Multi-national consortiums to coordinate and facilitate vaccine(s) evaluation – Experience with the Meningitis Vaccine Project

Accelerating the licensure of Lassa vaccines: Generating robust evidence on vaccine efficacy and safety

Abuja, 25th & 26th of October 2022

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Regional meningitis focal point

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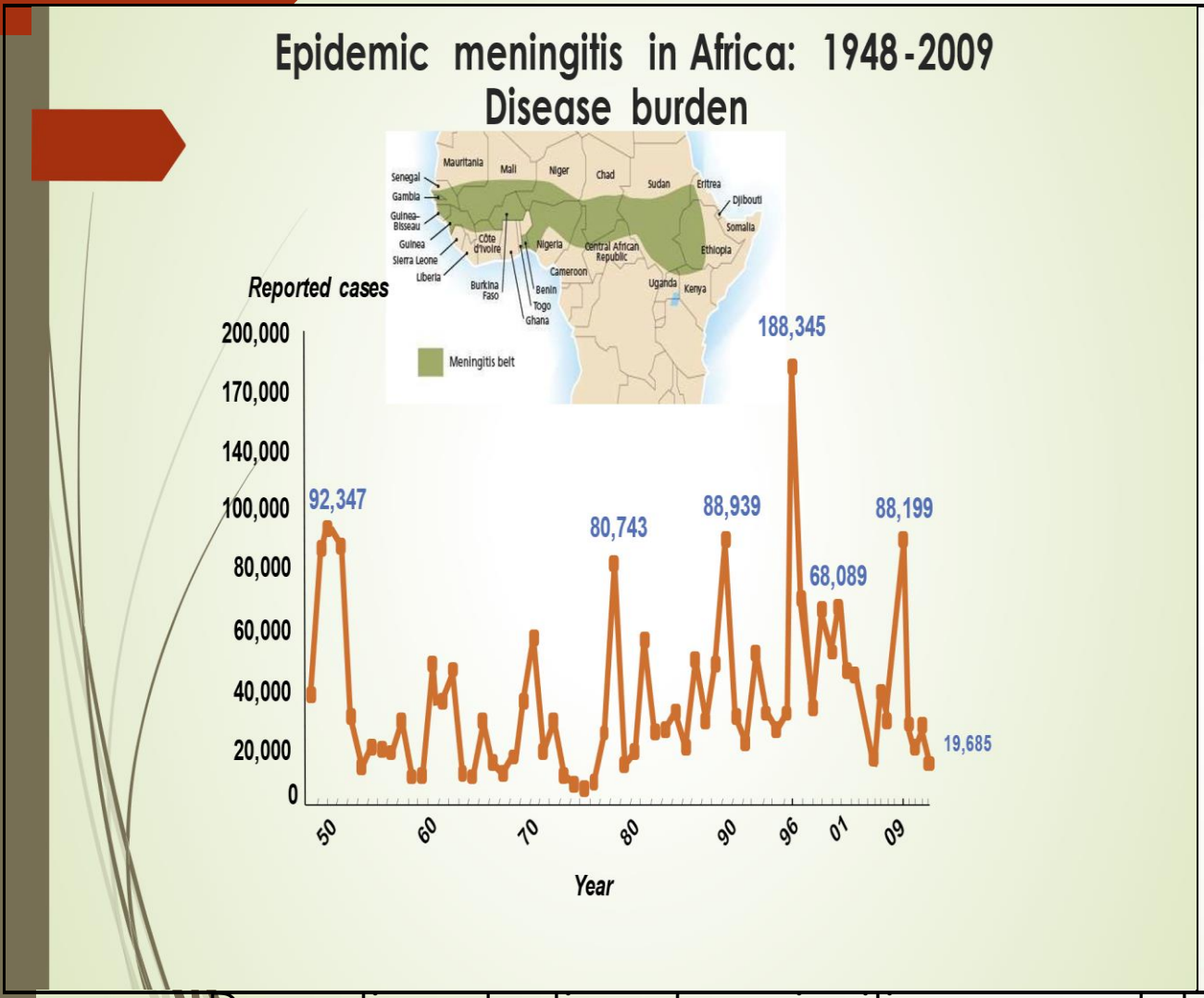
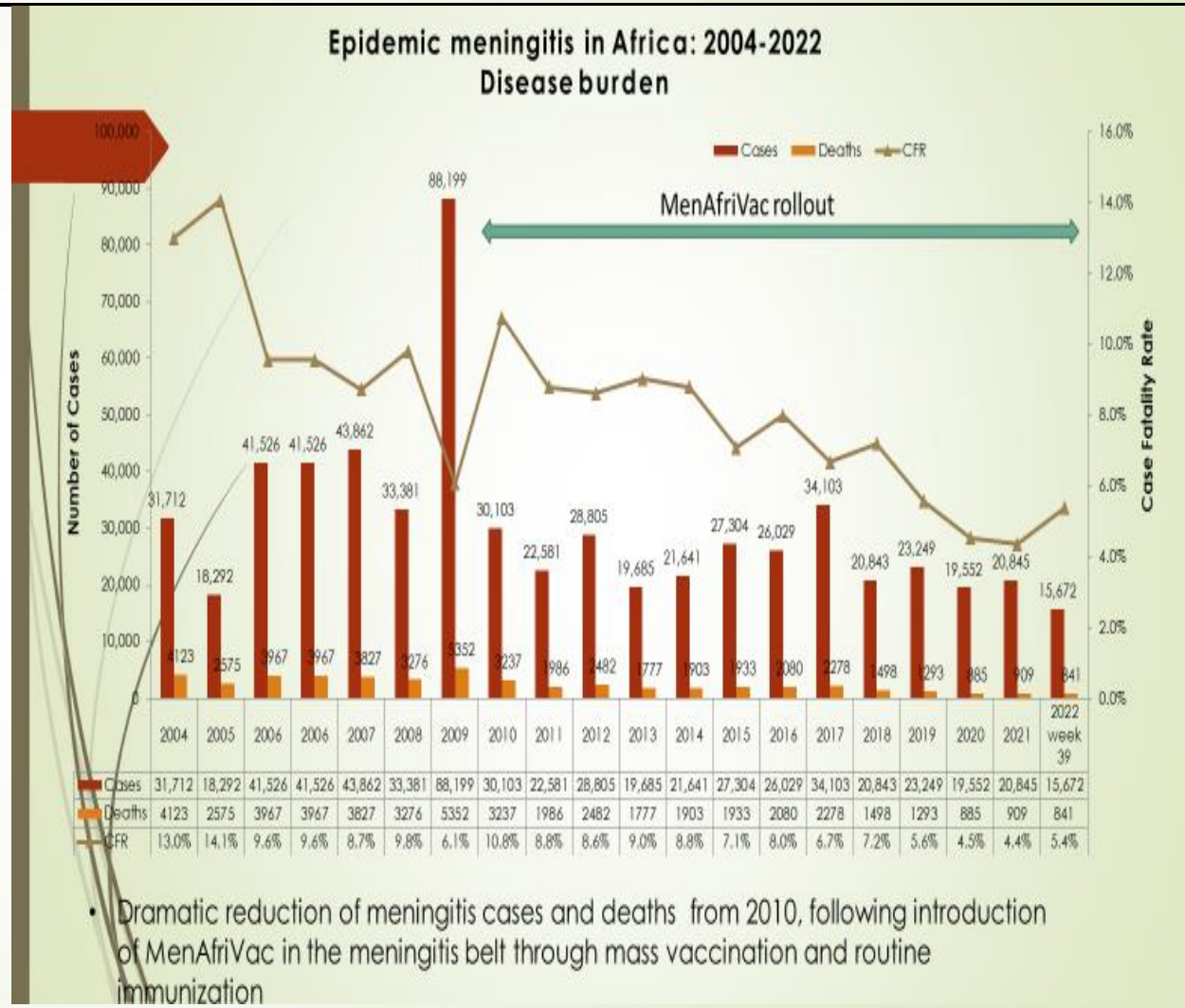
The public health problem: Epidemic meningitis in Sub-Saharan Africa

