The KIDS RESEARCH INSTITUTE AUSTRALIA

DISCOVER · PREVENT · CURE

Vaccines: research to licensure (discovery to submission)

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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 IV

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What phase of clinical trials will work out whether a vaccine has an impact on the clinical disease of interest?

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What phase of clinical trials will work out whether a vaccine has an impact on the clinical disease of interest?

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Learning outcomes

- Vaccine design to clinical testing – how does it work and what do we know when we have finished a trial?
- Outline the process of vaccine development, from research to licensure

Learning objectives

To understand:

- Vaccine development and trial pipeline: bench to submission
- Purpose and characteristics of vaccine trials: phase I to III

Diphtheria	**SARS-CoV-2**	**Measles**		
RSV	**Rotavirus**	**Pneumococcus**	**Human papillomavirus**	**Salmonella typhi**

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 III

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 antigen
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Human Challenge Models

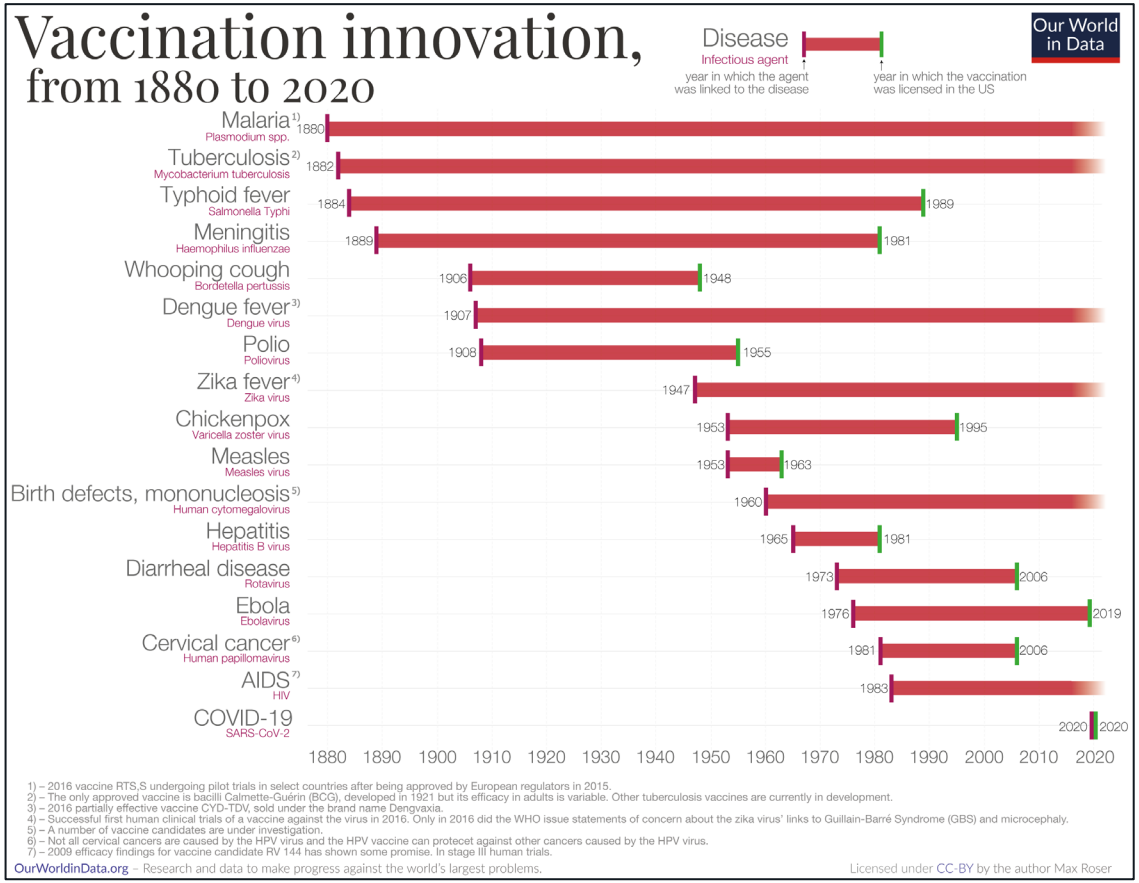
Phase Ia
Single Ascending Dose

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 a vaccine target



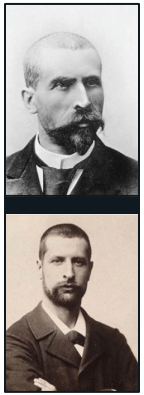
1821

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 (TAT)

1921

Park rolls out diphtheria campaign using TAT

Needed to test for immunity using the Schick test





1923

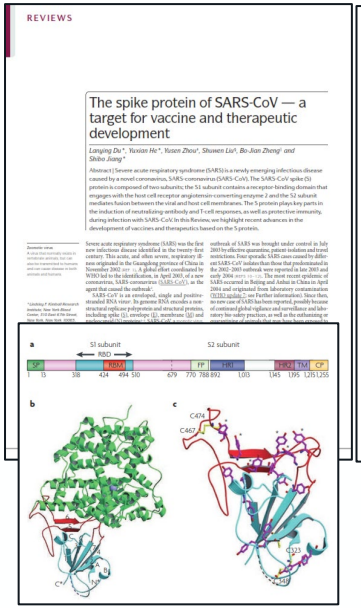
Gaston Ramon discovers way to inactivate toxin, creating a toxoid.

Product effective but immunogenicity not as great as diphtheria TAT.

1927

Gaston goes on to identify Alum as an adjuvant

Vaccine design: Choice of a vaccine target


REVIEWS

The spike protein of SARS-CoV — a target for vaccine and therapeutic development

Langlang Du*, Yuxian He*, Yanze Zhou*, Shuwen Liu*, Bo-Jian Zheng‡ and Shibo Jiang*

Abstract | Severe acute respiratory syndrome (SARS) is a newly emerging infectious disease caused by a novel coronavirus, SARS-coronavirus (SARS-CoV). The SARS-CoV spike (S) protein is composed of two subunits; the S1 subunit contains a receptor-binding domain that engages with the host cell receptor angiotensin-converting enzyme 2 and the S2 subunit mediates fusion between the viral and host cell membranes. The S protein plays key parts in the induction of neutralizing antibody and T cell responses, as well as protective immunity, during infection with SARS-CoV. In this Review, we highlight recent advances in the development of vaccines and therapeutics based on the S protein.

Zoonotic virus
A virus that normally exists in vertebrate animals, but can also be transmitted to humans and can cause disease in both animals and humans.

Severe acute respiratory syndrome (SARS) was the first new infectious disease identified in the twenty-first century. This acute, and often severe, respiratory illness originated in the Guangdong province of China in November 2002 [1–3]. A global effort coordinated by the World Health Organization (WHO) led to the end of the SARS outbreak in April 2003, of a new coronavirus, SARS-coronavirus (SARS-CoV), as the agent that caused the outbreak[4].

SARS-CoV is an enveloped, single and positive-stranded RNA virus. Its genome RNA encodes a non-structural replicase polyprotein and structural proteins, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins. To date, no new case of SARS has been reported, possibly because of continued global vigilance and surveillance and laboratory bio-safety practices, as well as the euthanizing or quarantining of civets that are the intermediate host of SARS-CoV[5–7]. However, the possibility of re-emergence of SARS-CoV from animal reservoirs or laboratory accidents cannot be ruled out[8–10]. Therefore, the development of vaccines and therapeutics to prevent and control SARS-CoV infection is still necessary.

outbreak of SARS was brought under control in July 2003 by effective quarantine, patient isolation and travel restrictions. Four sporadic SARS cases caused by different SARS-CoV isolates than those that predominated in the 2002–2003 outbreak were reported in late 2003 and early 2004 (REFS 11,12). The first case occurred in a SARS-scarred nurse in Beijing and Anhui in China in April 2004 and originated from laboratory contamination (TABLE 1; see Further information). Since then, no new case of SARS has been reported, possibly because of continued global vigilance and surveillance and laboratory bio-safety practices, as well as the euthanizing or quarantining of civets that are the intermediate host of SARS-CoV[5–7]. However, the possibility of re-emergence of SARS-CoV from animal reservoirs or laboratory accidents cannot be ruled out[8–10]. Therefore, the development of vaccines and therapeutics to prevent and control SARS-CoV infection is still necessary.


Article

A new coronavirus associated with human respiratory disease in China

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Check for updates

Wei Wu[1,2], Xu Zhao[1,2], Bin Yu[1,2], Yao-Wei Chen[1,2], Wen Wang[1,2], Zhi-Gang Song[1], Yi Hu[1,2], Zhao-Hu Tao[1], Jun-Hua Tian[1], Yuan-Yuan Pei[1], Ming-Li Yuan[1], Yu-Ling Zhang[1], Fa-Hui Dai[1], Yi Liu[1], Qi-Min Wang[1], Jian-Jun Zheng[1], Lin Xu[1], Edward C. Holmes[2,3] & Yong-Zhen Zhang[1,2,4]*

Emerging infectious diseases, such as severe acute respiratory syndrome (SARS) and Zika virus disease, present a major threat to public health[1–3]. Despite intense research efforts, how, when and where new diseases appear are still a source of considerable uncertainty. A severe respiratory disease was recently reported in Wuhan, Hubei province, China. As of January 26, 2020, at least 1,975 cases had been reported, and the first patient was hospitalized on 12 December 2019. Epidemiological investigations have suggested that the outbreak was associated with a seafood market in Wuhan. Here we study a single patient who was a worker at the market and who was admitted to the Central Hospital of Wuhan on 26 December 2019 while experiencing a severe respiratory syndrome that included fever, dizziness and a cough. Metagenomic RNA sequencing[4] of a sample of bronchoalveolar lavage fluid from the patient identified a new RNA virus strain from the family *Coronaviridae*, which is designated here 'WH-Human 1' coronavirus (and has also been referred to as '2019-nCoV'). Phylogenetic analysis of the complete viral genome (29,903 nucleotides) revealed that the virus was most closely related (89.1% nucleotide similarity) to a group of SARS-like coronaviruses (genus Betacoronavirus, subgenus Sarbecovirus) that had previously been found in bats in China[5]. This outbreak highlights the ongoing ability of viral spill-over from animals to cause severe disease in humans.

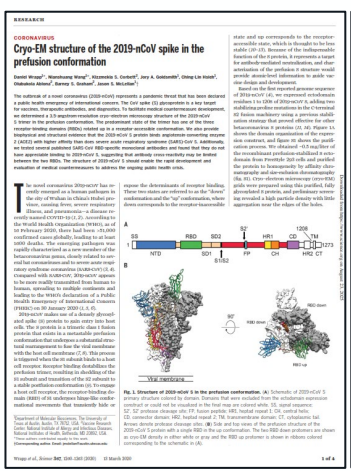
The patient studied was a 41-year-old man with no history of hepatitis, tuberculosis or diabetes. He was admitted to and hospitalized in the Central Hospital of Wuhan on 26 December 2019, 6 days after the onset of disease. The patient reported fever, chest tightness, unproductive cough, pain and weakness for 1 week on presentation (Table 1). Physical examination of cardiovascular, abdominal and neurological characteristics was that these were normal. Mild hypoxaemia was present (oxygen at 90–93% on room air). Laboratory tests but white blood cell and blood platelet counts were normal as a complete blood count test. Elevated level of C-reactive protein (41.4 mg/l of blood; reference range, 0–6 mg/l) was observed and the levels of aspartate aminotransferase, lactic dehydrogenase and creatine kinase were slightly elevated in blood chemistry tests. The patient had mild hypoxaemia with oxygen levels of 67 mm Hg as determined by an arterial blood gas test. On the first day of admission (a day after the onset of disease), chest radiographs were abnormal with air space shadowing such as ground-glass opacities, focal consolidation and patchy consolidation in both lungs (Extended Data Fig. 1). Computed tomography (CT) scans on day 3 revealed bilateral multiple mottling, lobar consolidation and patchy consolidation, especially in the lower lung (Extended Data Fig. 1a–d). A bronchoalveolar lavage fluid sample was collected on day 4 after the onset of disease (day 3 after admission) and was sent to the Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. [1]Department of Pulmonary and Critical Care Medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. [2]Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. [3]Sydney Institute for Infectious Diseases and Marie Bashir Institute for Infectious Diseases and Biosecurity, School of Life and Environmental Sciences and School of Medical Sciences, The University of Sydney, Sydney, New South Wales, Australia. [4]School of Public Health, Fudan University, Shanghai, China. *These authors contributed equally: Wei Wu, Xu Zhao, Bin Yu, Yao-Wei Chen, Wen Wang, Zhi-Gang Song, Yi Hu. ✉e-mail: zhangyongzhen@shphc.org.cn

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Novel coronavirus isolated



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


RESEARCH

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

David Wrapp[1†], Nianshuang Wang[1†], Kizzmekia S. Corbett[2], Jory A. Goldsmith[1], Ching-Lin Hsieh[1], Olubukola Abiona[2], Barney S. Graham[2], Jason S. McLellan[1]*

The outbreak of a novel coronavirus (2019-nCoV) represents a pandemic threat that has been declared a public health emergency of international concern. The CoV spike (S) glycoprotein is a key target for vaccines, therapeutic antibodies, and diagnostics. To facilitate medical countermeasure development, we determined a 3.5-angstrom-resolution cryo-electron microscopy structure of the 2019-nCoV S trimer in the prefusion conformation. The predominant state of the trimer has one receptor-binding domain (RBD) elevated to a receptor-accessible position. We also provide biochemical and structural evidence that the 2019-nCoV S protein binds angiotensin-converting enzyme 2 (ACE2) with higher affinity than does severe acute respiratory syndrome (SARS)-CoV S. Additionally, we tested several published SARS-CoV RBD-specific monoclonal antibodies and found that they do not appear to recognize binding to 2019-nCoV S, suggesting that antibody cross-reactivity may be limited between the two RBDs. The structure of 2019-nCoV S should enable the rapid development and evaluation of medical countermeasures to address the ongoing public health crisis.

The novel coronavirus 2019-nCoV has recently emerged as a human pathogen in the city of Wuhan in China's Hubei province, causing fever, severe respiratory illness, and pneumonia—a disease recently named COVID-19 [1, 2]. According to the World Health Organization (WHO), as of 30 February 2020, there had been >31,000 confirmed cases globally, leading to at least 1000 deaths. The emerging pathogen was rapidly characterized as a new member of the betacoronavirus genus, closely related to several coronaviruses found in bats, but not to any of the previously known coronavirus (SARS-CoV) [3, 4]. Although SARS-CoV is thought to have originated in bats, it was readily transmitted from human to human, spreading to multiple continents and leading to the WHO's declaration of a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 [5, 6, 7].

2019-nCoV makes use of a densely glycosylated spike (S) protein to fuse entry into host cells. The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation that undergoes a substantial structural rearrangement to fuse the viral membrane with the host cell membrane [7, 8]. This process is initiated when the S protein binds to its host cell receptor. Receptor-binding destabilizes the prefusion trimer, resulting in shedding of the S1 subunit and transition of the S2 subunit to a stable postfusion conformation [9]. To engage a host cell receptor, the receptor-binding domain (RBD) of S1 undergoes hinge-like conformational movements that transiently hide or expose the determinants of receptor binding. These two states are referred to as the "down" conformation and the "up" conformation, where down corresponds to the receptor-inaccessible state and up corresponds to the receptor-accessible state, which is thought to be less stable [10–13]. Because of the indispensable function of the S protein, it represents a target for antibody-mediated neutralization, and characterization of the prefusion S structure would provide atomic-level information to guide vaccine design and development.

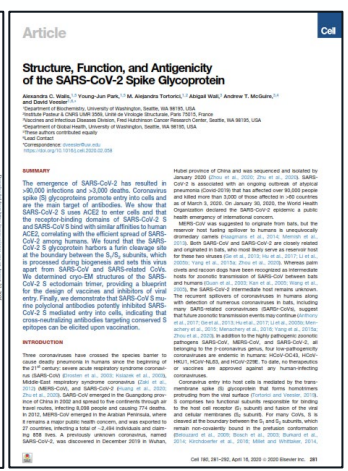
Based on the first reported genome sequence of 2019-nCoV [4], we expressed ectodomain residues 1 to 1206 of 2019-nCoV S, adding two stabilizing proline substitutions at the top of central S1 fusion machinery using a previous stabilization strategy that proved effective for other betacoronavirus S proteins [10, 14]. Figure 1A shows the domain organization of the expression construct, and figure 1B shows the purification process. We obtained ~0.5 mg/liter of the recombinant prefusion-stabilized S ectodomain from Freestyle 293 cells and purified the protein to homogeneity by affinity chromatography and size-exclusion chromatography (fig. S1). Cryo-electron microscopy (cryo-EM) grids were prepared using this purified, fully glycosylated S protein, and preliminary screening revealed a high particle density with little aggregation over the edges of the holes.

