Update on the Global Immunizations

The WHO Strategic Advisory Group of Experts on Immunizations (SAGE)

Jon S. Abramson, MD
Chair, Department of Pediatrics at Wake Forest School of Medicine
&
Chair of SAGE

World Health Organization

Disclosure

I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services

A Global View

Eight Millennium Development Goals (MDGs) (2000 – 2015)

- The eight MDGs set a bold vision for the entire international community to work towards a common end so that human development reaches everyone
  - Adopted by >190 countries in 2000
  - The goals use 1990 data as the starting point and are set to be achieved by 2015
  - 21 quantifiable targets measured by 60 indicators
  - If all MDGs are achieved, world poverty would be cut by half, and tens of millions of lives would be saved

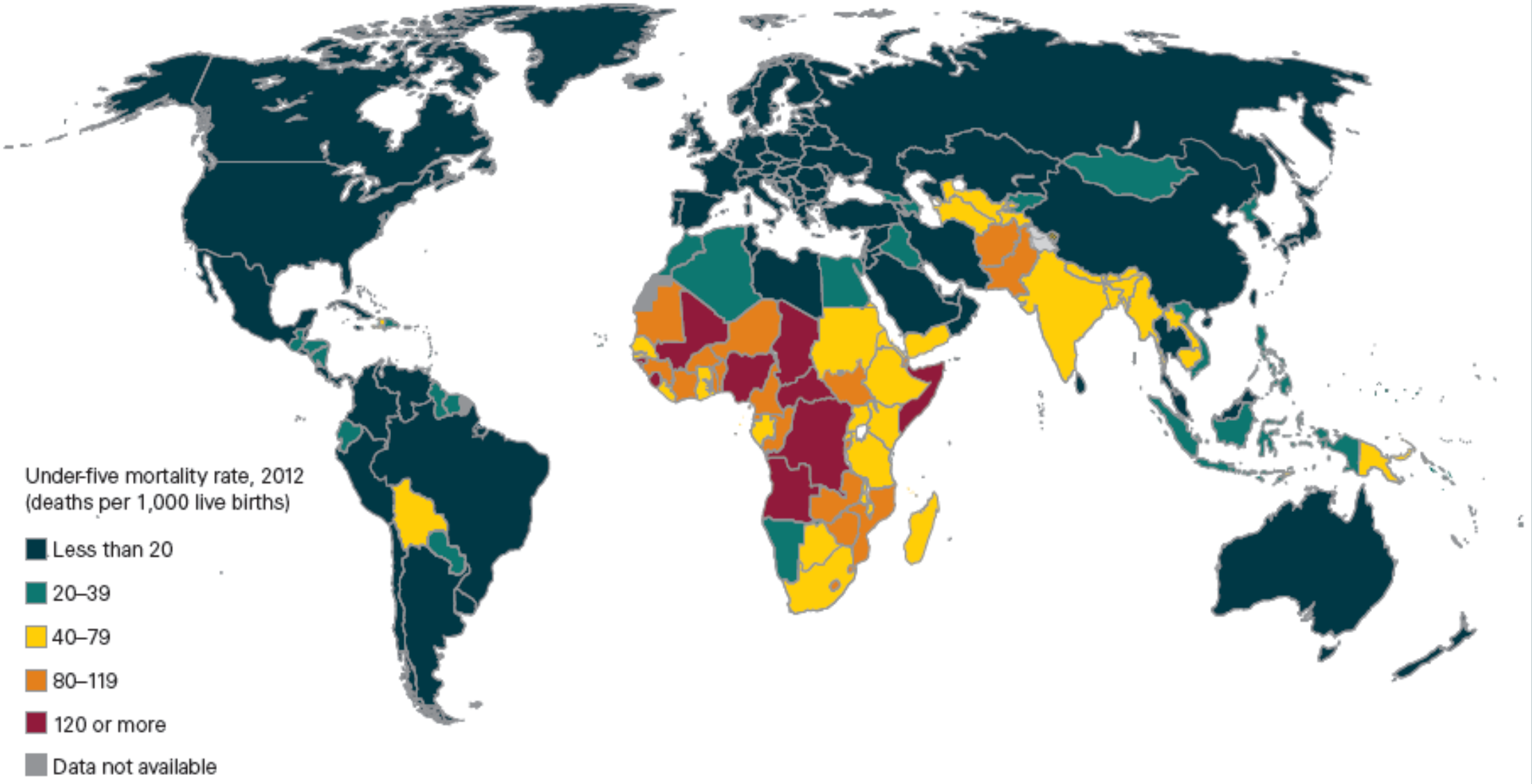
MDG # 4

Goal 4- Reduce mortality by two thirds in children <5 yrs of age

- In 1990 the mortality rate in children <5 yrs of age was ~160/1000 in low income countries as compared to 8/1000 in developed countries.
- By 2012 the mortality rate in low income countries was reduced to ~88/1000 in children <5 yrs of age (45%).
  - Global deaths decreased from ~12M to 6.6M
- ~17,000 fewer children <5 yrs died every day in 2012 than in 1990
- ~18,000 children <5 yrs still died every day in 2012.
- Many of the deaths in children <5 yrs in low income countries continue to be due to vaccine preventable diseases.

MAP 1

Children in Sub-Saharan Africa and Southern Asia face a higher risk of dying before their fifth birthday



Note: This map is stylized and not to scale. It does not reflect a position by UN IGME agencies on the legal status of any country or territory or the delimitation of any frontiers.

