Summary of the WHO Maternal Influenza Meeting on New Data and Implementation

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SAGE Maternal Immunization Session | April 15, 2015

Technical Consultation on Maternal Influenza Immunization Evidence and Implementation

- Closed meeting held 25-26 March in Geneva
- Meeting Objectives
  1. To **review new data** informing maternal influenza vaccine programmes
  2. To **discuss data gaps** in need of further efforts to strengthen uptake of maternal influenza immunization programmes, with a particular focus on low-resource settings
  3. To **discuss integration** of maternal influenza immunization into routine antenatal care services
  4. To **review the portfolio** of maternal influenza immunization activities being undertaken globally and to prioritize areas of need
- Co-chairs: Zulfiqar Bhutta and Kate O'Brien
- Agenda and List of Participants are available here:
  - http://webitpreview.who.int/entity/immunization/research/meetings_workshops/maternal_influenza_immunization_march15/en/index.html

Outline: Maternal Influenza Immunization Meeting Summary

- BMGF-funded RCTs
- Disease burden
- Vaccine safety
- Vaccine impact
- Implementation
- Survey
- Conclusion

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Hypothesis Generation: Mother's Gift Trial

- RCT of pneumococcal polysaccharide vaccine among pregnant women to protect youngest infants against pneumococcal disease:
  - Dhaka Bangladesh, 2004-05
  - 340 pregnant women (3rd trimester)
    - pneumococcal polysaccharide vaccine- PPV23 (intervention vaccine)
    - inactivated influenza vaccine (comparator vaccine)
    - (N.B. no placebo arm in the trial)
  - Follow-up through six months after birth

- Exploratory outcomes:
  - Febrile respiratory illness among infants and mothers
  - Lab-confirmed influenza among infants

Zaman, et. al. NEJM 2008
https://clinicaltrials.gov/ct2/show/NCT00142389

Hypothesis Generation: Mother's Gift Trial

- Influenza vaccine exposure decreased respiratory illness with fever:
  - 29% among infants
  - 36% among their mothers
- Vaccine efficacy against laboratory-confirmed influenza among infants through 6 months of age was 63% (95% CI: 5, 85)

Zaman, et. al. NEJM 2008

Mother's Gift Trial: Birth Outcomes of Babies, by Vaccine, and by Season of Birth

	Variable	PPV (n=166)	IIV (n=161)	*p* value	OR (95% CI)
All births	<2500 g	13 (7.8)	1 (4.4)	0.2	0.53 (0.2-1.4)
	SGA	63 (38.0)	45 (28.0)	0.05	0.63 (0.4-1.0)
	Preterm (<37 weeks)	14 (8.4)	10 (6.2)	0.4	0.72 (0.3-1.7)
	Mean birth weight, g	3027	3117	0.09	--

	Variable	PPV (n=58)	IIV (n=58)	*p* value	Adj. OR (95% CI)*
Born during the flu season	<2500 g	5 (8.6)	1 (1.7)	0.1	0.17 (0.02-1.63)
	SGA	26 (44.8)	15 (25.9)	0.05	0.44 (0.19-0.99)
	Preterm (<37 weeks)	4 (6.9)	2 (3.5)	0.3	0.32 (0.05-2.29)
	Mean birth weight, g	2978	3178	0.01	--

*Adjusted for gestational age at immunization, and interval from immunization to delivery.

Steinhoff, et. al. CMAJ. 2012

Maternal Influenza Immunization RCTs
BMGF Sponsored

- Test of hypothesis that maternal influenza vaccine could affect fetal outcomes, infant and maternal ds.
- Three RCTs in other low-resource settings
  - sufficiently powered to examine maternal flu effects both human immunodeficiency virus (HIV)-infected and uninfected populations of pregnant women
- Sites:
  - Mali (analysis ongoing)
  - Nepal (analysis ongoing)
  - South Africa (published 2014)

Study approach described Adegbola R. Am J Obstet Gynecol. 2012.; Clinicaltrials.gov
SA Study Madhi SA et al. NEJM 2014 Sep 4;371(10):918-31.

Maternal Influenza Immunization RCTs
BMGF Sponsored

Analysis Complete

- South Africa (2 cohorts)
  - HIV+ mothers (n= 194; 1 season of enrolment)
  - HIV- mothers (n= 2116; 2 seasons of enrolment)

Analysis Ongoing

- Mali (1 cohort, 2 years of enrolment)
- Nepal (2 cohorts, sequential 12-month enrolment)

NB: Not all primary analyses or secondary analyses presented at meeting

Madhi SA, et al. N Engl J Med. 2014

Maternal influenza vaccine RCTs: Vaccine Efficacy

- Not all VE data from the trials were presented
- Lab-confirmed influenza (cases mostly mild, not medically attended)
  - Mothers: VE 35%-70%
  - <6 months: VE 28%-61%
- Severe lab-confirmed influenza (i.e. hospitalized)
  - Trials not designed to evaluate this outcome
  - Few cases of hospitalized influenza identified
- Birth outcomes
  - Mixed results
    - 1 country: Significant effect on LBW (<2500g) and birth weight (g)
    - No fetal effects found in 2 of the 3 countries
    - More detailed analyses ongoing in all three trials

Maternal influenza vaccine RCTs Vaccine Safety

- No safety signal among mothers or infants
- Trials excluded women with chronic illness (apart from the HIV+ cohort in South Africa)
- Trials not sufficiently powered to:
  - Identify significant imbalances in rare outcomes
  - Identify significant imbalances in common safety events of public health importance (stillbirth, miscarriage, etc.)

Maternal influenza vaccine RCTs: Ongoing Analyses

- Primary publications from Nepal and Mali expected later in 2015
- Pooled analysis getting underway
  - by trial investigators
  - to evaluate associations between maternal influenza vaccine and less common safety and efficacy endpoints

Maternal influenza vaccine RCTs: What is unanswered from the trials?

- Vaccine performance among women with chronic illnesses
  - Excluded from trials
  - At risk for more severe influenza
  - At risk for worse birth outcomes
- Severe influenza in pregnant women and infants <6 mos.
  - Burden of disease (i.e. control arm)
  - Vaccine efficacy
  - Vaccine impact (vaccine-attributable rate reduction)

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Influenza Disease Burden

- Brad Gessner (AMP)
  - interim report from WHO Working Group to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling
- David Savitz (Brown University)
  - Perinatal epidemiologist
  - Expert review of studies on influenza vaccines and birth outcomes

Findings from Expert Review
Interim WHO Working Group Findings
(Disease epidemiology and vaccine)

- Pregnancy associated with influenza hospitalization but not other severe outcomes
  - Meta-analyses of observational data
- Data are non-representative
  - Most data from HICs and from 2009 pandemic
- Little evidence that maternal influenza substantially impacts birth outcomes
- Additional data are needed to more clearly assess maternal influenza immunization program impact

Findings from Expert Review
Influenza Vaccine Effect on Birth Outcomes

Does vaccination prevent development of influenza?	Yes
Does occurrence of influenza cause adverse pregnancy outcome?	Maybe • Empirical evidence is quite mixed: limited quantity, quality; heterogeneous results • Severe influenza may be related to preterm birth based on 2 studies • Little evidence that mild influenza affects pregnancy outcome
Does prevention of influenza through vaccination prevent adverse pregnancy outcome?	Maybe • Results of observational studies are heterogeneous, but generally show reduced risk of preterm birth and LBW/SGA • Some indication that births during influenza season show greater reduction in adverse outcomes

Slide courtesy D. Savitz

Does prevention of influenza through vaccination prevent adverse pregnancy outcome?

Savitz: Unresolved

Recommends caution with interpretation of studies:

- Studies generally fail in the analysis to properly align timing of pregnancy and influenza season
- Questionable plausibility of the magnitude of reported reduction in risk
- Unclear how fetal growth restriction would be affected by acute influenza illness
- Several methodologically strong observational studies show no reduced risk

Slide courtesy A. Yakubu

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Vaccine Safety
Maternal Influenza Vaccination

- 2014 GACVS Review
  - found no safety signals for inactivated influenza vaccine
- 3 recent systematic reviews
  - found no safety signals
- Data limitations
  - observational, not product-specific, and generally exclude 1st trimester
  - data quality issues from spontaneous reporting systems
  - no studies of sufficient size to evaluate rare safety outcomes (which may be of relevance to public health)
- There is a need for strengthened post-licensure safety monitoring to ensure capture of any signals

http://www.who.int/vaccine_safety/publications/safety_immunization_pregnancy/en
Fell DB, et al. BJOG. 2015.
Bratton KN, et al. Clin Infect Dis. 2015.
McMillan, M., et al.. The JBI Database of Systematic Reviews and Implementation Reports. 2014.

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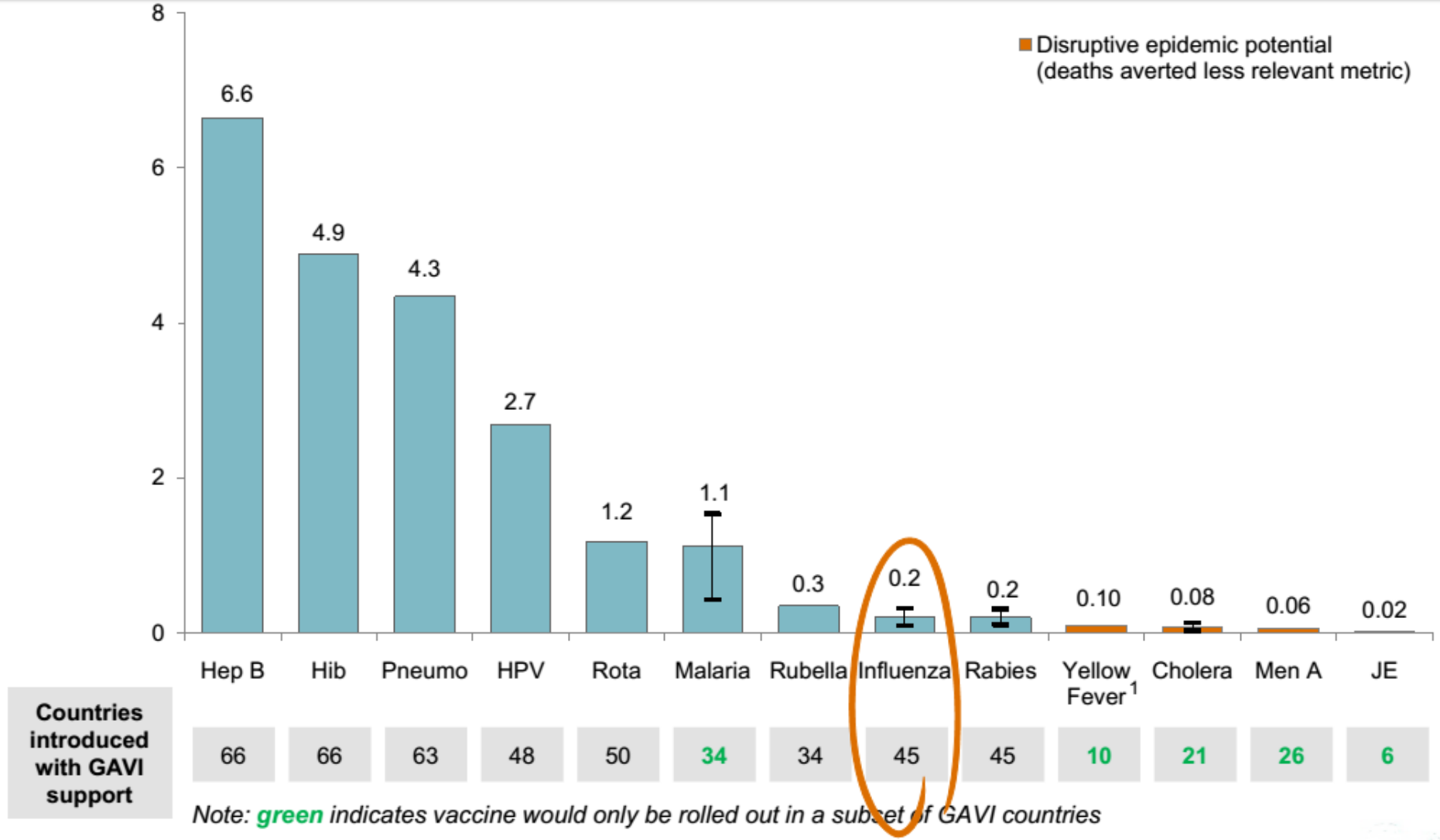
Vaccine Impact

Setting	Key considerations	Available Data
High income	• Cost-effectiveness • Averting complications in risk groups • Economic productivity	• Some health economic studies available • Most disease burden
Middle income	• Cost-effectiveness • Return on investment • Range of health indicators (mortality, health care utilisation, morbidity, productivity)	• Limited health economic data available • Limited disease burden data
Low income	• Mortality (most important) • Affordability • Cost-effectiveness	• No health economic data available • Minimal disease burden data

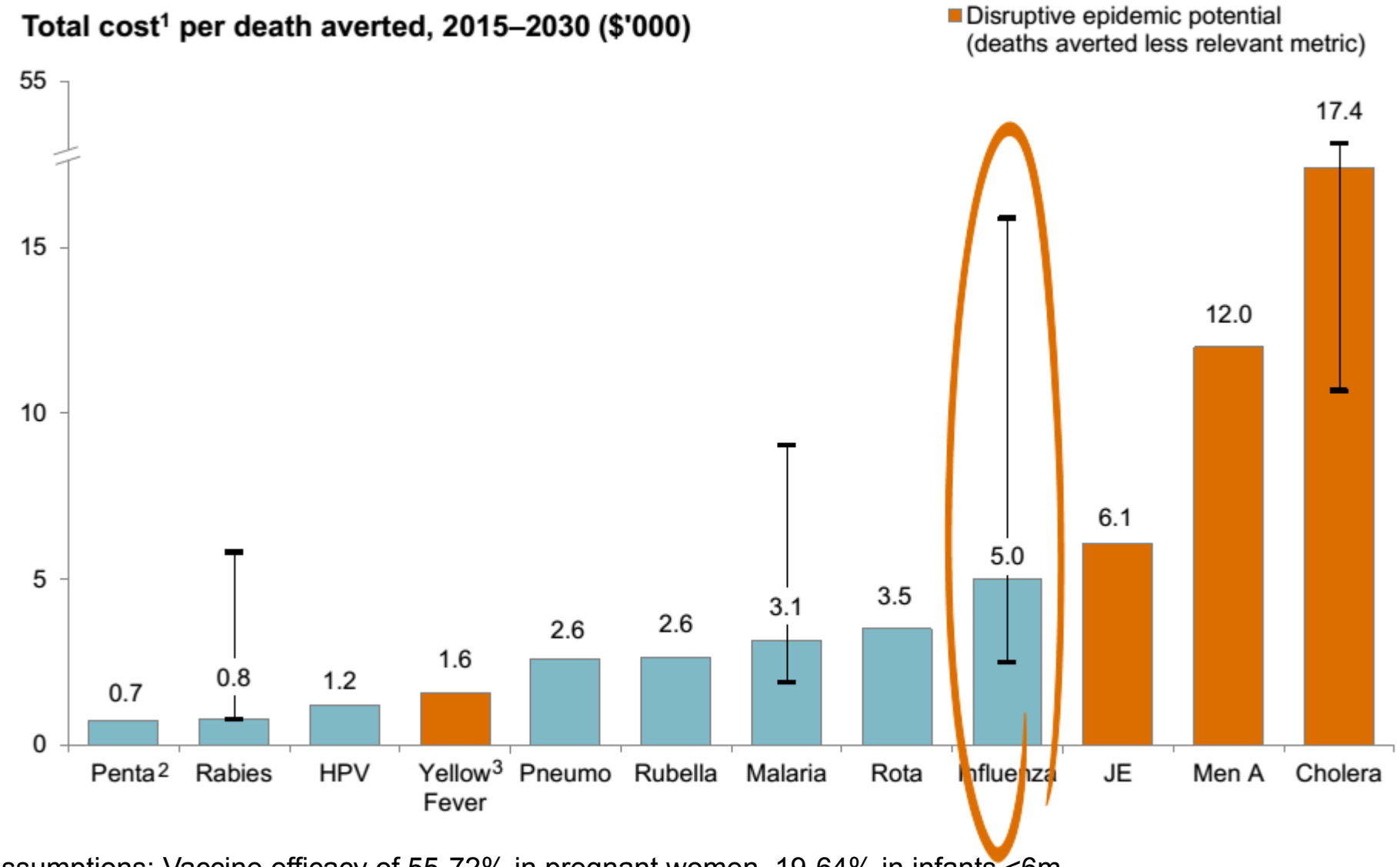
Slide courtesy M. Jit

2013 Gavi Model of Future Deaths Averted in Gavi-Eligible Countries (2015-2030), in millions



Assumptions: Vaccine efficacy of 55-72% in pregnant women, 19-64% in infants <6m.
http://www.gavi.org/library/gavi-documents/strategy/final-vis-analysis-2013--maternal-influenza/

2013 Gavi Model of Costs per Death Averted in Gavi-Eligible Countries (2015-2030), in $'000s



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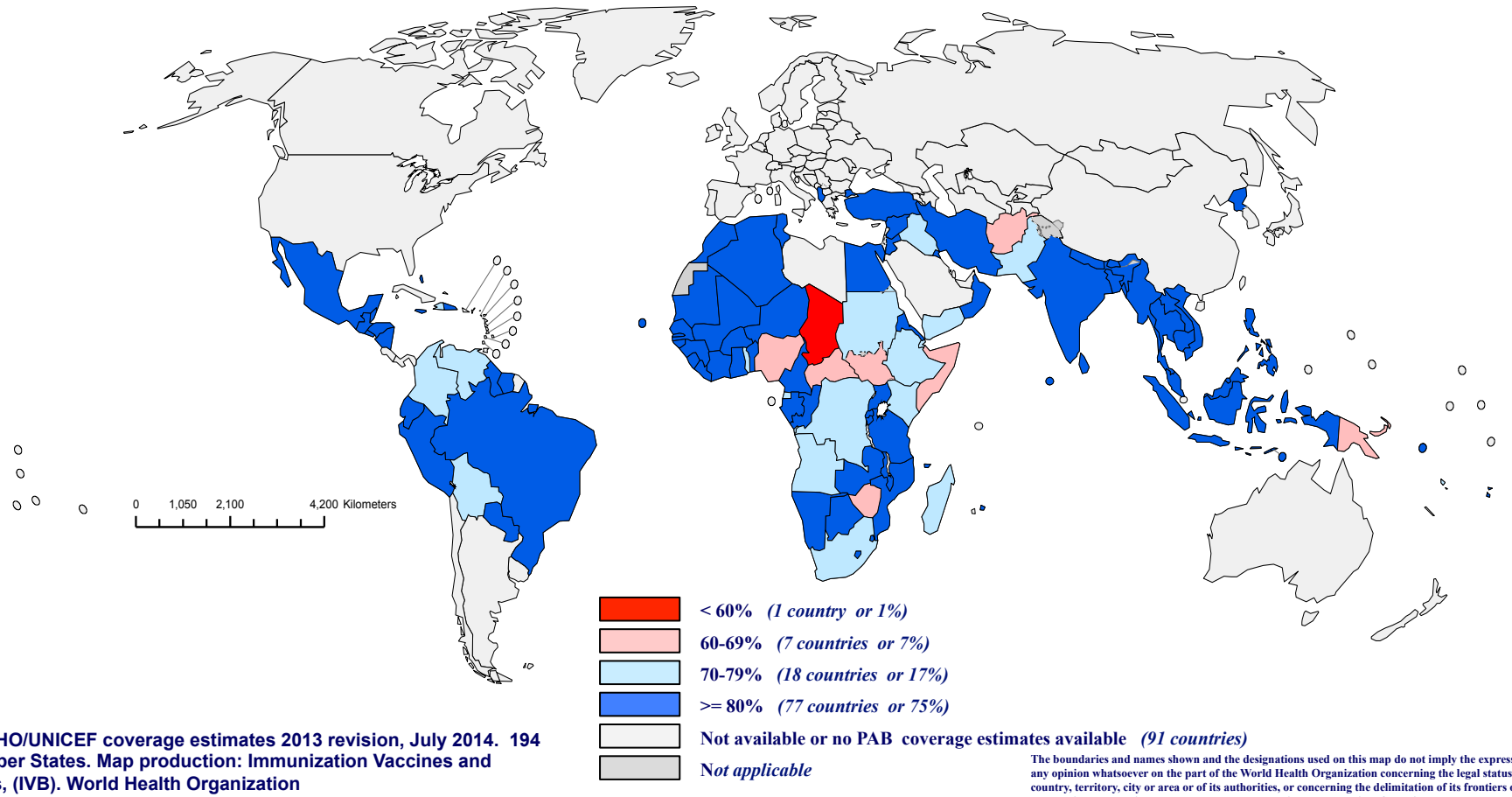
Implementation of Maternal Influenza Immunization Complex

