COMBINATION VACCINES: HOW AND WHY? LESSONS LEARNED.

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STRONG RATIONALE EXISTS FOR COMBINATION VACCINES

- Fewer injections
- Higher rate of compliance with complex vaccination schedule
- Better vaccine coverage
- Timely vaccination - schedule completed on time
- Reduced administration cost
- Lower storage space requirement
- Allows incorporation of additional vaccines in the schedule

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COMBINATIONS HAVE LED TO IMPROVED UPTAKE AND CLINICAL OUTCOMES VS. STANDALONE ALTERNATIVES *(THAILAND EXAMPLE)*

COMBINATION with HEPB SHOWED COVERAGE AND IMMUNOGENICITY GAINS

	DTPw + HB (separately)	Combined DTPw-HB	Net change
HB coverage (3rd dose)	83.8%	93.8%	+10%
Seroconversion rate	88.4%	94.8%	+6.4%

Notes: HB coverage (3rd dose) P-value=0.001
Source: Comparative evaluation of a combined DTP-HB vaccine in the EPI in Chiangrai Province, Thailand, Vaccine (2002);

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CASE FOR COMBINATION VACCINES? EVOLVING UNDERSTANDING OF ACCEPTANCE OF MULTIPLE INJECTIONS IN DEVELOPING WORLD

Some countries in the developing world are reluctant to have > 2 shots per visit…

NEPAL:

- Introduced **PCV at 6, 10 weeks and 9 months to avoid 3rd injection (with IPV + Penta) at 14 weeks**
- Given reduced interval between 6 and 10-week injections, concerns raised about immunogenicity
- Avoidance of three injections at 14-week visit prioritized

BANGLADESH:

- Bangladesh **introduced PCV and IPV** to routine immunization schedule in 2015 with Penta
- District EPI managers/mothers influence decision **18-week visit rather than a third injection at 14 weeks**

…But in the U.S., 3 injections in one visit is the norm

2015 U.S. Immunization Schedule

3 injections given at most visits from 2 to 15 months

4 injections given at 4 to 6 years of age

BUT THERE ARE OTHER CONSIDERATIONS

- Scientific/Technical
  - Immunological: “in the child’
  - Physicochemical: “in the vial”
  - Analytical; “in the lab”
- Commercial
  - Intellectual Property
  - Access to all valences
  - Access policies and pricing
- Strategic
  - Introduction of new vaccines

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SCIENTIFIC CHALLENGES: MULTIPLE TECHNICAL AND IMMUNO-LOGICAL BARRIERS CHALLENGE THE SUCCESS OF COMBINATIONS

"In the child"	"In the vial"	"In the lab"
Immune interference	Incompatibility of components	Analytical assay tests
Bystander interference	pH incompatibility over time	
Carrier-induced epitopic suppression	Variable absorption to adjuvant	

COMBO DEVELOPMENT CAN BE CHALLENGING AND IS NOT ALWAYS SUCCESSFUL…

…3 Case studies

CASE STUDY 1: GLOBORIX

Objective	• Heptavalent for the Meningitis belt, incorporating MenAC into infant series
Composition	• D, T, wcP, HepB, Hib, MenAC-TT
Challenges	• Somewhat reduced immunogenicity of Men • Timing/cost of product mismatched vs the development of MenAfrivac
Outcome	• File withdrawn following the Article 58 day 120 questions

CASE STUDY 2: HEXAVAC

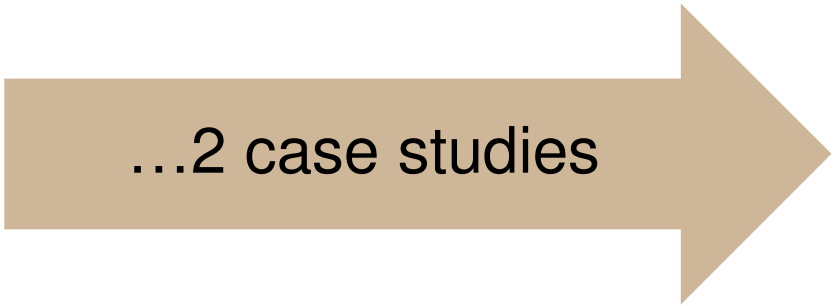
MERCK & SANOFI

Objective	• Hexavalent, primarily for Europe but other private markets as well.
Composition	• D, T, acP, HBV, Hib, IPV
Challenges	• Reduced HBV titers vs. licensed comparators • Few SIDS cases temporally associated (causality later excluded)
Outcome	• Licensed in 2000, suspended by EMA in 2005 • Large commitments for re introduction , vaccine ultimately withdrawn by manufacturer