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


Cell

Article

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

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SUMMARY

The emergence of SARS-CoV-2 has resulted in >90,000 infections and >3,000 deaths. Coronavirus spike (S) glycoproteins promote entry into cells and are the main target of antibodies. We show that SARS-CoV-2 S uses ACE2 to enter cells and that the receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2, correlating with the efficient spread of SARS-CoV-2 among humans. We found that the SARS-CoV-2 S glycoprotein harbors a furin cleavage site at the boundary between the S1/S2 subunits, which is processed during biogenesis and sets this virus apart from SARS-CoV and SARS-related CoVs. We determined cryo-EM structures of the SARS-CoV-2 S ectodomain trimer, providing a blueprint for the design of vaccines and inhibitors of viral entry. Finally, we demonstrate that SARS-CoV S mutants with enhanced ACE2 affinity can mediate efficient entry into human airway cells and are blocked by SARS-CoV antibodies, indicating that variants that may emerge in humans are likely to be covered by vaccines based on SARS-CoV S.

Hubei province of China and was sequenced and isolated by January 2020 (Zhou et al., 2020; Zhu et al., 2020). SARS-CoV-2 is associated with an ongoing outbreak of atypical pneumonia (Covid-2019) that has affected over 93,000 people and killed more than 3,200 of those affected in >80 countries as of March 3, 2020. On January 30, 2020, the World Health Organization declared the SARS-CoV-2 epidemic a public health emergency of international concern.

MERS-CoV was suggested to originate from bats, but the reservoir host fueling spillover to humans is unequivocally zoonotary camels (Haagmans et al., 2014; Memish et al., 2013b; Both SARS-CoV and SARS-CoV-2 are closely related and originated in bats, who most likely serve as reservoir host for these two viruses (Ge et al., 2013; Hu et al., 2017; Li et al., 2005; Yang et al., 2015a; Zhou et al., 2020a). Molecular determinants and racoon dogs have been recognized as intermediate hosts for zoonotic transmission of SARS-CoV between bats and humans (Guan et al., 2003; Kan et al., 2005; Wang et al., 2005). The recurrent spillovers of coronaviruses in humans along with detection of numerous coronaviruses in bats, including many SARS-related coronaviruses (SARSr-CoVs), suggest that future zoonotic transmission events may continue (Anthony et al., 2017; Ge et al., 2013; Hu et al., 2017; Li et al., 2005b; Menachery et al., 2015; Menachery et al., 2016; Yang et al., 2015a; Zhou et al., 2020). In addition to the highly pathogenic zoonotic pathogens SARS-CoV, MERS-CoV, and SARS-CoV-2, all emerging in the β-coronavirus genus, the low-pathogenicity coronaviruses are endemic in humans: HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E. To date, no therapeutics or vaccines are approved against any human-infecting coronaviruses.

Coronavirus entry into host cells is mediated by the transmembrane spike (S) glycoprotein that forms homotrimers protruding from the viral surface (Fehr and Perlman, 2015). Each monomer contains two subunits: S1, which is responsible for host cell receptor (S) subunit and fusion of the viral and cellular membranes (S2 subunit). For many CoVs, S is cleaved at the boundary between the S1 and S2 subunits, which remain non-covalently bound in the prefusion conformation (Belouzard et al., 2009; Bosch et al., 2003; Burkard et al., 2014; Kirchdoerfer et al., 2018; Millet and Whittaker, 2014;

Department of Veterinary and Biomedical Sciences, University of Minnesota, Saint Paul, MN, USA. [2]Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN, USA. *These authors contributed equally: Jun Wang, Yang Jin, Ke Xu. ✉e-mail: fengzj@ioz.ac.cn

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


Article

Structural basis of receptor recognition by SARS-CoV-2

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Check for updates

Jun Shang[1†], Gang Ye[1†], Ke Shi[2†], Yushun Wan[1†], Chuming Luo[1], Hideki Aihara[2], Qibin Geng[1], Ashley Auerbach[3] & Fang Li[1]*

A novel severe acute respiratory syndrome coronavirus (SARS-like coronavirus (SARS-CoV-2) recently emerged and is rapidly spreading in humans, causing COVID-19[1,2]. A key to tackling this pandemic is to understand the receptor recognition mechanism of the virus, which regulates its infectivity, pathogenesis and host range. SARS-CoV-2 and SARS-CoV recognize the same receptor—angiotensin-converting enzyme 2 (ACE2)—in humans[3,4]. Here we determined the crystal structure of the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 (engineered to facilitate crystallization) in complex with ACE2. In comparison with the SARS-CoV RBD, an ACE2-binding ridge in SARS-CoV-2 RBD has a more compact conformation; moreover, several residue changes in the SARS-CoV-2 RBD stabilize two virus-binding hotspots at the RBD–ACE2 interface. These structural features of SARS-CoV-2 RBD increase its ACE2-binding affinity. Additionally, we show that RaTG13, a bat coronavirus that is closely related to SARS-CoV-2, also uses human ACE2 as its receptor. The differences among SARS-CoV-2, SARS-CoV and RaTG13 in ACE2 recognition shed light on the potential animal-to-human transmission of SARS-CoV-2. This study provides guidance for intervention strategies that target receptor recognition by SARS-CoV-2.

The sudden emergence and rapid spread of SARS-CoV-2 is challenging global health and economy[1,2]. SARS-CoV-2 has caused many more infections, deaths and economic disruptions than SARS-CoV in 2002–2003[3]. The origin of SARS-CoV-2 remains unclear. Bats are considered the original source of SARS-CoV-2 because a closely related coronavirus, RaTG13, has been identified in bats[2]. Whether pangolins are the direct host that led to the public bat-to-human transmission of SARS-CoV-2 is unknown. Clinically approved vaccines or drugs that specifically target SARS-CoV-2 are also lacking. Receptor recognition by coronaviruses is an important determinant of viral infectivity, pathogenesis and host range[3,4]. It promotes a major target for vaccination and antiviral strategies[5]. Here we elucidate the structural and biochemical mechanisms of receptor recognition by SARS-CoV-2.

Receptor recognition by SARS-CoV has been extensively studied. A virus-surface spike protein mediates the entry of coronaviruses into host cells. The spike protein of SARS-CoV contains a RBD that specifically recognizes ACE2 as its receptor[3,4]. A series of crystal structures of the SARS-CoV RBD from different strains in complex with ACE2 from various species have been determined[6–8]. Our group previously showed that SARS-CoV RBD contains a core and a receptor-binding motif (RBM); the RBM mediates contacts with ACE2. The surface of ACE2 contains two virus-binding hotspots that are essential for SARS-CoV binding. Several naturally selected mutations in the SARS-CoV RBM surround these hotspots and regulate the infectivity, pathogenesis, and cross-species and human-to-human transmission of SARS-CoV[9,10].

Because of the sequence similarity between the spike proteins of SARS-CoV and SARS-CoV-2, it was recently predicted that SARS-CoV-2 also uses ACE2 as its receptor[11], which has been validated by other studies[12–14]. Here we determined the structural basis of receptor recognition by SARS-CoV-2 and compared the ACE2-binding affinity among SARS-CoV-2, SARS-CoV and RaTG13. Our findings identify the molecular and structural features of the SARS-CoV-2 RBM that result in tight ACE2 binding and provide insights into the animal origin of SARS-CoV-2, and can help to guide intervention strategies that target SARS-CoV-2–ACE2 interactions.

To understand the structural basis of ACE2 recognition by SARS-CoV-2, we aimed to crystallize the SARS-CoV-2 RBD–ACE2 complex. We engineered a major target for vaccination and antiviral strategies[5]. Here we elucidate the structural and biochemical mechanisms of receptor recognition by SARS-CoV-2.

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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

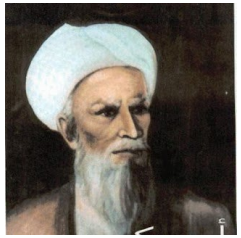
WHO declares COVID-19 a pandemic

December 2019 — January 2020 — February 2020 — March 2020 — April 2020

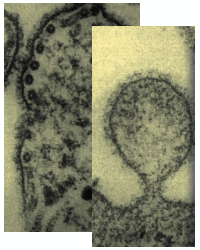
Vaccine design: Choice of the platform

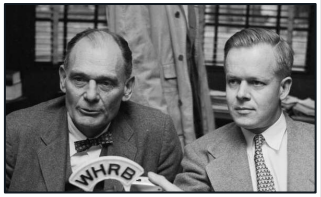
	Technology	Example pathogens
Protein	Purified antigen protein	Influenza, Diphtheria, Pertussis, Tetanus, Anthrax, COVID-19, RSV
	Protein-VLP (virus like particles)	Varicella, HPV, Hepatitis B, Malaria
Carbohydrate	Capsid Carbohydrate	Pneumococcal
	Carbohydrate-protein conjugate	Pneumococcal, Hib, Meningococcal 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

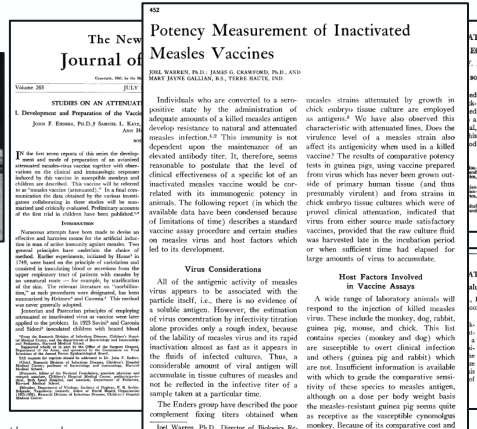


First clinical description attributed to Abu Bakr al-Razi





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



Potency Measurement of Inactivated Measles Vaccines

JOEL WARREN, PH.D., JAMES G. CRAWFORD, PH.D., AND MARY JAYNE GALLIAN, B.S., TERRE HAUTE, IND.

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.

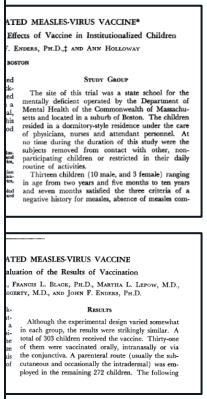
The Enders group have described the poor complement fixing titers obtained when measles strains attenuated by growth in chick embryo tissue culture are employed as antigens.[3] We have also observed this characteristic with attenuated lines. Does the virulence level of a measles strain also affect its 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 grade 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 receptive 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,

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

Measles Vaccine Clinical trials



ATED MEASLES-VIRUS VACCINE*

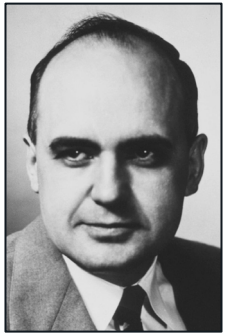
Effects of Vaccine in Institutionalized Children

ATED MEASLES-VIRUS VACCINE

aluation of the Results of Vaccination

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)

Later combined with attenuated Jeryl Lynn strain of Mump virus

9th Cent

1954

1960

1963

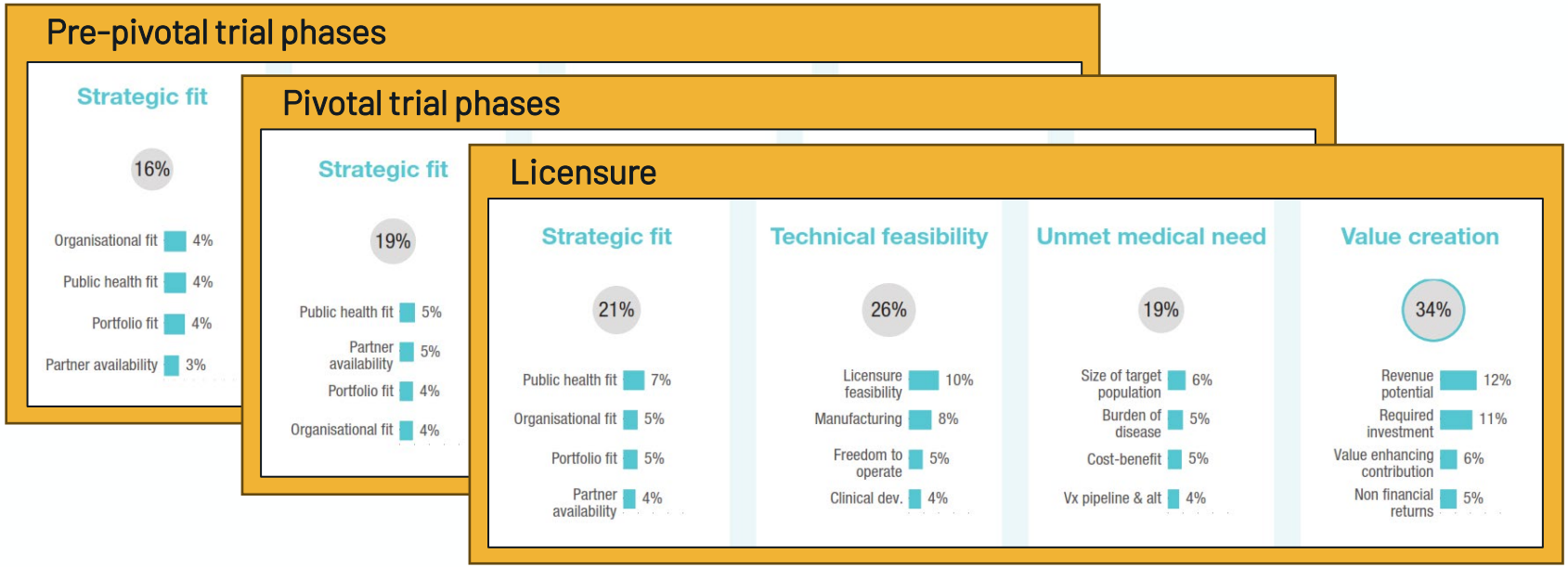
1960

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 company considerations



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

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

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 common/severe side effects and adverse reactions

Animal models have traditionally been a critical component to pre-clinical testing

Pre-clinical testing

Stage of development	Type of Study	Objective
Research	• Host-pathogen interactions & virulence • Immunological studies (humoral and cellular responses to vaccination) • Formulation-and-delivery studies • Vaccine efficacy • Vaccine mechanisms of action	• Identification of virulence factors (ie through KO strains) • Identification of virulence factors by in-vivo expression studies • **Characterisation of immune response following infection** • **Characterisation of the immune response following vaccination** • **Comparison of different formulations, different adjuvants, delivery systems and routes of immunisation** • Assessment of the protective ability of the vaccine in well-defined animal models • **Definition of correlates of protection to be used as clinical endpoints**
Development	• Antigen dose ranging studies • Toxicology studies • Stability studies • Lot to lot consistency	• **Evaluation of immunogenicity induced by different amount/combo of antigen** • Evaluation of the safety profile • **Assessment of the stability of the final formulation and define the proper storage conditions** • Demonstration that different vaccine lots maintain the same physicochemical and immunological properties
Quality Control	• *In vivo* potency studies • Rabbit pyrogenicity test	• **Demonstrate the immunogenicity of efficacy of each vaccine lot produced** • Demonstrate that the vaccine is no pyrogenic

Chiarot E et al, Current Opin Micro 2022. Animal models in vaccinology

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 and similar to human;** • **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:

- Invertebrate models (Galleria mellonella larvae, Zebrafish)
- 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

Use of alternatives being drive by both ethical, financial and often logistic factors

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 III

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

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Human Challenge Model

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

RSV	Rotavirus	Pneumococcus	Human papillomavirus	Salmonella typhi	SARS-CoV-2

Clinical trials

1956 — **RSV discovered**

1960s — **RSV vaccine development stalls**
Formalin-inactivated, pediatric RSV vaccine candidate shown to cause enhanced respiratory disease in RSV-naïve infants during first natural infection