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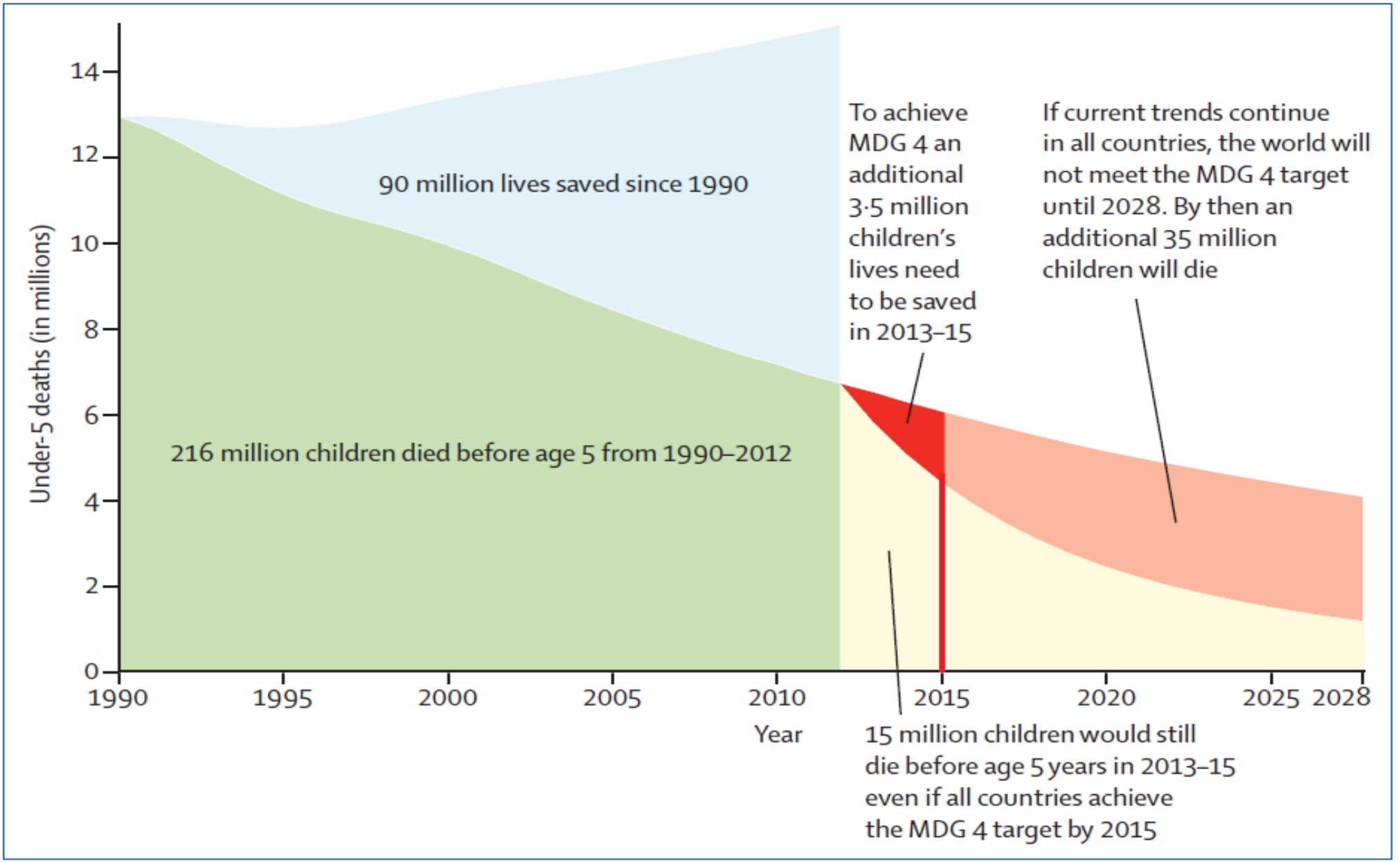
Number of lives saved and to be saved in children <5 yrs*



*Reproduced from committing to Child Survival: A Promise Renewed Progress Report 2013

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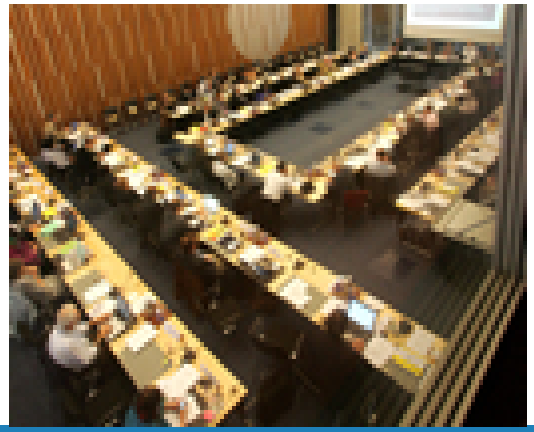
Overview of How SAGE Functions

Why SAGE was Formed

The WHO has a mandate to provide leadership on global policies, standards and norms and to support countries in applying these to national programs to improve health.

SAGE was established by the WHO Director General in 1999 as the principal advisory group to the WHO for vaccines and immunization.

SAGE provides recommendations on global policies and strategies for all vaccine-preventable diseases



SAGE Composition

Membership

15 independent experts from around the world serving in a personal capacity

Broad range of disciplines including epidemiology, public health, vaccinology, pediatrics, internal medicine, health economics, infectious diseases, immunology, drug/vaccine regulation, program management, immunization delivery, healthcare administration, vaccine safety

Spectrum of professional affiliation with geographical and diversity balance

Initial term of 3 years with provision for one additional term

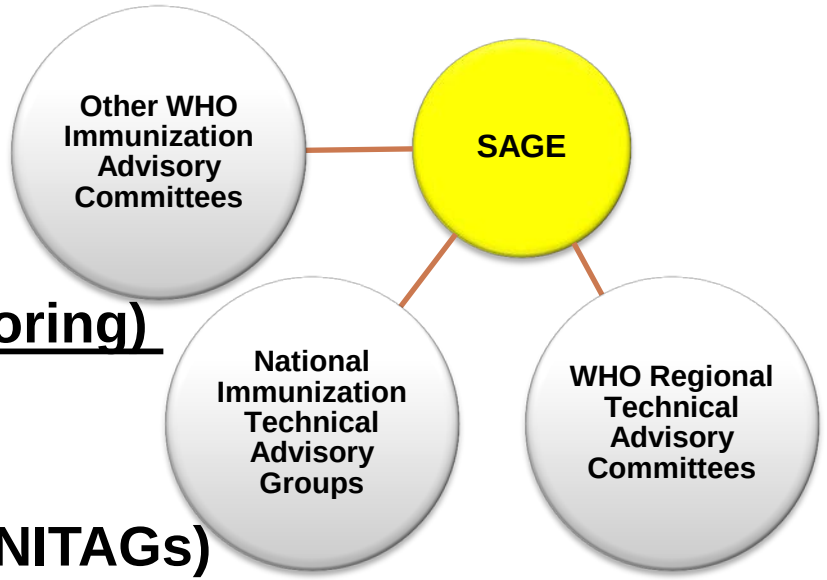
Strategic Collaboration

Advisory Bodies

SAGE collaborates with global, regional & national advisory bodies

WHO Immunization Advisory Committees

- Global Advisory Committee on Vaccine Safety
- Expert Committee on Biological Standardization
- Initiative for Vaccine Research Advisory Committee
- Immunization and Vaccines related Implementation Research Advisory Committee
- Immunization Practices Advisory Committee



