World Health Organization

15 Mar. 2016

Malaria Policy Advisory Committee (MPAC) Draft Meeting Agenda

Dates: 16-17 March 2016. Location: Salle A, WHO HQ, Geneva

Wednesday, 16 March 2016

Time	Session	Purpose	Type
9.00 am 10:00 am	Session 1: Welcome from Chair, MPAC *(K Marsh)* Report from the Director, GMP *(P Alonso)*	For information For information	open
10.30 am	**coffee**		
11.00 am 11:30 pm	Session 2: Update on RTS,S vaccine *(A. Bosman and V. Moorthy)* New WHO guidelines for iron supplementation/Presentation *(M.P. Solon)*	For information For information	open
12.15 pm	**lunch**		
1.15 pm 2.30 pm	Session 3: Drug Efficacy and Response Technical Expert Group/Presentation *(P. Ringwald)* Update on establishment of WHO advisory group on malaria eradication *(P. Alonso)*	Decision point (TBD) For information	open
3.00 pm	**coffee**		
3.30 pm 5.00 pm	Session 4: Working groups Conclusions of working groups	For information For discussion	open
5.30 pm	**End of day/ cocktail reception**		

Report from the Global Malaria Programme

Dr Pedro L. Alonso, Director

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

World Health Organization

Vision, goals, milestones and targets

Vision: A world free of malaria			
Goals	**Milestones**		**Targets**
	2020	**2025**	**2030**
1. Reduce malaria mortality rates globally compared with 2015	≥40%	≥75%	≥90%
2. Reduce malaria case incidence globally compared with 2015	≥40%	≥75%	≥90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

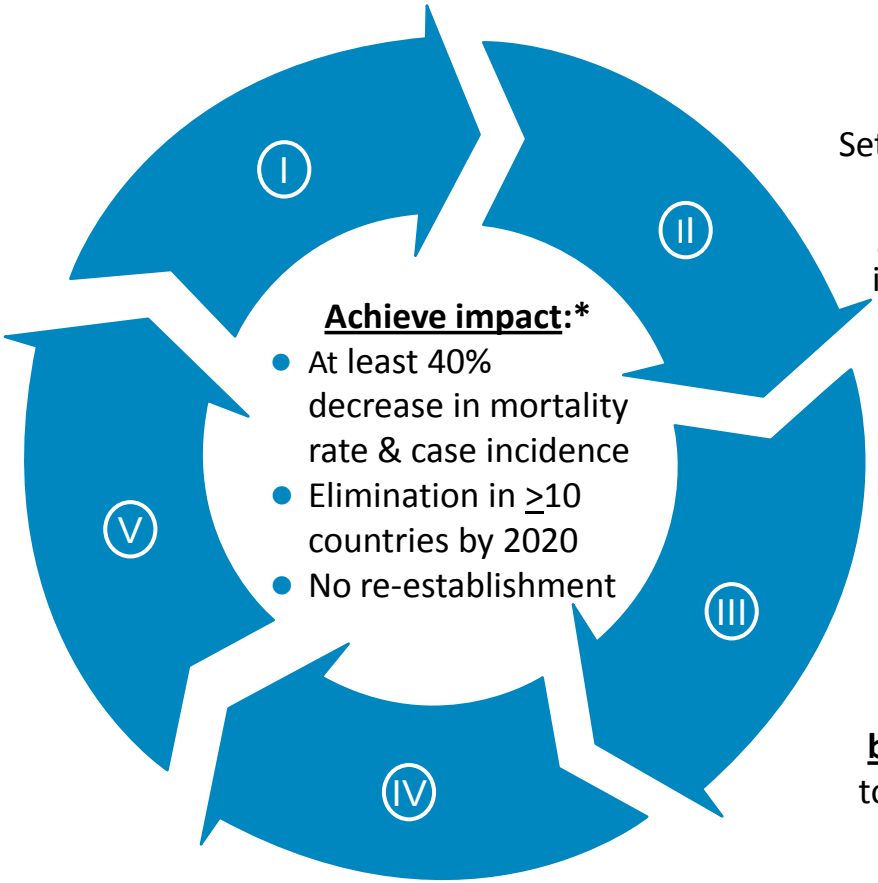
GMP strategy - core roles

I

In collaboration with the malaria community, address key **strategic questions** related to malaria control and elimination

II

Set, communicate & disseminate evidence-based **normative guidance**, policy advice and implementation guidance to support country action



III

Coordinate WHO **capacity building & technical support** to member states, jointly with Regions, ISTs and countries

V

Keep an **independent score** of global progress in malaria control and elimination, including **drug & insecticide resistance**

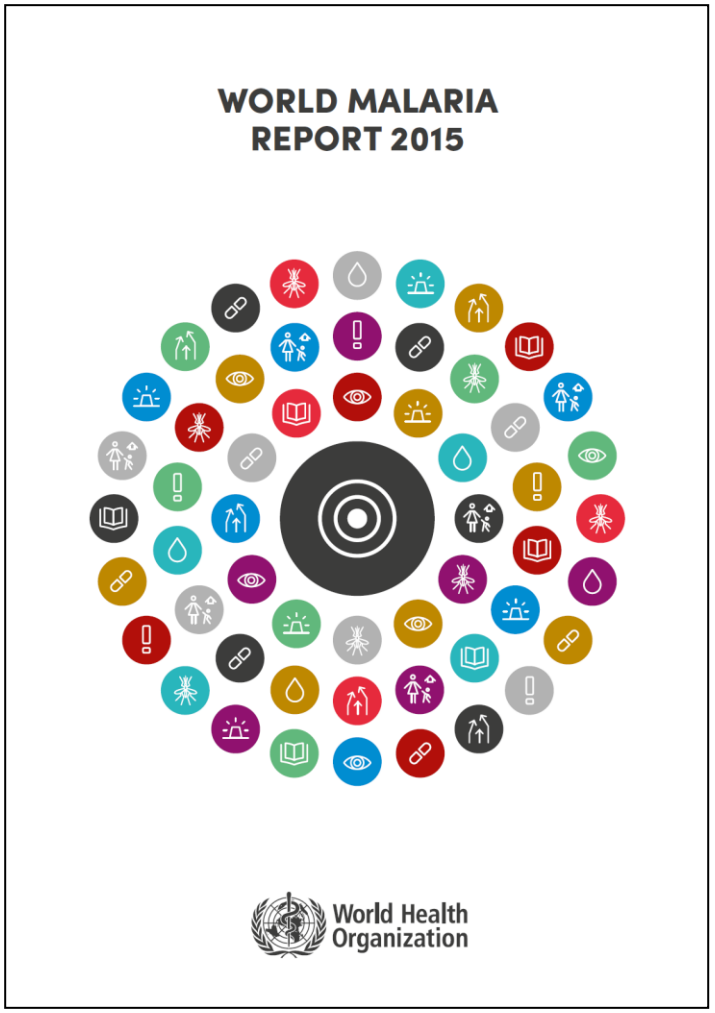
IV

Help countries develop & implement robust **surveillance** systems to generate quality data and use that data to achieve greater impact

* Global Technical Strategy objectives for 2020

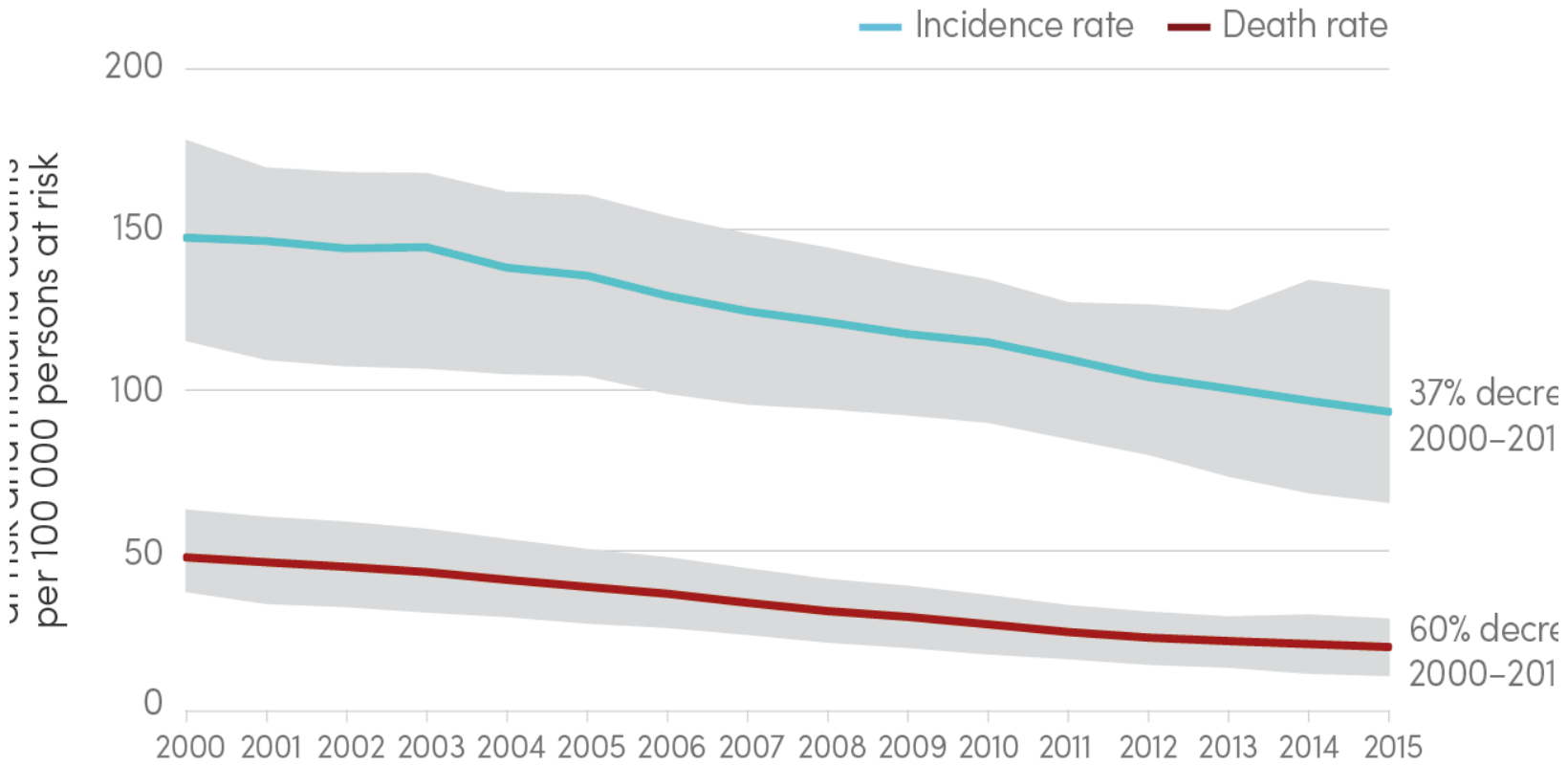
Keeping an independent score: global progress

- Launched at the European Parliament in Brussels on 9 December 2015
- Topics covered include: trends in infection prevealence, case incidence and mortality rates, coverage of key interventions, costs of malaria control and costs savings, remaining and emerging challenges.



Global trends in malaria incidence and mortality

imated malaria case incidence and death rate globally, 2000–2015



Source: WHO estimates

Reductions in malaria cases and deaths 2000–2015

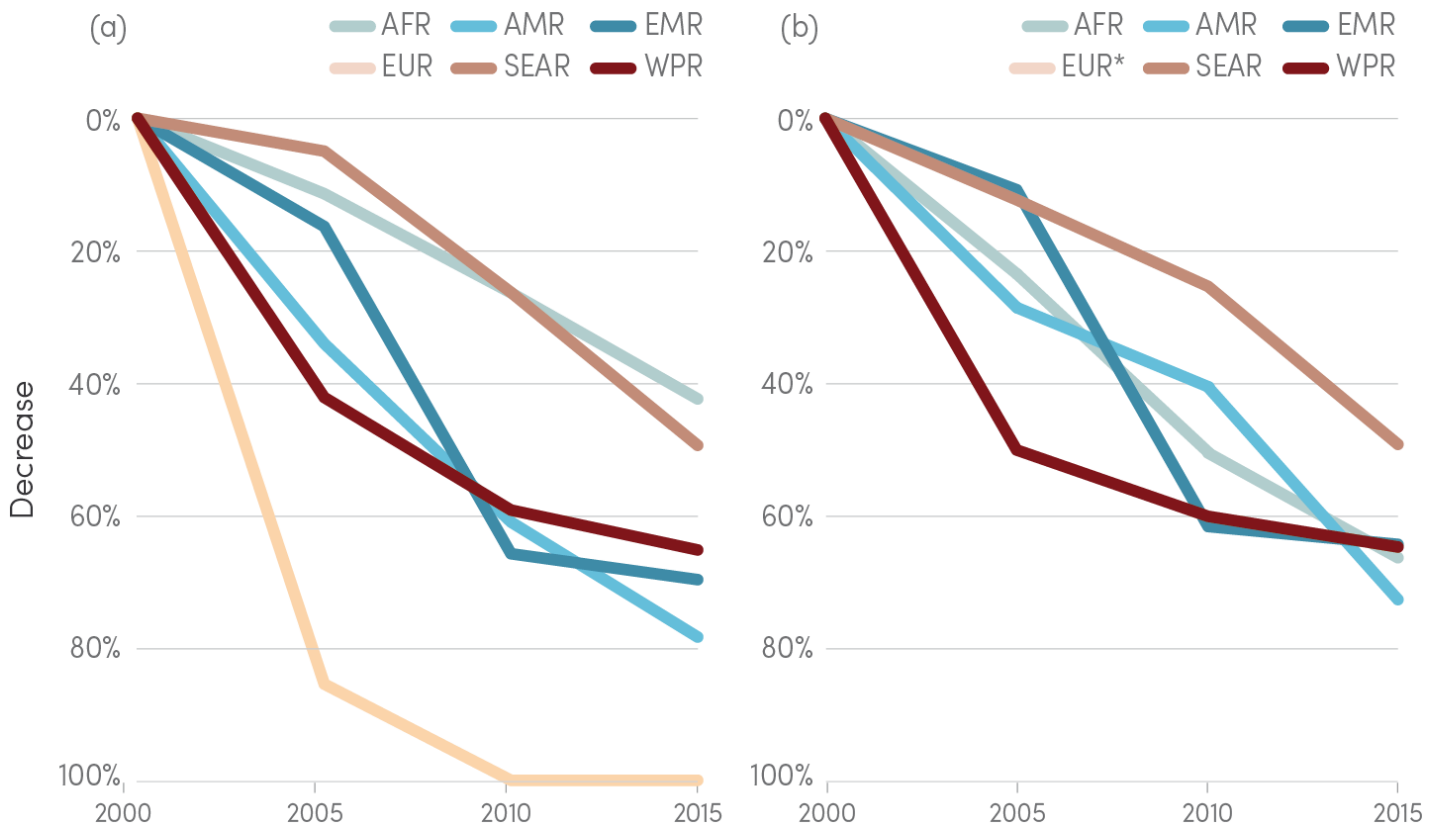
	Estimated number of malaria cases (000's)				Change	Estimated number of malaria deaths				Change
WHO region	**2000**	**2005**	**2010**	**2015**	**2000–2015**	**2000**	**2005**	**2010**	**2015**	**2000–2015**
African	214 000	217 000	209 000	188 000	-12%	764 000	670 000	499 000	395 000	-48%
Americas	2 500	1 800	1 100	660	-74%	1 600	1 200	1 100	500	-69%
Eastern Mediterranean	9 100	8 600	4 000	3 900	-57%	15 000	15 000	7 000	6 800	-51%
European*	36	5.6	0.2	0	-100%	0	0	0	0	
South-East Asia	33 000	34 000	28 000	20 000	-39%	51 000	48 000	44 000	32 000	-37%
Western Pacific	3 700	2 300	1 700	1 500	-59%	8 100	4 200	3 500	3 200	-60%
World	**262 000**	**264 000**	**243 000**	**214 000**	**-18%**	**839 000**	**738 000**	**554 000**	**438 000**	**-48%**
Lower bound	205 000	203 000	190 000	149 000		653 000	522 000	362 000	236 000	
Upper bound	316 000	313 000	285 000	303 000		1 099 000	961 000	741 000	635 000	

* There were no recorded deaths among indigenous cases in WHO European Region for the years shown.