1998 — **Short-acting mAb licensed**
Palivizumab

2010s — **Breakthroughs in RSV understanding spark product development renaissance**

2013 — **Key technology—RSV pre-fusion (F) protein**
- Pre-fusion conformation of the F protein discovered as safe and promising immune target
- Neutralizing antibodies target pre-F protein and prevent virus from fusing to and infecting host cells
- Removes risk of causing enhanced disease

2023 — **Long-acting mAb licensed**
Nirsevimab (pre-F)

2023 — **Maternal vaccine and vaccines for older adults licensed**
Recombinant pre-F vaccines approved in US and Europe

2024 — **Maternal vaccine approved in Australia**

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RESPIRATORY SYNCYTIAL VIRUS DISEASE IN INFANTS DESPITE PRIOR ADMINISTRATION OF ANTIGENIC INACTIVATED VACCINE[1, 2]

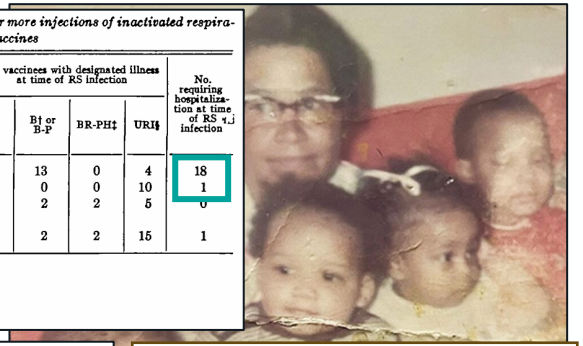
HYUN WHA KIM, JOSE G. CANCHOLA[3], CARL D. BRANDT, GLORIA PYLES, ROBERT M. CHANOCK, KEITH JENSEN, AND ROBERT H. PARROTT[4]

(Received for publication August 8, 1968)

RS virus infection and illness in groups of infants after receiving 1 or more injections of inactivated respiratory syncytial and parainfluenza vaccines

Vaccine received	No. vaccinees	No. vaccinees with later RS infection as indicated by			No. vaccinees with designated illness at time of RS infection				No. requiring hospitalization at time of RS infection
		Virus recovery	CF antibody rise	Virus recovery and/or CF rise	P*	B† or B-P	BR-PH‡	URI§	
RS lot 100	31	18	20	23	6	13	0	4	18
Para 1 lot 23	20	7	12	12	2	0	0	10	1
Trivalent parainfluenza lot 6279	20	7	9	9	0	2	2	5	0
Total parainfluenza	40	14	21	21	2	2	2	15	1

* P = Pneumonia.
† B = Bronchiolitis.
‡ BR-PH = Severe bronchitis-pharyngitis.
§ URI = Mild rhinitis, pharyngitis and/or bronchitis.



The severity of illness in the RS vaccinees was greater than in unvaccinated infants and children who were admitted to the hospital during the community wide outbreak of RS virus infection. The mean period of hospitalization of the RS vaccinees was 10.5 days, whereas the mean period of 30 age-matched unvaccinated infants with RS bronchiolitis and/or pneumonia was 6.7 days.

Two infants died, one at age 14 months, the other at age 16 months. Each had received three inoculations, one beginning at age two months, the other at age five months. The major findings at post mortem examination were extensive bronchopneumonia and patchy atelectasis with emphysema and pneumothorax in one infant.

Clinical trials – Maternal RSV vaccine

Background factors:
Issue of global importance
Common clinical outcome
High risk patient group
Previous concerns about safety

Clinical testing

Phase I
Phase II
Phase IV

	Phase I	Phase II	Phase III
Population			
Intervention	Safety	Identify optimal formulation, doses and schedules	Safety and efficacy
Comparator	Tens of participants	Safety	Thousands of participants
Outcome		Hundreds of participants	

Clinical trials – Maternal RSV vaccine

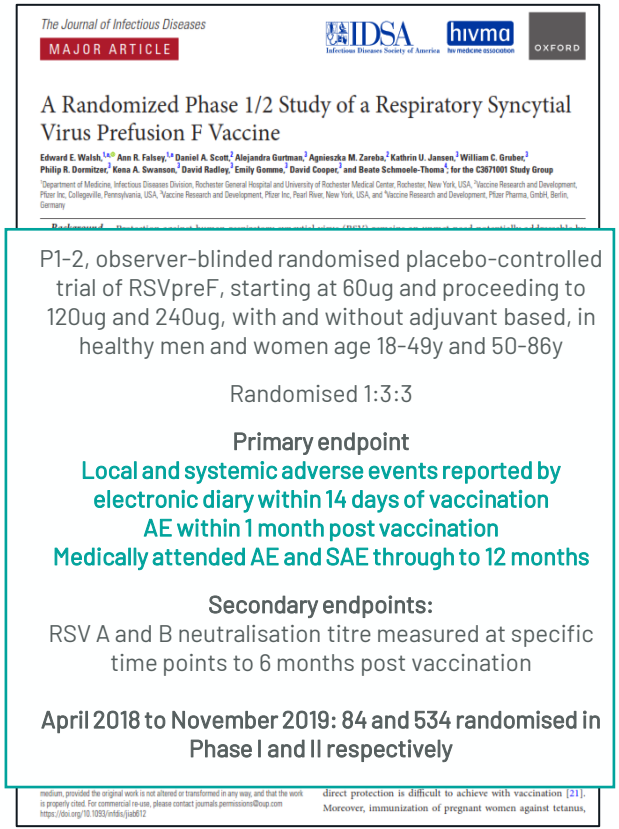
Background factors:
Issue of global importance
Common clinical outcome
High risk patient group
Previous concerns about safety

Clinical testing

Phase I
Phase II
Phase IV

	Phase I	Phase II	Phase III
Population	Healthy men and women	Healthy pregnant women	Healthy pregnant women
Intervention	Escalating doses with and without adjuvant	Two fixed doses with and without adjuvant	Single dose without adjuvant
Comparator	Placebo	Placebo	Placebo
Outcome	Safety outcomes in vaccine recipients Immunogenicity (2ndary)	Maternal and infant safety Immunogenicity at time of delivery (mother & infant)	Clinical outcomes in infants Severe RSV infections in infants aged <6m Maternal and infant safety

Clinical trials – Maternal RSV vaccine



The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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

Edward E. Walsh,[1,a] Ann R. Falsey,[1,a] Daniel A. Scott,[2] Alejandra Gurtman,[3] Agnieszka M. Zareba,[2] Kathrin U. Jansen,[3] William C. Gruber,[2] Philip R. Dormitzer,[2] Kena A. Swanson,[2] David Radley,[2] Emily Gomme,[2] David Cooper,[3] and Beate Schmoele-Thoma[4]; for the C3671001 Study Group

[1]Department of Medicine, Infectious Diseases Division, Rochester General Hospital and University of Rochester Medical Center, Rochester, New York, USA, [2]Vaccine Research and Development, Pfizer Inc, Collegeville, Pennsylvania, USA, [3]Vaccine Research and Development, Pfizer Inc, Pearl River, New York, USA, and [4]Vaccine Research and Development, Pfizer Pharma, GmbH, Berlin, Germany

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

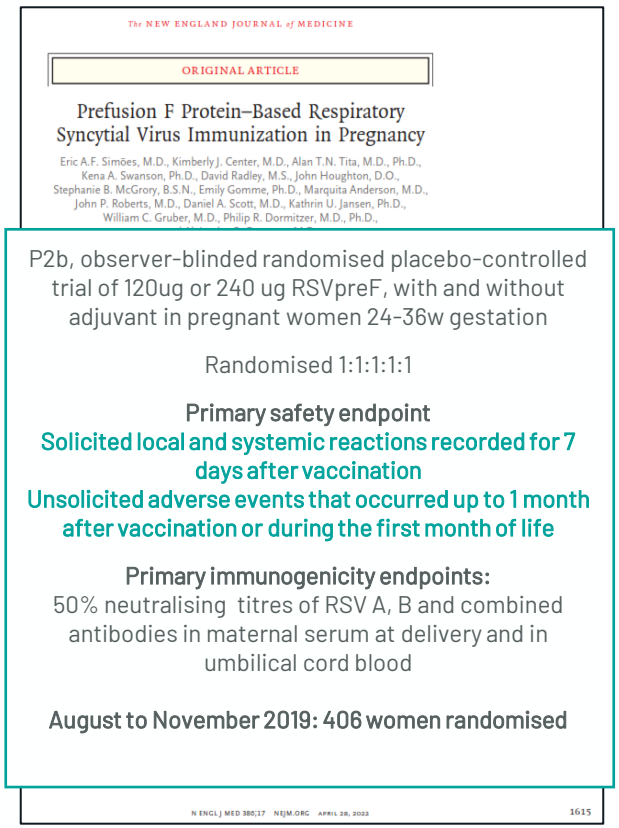
Primary endpoint

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



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. McGrory, 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 1:1:1:1:1

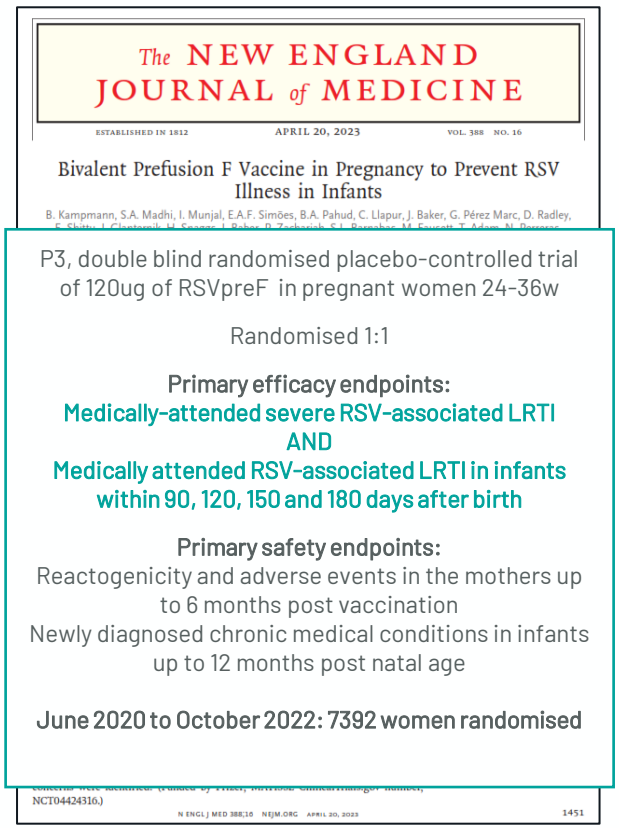
Primary safety endpoint

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

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley,

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

Randomised 1:1

Primary efficacy endpoints:

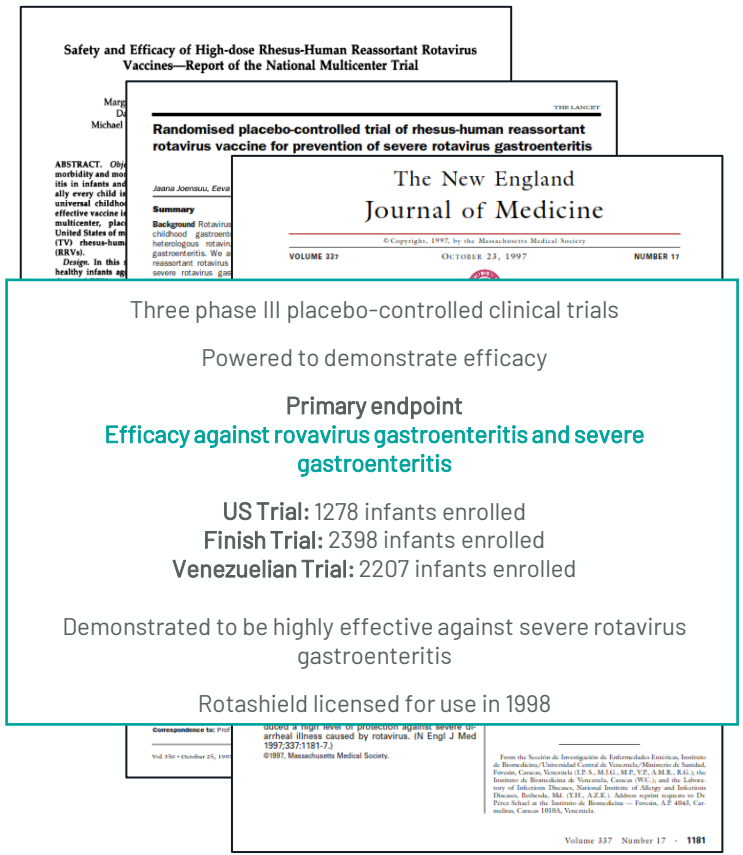
Medically-attended severe RSV-associated LRTI AND
Medically attended RSV-associated LRTI in infants within 90, 120, 150 and 180 days after birth

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

Rare safety endpoints


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

THE LANCET

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

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 337 OCTOBER 23, 1997 NUMBER 17

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Volume 337 Number 17 · 1181

Three phase III placebo-controlled clinical trials

Powered to demonstrate efficacy

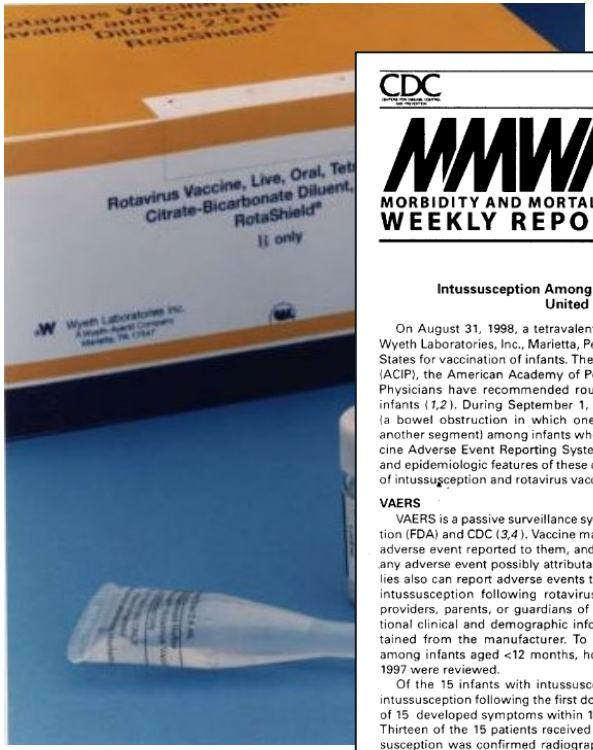
Primary endpoint

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



CDC

July 16, 1999 / 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 Measles Elimination — Southern Africa, 1996–1998
590 Recommendations of the Advisory Committee on Immunization Practices: Revised Recommendations for Routine Poliomyelitis 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 to 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 reaction, 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

Rare safety endpoints – 2nd gen. rotavirus vaccines

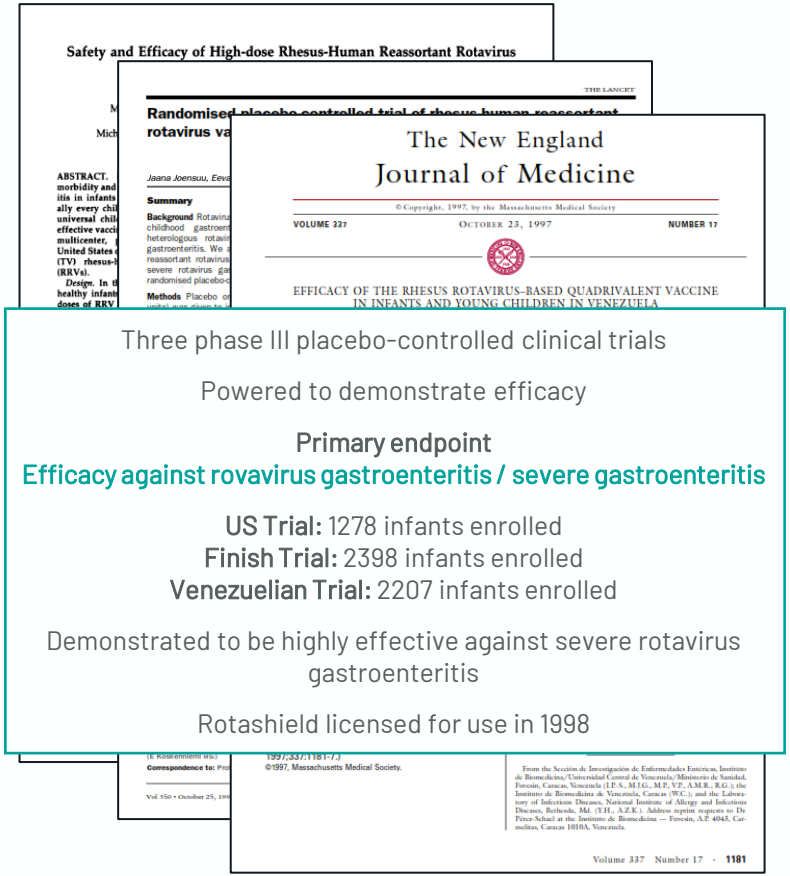
Background factors:
Issue of global importance
Common clinical outcome
Previous rare but significant safety signal (intussusception)

