SAGE recommendations on non-specific effects of vaccines and their implementation

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Topics

- Process of developing immunization policies
- The evolving immunization schedule
- SAGE recommendations on non-specific effects of vaccines (NSE) and related activities
- Final considerations

Immunization policies

Immunization policy advisory framework

Global

Strategic Advisory Group of Experts in Immunization (SAGE)

- Global policy recommendations & strategies
- Support regional/national challenges

Other WHO technical advisory committees

- Safety
- Standards
- Practices
- Burden assessment/ modelling

For example,

- Global Advisory Committee on Vaccine Safety (GACVS)
- Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC)

Regional

Regional Technical Advisory Group

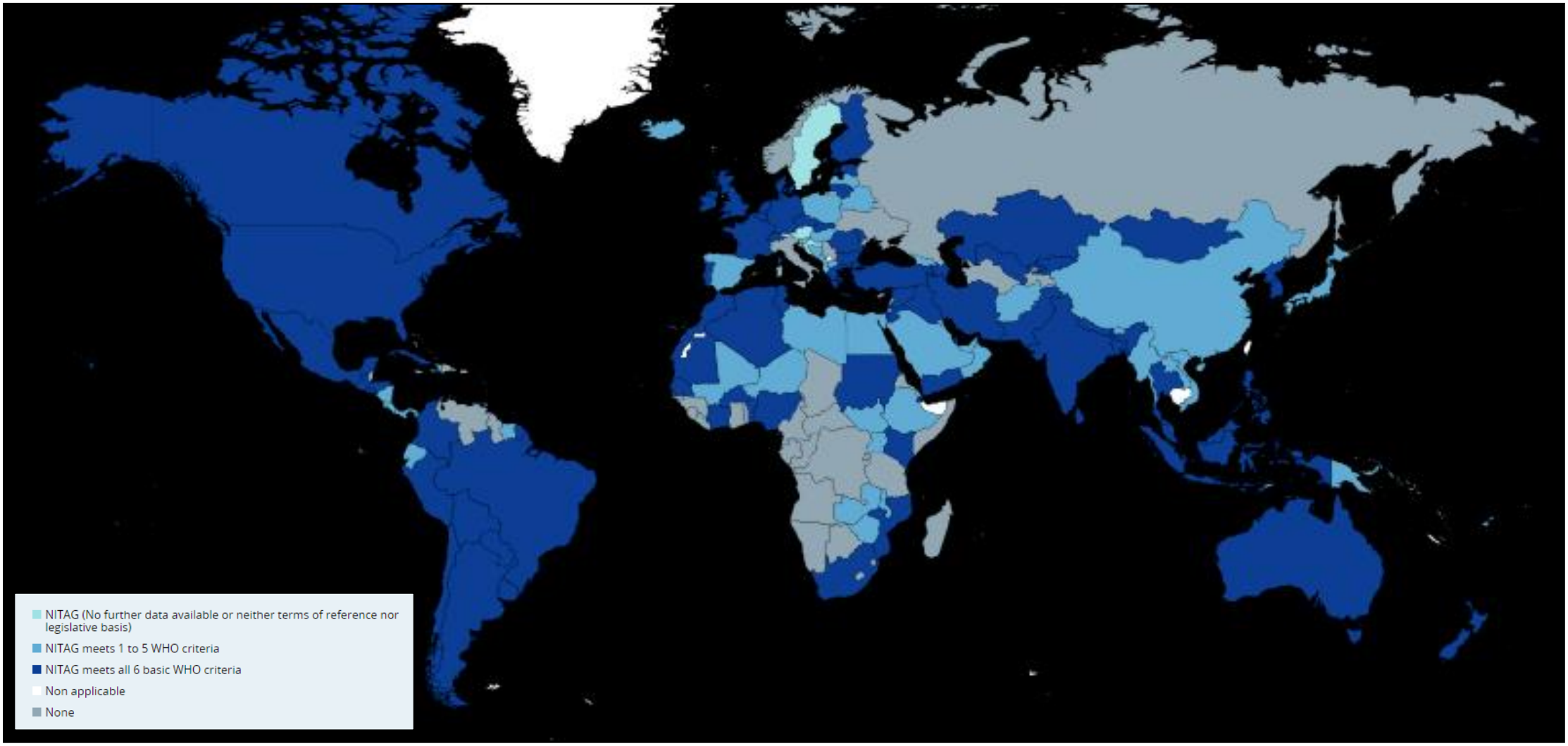
- Regional policies & strategies
- Identify & set regional priorities
- Monitor regional progress

