

Vaccines: research to implementation

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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

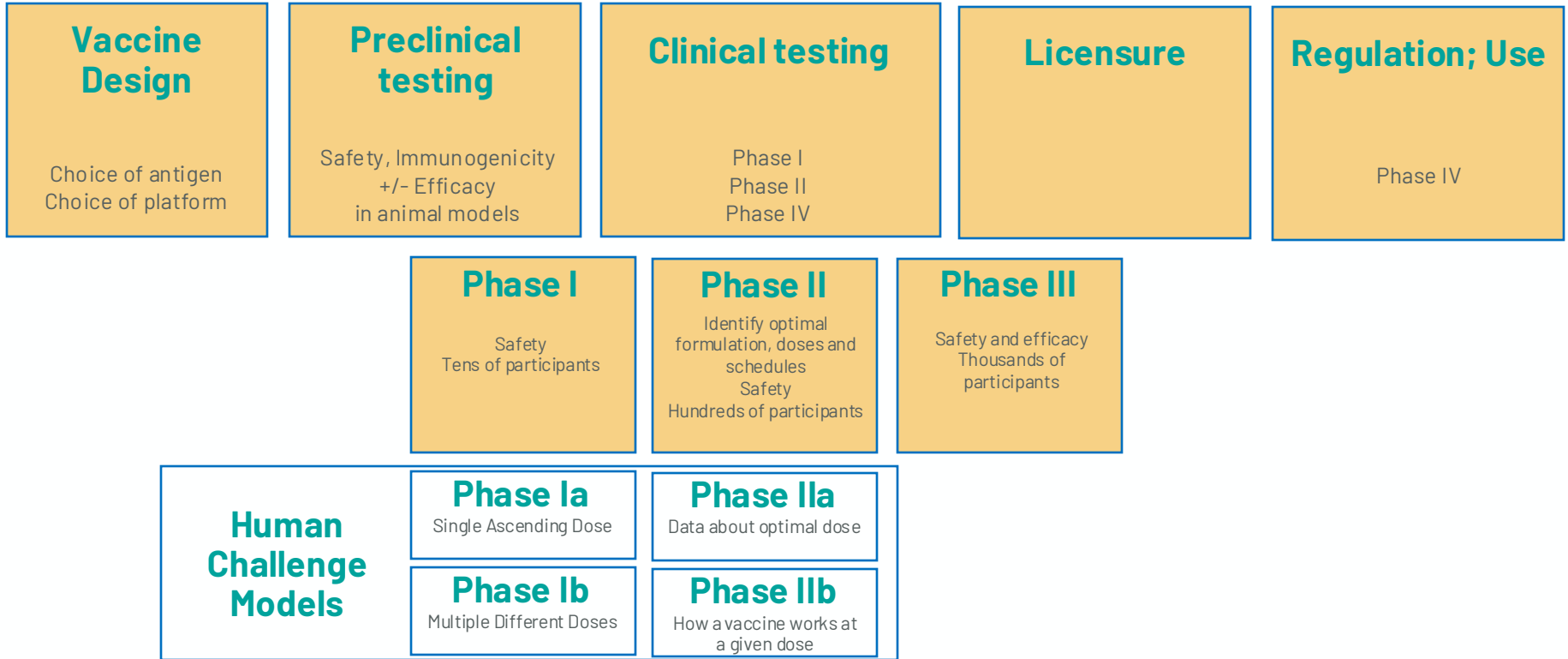
To understand:

