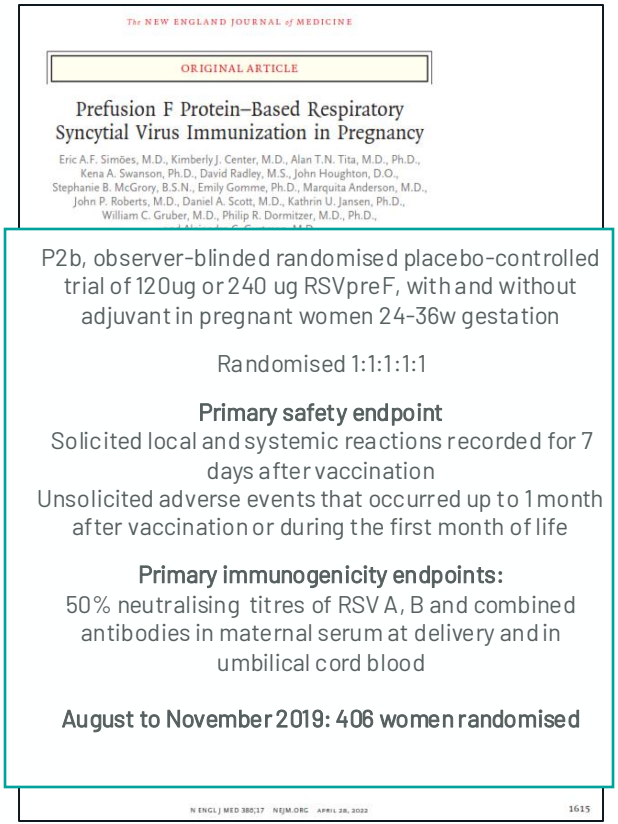
Primary endpoint

Local and systemic adverse events reported by electronic diary within 14 days of vaccination
AE within 1 month post vaccination
Medically attended AE and SAE through to 12 months

Secondary endpoints:

RSV A and B neutralisation titre measured at specific time points to 6 months post vaccination

April 2018 to Novembber 2019: 84 and 534 randomised in Phase I and II respectively



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy

P2b, observer-blinded randomised placebo-controlled trial of 120ug or 240 ug RSVpreF, with and without adjuvant in pregnant women 24-36w gestation

Randomised 1:1:1:1:1

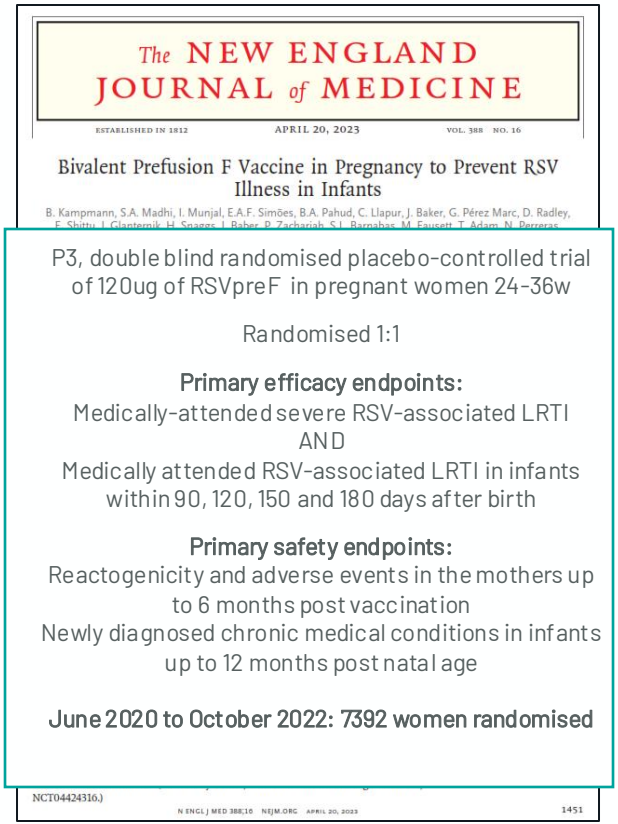
Primary safety endpoint

Solicited local and systemic reactions recorded for 7 days after vaccination
Unsolicited adverse events that occurred up to 1 month after vaccination or during the first month of life