National

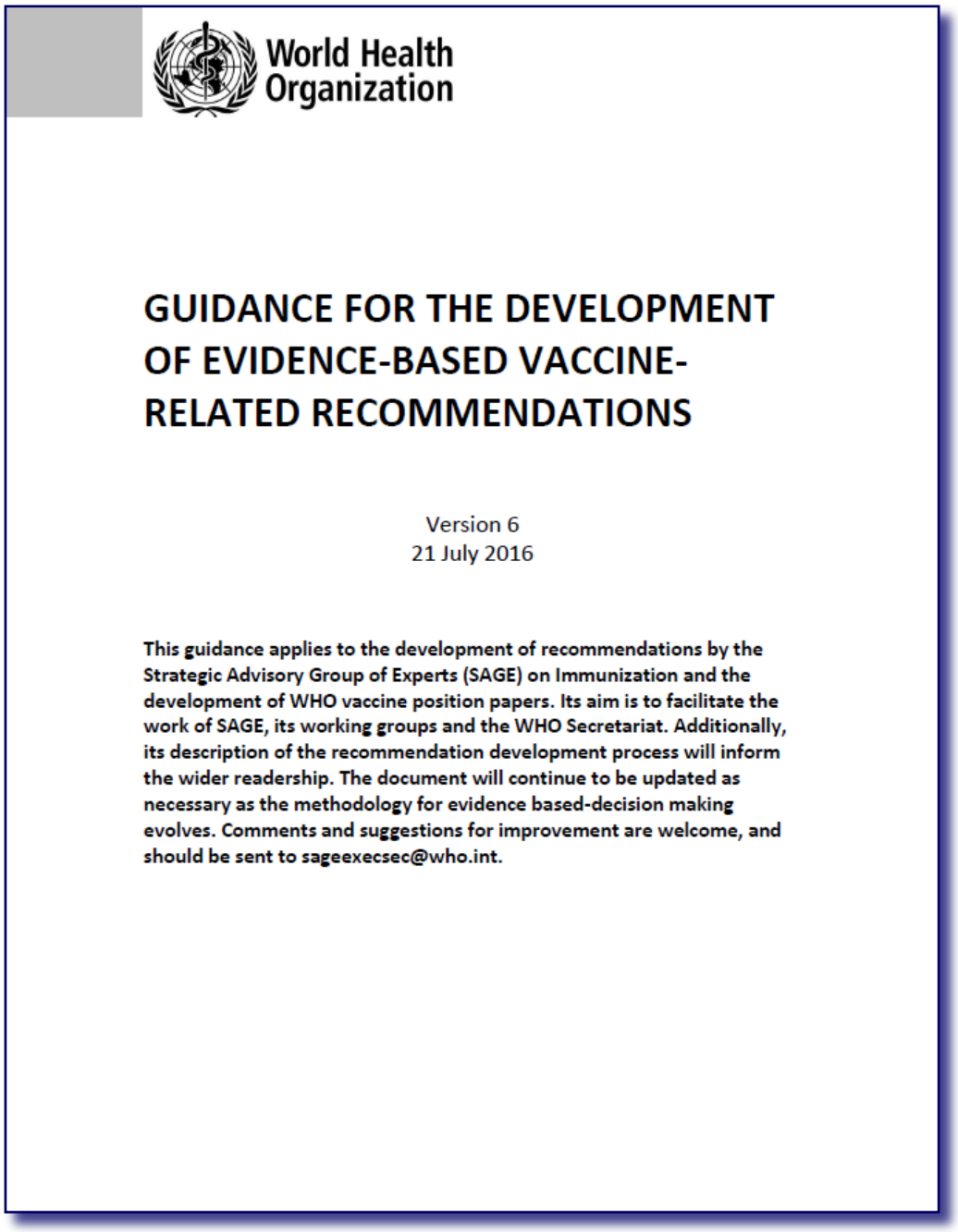
National Immunization Technical Advisory Group (NITAG)