WHO Regional Technical Advisory Committees (regional policies, strategies, priority-setting, monitoring)

6 WHO Regions: Africa, Americas Eastern Mediterranean, Europe, South-East Asia, Western Pacific

National Immunization Technical Advisory Groups (NITAGs) country-level policies, strategies, priority-setting, program implementation, monitoring)

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SAGE Recommendation Process

Committee Meetings

Meet 2x/yr with additional meetings as required (e.g., pandemic flu, DoV planning)

Open forum to ensure transparency. Observers include UNICEF, GAVI, Secretariat, Chairs of WHO Regional Offices and TAGs.

SAGE working groups address complex questions and are comprised of at least two SAGE members, WHO staff and additional external subject matter experts

SAGE considers working group recommendations. SAGE recommendations are made by **consensus** and not by majority vote.

The resulting evidence-based recommendations provide the basis for WHO vaccine position papers which inform country-level decision-making and program implementation. These recommendations also assist partner organizations (e.g., GAVI, non-profit organizations, and international professional associations).

Grading of SAGE Recommendations

Quality of Evidence and Strength of Recommendations: GRADE

To assess the quality of evidence, SAGE uses broadly endorsed Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

Rating method

Quality of evidence – Levels of confidence in estimate of effect (very little confidence, limited confidence, moderately confident, very confident

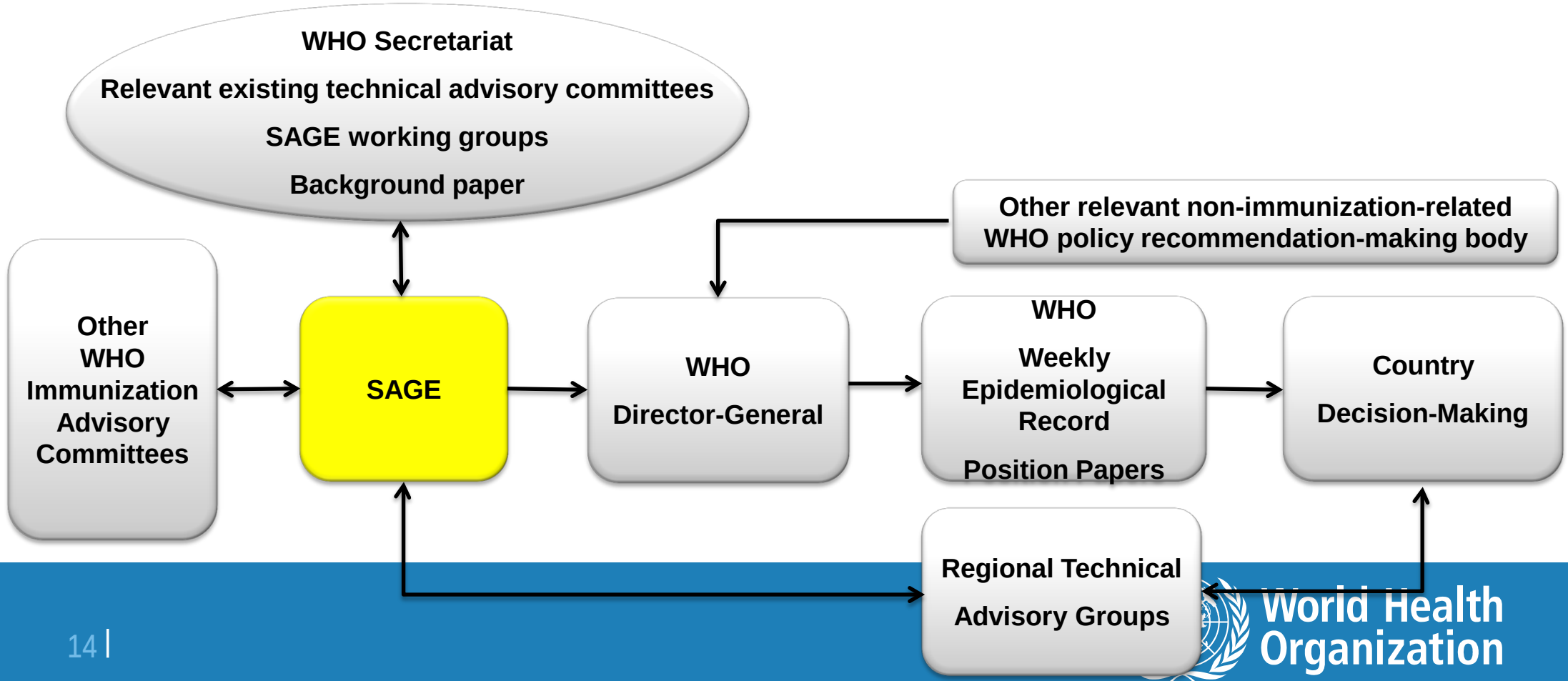
Strength of recommendations – Strong (benefits do, or do not, outweigh risks and burdens) or Weak (benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks)

How WHO Processes SAGE Recommendations

Conclusions and Recommendations

SAGE Chair briefs WHO Director-General on proceedings of each meeting

Conclusions and recommendations published in WHO's Weekly Epidemiological Report within 2 months



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Outside Review of SAGE

Impact of SAGE Recommendations

-An independent review in 2008 investigated the effects of recommendations formulated by SAGE

“SAGE recommendations have become a necessary step to the introduction and use of vaccines, especially in developing countries and, as a consequence, have clear and significant impact”

The independent review recommended that WHO

-Take immediate steps to consolidate and build on the successes of SAGE

-Rapidly disseminate recommendations at the country level

-Ensure immunization policies are coordinated within the wider framework of other possible preventive interventions

Decade of Vaccines (DoV) and the Global Action Plan (GVAP)

DoV
Vision and Mission

"We envision a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases".