Primary immunogenicity endpoints:

50% neutralising titres of RSV A, B and combined antibodies in maternal serum at delivery and in umbilical cord blood

August to November 2019: 406 women randomised



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 20, 2023 VOL. 388 NO. 16

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

P3, double blind randomised placebo-controlled trial of 120ug of RSVpreF in pregnant women 24-36w

Randomised 1:1

Primary efficacy endpoints:

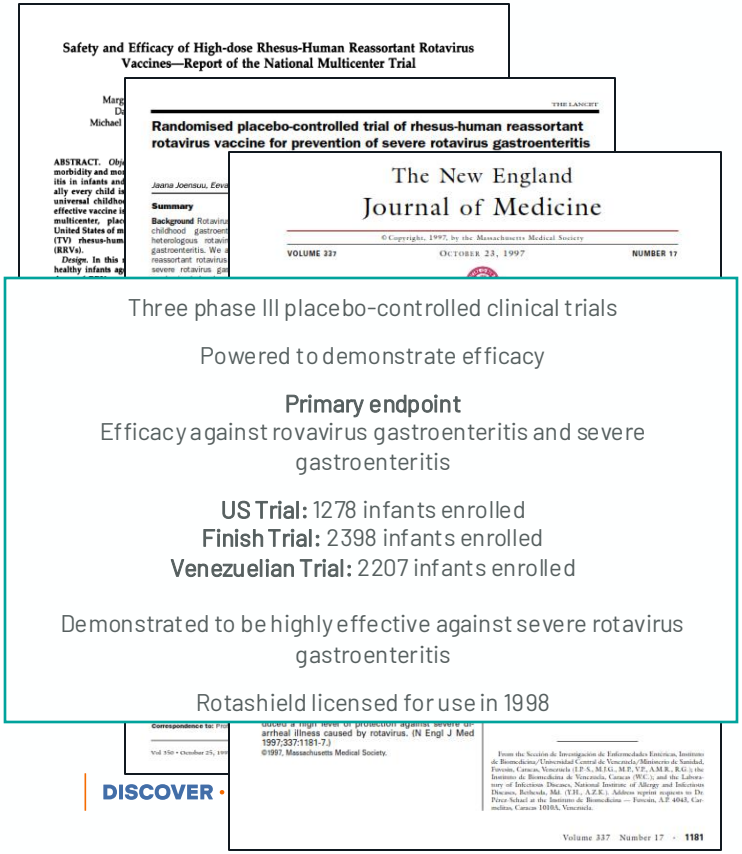
Medically-attended severe RSV-associated LRTI
AND
Medically attended RSV-associated LRTI in infants within 90, 120, 150 and 180 days after birth

Primary safety endpoints:

Reactogenicity and adverse events in the mothers up to 6 months post vaccination
Newly diagnosed chronic medical conditions in infants up to 12 months post natal age

