A vaccine meets a strategy:

Eliminating epidemic meningitis from Sub-Saharan Africa

Dr. Bernard Guyer Lecture in Public Health

Center for Community Health and Prevention
University of Rochester Medical Center

Rochester, NY, September 27, 2018

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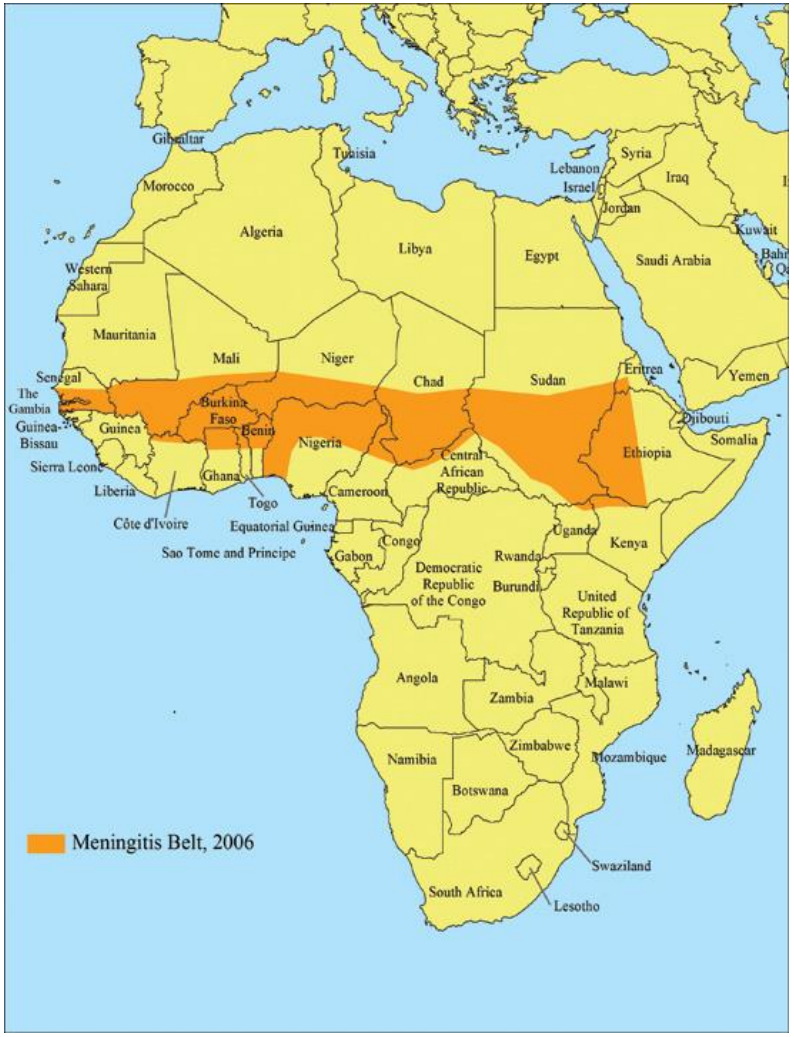
Disclosure

Dr. LaForce is employed by the Serum Institute of India where he serves as Director, Technical Services.

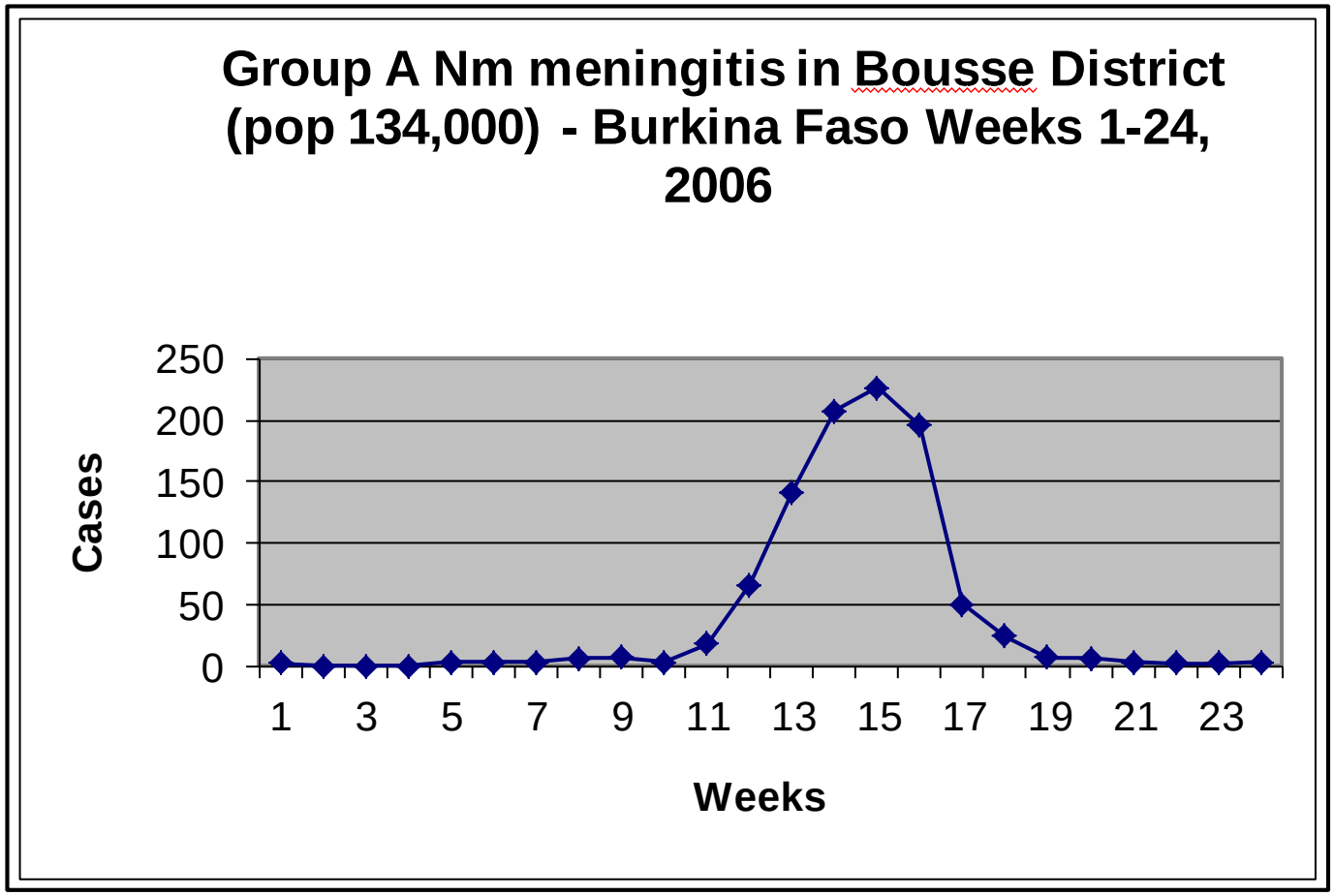
Meningitis belt in Sub-Saharan Africa

- Over 90 percent of global meningococcal disease occurs in the African meningitis belt
- Until recently 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.