- Until recently over 90 percent of global meningococcal disease occurred in the African meningitis belt
- One strain (Group A Nm) accounted for estimated 80% of all meningococcal cases.
- Focal epidemics occurred every year.
- Major epidemics occurred every 7-14 years.

Dramatic reduction of meningitis epidemics resulted to MenAfriVac roll out

Epidemic meningitis in Africa: 1948-2022
Disease burden





- Dramatic reduction of meningitis cases and deaths from 2010, following introduction of MenAfriVac in the meningitis belt through mass vaccination and routine immunization

Availability of Meningococcal Vaccines for Sub-Saharan Africa in 2001

- Only A/C PS vaccines were available and were largely used in reactive campaigns.
- The reactive campaigns were expensive, largely ineffective, but politically necessary.
- There were no Pharma plans to develop a Group A Nm conjugate vaccine for Africa.

Creation of the Meningitis Vaccine Project (MVP)

- **Under WHO leadership international meetings were held in in 2000 and 2001 that recommended that conjugate meningococcal vaccines be developed for Africa.**

- **In June 2001 MVP was created with Gates Foundation support as a 10 year partnership between WHO and PATH.**

Goal: to eliminate epidemic meningitis in Africa as a public health problem through the development, testing, licensure, and widespread use of conjugate meningococcal vaccines

Four pivotal events

- Better understanding the problem of epidemic meningitis from the African perspective from July 2001 to February 2002.
- The Meningitis Vaccine Project becomes a virtual vaccine company in March 2002.
- A new conjugation method is transferred from FDA/NIH to Serum Institute in December 2003.
- Serum Institute successfully accepts tech transfers and scales up production from laboratory to commercial scale (04-07) and licenses a new PsA-TT vaccine, *MenAfriVac* (2009).

Informing African partners while better understanding the problem – Fall 2001

- MVP discussions with African public health officials and WHO/AFRO (Harare, Niger, Burkina Faso, Nigeria) yielded consistent information:
  - Epidemic meningococcal meningitis was an important public health problem that African Ministries of Health wanted solved.
  - Cost of vaccine was the most important limiting factor to the introduction of new vaccines in Africa.
  - Success of MVP (widespread use of a Group A Nm conjugate vaccine in mass campaigns) would not be possible unless vaccines were priced less than $US 0.50 per dose.

MVP becomes a virtual vaccine company in March 2002

- MVP could not reach an agreement with major vaccine manufacturers and negotiations end in March 02.

- After consultations with MVP Technical and Management Committees and the Gates Foundation, MVP elected to become a virtual vaccine company with the goal of developing a Group A conjugate vaccine.

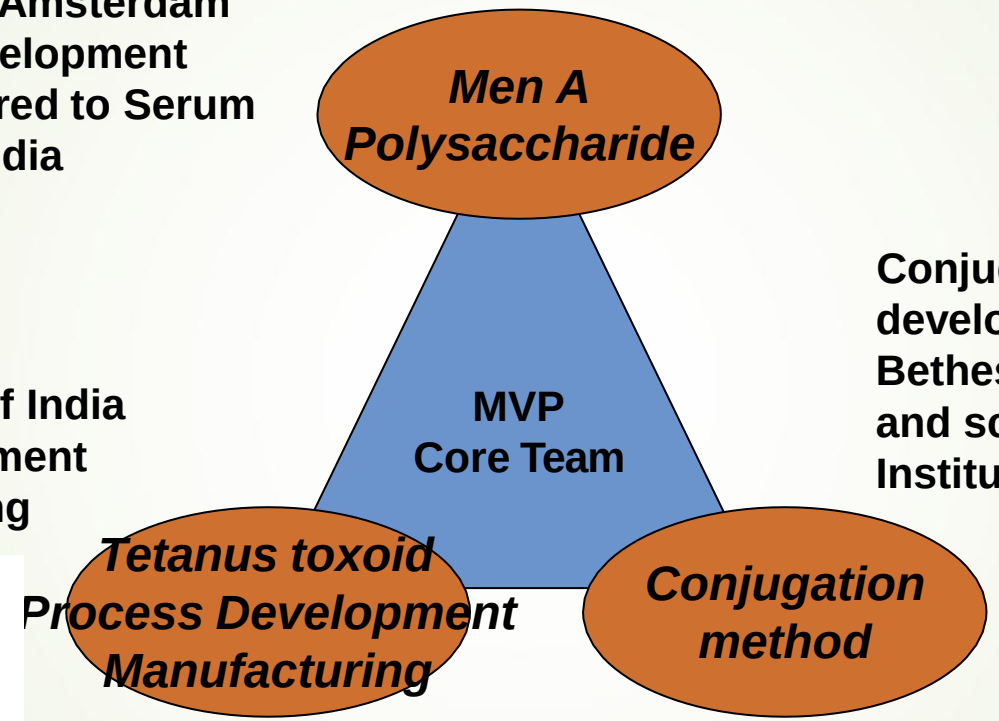
- Crucial elements in making this decision included:
  - Inputs from African public health officials on the importance of vaccine price.
  - Availability of a business plan commissioned by WHO indicating that “cost of goods” for making 25-50 million doses of a Men A conjugate vaccine could be as low as $US 0.20 per dose.