June 2020 to October 2022: 7392 women randomised

Clinical trials: rare endpoints



Three phase III placebo-controlled clinical trials

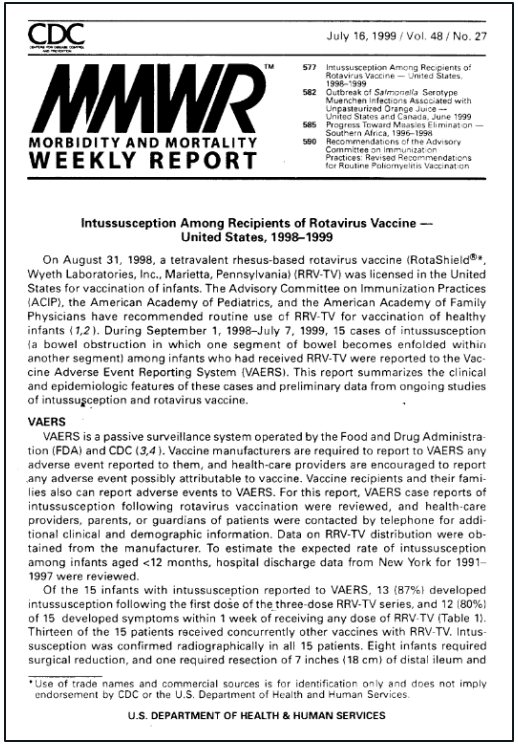
Powered to demonstrate efficacy

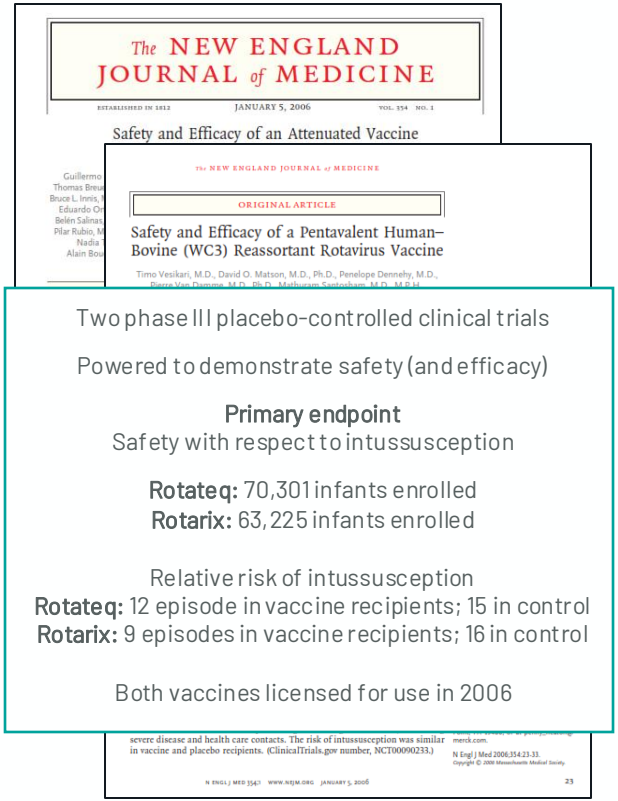
Primary endpoint
Efficacy against rovavirus gastroenteritis and severe gastroenteritis

US Trial: 1278 infants enrolled
Finish Trial: 2398 infants enrolled
Venezuelian Trial: 2207 infants enrolled

Demonstrated to be highly effective against severe rotavirus gastroenteritis

Rotashield licensed for use in 1998





Two phase III placebo-controlled clinical trials

Powered to demonstrate safety (and efficacy)

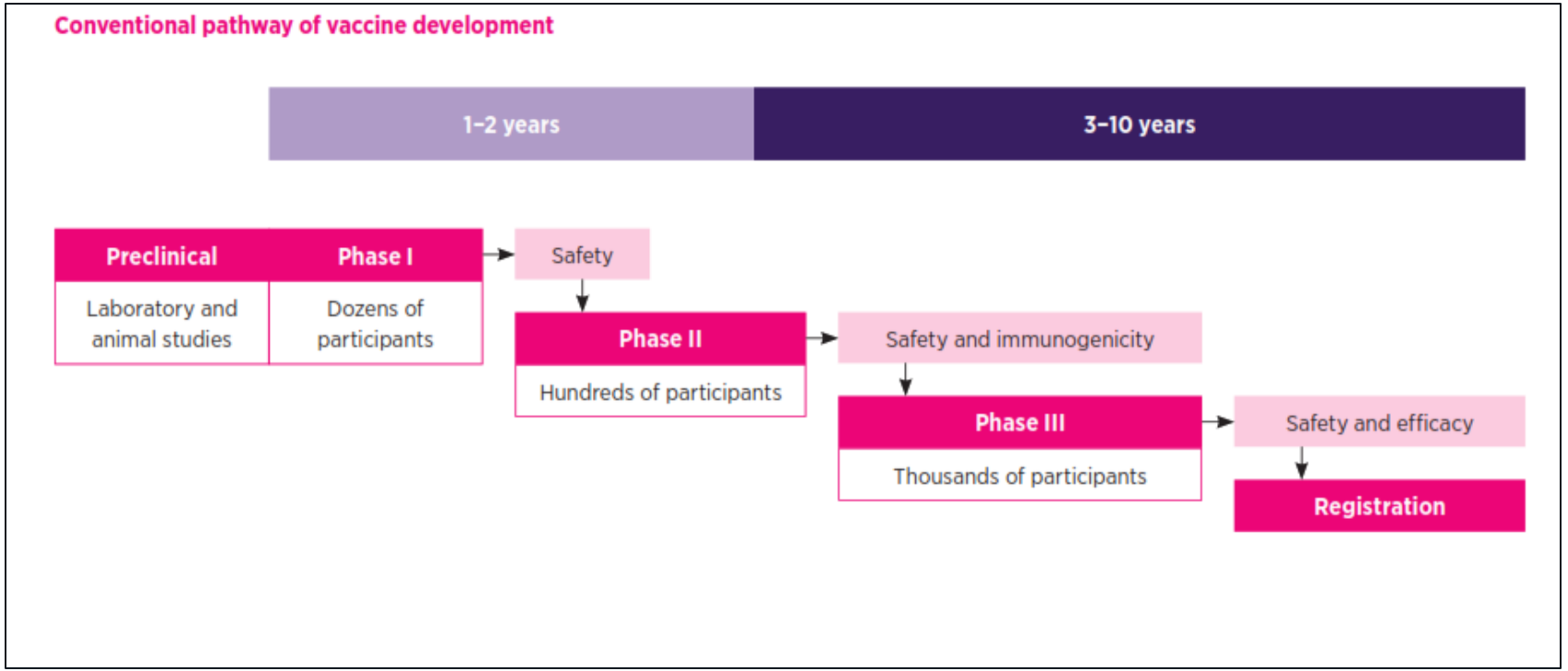
Primary endpoint
Safety with respect to intussusception