"The mission of the Decade of Vaccines is to extend, by 2020 and beyond, the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live."

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Why a DoV Now (2010 - 2020)?

Unique moment in time where increased funding meets scientific opportunity

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Goals for the DoV

- Achieve a world free of poliomyelitis
- Meet global and regional elimination targets
- Meet vaccination coverage targets in every region, country and community
- Develop and introduce new and improved vaccines and technologies
- Exceed the Millennium Development Goal 4 target for reducing child mortality

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Relationship of DoV to the GVAP

Global Vaccine Action Plan (GVAP) will be used to achieve the five DoV goals that contain six objectives.

Collaborative effort by international vaccine community to extend, by 2020 and beyond, the full benefits of immunization to all people

Endorsed in 2012 by 194 member countries at 65th World Health Assembly (WHO's decision-making body)

SAGE recommendations are used to support the WHO's contributions to the GVAP

Why has a New Vaccine Plan been Developed for the DoV?

- Continued unmet needs & many challenges
  - Opportunities exist to do much better
    - Elimination (e.g., measles) and eradication (i.e., polio) goals not on target
    - More rapid introduction and uptake of recently introduced vaccines would further decrease number of deaths
    - More rapid introduction and uptake of new vaccines this decade (e.g., malaria)
- The previous Global Immunization Vision and Strategy (GIVS) plan is now being replaced with the GVAP. The GIVS was created as a way to help meet some of the MDGs, but is no longer adequate to deal with the robust vaccine pipeline and the need to add newer vaccines into national programs

Moving from GIVS to GVAP

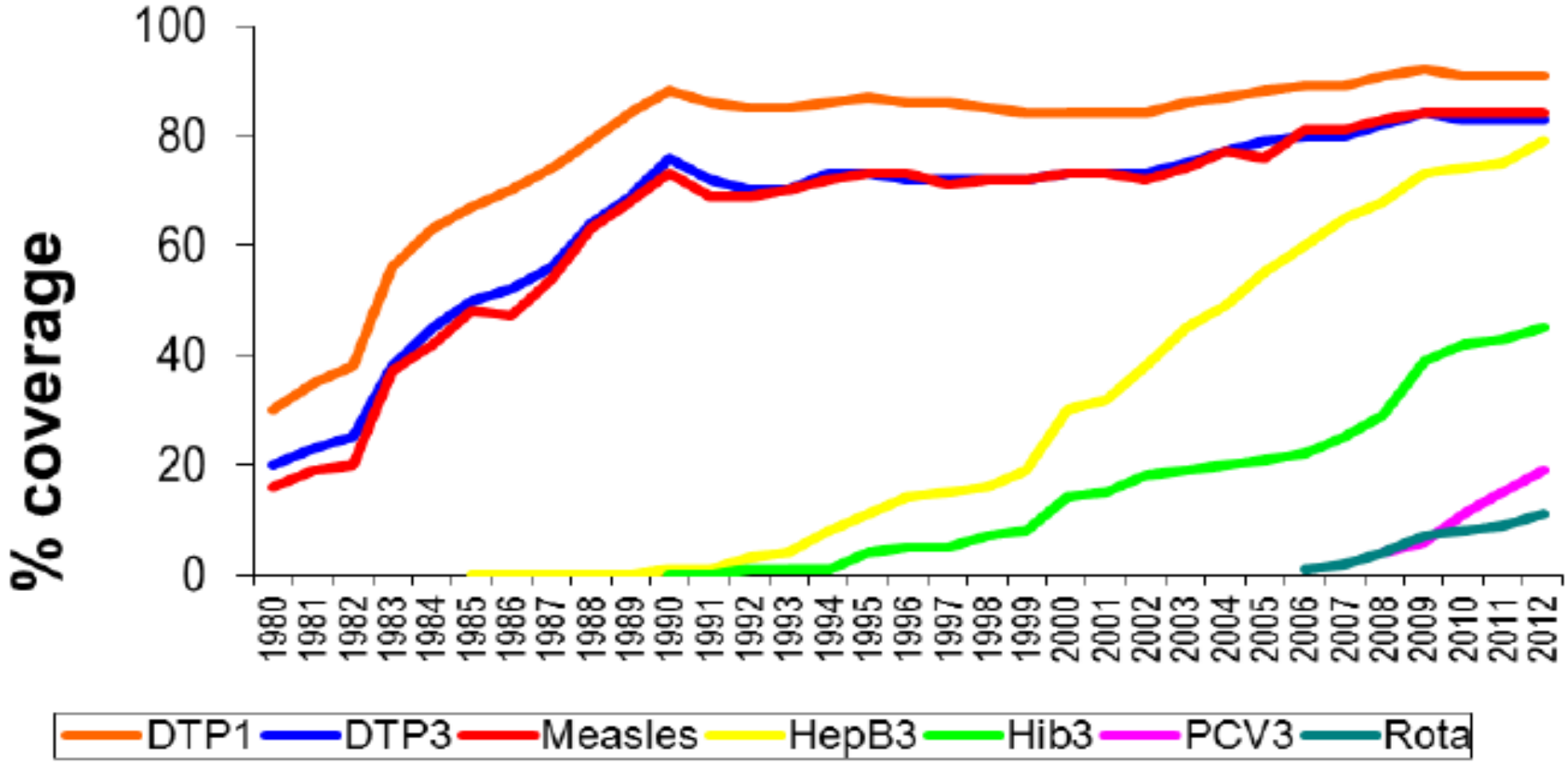
GIVS	GVAP
Focus on mortality	Focus on mortality, morbidity and economic impact
Top-down decision-making	Country ownership
Supply-side emphasis	Supply and demand-side interventions
Reaching Every District	Reaching Every Community
Immunization coverage	Comprehensive disease prevention and control / focus on surveillance
Access focus on low-income countries	Access focus on low and middle-income countries
A strategy (GIVS)	Predefined accountability framework that includes all stakeholder and not just countries

GVAP
Guiding Principles

- **Country ownership**
  - Countries have primary ownership and responsibility for establishing **good governance** and for providing effective and quality immunization services for all.
- **Shared responsibility and partnership**
  - Immunization is an **individual,** a **community** and a governmental responsibility that transcends borders and sectors
- **Equitable access**
  - Equitable access to immunization is a **core component of the right to health**
- **Integration**
  - Strong immunization systems, which are **part of the broader health systems** and closely coordinated with other primary health care delivery programs
- **Sustainability**
  - **Informed decisions** and implementation strategies, **appropriate** levels of **financial investments**, and improved **financial management and oversight**
- **Innovation**
  - The full potential of immunization realized only through **learning**, **continuous improvement, and innovation** across all aspects of immunization.