- 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

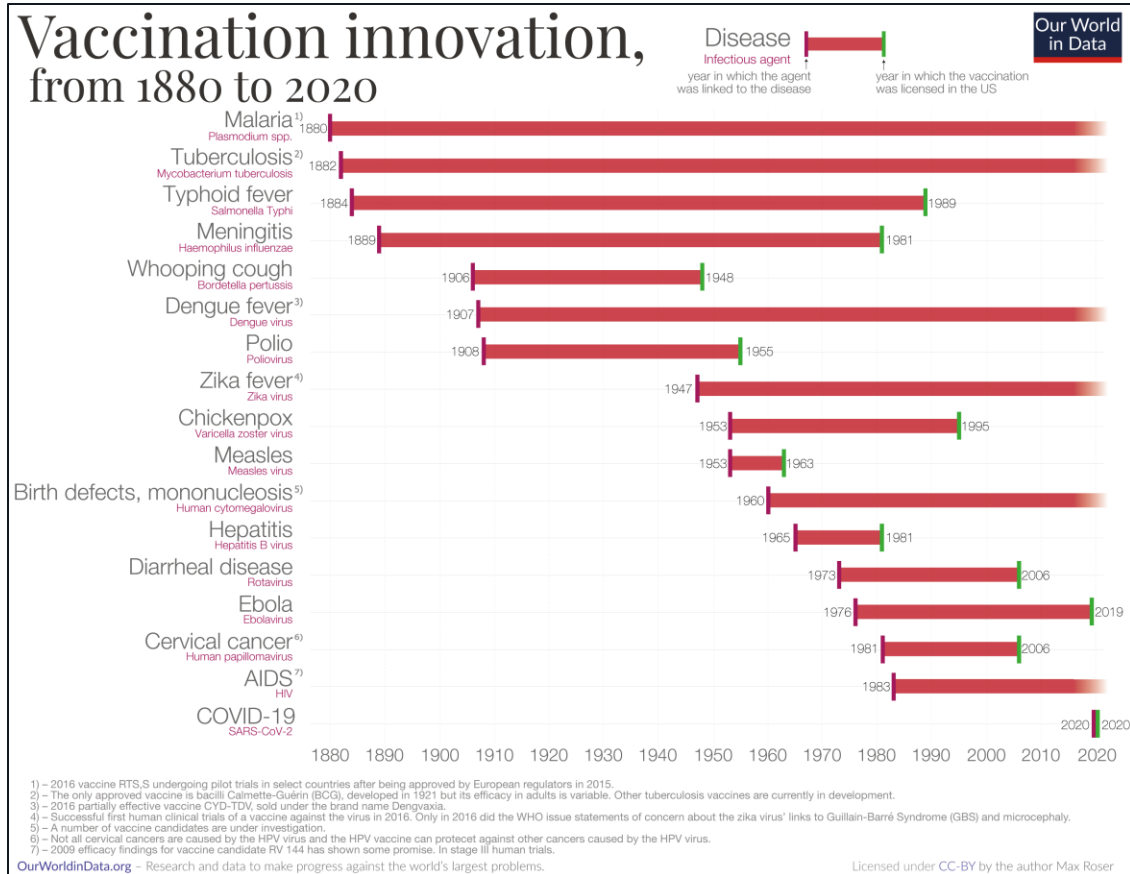
To provide real-world examples using meningococcal vaccines

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

The pipeline to a vaccine



The pipeline to a vaccine



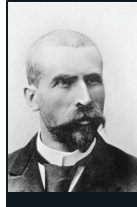
Vaccine design: Choice of the target



Clinical syndrome named by Pierre Bretonneau



Bacteria isolated by Edwin Klebs



Roux and Yersin discover toxin



Antisera against toxin generated by Behring and Shibusaburo

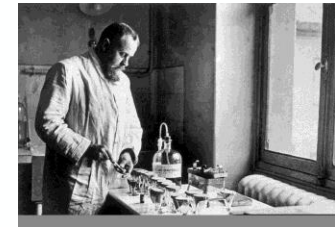


Diphtheria antisera generated - serum therapy became the treatment of choice



Behring develops diphtheria toxin-antitoxin (AT)

Park rolls out diphtheria campaign using diphtheria AT



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

1821

1883

1888

1890

1913

1921

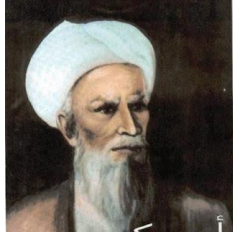
1923

1927

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
Nucleic acid	mRNA	COVID-19, influenza, RSV

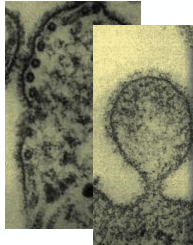
Vaccine design: Choice of platform



First clinical description attributed to Abu Bakr al-Razi



John Enders and Thomas Peebles 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

The New Journal of

Volume 202

JULY

STUDIES ON AN ATTENUATED Measles Virus
Development and Propagation of the Vaccine
JOHN F. ENDERS, DAVID S. PEEBLES, & KENNETH W. EDMONSTON, JR.

The first virus report of the series the description and study of propagation of an attenuated measles virus vaccine against such observations on the clinical and immunological reactions to this virus in susceptible children and children are described. This virus can be cultured in human amnion cells. In the development of a vaccine procedure to the culture medium containing in their media will be separated and virally inactivated. Preliminary reports of the first two children have been published.

Measles virus has been made to develop an effective and accurate model for the clinical studies in a series of active measles virus strains. The general principles have subjected the study of another. Further experiments, carried by Howe in 1954, were based on the principle of vaccination and the use of a vaccine procedure to the culture medium containing in their media will be separated and virally inactivated. Preliminary reports of the first two children have been published.

Potency Measurement of Inactivated Measles Vaccines

MEL WARREN, Ph.D.; JAMES G. CHAMFORD, Ph.D.; AND MARY JAVINE GALLAGHER, M.S.; THURGOOD SMITH, Ph.D.

Individuals who are converted to a seropositive state by the administration of adequate amounts of a killed measles antigen develop resistance to natural and attenuated measles infection.^{1,2} This immunity is not dependent upon the maintenance of an elevated antibody titer. It, therefore, seems reasonable to postulate that the level of clinical effectiveness of a specific lot of an inactivated measles vaccine would be correlated with its immunogenic potency in animals. The following report (in which the available data have been condensed because of limitations of time) describes a standard vaccine assay procedure and certain studies on measles virus and host factors which led to its development.

Virus Considerations

All of the antigenic activity of measles virus appears to be associated with the particle itself, i.e., there is no evidence of a soluble antigen. However, the estimation of virus concentration by infectivity titration alone provides only a rough index, because of the lability of measles virus and its rapid inactivation almost as fast as it appears in the fluids of infected cultures. Thus, a considerable amount of viral antigen will accumulate in tissue cultures of measles and not be reflected in the infective titer of a sample taken at a particular time.

The Enders group have described the poor complement fixing titer obtained when the virus was cultured in chick embryo cells. Department of Biological Research, Chas. Pfizer & Co., Inc., Terre Haute, Ind. Presented at the International Conference on Measles Infection, National Institutes of Health, Bethesda, Md., Nov. 7-9, 1961.

measles strains attenuated by growth in chick embryo tissue culture are employed as antigens.³ We have also observed this characteristic with attenuated lines. Does the virulence level of a measles strain also affect its antigenicity when used in a killed vaccine? The results of comparative potency tests in guinea pigs, using vaccine prepared from virus which has never been grown outside of primary human tissue (and thus presumably virulent) and from strains in chick embryo tissue cultures which were of proved clinical attenuation, indicated that virus from either source made satisfactory vaccines, provided that the raw culture fluid was harvested late in the incubation period or when sufficient time had elapsed for large amounts of virus to accumulate.

Host Factors Involved in Vaccine Assays

A wide range of laboratory animals will respond to the injection of killed measles virus. These include the monkey, dog, rabbit, guinea pig, mouse, and chick. This list contains species (monkey and dog) which are susceptible to overt clinical infection and others (guinea pig and rabbit) which are not. Insufficient information is available with which to guide the comparative sensitivity of these species to measles antigen, although on a dose per body weight basis the measles resistant guinea pig seems quite as responsive as the susceptible cynomolgus monkey. Because of its comparative cost and the frequent occurrence of naturally acquired measles, the monkey is not well suited to vaccine standardization. Therefore, we have developed a potency assay using guinea pigs, since the serum antibody concentration may be readily measured in a variety of ways.

ATTEN MEASLES-VIRUS VACCINE*

Effects of Vaccine in Institutionalized Children - ENDESS, Ph.D. and ANNE HOLLOWAY

JOHN F. ENDERS

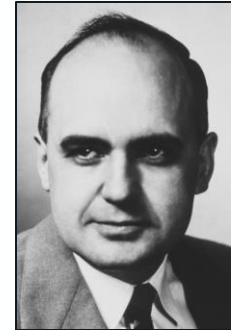
The site of this trial was a state school for the mentally deficient operated by the Department of Mental Health of the Commonwealth of Massachusetts and located in a suburb of Boston. The children resided in a dormitory-type residence under the care of physicians, nurses and attendant personnel. At no time during the duration of the study were the subjects removed from contact with other, non-participating children or restricted in their daily routine of activities. Thirteen children (10 males and 3 females) ranging in age from two years and five months to ten years and seven months satisfied the three criteria of a negative history for measles, absence of measles con-

ATTEN MEASLES-VIRUS VACCINE

ation - Results of Vaccination

FRANCIS E. BRUCE, Ph.D.; MARION L. LEVINSKY, M.D.; ROBERT, M.D.; and JOHN F. ENDESS, Ph.D.

Although the experimental design varied somewhat in each group, the results were strikingly similar. A total of 353 children received the vaccine. Thirty-one of them were vaccinated orally, intranasally or via the conjunctiva. A parotid smear (usually the subcutaneous and occasionally the intranasal) was employed in the remaining 272 children. The following