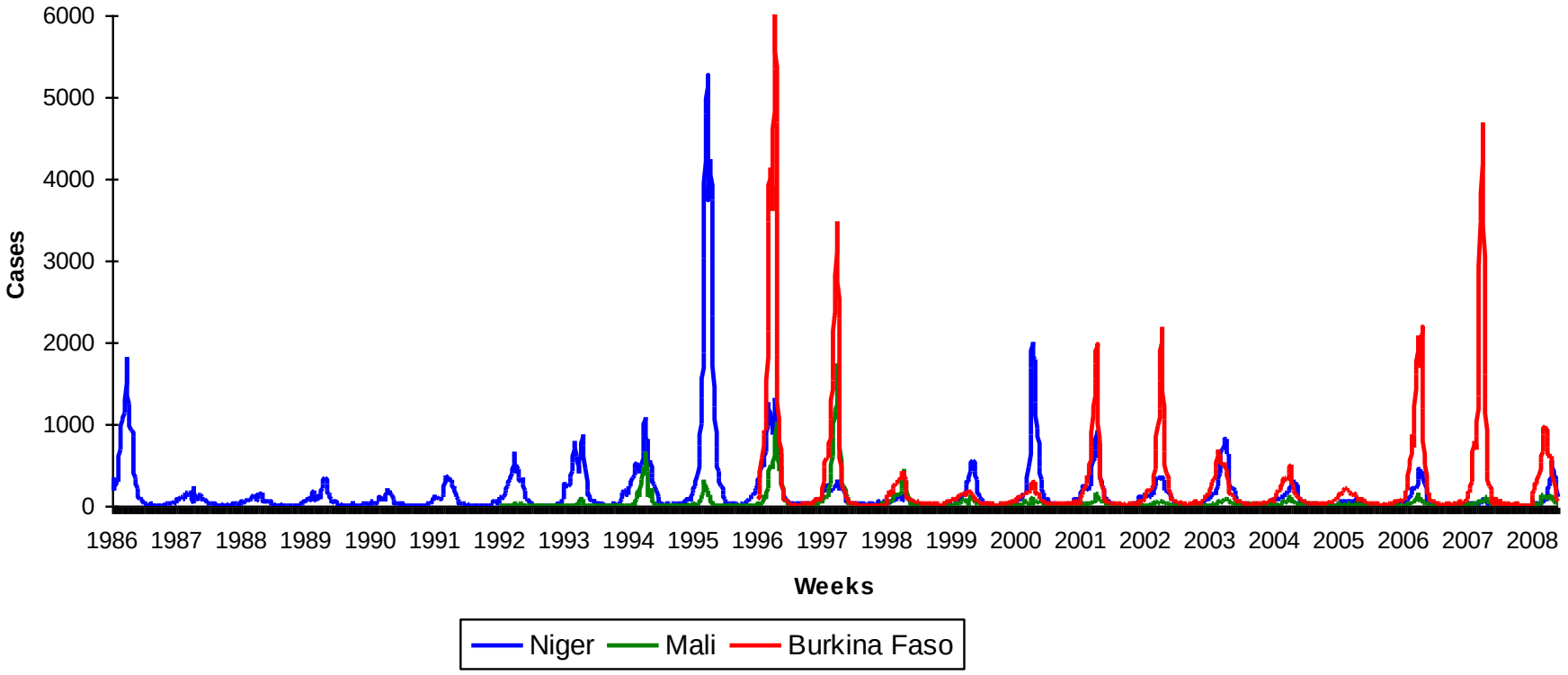
Economic context in meningitis belt countries

- Poorest countries in the world
- Few natural resources
- Inhospitable arid climate
- Per capita income 1-2 dollars per day
- Families have little to no “disposable income”



Total of 1003 cases of acute meningitis in 2006; incidence rate of 740 per 100,000

Meningitis by weekly reports in Burkina Faso (1997-2008), Mali (1992-2008) and Niger (1986-2008)



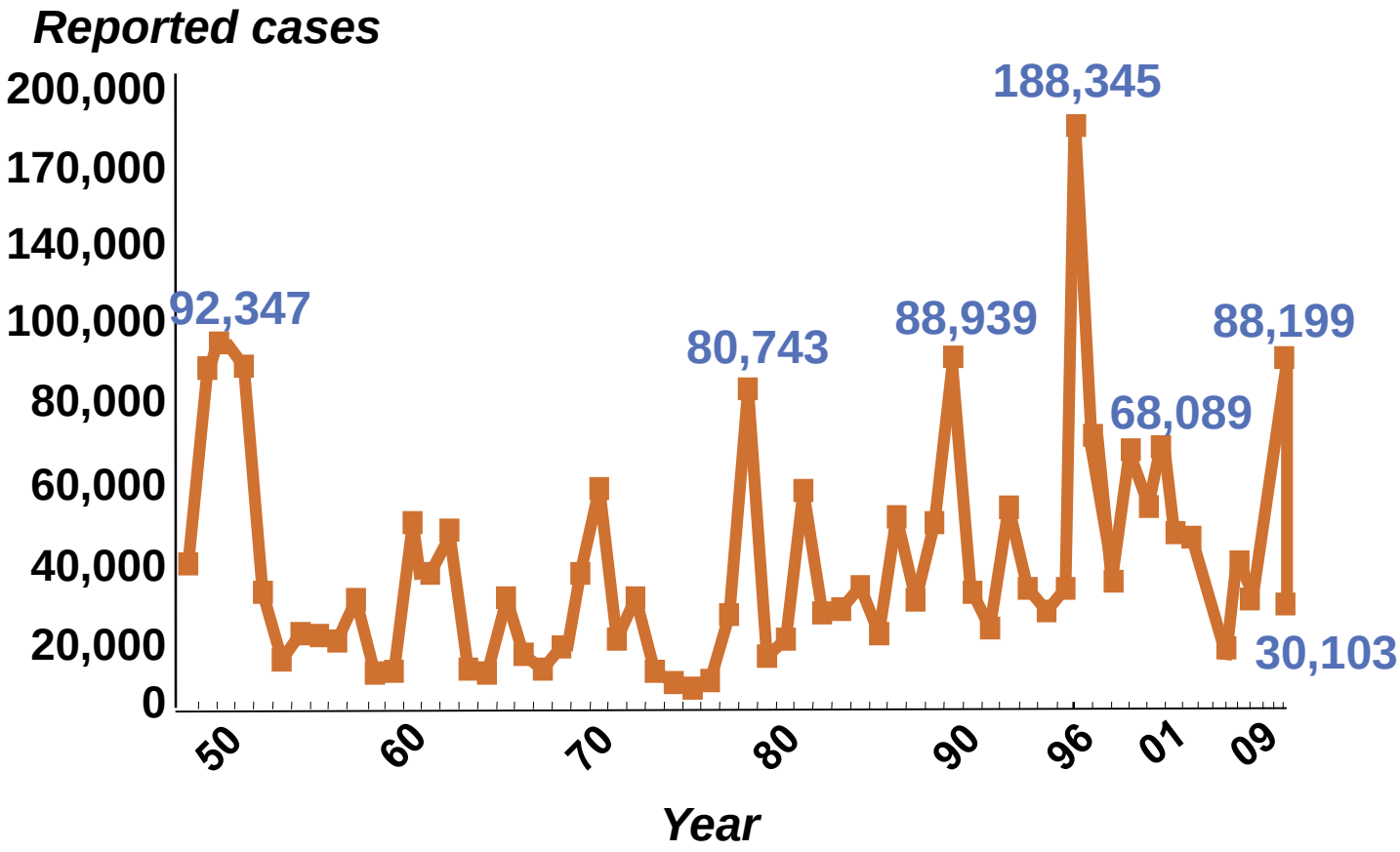
Average district incidence rates per 100 000 in epidemic and non epidemic years (1994-2007)

	Average district incidence rates (range)	
Country	**Epidemic years**	**Non epidemic years**
Burkina Faso	158 (54-353)	48 (18-115)
Mali	50 (1-141)	11 (0-29)
Niger	211 (10-834)	44 (2-118)