- National policies & strategies
- Prioritize problems & define optimal solutions
- Implement national programme & monitor impact

National Immunization Technical Advisory Groups (NITAG) by WHO evaluation criteria, July 2015



Source: http://www.nitag-resource.org/ (accessed 24/08/2016)



Factors that are taken into consideration when making recommendations include:

disease epidemiology and clinical profile; benefits and harms of the options; values pertaining to the importance of the desirable and undesirable effects; equity considerations; feasibility and resource implications including economic considerations; social values and preferences, and acceptability; health-system opportunities, and interaction with other existing intervention and control strategies.

In addition to study results themselves, consideration is given to methodology and study design.

http://www.who.int/immunization/policy/sage/en/

From evidence to recommendation

1. Problem identification, terms of reference, establishment of working group
2. Definition of critical questions
3. Systematic review of literature
4. Assessment of risk of bias
5. GRADE
6. Evidence to recommendation table
7. Draft recommendations
8. Presentation to SAGE
9. SAGE discussion, deliberation and decision
10. Publication as WHO vaccine position paper

* GRADE, Grading of Recommendations: Assessment, Development and Evaluation

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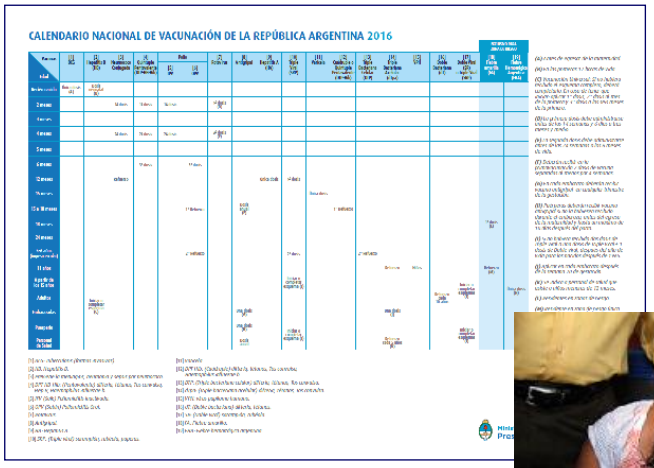
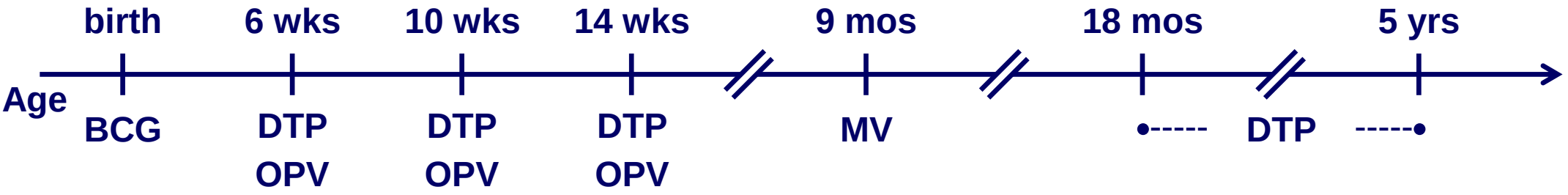

CALENDARIO NACIONAL DE VACUNACIÓN DE LA REPÚBLICA ARGENTINA 2016

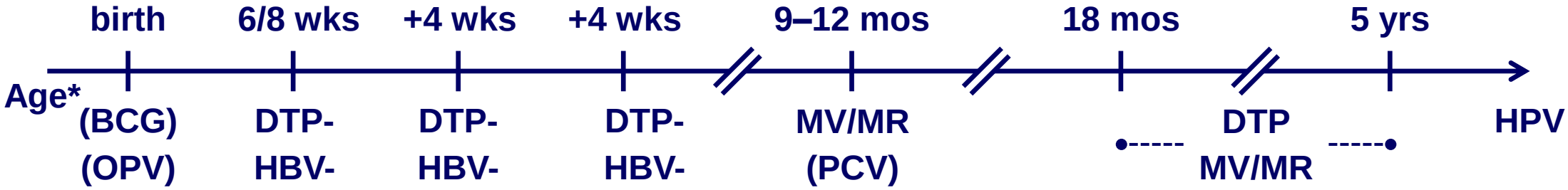
Immunization schedules

Immunization schedule, then and now

Early 1980s (6 antigens)