Source: *WHO estimates*

Regional trends in malaria incidence and mortality

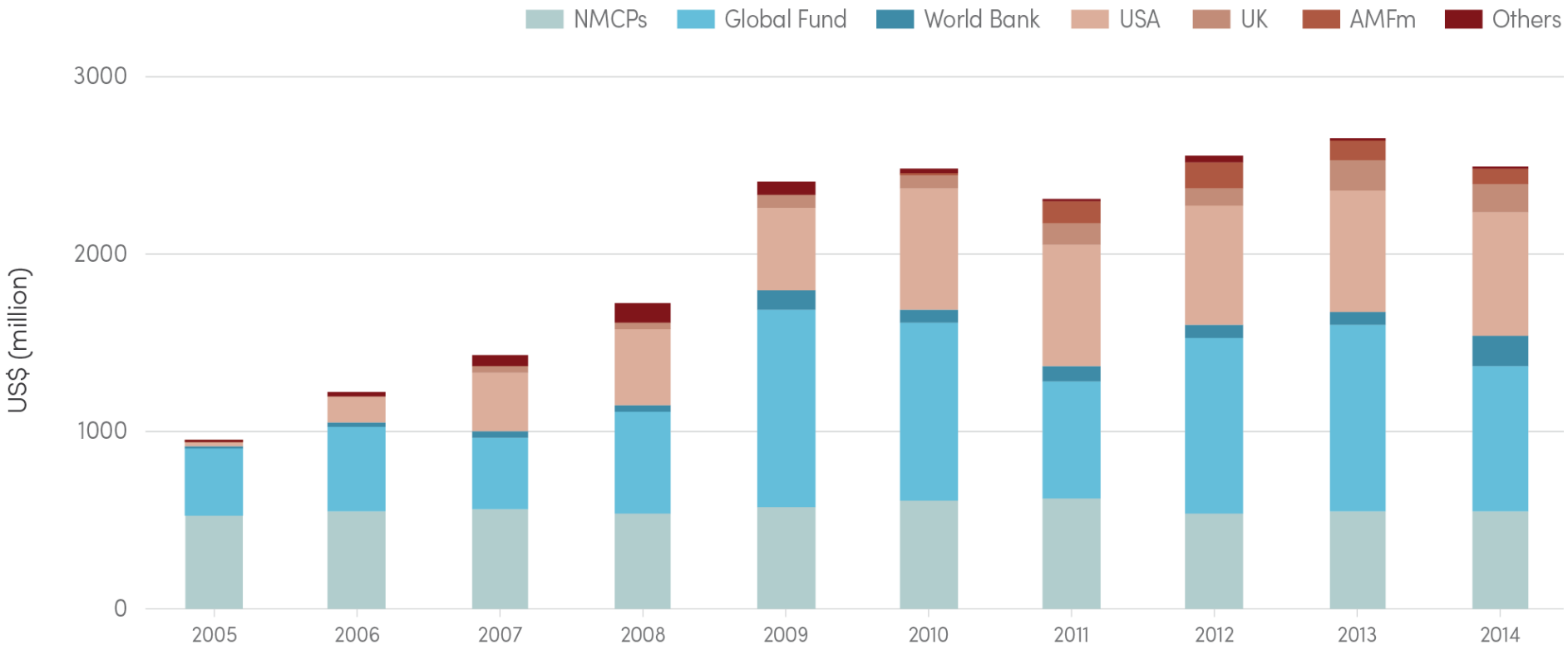
Percentage decrease in (a) estimated malaria case incidence and (b) malaria death rate, by WHO region, 2000–2015



Source: WHO estimates

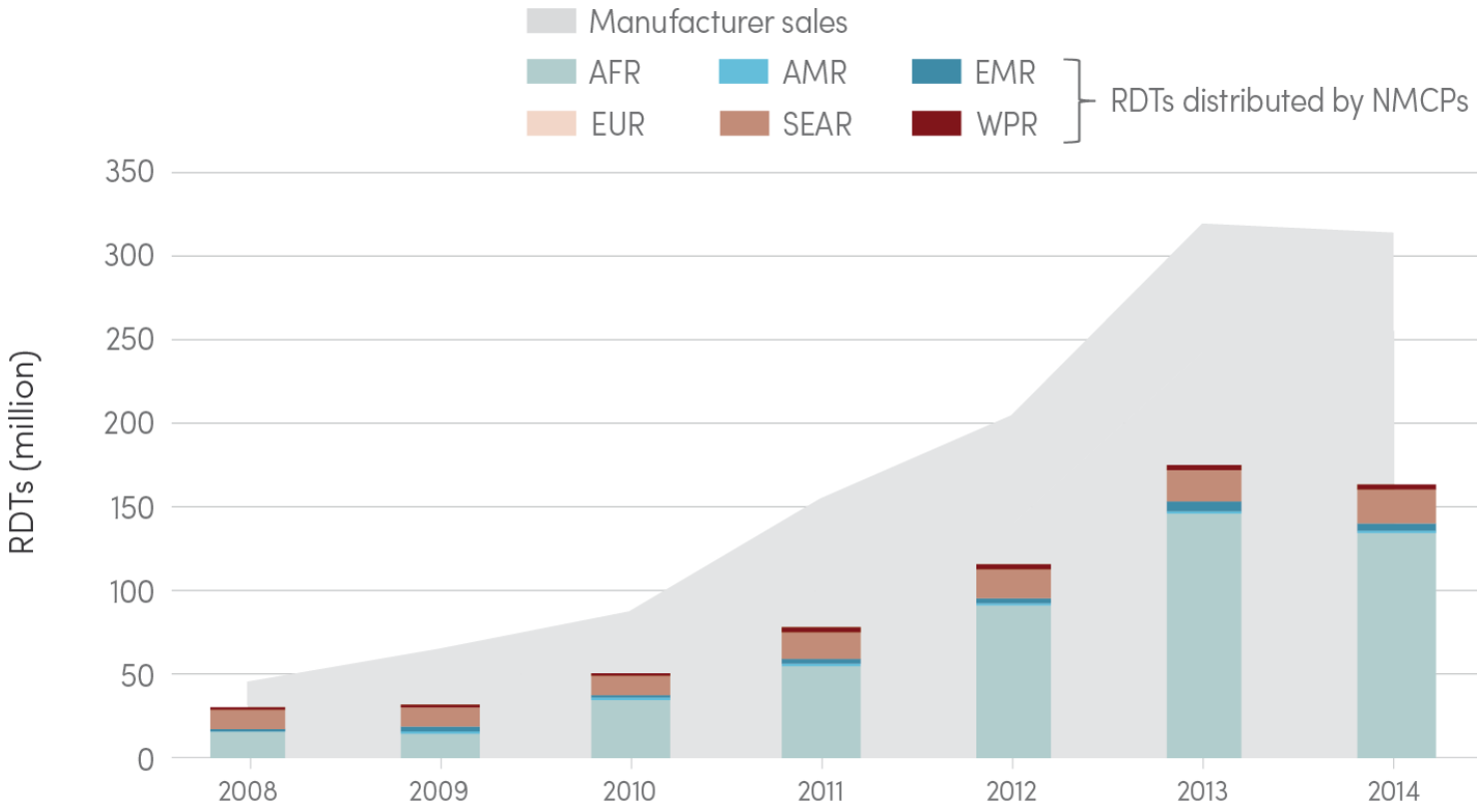
Global trends in financing by funding source

Investments in malaria control activities by funding source, 2005–2014



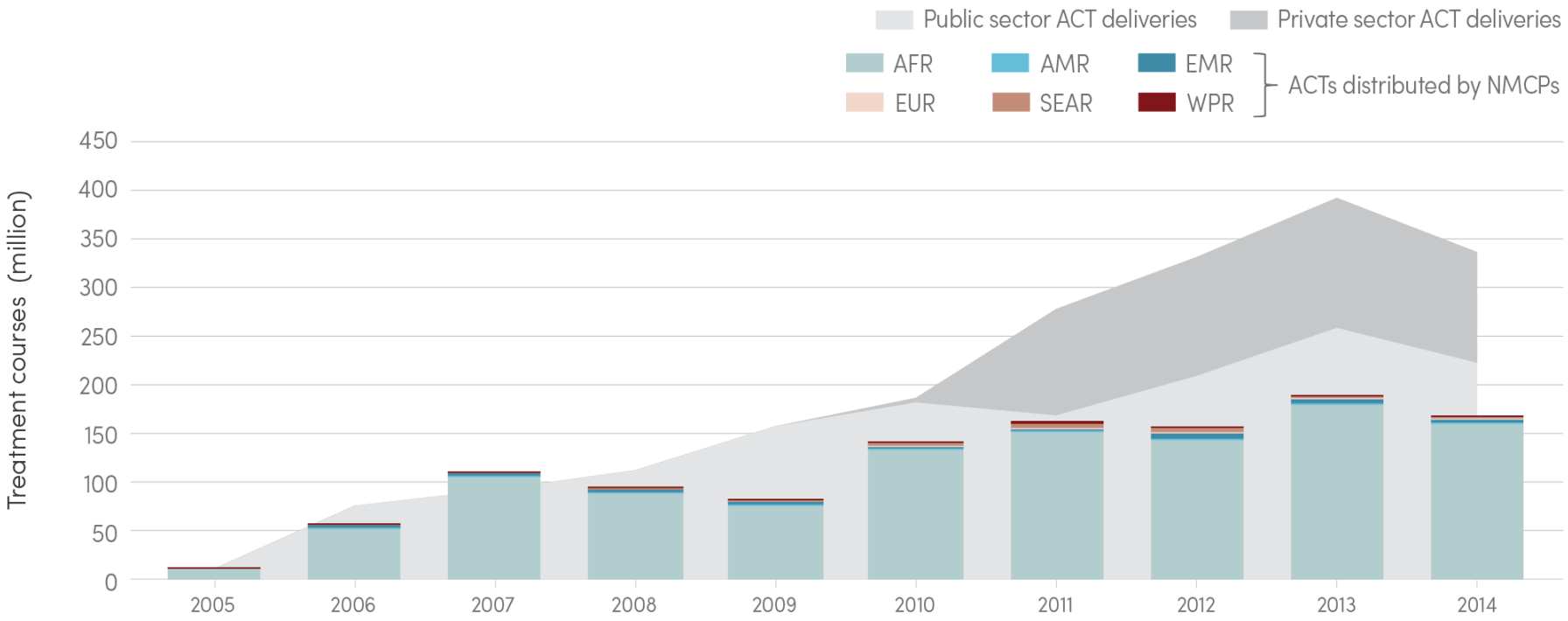
RDTs procured and distributed by region

Number of RDTs sold by manufacturers and distributed by NMCPs, by WHO region, 2005–2014

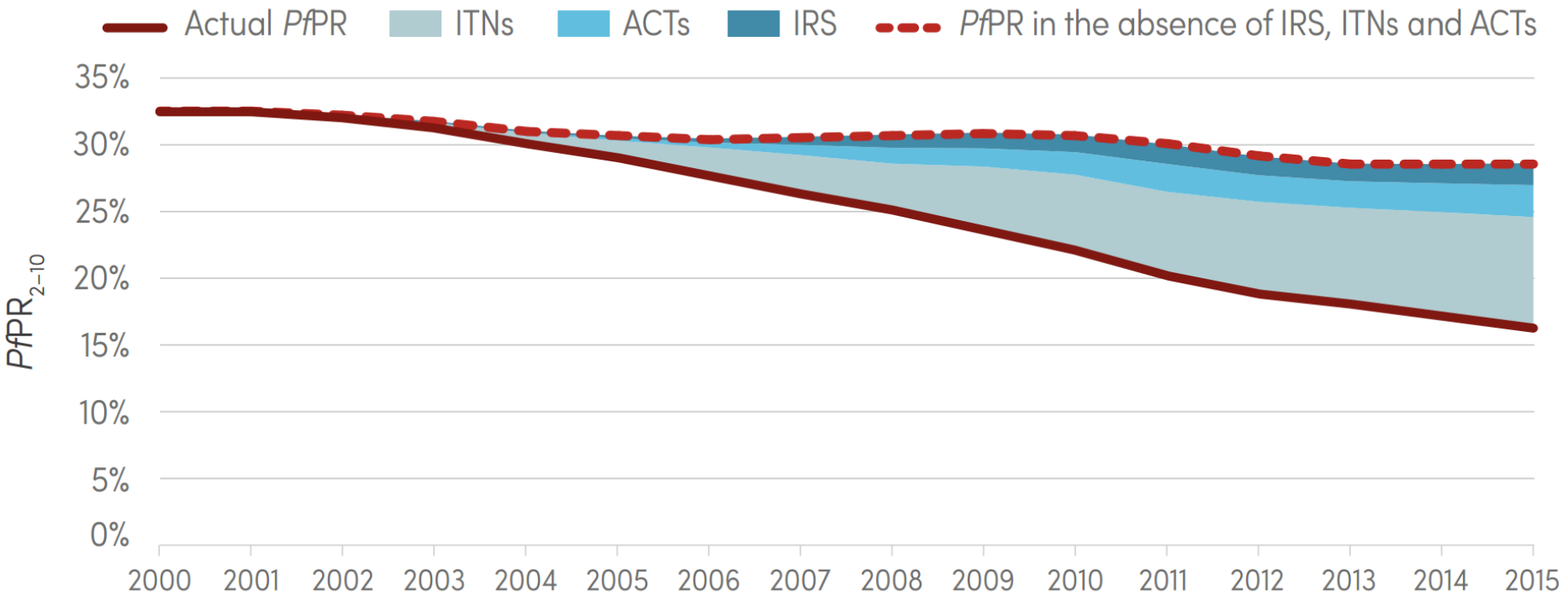


ACTs procured and distributed by region

Number of ACT treatment courses distributed by NMCPs, by WHO region, and ACT treatment courses delivered by manufacturers to the public and private* sector, 2005–2014

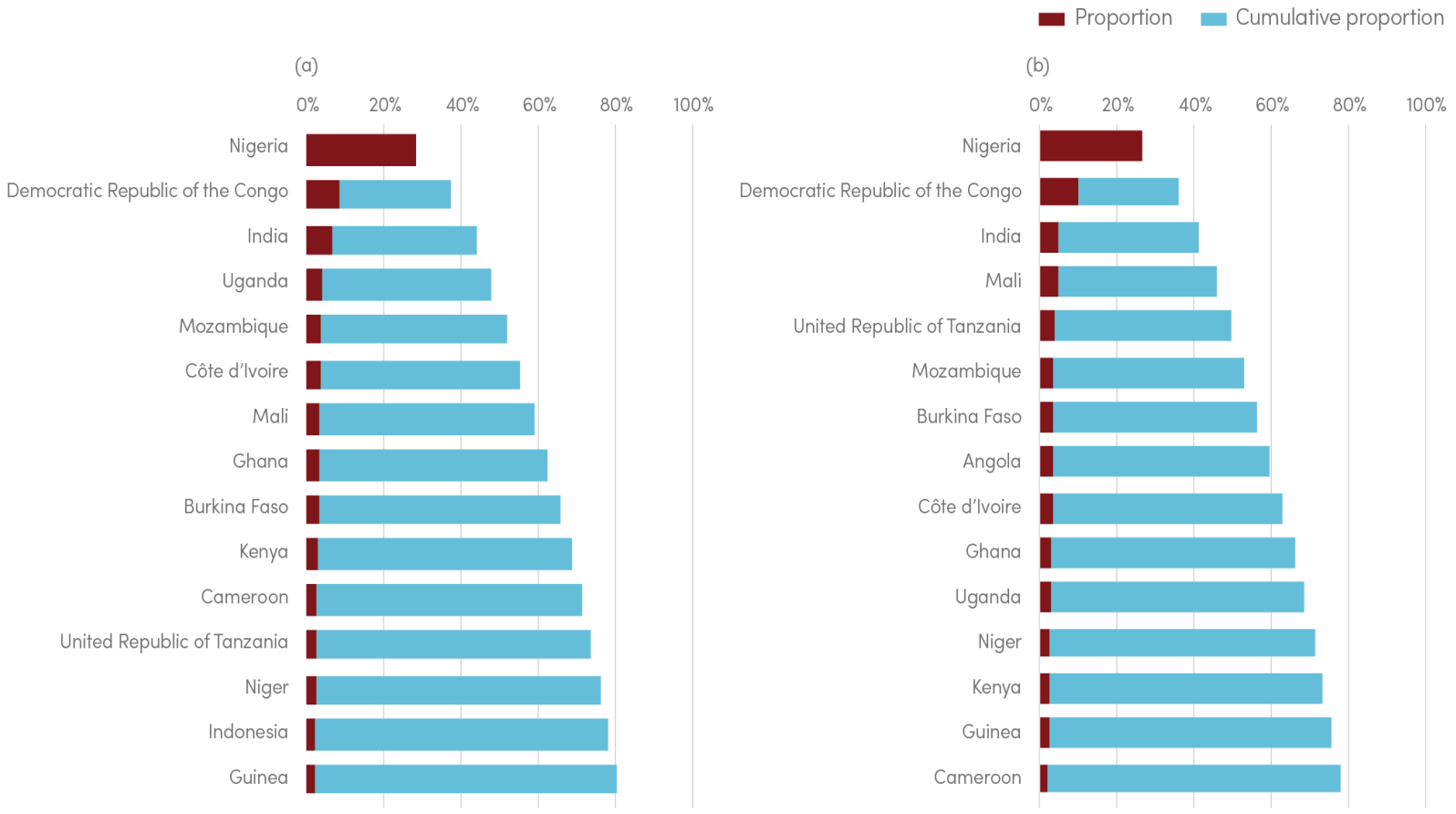


Relative impact of the different core malaria interventions



Continuing disease burden

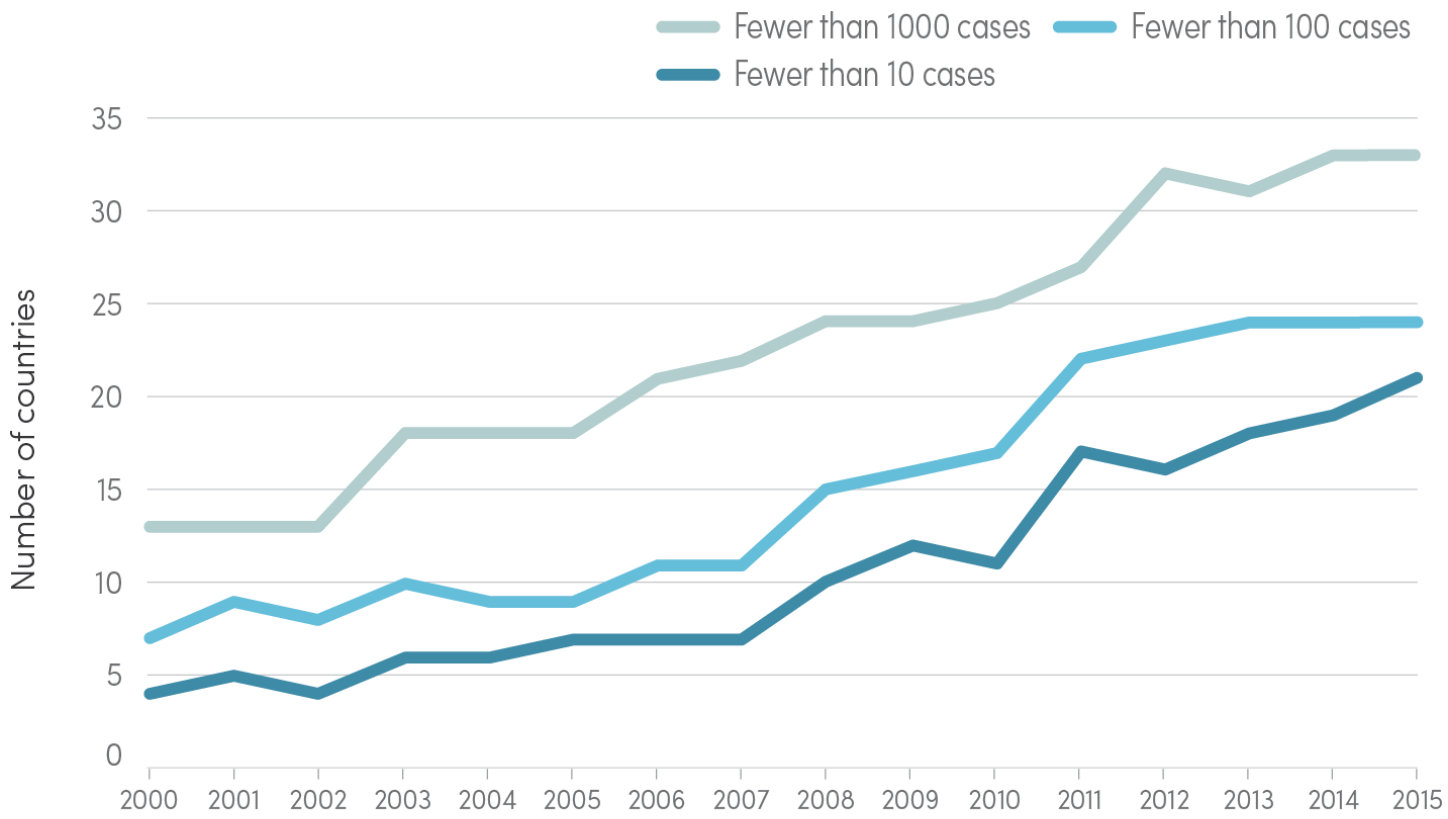
Estimated proportion, and cumulative proportion, of the global number of (a) malaria cases and (b) malaria deaths in 2015 for countries accounting for the highest share of the malaria disease burden



Source: WHO estimates

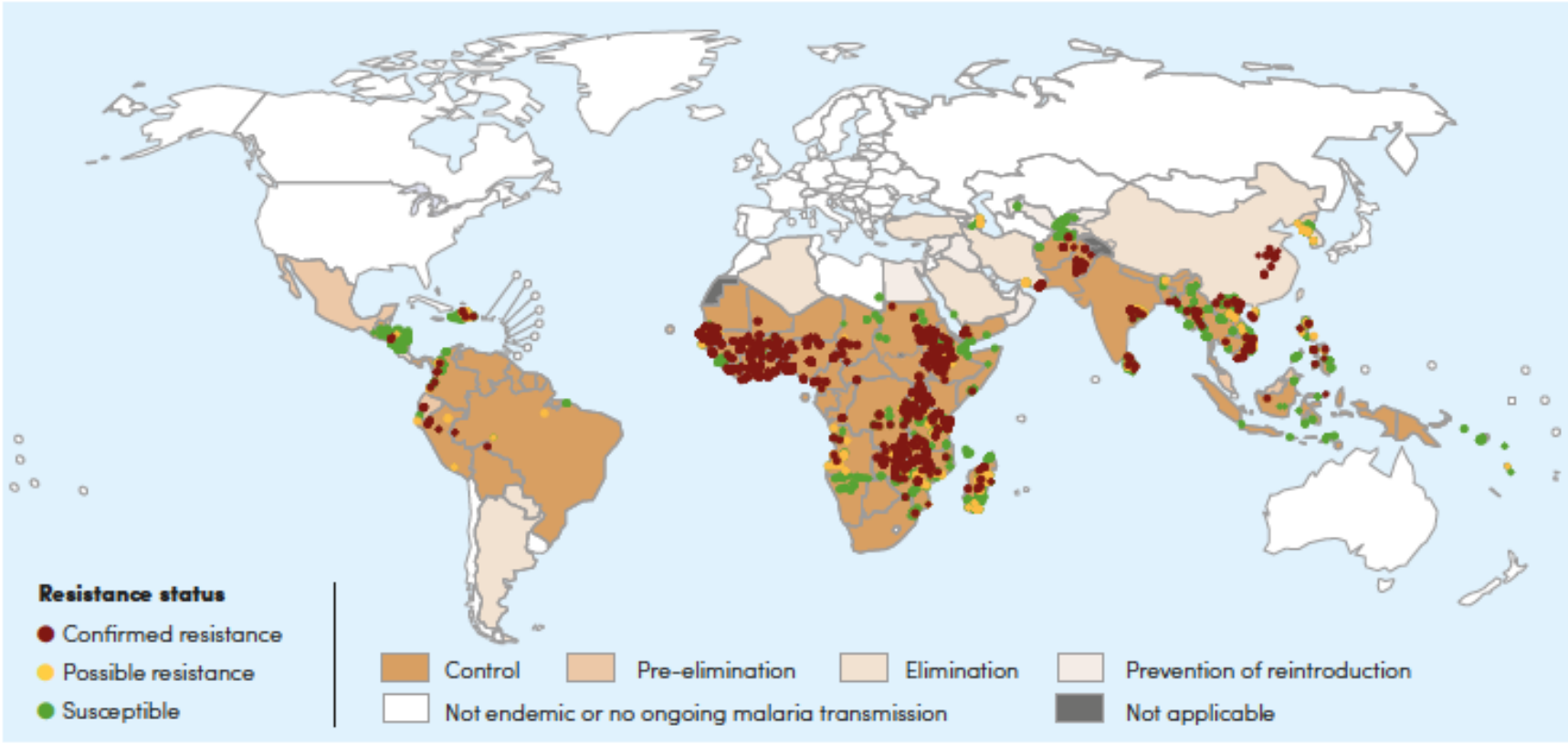
Country-level trends in malaria incidence

Number of countries with fewer than 1000, 100 and 10 cases, 2000–2015



Source: WHO estimates

Reported pyrethroid resistance status of malaria vectors, measured with insecticide bioassays since 2010



Data shown are for standard bioassays. Where multiple insecticide classes or types, mosquito species or time points were tested, the highest resistance status is shown.

Source: *National malaria control programme reports, African Network for Vector Resistance, Malaria Atlas Project, President's Malaria Initiative (United States), scientific publications.*

P. falciparum resistance to artemisinins has been detected in five countries in the Greater Mekong subregion. Chloroquine resistance in *P. vivax* has been confirmed in 10 countries

Further updates & new initiatives

Update on Roll Back Malaria Partnership

- RBM is currently operating under a Transition Support Team co-chaired by the Minister Parirenyatwa and Admiral Tim Ziemer
- Board Selection Committee appointed to select diverse members from the wide malaria community and related multisectoral communities including government, civil society, NGOs, private sector, donors, research and academia and representatives from affected countries.
- It should specifically include at least 7 members nominated by the affected countries
- Current Board members have until Tuesday to vote for or against the proposed Board, which is expected to meet four times per year

Normative function: recent WHO / GMP products

- Training module on malaria elimination – Feb 2016
- Malaria microscopy quality assurance manual (2) – Jan 2016
- A WHO external quality assurance scheme for malaria nucleic acid amplification testing. Meeting report – Dec 2015
- Conditions for use of LLINs treated with a pyrethroid and piperonyl butoxide – Dec 2015
- Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests – Dec 2015
- Results of WHO product testing of malaria RDTs: Round 6 (2014-2015) – Dec 2015
- Procedures for product testing and lot testing. Information for RDT manufacturers and procurers – Dec 2015
- Recommendations on intermittent screening and treatment in pregnancy and the safety of ACTs in the 1st trimester – Dec 2015
- Recommendations on the role of MDA, MSAT and FSAT for malaria – Nov 2015
- Information note on the risks associated with the scale back of vector control in areas where transmission has been reduced – Nov 2015
- Update on artemisinin and ACT resistance – Sept 2015
- Achieving the malaria MDG target: reversing the incidence of malaria 2000 – 2015 – Sept 2015

Implementation guidance to support country action

In SEARO

- WHO staff
- NMCP Managers and key staff
- Regional / national experts

To be done in other Regions

Inter- country Meeting on Cross-Border Collaboration to
Eliminate Malaria in South Asia
WHO Regional Office for South-East Asia
New Delhi, India
12-13 February 2016

World Health Organization
Regional Office for South-East Asia

Changing procurement criteria for RDTs to PQ

- WHO is harmonising internal systems and strengthening its prequalification programme for diagnostics, medicines, vaccines and insecticides for public health use.
- The product testing programme of malaria RDTs, managed by WHO/FIND/CDC Atlanta is the laboratory evaluation component of WHO prequalification of mRDTs.
- WHO prequalification, in addition to product testing, requires review of product dossier and inspection of manufacturing site(s).
- WHO is now considering a shift from product testing to prequalification as a requirement for procurement.
- The transition plan and risk assessment are under internal WHO discussion - a detailed presentation on this will follow.

Rectal artesunate (RAS)

- Recommended by WHO for pre-referral treatment of severe malaria since 2006 in Malaria Treatment Guidelines
- No quality product on the market – Mepha handover to Acino, which suspended production in 2016
- Strides & Cipla with support from MMV have submitted dossiers to WHO Prequalification in Dec 2015 (possible approval in 2016?)
- In many countries RAS is included in the malaria treatment policy, but no product is being deployed
- Uncontrolled large scale use of RAS, once approved, may lead to large scale exposure to artemisinin monotherapy
- WHO/GMP is working with MMV to design a demonstration project on rational use of RAS in selected African countries

Multi-agency efforts to scale-up IPTp

- In October 2012, WHO updated its policy on IPTp-SP, recommending that doses should be delivered at each antenatal care (ANC) visit after the first trimester - four ANC visits are recommended by WHO.
- For the 36 African countries in which the policy has been adopted, it is estimated that only 17% received three or more doses in 2014 (WMR, 2015).
- WHO/GMP is collaborating with CDC Atlanta, JHPiego, ISGlobal, Malaria Consortium, MMV and UNICEF to develop a demonstration project in six African countries to increase coverage of IPTp-SP delivered at ANC facilities through a complementary community-based approach.

UNITAID/IVCC grant to support access to new generation vector control products

- 1 Feb UNITAID/IVCC signed a US$ 65M grant to support African countries' access new generation vector control products
- WHO supports this initiative because effective vector control is a cornerstone of the Global Technical Strategy for Malaria 2016-30
- More importantly, until products with 2 AIs are available, the rotational use of insecticides with different modes of action remains the only effective resistance management strategy/approach
- The implementation of this project offers the oportunity to further build capacity both in leadership and in technical areas such as in resistance monitoring and management.

Innovation to Impact (I2I) in vector control

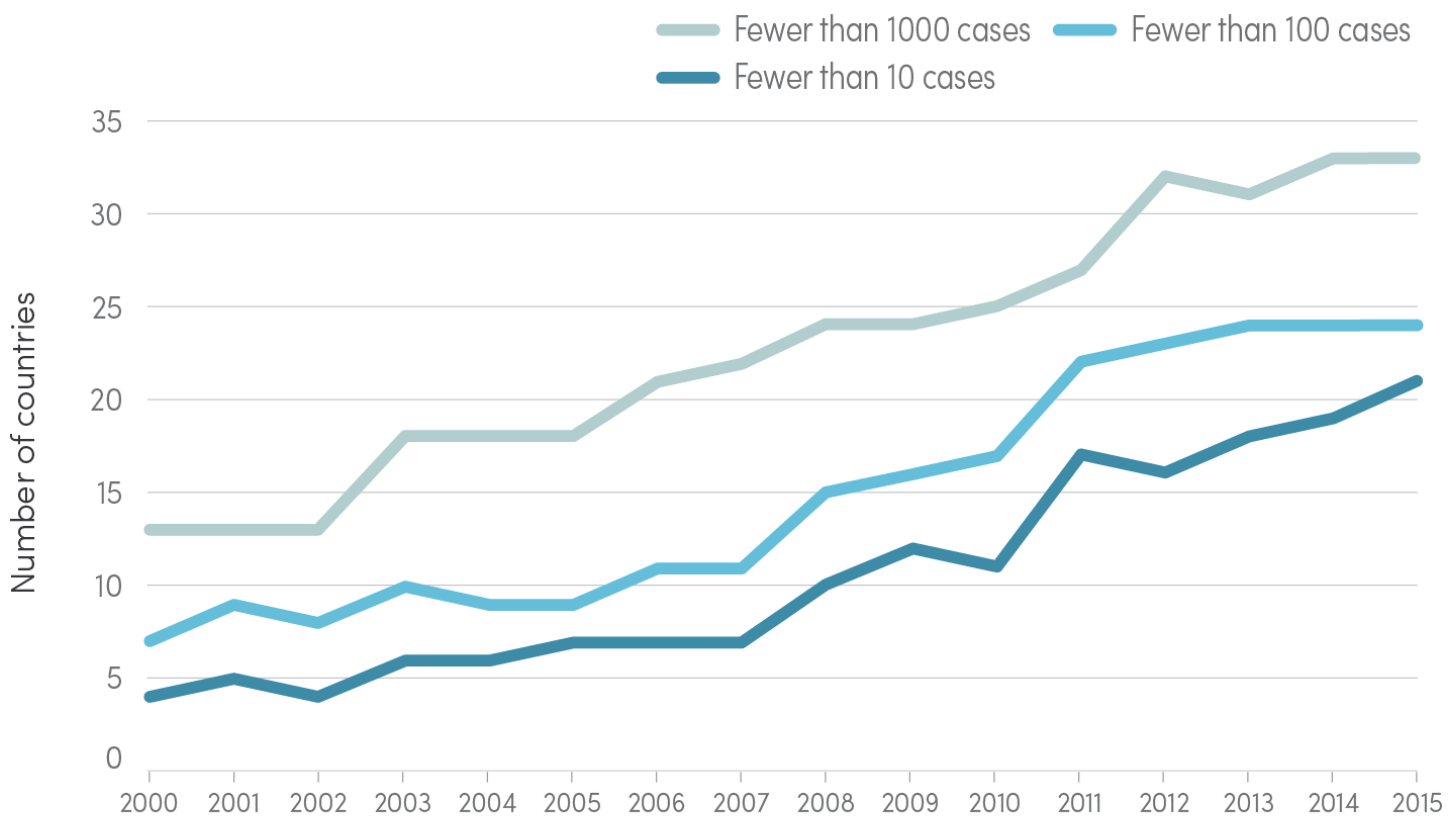
- Global initiative to support innovation and subsequent impact on VBDs – currently coordinated by IVCC with the aim of:
  - Increasing partnership for the development of innovative, high quality products
  - Establishing efficient evaluation systems through accredited GLP facilities with manufacturers generating their own data
  - Strengthening the normative guidance in WHO (GMP/NTD)
  - Support the effective use of vector control products through harmonized registration, procurement and M&E of interventions
- While this is a global initiative, with most of the expected changes happening in WHO, I2I is not a policy setting platform

GMP contribution to Zika response

- Part of the HTM team leading the WHO working group on vector control
- Developed a number of guidelines on vector control in support of the Zika response
  - Monitoring insecticide resistance in vectors
  - of Zika
  - Entomological surveillance
  - Vector control operations
- Just concluded an emergency expert consultation on new vector control tools against Zika
- One of our GMP staff is on loan to support the response in PAHO
- An opportunity for countries and WHO to strengthen capacity in entomology and vector control

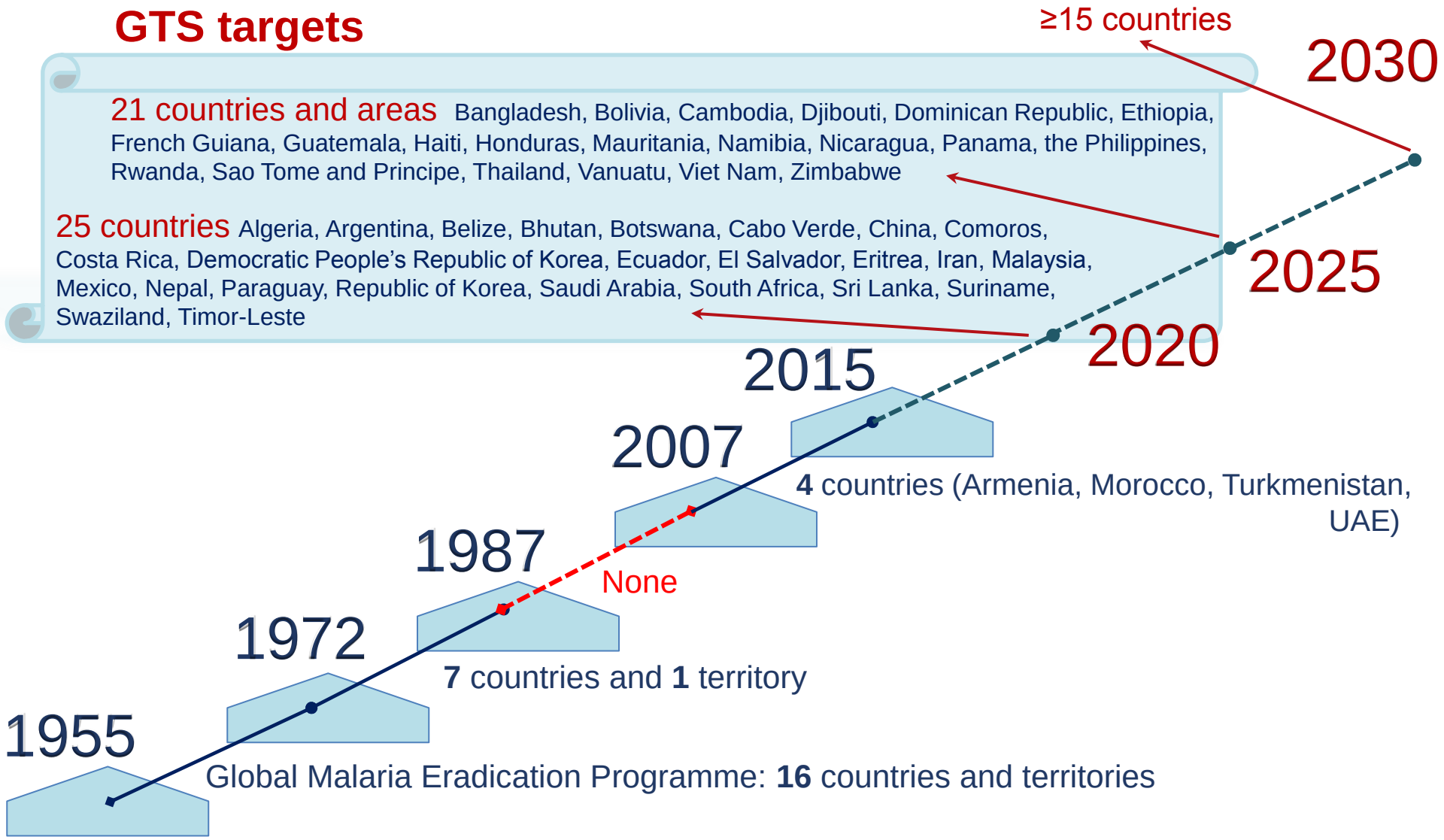
Supporting elimination countries

Number of countries with fewer than 1000, 100 and 10 cases, 2000–2015



Source: WHO estimates

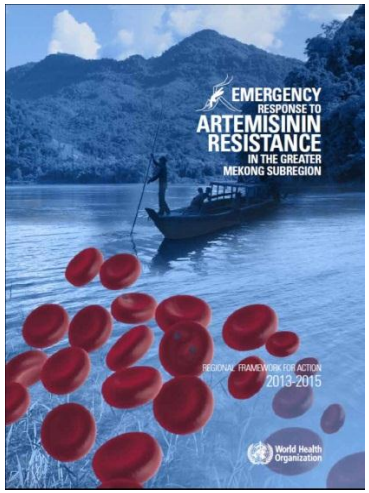
Countries certified as malaria-free by WHO: history and prospects

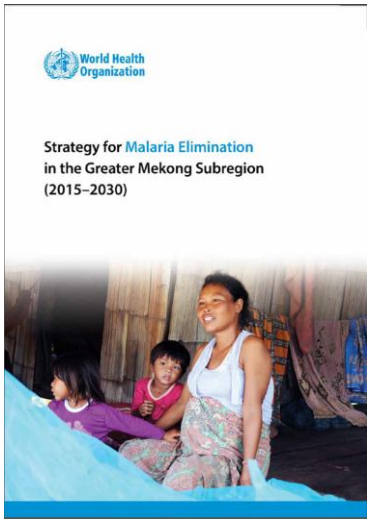


Countries aiming for malaria elimination: 2020 and 2025

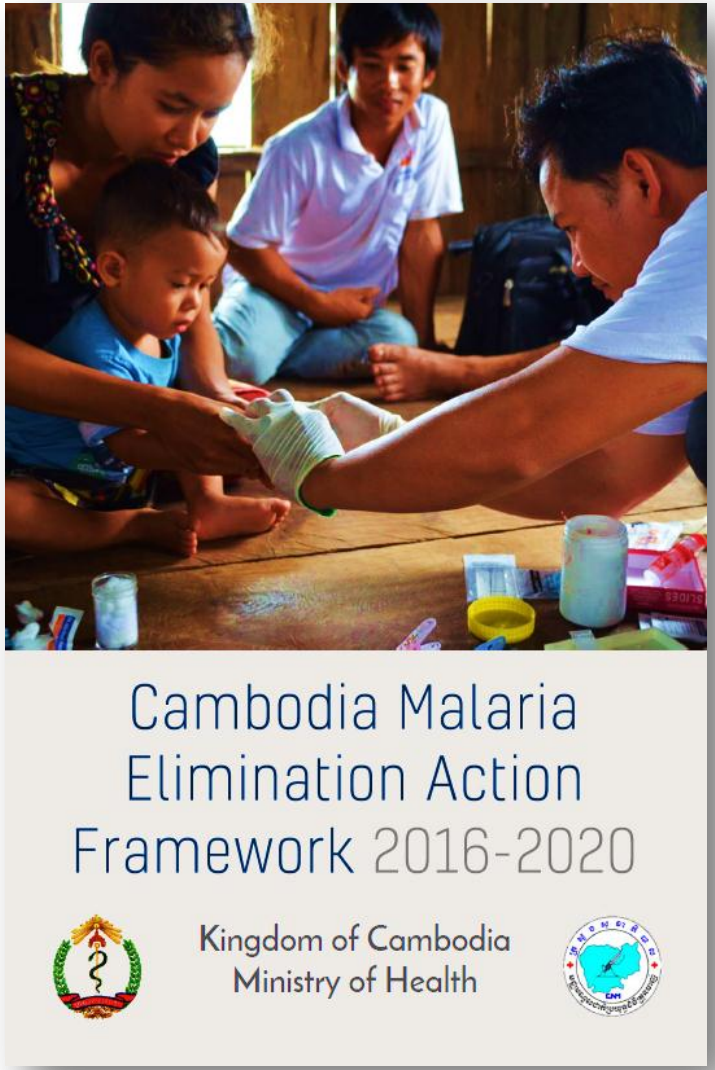
WHO region	Country	
	2020	2025
AFR	Algeria, Cabo Verde, Swaziland, Botswana, South Africa, Comoros, Eritrea Sub-national elimination: Tanzania (Zanzibar)	Ethiopia, Mauritania, Namibia, Rwanda, Sao Tome and Principe, Zimbabwe
AMR	Argentina, Belize, Costa Rica, Ecuador, El Salvador, Paraguay, Mexico, Suriname	Bolivia, Dominican Republic, French Guiana Guatemala, Haiti, Honduras, Nicaragua, Panama
EMR	Iran, Saudi Arabia	Afghanistan (*P. falciparum*), Djibouti Subnational elimination: Pakistan (Punjab Province) Somalia (Northern Zone , namely Somaliland and Puntland)
SEAR	Bhutan, DPRK, Nepal, Sri Lanka, Timor-Leste	Bangladesh, Myanmar (*P. falciparum*), Thailand
WPR	China, Republic of Korea, Malaysia	Cambodia, Vanuatu, the Philippines, Viet Nam

ERAR framework transition to elimination





- In April 2013, WHO launched the Emergency response to artemisinin resistance (ERAR) in the GMS;
- A regional hub was established in Phnom Penh, Cambodia, to support the coordination of activities relying on regional staff based in country offices;
- MPAC recommended in September 2014 the adoption of the goal of elimination of *P. falciparum* in the GMS by 2030;
- Subsequently, at the World Health Assembly in May 2015, WHO launched a Strategy for malaria elimination in the GMS (2015–2030), which was endorsed by all the GMS countries;
- As a transitional year, in 2016 the ERAR hub will fulfil the objectives agreed in ERAR project and help the countries to update their national strategic plans with the the goal to accelerate towards elimination;
- ERAR hub will evolve in 2017 with less staff at the regional level but stronger country offices.



Cambodia Malaria Elimination Action Framework 2016-2020

(MEAF)

National Framework for Malaria Elimination, India, 2016 – 2030 Launch

Ministry of Health & Family Welfare Goverment of India

World Health Organization India

National Framework for Malaria Elimination (NFME) in India 2016- 2030

Global **Malaria** Programme

World Health Organization

Technical Support

- Program review
- Updating and costing of NSP
- Development of annual workplan
- Programmatic and financial gap analysis in “redline countries”
- Resource mobilization
- Addressing technical and operational issues
- Training on malaria elimination

2016 Technical meetings

Meeting	Team	Date
Malaria Policy Advisory Committee	PSM	16-17 Mar
Consultation on preferred product characteristics for ivermectin as malaria transmission-blocking	PDT	Mar 30 – Apr 1
Technical consultation to review test procedures on monitoring insecticide resistance	EVC	7-8 Apr
Vector Control TEG	EVC	22-24 Jun
Cardiotoxicity of antimalarial medicines ERG	PDT	May
Elimination ERG	ELI	30-31 May
GTS evaluation taskforce	SEE	June
Malaria Eradication Advisory Group	PSM	June
Review of Seasonal Malaria Chemoprevention implementation	PDT	June
Field based quality control of malaria RDTs ERG	PDT	July

2016 Technical meetings (continued)

Meeting	Team	Date
Malaria Policy Advisory Committee	PSM	14-16 Sept
Chemotherapy TEG	PDT	Oct
Drug Resistance and Containment TEG	DER	Q3
Monitoring and evaluation of larval source management in control and elimination settings ERG	EVC	Q3
Consultation on inter-lab validation of net fabric strength	EVC	Q3
Review current recommendations to deploy PBO nets and next generation LLINs ERG	EVC	Q4

2016 Technical guidance

Guidance	Team	Date
Consolidated guidance on malaria prevention and control	PDT/ EVC	2017
Operational manual on MDA	PDT	Aug
Guidance manual on diagnostics in low transmission settings	PDT	Sept
Guidance for manufacturers on RDT product labelling and instructions for use	PDT	Q2
Malaria entomology and surveillance manual	EVC	Q2
Revised test procedures for monitoring insecticide resistance in malaria vectors	EVC	Q2
Framework for insecticide resistance management and national/regional plans	EVC	Q4
Monitoring LLIN durability and preferences for procurement decisions	EVC	Q2
Monitoring and evaluation of larval source management in control and elimination settings	EVC	Q3

2016 Technical guidance (continued)

Guidance	Team	Date
Technical criteria for equivalence of vector control products	EVC	Mar
Updated recommendations on areas where to deploy PBO nets and next generation LLINs	EVC	Q4
Monitoring & evaluation framework for the Global Technical Strategy	SEE	Q3
Guidance for malaria epidemics	SUR	Q4
Elimination field manual	ELI	Q4

Increasing the effectiveness of the WHO Malaria team

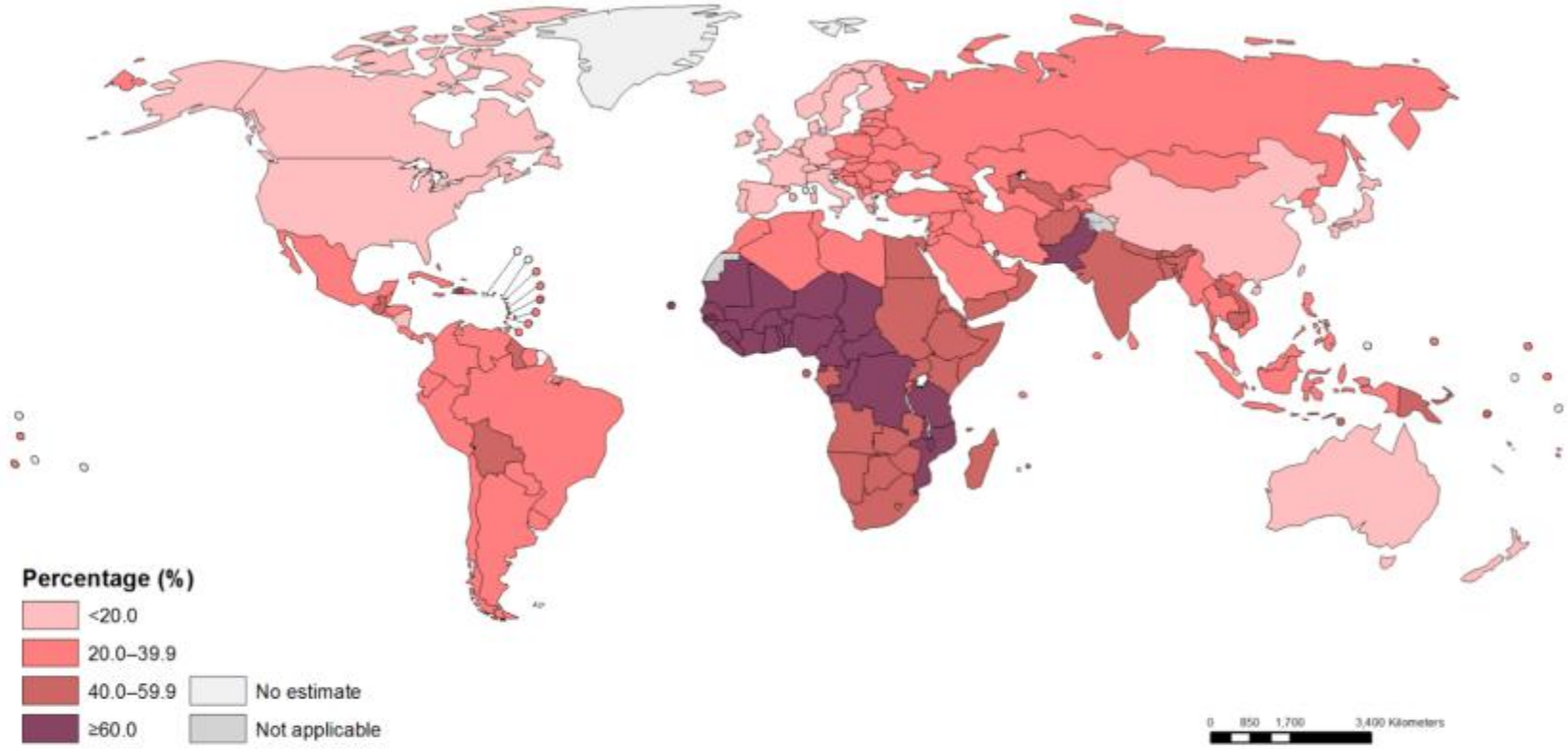
World Health Organization

Malaria Programme Area Network (PAN) Meeting
16 to 18 December 2015
Royal Plaza Montreux and Spa
Montreux, Switzerland

WHO Guideline: Daily iron supplementation in infants and children

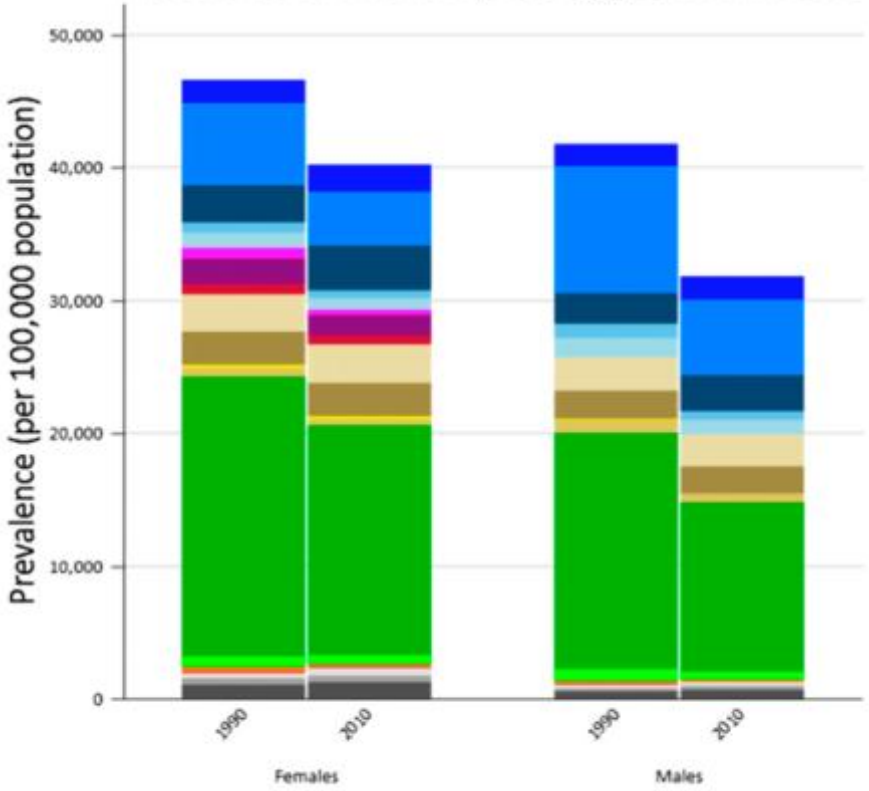
Pura Rayco-Solon
Department of Nutrition for Health and Development
World Health Organization
16 March 2016

Global estimates of the prevalence of anaemia in infants and children aged 6–59 months, 2011

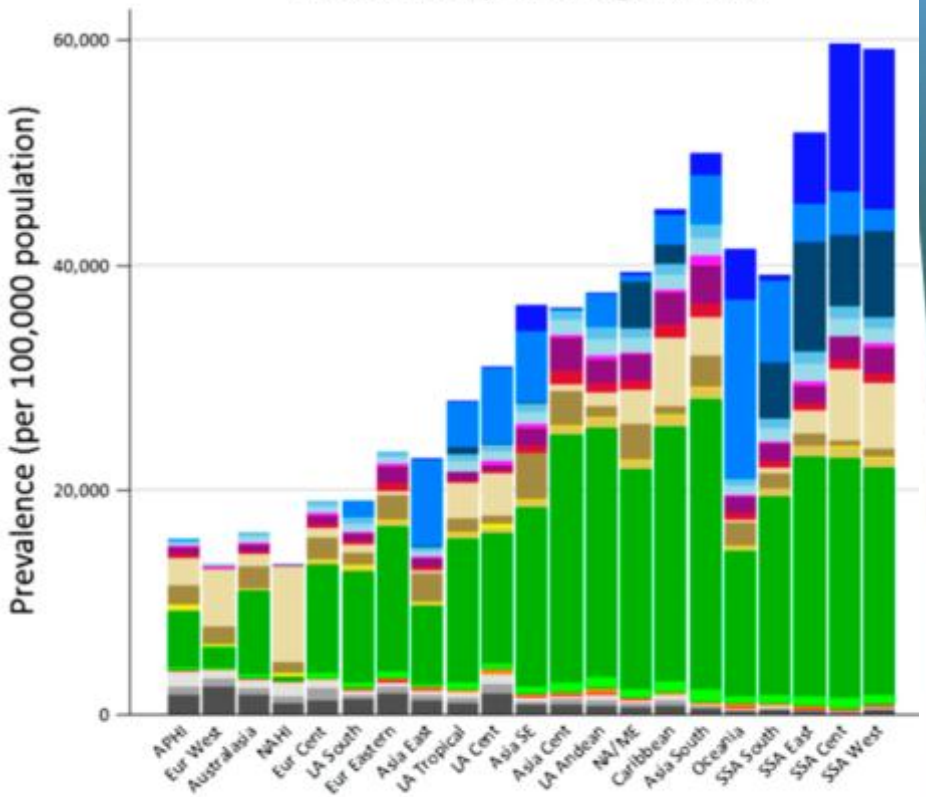


Source: WHO. The global anaemia prevalence in 2011. Geneva: World Health Organization; 2015.

Prevalence of Anemia by Etiology, 1990 and 2010

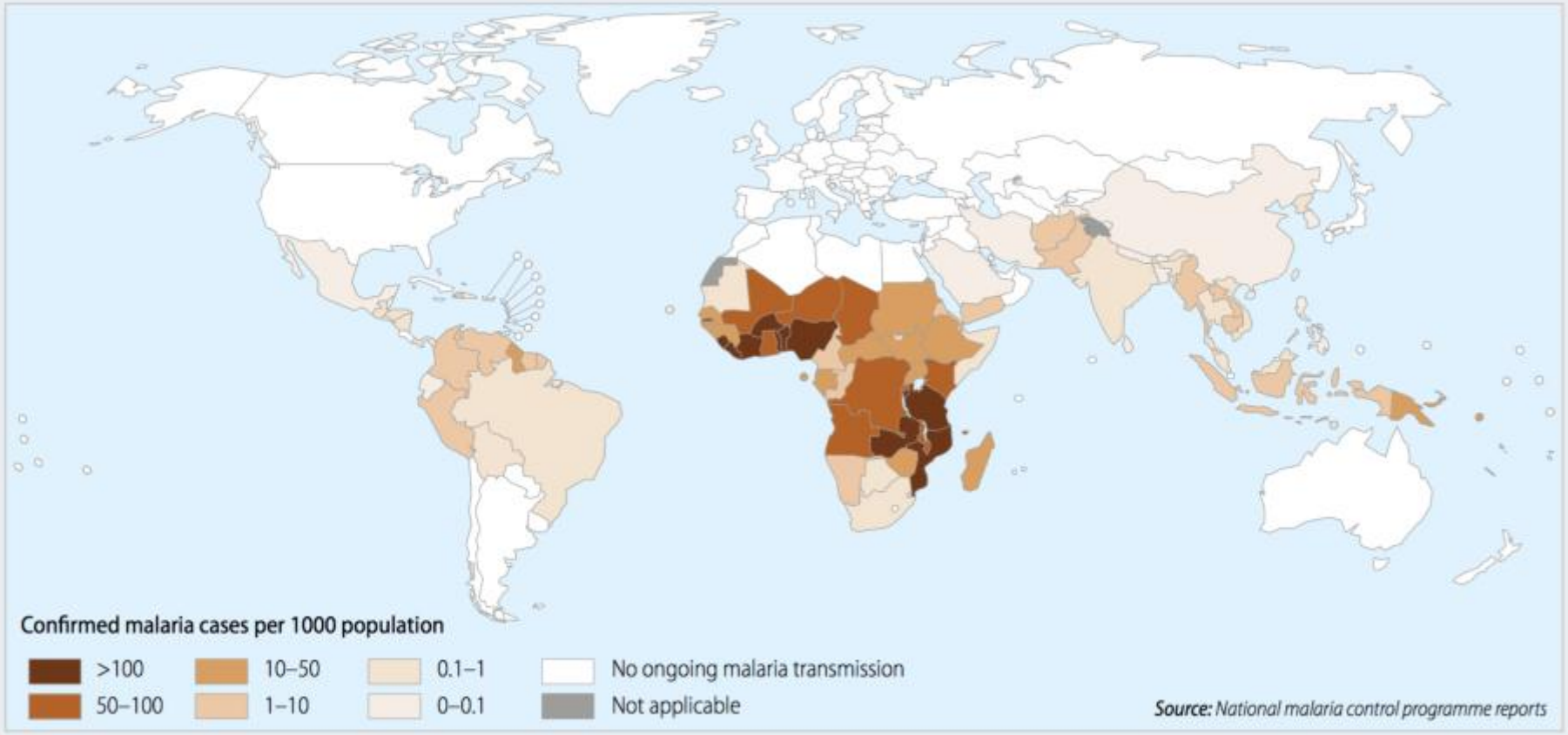


Prevalence by GBD Region, 2010



- Malaria
- Hookworm
- Schistosomiasis
- Other infectious diseases
- Other NTD
- Maternal hemorrhage
- Fibroids
- Other gynecological disorders
- Sickle cell
- Thalassemias
- G6PD deficiency
- Other hemog
- Iron-deficiency anemia
- Other endocrine
- Gastritis & duodenitis
- Peptic ulcer
- Diabetic CKD
- Hypertensive CKD
- Other CKD

Figure 1.1 Countries with ongoing transmission of malaria, 2013



Evidence & Programme Guidance
Department of Nutrition for Health and Development

World Health Organization

WHO/NHD/01.3
Distribution: General
English only

Iron Deficiency Anaemia

Assessment, Prevention, and Control

A guide for programme managers

Evidence & Programme Guidance
Department of Nutrition for Health and Development

World Health Organization

Table 10. Dosage schedules for iron supplementation to prevent iron deficiency anaemia

Age groups	Indications for supplementation	Dosage schedule	Duration
Low-birth-weight infants	Universal supplementation	Iron: 2 mg/kg body weight/day	From 2 months of age up to 23 months of age
Children from 6 to 23 months of age	Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%	Iron: 2 mg/kg body weight/day	From 6 months of age up to 23 months of age
Children from 24 to 59 months of age	Where anaemia prevalence is above 40 %	Iron: 2 mg/kg body weight/day up to 30 mg	3 months
School-aged children (above 60 months)	Where anaemia prevalence is above 40 %	Iron: 30 mg/day Folic acid: 250 µg/day	3 months
Women of childbearing age	Where anaemia prevalence is above 40 %	Iron: 60 mg/day Folic acid: 400 µg/day	3 months
Pregnant women	Universal supplementation	Iron: 60 mg/day Folic acid: 400 µg/day	As soon as possible after gestation starts - no later than the 3rd month - and continuing for the rest of pregnancy
Lactating women	Where anaemia prevalence is above 40 %	Iron: 60 mg/day Folic acid: 400 µg/day	3 months post-partum

Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial

Sunil Sazawal, Robert E Black, Mahdi Ramsan, Hababu M Chwaya, Rebecca J Stoltzfus, Arup Dutta, Usha Dhingra, Ibrahim Kabole, Saikat Deb, Mashavi K Othman, Fatma M Kabole

Summary

Background Anaemia caused by iron deficiency is common in children younger than age 5 years in eastern Africa. However, there is concern that universal supplementation of children with iron and folic acid in areas of high malaria transmission might be harmful.

Methods We did a randomised, placebo-controlled trial, of children aged 1–35 months and living in Pemba, Zanzibar. We assigned children to daily oral supplementation with: iron (12·5 mg) and folic acid (50 μg; n=7950), iron, folic acid, and zinc (n=8120), or placebo (n=8006); children aged 1–11 months received half the dose. Our primary endpoints were all-cause mortality and admission to hospital. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN59549825.

Findings The iron and folic acid-containing groups of the trial were stopped early on Aug 19, 2003, on the recommendation of the data and safety monitoring board. To this date, 24 076 children contributed a follow-up of 25 524 child-years. Those who received iron and folic acid with or without zinc were 12% (95% CI 2–23, p=0·02) more likely to die or need treatment in hospital for an adverse event and 11% (1–23%, p=0·03) more likely to be admitted to hospital; there were also 15% (−7 to 41, p=0·19) more deaths in these groups.

Interpretation Routine supplementation with iron and folic acid in preschool children in a population with high rates of malaria can result in an increased risk of severe illness and death. In the presence of an active programme to detect and treat malaria and other infections, iron-deficient and anaemic children can benefit from supplementation. However, supplementation of those who are not iron deficient might be harmful. As such, current guidelines for universal supplementation with iron and folic acid should be revised.

Lancet 2006; 367: 133–43

See Comment page 90

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Table 2

Effect of supplementation with iron and folic acid with or without zinc on serious adverse events, deaths, and admissions to hospital overall, by age group and by duration of supplement compared with placebo.

	Adverse events			Mortality			Hospital admission		
	Number	RR (95% CI)	p	Number	RR (95% CI)	p	Number	RR (95% CI)	p
Overall	2135	1·12 (1·02–1·23)	0·02	295	1·15 (0·93–1·41)	0·19	1840	1·11 (1·01–1·23)	0·03
Age group									
1–5 months	85	1·10 (0·75–1·60)	0·63	17	1·71 (0·63–4·64)	0·29	68	1·01 (0·67–1·52)	0·98
6–11 months	590	1·04 (0·90–1·20)	0·58	88	1·03 (0·71–1·48)	0·89	502	1·04 (0·89–1·22)	0·59
12–23 months	975	1·19 (1·06–1·33)	0·004	111	1·29 (0·90–1·84)	0·16	864	1·17 (1·04–1·33)	0·01
≥24 months	485	0·99 (0·85–1·16)	0·94	79	0·98 (0·67–1·42)	0·90	406	1·00 (0·84–1·18)	0·98
Duration of supplementation									
≤3 months	751	1·07 (0·94–1·21)	0·30	101	1·03 (0·73–1·45)	0·87	650	1·08 (0·94–1·23)	0·29
>3 months	1384	1·13 (1·03–1·25)	0·01	194	1·21 (0·94–1·57)	0·15	1190	1·12 (1·01–1·24)	0·03

	Adverse events		
	Number	RR (95% CI)	p
Overall	2135	1·12 (1·02–1·23)	0·02
Age group			
1–5 months	85	1·10 (0·75–1·60)	0·63
6–11 months	590	1·04 (0·90–1·20)	0·58
12–23 months	975	1·19 (1·06–1·33)	0·004
⩾24 months	485	0·99 (0·85–1·16)	0·94
Duration of supplementation			
⩽3 months	751	1·07 (0·94–1·21)	0·30
>3 months	1384	1·13 (1·03–1·25)	0·01

	Hospital admission		
	Number	RR (95% CI)	p
Overall	1840	1·11 (1·01–1·23)	0·03
Age group			
1–5 months	68	1·01 (0·67–1·52)	0·98
6–11 months	502	1·04 (0·89–1·22)	0·59
12–23 months	864	1·17 (1·04–1·33)	0·01
⩾24 months	406	1·00 (0·84–1·18)	0·98
Duration of supplementation			
⩽3 months	650	1·08 (0·94–1·23)	0·29
>3 months	1190	1·12 (1·01–1·24)	0·03

Table 3

Effects on overall adverse events, deaths, and admissions to hospital and on cause-specific adverse events in the two iron and folic acid groups compared with placebo

	Iron and folic acid (child-years' follow up 8402)			Iron, folic acid, and zinc (child-years' follow up 8548)			Placebo (child-years' follow up 8574)
	Number	RR (95%CI)	p	Number	RR (95% CI)	p	Number
Overall							
Adverse events	1036	1·10 (0·99–1·22)	0·09	1099	1·14 (1·03–1·27)	0·01	965
Deaths	149	1·16 (0·92–1·47)	0·21	146	1·12 (0·88–1·42)	0·35	130
Hospital admissions	887	1·08 (0·97–1·21)	0·16	953	1·14 (1·03–1·28)	0·02	835
Cause-specific adverse events							
Malaria-related causes	467	1·16 (1·00–1·34)	0·05	476	1·16 (1·01–1·34)	0·04	411
Infection-related causes	232	1·25 (1·01–1·53)	0·04	265	1·40 (1·14–1·71)	0·001	190
Smear positive	71	1·37 (0·96–1·95)	0·09	97	1·84 (1·31–2·57)	0·00	53
Smear negative	161	1·20 (0·94–1·53)	0·14	168	1·23 (0·97–1·56)	0·09	137
Diarrhoea	87	0·92 (0·68–1·25)	0·62	92	0·96 (0·72–1·29)	0·79	96
Smear positive	21	0·93 (0·51–1·70)	0·82	25	1·09 (0·61–1·94)	0·77	23
Smear negative	66	0·92 (0·65–1·31)	0·65	67	0·92 (0·66–1·29)	0·63	73
Other causes	108	0·99 (0·76–1·30)	0·96	127	1·15 (0·88–1·50)	0·32	111
Smear positive	18	0·97 (0·50–1·87)	0·34	30	1·58 (0·88–2·86)	0·13	19
Smear negative	90	1·00 (0·74–1·35)	0·99	97	1·06 (0·79–1·42)	0·71	92

Table 4

Effects of supplementation with iron and folic acid with or without zinc on adverse events overall and by iron status and anaemia (substudy)

	Iron and folic acid (with and without zinc)				Placebo	
	Children	Events (rate/ 100 child-years)	RR (95%CI)	p	Children	Events (rate/ 100 child-years)
Overall adverse events	1609	97 (6·46)	0·76 (0·52–1·09)	0·13	804	65 (8·55)
Zinc protoporphyrin (μmol/mol of haeme)						
<80	391	29 (7·86)	1·63 (0·72–3·66)	0·24	196	9 (4·83)
⩾80	1218	68 (6·00)	0·62 (0·41–0·93)	0·02	608	56 (9·76)
Haemoglobin (g/L)						
70–100	1018	52 (5·54)	0·59 (0·37–0·92)	0·02	455	40 (9·43)
>100	591	45 (8·00)	1·08 (0·58–1·98)	0·8	349	25 (7·44)
Iron replete and anaemic	127	10 (8·33)	2·00 (0·46–8·75)	0·36	52	2 (4·17)
Iron replete and non-anaemic	264	19 (7·63)	1·51 (0·57–3·98)	0·41	144	7 (5·06)
Iron deficient and anaemic	891	42 (5·13)	0·51 (0·31–0·83)	0·006	403	38 (10·11)
Iron deficient and non-anaemic	327	26 (8·29)	0·91 (0·42–1·98)	0·82	205	18 (9·09)

Lyon, France, 12–14 June 2006

Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas

World Health Organization Secretariat on behalf of the participants to the Consultation*

Evidence & Programme Guidance
Department of Nutrition for Health and Development

World Health Organization

TABLE 1. Strategies to control the iron status of infants and young children in malaria-endemic areas *(continued)*

Age group	Settings where screening system to detect iron deficiency and health services are available	Settings where screening system to detect iron deficiency is not available
	6–24 months	
All infants and young children	*Control of iron deficiency* Processed complementary foods fortified with iron or, if not available, Iron therapy for 3 months only to infants and young children detected with iron deficiency » Iron therapy should always be administered along with food and in conjunction with the measures to prevent and control malaria (see below) » It is advisable not to give supplemental folic acid *Prevention and control of malaria* Provision of insecticide-treated nets and vector control for prevention of malaria, and treatment of malaria illness with effective antimalarial drug therapy *General health care, including:* Breastfeeding and adequate complementary feeding Infection/parasitic disease control	*Control of iron deficiency* Processed complementary foods fortified with iron or, if not available, Iron therapy for 3 months only to infants and young children with clinical symptoms of severe anemia » Iron therapy should always be administered along with food and in conjunction with the measures to prevent and control malaria (see below) » It is advisable not to give supplemental folic acid *Prevention and control of malaria* Provision of insecticide-treated nets and vector control for prevention of malaria, and treatment of malaria illness with effective antimalarial drug therapy *General health care, including:* Breastfeeding and adequate complementary feeding Infection/parasitic disease control

WHO Guideline:
DAILY IRON SUPPLEMENTATION IN INFANTS AND CHILDREN

Evidence & Programme Guidance
Department of Nutrition for Health and Development

World Health Organization

A. Daily iron supplementation in infants and young children aged 6–23 months

Daily oral iron supplementation compared to placebo or control in infants and young children aged 6–23 months

Patient or population: infants and young children aged 6–23 months
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of Pparticipants (studies)	Quality of the evidence (GRADE)
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.61** (0.50 to 0.74)	4825 (17 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	**RR 0.30** (0.15 to 0.60)	2464 (9 RCTs)	⊕⊕⊕⊖ MODERATE [2]
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	**RR 0.14** (0.10 to 0.22)	2145 (6 RCTs)	⊕⊕⊕⊕ HIGH [3]
Growth measures (stunting)	**RR 1.10** (0.92 to 1.32)	1504 (3 RCTs)	⊕⊕⊕⊖ MODERATE [4]
Growth measures (wasting)	**RR 1.03** (0.65 to 1.64)	1504 (3 RCTs)	⊕⊕⊖⊖ LOW [5]
Mortality (all cause, acute respiratory infections, diarrhoea, malaria)	**Rate ratio 1.10** (0.91 to 1.34)	(3 RCTs)	⊕⊕⊖⊖ LOW [6]

*The **risk in the intervention** group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

Parishpa et al. Lancet Glob Health 2013; 1(2):e77-86.

B. Daily iron supplementation in children aged 24–59 months

Daily oral iron supplementation compared to placebo or control in children aged 24–59 months

Patient or population: children aged 24–59 months
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.98** (0.88 to 1.08)	359 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1]
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	Not estimable	None of the studies reported on this outcome.	
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	Not estimable	None of the studies reported on this outcome.	
Growth measures (height *Z*-score)	The mean growth measures (height *Z*-score) in the intervention group was **0.01 *Z*-score lower** (1.14 lower to 0.12 higher)	634 (3 RCTs)	⊕⊕⊖⊖ LOW [2]
Growth measures (weight *Z*-score)	The mean growth measures (weight *Z*-score) in the intervention group was **0.04 *Z*-score lower** (0.12 lower to 0.05 higher)	634 (3 RCTs)	⊕⊕⊖⊖ LOW [3]
Mortality	Not estimable	None of the studies reported on this outcome.	

*The **risk in the intervention** group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention **(and its 95% CI).**
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

Thompson, et al. Pediatrics 2013; 131(4):739-53.

C. Daily iron supplementation in children aged 60 months and older

Daily oral iron supplementation compared to placebo or control in children aged 60 months and older

Patient or population: children aged 60 months and older
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.50** (0.39 to 0.64)	1763 (7 RCTs)	⊕⊕⊕⊖ MODERATE[1]
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	**RR 0.21** (0.07 to 0.63)	1020 (5 RCTs)	⊕⊕⊖⊖ LOW[2]
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	**RR 0.12** (0.02 to 0.66)	334 (2 RCTs)	⊕⊕⊕⊖ MODERATE[3]
Growth measures (height *Z*-score)	The mean growth measures (height *Z*-score) in the intervention group was **0.09 *Z*-score higher** (0.01 higher to 0.17 higher)	1318 (5 RCTs)	⊕⊕⊕⊖ MODERATE[4]
Growth measures (weight *Z*-score)	The mean growth measures (weight *Z*-score) in the intervention group was **0.1 *Z*-score higher** (0.03 lower to 0.23 higher)	1318 (5 RCTs)	⊕⊕⊖⊖ LOW[5]
Mortality (all cause, acute respiratory infections, diarrhoea, malaria)	not estimable		

*The **risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

Low, et al. CMAJ 2013; 185(17):e791-802.

Cochrane Library

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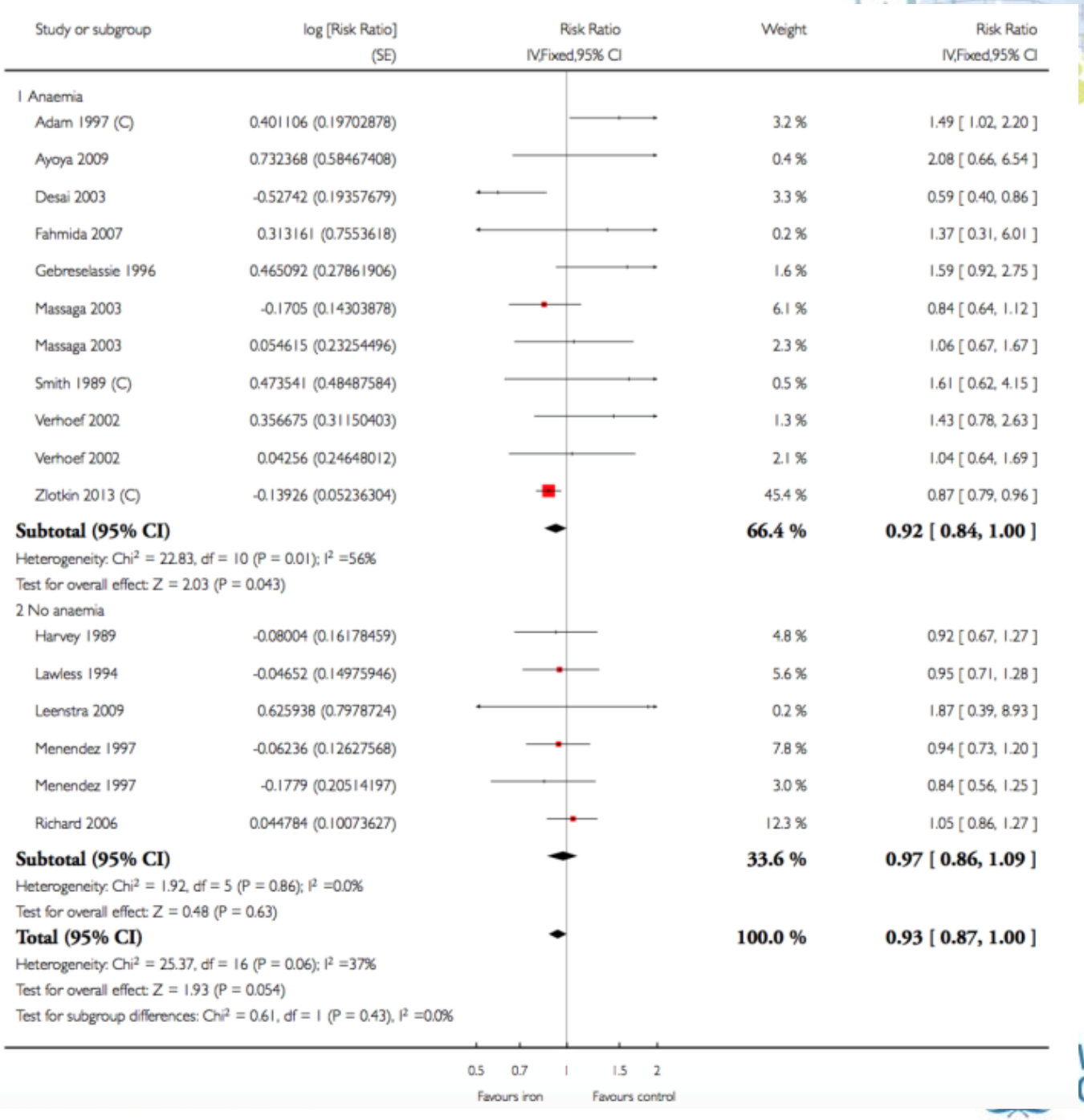
Oral iron supplements for children in malaria-endemic areas (Review)

Neuberger A, Okebe J, Yahav D, Paul M

Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD006589.

Evidence & Programme Guidance
Department of Nutrition for Health and Development

World Health Organization



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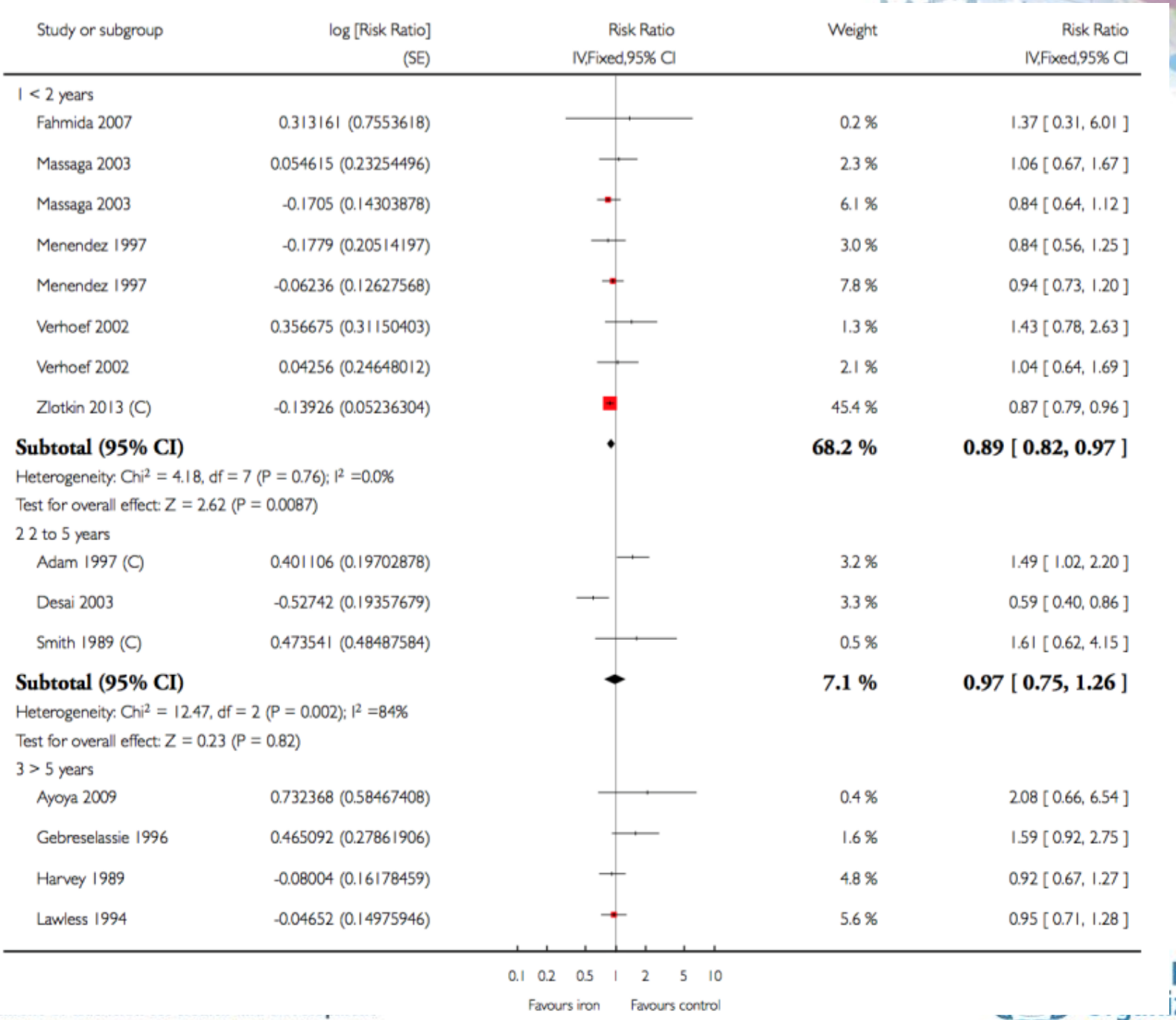
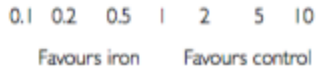
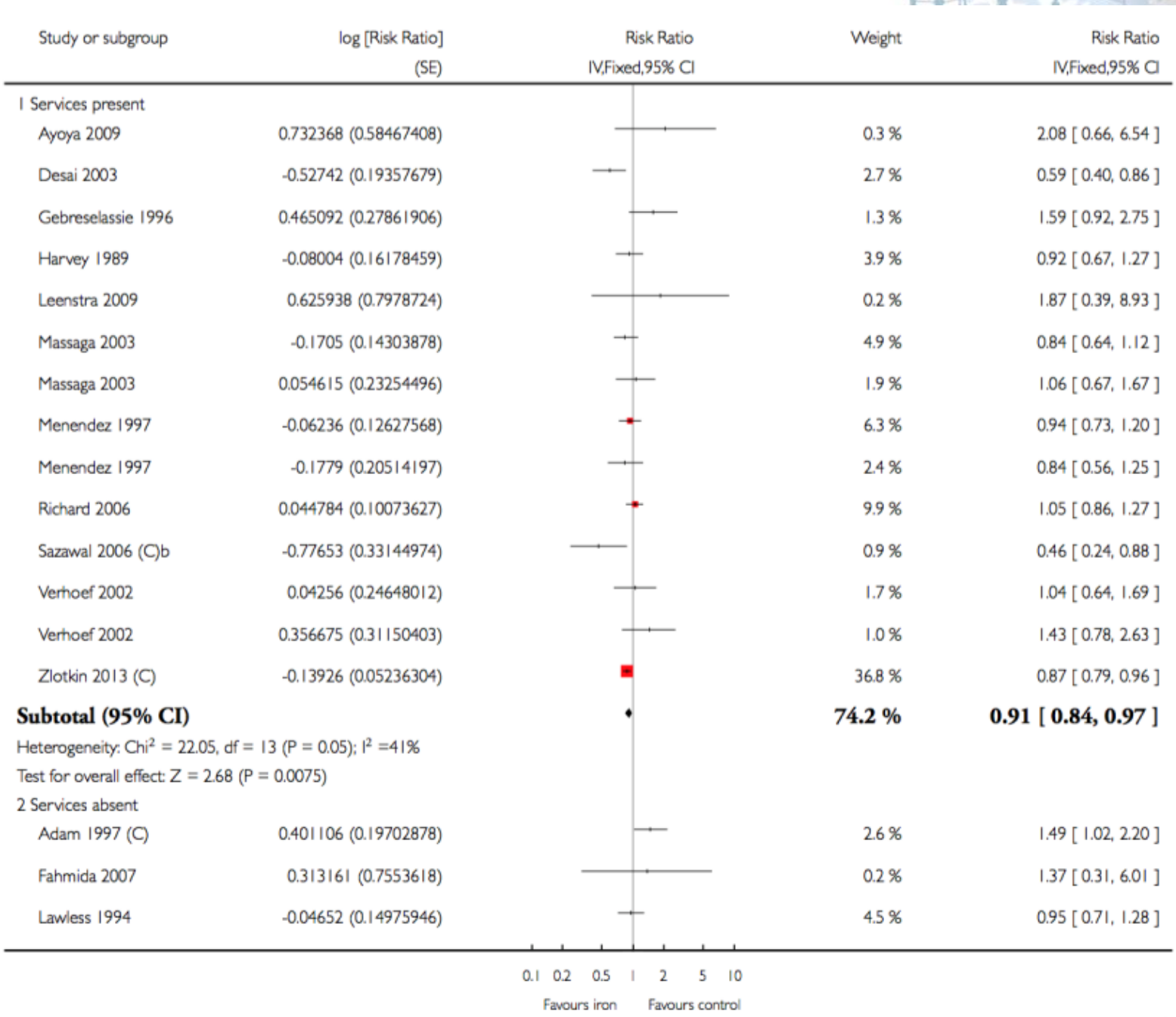

Study or subgroup
log [Risk Ratio] (SE)
Risk Ratio IV,Fixed,95% CI
Weight
Risk Ratio IV,Fixed,95% CI
1 < 2 years
Fahmida 2007 0.313161 (0.7553618) 0.2 % 1.37 [0.31, 6.01]
Massaga 2003 0.054615 (0.23254496) 2.3 % 1.06 [0.67, 1.67]
Massaga 2003 -0.1705 (0.14303878) 6.1 % 0.84 [0.64, 1.12]
Menendez 1997 -0.1779 (0.20514197) 3.0 % 0.84 [0.56, 1.25]
Menendez 1997 -0.06236 (0.12627568) 7.8 % 0.94 [0.73, 1.20]
Verhoef 2002 0.356675 (0.31150403) 1.3 % 1.43 [0.78, 2.63]
Verhoef 2002 0.04256 (0.24648012) 2.1 % 1.04 [0.64, 1.69]
Zlotkin 2013 (C) -0.13926 (0.05236304) 45.4 % 0.87 [0.79, 0.96]
Subtotal (95% CI) 68.2 % 0.89 [0.82, 0.97]
Heterogeneity: Chi² = 4.18, df = 7 (P = 0.76); I² =0.0%
Test for overall effect: Z = 2.62 (P = 0.0087)
2 2 to 5 years
Adam 1997 (C) 0.401106 (0.19702878) 3.2 % 1.49 [1.02, 2.20]
Desai 2003 -0.52742 (0.19357679) 3.3 % 0.59 [0.40, 0.86]
Smith 1989 (C) 0.473541 (0.48487584) 0.5 % 1.61 [0.62, 4.15]
Subtotal (95% CI) 7.1 % 0.97 [0.75, 1.26]
Heterogeneity: Chi² = 12.47, df = 2 (P = 0.002); I² =84%
Test for overall effect: Z = 0.23 (P = 0.82)
3 > 5 years
Ayoya 2009 0.732368 (0.58467408) 0.4 % 2.08 [0.66, 6.54]
Gebreselassie 1996 0.465092 (0.27861906) 1.6 % 1.59 [0.92, 2.75]
Harvey 1989 -0.08004 (0.16178459) 4.8 % 0.92 [0.67, 1.27]
Lawless 1994 -0.04652 (0.14975946) 5.6 % 0.95 [0.71, 1.28]
0.1 0.2 0.5 1 2 5 10
Favours iron
Favours control

(. . . *Continued*)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Leenstra 2009	0.625938 (0.7978724)		0.2 %	1.87 [0.39, 8.93]
Richard 2006	0.044784 (0.10073627)		12.3 %	1.05 [0.86, 1.27]
Subtotal (95% CI)			**24.8 %**	**1.04 [0.91, 1.20]**
Heterogeneity: Chi^2 = 5.15, df = 5 (P = 0.40); I^2 =3%				
Test for overall effect: Z = 0.60 (P = 0.55)				
Total (95% CI)			**100.0 %**	**0.93 [0.87, 1.00]**
Heterogeneity: Chi^2 = 25.37, df = 16 (P = 0.06); I^2 =37%				
Test for overall effect: Z = 1.93 (P = 0.054)				
Test for subgroup differences: Chi^2 = 3.56, df = 2 (P = 0.17), I^2 =44%				




Study or subgroup
log [Risk Ratio] (SE)
Risk Ratio IV,Fixed,95% CI
Weight
Risk Ratio IV,Fixed,95% CI
1 Services present
Ayoya 2009 0.732368 (0.58467408) 0.3 % 2.08 [0.66, 6.54]
Desai 2003 -0.52742 (0.19357679) 2.7 % 0.59 [0.40, 0.86]
Gebreselassie 1996 0.465092 (0.27861906) 1.3 % 1.59 [0.92, 2.75]
Harvey 1989 -0.08004 (0.16178459) 3.9 % 0.92 [0.67, 1.27]
Leenstra 2009 0.625938 (0.7978724) 0.2 % 1.87 [0.39, 8.93]
Massaga 2003 -0.1705 (0.14303878) 4.9 % 0.84 [0.64, 1.12]
Massaga 2003 0.054615 (0.23254496) 1.9 % 1.06 [0.67, 1.67]
Menendez 1997 -0.06236 (0.12627568) 6.3 % 0.94 [0.73, 1.20]
Menendez 1997 -0.1779 (0.20514197) 2.4 % 0.84 [0.56, 1.25]
Richard 2006 0.044784 (0.10073627) 9.9 % 1.05 [0.86, 1.27]
Sazawal 2006 (C)b -0.77653 (0.33144974) 0.9 % 0.46 [0.24, 0.88]
Verhoef 2002 0.04256 (0.24648012) 1.7 % 1.04 [0.64, 1.69]
Verhoef 2002 0.356675 (0.31150403) 1.0 % 1.43 [0.78, 2.63]
Zlotkin 2013 (C) -0.13926 (0.05236304) 36.8 % 0.87 [0.79, 0.96]
Subtotal (95% CI) 74.2 % 0.91 [0.84, 0.97]
Heterogeneity: Chi² = 22.05, df = 13 (P = 0.05); I² =41%
Test for overall effect: Z = 2.68 (P = 0.0075)
2 Services absent
Adam 1997 (C) 0.401106 (0.19702878) 2.6 % 1.49 [1.02, 2.20]
Fahmida 2007 0.313161 (0.7553618) 0.2 % 1.37 [0.31, 6.01]
Lawless 1994 -0.04652 (0.14975946) 4.5 % 0.95 [0.71, 1.28]
0.1 0.2 0.5 1 2 5 10
Favours iron
Favours control

(. . . *Continued*)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Sazawal 2006 (C)a	0.14842 (0.07466062)		18.1 %	1.16 [1.00, 1.34]
Smith 1989 (C)	0.473541 (0.48487584)		0.4 %	1.61 [0.62, 4.15]
Subtotal (95% CI)			**25.8 %**	**1.16 [1.02, 1.31]**
Heterogeneity: Chi^2 = 3.84, df = 4 (P = 0.43); I^2 =0.0%				
Test for overall effect: Z = 2.34 (P = 0.019)				
Total (95% CI)			**100.0 %**	**0.97 [0.91, 1.03]**
Heterogeneity: Chi^2 = 37.29, df = 18 (P = 0.005); I^2 =52%				
Test for overall effect: Z = 1.11 (P = 0.26)				
Test for subgroup differences: Chi^2 = 11.40, df = 1 (P = 0.00), I^2 =91%				

Review: Oral iron supplements for children in malaria-endemic areas

Comparison: 1 Iron versus placebo or no treatment

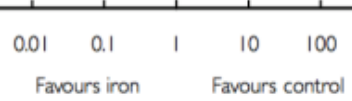
Outcome: 6 Clinical malaria with high-grade parasitaemia or requiring admission