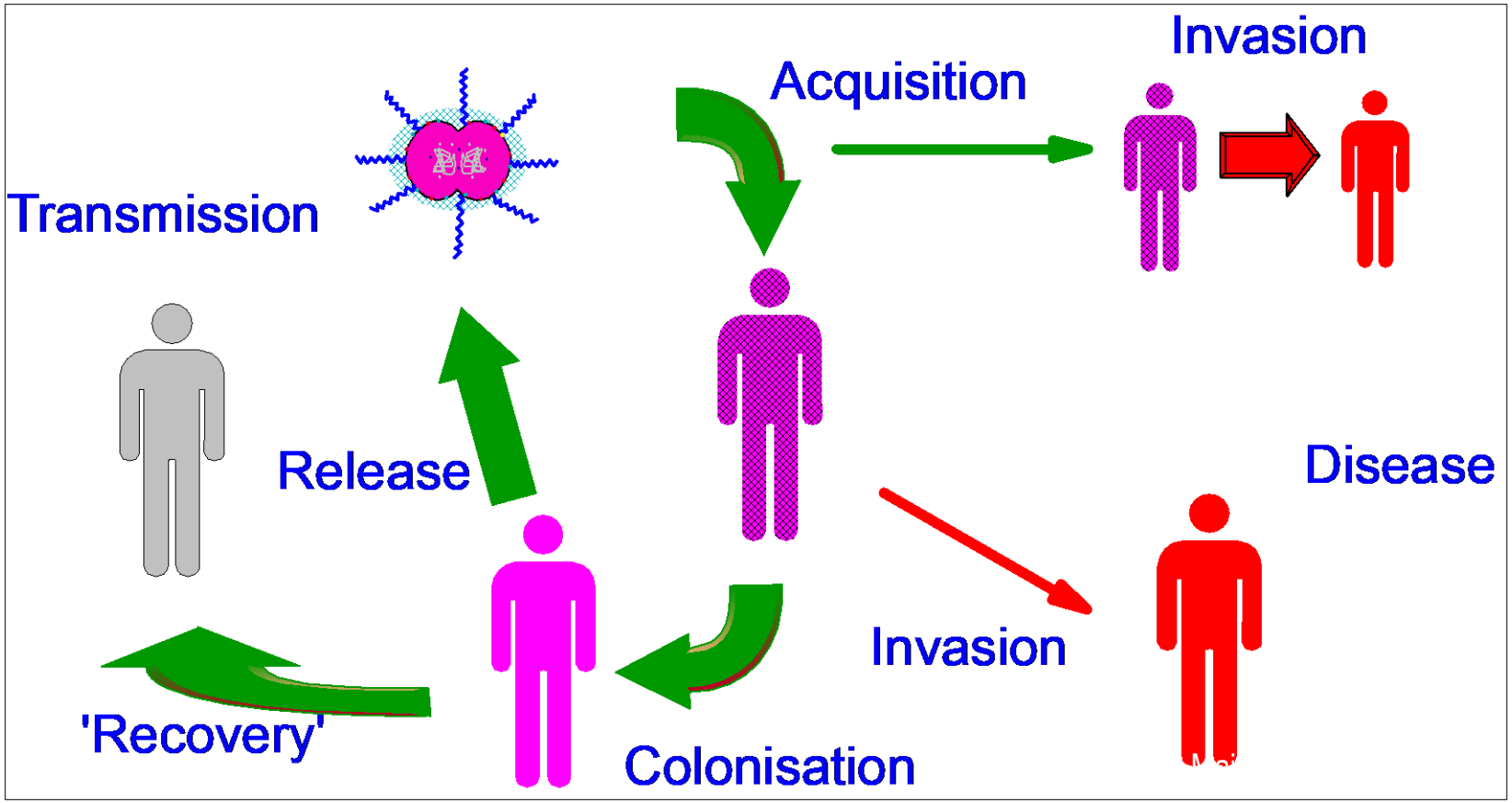
(In recent years US meningococcal incidence rates have ranged between 0.1 to 0.3 cases per 100,000 population)


RICE

Epidemic meningitis in Africa

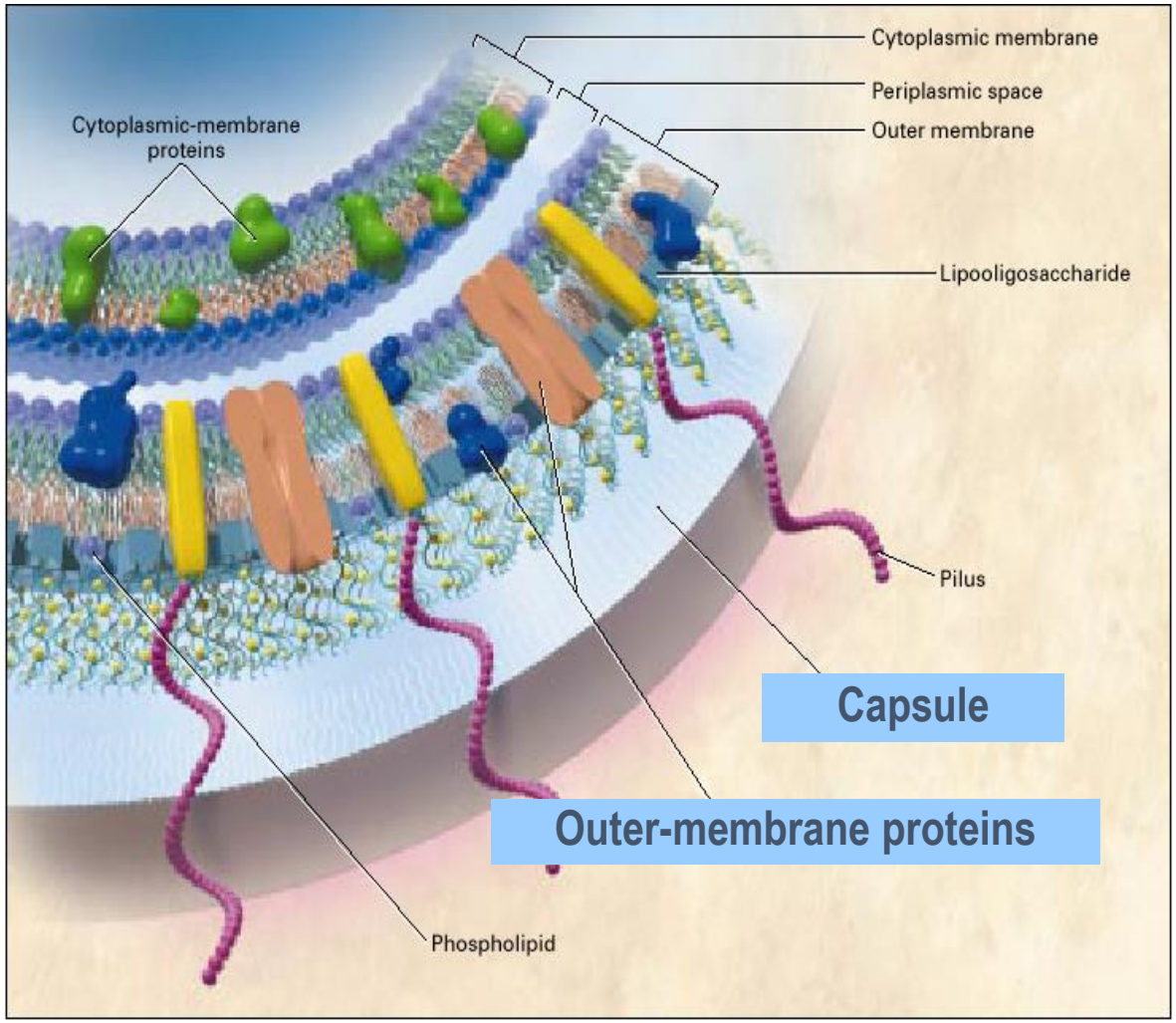


Flow of *Neisseria meningitidis* through a population



Courtesy Dr. Martin Maiden

Meningococcal structure: antigens for vaccines



Meningococcal capsular sugars are antigenic and were the basis for A/C polysaccharide (PS) vaccines developed in the 60s

By 2005 a conjugate multivalent (A/C/Y/W) vaccine was developed for US and European markets

Properties of Meningococcal Vaccines

Immunogenicity	Polysaccharide vaccines	Conjugate vaccines
5 year olds-adults	High	High
Young children	Poor	High
Response to booster	Poor	High
Quality of antibody in children		
Avidity	Low	High
Bactericidal activity	Low	High
Induction of memory	No	Yes
Effect on colonization	No	Yes

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

- The terrible 1996 meningitis epidemic in 1996 led African public health officials to ask WHO for help.