CASE STUDY 3: PROQUAD

Objective	• Increase compliance and timeliness of MMR and varicella vaccination • Reduced number of injections • Target HIC market
Composition	• Measles, Mumps, Rubella, Varicella
Challenges	• Higher varicella titers required for adequate immunogenicity • Elevated febrile seizure risk identified post-licensure
Outcome	• Licensed in 2005 • In 2009, new ACIP recommendation as a 2nd dose at 4-6 years only

…BUT SUCCESSFUL COMBINATIONS HAVE LED TO EFFECTIVE VACCINES WITH GLOBAL IMPACT



CASE STUDY 1: PENTA

Objective	• Pentavalent infant vaccine for L&MICs
Composition	• Diphtheria, Tetanus, wcPertussis, HepB, Hib
Advantages	• Emerged as successor to DTP • Shots reduced from 9 to 3 • Allowed the introduction of Hib
Outcome	• After hiccups, now available in world's 73 poorest countries from 6 manufacturers • Increased coverage

Source: Gavi: Pentavalent Vaccine Support

CASE STUDY 2: MMR

Objective	• Trivalent pediatric combination for the world
Composition	• Measles, Mumps, Rubella
Advantages	• Available for >40 years • Components developed as individual vaccines prior to combination
Outcome	• Similar titers elicited vs. standalone vaccines • Where widely used, >99% reduction in incidence of each disease

Source: Development of Combination Vaccines (Vaccine, 2009); BioSpectrumIndia; UNICEF: Facts for Life; Merckvaccines.com

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ANTIGEN AVAILABILITY AND INTELLECTUAL PROPERTY HAVE IMPACTED THE DEVELOPMENT OF COMBINATION VACCINES…

Introduction

- **Combination vaccines first emerged in vaccinology in 1949** when DTP was licensed
- As the number of available vaccines grew and the **immunization got crowded, the incentive to reduce the number of injections grew**, particularly for the primary schedule in infants
- The **stage was set for hexavalent combinations in the 1990s** with the availability of HepB and Hib and a shift to IPV

Main drivers

Antigen availability

Initially, **no manufacturer had all the valences** available **to make a hexavalent**

Intellectual property

Vaccines had become commodities but **IP covering recHepB became a huge driving force**

…AND HAVE SHAPED THE DEVELOPED WORLD VACCINE INDUSTRY!

Combination strategies varied by player

Sanofi and Merck

- Formed a joint venture in Europe in 1994
- Started development of Hexavac

GSK

- Elected to go “alone”
- Obtained D and T through a agreement with Chiron Behring

Other players

- Excluded from the combo market in the developed world
- e.g. Sclavo/Chiron despite an excellent acP

Future developments

- In the developing world, a lot of movement is taking place already between DCVMs and MNCs; it can be expected that combination vaccines will drive further change in the landscape