- Country experiences showed complexities of delivering maternal immunization (e.g. maternal tetanus, maternal flu vaccine)
  - Alignment of priorities between MNCH and Immunization
  - Regulatory challenges
  - Supply and logistics
  - Delivery strategy and responsibility
  - Limited demand/recognition of disease
  - Challenges maintaining coverage
  - Program sustainability
- No clear global champion(s)
- No identified funding mechanism for low-resource settings
- A dedicated multi-functional team to drive strategy, coordination and engagement is essential

Need for Implementation Research

- Limited implementation research of maternal immunization, globally
- Demonstration projects of other interventions have generated generalizable data regarding implementation (e.g. HPV, malaria prevention in pregnancy)
- Demonstration projects can
  - Identify, understand and address barriers to effective implementation
  - Assess feasibility of program introduction in key settings

MNTE as a programmatic opportunity: Protection at birth (PAB) coverage against tetanus, 2013

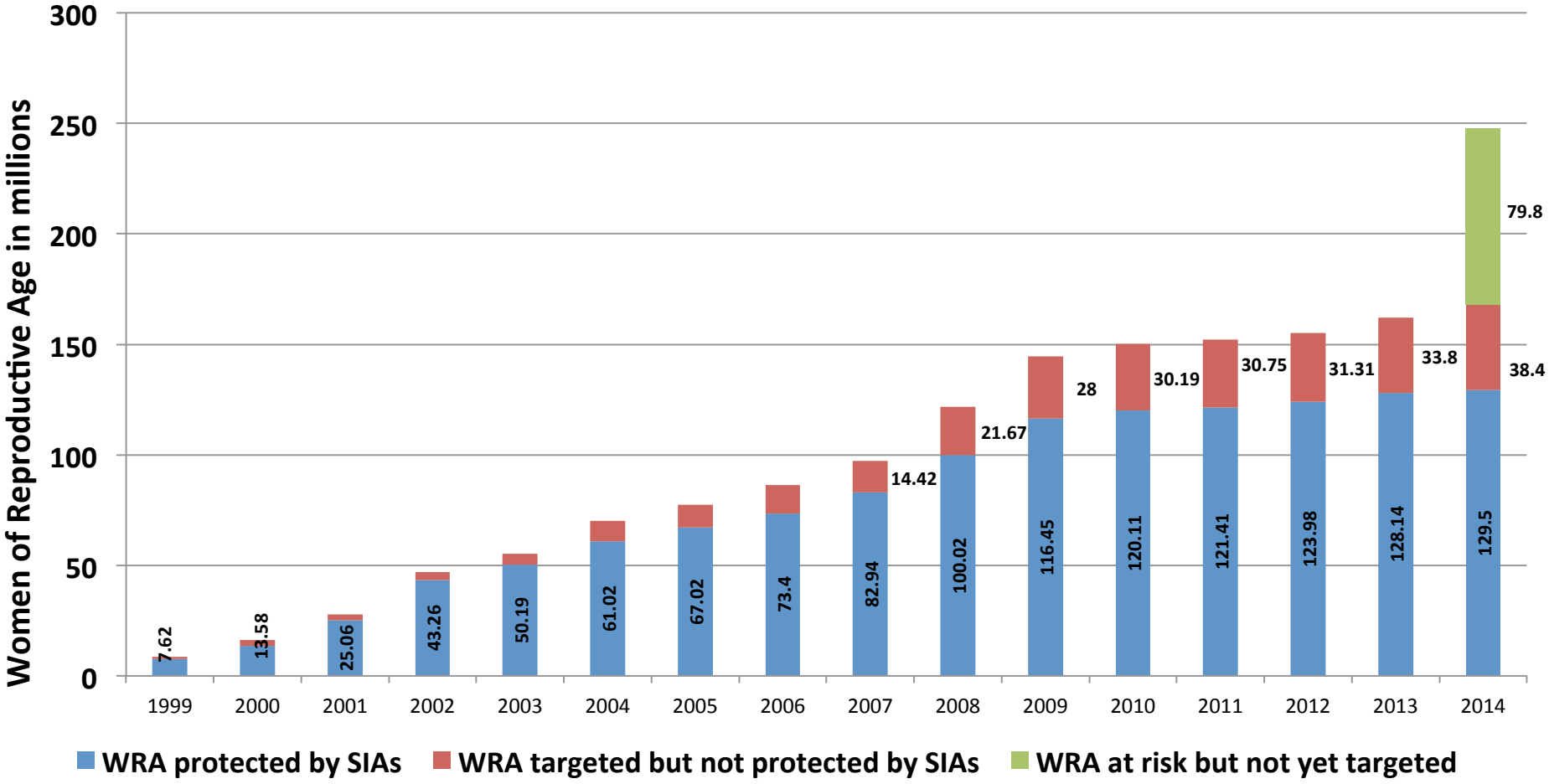


Source: WHO/UNICEF coverage estimates 2013 revision, July 2014. 194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 30 July 2014

Slide courtesy A. Yakubu

MNTE as a programmatic opportunity: Women protected by at-least 2 doses of TT/Td

1999-2014



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Before and After Survey of Participants

- 22 Questions asking whether:
  - There are sufficient data for program investment globally
  - The data justify strengthened policy statements
- Multiple domains:
  - Disease burden mothers, infants <6 months, fetal effects
  - Vaccine performance
  - Program impact
  - Vaccine safety
  - Data needs for integration into routine antenatal care

Before and After Survey of Participants

- Disease burden an area of insufficient data
  - particularly influenza effect on birth outcomes,
- Program impact area with least sufficient data
- Vaccine safety area with most sufficient data
- Recommendations:
  - Current SAGE position adequate given the data
  - Further data collection on integration of vaccine programmes into antenatal care platforms in low-resource settings strongly supported

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Conclusion

- Substantial data will become available in 2015/2016
  - 2 RCTs (Nepal, Mali)
  - Pooled analysis of SA, Nepal, Mali
  - Influenza workgroup systematic reviews
- Data presented at the meeting support the existing, permissive SAGE policy recommendation
- More data needed before strengthened policy recommendation should be considered
  - Disease burden (mothers, infants)
  - Vaccine-attributable rate reduction of severe influenza disease
  - Vaccine effect on birth outcomes
- There is a need to generate generalizable data regarding vaccine delivery / integration into ANC

Thank you