- 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*

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
  - Cost of vaccine was the most important limiting factor to the introduction of new vaccines in Africa
  - **Success of MVP (widespread use of a conjugate meningococcal vaccine in mass campaigns) would not be possible unless vaccines were priced less than $US 0.50 per dose**

MVP negotiations with Pharma (01-02)

- Meetings with Chiron, Baxter and GSK (September 2001 – March 2002)

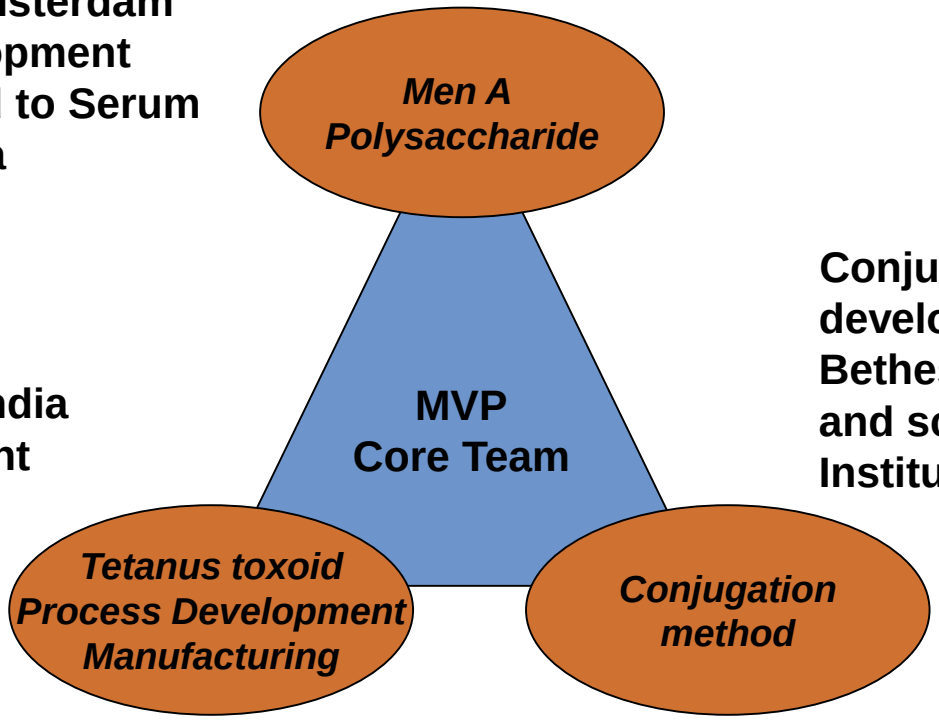
- Key issues in the negotiations included:
  - Vaccine price
  - Guaranteed purchase (effect of volume on price)
  - Investments to increase manufacturing capacity
  - Creating a “no risk” model

MVP becomes a virtual vaccine company in March 2002

- MVP could not reach an agreement with major vaccine manufacturers and negotiations ended in March 02
- Instead, MVP chose to become a virtual vaccine company to develop a Group A conjugate vaccine.
- Crucial elements in making this decision included
  - Inputs from African public health officials on the importance of a low 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 annually could be as low as $US 0.20 per dose.

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

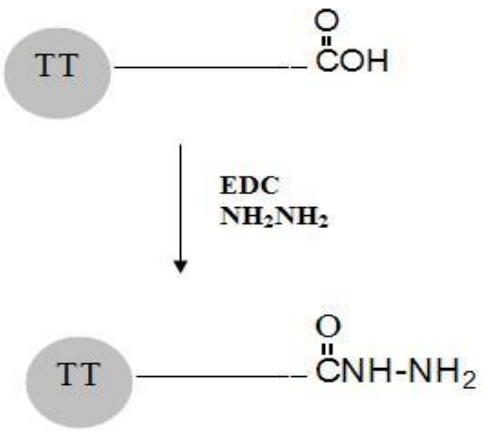
Serum Institute of India process development and manufacturing

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

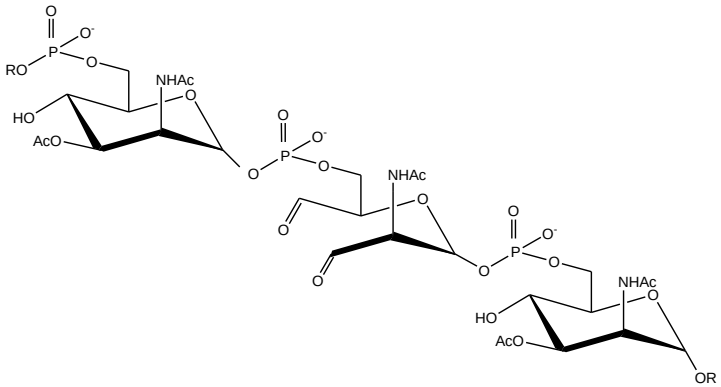
Target price US$ <0.50/dose

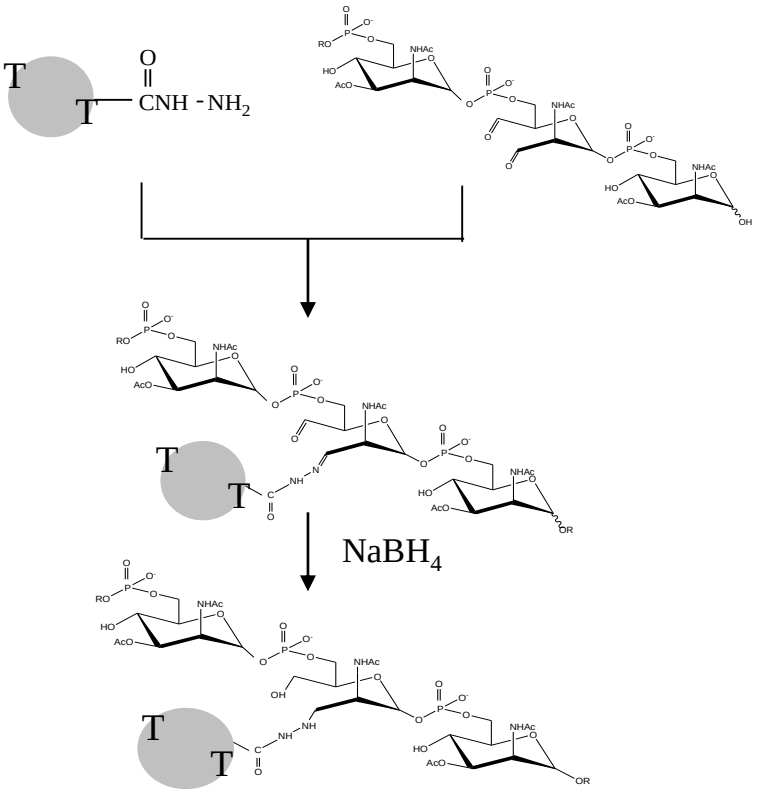
Lee/Frasch (FDA) conjugation method

Derivatized TT (TTH)

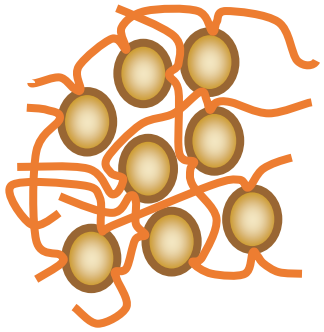


Periodate activation of PsA



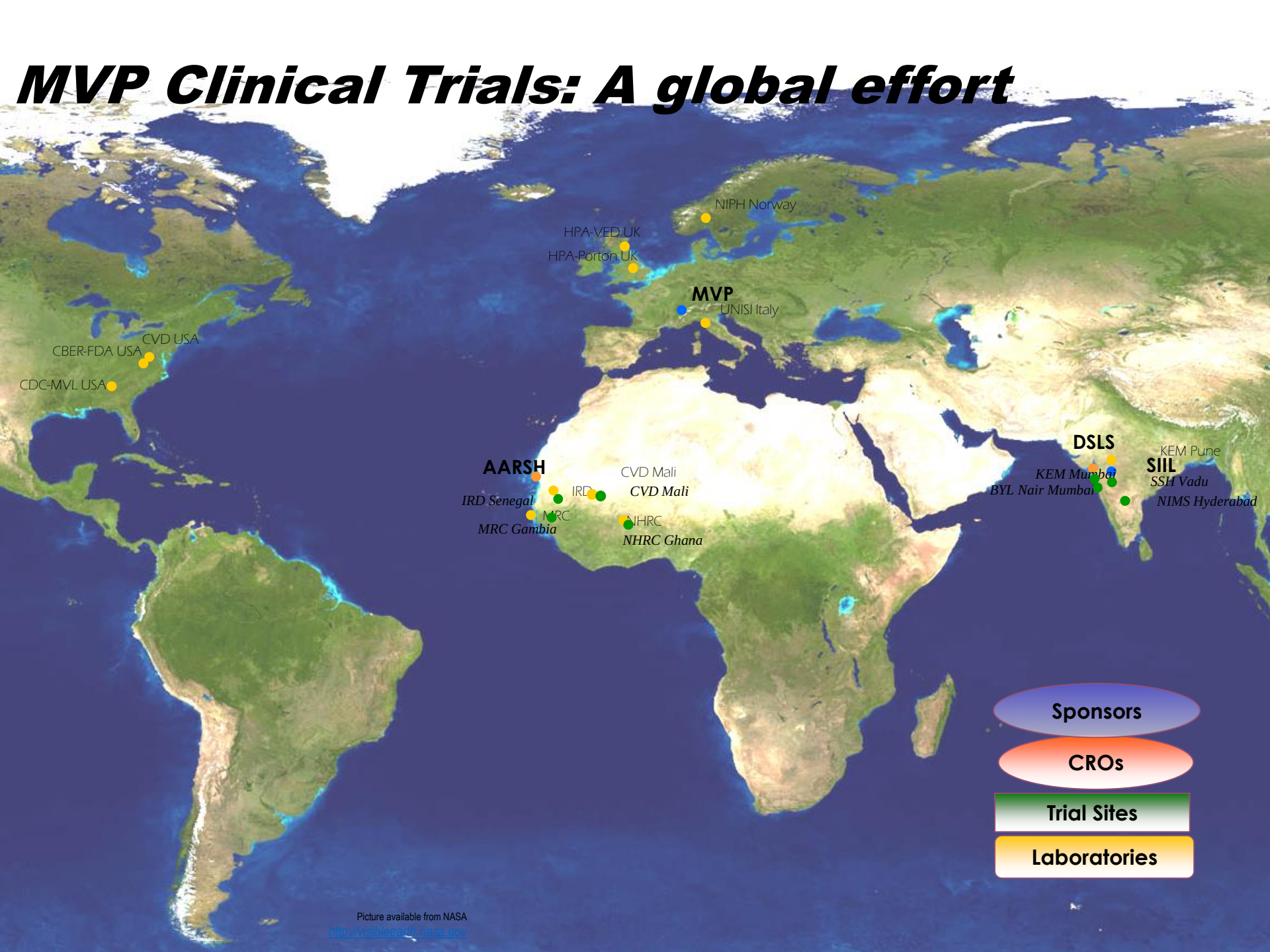


PsA-TT conjugate forms a "lattice" configuration



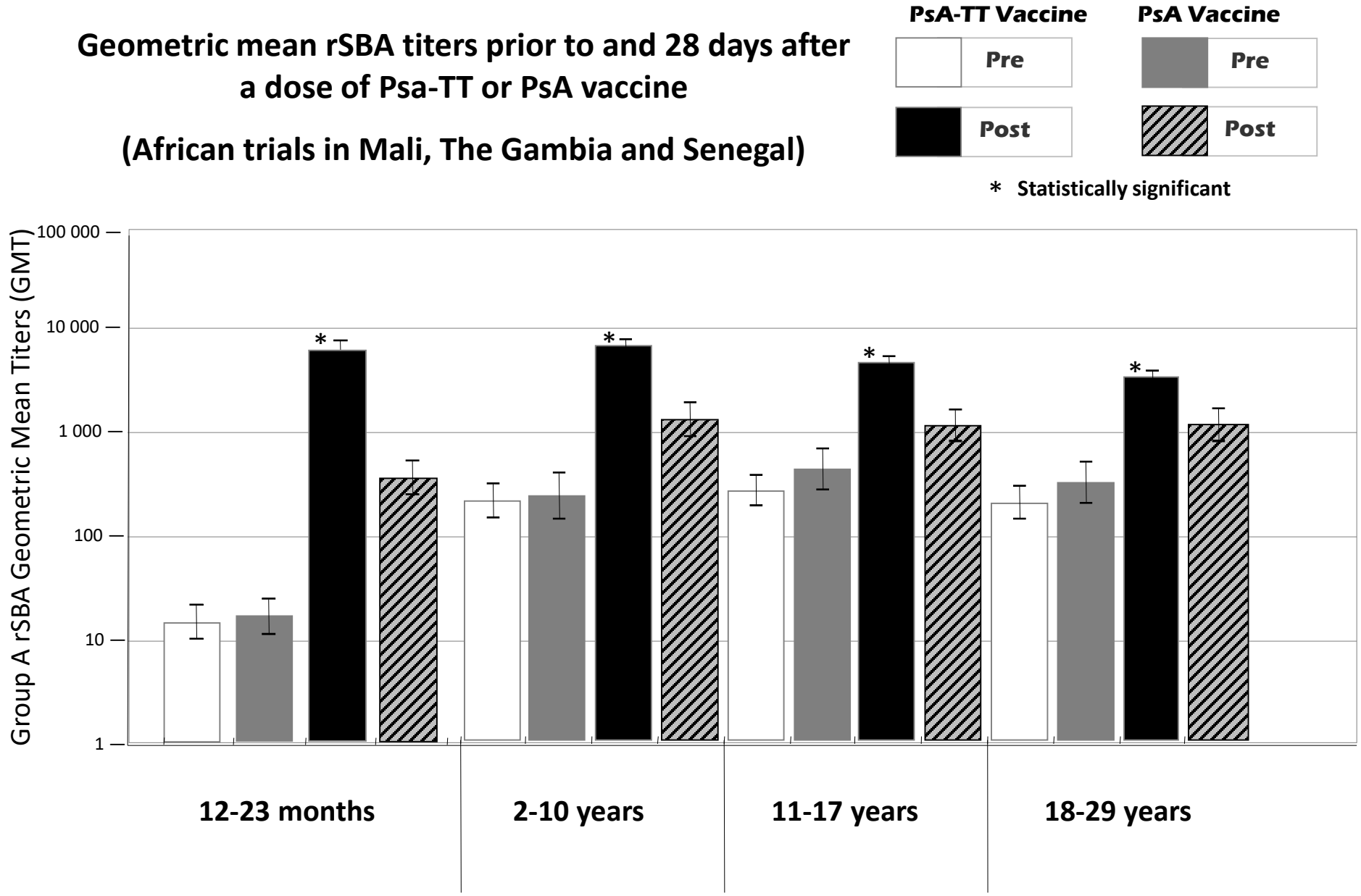

MenAfriVac
10 mcg
10 to 33 mcg
SHAKE WELL BEFORE
Meets W.H.O. requ
MFG. LIC. No.
INSTITUTE OF INDIA LTD.
Pune 411 028, INDIA
5 ml
Diluent for
Meningococcal A
Conjugate Vaccine
0.5ml for 1
INSTITUTE OF INDIA LTD.

MVP Clinical Trials: A global effort



Geometric mean rSBA titers prior to and 28 days after a dose of Psa-TT or PsA vaccine

(African trials in Mali, The Gambia and Senegal)



Potency and safety of vaccine

- ***Results from eight clinical trials showed that PsA-TT (10µg) when administered to African 1-29 year-olds***
  - Was well tolerated and safe in any of the age groups evaluated (infants to 29-year-olds)
  - Was highly immunogenic
    - Superior immunogenicity *vs.* licensed PS vaccine
    - Induced immune memory
    - Bactericidal antibodies were sustained
  - Boosted anti-tetanus immunity

Licensure and Prequalification of PsA-TT (*MenAfriVac*™)

- *MenAfriVac™* licensed by Drugs Controller General of India in December 2009.

- WHO prequalification awarded in June 2010.

Dec. 6, 2010 - Official launch day – President of Burkina Faso

Official launch day – health workers


Safety Box


simSafe 5L
Safety Box
BIOHAZARD

Burkina Faso campaign: 6-15 December

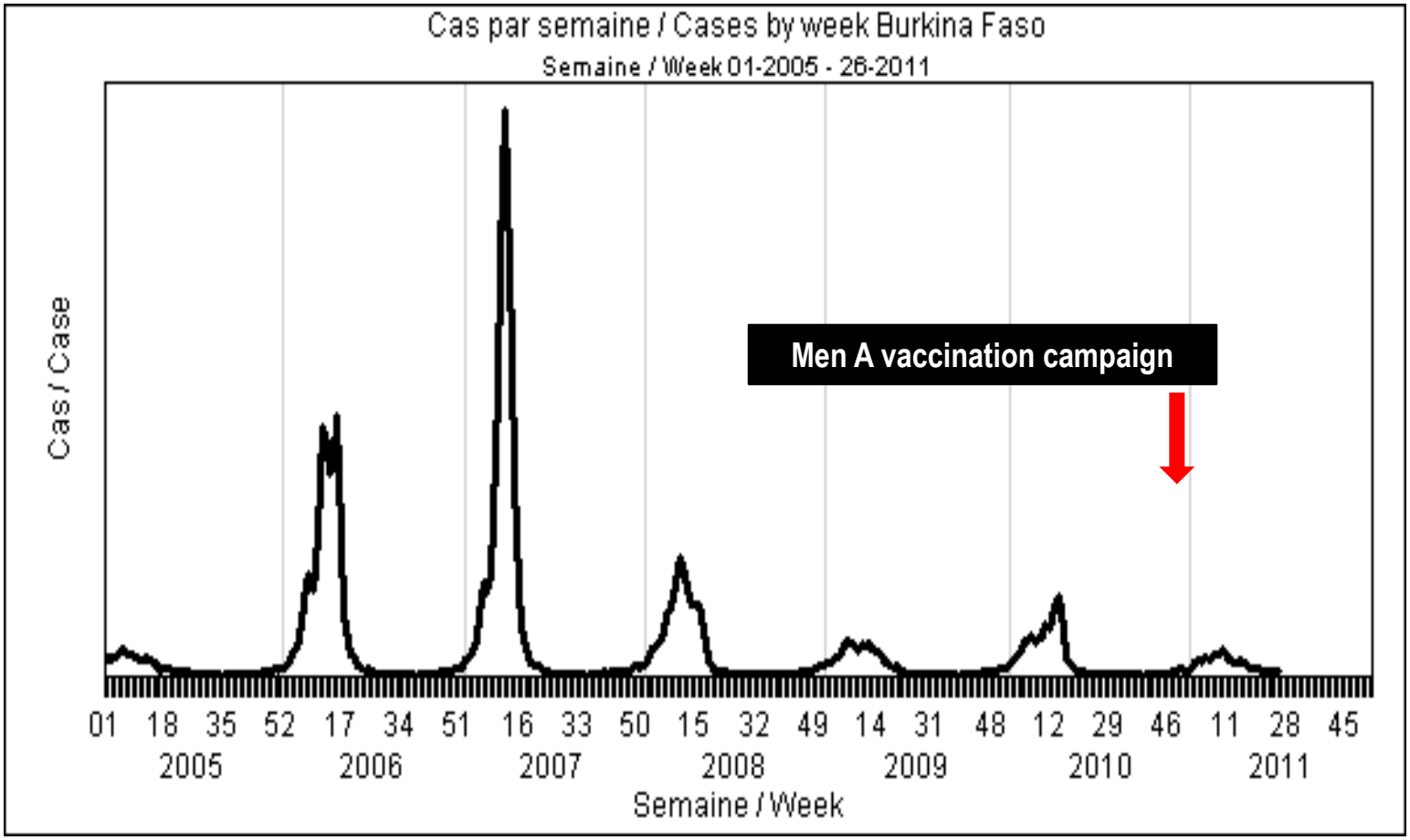
- **Target** population: 10,677,781 Burkinabes between 1 and 29 years of age

- **Duration** of the campaign: 10 days

- **Results**: 10.8 million persons immunized

Very successful campaign with high acceptance !

Meningitis cases by week – Burkina Faso



2011 bacteriologic data – Burkina Faso

	№	Percent
Reported meningitis cases	3875	
Number of CSF specimens	3412	88.1
Number of CSF sent for lab confirmation	3318	97.2

22% in 2007

Bacteriologic results (PCR, latex or culture)

Contaminated	609	18.3
Negative	1552	46.8
Positive	1157	34.9
Total	3318	100

9% in 2007

Distribution of pathogens (% based on positive samples)

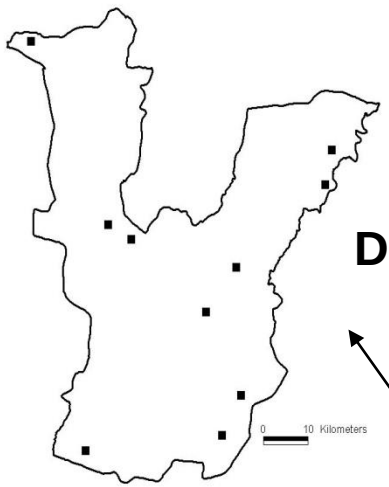
NmA	1 (0.1%)	Pneumococcus	837 (72.3%)
NmX	161 (13.9%)	Hib	43 (3.7%)
NmW135	110 (9.5%)	Other	3 (0.3%)
Nm indeterminant	2 (0.2%)		

Reported meningitis cases with percent distribution of Group A meningococci Burkina Faso, 2005-2012 (wk 26)

Year	Cases	% Men A
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	0.4
2012 (wk 26)	5,987	0.0

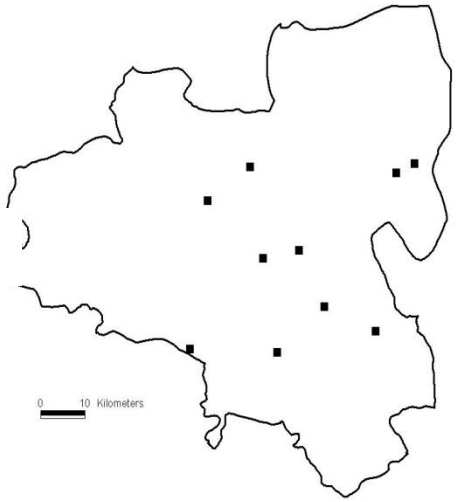
Carriage study results: Burkina Faso

Representative sampling of 1-29 year old Burkinabes

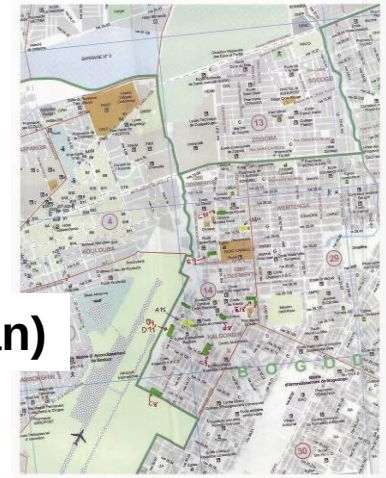


Dandé (rural)

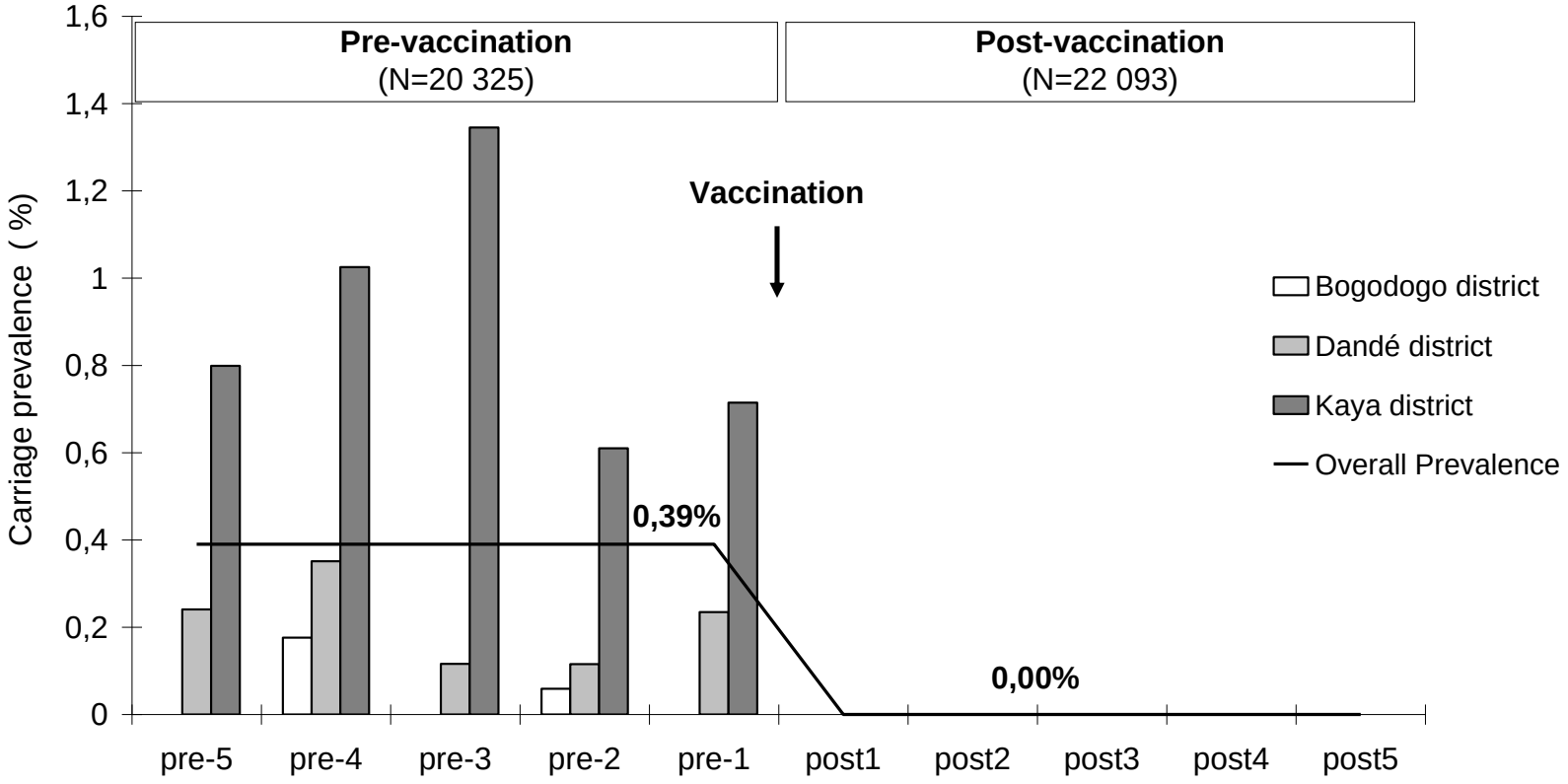
Kaya (rural)