Current recommendations (12[13] + 12 antigens)



* Minimum ages & intervals are reported

Twelve vaccines for certain regions, high-risk populations or programmes with certain characteristics: JE, YF, tick-borne encephalitis, typhoid, cholera, meningococcal, HAV, rabies, dengue, mumps, influenza, varicella

Wks/mos/yrs: Recommended age of administration in weeks/months/years of age
Current schedule: http://www.who.int/immunization/policy/immunization_tables/en/

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Table 2: Summary of WHO Position Papers - Recommended Routine Immunizations for Children

Antigen		Age of 1st Dose	Doses in Primary Series	Interval Between Doses			Booster Dose	Considerations (see footnotes for details)
				1st to 2nd	2nd to 3rd	3rd to 4th		
Recommendations for all children								
BCG [1]		As soon as possible after birth	1					Exceptions HIV
Hepatitis B [2]	**Option 1**	As soon as possible after birth (<24h)	3	4 weeks (min) with DTP1	4 weeks (min) with DTP3			Premature and low birth weight Co-administration and combination vaccine High risk groups
	Option 2	As soon as possible after birth (<24h)	4	4 weeks (min) with DTP1	4 weeks (min) with DTP2	4 weeks (min),with DTP3		
Polio [3]	**bOPV + IPV**	6 weeks (see footnote for birth dose)	4 (IPV dose to be given with bOPV dose from 14 weeks)	4 weeks (min) with DTP2	4 weeks (min) with DTP3			bOPV birth dose Transmission and importation risk criteria
	IPV / bOPV Sequential	8 weeks (IPV 1st)	1-2 IPV 2 bOPV	4-8 weeks	4-8 weeks	4-8 weeks		
	IPV	8 weeks	3	4-8 weeks	4-8 weeks		(see footnote)	IPV booster needed for early schedule (i.e. first dose given <8 weeks)
DTP [4]		6 weeks (min)	3	4 weeks (min) - 8 weeks	4 weeks (min) - 8 weeks		1-6 years of age (see footnote)	Delayed/ interrupted schedule Combination vaccine; maternal immunization
***Haemophilus influenzae* type b** [5]	**Option 1**	6 weeks (min) 59 months (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3		(see footnote)	Single dose if >12 months of age Not recommended for children > 5 yrs Delayed/ interrupted schedule Co-administration and combination vaccine
	Option 2		2-3	8 weeks (min) if only 2 doses 4 weeks (min) if 3 doses	4 weeks (min) if 3 doses		At least 6 months (min) after last dose	
Pneumococcal (Conjugate) [6]	**Option 1**	6 weeks (min)	3	4 weeks (min)	4 weeks		(see footnote)	Vaccine options Initiate before 6 months of age Co-administration HIV+ and preterm neonates booster
	Option 2	6 weeks (min)	2	8 weeks (min)			9-15 months	
Rotavirus [7]	**Rotarix**	6 weeks (min) with DTP1	2	4 weeks (min) with DTP2				Vaccine options Not recommended if > 24 months old
	Rota Teq	6 weeks (min) with DTP1	3	4 weeks (min) - 10 weeks with DTP2	4 weeks (min) with DTP3			
Measles [8]		9 or 12 months (6 months min, see footnote)	2	4 weeks (min) (see footnote)				Combination vaccine; HIV early vaccination; Pregnancy
Rubella [9]		9 or 12 months with measles containing vaccine	1					Achieve and sustain 80% coverage Combination vaccine and Co-administration; Pregnancy
HPV [10]		As soon as possible from 9 years of age (females only)	2	6 months (min 5 months)				Target 9-13 year old girls Pregnancy Older age ≥ 15 years 3 doses HIV and immunocompromised

Refer to http://www.who.int/immunization/documents/positionpapers/ for table & position paper updates.