Clinical testing

Phase I
Phase II
Phase III

	Phase I	Phase II	Phase III
Population	Healthy adults, then toddlers, then infants	Healthy infants	Healthy infants
Intervention	Two-three doses of rotavirus vaccine strain	Two-three doses of rotavirus vaccine strain	Two-three doses of rotavirus vaccine strain
Comparator	Placebo	Placebo	Placebo
Outcome	Solicited symptoms including fever, diarrhoea Immunogenicity and shedding (2ndary)	Solicited symptoms including fever, diarrhoea Efficacy (2ndary)	Intussusception Any SAE Severe rotavirus gastroenteritis

Rare safety endpoints – 2nd gen. rotavirus vaccines



Three phase III placebo-controlled clinical trials

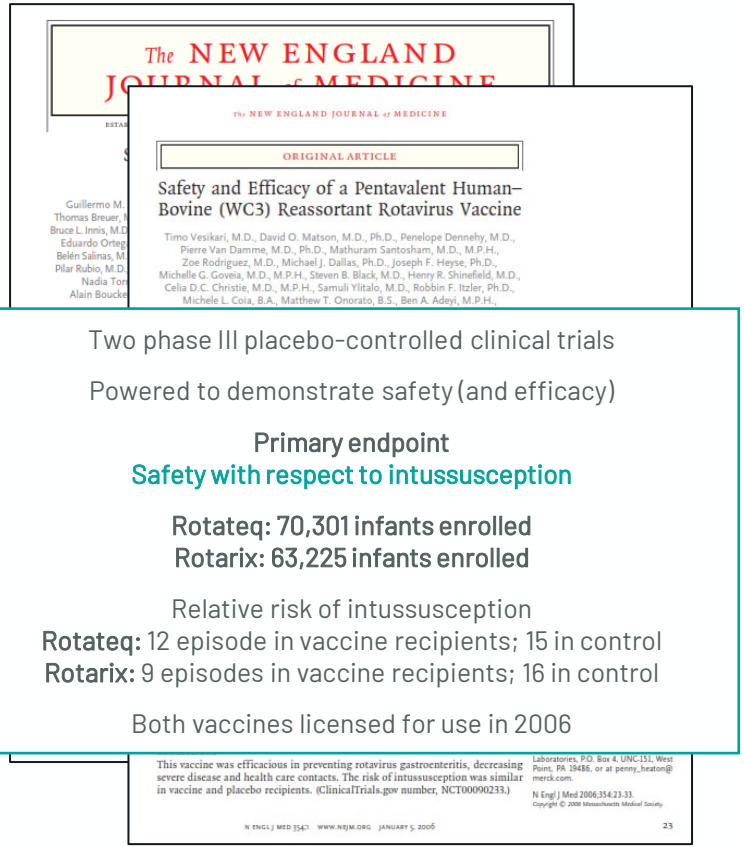
Powered to demonstrate efficacy

Primary endpoint
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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)

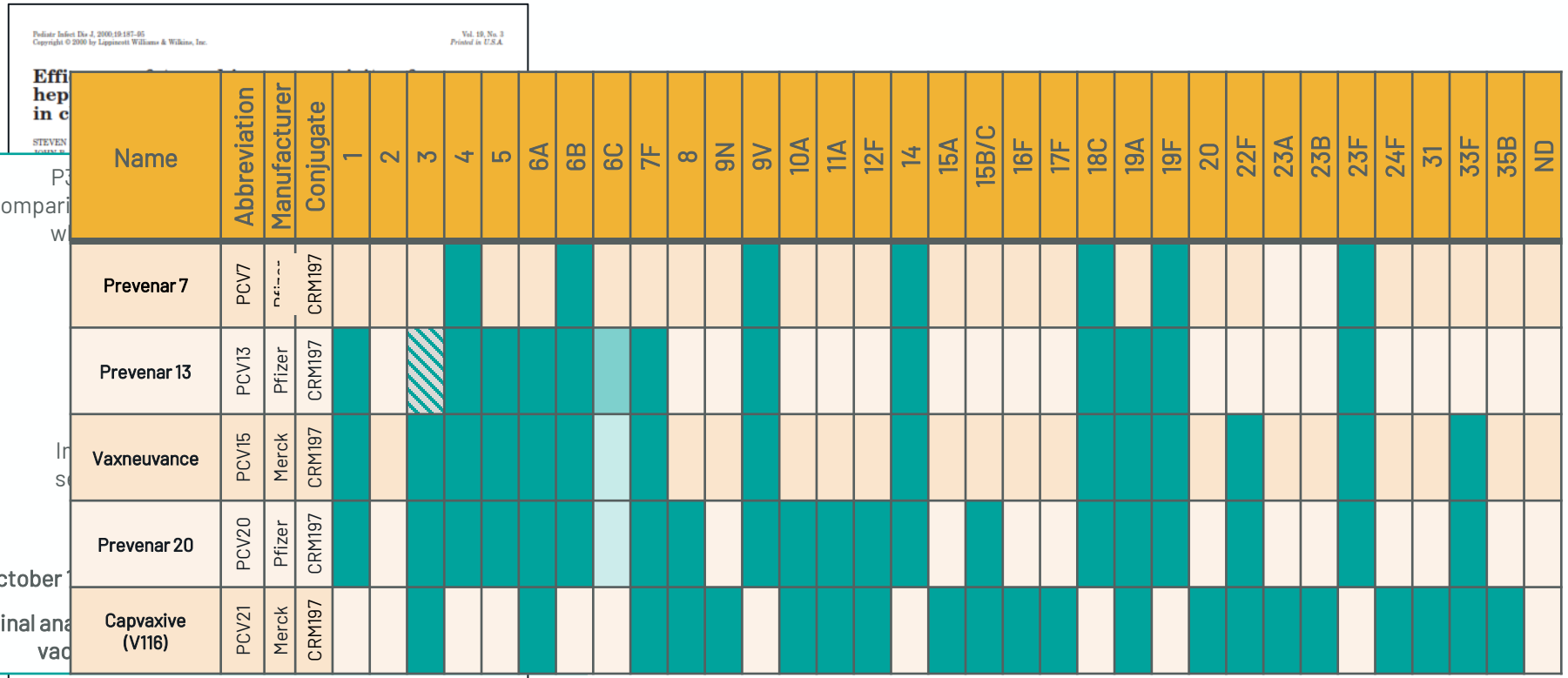
Primary endpoint
Safety with respect to intussusception

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

Broader protection



Broader protection – higher valency PCV in children

Background factors:
Issue of global importance
Uncommon clinical outcome
Existing phase III data for vaccines with fewer serotypes

Clinical testing

Phase I
Phase II
Phase III

	Phase I	Phase II	Phase III
Population	Healthy adults aged 18-49 years	Healthy infants	Healthy infants
Intervention	1 dose of PCV20	4 doses of PCV20	4 doses of PCV20
Comparator	1 dose of dTpa	4 doses of PCV13	4 doses of PCV13
Outcome	Serotype specific antibody titres after dose 1 Safety: local and systemic events within 14d of dose 1	Safety: local and systemic events within 7d of dose 1 and 1m of dose 3/4	Serotype specific antibody titres after dose 4 Proportion with a serotype specific IgG concentration

Broader protection – higher valency PCV in children

Pediatr Infect Dis J. 2000;19:187–95
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Vol. 19, No. 3
Printed in U.S.A.

Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children

STEVEN BLACK, MD, HENRY SHINEFIELD, MD, BRUCE FIREMAN, MA, EDWIN LEWIS, MPH, PAULA RAY, MPH,

P3, double blind randomised controlled trial comparing 7vPCV and conjugate MenC vaccine (CRM197) given at 2,4,6 and 12-15 months of age

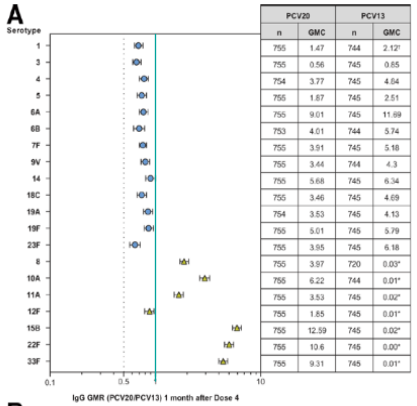
Randomised 1:1

Primary endpoints:
IPD caused by a vaccine serotype

Secondary endpoints:
Impact on IPD due to any serotype
Impact on otitis media visits, OM episodes, severe OM episodes and grommit insertion
Vaccine safety
Immunogenicity

October 1995 and August 1998: 37868 children randomised

Final analysis: 39 episodes in controls vs 1 episode in PCV vaccinated (efficacy 97.4%; 82.7-99.9)



Serotype	PCV20 n	PCV20 GMC	PCV13 n	PCV13 GMC
1	755	1.47	744	2.12†
3	755	0.56	745	0.65
4	754	3.77	745	4.64
5	755	1.87	745	2.51
6A	755	9.01	745	11.69
6B	753	4.01	744	5.74
7F	755	3.91	745	5.18
9V	755	3.44	744	4.3
14	755	5.68	745	6.34
18C	755	3.46	745	4.69
19A	754	3.53	745	4.13
19F	755	5.01	745	5.79
23F	755	3.95	745	6.18
8	755	3.97	720	0.03*
10A	755	6.22	744	0.01*
11A	755	3.53	745	0.02*
12F	755	1.85	745	0.01*
15B	755	12.59	745	0.02*
22F	755	10.6	745	0.00*
33F	755	9.31	745	0.01*

Serotype	PCV20 n	PCV20 GMC	PCV13 n	PCV13 GMC
1	833	0.74	802	1.14
3	833	0.36	802	0.51
4	833	0.75	802	1.08
5	833	0.66	802	0.96
6A	833	1.95	802	2.69
6B	831	0.61	801	1.02
7F	833	1.71	802	2.29
9V	833	0.87	802	1.21
14	832	2.16	802	2.72
18C	833	1.31	802	1.71
19A	833	0.72	802	0.91†
19F	833	1.59	802	2.00
23F	833	0.82	802	1.25
8	833	1.8	794	0.02*
10A	833	1.21	803	0.01*
11A	833	1.39	803	0.02*
12F	833	0.55	803	0.01*
15B	833	4.4	803	0.03*
22F	833	3.71	803	0.01*
33F	833	1.49	802	0.02*

VACCINE REPORTS
OPEN

A Phase Three Study of the Safety and Immunogenicity of a Four-dose Series of 20-Valent Pneumococcal Conjugate Vaccine in Healthy Infants

Shelly Senders, MD, Nicola P. Klein, MD, PhD,† Noor Tamimi, MD,‡ Allison Thompson, MD,§ Gary Baugher, PharmD,‡ James Trammel, MS,‡ Yahong Peng, PhD,‡ Peter Giardina, PhD,§*

P3, double blind randomised controlled trial comparing 20vPCV and 13vPCV when given at 2,4,6 and 12-15 months of age

Randomised 1:1

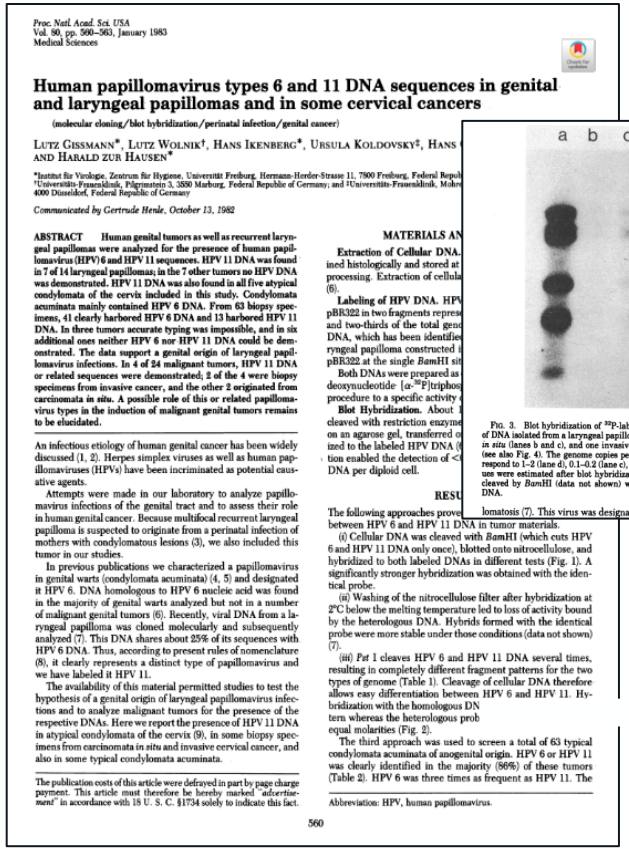
Primary endpoints:
Serotype specific IgG geometric mean concentrations (GMC) 1 month after dose 4
Proportion with predefined serotype-specific IgG concentrations 1 month after dose 3

Secondary endpoints:
Additional serological endpoints
Safety outcomes

May 2020 and September 2022: 1997 children randomised

Final analysis: GMCs were noninferior in all 13 matched serotypes in the 20v and 13v vaccine

Long term impacts



Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 560–563, January 1983
Medical Sciences

Human papillomavirus types 6 and 11 DNA sequences in genital and laryngeal papillomas and in some cervical cancers

(molecular cloning/blot hybridization/perinatal infection/genital cancer)

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Communicated by Gertrude Henle, October 13, 1982

ABSTRACT **Human genital tumors as well as recurrent laryngeal papillomas were analyzed for the presence of human papillomavirus (HPV) 6 and HPV 11 sequences. HPV 11 DNA was found in 7 of 14 laryngeal papillomas; in the 7 other tumors no HPV DNA was demonstrated. HPV 11 DNA was also found in all five atypical condylomata of the cervix included in this study. Condylomata acuminata mainly contained HPV 6 DNA. From 63 biopsy specimens, 41 clearly harbored HPV 6 DNA and 13 harbored HPV 11 DNA. In three tumors accurate typing was impossible, and in six additional ones neither HPV 6 nor HPV 11 DNA could be demonstrated. The data support a genital origin of laryngeal papillomavirus infections. In 4 of 24 malignant tumors, HPV 11 DNA or related sequences were demonstrated; 2 of the 4 were biopsy specimens from invasive cancer, and the other 2 originated from carcinomata *in situ*. A possible role of this or related papillomavirus types in the induction of malignant genital tumors remains to be elucidated.**

An infectious etiology of human genital cancer has been widely discussed (1, 2). Herpes simplex viruses as well as human papillomaviruses (HPVs) have been incriminated as potential causative agents.

Attempts were made in our laboratory to analyze papillomavirus infections of the genital tract and to assess their role in human genital cancer. Because multifocal recurrent laryngeal papilloma is suspected to originate from a perinatal infection of mothers with condylomatous lesions (3), we also included this tumor in our studies.

In previous publications we characterized a papillomavirus in genital warts (condylomata acuminata) (4, 5) and designated it HPV 6. DNA homologous to HPV 6 nucleic acid was found in the majority of genital warts analyzed but not in a number of malignant genital tumors (6). Recently, viral DNA from a laryngeal papilloma was cloned molecularly and subsequently analyzed (7). This DNA shares about 25% of its sequences with HPV 6 DNA. Thus, according to present rules of nomenclature (8), it clearly represents a distinct type of papillomavirus and we have labeled it HPV 11.

The availability of this material permitted studies to test the hypothesis of a genital origin of laryngeal papillomavirus infections and to analyze malignant tumors for the presence of the respective DNAs. Here we report the presence of HPV 11 DNA in atypical condylomata of the cervix (9), in some biopsy specimens from carcinomata *in situ* and invasive cervical cancer, and also in some typical condylomata acuminata.