Bogodogo (urban)



Carriage of Group A *Neisseria meningitidis* before and after *MenAfriVac* campaign



Observations on vaccine impact

Consistent with vaccine derived herd immunity

- Disappearance of Group A meningococcal meningitis
- Absence of Group A meningococci in carriage studies

Why such a powerful effect ?

- *The PsA-TT vaccine was* a potent vaccine and very high coverage rates were attained.
- Background rates of Men A carriage in Burkina Faso were low at the time of introduction (about 0.4%).
- Immunity against Group A meningococcus elevated in light of the 2006-2008 epidemic years that involved all districts.

Importance of Basic Reproductive Rate (R_0)

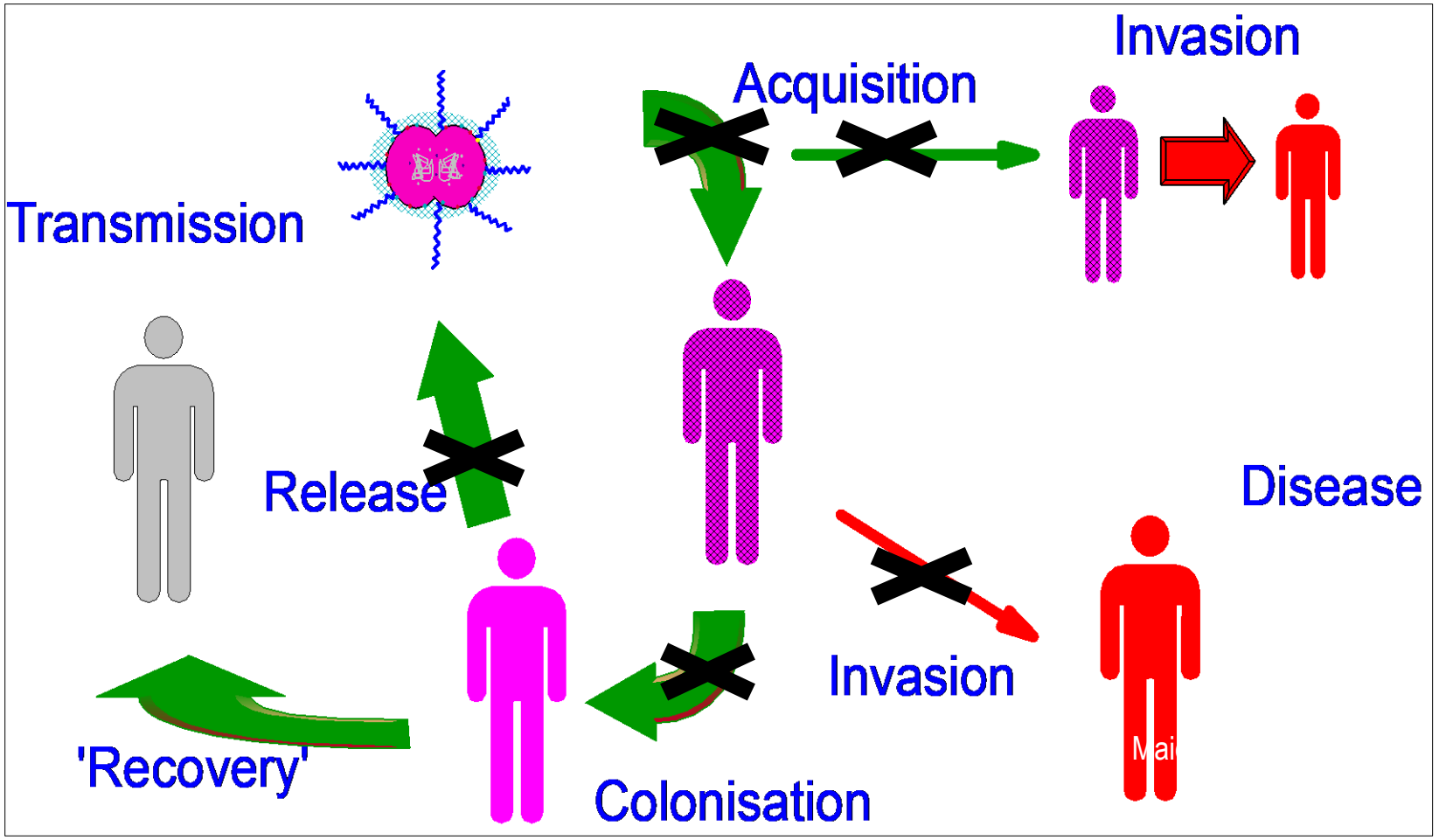
- The Basic Reproductive Rate (R_0) defines the transmission potential of an infectious agent. When R_0 falls to than 1 the agent in question disappears from a population

  - $R_0 = c\ p\ d$
    - c is no. of contacts per unit time (no vaccine effect)
    - *p* is transmission rate per contact
    - *d* is duration of infectiousness