DoV
Highlights of Progress to Date

Global coverage estimates, 1980-2012
DTP1, DTP3, Measles, HepB3, Hib3, PCV3 and Rota3



Source: WHO and UNICEF estimates of national routine immunisation coverage, 2012 data revision (completed July 2013). Date of graph: 22 July 2013

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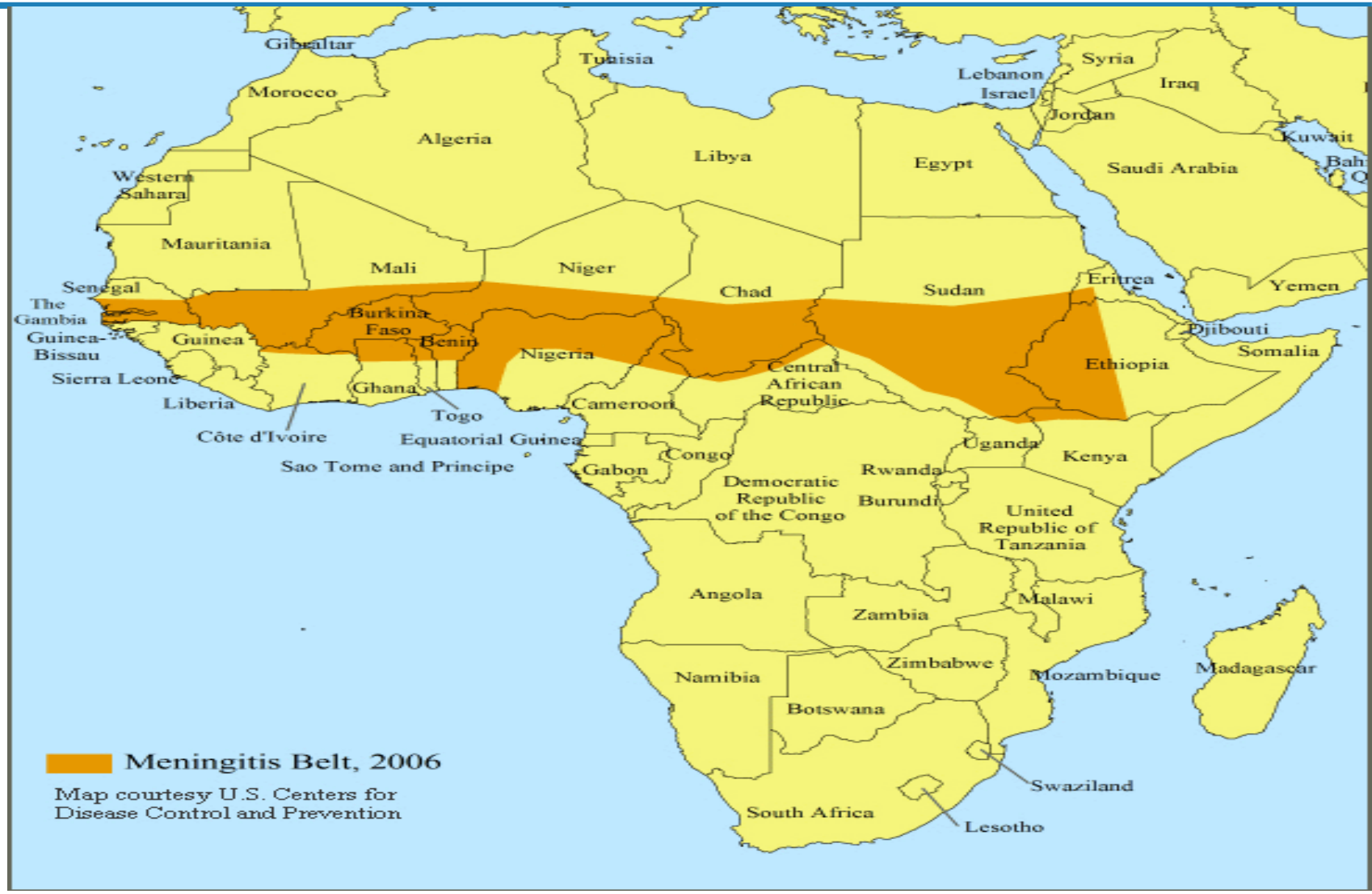
New WHO Vaccine Recommendations Since 2010

- Conjugated Meningococcal A- focus on African meningitis belt with an inexpensive ($0.50) vaccine
- Conjugated Pneumococcal- widespread global use with help of GAVI price shaping
- Dengue- not recommended due to lack of efficacy for serotype 2
- Hepatitis A- decreasing the cost by recommending one dose instead of two
- Influenza- pregnant women given highest priority
- Rotavirus- removal of age restriction allows additional lives to be saved
- Tick-borne encephalitis- consider use based on geographical disease incidence
- Yellow fever vaccine- only one dose needed and use in pregnant and lactating women should be considered based on risk-benefit assessment

Impact of vaccines noted in red will be briefly discussed

The “Meningitis Belt” of sub-Saharan Africa

430 million people live in the meningitis belt



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Meningococcal Disease

- The meningococcal meningitis belt in sub-Saharan Africa spans from Senegal in the west to Ethiopia in the east
  - Epidemics due to serotype A occur every 7 – 12 yrs
  - In 2009 ~88,000 cases and ~10,000 deaths
  - In conjunction with the Gates Foundation a massive immunization program using a conjugated meningococcal A vaccine ($0.50/ dose) has been initiated in this region for everyone 1 – 29 yrs of age.
  - In the 6 countries where the vaccine has been used to date the disease incidence has decreased >95%

Assessment of Influenza Risk and Influenza Vaccine Characteristics in Various Risk Groups