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MATERIALS AN

Extraction of Cellular DNA. ined histologically and stored at processing. Extraction of cellula (6).

Labeling of HPV DNA. HPV pBR322 in two fragments represe and two-thirds of the total geno DNA, which has been identifie ryngeal papilloma constructed i pBR322 at the single *Bam*HI sit

Both DNAs were prepared as deoxynucleotide [α-^{32}P]triphos procedure to a specific activity

Blot Hybridization. About cleaved with restriction enzyme on an agarose gel, transferred o ized to the labeled HPV DNA (tion enabled the detection of <(DNA per diploid cell.

RESU

The following approaches prove between HPV 6 and HPV 11 DNA in tumor materials.

(i) Cellular DNA was cleaved with *Bam*HI (which cuts HPV 6 and HPV 11 DNA only once), blotted onto nitrocellulose, and hybridized to both labeled DNAs in different tests (Fig. 1). A significantly stronger hybridization was obtained with the identical probe.

(ii) Washing of the nitrocellulose filter after hybridization at 2°C below the melting temperature led to loss of activity bound by the heterologous DNA. Hybrids formed with the identical probe were more stable under those conditions (data not shown) (7).

(iii) *Pst* I cleaves HPV 6 and HPV 11 DNA several times, resulting in completely different fragment patterns for the two types of genome (Table 1). Cleavage of cellular DNA therefore allows easy differentiation between HPV 6 and HPV 11. Hybridization with the homologous DN tern whereas the heterologous prob equal molarities (Fig. 2).

The third approach was used to screen a total of 63 typical condylomata acuminata of anogenital origin. HPV 6 or HPV 11 was clearly identified in the majority (86%) of these tumors (Table 2). HPV 6 was three times as frequent as HPV 11. The

Abbreviation: HPV, human papillomavirus.

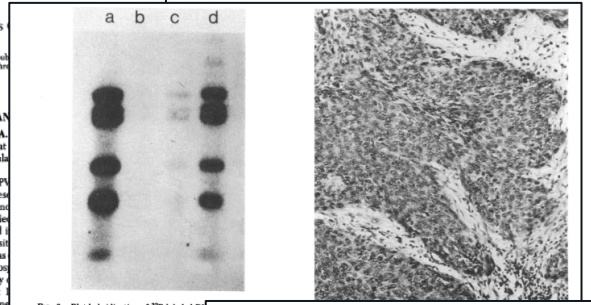
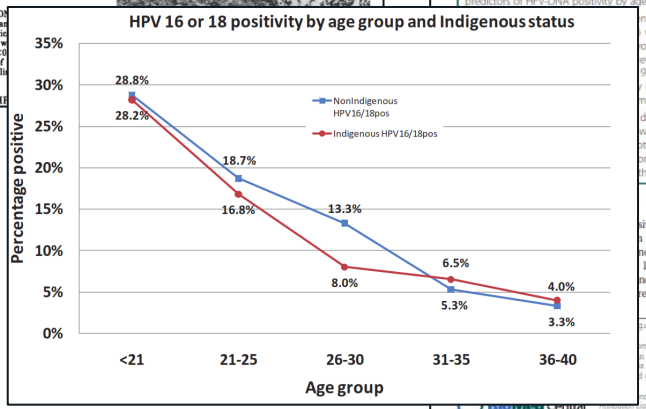
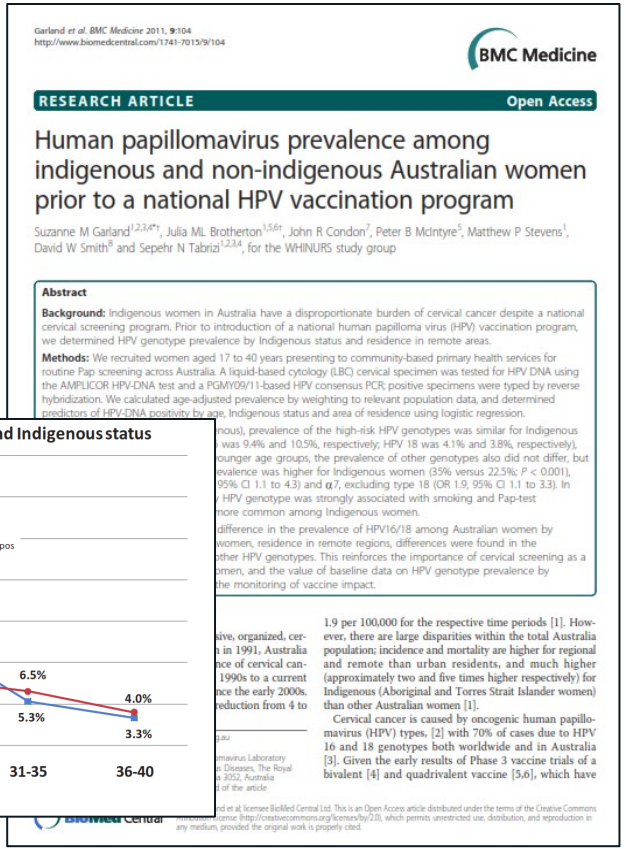


FIG. 3. Blot hybridization of ^{32}P-labeled DN of DNA isolated from a laryngeal papilloma (las *in situ* (lanes b and c), and one invasive cervic (see also Fig. 4). The genome copies per cell w respond to 1–2 (lane d), 0.1–0.2 (lane c), and <0 ues were estimated after blot hybridization of cleaved by *Bam*HI (data not shown) which li DNA.

lomatosis (7). This virus was designated HI





Garland *et al. BMC Medicine* 2011, **9**:104
http://www.biomedcentral.com/1741-7015/9/104

BMC Medicine

RESEARCH ARTICLE Open Access

Human papillomavirus prevalence among indigenous and non-indigenous Australian women prior to a national HPV vaccination program

Suzanne M Garland[1,2,3,4*†], Julia ML Brotherton[1,5,6†], John R Condon[7], Peter B McIntyre[5], Matthew P Stevens[1], David W Smith[8] and Sepehr N Tabrizi[1,2,3,4], for the WHINURS study group

Abstract

Background: Indigenous women in Australia have a disproportionate burden of cervical cancer despite a national cervical screening program. Prior to introduction of a national human papilloma virus (HPV) vaccination program, we determined HPV genotype prevalence by Indigenous status and residence in remote areas.

Methods: We recruited women aged 17 to 40 years presenting to community-based primary health services for routine Pap screening across Australia. A liquid-based cytology (LBC) cervical specimen was tested for HPV DNA using the AMPLICOR HPV-DNA test and a PGMY09/11-based HPV consensus PCR; positive specimens were typed by reverse hybridization. We calculated age-adjusted prevalence by weighting to relevant population data, and determined predictors of HPV-DNA positivity by age, Indigenous status and area of residence using logistic regression.

nous), prevalence of the high-risk HPV genotypes was similar for Indigenous was 9.4% and 10.5%, respectively; HPV 18 was 4.1% and 3.8%, respectively), ounger age groups, the prevalence of other genotypes also did not differ, but evalence was higher for Indigenous women (35% versus 22.5%; $P < 0.001$), 95% CI 1.1 to 4.3) and α7, excluding type 18 (OR 1.9, 95% CI 1.1 to 3.3). In HPV genotype was strongly associated with smoking and Pap-test more common among Indigenous women.

difference in the prevalence of HPV16/18 among Australian women by women, residence in remote regions, differences were found in the other HPV genotypes. This reinforces the importance of cervical screening as a omen, and the value of baseline data on HPV genotype prevalence by he monitoring of vaccine impact.

sive, organized, cer- n in 1991, Australia nce of cervical can- 1990s to a current nce the early 2000s. eduction from 4 to

1.9 per 100,000 for the respective time periods [1]. However, there are large disparities within the total Australia population; incidence and mortality are higher for regional and remote than urban residents, and much higher (approximately two and five times higher respectively) for Indigenous (Aboriginal and Torres Strait Islander women) than other Australian women [1].

Cervical cancer is caused by oncogenic human papillomavirus (HPV) types, [2] with 70% of cases due to HPV 16 and 18 genotypes both worldwide and in Australia [3]. Given the early results of Phase 3 vaccine trials of a bivalent [4] and quadrivalent vaccine [5,6], which have

mavirus Laboratory s Diseases, The Royal 3052, Australia d of the article

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Long term impacts – HPV vaccine

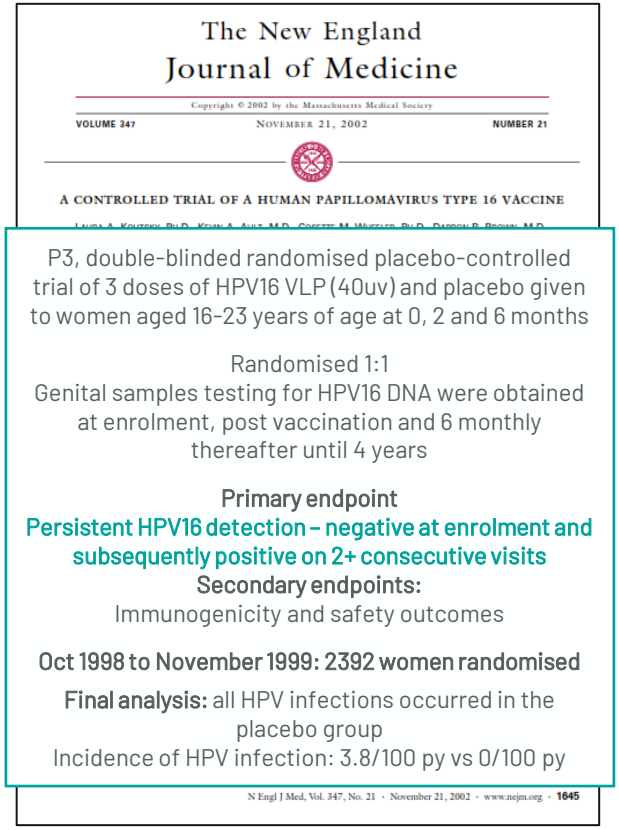
Background factors:
Issue of global importance
A broad range of important clinical outcomes some with a long incubation period (cervical Ca)

Clinical testing

Phase I
Phase II
Phase III

	Phase I	Phase II	Phase III
Population	Healthy adult females and males	Healthy adult females	Healthy adult females
Intervention	Escalating doses with and without adjuvant HPV16 L1 VLP	Three dose of 40ug HPV16 L1 VLP + alum	Three dose of 40ug HPV16 L1 VLP + alum
Comparator	Placebo	Placebo	Placebo
Outcome	Solicited symptoms for 7d HPV16 Immunogenicity	Solicited symptoms for 7d HPV16 Immunogenicity	Persistent HPV-16 infection All adverse events for 14d

Long term impacts – HPV vaccine


The New England Journal of Medicine

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VOLUME 347 NOVEMBER 21, 2002 NUMBER 21

A CONTROLLED TRIAL OF A HUMAN PAPILLOMAVIRUS TYPE 16 VACCINE

P3, double-blinded randomised placebo-controlled trial of 3 doses of HPV16 VLP (40uv) and placebo given to women aged 16-23 years of age at 0, 2 and 6 months

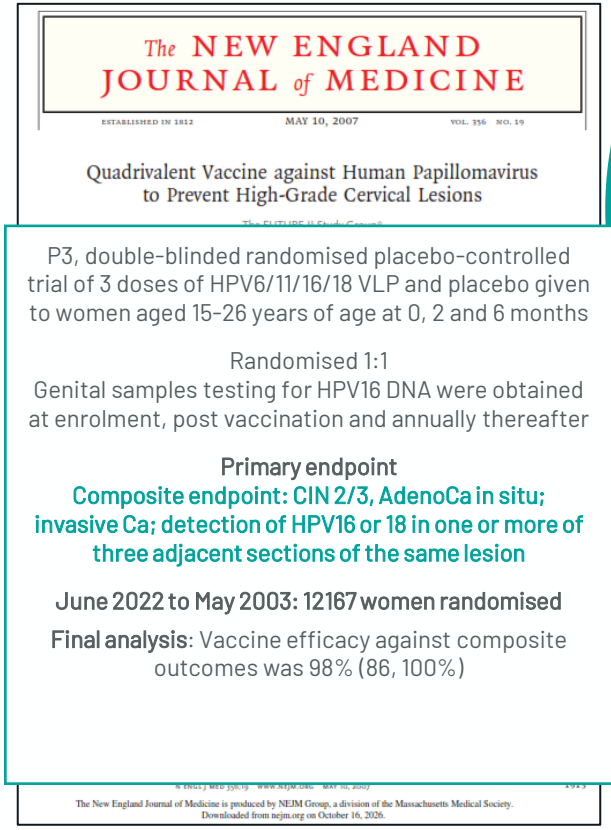
Randomised 1:1
Genital samples testing for HPV16 DNA were obtained at enrolment, post vaccination and 6 monthly thereafter until 4 years

Primary endpoint
Persistent HPV16 detection – negative at enrolment and subsequently positive on 2+ consecutive visits
Secondary endpoints:
Immunogenicity and safety outcomes

Oct 1998 to November 1999: 2392 women randomised

Final analysis: all HPV infections occurred in the placebo group
Incidence of HPV infection: 3.8/100 py vs 0/100 py

N Engl J Med, Vol. 347, No. 21 · November 21, 2002 · www.nejm.org · 1645


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2007 VOL. 356 NO. 19

Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions

P3, double-blinded randomised placebo-controlled trial of 3 doses of HPV6/11/16/18 VLP and placebo given to women aged 15-26 years of age at 0, 2 and 6 months

Randomised 1:1
Genital samples testing for HPV16 DNA were obtained at enrolment, post vaccination and annually thereafter

Primary endpoint
Composite endpoint: CIN 2/3, AdenoCa in situ; invasive Ca; detection of HPV16 or 18 in one or more of three adjacent sections of the same lesion

June 2022 to May 2003: 12167 women randomised

Final analysis: Vaccine efficacy against composite outcomes was 98% (86, 100%)

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on October 16, 2026.