This table summarizes the WHO vaccination recommendations for children.The ages/intervals cited are for the development of country specific schedules and are not for health workers.

National schedules should be based on local epidemiologic, programmatic, resource & policy considerations. While vaccines are universally recommended, some children may have contraindications to particular vaccines.

Recommended immunization schedule for vaccine against *Haemophilus influenzae* type b

Antigen	Age of 1st dose	Doses in primary series	Interval between doses		Booster dose
			1st to 2nd	2nd to 3rd	
Hib	6 wks (min) 59 mts (max)				
3+0		3	4 wks (min) w/ DTP2	4 wks (min) w/ DTP3	
2+1, 3+1		2	8 wks (min) if 2 doses		>6 months (min) after last dose
		3	4 wks (min) if 3 doses	4 wks (min) if 3 doses	

Wks, weeks; mts, months
Source: http://www.who.int/immunization/policy/immunization_tables/en/

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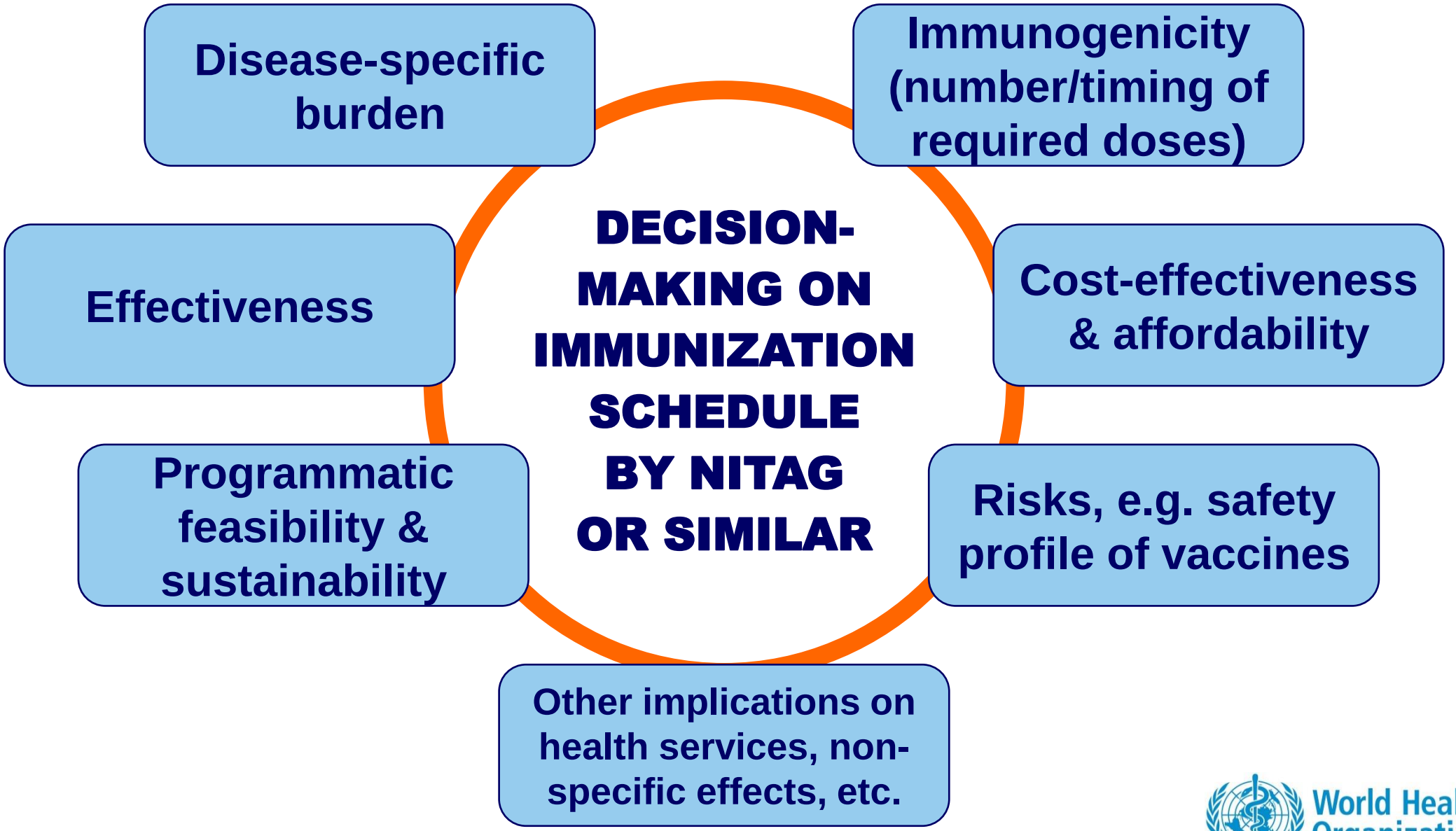
Some criteria considered in decision-making on a national immunization schedule



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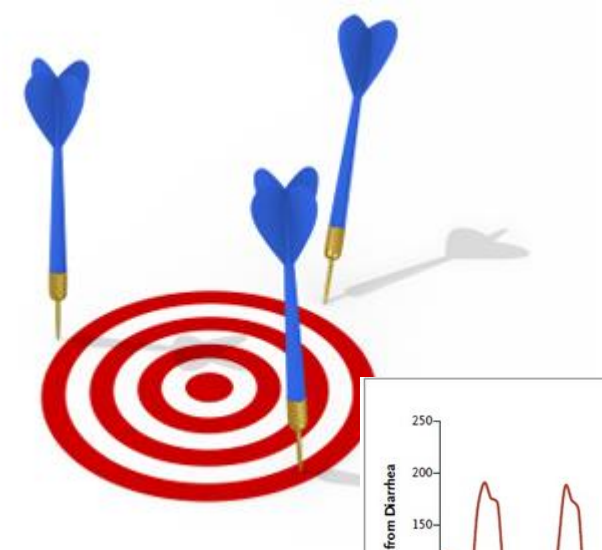

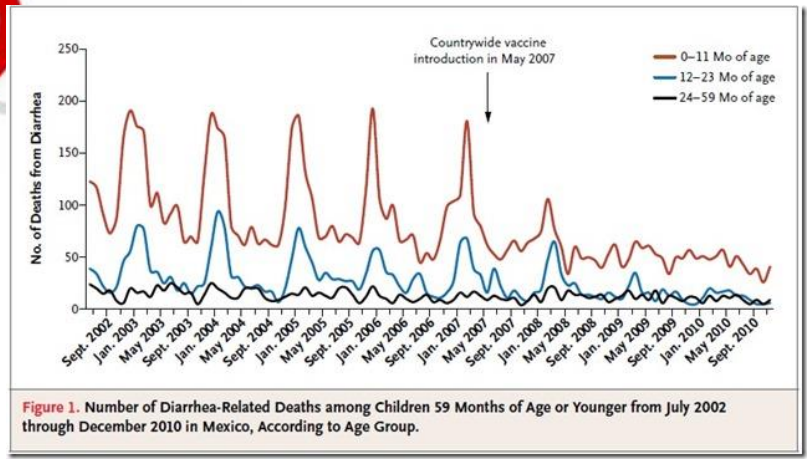

Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through December 2010 in Mexico, According to Age Group.

Non-specific effects of vaccines

Actions and recommendations on NSE October 2012–April 2014

Oct 2012	Nov 2012–Mar 2013	Apr 2013	Apr 2013–Mar 2014	Apr 2014
SAGE requested NSE to be discussed	Scope and review questions outlined Protocols and tools drafted SAGE working groups (WG) established	SAGE reviewed protocols of epidemiologic and immunologic systematic reviews, and stressed primary task of WG to review effects on childhood mortality by BCG/DTP/MV	Systematic reviews carried out They included quality and bias checks and GRADE conclusions Final reports submitted to SAGE	SAGE meeting…