Rotateq: 70,301 infants enrolled
Rotarix: 63,225 infants enrolled

Relative risk of intussusception
Rotateq: 12 episode in vaccine recipients; 15 in control
Rotarix: 9 episodes in vaccine recipients; 16 in control

Both vaccines licensed for use in 2006

Clinical trials: the need for speed



McIntyre P et al, Australian Prescriber 2021

Clinical trials: the need for speed

18th November 2020: Phase III

14th Jul

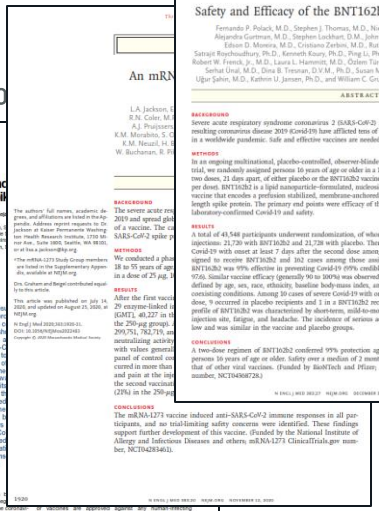
9th March 20

3rd February 2


The NEW ENGLAND JOURNAL of MEDICINE

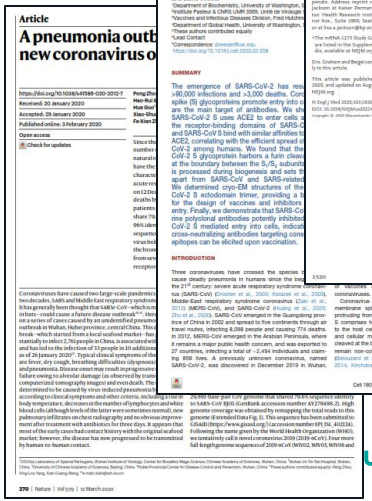
ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

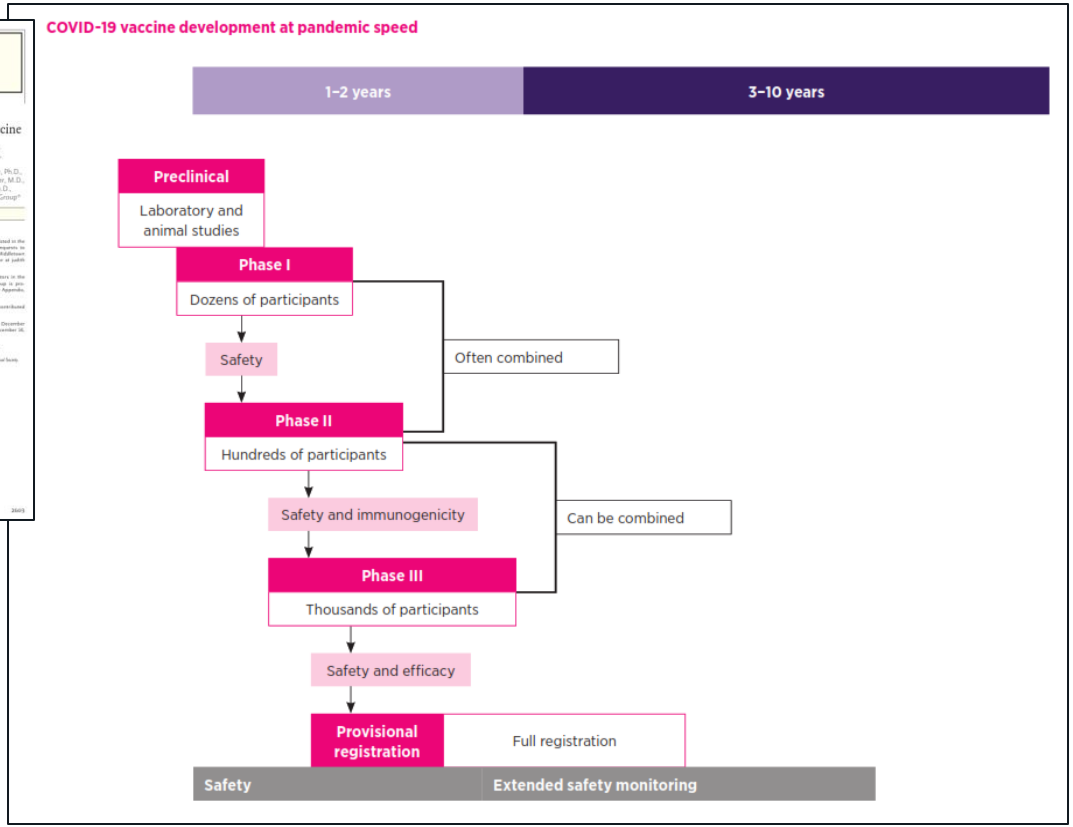

An mRN


Article

Structure, Function, and
of the SARS-CoV-2 Spik

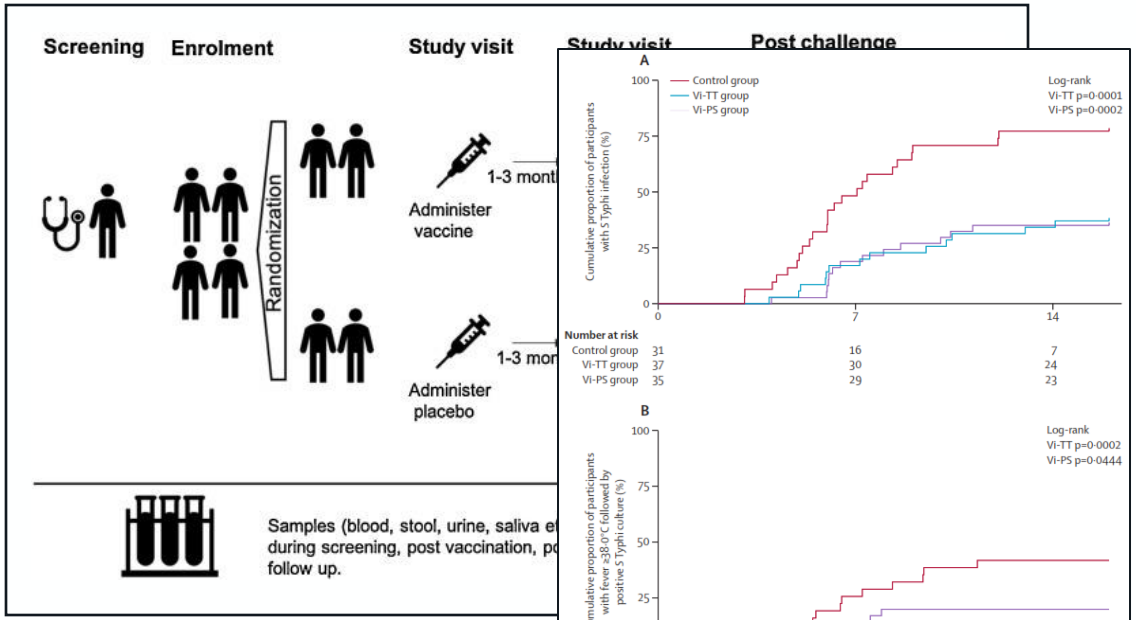

Article

A pneumonia outb
new coronavirus o

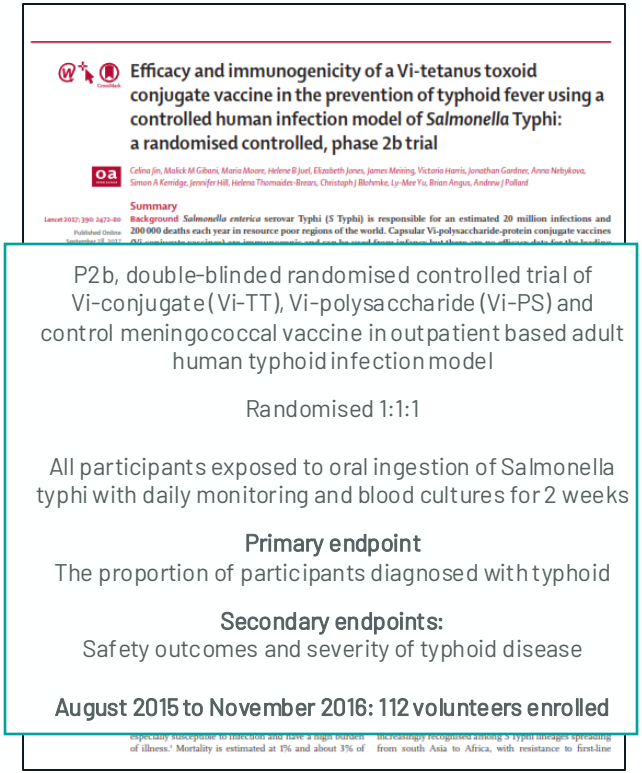


McIntyre P et al, Australian Prescriber 2021

Clinical trials: uncommon infections



Human Challenge Models



Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella* Typhi: a randomised controlled, phase 2b trial

Celina Jin, Malick M Gibani, Maria Moore, Helene B Juel, Elizabeth Jones, James Meiring, Victoria Harris, Jonathan Gardner, Anna Nebykova, Simon A Kerridge, Jennifer Hill, Helena Thomaides-Brears, Christoph J Blohmke, Ly-Mee Yu, Brian Angus, Andrew J Pollard

Summary

Background *Salmonella enterica* serovar Typhi (S Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines

P2b, double-blinded randomised controlled trial of Vi-conjugate (Vi-TT), Vi-polysaccharide (Vi-PS) and control meningococcal vaccine in outpatient based adult human typhoid infection model

Randomised 1:1:1

All participants exposed to oral ingestion of Salmonella typhi with daily monitoring and blood cultures for 2 weeks

