Development of a Vaccine Multi-Dose Vial: Rationale and Strategy

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WCBP 2018
Washington, DC Jan 30-Feb 1, 2018

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

Overview

- We have developed a multi-dose version of Prevenar 13® in support of vaccinating populations against pneumococcal disease.

- Development of this multi-dose vaccine (MDV) involved a close partnership between Pfizer and the World Health Organization (WHO) to vaccinate children in countries served by The Global Vaccine Alliance (GAVI).

- The two key considerations from the development of the Prevenar 13® MDV are:

  – Close communication and collaboration with regulatory authorities and support agencies who are driving for increased vaccination in underserved communities

  – Taking advantage of established technical expertise and Know How from Prevenar 13® to develop the MDV

Prevenar 13®

- The WHO estimates that up to 1 million children less than 5 years of age die each year from pneumococcal diseases

- Prevenar 13® is
  - in the EU, approved for active immunization for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to 17 years of age.
  - approved in at least 150 countries and is the most widely used pneumococcal conjugate vaccine in the world.
  - included in the pediatric National Immunization Programs of 102 countries
  - approved for use in adults, 50 years of age or older, in more than 100 countries.

- Prevenar 13® is composed of a suspension of polysaccharides (1,3,4,5,6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) individually conjugated to a nontoxic mutant of Cross Reactive Material (CRM_{197})
- All conjugates are subsequently formulated with AlPO4, PS80 and 2-PE (for MDV)

Logistical Drivers

- Until recently, Prevenar 13® was available only as a single use pre-filled syringes or vial

- For infant vaccination in the US, children receive Prevenar 13® in a four-dose vaccination series while in developing countries they receive it in three-dose vaccination series.

- The WHO has recognized that multi-dose vials have advantages over single-dose configurations by improving the logistics of immunization programs in developing countries
  - Reduced volume of cold-chain per dose
  - Increased flexibility in safely handling opened vials
  - Overall reduced cost per dose

- On this basis, we agreed to develop a Prevenar 13 ® multi-dose vial containing four doses with preservative

See Bulletin of the World Health Organization 2003; 81

Choice of Preservative

- Preservative choice depended on technical feasibility as well as awareness of public concerns regarding the use of thiomersal

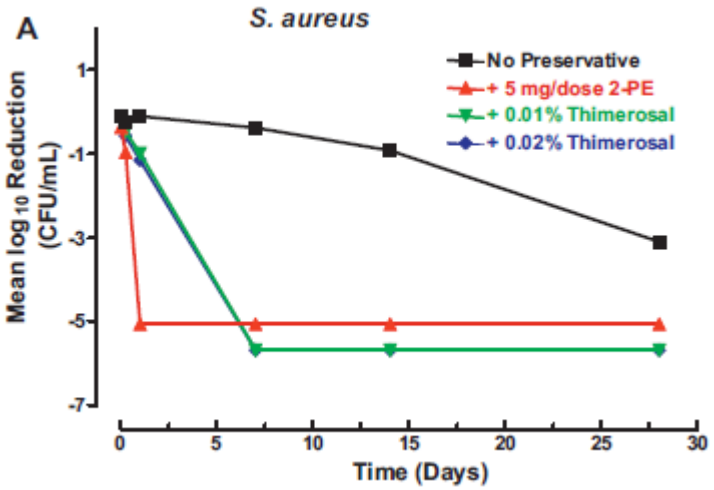
- 2-Phenoxyethanol (2-PE) was identified as a viable option for assessment
  - Previously assessed in several hepatitis, polio and DPT vaccines
  - Currently utilized in several vaccines at levels of 2.5 to 5.0 mg/dose.

- Prevenar 13 ® formulations were prepared including 5 mg/dose 2-PE and evaluated for preservative effectiveness by two methods:
  - Single challenge method according to guidelines set by European Pharmacopoeia 5.1.3
  - Multiple challenge studies as per WHO Open Vial policy.

