

GVIRF 2016: New Combination Vaccines: How and Why?	
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Session Outline	<p>Chair: R. Clemens</p> <p>Opening remarks: R. Clemens</p> <p>Presentations: M. De Wilde, P. Dull, M. Malhame</p>
Objectives of the session	<p><i>To discuss:</i></p> <ul style="list-style-type: none"> • Successful and unsuccessful combination vaccines and what determined their fate • Manufacturing, clinical, regulatory and operational challenges of combination vaccines • Current and future vaccine landscape which drives the need for new combination vaccines • In-market barriers and opportunities that guide appropriate combination vaccines
Main outcome	<ul style="list-style-type: none"> • Current vaccine candidates in development present public health opportunities and challenges for introducing as stand-alone vaccine. • Benefits of combination vaccines can outweigh downsides. Therefore, combination vaccine strategy should be actively explored with careful consideration of the challenges outlined below. • For successful implementation of combination vaccine strategies, maximizing impact and reducing time to market, leverage learnings from past combination vaccines development and introduction. • Be strategic in identifying the right combinations based on epidemiology, technical feasibility, and impact
Summary (400-500 words)	<p>As more important and lifesaving vaccines become available, the childhood vaccination schedule is becoming increasingly crowded. Immunization programs are facing constraints on the number of injections per visit that will be accepted, and on the system resources available for vaccination. To address these constraints, some countries have increased the number of visits to accommodate additional injections or reduced the number of doses of specific vaccines to limit the total number of injections while retaining effectiveness. Combination vaccines are an important approach to maximize protection while minimizing the burden on immunization systems and families.</p> <p>Successful combination vaccines are the mainstay of infant immunization schedules and have had global impact. Measles, mumps, and rubella (MMR) vaccines were originally developed as individual vaccines: the MMR combination has now been available for over 40 years and is used in more than 100 countries. DTPw Penta vaccine, combining diphtheria, whole-cell pertussis, tetanus, hepatitis B and</p>

HiB, is supplied by 6 manufacturers and used in all 73 Gavi countries, representing a robust global market.

Development of combinations face many challenges. First, the components must be physicochemically compatible. New technologies such as frangible seals, micropellets, mRNA technology, and delayed release formulations have the potential to allow novel combinations of poorly compatible components. Second, each of the combined antigens must be safe and efficacious when administered. When correlates of protection have been established for all of the component antigens, clinical evaluation can be simplified substantially. Third, the vaccine manufacturer must have the necessary intellectual property rights for all the vaccine components. Intellectual property considerations have driven the formation of joint ventures and licensing agreements, and have also excluded specific antigens from incorporation in combination vaccines.

Three case studies illustrate these challenges. Globorix, a 7-valent vaccine combining penta and meningitis serogroups A and C, was dropped due to a somewhat reduced immunogenicity of the meningococcal antigens and anticipated competition from MenAfriVac. Hexavac, a 6-valent vaccine combining DTaP Penta and inactivated polio vaccine, was ultimately withdrawn by the manufacturer due to reduced hepatitis B titers and a safety signal (causality later excluded). Proquad, a combination of MMR and varicella, has been associated with an elevated risk of febrile seizures, and the recommendation has therefore been changed to use only as a 2nd dose.

Regardless of these challenges, new combination vaccines remain attractive, particularly in three areas: maternal immunization, adding additional antigens to DTPw Penta-based immunization in infants, and vaccines for enteric diarrheal diseases in infants. Maternal immunization relies on an efficient transfer of maternal antibodies to neonates. This vaccination could be given during the third trimester in a single visit (e.g. RSV, GBS, influenza). Given the success of the DTPw Pentavalent vaccines, additional antigens can be considered for incorporation, such as injectable rotavirus vaccine, reduced dose IPV, Norovirus vaccine, monovalent or multivalent meningococcal components. The enteric platform takes advantage of similar epidemiological pattern of different pathogens causing enteric diarrheal diseases such as Shigella and ETEC.

For combination vaccines to achieve the greatest impact, several factors must be considered. Supply security for the combination requires supply security for all components of the vaccine. When multiple combination vaccines are made with bulk antigen from a single supplier, there may be hidden risks to supply. Regional diseases

	<p>may benefit from region-specific combinations, and offer improvements in coverage and efficiency if programmatic requirements are satisfied. Finally, cost-effectiveness remains an important consideration as antigens are added. Converging on broadly used combinations such as DTPw Penta and MMR can lower per dose costs through economies of scale, and improve the value proposition for combination vaccines.</p>
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