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

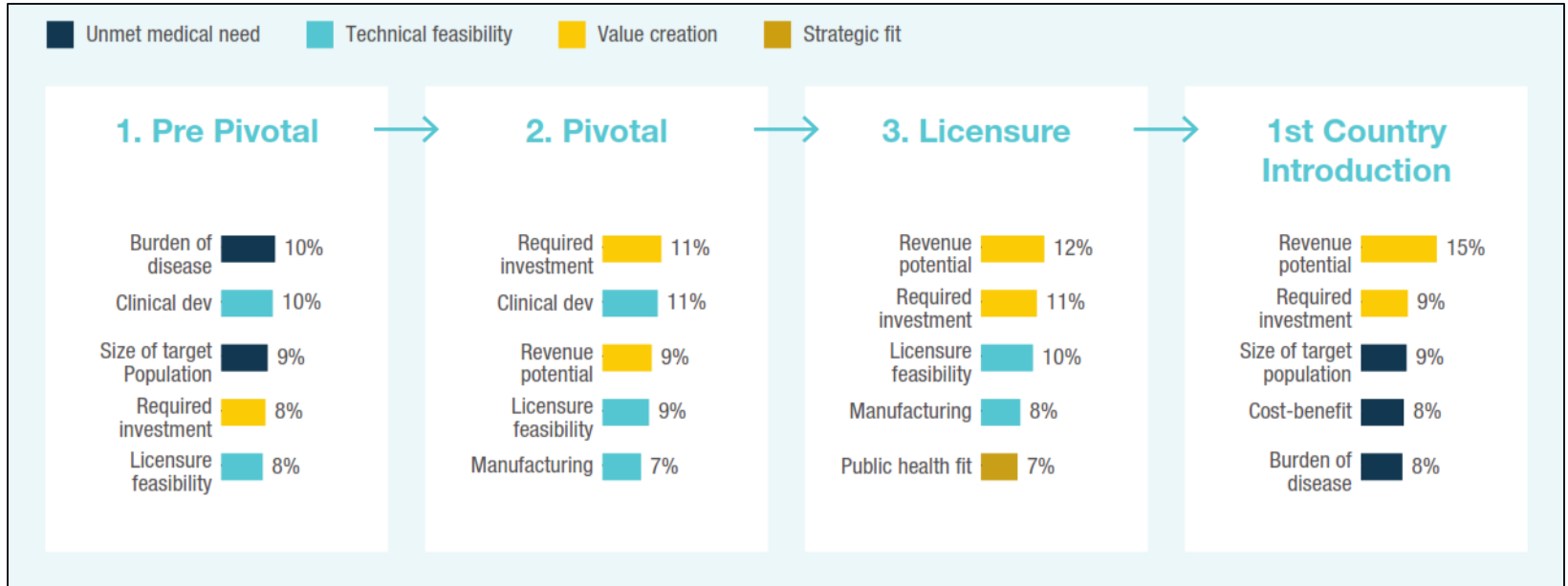
9th Cent → 1954 → 1960 → 1963 → 1960

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



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	<p>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);</p>	<p>Small size; Limited access to mucosal surfaces / immune compartments; manipulation of neonates very difficult; short life span</p>
Rabbit	<p>Moderate costs; good serum donors; longer life span; hemochorial placentation</p>	<p>Larger infrastructure requirements to house large numbers, fewer reagents available</p>
Ferret	<p>Moderate costs; outbred species; Excellent model for respiratory viral infections; Greater access to mucosal compartments</p>	<p>Small size, difficult to handle, require specific training and infrastructure</p>
Pig	<p>Moderate costs; ready access to mucosal surfaces Outbred species; similar physiology to humans; Access to fetal tissue; easy mucosal vaccine delivery</p>	<p>Requires dedicated facilities and training; rapid growth; host to endogenous retroviruses</p>
Sheep, Cattle	<p>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</p>	<p>Moderate to high cost; Requires dedicated facilities and training; long breeding cycle</p>
Non-human primate	<p>Physiology very similar to humans; easy access to mucosal surfaces and many immune compartments; Immune functions well defined; hemochoiral placentation</p>	<p>Very high cost; Requires dedicated facilities training; Long breeding cycle; immune system develops post partum</p>

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

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 Model

Phase Ia

Single Ascending Dose

Phase IIa

Data about optimal dose

Phase Ib

Multiple Different Doses

Phase IIb

How a vaccine works at
a given dose

Clinical trials

The Journal of Infectious Diseases

MAJOR ARTICLE



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

Edward E. Walsh,^{1,6*} Ann R. Falsley,^{1,6} Daniel A. Scott,^{1,6} Alejandra Gutman,⁷ Agnieszka M. Zareba,⁷ Kathrin U. Jansen,¹ William C. Gruber,¹

Philip R. Dormitzer,^{1,6} Kena A. Swanson,¹ David Radley,¹ Emily Gomme,¹ David Cooper,¹ and Beate Schmechel-Thoma,¹ for the 42071001 Study Group

Department of Medicine, Infectious Diseases Division, Rochester General Hospital and University of Rochester Medical Center, Rochester, New York, USA, ¹Vaccine Research and Development, Pfizer Inc, Collegeville, Pennsylvania, USA, ²Vaccine Research and Development, Pfizer Inc, Pearl River, New York, USA, and ³Vaccine Research and Development, Pfizer Pharma GmbH, Berlin, Germany

Background. Protection against human respiratory syncytial virus (RSV) infection cannot be achieved by a live-attenuated 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 November 2019: 84 and 534 randomised in Phase I and II respectively

medRxiv preprint doi: <https://doi.org/10.1101/2023.04.06.23281102>; this version posted April 10, 2023. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license.

direct protection is difficult to achieve with vaccination [21]. Moreover, immunization of pregnant women against tetanus,

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy

Eric A. F. Simões, M.D., Kimberly J. Center, M.D., Alan T.N. Tita, M.D., Ph.D.,

Kena A. Swanson, Ph.D., David Radley, M.S., John Houghton, D.O.,

Stephanie B. McGroarty, B.S.N., Emily Gomme, Ph.D., Marquita Anderson, M.D.,

John P. Roberts, M.D., Daniel A. Scott, M.D., Kathrin U. Jansen, Ph.D.,

William C. Gruber, M.D., Philip R. Dormitzer, M.D., Ph.D.,

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

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

N ENGL J MED 385:17 NEJM.ORG APRIL 26, 2023

1615

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

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Ulapur, J. Baker, G. Pérez Marc, D. Radley, F. Shittu, I. Glasteynik, H. Sengco, I. Baber, P. Zachariah, S.I. Barnabas, M. Faucett, T. Adam, N. Borrero

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

NCT04424316

N ENGL J MED 388:16 NEJM.ORG APRIL 20, 2023

1451

Clinical trials: rare endpoints

Safety and Efficacy of High-dose Rhesus-Human Reassortant Rotavirus Vaccines—Report of the National Multicenter Trial

Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis

ABSTRACT. Only morbidity and mortality in infants and ally every child in universal children effective vaccine in multicenter, place United States of a (TV) rhesus-human (RRV). Design. In this healthy infants age

The New England Journal of Medicine
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 VOLUME 337 OCTOBER 23, 1997 NUMBER 17

Three phase III placebo-controlled clinical trials
 Powered to demonstrate efficacy
 Primary endpoint
 Efficacy against rotavirus 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

DISCOVER

CDC
 July 16, 1998 / Vol. 48 / No. 27

MMWR
 MORBIDITY AND MORTALITY WEEKLY REPORT

577 Intussusception Among Recipients of Rotavirus Vaccine — United States, 1998–1999
 582 Outbreak of Salmonella Serotype Muenchen Infections Associated with Unpasteurized Orange Juice — United States and Canada, June 1999
 585 Progress Toward Malaria Elimination — Southern Africa, 1986–1996
 590 Recommendations of the Advisory Committee on Immunization Practices: Revised Recommendations for Routine Poliovirus Vaccination

Intussusception Among Recipients of Rotavirus Vaccine — United States, 1998–1999

On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine (RotaShield®*, Wyeth Laboratories, Inc., Marietta, Pennsylvania) (RRV-TV) was licensed in the United States for vaccination of infants. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians have recommended routine use of RRV-TV for vaccination of healthy infants (1,2). During September 1, 1998–July 7, 1999, 15 cases of intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment) among infants who had received RRV-TV were reported to the Vaccine Adverse Event Reporting System (VAERS). This report summarizes the clinical and epidemiologic features of these cases and preliminary data from ongoing studies of intussusception and rotavirus vaccine.

VAERS

VAERS is a passive surveillance system operated by the Food and Drug Administration (FDA) and CDC (3,4). Vaccine manufacturers are required to report VAERS any adverse event reported to them, and health-care providers are encouraged to report any adverse event possibly attributable to vaccine. Vaccine recipients and their families also can report adverse events to VAERS. For this report, VAERS case reports of intussusception following rotavirus vaccination were reviewed, and health-care providers, parents, or guardians of patients were contacted by telephone for additional clinical and demographic information. Data on RRV-TV distribution were obtained from the manufacturer. To estimate the expected rate of intussusception among infants aged <12 months, hospital discharge data from New York for 1991–1997 were reviewed.

Of the 15 infants with intussusception reported to VAERS, 13 (87%) developed intussusception following the first dose of the three-dose RRV-TV series, and 12 (80%) of 15 developed symptoms within 1 week of receiving any dose of RRV-TV (Table 1). Thirteen of the 15 patients received concurrently other vaccines with RRV-TV. Intussusception was confirmed radiographically in all 15 patients. Eight infants required surgical reduction, and one required resection of 7 inches (18 cm) of distal ileum and

* Use of trade names and commercial sources is for identification only and does not imply endorsement by CDC or the U.S. Department of Health and Human Services.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

The NEW ENGLAND JOURNAL of MEDICINE
 ESTABLISHED IN 1812 JANUARY 5, 2006 VOL. 354 NO. 1

Safety and Efficacy of an Attenuated Vaccine

ORIGINAL ARTICLE

Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine

Guillermo Thomas Brevi, Bruce L. Irwin, Eduardo Ori Belkin Salinas, Pilar Rubio, M. Nadia Alain Bori

Time Veclairi, M.D., David O. Matson, M.D., Ph.D., Penelope Dennysh, M.D., Bruce Alan Patton, M.D., Ph.D., Malibu, Calif. (UCLA), 44 P. 44 P. 44

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

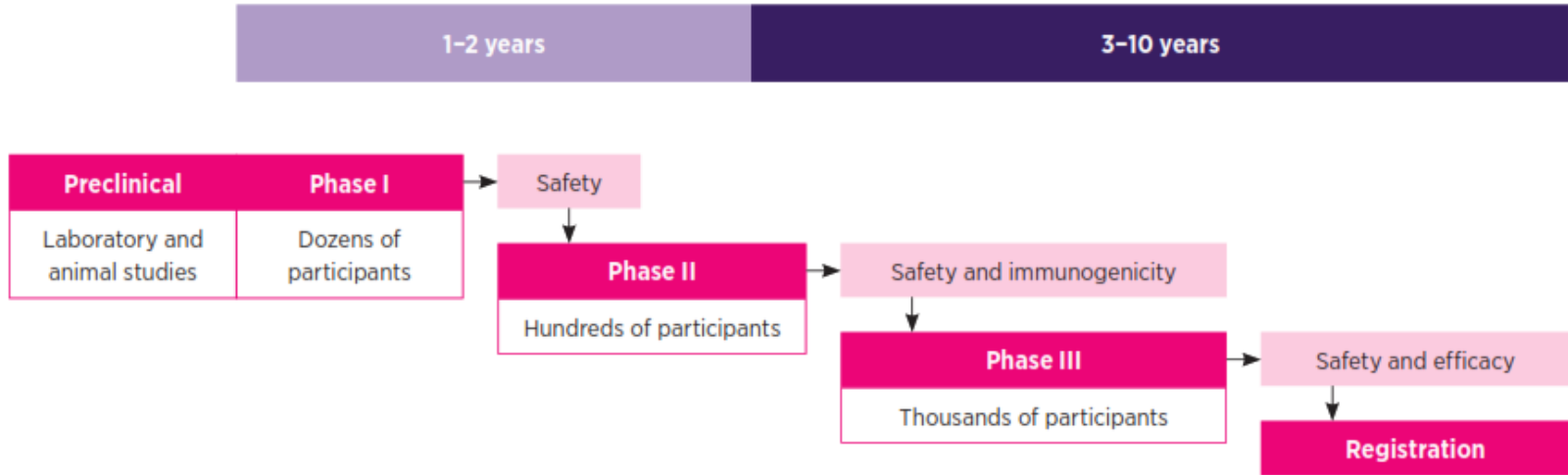
severe disease and health care contacts. The risk of intussusception was similar in vaccine and placebo recipients. (ClinicalTrials.gov number, NCT00090233.)

merck.com
 N Engl J Med 2006;354:23-33
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n engl j med 354(1) www.nejm.org january 5, 2006 23

Clinical trials: the need for speed

Conventional pathway of vaccine development



Clinical trials: the need for speed

18th November 2020: Phase III

COVID-19 vaccine development at pandemic speed

1-2 years

3-10 years



14th Jul

An mRNA

9th March 2020

Article

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

Antonio G. Nisli, Young-Jin Park, M. Anand Sivasankaran, et al.

L.A. Jackson, L. S. Coia, M. A. J. Pugliese, K.M. Heffernan, S.C. K.M. Heffernan, H.P. W. Boorman, H.P.

The authors full names, academic degrees, and affiliations are listed in the text.

BACKGROUND
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein is the main target of antibodies. We used cryo-electron microscopy to determine the structure of the spike glycoprotein.

RESULTS
The spike glycoprotein is a class II type I transmembrane protein. It consists of a single extracellular domain, a single transmembrane domain, and a single cytoplasmic tail. The spike glycoprotein is a class II type I transmembrane protein.

CONCLUSIONS
The spike glycoprotein is a class II type I transmembrane protein. It consists of a single extracellular domain, a single transmembrane domain, and a single cytoplasmic tail.

INTRODUCTION
Three coronaviruses have crossed the species barrier to infect humans since the late 19th century: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.

CONCLUSIONS
The spike glycoprotein is a class II type I transmembrane protein. It consists of a single extracellular domain, a single transmembrane domain, and a single cytoplasmic tail.

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3rd February 2020

Article

A pneumonia outbreak associated with a new coronavirus identified in a large hospital in Wuhan, China

Wang, Nishiura, et al.

Abstract text describing the pneumonia outbreak and the identification of a new coronavirus.

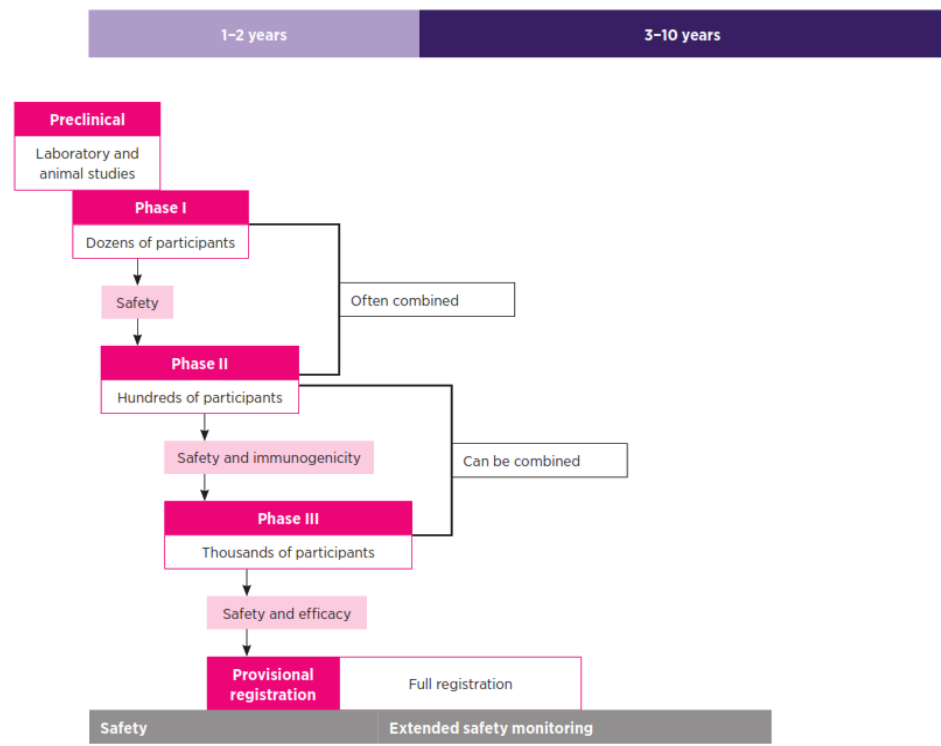
INTRODUCTION
A pneumonia outbreak associated with a new coronavirus identified in a large hospital in Wuhan, China.

RESULTS
A pneumonia outbreak associated with a new coronavirus identified in a large hospital in Wuhan, China.

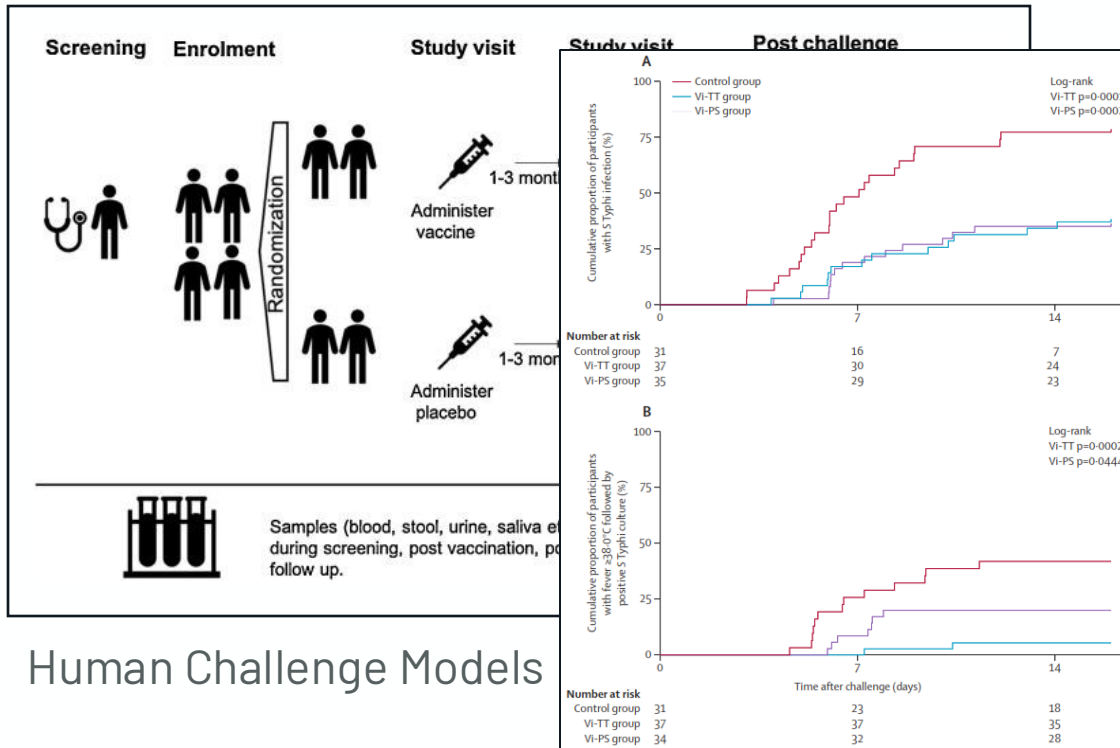
CONCLUSIONS
A pneumonia outbreak associated with a new coronavirus identified in a large hospital in Wuhan, China.

INTRODUCTION
A pneumonia outbreak associated with a new coronavirus identified in a large hospital in Wuhan, China.

CONCLUSIONS
A pneumonia outbreak associated with a new coronavirus identified in a large hospital in Wuhan, China.



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

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

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

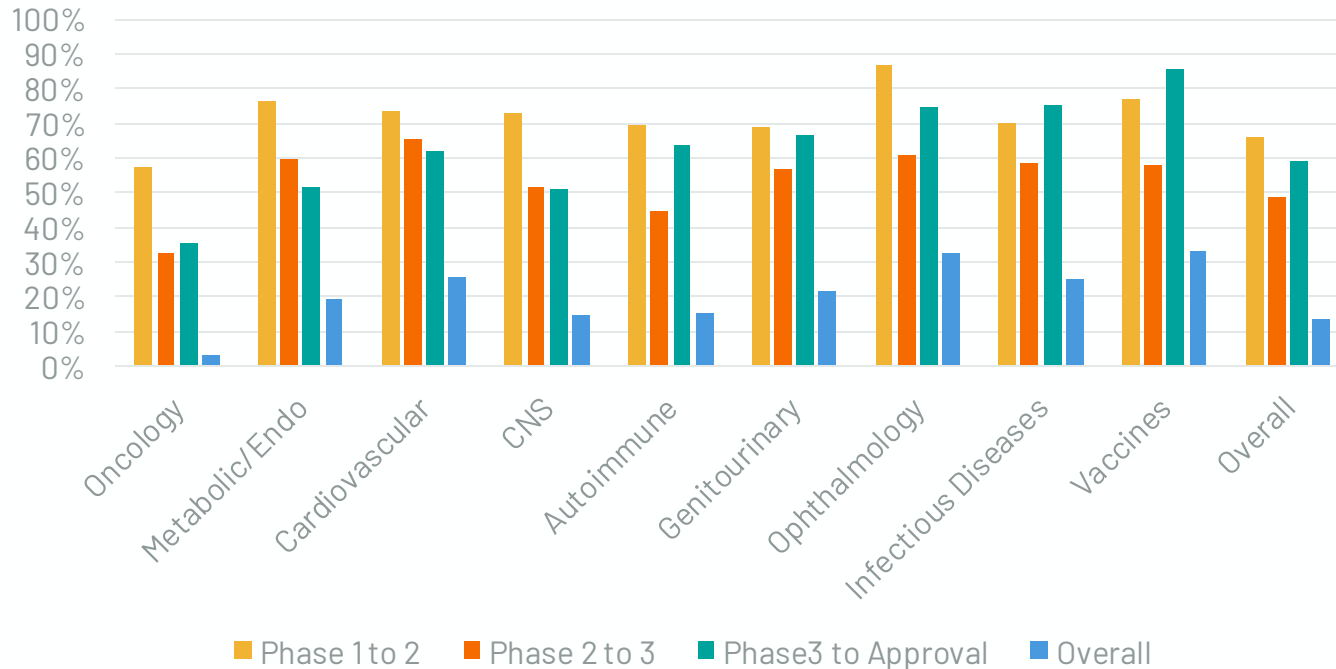
Secondary endpoints:
Safety outcomes and severity of typhoid disease

August 2015 to November 2016: 112 volunteers enrolled

especially susceptible to infection and have a high burden of increasing recognition among 11 pilot strategies spreading of illness.* Mortality is estimated at 1% and about 3% of from south Asia to Africa, with resistance to first-line

Clinical trials - success

Probability of success entering clinical trials:
2000-2015



Clinical trials

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 Model

Phase Ia

Single Ascending Dose

Phase IIa

Data about optimal dose

Phase Ib

Multiple Different Doses

Phase IIb

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

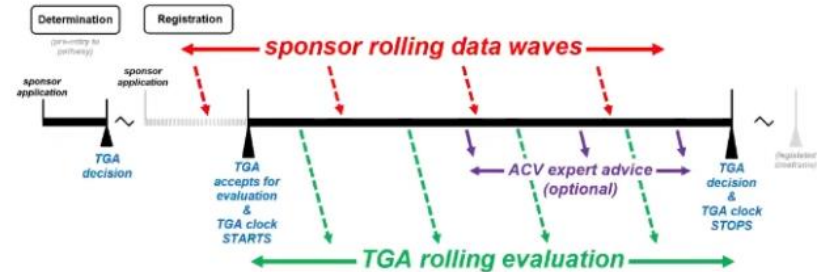
Standard (full) submission – in Australia, vaccines are evaluated as prescription medicines, not biological

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

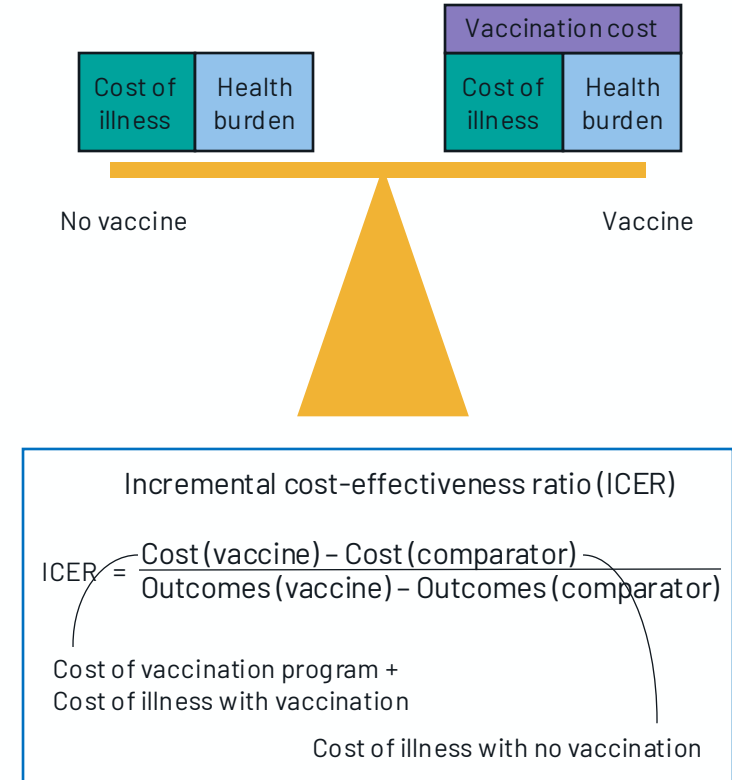
All new vaccines and extended cohorts for existing NIP vaccines must be recommended by the PBAC as **clinically and cost-effective** for the NIP.

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



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 term vaccinations