Lowe and Southern, 1994, Lett Appl Microbiol 18 (2) 115-6
EP 5.1.3
WHO Multi-Dose Vial Policy (2014 Revision)

PET Results – Single Challenge Method

- 30 mLs of Prevenar 13® spiked with various levels of preservatives
- Inoculated to 10^5-10^6 CFU/mL in triplicate with a suspension of test organism
  - *P. aeruginosa*
  - *S. aureus*
  - *C. albicans*
  - *A. niger*
- Incubated at 20-25ºC
- Samples plated and counted at 6h, 24h, 7d, 14d and 28d post inoculation



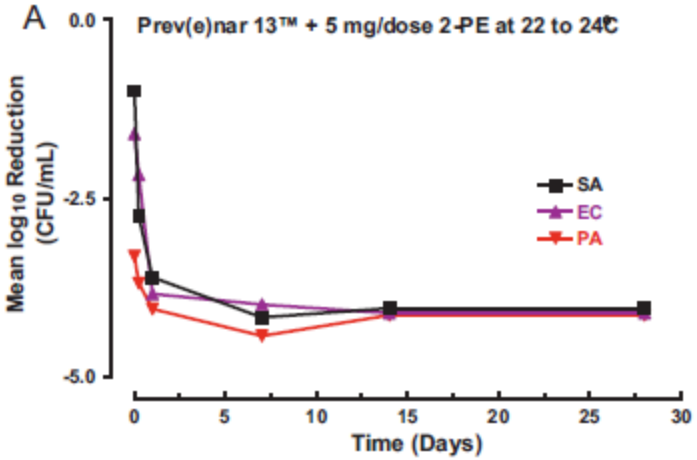
- Data for *S. aureus* are presented above and are representative of all samples
- 2-PE met the EP antimicrobial effectiveness requirement of EP

Khandkhe et al, Vaccine 29 (2011) 7144-7153

PET Results – Multiple Challenge Method

- 30 mLs of Prevenar 13® spiked with various levels of preservatives
- Inoculated to $5x10^3$ CFU/mL in triplicate with a suspension of test organism
  - *P. aeruginosa*
  - *S. aureus*
  - *E coli*
  - *B. subtilis*
- Incubated at 22-24ºC and 2-8ºC
- Suspensions were sampled and re-challenged ($5x10^3$ CFU/mL) at 6h, 24h, 7d and 14d post inoculation

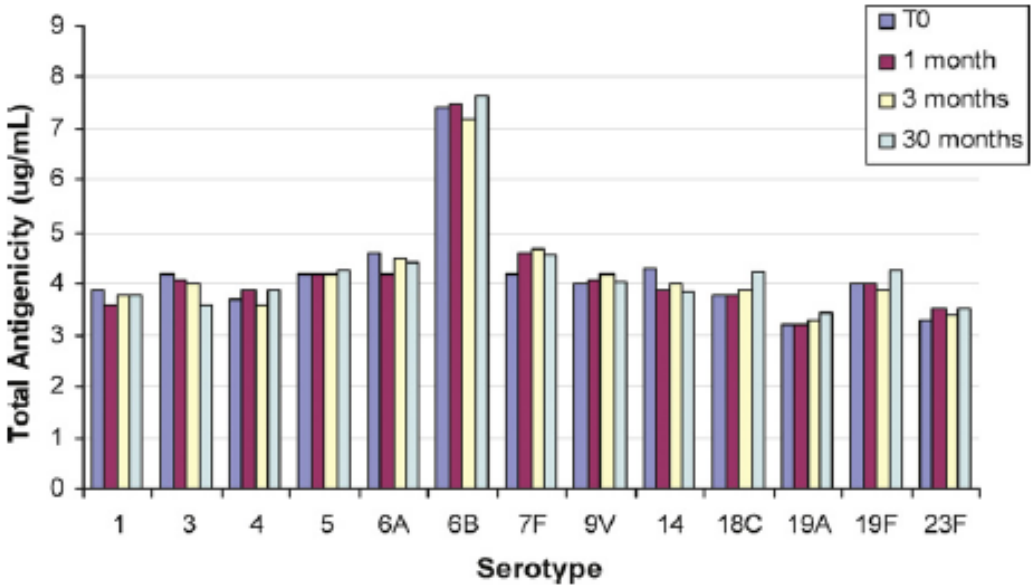
Khandkhe et al, Vaccine 29 (2011) 7144-7153



- Data for *S. aureus* are presented above and are representative of all samples
- *B. subtilis* viability was significantly reduced in the absence of preservative
- 2-PE met the EP antimicrobial effectiveness requirement of WHO Open Vial Policy

2-PE: Effect on Prevenar 13® Antigenicity

- Prevenar 13® formulations containing 5 mg/dose 2-PE were assessed for antigenicity by nephelometry. No differences were observed.
- There was no impact on antigenicity or other quality attributes over 30 months at 2-8°C.
- Preservative effectiveness was demonstrated for full shelf-life.