Actions and recommendations on NSE April 2014–August 2016

Apr 2014	Sept 2015	Feb 2015	Jun 2015	Jul 2015–Aug 2016
Based on systematic reviews, SAGE concluded that evidence did not support schedules changes, but recommended IVIR-AC to outline research questions and study designs	IVIR-AC echoed SAGE proposition for high-quality prospective studies to address policy relevant questions and with immunologic analyses (nested)	Ad-hoc expert group on immunological convened at Oxford University It identified opportunities to define immunologic effect mechanisms in interventional studies	IVIR-AC re-iterated SAGE conclusions that further observational studies are unlikely to inform policy It emphasised importance of randomized trial, w/ nested immunologic studies	Research questions systematized and prioritized IVIR-AC assessed progress in June 2016 Ongoing work by ad-hoc expert group on clinical trials

SAGE specific conclusions, April 2014

- BCG
  - SAGE concluded that the evidence does not support a change in policy for BCG immunization
  - Current WHO recommended schedule has a beneficial effect on all-cause mortality and this should be emphasized
- Measles-containing vaccines
  - SAGE concluded that the evidence does not support a change in policy for measles vaccine
  - Current WHO recommended schedule for current standard titre measles-containing vaccine has a beneficial effect on all-cause mortality in children
- DTP
  - SAGE concluded that the evidence does not support a change in policy for DTP and emphasized the benefit of DTP in preventing disease and the importance of the current recommendation

Wkly Epimiol Rep 2014, 89:233–235

SAGE recommendations, April 2014

- NSEs on all-cause mortality warrant further research
- IVIR-AC should
  - Advise on priority research questions to inform policy decisions and on study designs to answer them
  - Assess use of high quality randomized controlled trials where feasible, with sufficient power to explore sex differences and a priori defined and standardized immunological endpoints
- Future research should draw on a broad investigator pool and from a wide range of geographic locations using standardized protocols
- Additional observational studies are unlikely to contribute to policy decision-making and therefore should not be encouraged

Wkly Epimiol Rep 2014, 89:233–235

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Weekly epidemiological record
Relevé épidémiologique hebdomadai

19 AUGUST 2016, 91th YEAR / 19 AOÛT 2016, 91e ANNÉE
No 33, 2016, 91, 389–396
http://www.who.int/wer

Contents

Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC): summary of conclusions and recommendations, 30 May – 1 June 2016 meeting

1. **Reaffirmed importance of clinical trials and acknowledged progress made**
2. **Endorsed design of one or more protocols**
3. **Will continue to guide and review future work**

Session 2: Non-specific effects (NSEs) of vaccines

Introduction

The IVIR-AC meeting in 2015 emphasized the importance of randomized trials within nested immunological studies. The Committee considered priority questions for NSE clinical trials, including trial designs for each priority question, as proposed by the participants of an ad-hoc consultation in February 2016.

Recommendations

- IVIR-AC considered the conclusion of the IVIR-AC meetings in 2014 and 2015[2] that further observational studies are unlikely to inform public health decision-making, thus reaffirming the importance of randomized clinical trials. The Committee acknowledged the progress made towards the refinement of priority research questions and trial designs resulting from the ad-hoc expert consultation, and also recommended that any trial design proposed should have its own rationale.
- IVIR-AC endorsed the designing of one or more protocols to assess the prospective non-specific effects of immunization on mortality. The work of the WHO Secretariat needs to be completed in preparing the protocols for the questions identified and trials outlined during the ad-hoc expert consultation of February 2016. These generic protocols would enable harmonized implementation of the trials across multiple settings. While further development of all the proposed trial designs is important, IVIR-AC recognizes that full evaluation necessitates a complete protocol. IVIR-AC will help inform decisions on feasibility and the selection of designs, and formulate questions.
- IVIR-AC members will continue to guide future WHO consultations, and review and comment on the protocols while being developed.

Wkly Epimiol Rep 2016, 91:390–391

Next steps

- Continue work on research questions and design of related clinical trials (generic protocols)
- Submit to IVIR-AC for advice on the pertinence of proposed approach
- Seek comments from research community
- Consolidate feedback and adjust under IVIR-AC guidance
- Share with SAGE

Final considerations

- Established process for decision-making on immunization policies
- Clear SAGE and IVIR-AC recommendations on what evidence is needed on NSE
- WHO Secretariat is working with a broad group of experts to draft generic protocols for potential clinical trials

Thank you

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