P3: HPV6/11/16/18 VLP 3 dose efficacy against external anogenital and vaginal lesions in women

P3: HPV6/11/16/18 VLP 3 dose efficacy against anogenital / external genital lesions in men (MSM)

P3: HPV-9v VLP 3 dose vaccine efficacy against cervical, vulvar and vaginal lesions in women aged 16-26y

P3: HPV-9v VLP 3 dose immunogenicity, and safety in girls and boys aged 9-15 years

P3: HPV-9v VLP 1 dose vaccine efficacy against cervical, vulvar and vaginal lesions in women aged 15-20y

P3: HPV-9v VLP 1 dose immunogenicity and safety in girls aged 9- 14 year

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 III

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 Ib
Multiple Different Doses

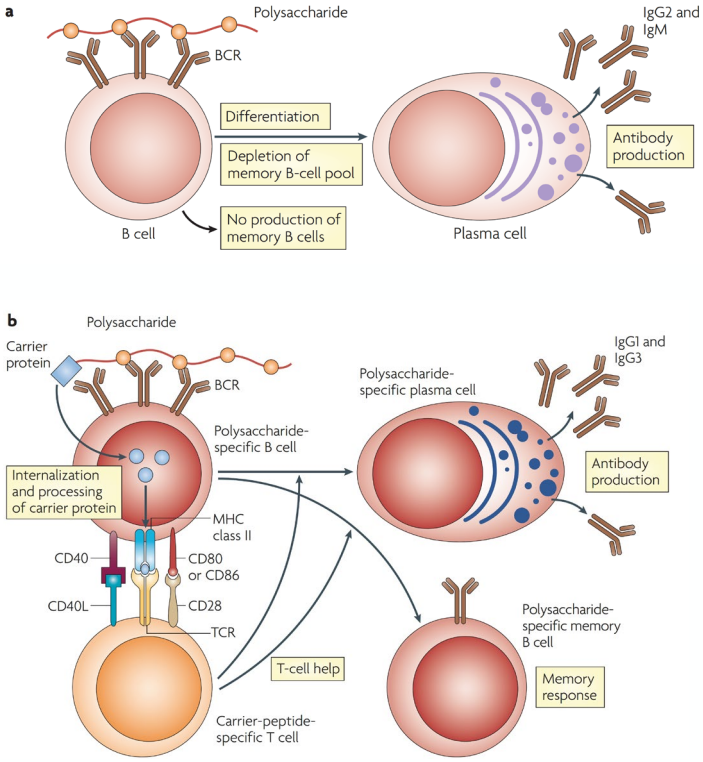
Phase IIa
Data about optimal dose

Phase IIb
How a vaccine works at a given dose

RSV	Rotavirus	Pneumococcus	Human papillomavirus	Salmonella typhi	SARS-CoV-2

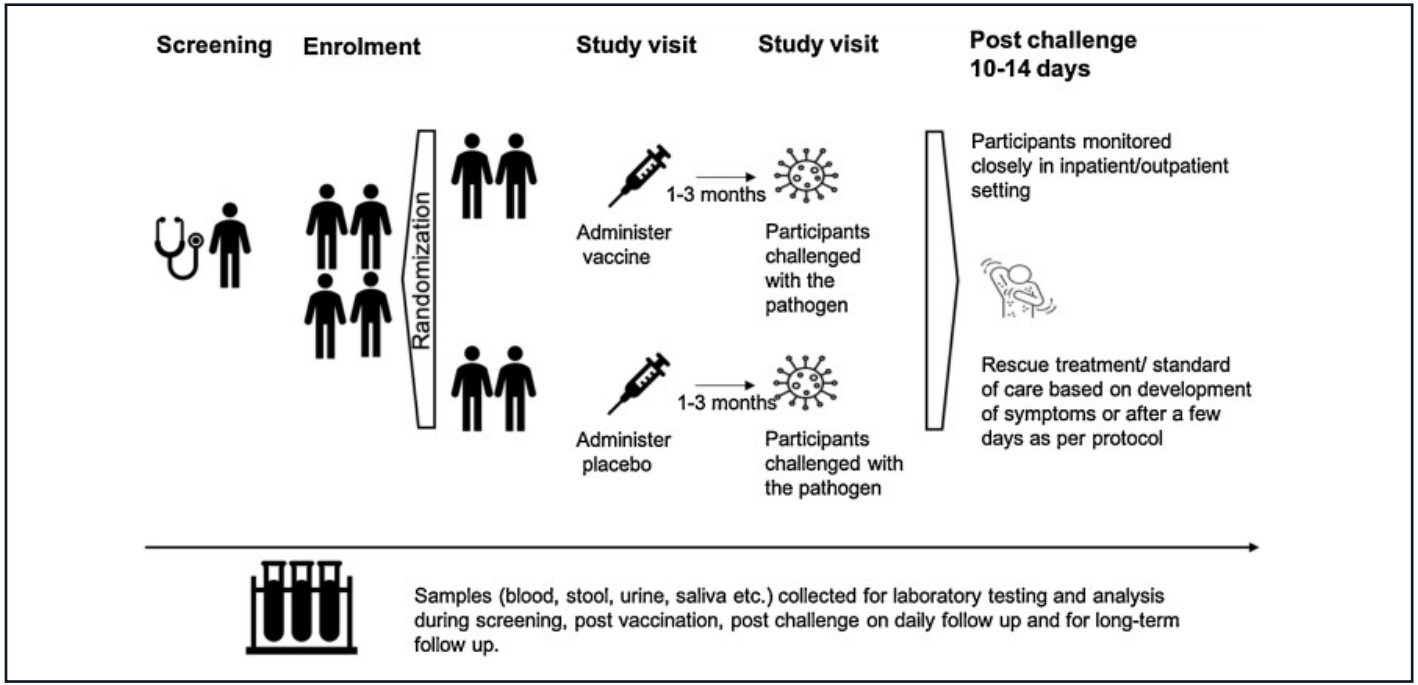
Uncommon infections – *S. typhi* vaccines

Vaccine type	Ty21a Vaccine	Vi Capsular polysaccharide vaccine
Composition	Live attenuated	Subunit
Immunogenic properties	Chemically mutated Ty2 strain of S. typhi	Purified Vi capsular polysaccharide of Ty2 S. typhi strain
Quality Control	Elicits mucosal IgA and serum IgG antibodies against O, H, and other antigens, as well as cell-mediated responses No booster effect has been shown	Elicits serum IgG Vi antibodies T-cell independent (no booster response)
Route of administration	Oral	Parenteral (subcutaneous or intramus cular)
Minimum age	2 years old for liquid formulation and 5 years old for capsule formulation	2 years old
Formulation	Enteric-coated capsules, or Liquid suspension	Solution of 25 µg combined with buffer
Number of doses	3 to 4	1
Storage requirements	Requires storage at 2º to 8ºC	Requires storage at 2º to 8ºC
Shelf life	14 days at 25 °C	6 months at 37 °C 2 years at 22 °C
Safety/tolerability	High	High
Efficacy at 3 years (95% CI)	51% (36–62%)	55% (30–70%)
Length of protection	At least 5–7 years	At least 3 years



Syed KA, CID 2020; Pollard A, Nature Reviews 2009;

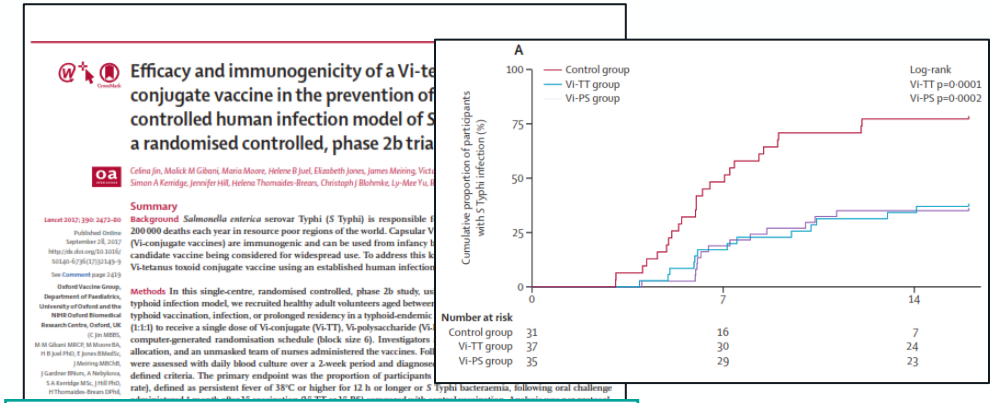
Uncommon infections – *S. typhi* vaccines



Human Challenge Models

Sekhar A et al, Semin Immunol 2020

Uncommon infections – *S. typhi* vaccines


Efficacy and immunogenicity of a Vi-te
conjugate vaccine in the prevention of
controlled human infection model of S
a randomised controlled, phase 2b tria

Celina Jin, Malick M Gibani, Maria Moore, Helene B Juel, Elizabeth Jones, James Meiring, Victo
Simon A Kerridge, Jennifer Hill, Helena Thomaides-Brears, Christoph J Blohmke, Ly-Mee Yu, E

Summary

Background *Salmonella enterica* serovar Typhi (*S* Typhi) is responsible
200 000 deaths each year in resource poor regions of the world. Capsular V
(Vi-conjugate vaccines) are immunogenic and can be used from infancy b
candidate vaccine being considered for widespread use. To address this k
Vi-tetanus toxoid conjugate vaccine using an established human infection

Methods In this single-centre, randomised controlled, phase 2b study, us
typhoid infection model, we recruited healthy adult volunteers aged between
typhoid vaccination, infection, or prolonged residency in a typhoid-endemic
(1:1:1) to receive a single dose of Vi-conjugate (Vi-TT), Vi-polysaccharide (Vi-
computer-generated randomisation schedule (block size 6). Investigators
allocation, and an unmasked team of nurses administered the vaccines. Foll
were assessed with daily blood culture over a 2-week period and diagnose
defined criteria. The primary endpoint was the proportion of participants
rate), defined as persistent fever of 38°C or higher for 12 h or longer or *S* Typhi bacteraemia, following oral challenge

P2b, double-blinded randomised controlled trial of Vi-conjugate (Vi-TT), Vi-polysaccharide (Vi-PS) and control meningococcal ACWY 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

P3, double-blinded randomised controlled trial of Vi-conjugate (Vi-TT) and meningococcal A vaccine in children aged 9m to 16y living in Nepal

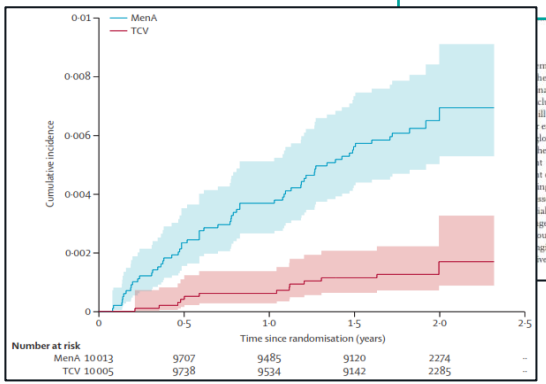
Randomised 1:1

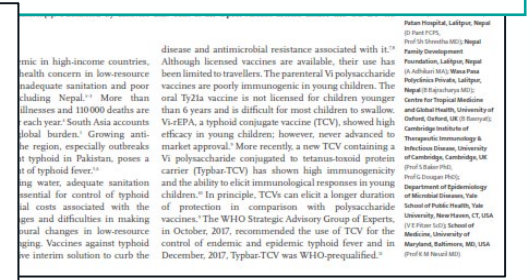
Primary endpoint
Blood culture confirmed typhoid fever

Secondary endpoints:
Incidence of BC confirmed typhoid with 3d of fever
Incidence of BC confirmed paratyphoid fever
Number and duration of inpatient and outpatient fever
Length of hospitalisations

November 2017 to April 2018: 20019 children enrolled

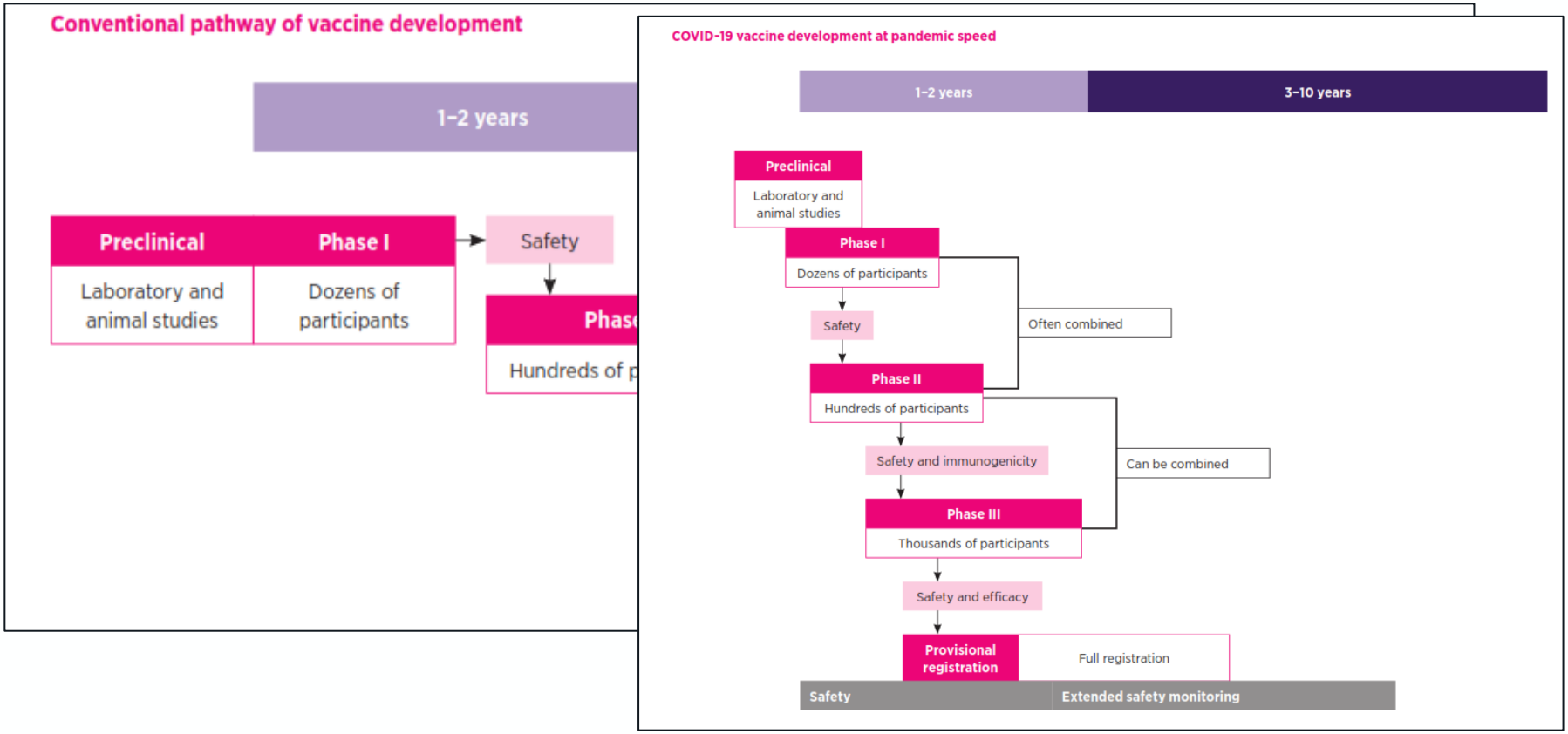
Vaccine efficacy: 79.0% (31.9 to 88.5)




disease and antimicrobial resistance associated with it.[7,8] Although licensed vaccines are available, their use has been limited to travellers. The parenteral Vi polysaccharide vaccines are poorly immunogenic in young children. The oral Ty21a vaccine is not licensed for children younger than 6 years and is difficult for most children to swallow. Vi-rEPA, a typhoid conjugate vaccine (TCV), showed high efficacy in young children; however, never advanced to market approval.[9] More recently, a new TCV containing a Vi polysaccharide conjugated to tetanus-toxoid protein carrier (Typbar-TCV) has shown high immunogenicity and the ability to elicit immunological responses in young children.[10] In principle, TCVs can elicit a longer duration of protection in comparison with polysaccharide vaccines.[4] The WHO Strategic Advisory Group of Experts, in October, 2017, recommended the use of TCV for the control of endemic and epidemic typhoid fever and in December, 2017, Typbar-TCV was WHO-prequalified.[11]

Sekhar A et al, Semin Immunol 2020

The need for speed



McIntyre P et al, Australian Prescriber 2021

The need for speed – SARS-CoV-2

3rd February 2020: First sequence



Article

A pneumonia outbreak associated with a new coronavirus of probable bat origin

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Open access
Check for updates

Peng Zhou[1,2], Xing-Lou Yang[1,2], Xian-Guang Wang[1,2], Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,2], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[1], Hui-Dong Chen[1], Jing Chen[1], Yun Luo[1,2], Hua Guo[1,2], Ren-Di Jiang[1,2], Mei-Qin Liu[1,2], Ying Chen[1,2], Xu-Rui Shen[1,2], Xi Wang[1,2], Xiao-Shuang Zheng[1,2], Kai Zhao[1,2], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[1], Bing Yan[1], Fa-Xian Zhan[1], Yan-Yi Wang[1], Geng-Fu Xiao[1] & Zheng-Li Shi[1]✉

Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats[1–4]. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans[5–7]. Here we report the identification and characterization of a new coronavirus (2019-nCoV) which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Full-length genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of SARSr-CoV. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

Coronaviruses have caused two large-scale pandemics in the past two decades, SARS and Middle East respiratory syndrome (MERS)[8,9]. It has generally been thought that SARSr-CoV—which is mainly found in bats—could cause a future disease outbreak[4,6,7]. Here we report on a series of cases caused by an unidentified coronavirus (see Extended Data Table 1). As a laboratory investigating CoV, we first used pan-CoV PCR primers to test these samples[10], given that the outbreak occurred in winter and in a market—the same environment as SARS infections. We found five samples to be PCR-positive for CoVs. One sample (WIV04), collected from the bronchoalveolar lavage fluid (BALF), was analysed by metagenomics analysis using next-generation sequencing to identify potential aetiological agents. Of the 10,038,758 total reads—of which 1,582 total reads were retained after filtering of reads from the human genome—1,379 (87.1%) sequences matched the sequence of SARSr-CoV (Fig. 1a). By de novo assembly and targeted PCR, we obtained a 29,901 base-pair CoV genome that shared 79.6% sequence identity to SARS-CoV BJ01 (GenBank accession number AY278488.2). High genome coverage was obtained by remapping the total reads to this genome (Extended Data Fig. 1). This sequence has been submitted to GISAID (https://www.gisaid.org/) (accession number EPI_ISL_402124). Following the name given by the World Health Organization (WHO), we tentatively call it novel coronavirus 2019 (2019-nCoV). Four more full-length genome sequences of 2019-nCoV (WIV02, WIV05, WIV06 and

Samples from seven patients with severe pneumonia (six of whom are sellers or deliverymen from the seafood market), who were admitted to the intensive care unit of Wuhan Jin Yin-Tan Hospital at the beginning of the outbreak, were sent to the laboratory at the Wuhan Institute of Virology (WIV) for the diagnosis of the causative pathogen (Extended Data Table 1). As a laboratory investigating CoV, we first used pan-CoV PCR primers to test these samples[10], given that the outbreak occurred in winter and in a market—the same environment as SARS infections. We found five samples to be PCR-positive for CoVs. One sample (WIV04), collected from the bronchoalveolar lavage fluid (BALF), was analysed by metagenomics analysis using next-generation sequencing to identify potential aetiological agents. Of the 10,038,758 total reads—of which 1,582 total reads were retained after filtering of reads from the human genome—1,379 (87.1%) sequences matched the sequence of SARSr-CoV (Fig. 1a). By de novo assembly and targeted PCR, we obtained a 29,901 base-pair CoV genome that shared 79.6% sequence identity to SARS-CoV BJ01 (GenBank accession number AY278488.2). High genome coverage was obtained by remapping the total reads to this genome (Extended Data Fig. 1). This sequence has been submitted to GISAID (https://www.gisaid.org/) (accession number EPI_ISL_402124). Following the name given by the World Health Organization (WHO), we tentatively call it novel coronavirus 2019 (2019-nCoV). Four more full-length genome sequences of 2019-nCoV (WIV02, WIV05, WIV06 and Hubei province of China and was sequenced and isolated by January 2020 (Zhou et al., 2020; Zhu et al., 2020). SARS-CoV-2 is associated with an ongoing outbreak of atypical pneumonia (Covid-2019) that has affected over 90,000 people and killed more than 3,000 of those affected in >80 countries as of March 3, 2020. On January 30, 2020, the World Health Organization declared the SARS-CoV-2 epidemic a public health emergency of international concern.

MERS-CoV was suggested to originate from bats, but the reservoir host fueling spillover to humans is unequivocally dromedary camels (Hasanin et al., 2014; Memish et al., 2013). Both SARS-CoV and SARS-CoV-2 are closely related and originated in bats, who most likely serve as reservoir host for these two viruses (Ge et al., 2013; Hu et al., 2017; Li et al., 2005b; Yang et al., 2015a; Zhou et al., 2020). Whereas palm civets and racoon dogs have been recognized as intermediate hosts for zoonotic transmission of SARS-CoV between bats and humans (Guan et al., 2003; Kan et al., 2005; Wang et al., 2005), the SARS-CoV-2 intermediate host remains unknown. The recurrent spillovers of coronaviruses in humans along with detection of numerous coronaviruses in bats, including many SARS-related coronaviruses (SARSr-CoVs), suggest that future zoonotic transmission events may continue (Anthony et al., 2017; Ge et al., 2013; Hu et al., 2017; Li et al., 2005b; Menachery et al., 2015; Menachery et al., 2016; Yang et al., 2015a; Zhou et al., 2020). In addition to the highly pathogenic zoonotic pathogens SARS-CoV, MERS-CoV, and SARS-CoV-2, all belonging to the β-coronavirus genus, four low-pathogenicity coronaviruses are endemic in humans: HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E. To date, no therapeutics or vaccines are approved against any human-infecting coronaviruses.

Coronavirus entry into host cells is mediated by the trans-membrane spike (S) glycoprotein that forms homotrimers protruding from the viral surface (Fehr and Perlman, 2015). S comprises two functional subunits responsible for binding to the host cell receptor (S_1 subunit) and fusion of the viral and cellular membranes (S_2 subunit). For many CoVs, S is cleaved at the boundary between the S_1 and S_2 subunits, which remain non-covalently bound in the prefusion conformation (Belouzard et al., 2009; Bosch et al., 2003; Bukreyev et al., 2014; Kirchdoerfer et al., 2016; Millet and Whittaker, 2014,

9th March 2020: Vaccine design



Article

Cell

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

Alexandra C. Walls,[1,5] Young-Jun Park,[1,5] M. Alejandra Tortorici,[1,2] Abigail Wall,[1] Andrew T. McGuire,[3,4] and David Veesler[1,6,*]

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https://doi.org/10.1016/j.cell.2020.02.058

SUMMARY

The emergence of SARS-CoV-2 has resulted in >90,000 infections and >3,000 deaths. Coronavirus spike (S) glycoproteins promote entry into cells and are the main target of antibodies. We show that SARS-CoV-2 S uses ACE2 to enter cells and that the receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2, correlating with the efficient spread of SARS-CoV-2 among humans. We found that the SARS-CoV-2 S glycoprotein harbors a furin cleavage site at the boundary between the S_1/S_2 subunits, which is processed during biogenesis and sets this virus apart from SARS-CoV and SARS-related CoVs. We determined cryo-EM structures of the SARS-CoV-2 S ectodomain trimer, providing a blueprint for the design of vaccines and inhibitors of viral entry. Finally, we demonstrate that SARS-CoV S murine polyclonal antibodies potently inhibited SARS-CoV-2 S mediated entry into cells, indicating that cross-neutralizing antibodies targeting conserved S epitopes can be elicited upon vaccination.

INTRODUCTION

Three coronaviruses have crossed the species barrier to cause deadly outbreaks in humans since the beginning of the 21st century: severe acute respiratory syndrome coronavirus (SARS-CoV) (Drosten et al., 2003; Ksiazek et al., 2003), Middle-East respiratory syndrome coronavirus (Zaki et al., 2012) (MERS-CoV), and SARS-CoV-2 (Huang et al., 2020; Zhu et al., 2020). SARS-CoV emerged in the Guangdong province of China in 2002 and spread to five continents through air travel routes, infecting 8,098 people and causing 774 deaths. In 2012, MERS-CoV emerged in the Arabian Peninsula, where it remains a major public health concern, and was exported to 27 countries, infecting a total of ~2,494 individuals and claiming 858 lives. A previously unknown coronavirus, named SARS-CoV-2, was discovered in December 2019 in Wuhan,

14th July 2020: Phase I



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson II, M. Padilla, J.R. Mascola, K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, and J.H. Beigel, for the mRNA-1273 Study Group*

ABSTRACT

BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and spread globally, prompting an international effort to accelerate development of a vaccine. The candidate vaccine mRNA-1273 encodes the stabilized prefusion SARS-CoV-2 spike protein.

METHODS

We conducted a phase 1, dose-escalation, open-label trial including 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 μg, 100 μg, or 250 μg. There were 15 participants in each dose group.

RESULTS

After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti–S-2P antibody geometric mean titer [GMT], 40,227 in the 25-μg group, 109,209 in the 100-μg group, and 213,526 in the 250-μg group). After the second vaccination, the titers increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively). After the second vaccination, serum-neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (27%) in the 250-μg dose group reported one or more severe adverse events.

CONCLUSIONS

The mRNA-1273 vaccine induced anti–SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified. These findings support further development of this vaccine. (Funded by the National Institute of Allergy and Infectious Diseases and others; mRNA-1273 ClinicalTrials.gov number, NCT04283461).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jackson at Kaiser Permanente Washington Health Research Institute, 1730 Minor Ave., Suite 1600, Seattle, WA 98101, or at lisa.a.jackson@kp.org.

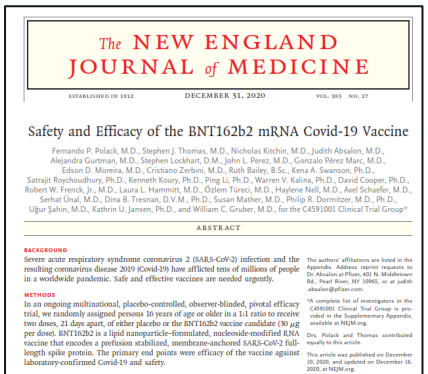
*The mRNA-1273 Study Group members are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Graham and Beigel contributed equally to this article.

This article was published on July 14, 2020, and updated on August 25, 2020, at NEJM.org.

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18th November 2020: Phase III



The NEW ENGLAND JOURNAL of MEDICINE

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Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

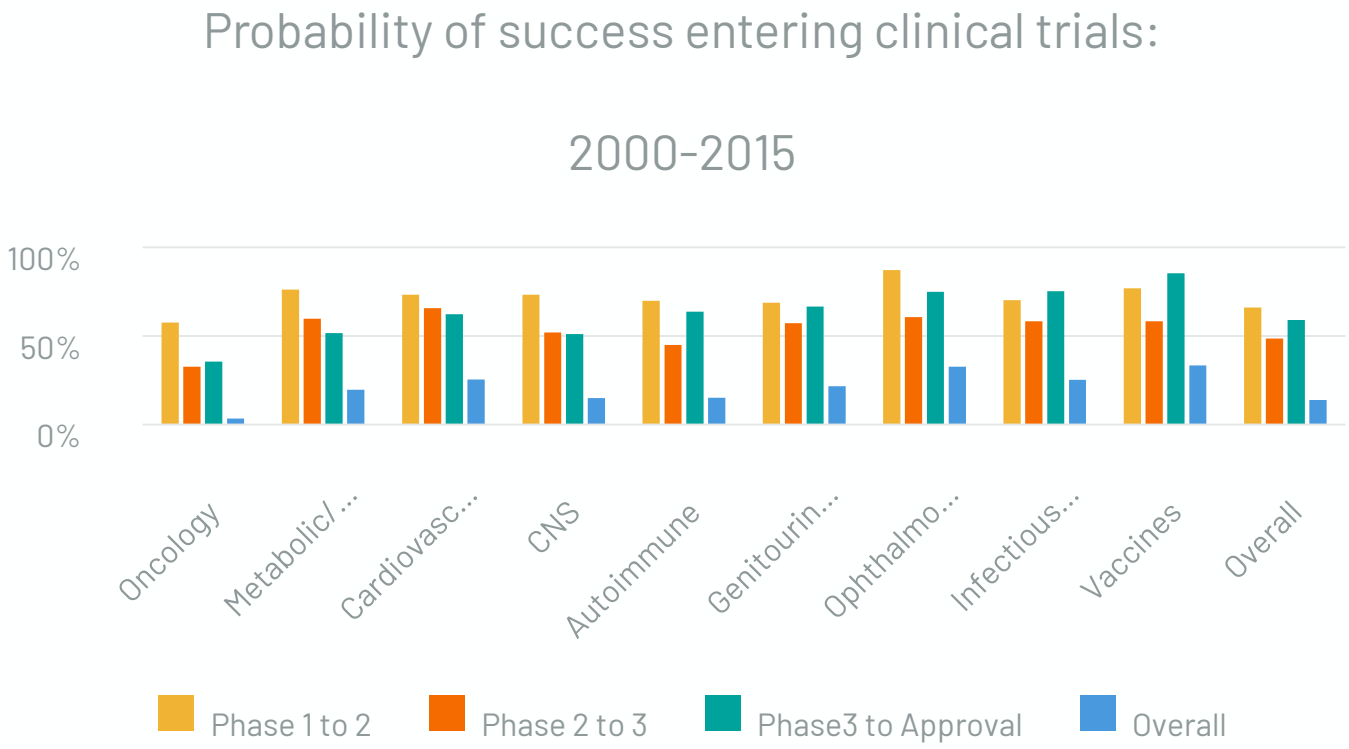
*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

This article was published on December 10, 2020, and updated on December 16, 2020, at NEJM.org.

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Clinical trials - success



Chi Heem Wong et al, Biostatistics 2019

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 Ib
Multiple Different Doses

Phase IIa
Data about optimal dose

Phase IIb
How a vaccine works at a given dose

Summary

Vaccine development, from research to licensure, follows a series of key and carefully designed steps, from vaccine design, through preclinical testing and clinical trials.

There is significant variability in both preclinical testing and clinical trial design, informed by many features including:

- The pathogen
- The epidemiology of the problem: incidence, age group at risk
- The outcome one is trying to prevent
- The immune response that one is trying to generate / replicate
- The potential safety of the vaccine

Summary

Following a successful pathway through vaccine design, preclinical testing and clinical trials, we know that a vaccine is:

- Safe against common/uncommon adverse events

  although safety against rare adverse events may not be identified
- Immunogenic (and hopefully which components of the immune system immune system are activated)

  although correlate of protection may not be established
- Effective against clinically relevant endpoints related to disease control

  although efficacy against the ultimate clinically-relevant endpoint and RWE may not be known
- Ready for licensure

DISCOVER · PREVENT · CURE

Vaccines: licensure to policy (submission to program)

Chris Blyth
Head | Wesfarmers Centre of Vaccines and Infectious Diseases, The Kids Research Institute Australia
Professor | School of Medicine, University of Western Australia
Infectious Diseases Physician | Perth Children's Hospital
Clinical Microbiologist | PathWest Laboratory Medicine WA

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 Ib
Multiple Different Doses

Phase IIa
Data about optimal dose

Phase IIb
How a vaccine works at a given dose

Quiz

In Australia, 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

Quiz

In Australia, who is responsible for negotiating the price that the government pays for a vaccine?

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- ATAGI
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Quiz

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Learning objectives

To understand:

- Pathway from licensure to policy: Australia and other high-income countries



Key groups in the Australian context

Therapeutic Goods Administration (TGA)
Australian Committee on Vaccines (ACV)
Australian Technical Advisory Group on Immunisation (ATAGI)
Pharmaceutic Benefits Advisory Committee (PBAC)

National Immunisation Branch, Dept of Health, Disability and Ageing
Jurisdictional Immunisation Programs / Coordinators

Key groups in the international context

Regulators:

- US Food and Drug Adminstration (FDA)
- UK Medicines &Healthcare products Regulatory Agency (MHRA)
- European Medicines Agency (EMA)

Immunisation Technical Advisory Groups:

- US Advisory Committee on Immunization Practices (ACIP)
- UK Joint Committee on Vaccination and Immunisation (JCVI)
- Individual European NITAGs

Therapeutics Goods Administration

Part of the Australian Government Dept of Health, Disability and Ageing

To regulate therapeutic goods for safety, efficacy, performance and quality to help protect and improve health of Australians

Australia's regulatory authority for therapeutic goods such as:

- Prescription medicines
- Non-prescription medicines
- Vaccines
- Medical devices
- Blood and blood products
- Sunscreens
- Vitamins
- Software and AI-based medical devises

Therapeutics Goods Administration

Statutory committees

Advisory Committee on Biologicals (ACB)

Information on the role and membership of ACB and proposed meeting dates.

Advisory Committee on Complementary Medicines (ACCM)

Information on the role and membership of ACCM and proposed meeting dates.

Advisory Committee on Chemicals Scheduling (ACCS)

Information on the role and membership of ACCS and proposed meeting dates and decision timeframes.

Advisory Committee on Medicines (ACM)

Information on the role and membership of ACM and proposed meeting dates.

Advisory Committee on Medical Devices (ACMD)

Information on the role and membership of Advisory Committee on Medical Devices (ACMD) and proposed meeting dates.

Advisory Committee on Medicines Scheduling (ACMS)

Information on the role and membership of ACMS and proposed meeting dates and decision timeframes.

Advisory Committee on Vaccines (ACV)

Information on the role and membership of ACV and proposed meeting dates.

Non-statutory committees

Australian Influenza Vaccine Committee (AIVC)

Information on the role and membership of Australian Influenza Vaccine Committee (AIVC) and proposed meeting dates.

Complementary and OTC Medicines Regulatory and Technical Consultative Forum (ComTech)

ComTech facilitates consultation between the TGA and representatives from the complementary and over-the-counter medicines industries.

Human Research Ethics Committee and Therapeutic Goods Administration Clinical Trials Discussion Forum

Information on the terms of reference, membership and meetings of the Human Research Ethics Committee and Therapeutic Goods Administration Clinical Trials Discussion Forum (the Forum).