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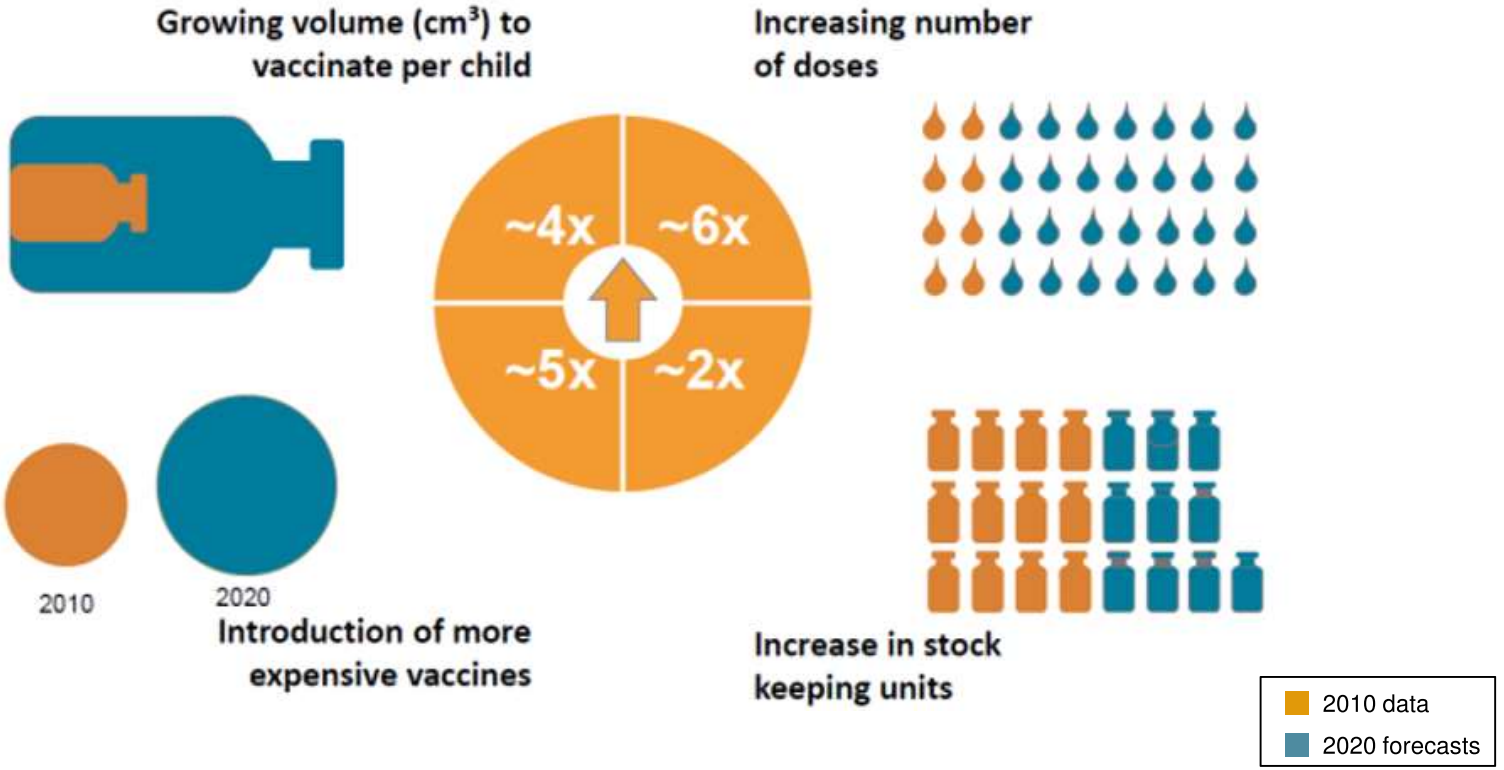
THE INTRODUCTION OF NEW VACCINES WILL FURTHER INCREASE COMPLEXITY



Note: All figures are based on GAVI-funded vaccines only

Source: Chart from GAVI Immunization supply chain strategy presentation, 2014: http://www.peoplethatdeliver.org/sites/peoplethatdeliver.org/files/2.%20GAVI%20SCS.pdf; UNICEF Supply 2012 financial report; 2010 GAVI Shipment data; 2012 GAVI SDF Forecast, including volume for future GAVI graduated countries; 2010 vaccines include YF, Measles, Penta, OPV; 2020 vaccines add Rota, Pneumo, HPV; Cost comparison based on 2013 prices; Stock keeping units estimates based on 2009 data for 2010 and 2013 forecast for 2020

COMBOS ADDRESS CONCERNS ACROSS EACH OF THESE AREAS

- Simplifying administration by decreasing volumes and combining antigens into fewer shots
- Providing greater access to vaccines in the developing world via material cost savings
- Minimizing cold chain supply challenges by decreasing the number of SKUs and total shipment volume required

GOING FORWARD: CONSIDERATIONS FOR NEW COMBINATIONS

- Epidemiology (age group and geography of burden)
- Technical and immunological risks
  - CMC complexity (formulation, analytical, failure rate)
- Route of administration (oral versus parenteral)
- Regulatory pathway
  - e.g. do correlates exist for all antigens?
  - e.g. article 58 vs local vs other
- Needed partnerships/licenses