Risk Group	Feasibility of Delivery	Disease Severity	Vaccine Effectiveness	Indirect Benefits
Pregnant women	++	+++	+++	++
Healthcare workers	++	+	+++	+
Children, 2-5 yrs	+	++	++	-
Children, < 2 yrs	++	+++	+	-
Elderly	+	+++	+	-
Underlying Health Conditions	+	+++	+	-

Use of Influenza Vaccine
SAGE Recommendations

- In countries using or considering introducing seasonal influenza vaccination SAGE recommends that:
  - Influenza vaccination of all pregnant women as the highest priority group
  - Based on local circumstances (e.g. burden of disease, vaccine availability, cost-effectiveness considerations, competing priorities, and programmatic constraints), countries consider annual influenza vaccination of healthcare workers, children (< 2 yrs and 2-5 yrs of age), the elderly, and individuals with underlying health conditions. Countries should decide the relative priority to assign to targeting these groups for influenza vaccination.

Rotavirus (RV) Disease

- In 2009 the WHO recommended that RV vaccine for infants be included in all national immunization programs.
  - In countries where deaths due to diarrhea account for ≥10% of mortality among children <5 yrs, the introduction of the vaccine is strongly recommended.
  - Due to concerns about intussusception, the 1st dose should be given before 15 weeks and last dose by 32 weeks
- In 2013 this age restriction was removed to enable children with delayed immunizations to receive the vaccine

Risk-Benefit Considerations for Removing the Age Restrictions for Rotavirus Vaccine?

	Median (5th and 95th percentiles)	
	Rotavirus Deaths Averted	Associated Intussusception Deaths
Restricted	**156,100 (110,100 to 201,800)**	**288 (99 to 688)***
No age restriction	**199,200 (140,700 to 255,400)**	**605 (310 to 1,133)***
No age restriction (vs. age restriction)	**43,100 additional rotavirus deaths averted (30,600 to 53,500)**	**317 additional IS deaths associated (211 to 445)**

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Yellow Fever (YF) Vaccine

In April 2013 SAGE reviewed its previous recommendation on YF vaccine and made the following changes to its recommendations:

1) Only one, rather than 2 doses, is needed to provide lifelong protection and that the vaccine should be considered for use in pregnant and lactating women based on risk vs benefit in the particular setting.

- The vaccine is very effective with only 12 suspected cases of YF disease has been detected in vaccinated people since the introduction of YF vaccination in the 1930s and the duration of protection due to YF vaccine is at least 20 years and probably for life.

- A systematic review identified 6 studies indicating that a high proportion of vaccine recipients (>90%) have detectable levels of serum neutralizing antibodies >20 years post YF vaccination.

- In a study of antibody levels in US World War II veterans, >80% had neutralizing antibodies 30–35 years after a single dose of YF vaccine.

Yellow Fever (YF) Vaccine

2) Based on the high mortality due to YF disease the vaccine should not be contraindicated in pregnant or lactating women, but rather the use of the vaccine in this population be based on the risk of contracting disease in the particular geographical setting

- Mortality rates due to YF are 10% – 30% with ~30 000 deaths currently occurring per year (90% in Africa).

- Over 540 million doses of YF vaccine have been administered and there have been no reports of vaccine-related viscerotropic or neurotropic disease in pregnant women.

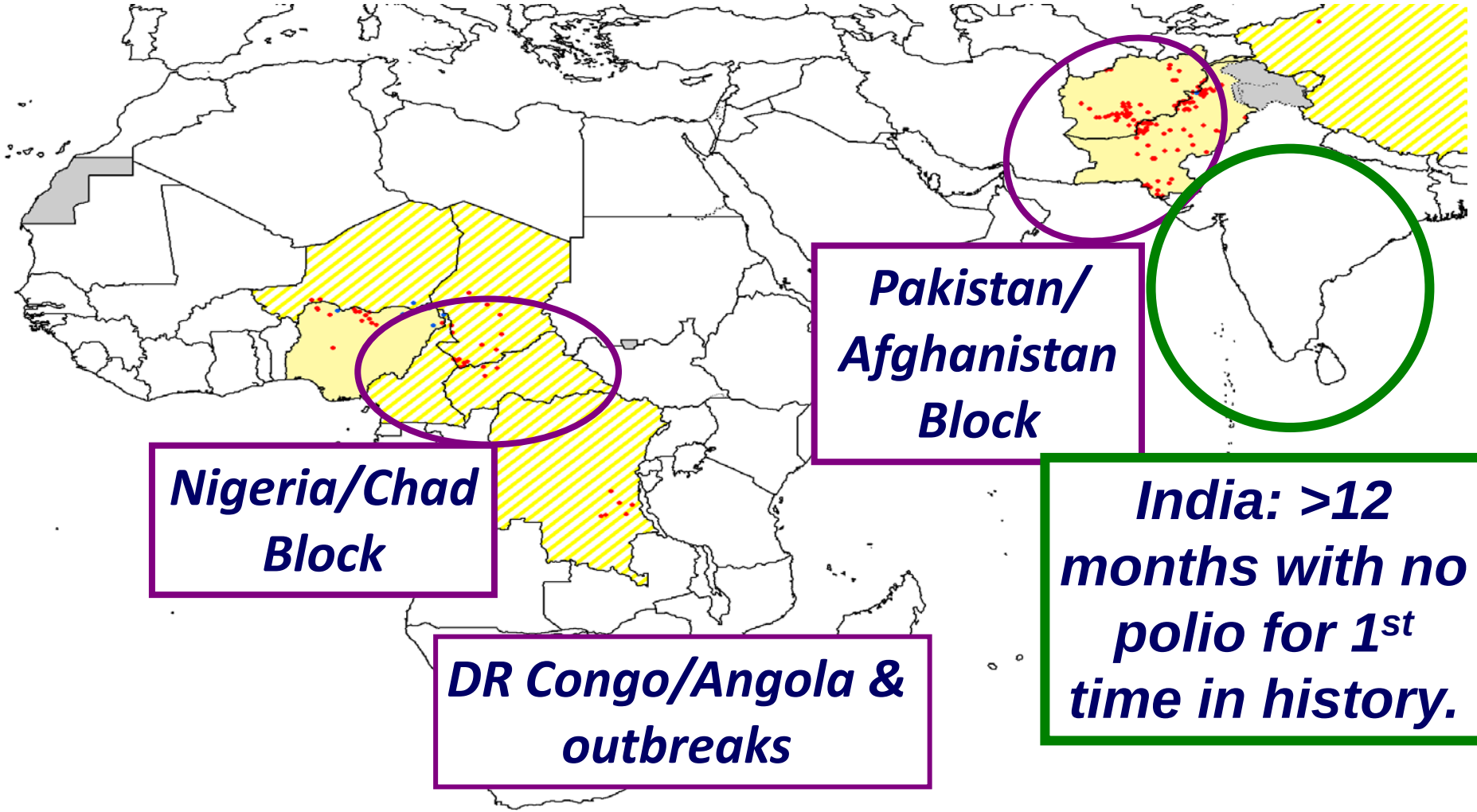
- There have been 3 cases of viscerotropic disease in newborns of lactating women who received the vaccine.

DoV
Highlights of Ongoing Topics

Current SAGE Working Groups and Topics*

- GVAP WG- ongoing
- Hepatitis E WG- just formed
- Japanese Encephalitis vaccine WG- just formed
- Malaria vaccine- preliminary data from RTS,S/AS01 trial reviewed
- Pertussis vaccine- global switch to acellular pertussis vaccine has been put on hold
- Polio vaccine- pre- and post-eradication issues
- Pregnancy and lactation- expanding use of vaccine in this population
- Varicella-Zoster vaccine- recommendations to be presented in April 2014
- Vaccine Hesitancy- ongoing
- Vaccine non-specific effects- ongoing

Polio Cases this Year (through April 2012)



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Polio Eradication

- Two eradication deadlines for polio eradication have past and the global effort is now costing greater than $1 billion/yr

- In 2011 the eradication of polio was designated by the WHO to be a **global emergency**.

"Loss of this opportunity to eradicate polio would be extremely tragic and unacceptable and a waste of the considerable investment already made in polio eradication with consequences for all of immunization activities, especially in the poorest countries. Any diminution of polio eradication activities due to a lack of funds is completely unacceptable. We urge all governments and partners to act immediately to meet the polio eradication funding needs if we are to wipe out this crippling disease."

- SAGE currently has the oversight responsibilities for the pre and post-vaccination recommendations

Integration of Vaccines Delivery with Other Services

Currently the polio program is the most integrated with other services and further integration of other vaccine and services will enhance the impact of the DoV

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Use of Vaccines in Pregnant and Lactating Women

The Problem

During the past few years SAGE has been asked to consider the use of vaccines that while not always specifically aimed at pregnant and lactating women could benefit them and their infant. Examples of this include use of the conjugated A meningococcal vaccine in the SIA campaigns in Africa, influenza vaccine, yellow fever vaccine and pertussis antigen containing vaccines.

This issue has existed for a long time with no real progress. The companies exclude pregnant women from vaccine trials due to litigation concerns. The regulatory agencies, given essentially no data for pregnant women, have little leeway in how the vaccine is labeled. Pregnancy registries are required, but decades go by and the labeling rarely changes.

This is similar to what occurred for a very long time with many of the drugs used in children in the US until finally a law was passed that give the FDA authority to require studies in children which has resulted in a substantial number of drug labeling changes specifically related to use of these drugs in children.

SAGE has repeatedly expressed its concerns that the current regulatory labeling hinders the use of these vaccines pregnant or lactating women to protect themselves and/or their baby from vaccine preventable diseases are not an appropriate assessment of the risk/benefit analysis, at least for all inactivated vaccines.

At the Nov 2013 meeting SAGE will be discussing what further role it can have to move this issue forward.

Acknowledgments

- Phil Duclos, Executive Secretariat of SAGE
- Helen Rees, Immediate-past Chair of SAGE

Questions and Comments

FIGURE 1 Under-five mortality declined in all regions between 1990 and 2012

Under-five mortality rate, by Millenium Development Goal region, 1990 and 2012 (deaths per 1,000 live births)