Point-of-care Manufacturing of Medical Devices Steering Committee and Working Groups

Information on the role and membership of the POC Manufacturing of Medical Devices Steering Committee and Working Groups

Regulatory and Technical Consultative Forum for Medical Devices (RegTech Forum)

Information on the terms of reference, membership, and meetings of the Regulatory and Technical Consultative Forum for Medical Devices (RegTech Forum)

Technical Reference Group for Software as a Medical Device (SaMD) and Artificial Intelligence (AI)

Information on the role and membership of the Technical Reference Group for SaMD and AI.

Therapeutic Goods Advertising Consultative Forum (TGACF)

Information on role and membership of TGACF

Advisory Committee on Vaccines (ACV)

Statutory committing providing independent medical and scientific advice to the Minister of Health and the TGA on issues related to the safety, quality and efficacy of vaccines on issues including:

- Pre-market assessment
- Post-market monitoring
- Safe use in immunisation programs

Australian Technical Advisory Group on Immunisation

Ministerially appointed committee, whose role it is to:

- Advise the Minister on the medical administration of vaccines available in Australia, including those available through the National Immunisation Program (NIP)
- Provide advice to research organisations on current immunisation research and areas that need more research
- Provide industry sponsors with pre-submission advice for potential submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) on vaccine effectiveness and use in Australia
- Consult with relevant organisations to produce the Australian Immunisation Handbook
- Consult with relevant organisations in implementing immunisation policies, procedures and vaccine safety.

Pharmaceutical Benefits Advisory Committee

Independent expert body appointed by the Australian Government

Its primary role is to recommend new medicines for listing on the Pharmaceutics Benefits Scheme (PBS) and vaccines for listing on the National Immunisation Program (NIP)

A new medicine or vaccine cannot be listed unless the committee makes a positive recommendation

Supported by:

- Drug Utilisation sub-committee
- Economic sub-committee

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

Licensure

TGA

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

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 first 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 a biological product

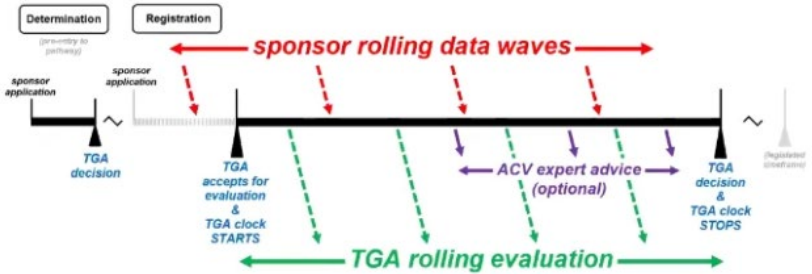
Provisional review – new vaccine and/or indication, preventing a serious condition, providing a major therapeutic advance **and** favourable efficacy or safety. Must plan to submit comprehensive clinical data

c
e

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

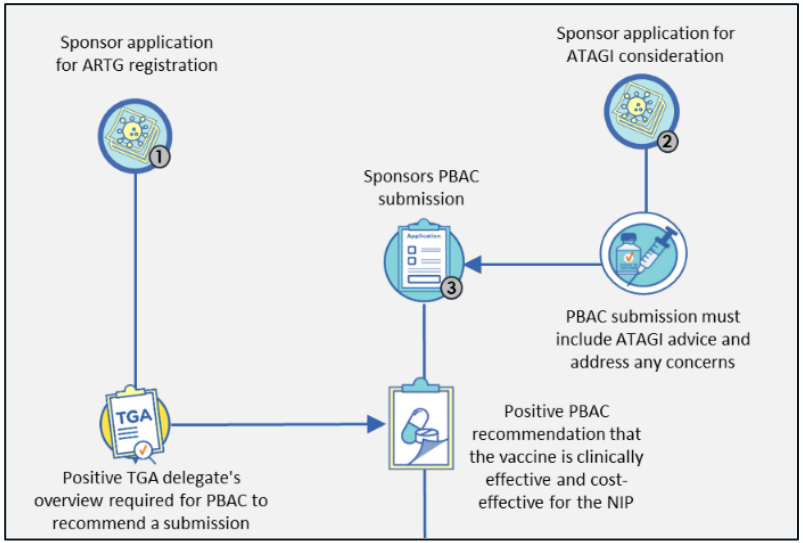
- Limited data on duration of protection

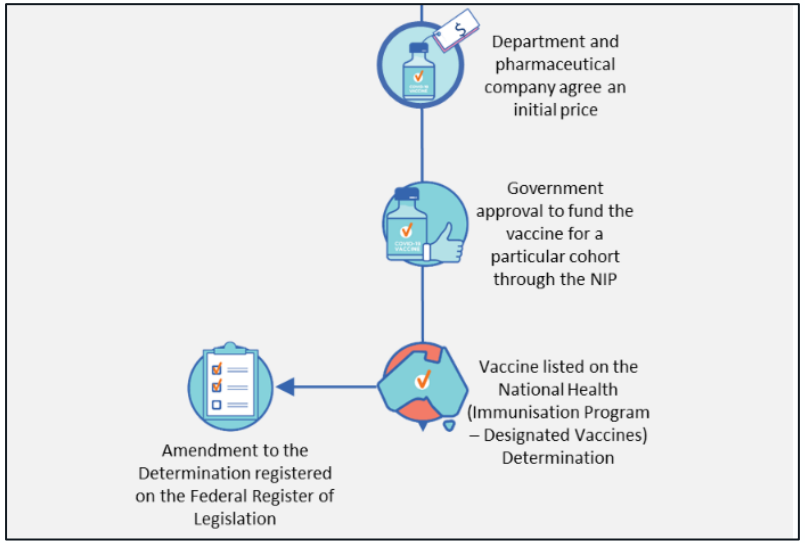
PBAC recommendation

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

PBAC considers health need, clinical efficacy/effectiveness and cost-effectiveness, informed by ATAGI advice





www.health.gov.au/sites/default/files/2024-09/health-technology-assessment-policy-and-methods-review-final-report_0.pdf

Key definitions

Efficacy – a measure of how well the vaccine works (the proportion reduction in cases amongst vaccinated persons compared with unvaccinated persons), in an ideal situation (e.g. in a clinical trial)

Effectiveness – a measure of how well the vaccine works (the proportion reduction in cases amongst vaccinated persons compared with unvaccinated persons, in real world situations (e.g. routine clinical or programmatic use)

Cost effectiveness - a measure of the value of an intervention (health benefits relative to costs)

Efficacy or Effectiveness

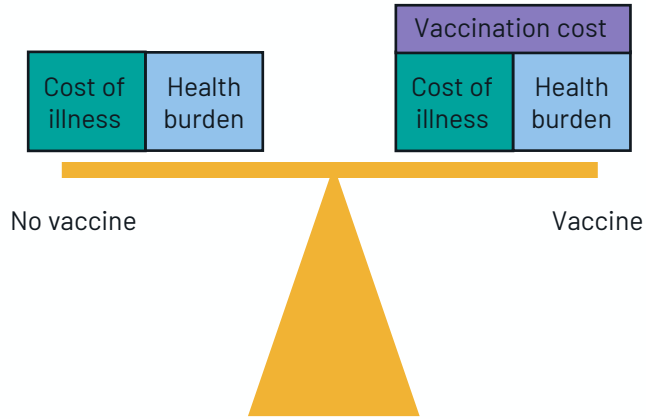
Can measure various endpoints: any disease (clinical presentation; lab-confirmed cases); severe disease; hospitalisation

Can measure in various population

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)

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

Cost of vaccination program + Cost of illness with vaccination

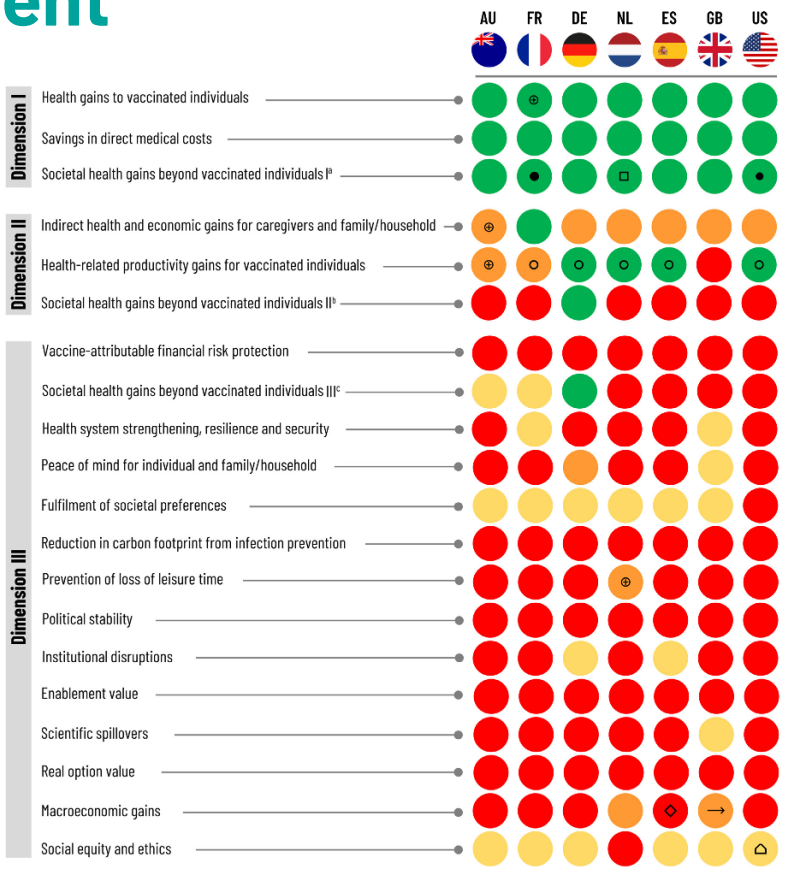
Cost of illness with no vaccination

Health Technology Assessment

Factors considered in an EE vary by country/jurisdiction:

Three dimensions:

1) Health gains from a payer perspective (direct costs)
2) Health gains from a societal perspective (indirect costs)
3) Additional gains: equity; health system gains.



Postma M et al, Vaccine 2022

Maternal RSV vaccine: Abrysvo

PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE (PBAC) MEETING OUTCOMES
MARCH 2024 PBAC MEETING

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	DRUG TYPE AND USE	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME	
RESPIRATORY SYNCYTIAL VIRUS VACCINE Injection 0.5 mL Abrysvo® PFIZER AUSTRALIA PTY LTD Category 1 (New NIP listing)	Prevention of lower res tract disease caused by re syncytial virus (RS			The PBAC did not recommend recombinant syncytial pre-fusion F protein vaccine (RSVpreF) for the prevention of lower respiratory tract illness (LRTI) caused by RSV in infants from birth through 6 months of age by active immunisation of pregnant women. The PBAC noted the clinical trial evidence presented in the submission showed there was a reduced risk of medically attended lower respiratory tract illness (MA-LRTI) and severe MA-LRTI due to RSV among infants during the first

PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE (PBAC) MEETING OUTCOMES
MAY 2024 PBAC MEETING

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	DRUG TYPE AND USE	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME	
RESPIRATORY SYNCYTIAL VIRUS VACCINE Injection (0.5 mL) Abrysvo® PFIZER AUSTRALIA PTY LTD (New NIP listing)	Prevention of lower respiratory tract disease caused by respiratory syncytial virus (RSV)	A resubmission requesting a National Immunisation Program (NIP) listing for recombinant syncytial pre-fusion F protein vaccine for the prevention of lower respiratory tract illness caused by RSV in infants from birth through to 6 months of age by the active immunisation of pregnant women.	Recommended	The PBAC recommended that respiratory syncytial virus vaccine (Abrysvo®, RSVpreF) be a designated vaccine for the purposes of the *National Health Act 1953* for the prevention of lower respiratory tract illness (LRTI) caused by RSV in infants from birth through 6 months of age by active immunisation of pregnant women. The PBAC considered that the vaccine was superior to no vaccine in terms of effectiveness, based on the reduced risk of medically attended-lower respiratory tract illness (MA-LRTI) and severe MA-LRTI due to RSV among infants during the first 6 months of life. The PBAC considered that the adverse event profile of RSVpreF was acceptable compared to placebo. The PBAC noted that the resubmission had offered a lower price compared with the price considered by the PBAC in March 2024, and had accepted most of its advice arising from that meeting. However, the resubmission had not accepted the PBAC's advice regarding the estimates of vaccine efficacy (VE) to be applied in the economic evaluation. The PBAC maintained its advice from the March 2024 meeting, that clinical trial data with 12 months of follow-up be used to inform the VE, rather than with 6 months of follow-up as proposed by the resubmission. The PBAC noted using clinical trial data with 12 months of follow-up to inform the VE resulted in an ICER that was unacceptably high. On this basis, the PBAC considered that a price reduction would be required to ensure the vaccine is cost-effective in the proposed circumstances of use.

PBAC minutes: March 2024 and May 2024

Maternal RSV vaccine: Zoster

NOVEMBER 2018 PBAC OUTCOMES – 1ST TIME DECISIONS NOT TO RECOMMEND

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	DRU
VARICELLA ZOSTER RECOMBINANT VACCINE Injection [1 vial] (&) adjuvant substance diluent [0.5 mL vial], 1 pack Shingrix® GlaxoSmithKline Australia Pty Ltd New listing (Major Submission)	Prev zoste

PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE (PBAC) MEETING OUTCOMES
MARCH 2023 PBAC MEETING

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	DRUG TYPE AND USE	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME	
VARICELLA ZOSTER VIRUS RECOMBINANT VACCINE Injection [1 vial] & adjuvant substance diluent [0.5 mL vial] Shingrix® GlaxoSmithKline Australia Pty Ltd Standard re-entry submission (New PBS listing)	Pr			The PBAC recommended that varicella virus recombinant vaccine (RZV, Shingrix®) be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of HZ and post-herpetic neuralgia. The PBAC considered the range of incremental cost effectiveness ratios presented in the

PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE (PBAC) MEETING OUTCOMES
JULY 2023 PBAC MEETING

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	DRUG TYPE AND USE	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME	
VARICELLA ZOSTER VIRUS RECOMBINANT VACCINE Injection [1 vial] & adjuvant substance diluent [0.5 mL vial] Shingrix® GlaxoSmithKline Australia Pty Ltd Early resolution submission (New listing)	Prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN)	Resubmission to request a National Immunisation Program (NIP) listing for the prevention of herpes zoster and post - herpetic neuralgia, for non - Indigenous individuals aged 65 to 69 years and individuals aged 71 years and older.	Recommended	The PBAC recommended that varicella zoster virus recombinant vaccine (RZV, Shingrix®) be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of HZ and for individuals aged 65 years (primary program) and older (catch-up program). The PBAC considered, based on the reduced price proposed, that RZV is cost-effective with the age for the primary program lowered to 65 years (compared with the March 2023 recommendation for vaccination at age 70 years) and with there being no upper age limit for the catch-up program. The PBAC noted the cost - effectiveness relies on accepting the long term modelled vaccine efficacy, and in this context considered that the cost-effectiveness of RZV should be reassessed if a booster dose is required or if long-term efficacy is less than predicted. The PBAC noted the total cost of the program was high. RZV will be listed on the NIP as of the 1 November 2023 for non - Indigenous individuals aged 70 years, Aboriginal and Torres Strait Islander individuals aged ≥ 50 years and immunocompromised individuals aged ≥ 18 years with conditions at high risk of HZ infection (based on the PBAC's March 2023 recommendation).

PBAC minutes: November 2018, March 2023, July 2023

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

There will be opportunity for further price negotiations as part of the NIP vaccine procurement process

Actual purchasing arrangements are subject to the outcomes of a NIP vaccine procurement process - no vaccine is guaranteed to be purchased for supply on the NIP

All amendments to the Determination are registered on the Federal Register of Legislation

A vaccine must be approved by Government and listed on the Determination before any contract for supply can be executed.

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

Summary

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

- Key decision about vaccine target and platform, health need and commercial viability are made ahead of trials and licensure
- Trials normally progress in a careful designed step-wise process
- But when there is financial and global commitment, studies can happen in parallel (and quickly)

Summary

Licensure and inclusion in programs in high-income countries is driven by numerous peak committees including the regulator and immunisation technical advisory groups

- In Australia, TGA, ATAGI, PBAC and Governments all play an important role
- To be included in the NIP, there needs to be a health need and considered to be clinically and cost-effective

Post licensure studies are very important to monitor rare safety events, demonstrate real-world effectiveness and long term vaccination impacts