FDA and the NIH step up - 2003

- In June 2003 Carl Frasch from FDA indicated that a robust conjugation method for NmA had been developed by Robert Lee at CBER/FDA.
- Discussions with FDA begin in late June; confirmatory testing of the CBER/FDA vaccine was done by Dan Granoff in October 2003.
- Technology transfer of the FDA conjugation method to a Serum Institute team began in during the 2003 Christmas holiday.

Men A Vaccine development model

A PS produced by SynCo BioPartners, Amsterdam for initial development then transferred to Serum Institute of India



Conjugation method developed at CBER/FDA, Bethesda, USA, transferred and scaled-up at Serum Institute of India

Serum Institute of India process development and manufacturing

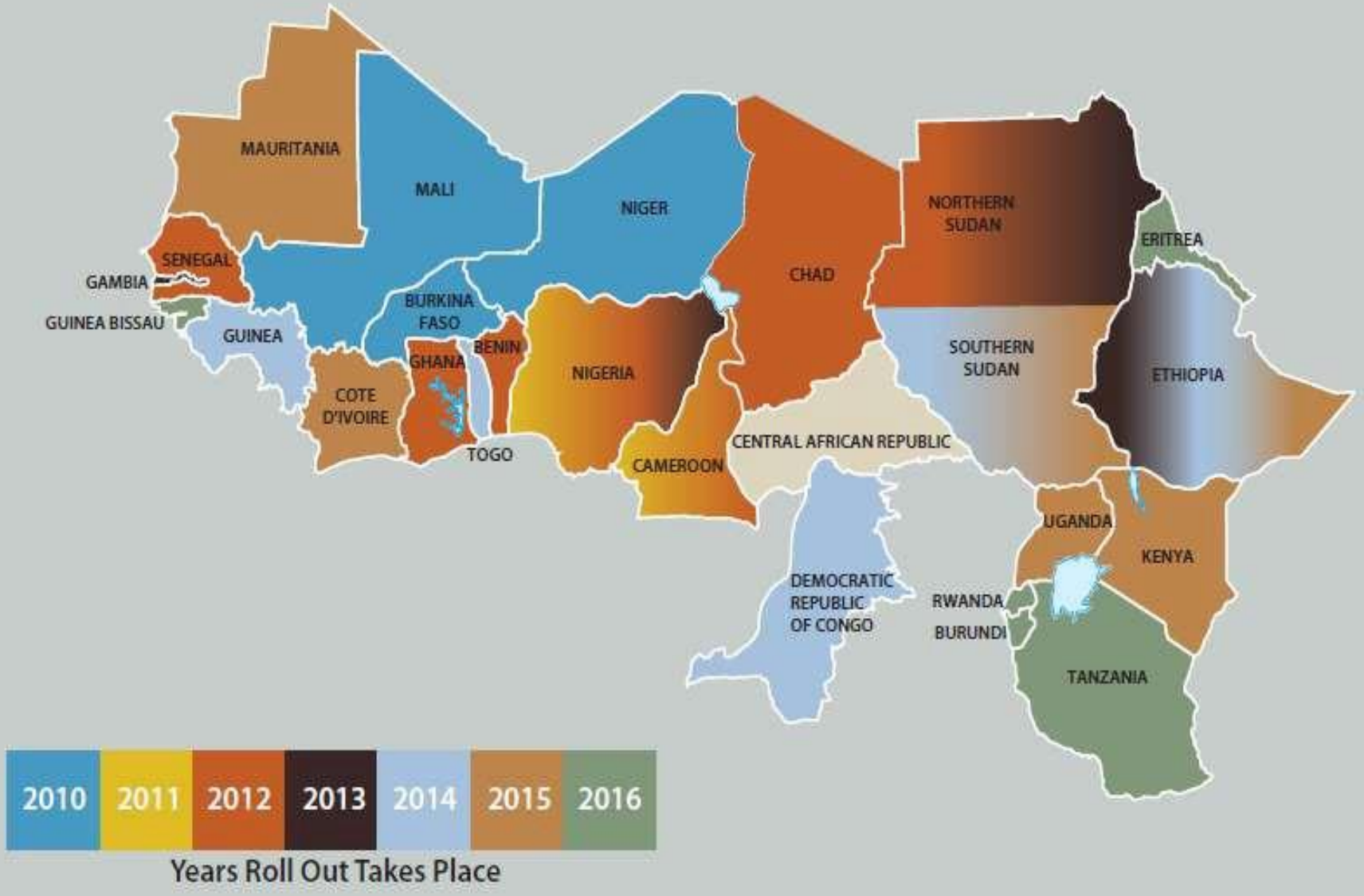
Lyophylization and stabilization tech transfer from Aerial in France to Serum Institute

Target price US$ <0.50/dose

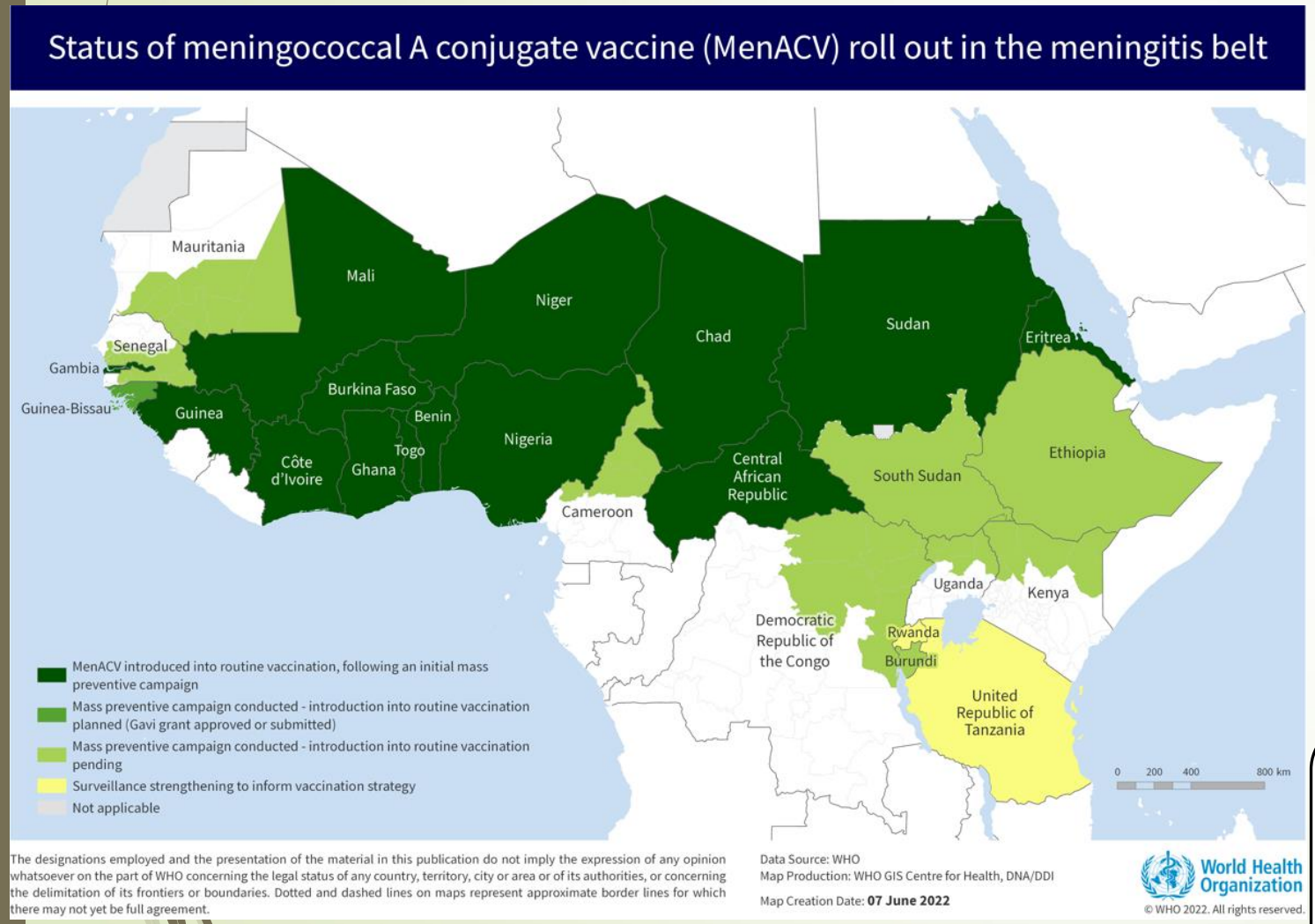
Clinical trials, licensure and introduction 2005 - 2010