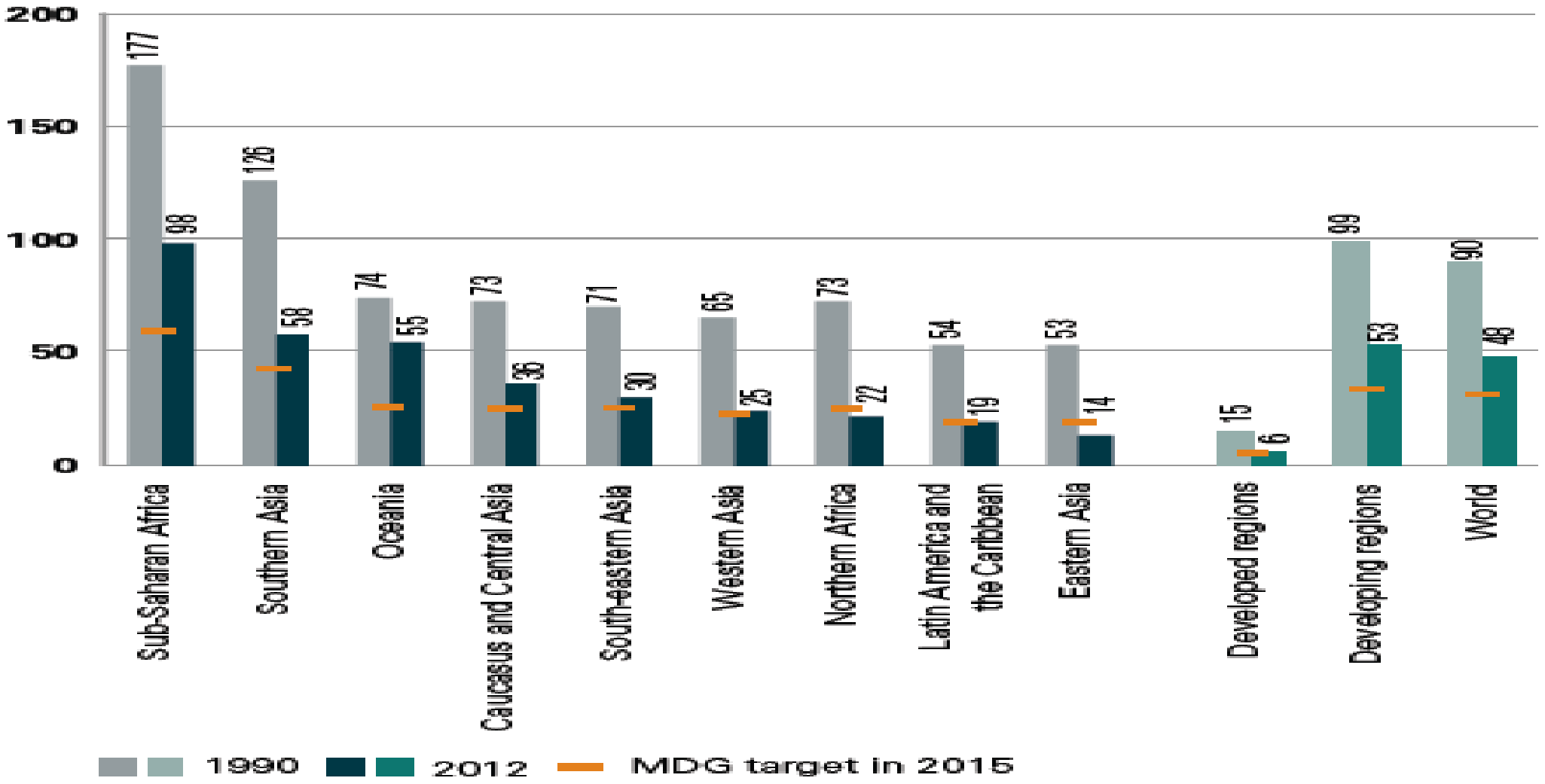

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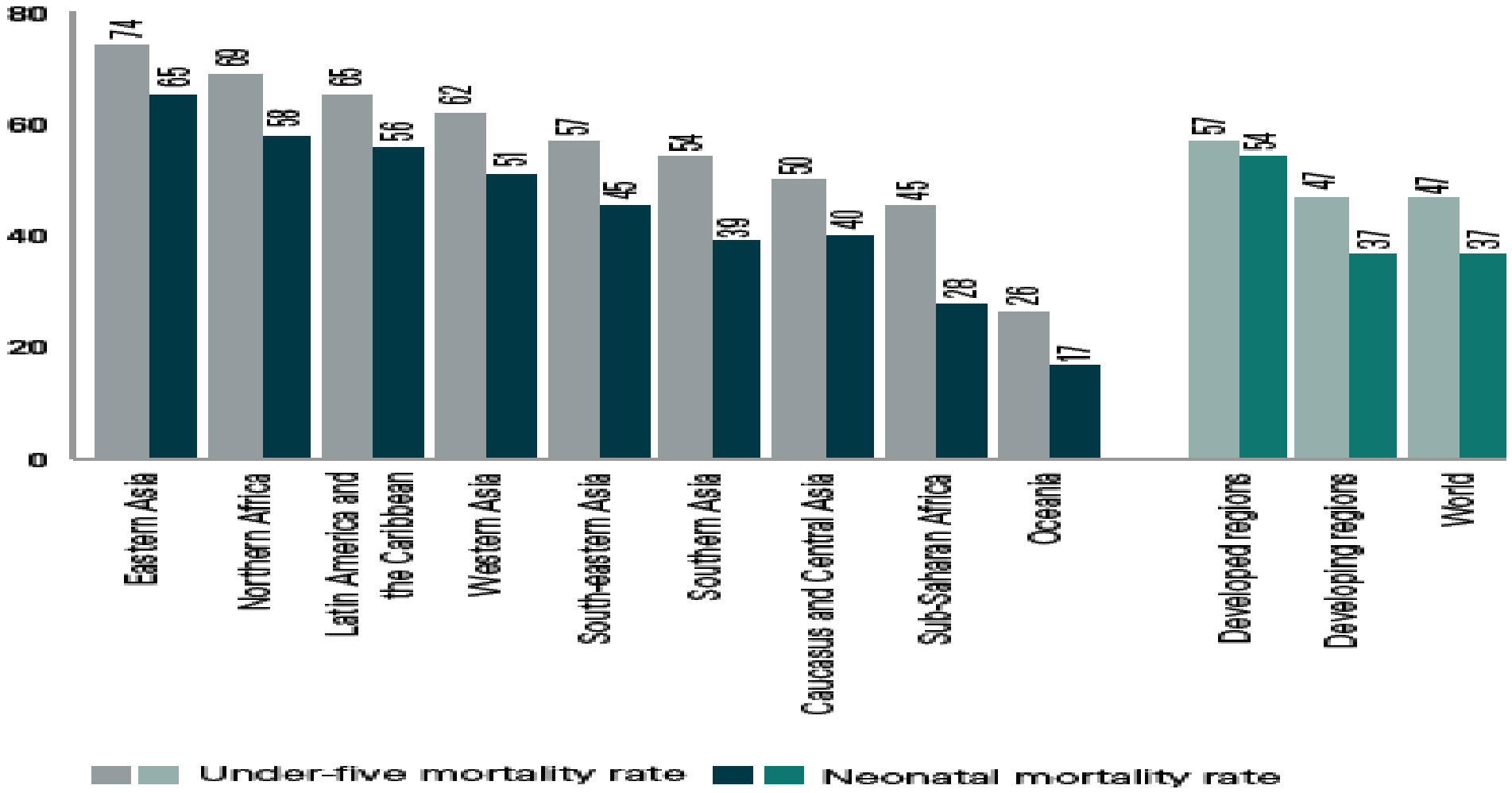
FIGURE 3

Decline in the neonatal mortality rate is slower than the decline in under-five mortality rate in all regions

Decline in under-five mortality rate and neonatal mortality rate, by Millennium Development Goal region, 1990–2012 (percent)



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Evidence-Based Decision-Making

Decision-Making Considerations

In making its recommendations, SAGE considers a variety issues

- **Disease epidemiology**
- **Clinical characteristics**
- **Vaccine and immunization characteristics**
- **Economic considerations**
- **Potential of integration with other health system opportunities**
- **Social, legal and ethical considerations**