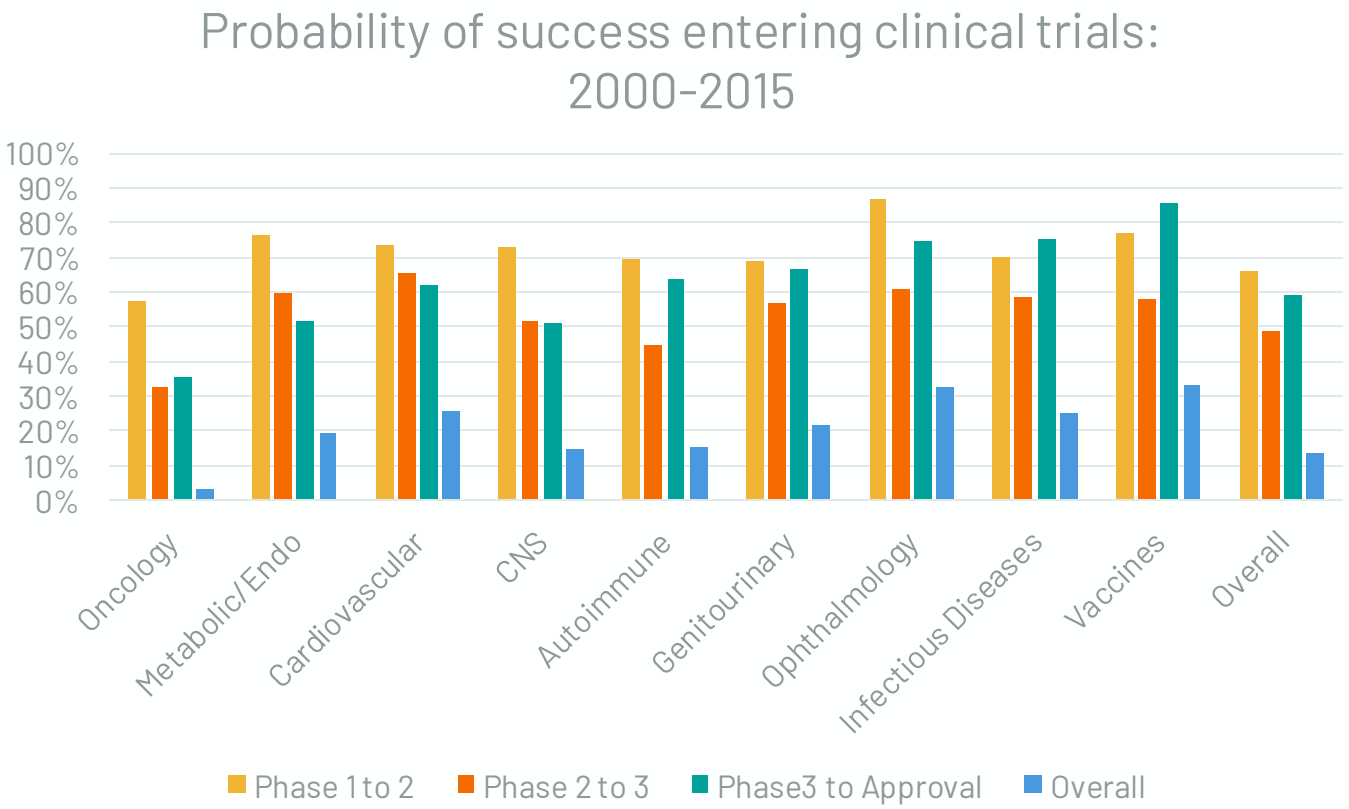
Primary endpoint
The proportion of participants diagnosed with typhoid

Secondary endpoints:
Safety outcomes and severity of typhoid disease

August 2015 to November 2016: 112 volunteers enrolled

Sekhar A et al, Semin Immunol 2020

Clinical trials - success



Chi Heem Wong et al, Biostatistics 2019

Clinical trials

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Licensure

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Single Ascending Dose

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Multiple Different Doses

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Data about optimal dose

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How a vaccine works at a given dose

Licensure

Method of licensure varies by country

The sponsor (normally the manufacturer) must follow a multi-step process

- An independent review of clinical trials
- Inspection of manufacturing facility
- Usability testing of the product label and product information

In Australia, vaccines are reviewed by the Therapeutics Goods Administration

Internationally, other regulators include: FDA, Health Canada, EMA

TGA pathways for vaccines

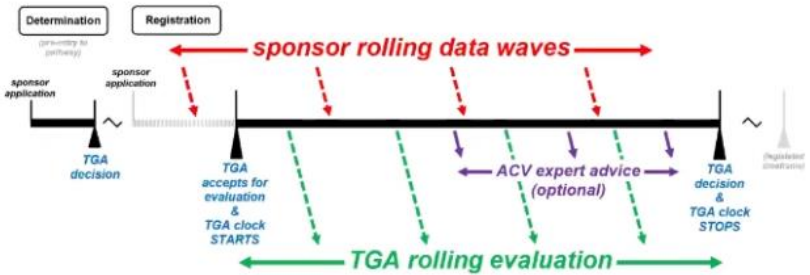
Standard (full) submission – in Australia, vaccines are evaluated as prescription medicines, not biological