- Clinical trials of the PsA-TT vaccine begin in 2005.
- *SII* is granted an export license for *MenAfriVac* by the Drugs Controller General of India in December 2009.
- WHO prequalification granted in June 2010.
- PsA-TT introduced in Burkina Faso, Mali and Niger in December 2010: 20 million doses administered ($US 0.40/ dose)

MenAfriVac Roll-Out Plan 2010-2016



MenAFriVac roll out as of October 2022



24 countries conducted mass campaigns

350 million 1-29 year-olds vaccinated Dec 2010 – Oct 2022

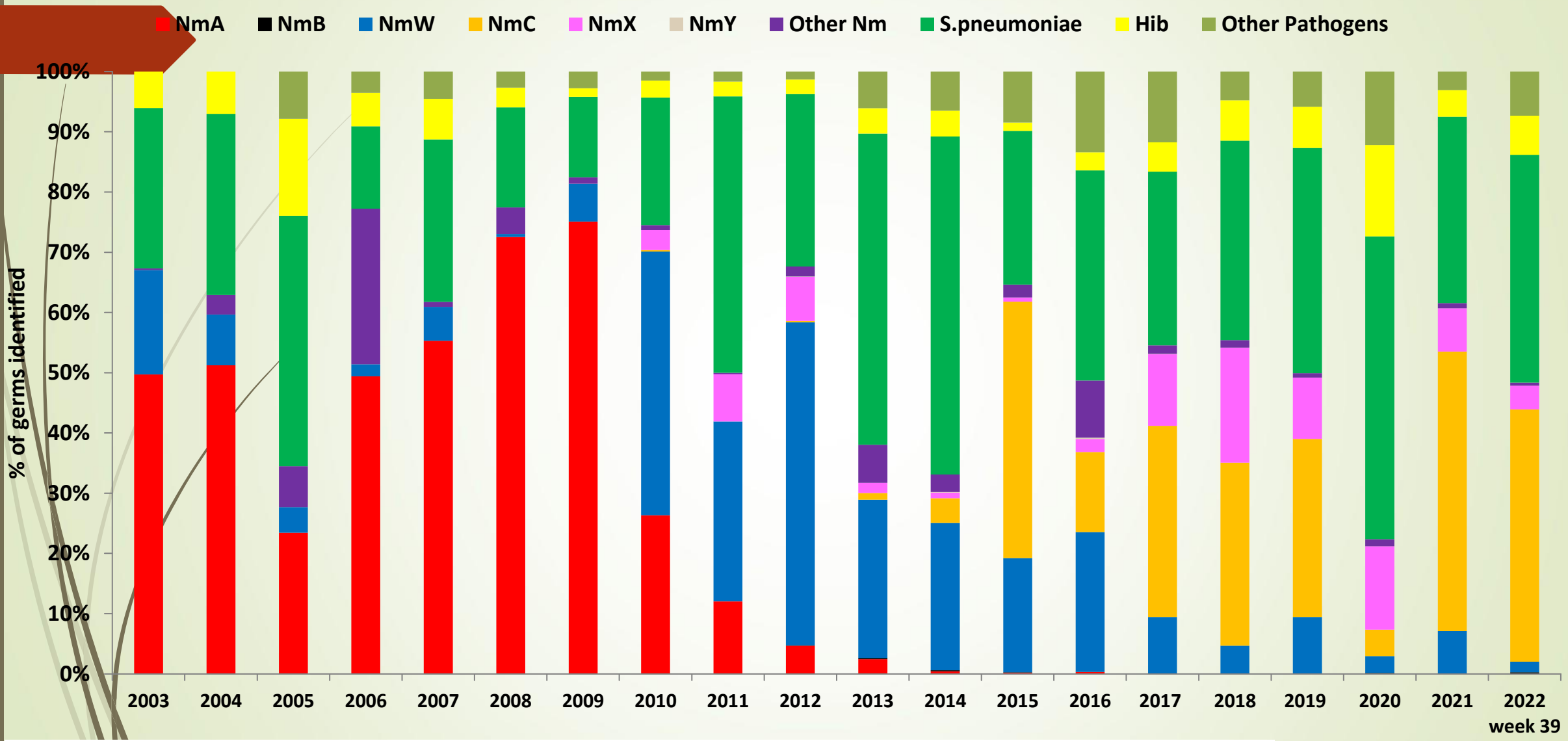
14 countries introduced into routine

No confirmed case of NmA in countries of the meningitis belt in 2018-2022
Ongoing efforts to sustain the impact of campaigns through routine immunization

Mass preventive vaccination campaigns 2010 – 2022

#	Country	Year	Target	# people Vaccinated	Admin coverage (%)	Coverage survey (%)
1	Burkina Faso	2010	11,133,831	11,425,391	102.6	95.9
		2016[3]	3,956,618	4,152,737	105.0	95.2
2	Mali	2010-2011	10,854,599	11,109,484	102.3	96.0
		2017[3]	3,328,000	3,483,991	104.7	N/C[4]
3	Niger	2010-2011	10,870,817	10,575,365	97.3	91.0
		2019[3]	6,072,802	6,316,857	104.0	95.2
4	Chad	2011-2012	9,223,913	8,732,251	94.7	84.0
		2018;2021[3]	4,208,522	4,342,986	103.1	82.0
5	Cameroon	2011-2013	6,727,388	6,725,245	100.0	73.5
6	Nigeria	2011-2014	83,695,197	87,062,324	104.0	69.9
		2019-2021[3]	33,452,572	33,030,640	99.7	90.0
7	Benin	2012	2,595,654	2,718,459	104.7	96.0
		2022[3]	1,573,504	1,678,660	106.7	89.0
8	Ghana	2012	3,098,348	3,038,393	98.1	90.1
		2016[3]	679,508	666,688	98.1	96.6
9	Senegal	2012	4,383,255	4,216,691	96.2	96.2
10	Sudan	2012-2013	24,823,640	23,521,440	94.8	94.0
		20163	5,226,139	5,278,401	101	N/C
11	Gambia	2013	1,177,923	1,229,509	104.4	96.6
		2019[3]	416,614	384,013	92.2	93.0
12	Ethiopia	2013-2015	61,748,268	61,059,389	98.9	96.0
13	Cote d'Ivoire	2014	4,271,669	4,587,056	107.4	N/C
		2018[3]	894,465	933,070	104.3	N/C
14	Mauritania	2014	1,610,523	1,561,720	97.0	N/C
15	Togo	2014;2017	2,906,816	2,967,981	102.1	98.1
		2021[3]	1,356,252	1,254,202	95.0	96.0
16	Guinea	2014-2015	3,005,423	2,880,334	95.8	92.7
		2022[3]	1,179,646	1,117,360	94.7	N/C
17	DRC	2016	18,205,784	18,058,535	99.2	N/C
18	Guinea-Bissau	2016	1,277,088	1,150,136	90.1	N/C
19	South Sudan	2016-2018	7,137,992	5,872,987	82.3	N/C
20	CAR[2]	2017	3,658,248	3,220,358	88.0	93.6
21	Uganda	2017	6,899,267	7,265,931	105.3	89.0
22	Burundi	2018	7,867,785	7,968,553	101.3	98.0
23	Kenya	2019	3,122,735	2,054,620	65.8	82.0
24	Eritrea[2]	2019	2,659,089	2,507,521	94.3	99.6
	Total		352,869,447	352,701,665	99.6	N/A[5]

Meningitis pathogens identified, 2003-*2022



Before 2010, NmA was the main pathogens isolated

After 2010, the prominent pathogens identified were NmC, Sp, and NmW

Distribution of Group A meningococci—Burkina Faso, 2005- 2016

Year	Meningitis cases	% Group A Nm
2005	3,626	11.6
2006	19,134	84.6
2007	26,878	91.1
2008	10,401	79.2
2009	4,723	30.1
2010	6,732	24.9
Introduction of MenAfriVac in December 2010		
2011	3,875	0.1
2012	6,797	0.0
2013	2,512	0.0
2014	3,476	0.0
2015	2,927	0.5
2016	2,645	0.0

The *MenAfriVac* report card: development costs and impact

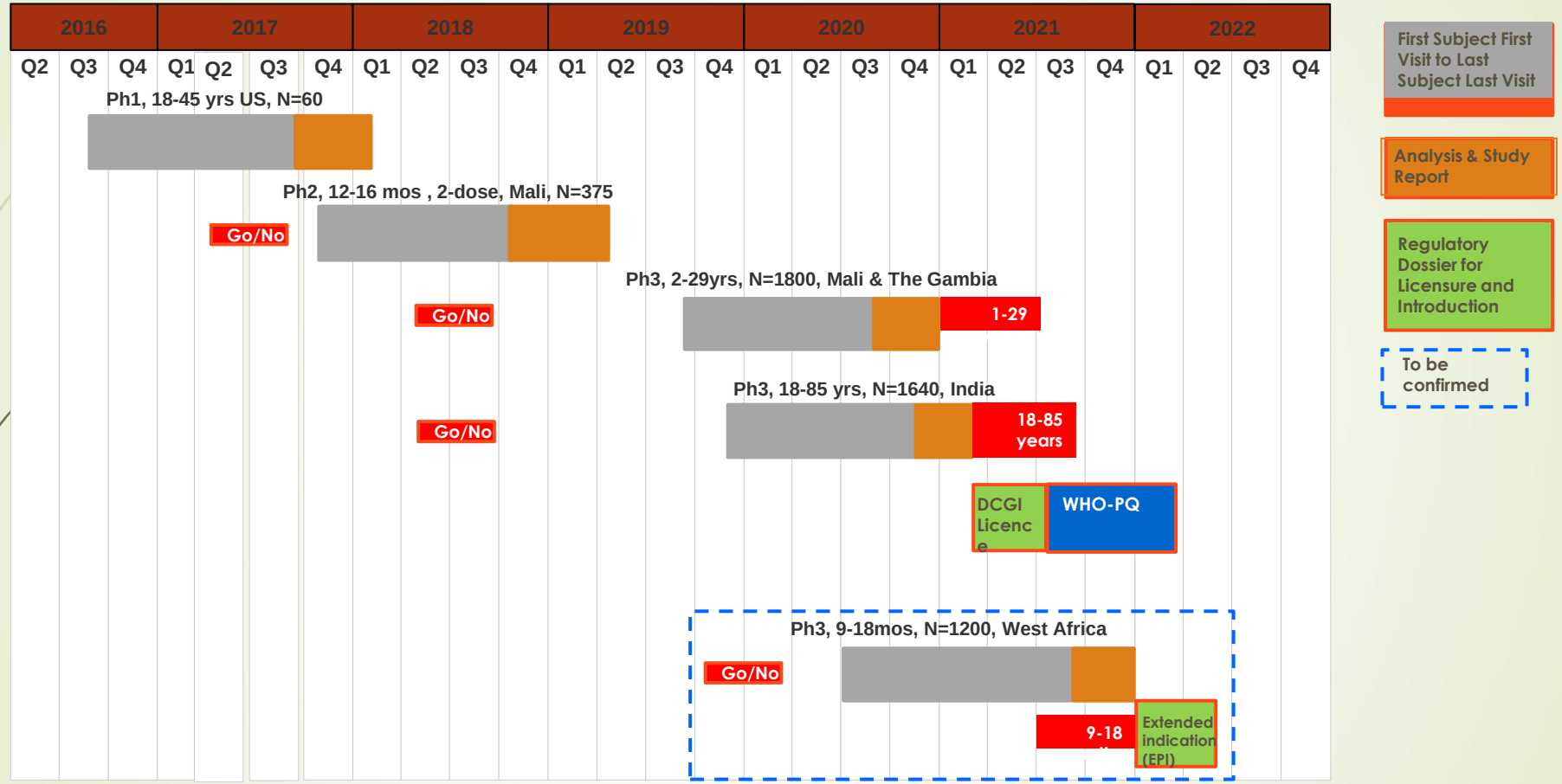
- Total development cost at about $US 100 million
- Enthusiastic acceptance of the new vaccine by African Ministries of Health.
- From 2010 to 2022 over 350 million Africans have received a dose of *MenAfriVac*.

Group A Neisseria meningitidis disease has disappeared from Sub-Saharan Africa.

Lessons learned: getting the science right

- There is nothing more important than the quality, safety and effectiveness of the final vaccine product.
  - The preclinical and clinical studies of the PsA-TT vaccine were all consistent: the vaccine was potent, safe and better than existing polysaccharide vaccines.
  - A clear road map (Men C conjugate vaccine) indicated that herd immunity was likely if the right age group was well vaccinated with the PsA-TT vaccine.

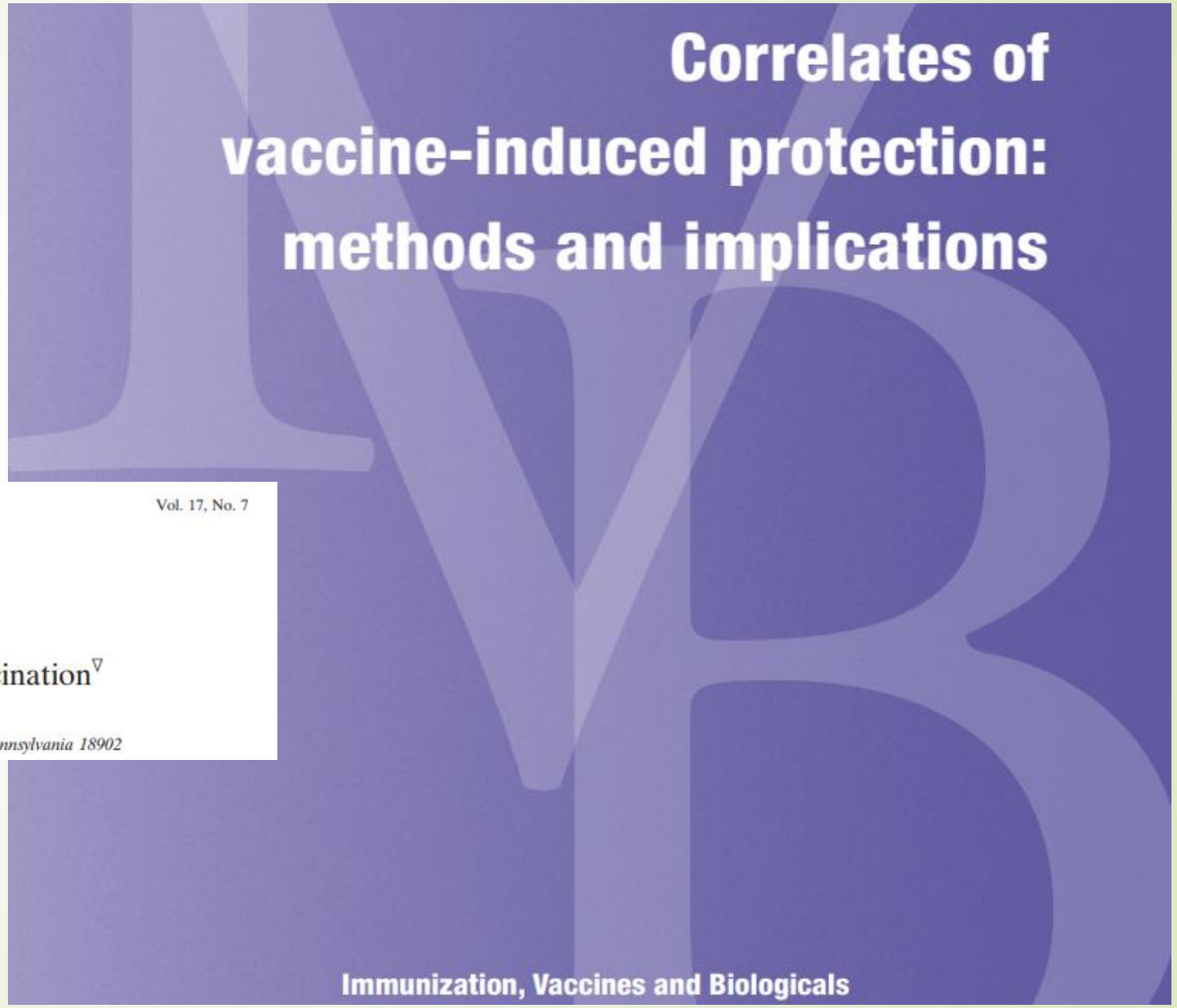
Lessons learned: After Phase 2 things happen fast – the NmCV-5 Clinical Development Plan



- Initial WHO PQ anticipated around Q2-Q4 2022.

Lessons learned: make sure that your correlates of protection are acceptable to regulatory bodies

USFDA - **Correlate of protection:** "Generally, a laboratory parameter that has been shown to be associated with protection from clinical disease" (Tiernan, 92).



CLINICAL AND VACCINE IMMUNOLOGY, July 2010, p. 1055–1065 Vol. 17, No. 7
1556-6811/10/$12.00 doi:10.1128/CVI.00131-10

MINIREVIEW

Correlates of Protection Induced by Vaccination▽

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Correlates and surrogates of protection

Comparison of definitions of correlates and surrogates of protection

	Plotkin (2008)	Qin et al. (2007)
Correlate of protection / risk	Immune response closely related to protection / that provides protection	Immune response whose presence is associated with low risk of disease/ infection
Surrogate of protection	Immune response that is not in itself protective, but which substitutes for the true correlate	Correlate that predicts accurately the level of VE, i.e. for which it can be shown that it is responsible for protection

Figure 1. Simple illustration of the induction of protective immunity by a vaccine

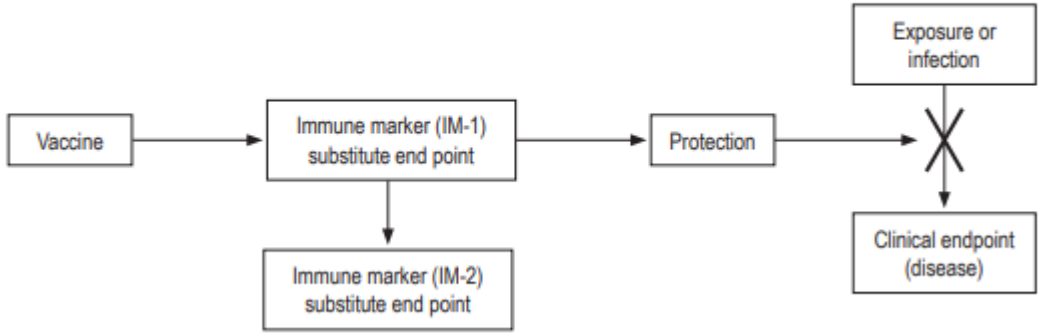
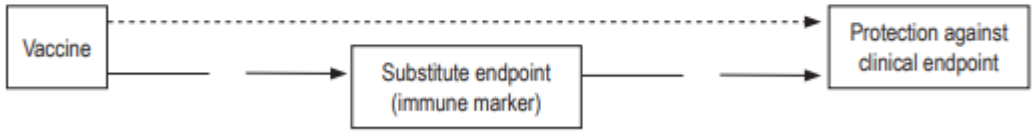
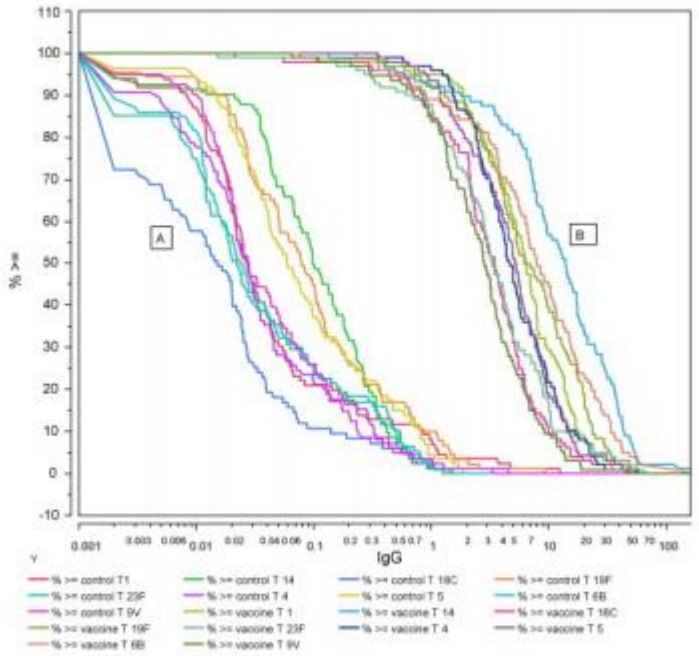


Figure 8. Simplest possible relationship between vaccine, substitute endpoint and clinical endpoint



Define a workable correlate of protection

Figure 9. Reverse cumulative distribution of antibody titres to each vaccine serotype in children receiving placebo or three doses of 9-valent pneumococcal conjugate vaccine

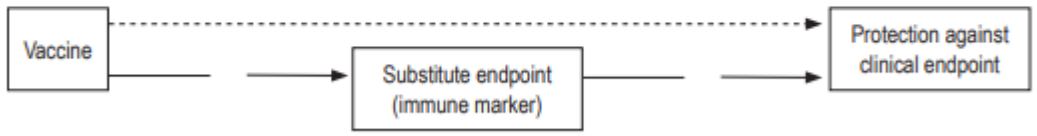


A, placebo; B, pneumococcal conjugate vaccine

Source: Reprinted from Saaka et al. (15) with permission from Elsevier.

- Men C conjugate vaccine was licensed in the UK as a result of phase II immunogenicity studies.
- These compared serum bactericidal assay titers induced by the new vaccine to those induced by a licensed serogroup C polysaccharide vaccine, which demonstrated direct evidence of efficacy and accepted correlates of protection.
- The studies used rabbit complement (rSBA) with the "gold standard" criterion for protection based on serum bactericidal assay titers using human complement (hSBA).
- Paired sample studies using both rSBA and hSBA showed that 85% of individuals with rSBA <8 had hSBA <4, and 93% of those with rSBA titres ≥128 had hSBA titres ≥4.
- However, for those with rSBA titres between 8 and 128, protection could be assumed if the rSBA titers rose fourfold as a consequence of vaccination. Thus, each step in Figure 8 was measured.

Figure 8. Simplest possible relationship between vaccine, substitute endpoint and clinical endpoint



The Prentice criteria (1989)

Four criteria for validation of a surrogate endpoint can be adapted for vaccine trials as follows:

1. Protection against the clinical endpoint is significantly related to having received the vaccine (the dotted line in Figure 8);

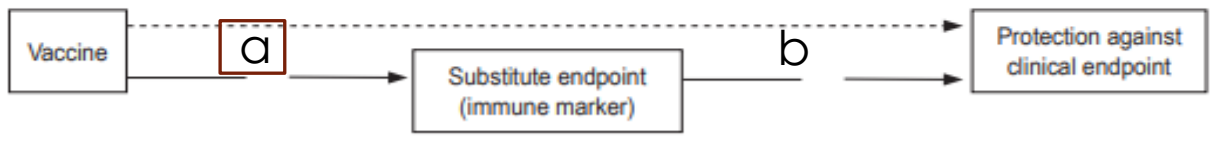
2. The substitute endpoint is significantly related to the vaccination status (step a in Figure 8);

3. The substitute endpoint is significantly related to protection against the clinical endpoint (step b in Figure 8);

4. The full effect of the vaccine on the frequency of the clinical endpoint is explained by the substitute endpoint, as it lies on the sole causal pathway.

If the full effect of the vaccine is mediated via the immune marker (criterion iv), the incidence of the clinical endpoint should be the same among vaccinated and unvaccinated individuals at any particular titer.

Figure 8. Simplest possible relationship between vaccine, substitute endpoint and clinical endpoint



Lessons learned: African engagement

- The African meningitis problem is an African problem and will be solved by Africans. MVP emphasized the following points:
  - Understanding the meningitis problem from the African point of view.
    - Making sure that the vaccine was affordable **as defined by Africans.**
    - Listening to Africans: from villagers to ministers
      - Choice of His Excellency, Blaise Campaore as the MVP "Patron"
      - Establishment of an MVP/WHO office in Ouagadougou, Burkina Faso
      - Investing in African communication expertise

Lessons learned: Working with WHO

- WHO's Expanded Program on Immunization (EPI) is the most important international immunization group in Africa.
  - WHO/AFRO and HQ were involved in every phase of MVP.
  - Regular visits to AFRO (Harare/Brazza) were part of the MVP work plan.
    - African EPI meetings were a priority to present a status report and to solicit advice.
    - A WHO/AFRO/MVP Advisory Group was established in 2004 and met regularly. The group was headed by Dr. Francis Nkrumah and members provided important counsel.
- Working with WHO required patience, tact and time and was a key element in MVP's success.

Lessons learned: Partnerships

- MVP had over 30 active partnerships.

- For partnerships to succeed:
  - Understanding partner needs – money, recognition, public service, etc…
  - Focusing on the goal and how the partner contribution fits in
  - Actively communicating, preferably face to face – using meetings to bind partners together
    - Current status in meeting the project's goal
    - Recognizing partner contributions
    - What were the current challenges

In collaboration with Health Authorities of 26 countries in Sub-Saharan Africa and of India

Men A-related opportunities for Serum Institute*

- Access to conjugate vaccine technology, IP and know-how.
- Close collaboration with PATH, WHO (HQ/AFRO), UNICEF and GAVI
- High visibility of the project in African countries
- Lowering the financial risk at Serum Institute.
  - $US 6.5 million to SII to support the Men A development work
  - $US 37 million for clinical trial costs in Africa and India
  - $US 3 million for filing the regulatory dossiers
- International recognition to Serum Institute

**Kulkarni et al, CID 2015:61 (Suppl 5); S483-S488*

Suggestion 1: Know the market and the pricing limits.

- Understand vaccine pricing limits from the very beginning.
- Demand matters - How will the vaccine be used?
  - As an EPI antigen
  - As a stockpile vaccine (epidemic response).
  - As a preventive vaccine

Suggestion 2: Understand Country, WHO, UNICEF and GAVI goals

- Make sure you understand what the end user (customer) wants.
- GAVI, WHO and country MOH are all key players and they all have their own interests, biases and priorities.
  - Matching priorities is a useful exercise.
  - Competing diseases and epidemics (like Ebola) are always important.
  - Political realities line rebel activities are real and are disruptive.

Suggestion 3: Prepare a quality investment case

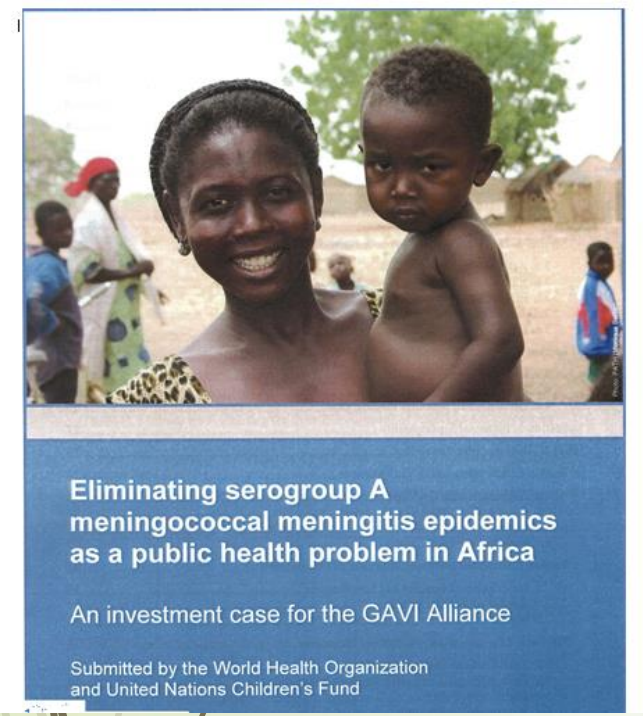


Table of Contents

Executive Summary i
Part I. The Proposed Investment 1
Section 1. The Objective I
Section 2. Description of the Problem 2
2.a. The disease 2
2.b. The challenges 5
2.c. Recent progress 7
Section 3. Description of the Proposed Investment 9
3.a. Activities to be carried out 9
3.b. Introduction strategies for different country environments 14
3.c. Project management 15
3.d. Partner roles and responsibilities 18
3.e. Implementation timeline 20
Section 4. Proposal Cost and Funding Needs 21
4.a. Cost of the proposal 21
4.b. Financing: sources of funds 26
4.c. Discussion of potential funding gaps 27
Section 5. Financial Sustainability 27

Part II. Rationale for Investing 29

Section 6. Relevance to GAVI Objectives 29

6.a. Alignment with GAVI priorities 29
6.b. Contribution to GAVI milestones 31
6.c. Consistency with GAVI concept of "value added" 31
6.c. Target countries 32

Section 7. Expected Incremental Impact of Investment 33

7.a. Description of benefits and beneficiaries 33
7.b. Burden of disease: baseline 34
7.c. Impact of investment on burden of disease 35

Section 8. Constraints and Probability of Success 35

8.a. Social and cultural constraints 36
8.b. Epidemiological and environmental constraints 36
8.c. Technical constraints 37
8.d. Institutional constraints 37
8.e. Point-counterpoint process 37
8.f. Critical risks 38

Section 9. Economic Analysis 38

9.a. Cost-effectiveness analysis 38
9.b. Sensitivity analysis 42
9.c. Market analysis 42
9.d. Equity impact and gender-related considerations 44

Part III. Monitoring and Evaluating Implementation **45**

Section 10. Success and Milestones 45

10.a. Process indicators 45
10.b. Data and information required 46
10.c. Monitoring and evaluation responsibilities and process 47
10.d. Monitoring and evaluation timetable 47

Part IV. Annexes **48**

Annex A. Meningitis and Meningitis Epidemics in Africa 48

Annex B. Challenges to Sufficient Vaccine Supply for Epidemic Response 53

Annex C. *N Meningitidis* Disease Transmission, Herd Immunity, and the Role of Mass Vaccination Campaigns With Men A Conjugate Vaccines in the Induction of Robust Herd Immunity 55

Annex D. Information About MenAfriVac™ 59

Annex E. Description of the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control 81

Annex F. Project Costs and Financing 83

Annex G. Assumptions Used to Create the Disease Burden Model 99

Annex H. Methods for Estimating the Cost-Effectiveness of Strategies for Introducing Men A conjugate Vaccine in Hyperendemic Countries in Sub-Saharan Africa 02

Annex I. Decision Tree for Bivalent (A/C) or Trivalent (A/C/W) Polysaccharide (Ps) Vaccine Use 108

Annex J. The Enhanced Epidemic Meningitis Surveillance 110

Annex K. Analysis of Potential Overlaps Between the Meningitis Investment Case and Other Proposed GAVI-funded Activities 114

Suggestion 4: Find a partner who will measure impact

- How will you measure success or failure?
- Vaccine development lessons.
- Vaccine acceptance – was the product used?
- What was accomplished from a public health perspective (partner)?


World Health Organization
Department of Immunization, Vaccines and Biologicals (IVB)
Initiative for Vaccine Research (IVR)
Meningitis Vaccine Project Meeting : A Scientific Workshop
at
Serum Institute of India Ltd., Pune, India
10 - 12 February 2010