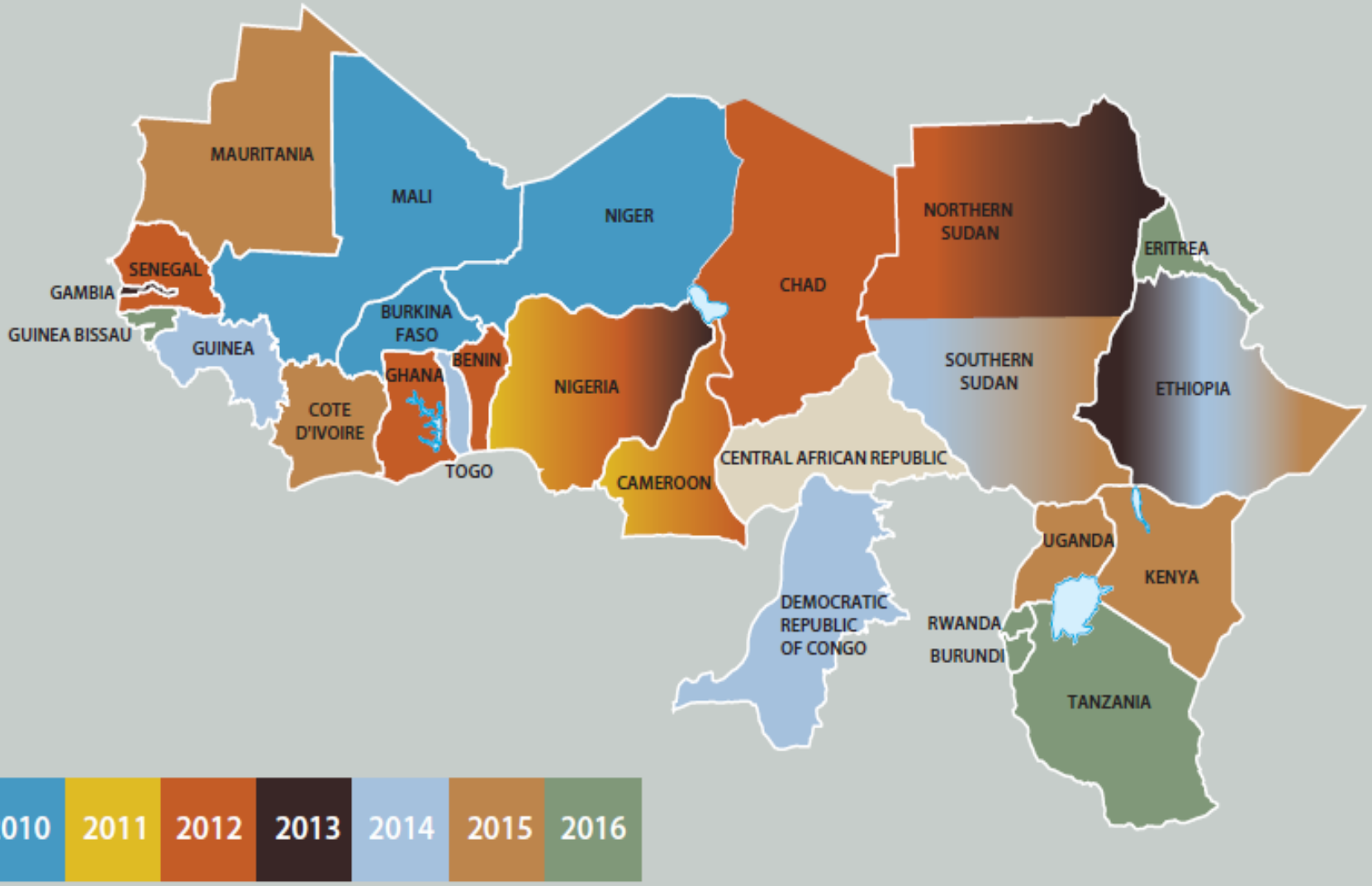
- Study results
  - We know that PsA-TT blocks colonization; therefore *p* falls
  - We think that PsA-TT shortens carriage (would also decrease *d)*

    - **Overall PsA-TT impact on R_0 = *c p* ↓ *d* ↓**

What happened? Impact of a conjugate vaccine on circulation of Group A meningococci



MenAfriVac Roll-Out Plan 2010-2016



CS226906-A

A report card for the MenA vaccine

Costs	$US (mil)	Savings	$US (mil)
Developing and testing the vaccine	100	Family costs saved over 10 years (1 million cases at $110/case) plus $10/month for disabled)	240
Mass vaccination programs for 280 million persons ($1.40 pp)	390	Savings from no longer doing reactive campaigns (5 mil/year at $3.00 per person)	150
EPI coverage over 10 years (birth cohort about 12 million/year with vaccine at 0.50 per dose	60	Country savings: clinical and laboratory costs ($60 per case)	60
100 million $US to prevent 1,000,000 cases and 200,000 disabilities.			
Total	550		450

Remaining problems

- Non-A *N meningitidis* cause epidemics
  - 2002 Group W epidemic in Burkina Faso (>10,000 cases)
  - 2004-6 Group X epidemics in Niger (>4,000 cases)
  - 2015-2018 Group C epidemics in Nigeria, and Niger (>16,000 cases)

Urgent need for an affordable polyvalent meningococcal conjugate vaccine active against Groups C, Y, W and X strains

Development of an ACYWX conjugate vaccine

- A new ACYWX meningococcal conjugate vaccine has been developed through a PATH/Serum Institute collaboration with funding from the UK's Department for International Development (DFID).

- IND filed with US/FDA in 2016;

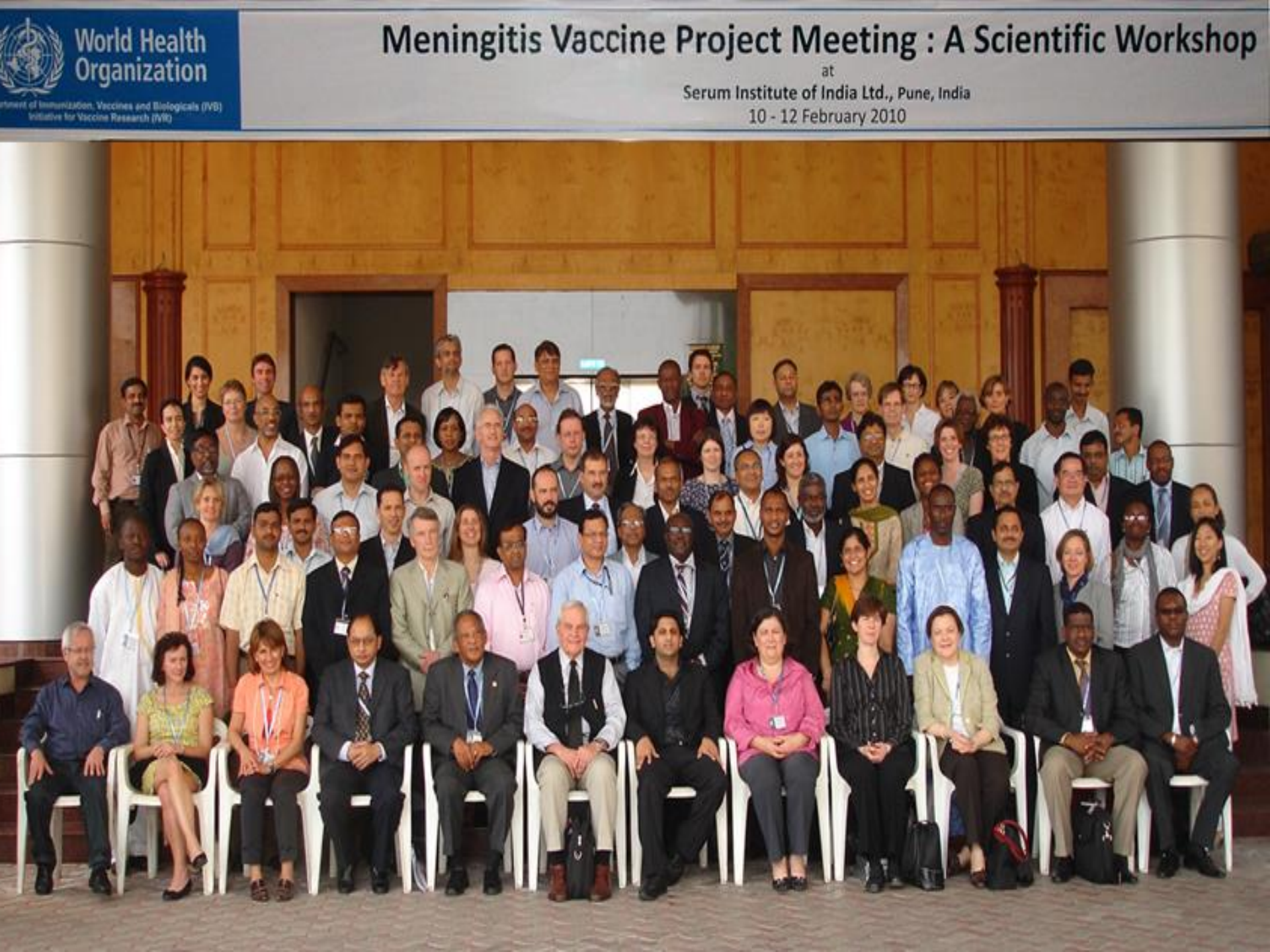
  - Phase 1 study in Baltimore completed in 2017.
  - Phase 2 study in Malian toddlers completed in 2018.

- ACYWX conjugate vaccine very immunogenic; no safety issues.

African challenges over the next 10 years

- Ensure that Men A conjugate vaccine is included as an EPI vaccine in meningitis belt countries.
- Maintain strong case based surveillance in selected countries and continue to improve epidemiologic and laboratory capabilities for all countries.
- Support WHO regional and country epidemic response activities.
- Assess introduction strategies for new Nm polyvalent vaccines.

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


World Health Organization
Meningitis Vaccine Project Meeting : A Scientific Workshop
at
Serum Institute of India Ltd., Pune, India
10 - 12 February 2010


KICK MENINGITIS
OUT OF AFRICA

The Meningitis Vaccine Project