Provisional review – new vaccine and/or indication, preventing a serious condition, providing a major therapeutic advance **and** favourable efficacy or safety. Must plan to submit comprehensive clinical data

TGA pathways for vaccines: COVID-19

Most countries granted temporary emergency authorisations

Provisional review – new vaccine and/or indication, preventing a serious condition, providing a major therapeutic advance **and** favourable efficacy or safety.
Must plan to submit comprehensive clinical data



In Australia, provisional pathway used, to enable early access

- Limited data on duration of protection

Pathway to including a vaccine in the NIP

TGA

All vaccines must be registered by the Therapeutic Goods Administration (TGA) as **clinically safe and effective** for use in Australia.

A positive TGA delegate's overview must be provided in order for the Pharmaceutical Benefits Advisory Committee (PBAC) to consider recommending a submission
Full TGA registration is required before Government approval can be sought to fund a vaccine for a particular cohort through the NIP

PBAC

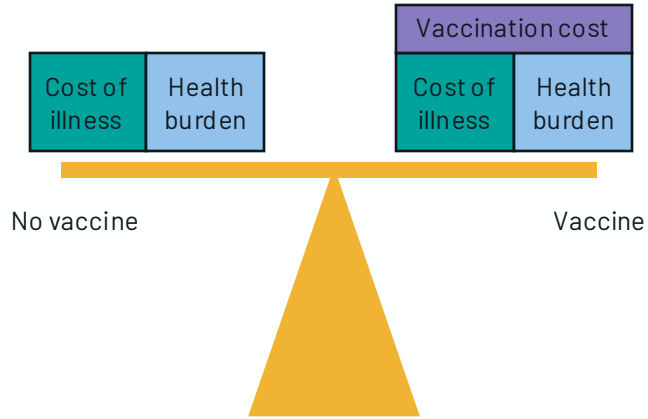
All new vaccines and extended cohorts for existing NIP vaccines must be recommended by the PBAC as **clinically and cost-effective** for the NIP

Clinical advice from ATAGI must accompany all vaccine submissions to the PBAC and submissions must address all matters raised in the ATAGI advice where appropriate (refer to information on ATAGI pre-submission advice below). For further information regarding the PBAC process please refer to the PBAC Guidelines

Health Technology Assessment

Alongside clinical efficacy and safety, an economic evaluation (EE) is typically used as a tool to quantify health benefits and costs of the intervention, relative to the comparator.

- Consideration of cost-effectiveness or "value for money"
- Consideration of affordability or budget impact, and financial sustainability of a vaccination program



Incremental cost-effectiveness ratio (ICER)

$$\text{ICER} = \frac{\text{Cost (vaccine)} - \text{Cost (comparator)}}{\text{Outcomes (vaccine)} - \text{Outcomes (comparator)}}$$

Cost of vaccination program + Cost of illness with vaccination

Cost of illness with no vaccination

Phase IV: post marketing studies

Ongoing post-licensure surveillance to evaluate vaccine effectiveness and safety:

Safety (critical to assess rare side effects):

- Passive receipt of AE from providers and vaccinated individuals
- Active surveillance for adverse events through targeted programs
- AEFI and AE signal investigation

Coverage and effectiveness (critical to collect real world use data)

- Ongoing evaluation of programs to identify vaccine and schedule effectiveness, coverage and programmatic gaps

High income vs Low-middle income country

Key considerations in vaccine development for LMICs:

- Safety and efficacy of candidate vaccines and duration protection
  - Demonstrated efficacy in LMICs
  - Differences in epidemiology / serotype
- Public health need (burden, severity, community impact)
- Vaccine characteristics
- Vaccine and program cost / implementability
- Partnerships to support introduction

Summary

Vaccines progress from pre-clinical to clinical studies, licensure, use

- Key decision about vaccine target, platform, health need and commercial viability are made ahead of trials
- Trials normally progress in a careful designed step-wise process
- But when there is financial and global commitment, studies can happen in parallel
- TGA, ATAGI, PBAC and Governments all play an important role
- Post licensure studies are very important to monitor rare safety events and long erm vaccinations