Khandkhe et al, Vaccine 29 (2011) 7144-7153

Global Health Community Engagement

- Pfizer repeatedly met with WHO officials to discuss feasibility and value of a MDV dosage form for Prevenar 13®.

- It was important to gain agreement on the appropriate testing criteria for the preservative effectiveness test. WHO agreed that the Ph.Eur. “B” criteria were appropriate.

- 5 mg/dose 2-PE was recommended as an effective approach to preserve the opened vials as well as take advantage of precedent.

  – Subsequent assessment of the level of 2-PE concluded that 4 mg/mL was optimal as a preservative and reducing the level of 2-PE exposure to infants.

  – This was discussed via the Scientific Advice process with EMA

Next Steps

- Clinical supplies were produced and a clinical trial verified the effectiveness of Prevenar 13® vaccine in the presence of 2-PE

- A Phase 3, Randomized, Open-label Trial to Evaluate the Safety, Tolerability and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine Formulated in Multidose Vials Given With Routine Pediatric Vaccinations in Healthy Infants

- 500 healthy infants were enrolled between January and September 2014.
  - 3 doses per infant
  - Comparator was the Prevenar 13® vaccine pre-filled syringe (50:50)
  - Trial was conducted in cooperation with the Medical Research Council Unit, and the Fajikunda Major Health Centre, The Gambia

- The preserved MDV formulation was well tolerated and provided comparable serotype-specific pneumococcal IgG antibody concentrations compared to the pre-filled syringe

Clinical Trials.gov

Global Health Community Engagement

- EMA agreed that the MDV presentation would be submitted, under the original Prevenar 13® license, through a variation (Type II).

- Close communication between Pfizer, EMA and WHO was essential to ensure that once the Type II variation was approved by EMA, WHO could initiate their review as part of the pre-qualification process.

- On April 1, 2016, the CHMP approved the MDV of Prevenar 13®. The primary benefits include:
  - 75% reduction in temperature-controlled supply chain requirements
  - 75% reduction in UNICEF related shipping costs
  - 75% reduction in storage requirements at national, regional, district and community levels

- Once approval was received, Pfizer applied to WHO for prequalification which would allow global use of the Prevenar 13® MDV by United Nations agencies that require WHO prequalification including GAVI. Prequalification was received July 18, 2016.

Summary

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- The two key considerations from the development of the Prevenar 13® MDV are:
  - Close communication and collaboration with regulatory authorities and support agencies who are driving for increased vaccination in underserved communities
  - Taking advantage of established technical expertise and Know How from Prevenar 13® to develop the MDV

Acknowledgements

Vaccines R&D
- Barry Ballan
- Lynn Phelan
- Lakshmi Khandke
- Cindy Yang
- Ksenia Krylova
- Kathrin U. Jansen
- Abbas Rashidgaigi
- Annaliesa Anderson
- Marja van Ziejl

GCMC
- Nathalie Dubois
- Jacqueline Dias

BTxPharmSci
- Li Li

PGS (Manufacturing)
- Gary Wyrick

DSRD
- David W. Clarke

Clinical Team
- Alejandra Gurtman Clinical Lead
- France Laudat Clinical Study lead
- Kimberly J. Center Clinical Study lead
- Daniel A. Scott Clinical Franchise lead

WSR
- Mary Allin

Emilio Emini – VRD Head during development.

Pfizer Biologic Medicines You May Recognize

Article 58

- Introduced in 2004 to help increase access to medicines in various developing countries
- Emphasis on medicines to treat or prevent diseases of major health interest
- Process
  - CHMP conducts a scientific assessment
  - After consultation with the WHO, adopts a scientific opinion
  - For positive opinions, issues an European Public Assessment report (EPAR)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp