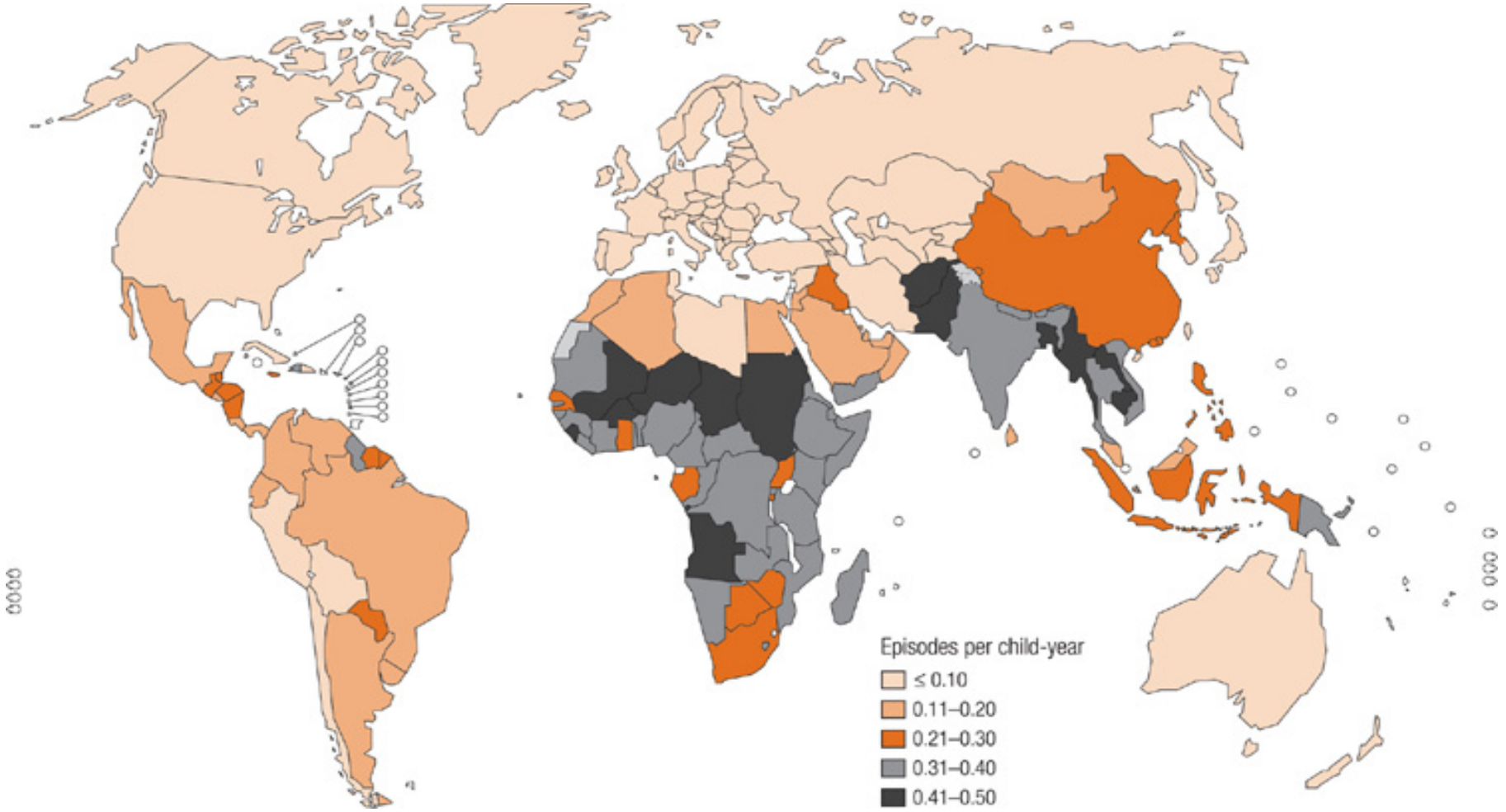
PNEUMOCOCCOL VACCINE DEMAND & UPDATE ON STRATEGY

Incidence of childhood clinical pneumonia at the country level



Source: Rudan et al, Bulletin of the WHO, May 2008 http://www.who.int/bulletin/volumes/86/5/07-048769.pdf,

AFR, African Region; AMR, Americas Region; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region.

What is a strategic demand forecast?

Estimates country adoption dates over a 20 year period early adopters, early majority and late adopters;

- **Estimates number of doses each country will uptake, the timing of introduction and the rate of uptake;**
- **Assumes a price that gives incentives for countries, donors, and suppliers to sustain vaccination;**
- **Analyzes the supply environment to assure adequate supply to meet demand from countries;**

Inputs to demand forecast

Global market assessment of pneumococcal vaccine.

Analysis of the supply environment:

Supply strategy working group

Product profile

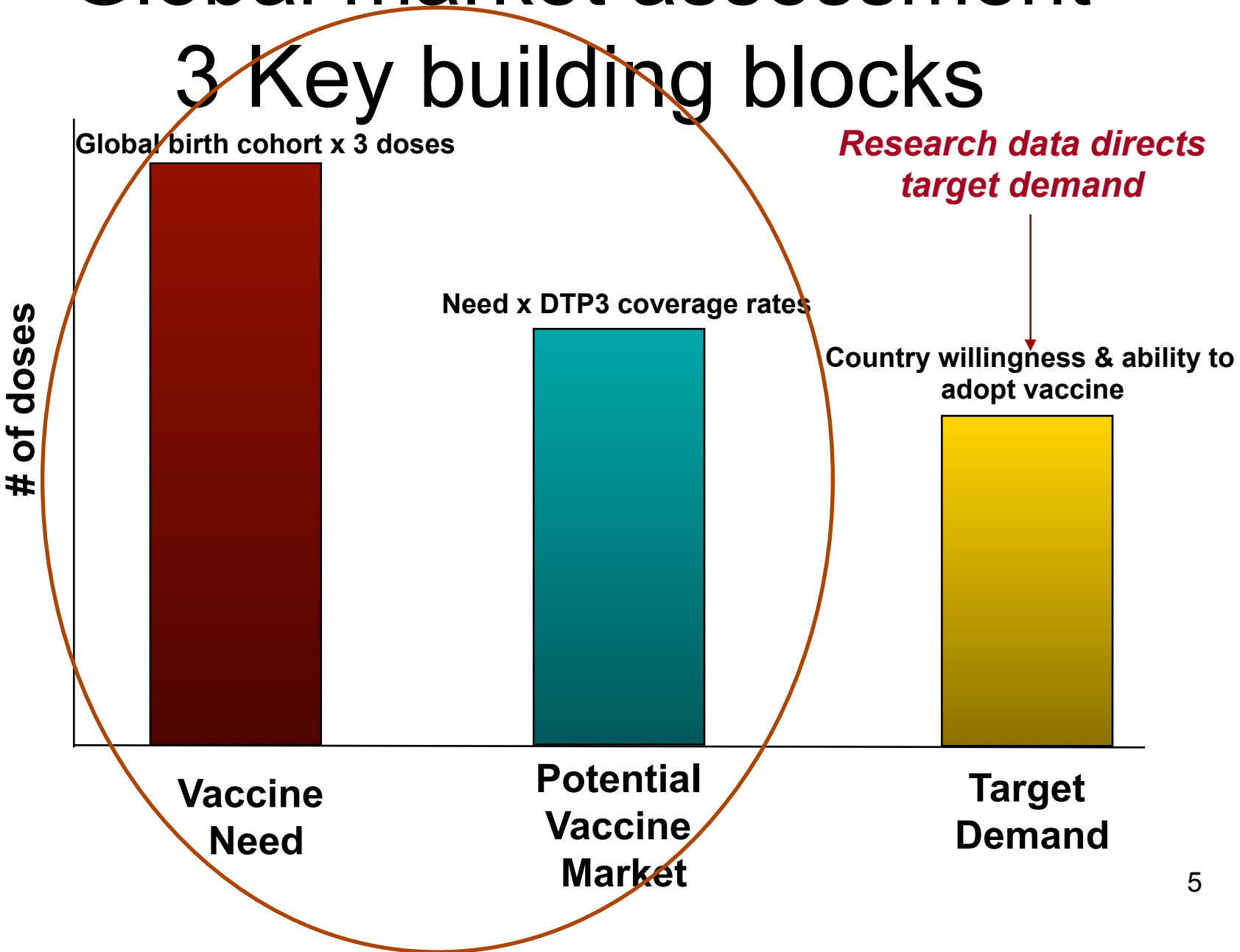
Cost analysis

Product portfolio

Country analysis; quantitative & qualitative

Financing requirements

Global market assessment
3 Key building blocks



Vaccine market size
Key analysis results: Potential vaccine market

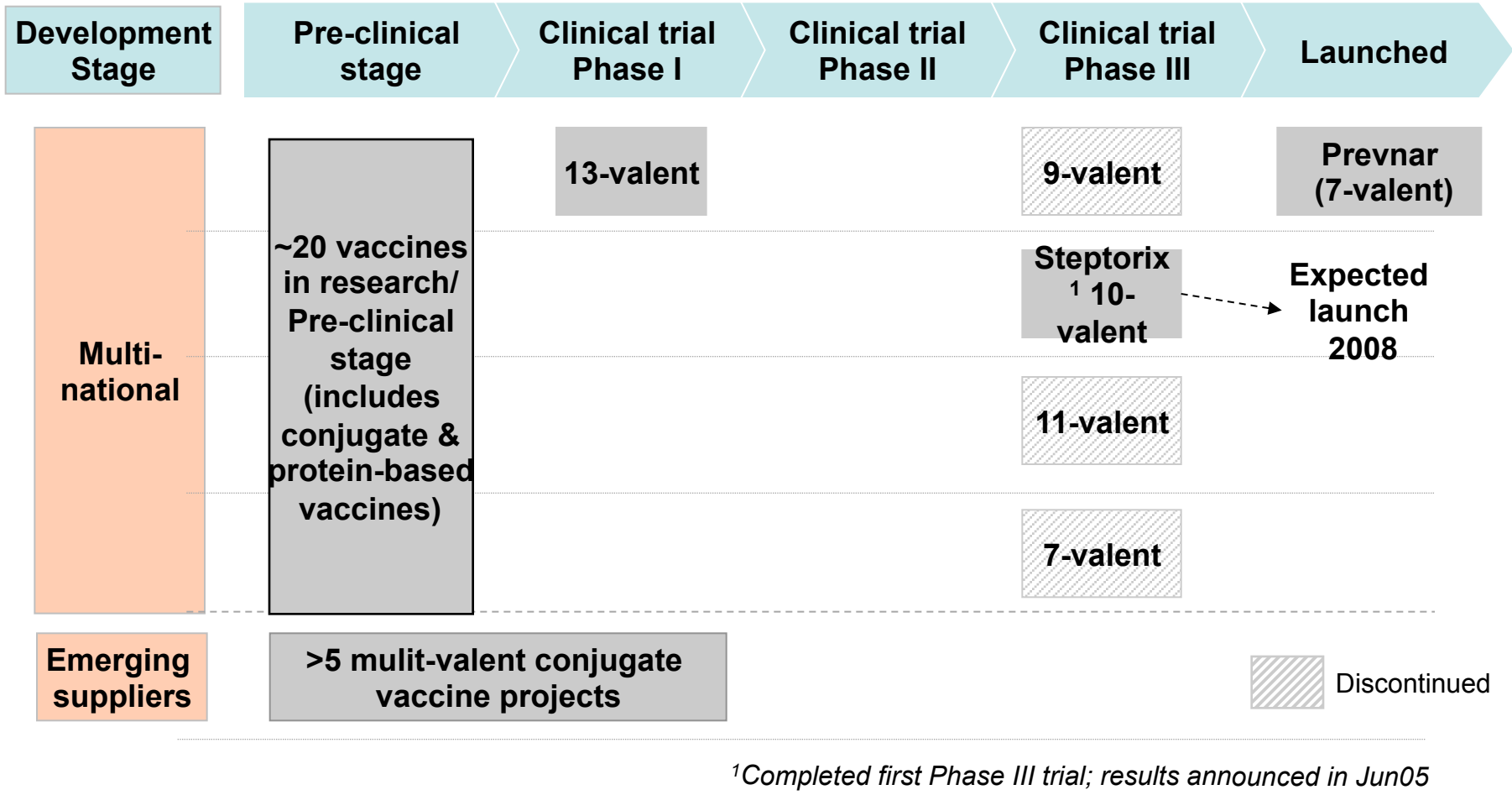
	Low Income	Middle Income	High Income	Total
Total Vaccine Market (Doses in millions)	**178**	**131**	**43**	**352**
Total Vaccine Market (US $millions)	**$1,342**	**$3,453**	**$2,368**	**$7,163**

Low Income Markets Value = $1.3 billion

**Low & Middle Income prices are PneumoADIP estimates;*
High Income prices based on CDC price list 2005 (http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm)

Pneumococcal vaccine pipeline (2005)

As of 2010, the 10-valent and 13-valent are now launched



[1]*Completed first Phase III trial; results announced in Jun05*

Source: BCG Global Supply Strategy 2005

PneumoADIP team analysis

Vaccine supply environment

*Supplier Scenario – Base Case**

2005-2009	2010-2015	2016-2025
• 1 supplier in the market with 100% of market share	•Two suppliers in 2010 and share market	•Third supplier enters market in 2015 (emerging supplier) •Three suppliers share market •Possible 4th supplier enters market.

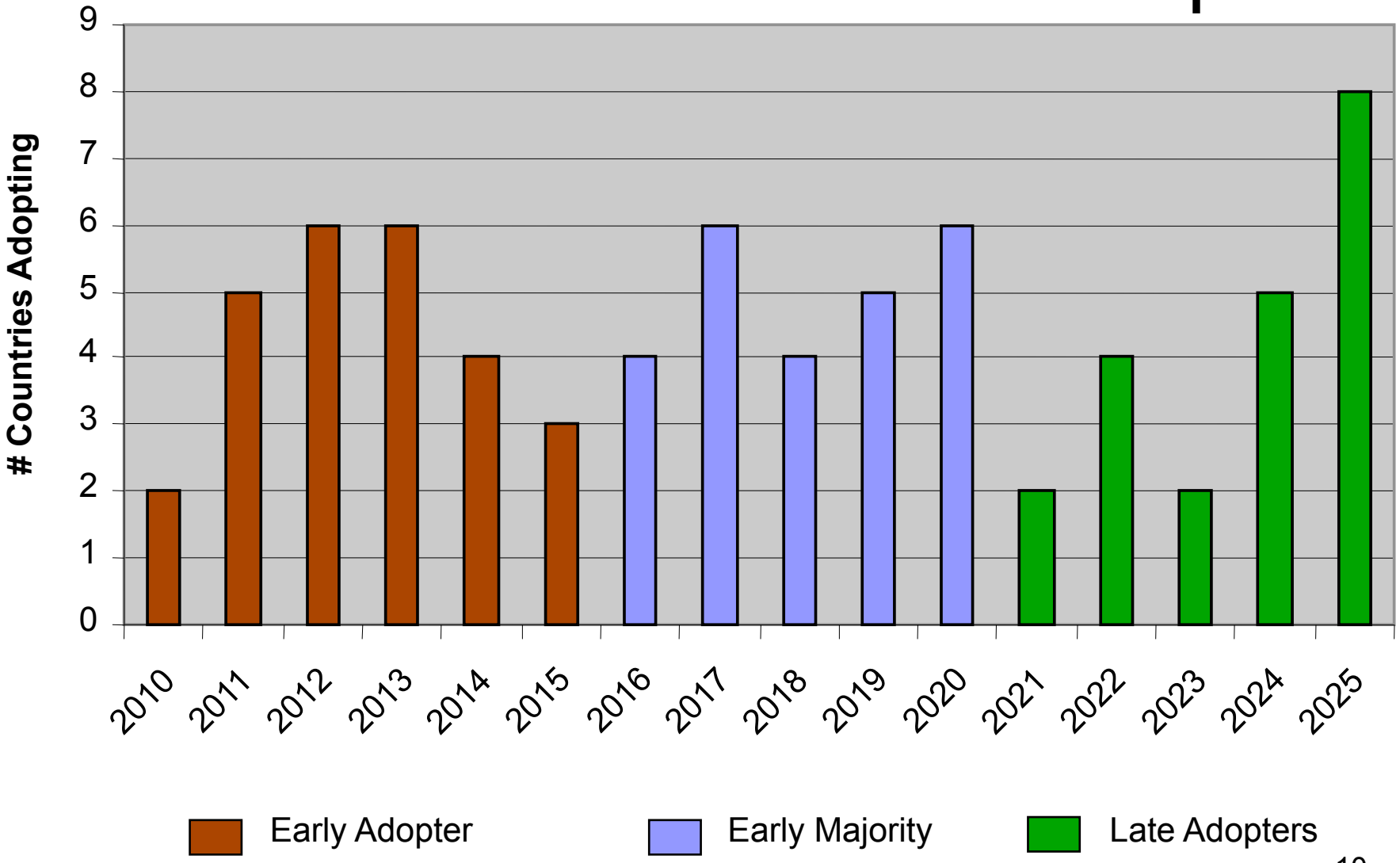
* *For potential solution set analysis purposes only; not discussed with suppliers*

Pneumo strategy

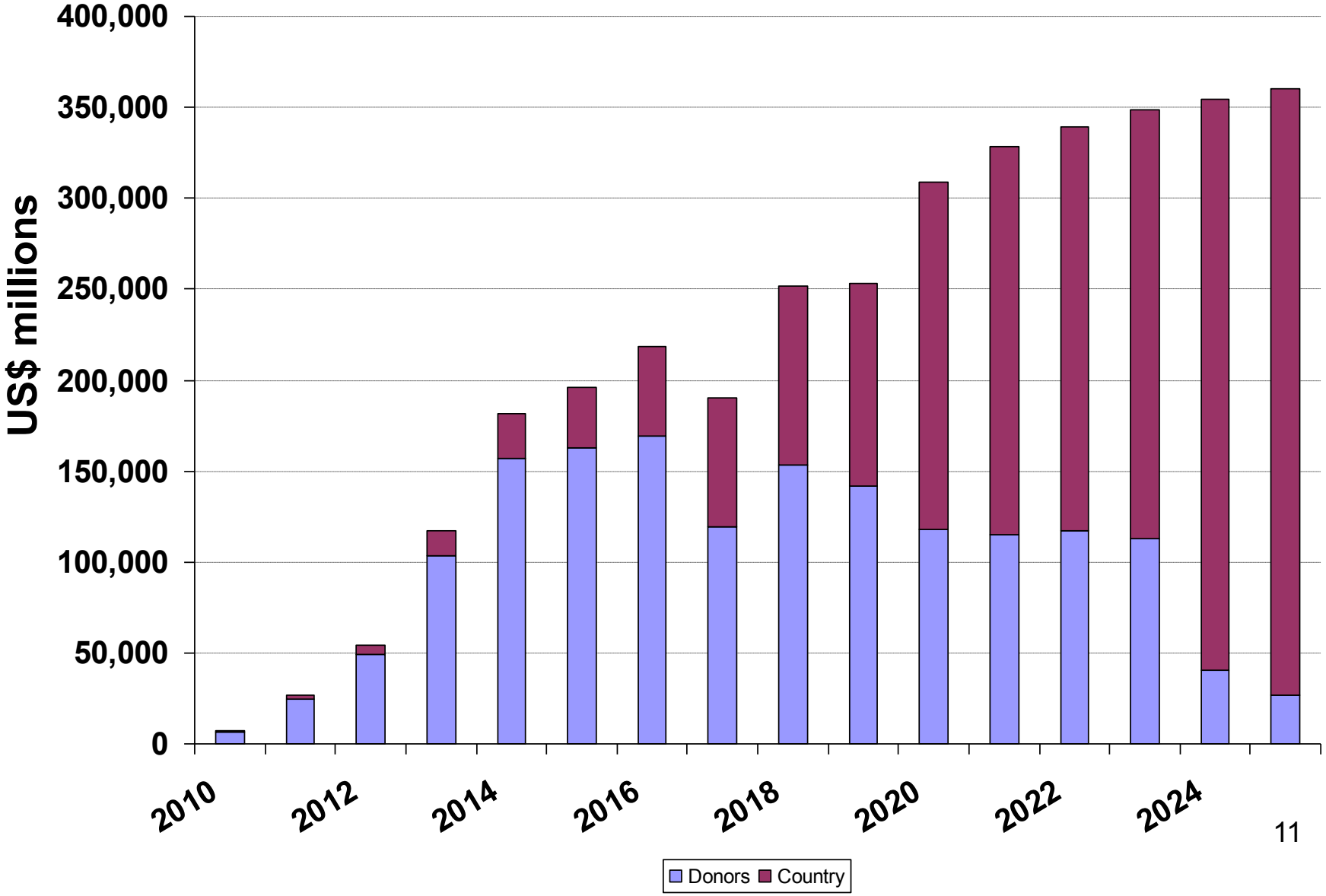
- **First stage = $200m on Prevnar**
  - *the current 7-valent vaccine, Prevnar, in 4-6 countries ahead of use by 2010 of a 10-13 valent vaccine*
- **Demand forecast 2010-2025/2030**
  - "Prevents 3.6m child deaths by 2025"
  - "Prevents 5.4m child deaths by 2030"
- **Some thoughts about these figures**

Country Analysis / Segmentation

Willingness & Ability to Adopt



Strategic demand financing requirements



Efforts to establish the value of pneumo vaccination

Disease burden/cost-effectiveness

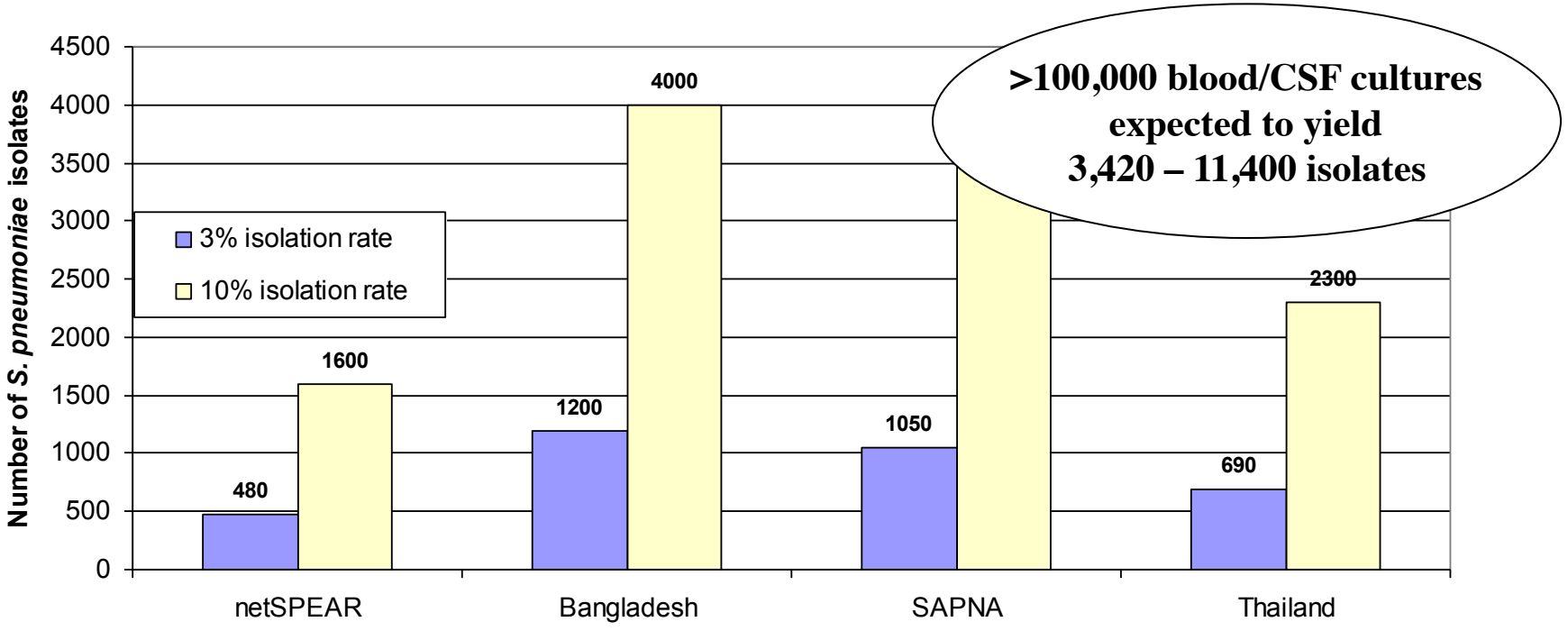
- WHO global disease burden estimates
  - –Version 1 by January 2005 (WHO/VAM with support from PneumoADIP)
- Global/regional cost-effectiveness analysis
  - –Global and regional analyses incorporating WHO disease burden estimates by Q3 2005
- PneumoBAT development
  - –With WHO (IVR, EPI & VAM) and CDC, tool to link local available data with trial data and provide range of disease burden estimates (fashioned after Hib rapid assessment tool)

Efforts to establish the value of pneumo vaccination

Vaccine impact

- Alternative vaccine regimens research (1-2 dose immunogenicity)
  - With WHO/IVR and using Wyeth 7-valent vaccine in Gambia/Philippines in 2005
- Analysis of efficacy of vaccine vs. pneumonia with elevated CRP/Procalcitonin
  - So. Africa, Gambia, Philippines (with WHO/IVR)
- Asian field site development
  - To assess health impact of routine pneumococcal vaccination

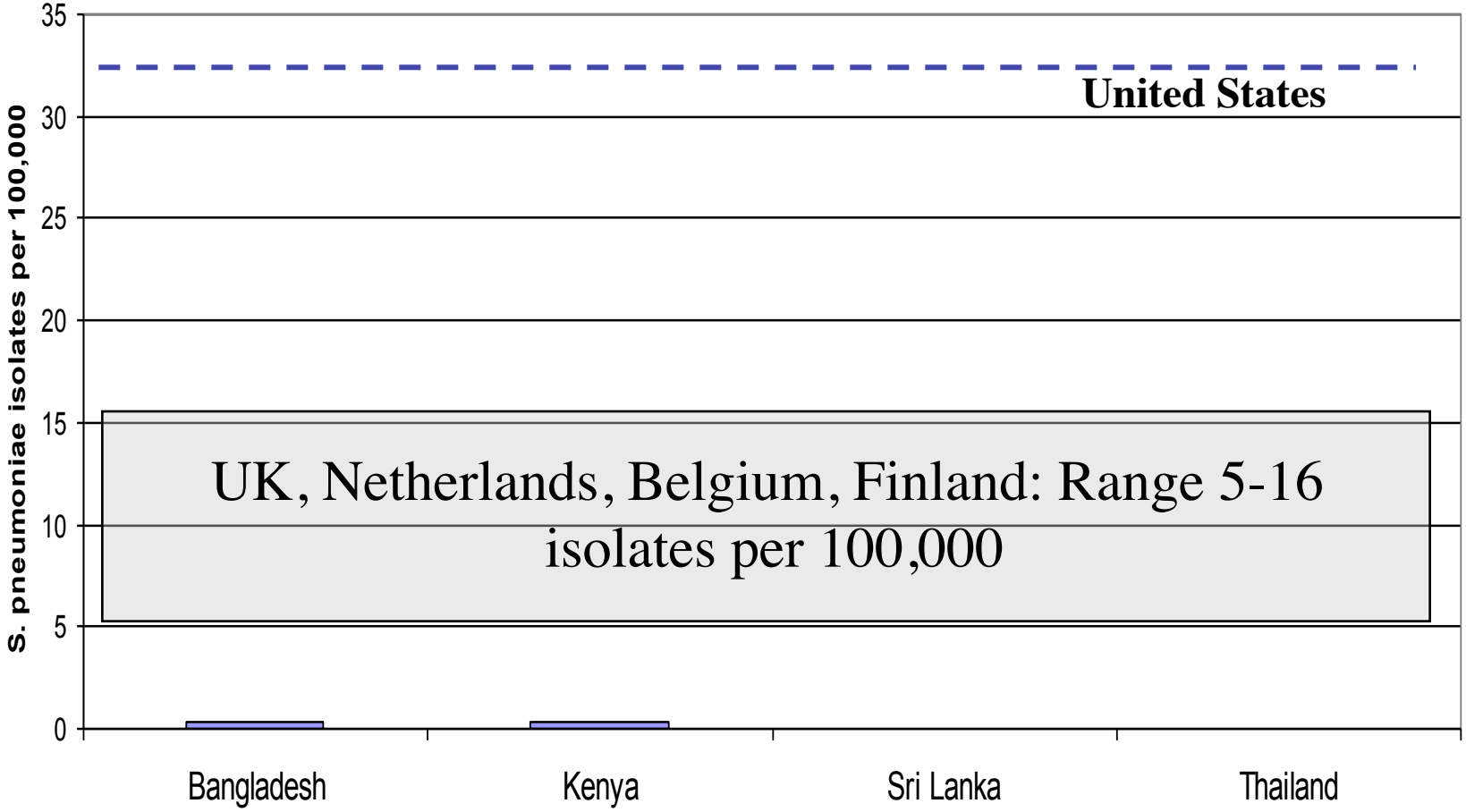
Expected Number of *S.pneumoniae* Isolates Collected with PneumoADIP Support, by Surveillance Network



16,000	40,000	35,000	23,000
Exp. Blood/CSF cultures			

** Projections based on No. Blood Cx & 3%, 5% and 10% positive

S. pneumoniae isolates/100,000 (target population***) without and with PneumoADIP investment

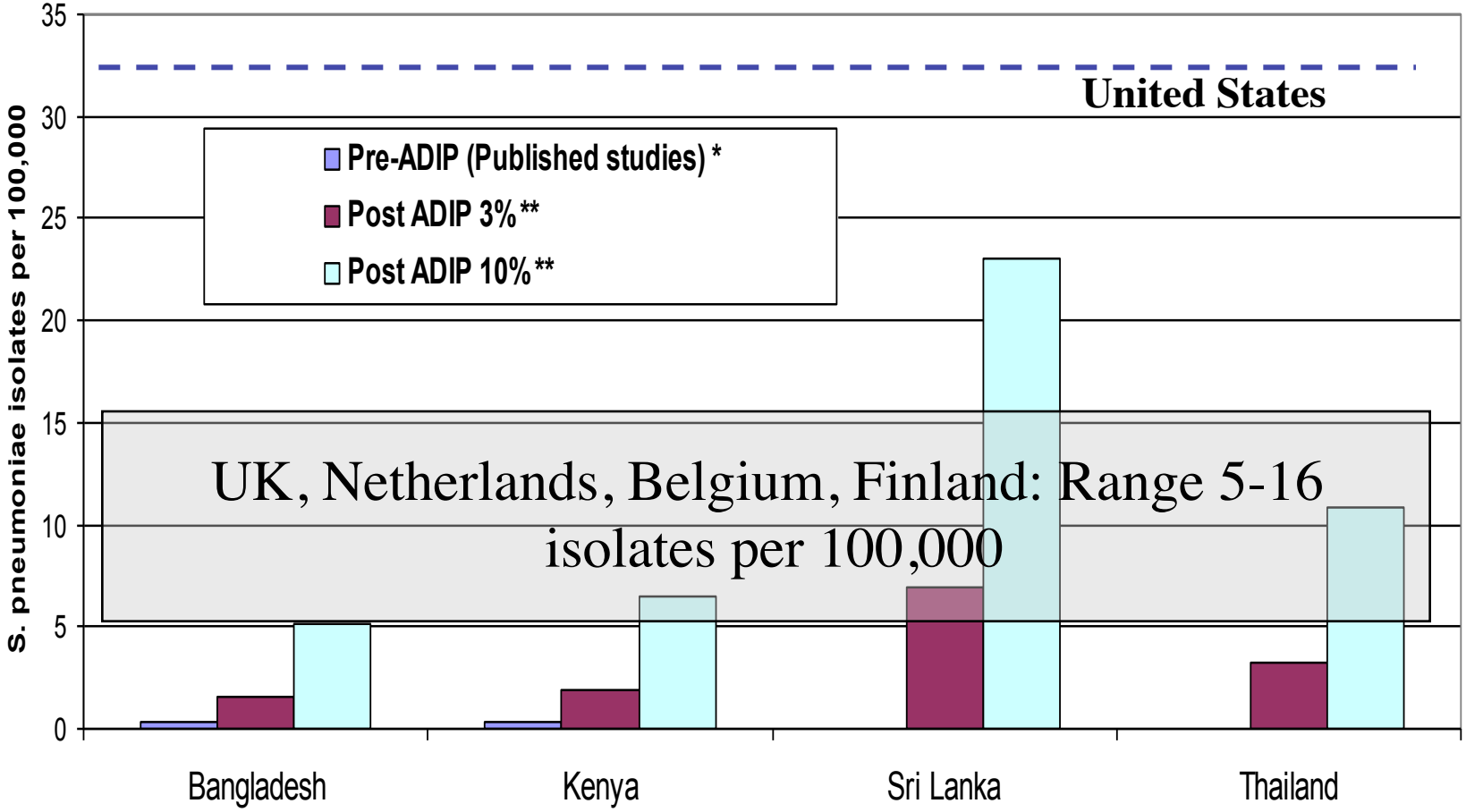


* Published studies: Hausdorff 2000, Saha 1997, Scott 1998

** Projections based on No. Blood Cx & 3%, 5%, and 10% positive

*** Target population (under five) UN Statistics Division 1995 and 2004

S. pneumoniae isolates/100,000 (target population***) without and with PneumoADIP investment

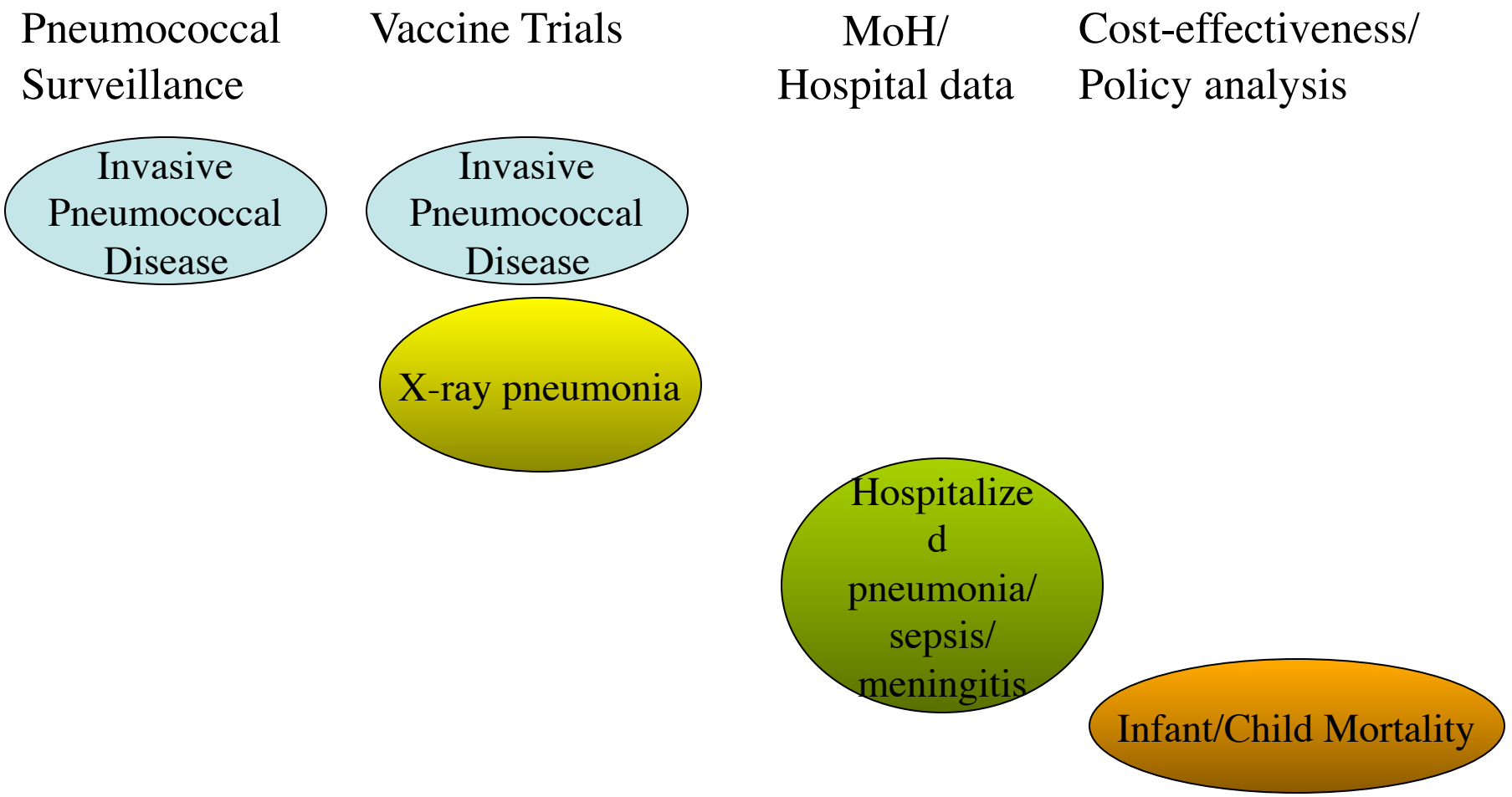


* Published studies: Hausdorff 2000, Saha 1997, Scott 1998

** Projections based on No. Blood Cx & 3% and 10% positive

*** Target population (under five) UN Statistics Division 1995 and 2004

Key challenge ahead: Linking research – surveillance – policy analysis



Pneumococcal conjugate questions

Outstanding questions	Research response *(ongoing or planned)*
• Herd immunity and coverage for herd immunity	• Conduct impact evaluation: modelling (age structured) and CEA
• Dose and timing of primary vaccination	• Review of evidence for various schedules
• Booster needs	• Promote PCV studies on alternative schedules
• Geographic differences in epidemiology	• Review of local relevant data on disease burden

Estimated costs (2007-15)

Costs to GAVI

	Years 2007-2010	**Years 2011-2015**	**Total**
Vaccine costs	$87-$149 million	$415-$926 million	$502-$1075 million
Strategic & Technical costs	$40 million	$25 million	$65 million
Total	$127-189 million	$440 - $951 million	$567-$1140 million

Estimated costs (2007-15)

Country co-payments

	Years 2007-2010	**Years 2011-2015**	**Total**
Country co-payments	$6 million	$15-25 million	$21-31 million

PANDEMIC FLU POLICY ISSUES

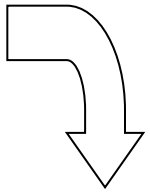
Development of a pandemic influenza vaccine

Supplied by WHO labs

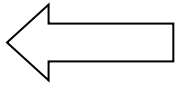
Highly pathogenic H5N1 virus

WHO labs

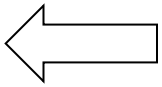
Attenuate virus by reverse genetics



Virus growth, Virus inactivation, Formulation



License vaccine



Vaccine available

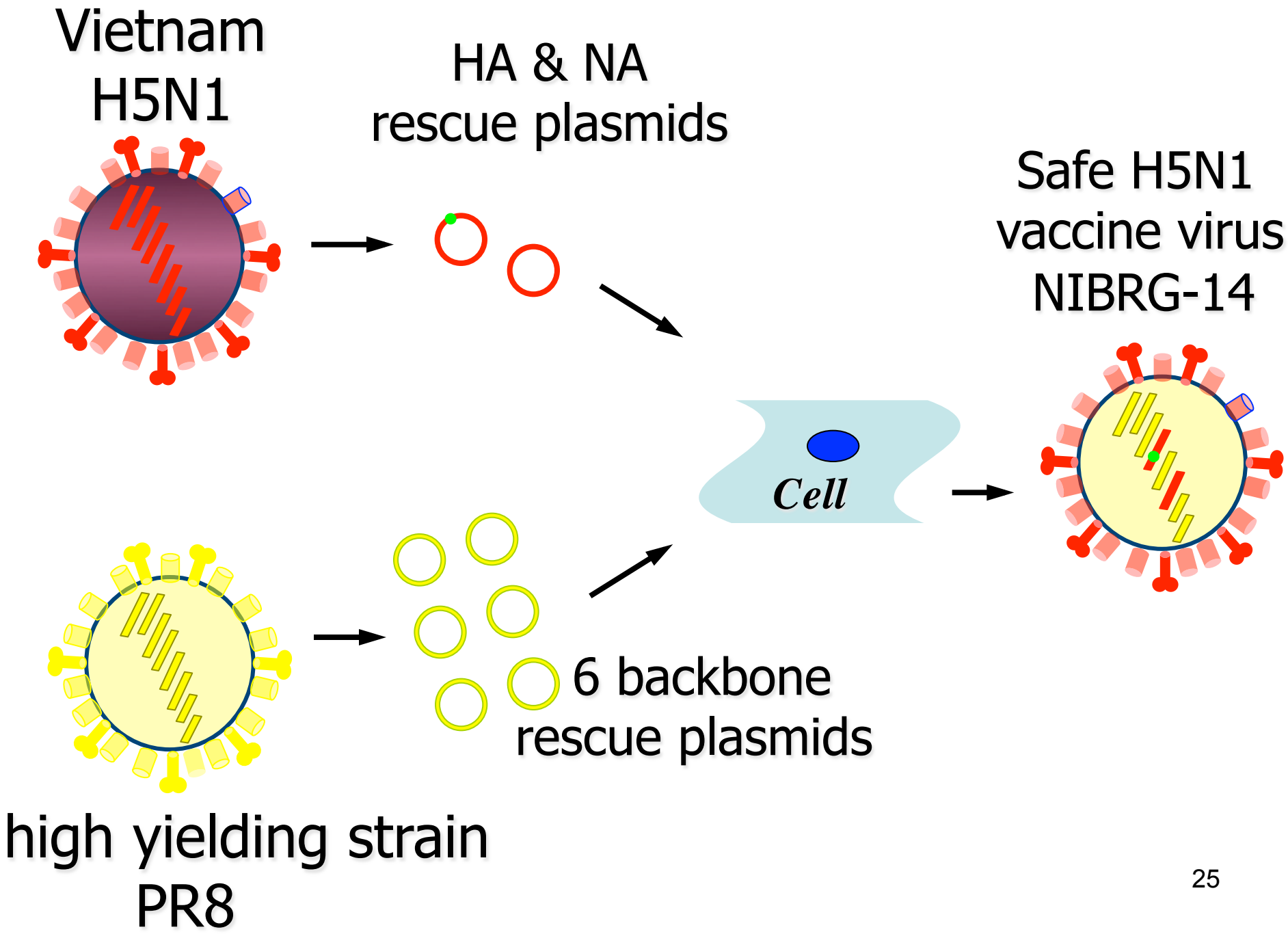
Vaccine manufacturers, government health authorities

Major issues affecting pandemic vaccine supply

- Supply of vaccine viruses
- Speed of response
- Vaccine efficacy
- Regulatory issues

Supply of vaccine viruses

- Viruses causing H5N1 infection can take several weeks to become available to WHO lab network
- Intellectual property for reverse genetics


Vietnam
H5N1
HA & NA
rescue plasmids
Safe H5N1
vaccine virus
NIBRG-14
Cell
6 backbone
rescue plasmids
high yielding strain
PR8

Supply of vaccine viruses

Intellectual property for reverse genetics

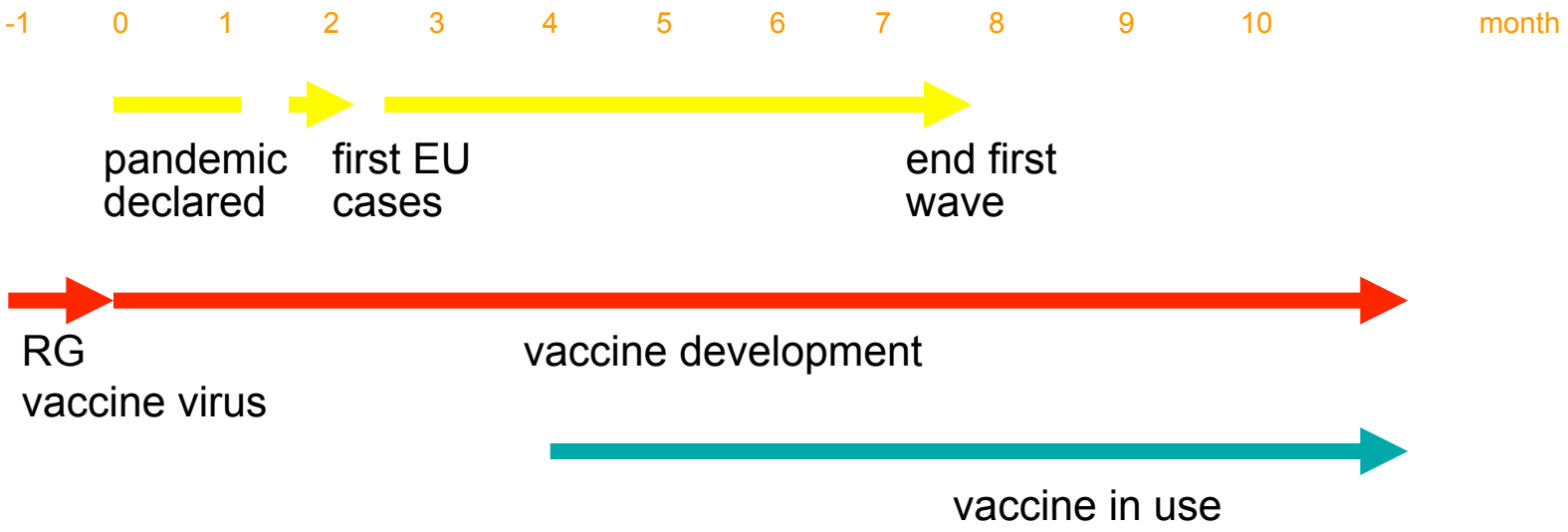
IPRs for the reverse genetics (RG) technology used in the preparation of influenza pandemic vaccine strains do not represent an obstacle for the development of pandemic vaccines and there is nothing specific about IPRs for RG that can justify exceptional approaches.

These rights cannot be dealt with as a group by the industry due to
anti-trust issues; thus, IVS international company members will have to negotiate separately with patent holders through normal commercial negotiations on an individual basis to use the IPRs involved in RG technology.

Supply of vaccine viruses

- Delays in obtaining licences for using products of reverse genetics may affect supply of pandemic vaccines
- Should there be research efforts to challenge current IP situation for reverse genetics?

Timetable for pandemic vaccine availability



Strategies to speed up vaccine availability

- Stockpile vaccine
  - Will it be the correct strain?
- Immunise beforehand – prime populations
  - Will it be the correct strain?
- Production of vaccine viruses in advance – a library of reagents – 2 months saved
  - Will vaccine produced from library virus protect against pandemic activity?
- Antigen sparing strategies
  - Vaccine will ‘go further’

Strategies to speed up vaccine availability

- Strategies depend on more information on:
  - Immunity provided by adjuvanted pandemic vaccines
  - Immunity afforded by ‘mis-matched’ vaccines

Public-funded research is moving very slowly and private research is directed towards licensing products

Public-private partnerships?

Role of WHO and other international organisations?

Vaccine efficacy 1

Correlates of influenza vaccine efficacy (seasonal influenza)

- HI antibody response ≥40 (*Hobson et al, 1972*)
- EU licensing criteria for pandemic vaccines depend on serum antibody responses

Problems

- There are no established correlates of immunity against pandemic influenza
- Serology tests are highly variable
- Established correlates are not suitable for next generation vaccines

Vaccine efficacy 2

Formulation of pandemic vaccines

- Alum adjuvanted split H5N1 vaccines need two doses of 15 µg
- Better adjuvants (MF59, AS03) offer promise of antigen sparing capacity
- Novel adjuvants or presentation systems offer promise of broad spectrum immunity

Need research into correlates of immunity and better pandemic vaccines

Regulatory issues

Pandemic vaccines are likely to be adjuvanted, monovalent, different antigen content, two dose schedule. They are not currently licensed and quality control procedures are not adequate

- EU (CHMP) *Guideline on dossier structure and content for pandemic influenza vaccines Market Authorisation, 2005*
- WHO guidelines on regulatory preparedness for human pandemic influenza vaccines
  - Regulatory pathways
  - Scientific and clinical assessment
  - Quality control preparedness
  - Post-marketing surveillance

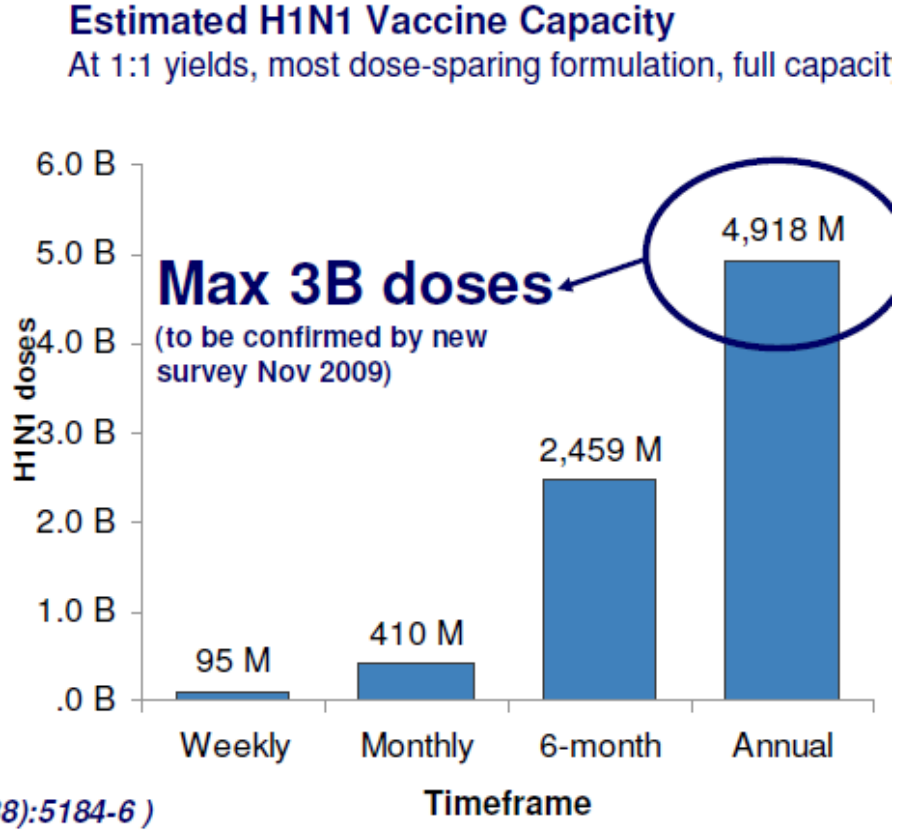
Some sums

- Current global capacity, seasonal influenza vaccine 300 million doses, trivalent vaccine (at 15µg hemagglutinin, HA, per dose), within about 6 months
- Based on three different inactivated (killed) viruses from three circulating strains (A/H3N2, A/H1N1 and B serotypes), selected by WHO
- In a pandemic, monovalent, such that at same production yields and the same 15µg HA formulation – 900 million doses
- Little prior exposure = need two doses = at most 450 million people vaccinated
- But yields of HA antigen are 30%-50% of the normal levels.
- 450m doses at 30µg HA per dose = 225m persons covered at two doses per person
- At 30-50%, less than about 100m population covered globally.
- To cover 3.6bn we will need 7.2bn doses, some 30 or more times what we can currently achieve
- At 1.875µg HA per dose, this is theoretically possible in less than 6 months
- The issue would then be distribution of it!

Global pandemic (H1N1) 2009 vaccine production capacity: less than 3bn doses/year

Assumptions / Methodology

- Survey sent to 36 potential influenza vaccine manufacturers
  - 100% response rate
  - All 21 current influenza vaccine producers responded
  - 26 manufacturers that intend to produce pandemic vaccines
  - Includes LAIV and one recombinant vaccine capacity
- Survey assumes
  - 1:1 H1N1 to seasonal yields
  - Most dose sparing formulation for **each** manufacturer
  - Use of full production capacity



Source: WHO survey (Collin N. et al, Vaccine 2009. 27(38):5184-6)

Status of pandemic (H1N1) 2009 vaccine donation to WHO

Donations from manufacturers: GSK, Sanofi Pasteur, CSL, MedImmune

156 million doses

Donation from 12 governments of up to 10% of domestic vaccine supply (or equivalent capacity, or cash, or mixture of the above): Australia, Brazil, France, Germany, Italy, Japan, New Zealand, Norway, Switzerland, Thailand, UK and USA

Up to 50 million doses?

Delivery schedule: starting December 2009 over a 12 month period

Prequalification of H1N1 vaccines: November 2009 to early 2010 for vaccine donated to WHO

One way: Technology Transfer

Initial seed grants for technology transfer to produce influenza (seasonal and H5N1) vaccines to 11 manufacturers:

- Brazil (2007)
- Indonesia (2007)
- Thailand (2007)
- Egypt (2009)
- Korea (2009)
- Serbia (2009)
- India (2007)
- Mexico (2007)
- Vietnam (2007)
- Iran (2009)
- Romania (2009)

Programme financed by US-HHS, Japan, Canada, UK, ADB

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Programme financed by US-HHS, Japan, Canada, UK, ADB

One way: Technology Transfer

Significant progress reported from all developing country vaccine manufacturers

- New blending/filling facilities completed or under construction (Indonesia/Mexico)
- Licensure of new seasonal vaccine (Indonesia)
- Inactivated H1N1 vaccine clinical trials completed or planned for 2009 (Korea, India) or 2010 (Indonesia, Brazil, Romania, Vietnam)
- Live Attenuated Influenza Vaccine (LAIV) technology sub-licensed from WHO for increased pandemic surge capacity (Thailand, India, *China*). Excellent yields (Thailand: 100 doses/egg, liquid; India: 50 doses/egg, lyophilized), promising preclinical data in several animal models, clinical trials to start in 2009.

The WHO technology transfer "hub" at the Netherlands Vaccine Institute (NVI) is operational since early 2009

WHO and pandemic vaccine supply

WHO Global agenda on influenza surveillance and control

- Develop strategies for the utilization of vaccines --- for a pandemic
- Advocate research on pandemic vaccines

Most of the issues covered in this part of the presentation are within WHO's plans, but progress has been slow, but seems to have picked up recently.