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Adam 1997 (C)	0.19062 (0.260213)		3.4 %	1.21 [0.73, 2.02]
Ayoya 2009	-0.08338 (1.401116)		0.1 %	0.92 [0.06, 14.34]
Massaga 2003	-0.19845 (0.104701)		21.1 %	0.82 [0.67, 1.01]
Massaga 2003	0.122218 (0.290672)		2.7 %	1.13 [0.64, 2.00]
Smith 1989 (C)	0.350657 (0.416318)		1.3 %	1.42 [0.63, 3.21]
Zlotkin 2013 (C)	-0.11653 (0.05692438)		71.3 %	0.89 [0.80, 1.00]
Total (95% CI)			**100.0 %**	**0.90 [0.81, 0.98]**

Heterogeneity: $Chi^2 = 3.92$, df = 5 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 2.30 (P = 0.022)

Test for subgroup differences: Not applicable



D. Daily iron supplementation in infants and children in malaria-endemic areas

Daily oral iron supplementation compared to placebo or control in infants and children in malaria-endemic settings

Patient or population: infants and children (aged 6 months to 18 years)
Intervention: iron supplementation1
Comparison: placebo or control
Setting: malaria-endemic areas

Outcomes		Relative effect* (95% CI)	Number of articipants (studies)	Quality of the evidence (GRADE)
Clinical malaria (fever >37.5 °C and any parasitaemia), all		**RR 0.93** (0.87 to 1.00)	7168 (14 RCTs)	⊕⊕⊕⊖ MODERATE[2]
Clinical malaria by age:[3]	6–23 months	**RR 0.89** (0.82 to 0.97)	3720 (5 RCTs)	
	24–59 months	**RR 0.97** (0.75 to 1.26)	1415 (3 RCTs)	
	60 months or older	**RR 1.04** (0.91 to 1.20)	2033 (6 RCTs)	
Clinical malaria by baseline anaemia:[4]	Anaemic at baseline	**RR 0.92** (0.84 to 1.00)	2112 (9 RCTs)	
	Non-anaemic at baseline	**RR 0.97** (0.86 to 1.09)	4986 (5 RCTs)	
Clinical malaria by availability of malaria-prevention and treatment programme:[5]	Yes (malaria-prevention and treatment programme available)	**RR 0.91** (0.84 to 0.97)	5586 (7 RCTs)	
	No (malaria-prevention and treatment programme not available or unclear)	**RR 1.16** (1.02 to 1.31)	19 086 (9 RCTs)	
Severe malaria (clinical malaria with high-grade parasitaemia)		**RR 0.90** (0.81 to 0.98)	3421 (6 RCTs)	⊕⊕⊕⊕ HIGH
All-cause mortality		**Risk difference 0.00** (0.00 to 0.01)	7576 (18 RCTs)	⊕⊕⊕⊖ MODERATE[6]

Recommendations[1]

- Daily iron supplementation is recommended as a public health intervention in infants and young children aged 6–23 months, living in settings where anaemia is highly prevalent,[2] for preventing iron deficiency and anaemia (*strong recommendation, moderate quality of evidence*).

Table A. Suggested scheme for daily iron supplementation in infants and young children aged 6–23 months

TARGET GROUP	**Infants and young children (6–23 months of age)**
SUPPLEMENT COMPOSITION	10–12.5 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 10–12.5 mg of elemental iron equals 50–62.5 mg of ferrous sulfate heptahydrate, 30–37.5 mg of ferrous fumarate or 83.3–104.2 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

- Daily iron supplementation is recommended as a public health intervention in preschool-age children aged 24–59 months, living in settings where anaemia is highly prevalent,[2] for increasing haemoglobin concentrations and improving iron status (*strong recommendation, very low quality of evidence*).

Table B. Suggested scheme for daily iron supplementation in children aged 24–59 months

TARGET GROUP	**Preschool-age children (24–59 months of age)**
SUPPLEMENT COMPOSITION	30 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups/tablets
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

- Daily iron supplementation is recommended as a public health intervention in school-age children aged 60 months and older, living in settings where anaemia is highly prevalent,[2] for preventing iron deficiency and anaemia (*strong recommendation, high quality of evidence*).

Table C. Suggested scheme for daily iron supplementation in school-age children (5–12 years of age)

TARGET GROUP	**School-age children (5–12 years of age)**
SUPPLEMENT COMPOSITION	30–60 mg elemental iron[a]
SUPPLEMENT FORM	Tablets or capsules
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate or 250–500 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

In malaria-endemic areas, the provision of iron supplementation in infants and children should be done in conjunction with public health measures to prevent, diagnose and treat malaria

Strong recommendation

High quality of evidence

RECOMMENDATION

REMARKS

In malaria-endemic areas, iron supplementation does not increase the risk of clinical malaria or death when regular malaria-surveillance and treatment services are provide.

The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas.

In the presence of surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation.

WHO Guideline: Daily iron supplementation in infants and children

http://www.who.int/nutrition/publications/micronutrients/guidelines/daily_iron_supp_childrens/en/

GUIDELINE

DAILY IRON SUPPLEMENTATION

in infants
and children

2016

World Health Organization

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DAILY IRON SUPPLEMENTATION IN INFANTS AND CHILDREN

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CONTENTS

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WHO GUIDELINE[1]: DAILY IRON SUPPLEMENTATION IN INFANTS AND CHILDREN

EXECUTIVE SUMMARY

Approximately 300 million children globally had anaemia in 2011. Deficiency in iron, a mineral necessary to carry oxygen in haemoglobin, is thought to be the most common cause of anaemia. Iron deficiency can result from inadequate intake or absorption of dietary iron, increased need in periods of growth, increased losses from menstruation in adolescent girls, or infection by intestinal helminths, such as schistosomiasis or hookworm infestation, in areas endemic to these parasites.

Iron is an essential nutrient for development and cell growth in the immune and neural systems, as well as in regulation of energy metabolism and exercise. The economic costs of iron deficiency anaemia from annual physical productivity losses have been calculated to be around US$ 2.32 per capita, or 0.57% of gross domestic product in low- and middle-income countries. The WHO has consistently recommended oral iron supplementation as one of the interventions that can reduce the prevalence of anaemia.

Iron is required for the survival and virulence of many pathogens. Concerns have been expressed on a possible increased risk of malaria with iron interventions in malaria-endemic areas, particularly among iron-replete children. On the other hand, screening to identify iron deficiency in children prior to iron supplementation is not feasible in many malaria-endemic settings. Given the importance and magnitude of anaemia globally, particularly in areas where malaria transmission is intense, an assessment of all available evidence has been carried out, to examine the safety and effectiveness of iron supplementation in children, including in malaria-endemic areas.

Purpose of the guideline

This guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the *Sustainable Development Goals* (SDGs) *(1)*, the global targets set in the *Comprehensive implementation plan on maternal, infant and young child nutrition (2)* and the *Global strategy for women's, children's, and adolescents' health (2016–2030) (3).* The recommendations in this guideline are intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of programmes for anaemia prevention and control, and in nutrition actions for public health.

The recommendations supersede those of previous WHO guidelines on iron supplementation in children where they pertain specifically to daily oral iron supplementation among infants and children.

Guideline development methodology

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development (4).* The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed *(5)*, to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

[1] This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area, and is not expected to cover the full scope of the condition or public health problem. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

The guideline development group consisted of content experts, methodologists and representatives of potential stakeholders and beneficiaries. One guideline group participated in a meeting concerning this guideline, held in Geneva, Switzerland, on 20–25 February 2010, where the guideline was scoped. A second guideline group participated in a meeting held in Geneva, Switzerland, on 14–18 March 2011, to discuss the safety of iron supplementation in children living in areas of high malaria transmission, and a third meeting was convened in Geneva, Switzerland, on 23–26 June 2014, where the guideline was finalized. Two experts served as technical peer-reviewers of the draft guideline.

Available evidence

The available evidence comprised four systematic reviews that followed the procedures of the *Cochrane handbook for systematic reviews of interventions (6)* and assessed the effects of daily iron supplementation in infants, preschool-age and school-age children, as well as the effect of iron on the incidence and severity of malaria, including deaths in children living in malaria-endemic settings. The reviews included individually randomized and cluster-randomized controlled trials. All studies compared a group of children who received iron supplementation to a group that did not receive iron. For systematic reviews done prior to 2013, the WHO Secretariat conducted an additional search on PubMed (June 2014) prior to the meeting of the guideline development group. In addition, in August 2015, a full literature search was performed as part of the review of evidence for malaria and iron supplementation. These searches did not identify any relevant additional studies.

The overall quality of the available evidence for daily iron supplementation in children and in malaria-endemic settings varied from high to very low for the critical outcomes of anaemia, iron deficiency and iron deficiency anaemia. The quality of evidence was moderate to very low for morbidity, mortality and growth measurements. The evidence for clinical malaria as an outcome in studies conducted in malaria-endemic settings was considered of high to moderate quality.

Recommendations[1]

- Daily iron supplementation is recommended as a public health intervention in infants and young children aged 6–23 months, living in settings where anaemia is highly prevalent,[2] for preventing iron deficiency and anaemia (*strong recommendation, moderate quality of evidence*).

Table A. Suggested scheme for daily iron supplementation in infants and young children aged 6–23 months

TARGET GROUP	**Infants and young children (6–23 months of age)**
SUPPLEMENT COMPOSITION	10–12.5 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 10–12.5 mg of elemental iron equals 50–62.5 mg of ferrous sulfate heptahydrate, 30–37.5 mg of ferrous fumarate or 83.3–104.2 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

[1] The recommendations supersede those of previous WHO guidelines on iron supplementation in children where they pertain specifically to daily oral iron supplementation among infants and children.

[2] Where the prevalence of anaemia is 40% or higher in this age group. For the latest estimates, please refer to the Vitamin and Mineral Nutrition Information System (VMNIS) hosted at WHO *(7)*.

- Daily iron supplementation is recommended as a public health intervention in preschool-age children aged 24–59 months, living in settings where anaemia is highly prevalent,[2] for increasing haemoglobin concentrations and improving iron status (*strong recommendation, very low quality of evidence*).

Table B. Suggested scheme for daily iron supplementation in children aged 24–59 months

TARGET GROUP	**Preschool-age children (24–59 months of age)**
SUPPLEMENT COMPOSITION	30 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups/tablets
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

- Daily iron supplementation is recommended as a public health intervention in school-age children aged 60 months and older, living in settings where anaemia is highly prevalent,[2] for preventing iron deficiency and anaemia (*strong recommendation, high quality of evidence*).

Table C. Suggested scheme for daily iron supplementation in school-age children (5–12 years of age)

TARGET GROUP	**School-age children (5–12 years of age)**
SUPPLEMENT COMPOSITION	30–60 mg elemental iron[a]
SUPPLEMENT FORM	Tablets or capsules
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate or 250–500 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

- In malaria-endemic areas, the provision of iron supplementation in infants and children should be done in conjunction with public health measures to prevent, diagnose and treat malaria (*strong recommendation, high quality of evidence*).

Remarks

The remarks in this section are intended to give some considerations for implementation of the recommendations, based on the discussion of the guideline development group.

- Daily oral iron supplementation is a preventive strategy for implementation at the population level. If a child is diagnosed with anaemia, national guidelines for the treatment of anaemia should be followed.

- If the prevalence of anaemia is 20–40%, intermittent regimens of iron supplementation can be considered.

- The selection of the most appropriate delivery platform should be context specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements.

- In malaria-endemic areas, iron supplementation does not increase the risk of clinical malaria or death when regular malaria-surveillance and treatment services are provided. Oral iron interventions should not be given to children who do not have access to malaria-prevention strategies (e.g. provision of insecticide-treated bednets and vector-control programmes), prompt diagnosis of malaria illness, and treatment with effective antimalarial drug therapy.

- The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas. There is no need to screen for anaemia prior to iron supplementation in settings where anaemia is highly prevalent.

- Since malaria infection occurs in early infancy and is especially dangerous at this age, in malaria-endemic areas, iron supplements should only be given to infants who sleep under insecticide-treated bednets, and where all episodes of malaria illness can be promptly treated with effective antimalarial drug therapy according to national guidelines.

- In the presence of comprehensive surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation. Insufficient and inequitable health-care services are associated with an increase in risks in general.

Research priorities

Discussions between the members of the WHO guideline development group and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on iron supplementation in infants and children, particularly in the following areas:

- the optimal dose, schedule and duration of iron supplementation; the effect of different doses and durations of iron supplementation on different severity, prevalence or causes of anaemia in all WHO regions;

- additional data on the safety of iron supplementation (liver damage; iron overload after continuing the supplementation programme for a number of years; iron supplementation given in conjunction with other interventions; insulin resistance; effects in non-anaemic or non-iron-deficient children);

- the effect of adding other micronutrients to the iron supplement on haemoglobin concentrations and the prevalence of anaemia;

- implementation research on effective behaviour-change strategies for sustained adherence and innovative delivery mechanisms for iron supplements;

- additional long-term studies on functional outcomes (e.g. cognitive and motor development).

SCOPE AND PURPOSE

This guideline provides global, evidence-informed recommendations on daily iron supplementation in infants and children, as a public health intervention for the prevention of anaemia and iron deficiency. It also includes recommendations for iron supplementation in countries where malaria is prevalent.

The guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Sustainable Development Goals (SDGs) *(1),* in particular, Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture. It will also support Member States in their efforts to achieve the global targets set in the *Comprehensive implementation plan on maternal, infant and young child nutrition*, as endorsed by the Sixty-fifth World Health Assembly in 2012, in resolution WHA65.6 *(2)*, and the *Global strategy for women's, children's, and adolescents' health (2016–2030) (3).*

The recommendations in this guideline are intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of programmes for anaemia prevention and control, and in nutrition actions for public health. This document presents the key recommendations and a summary of the supporting evidence.

BACKGROUND

Approximately 300 million children globally had anaemia in 2011 *(8, 9)*. The highest prevalence of anaemia is among children aged under 5 years and women *(10, 11)*. South Asia and central and west Africa continue to have the highest burden of anaemia *(9–11).*

Anaemia is characterized by a decrease in the number of red blood cells, sometimes with changed size or shape of the red blood cells, to a level that impairs the normal physiological capacity of the blood to transport oxygen to cells around the body. Anaemia is measured most reliably by a fall in haemoglobin concentration and can indicate poor nutrition and health *(12, 13).* Anaemia has been estimated to cause 68.4 million years lost to disability in 2010, or 8.8% of disability from all conditions that year *(11).*

Deficiency in iron, a mineral necessary to carry oxygen in haemoglobin, is thought to be the most common cause of anaemia *(10–14).* Iron deficiency can result from inadequate intake or absorption of dietary iron, increased need for iron in periods of growth or pregnancy, increased losses from menstruation, or infection with intestinal helminths such as schistosomiasis or hookworm infection, in areas where these infestations are endemic *(12–16).* Other important causes of anaemia include infections such as malaria, tuberculosis and HIV; other nutritional deficiencies such as of folate and vitamins B_{12}, A and C; genetic conditions and haemoglobinopathies such as sickle cell disease and thalassaemia; and chronic kidney disease *(9–11)*. Iron is an essential nutrient in development and cell growth in the immune and neural systems, as well as in regulation of energy metabolism and exercise *(17,18)*. Approximately 38–62% of anaemia is responsive to iron supplementation. In malaria-hyperendemic settings, only 6–32% of anaemia is responsive to iron supplementation *(19).*

Iron deficiency affects approximately two billion people worldwide; of these, about 500 million have anaemia *(20).* The economic costs of iron deficiency anaemia from annual physical productivity losses have been calculated to be around US$ 2.32 per capita, or 0.57% of gross domestic product in low- and middle-income countries *(21)*. WHO has consistently recommended iron supplementation as one of the interventions that can decrease rates of anaemia *(22, 23).*

Iron deficiency anaemia has been correlated with suboptimal mental and motor development in children *(24–33)* and women *(34)*, though some of the effects reported may be due to confounding *(35)*. Iron supplementation has been shown to improve some of the mental or motor outcomes *(18, 36–40)*, but the effects of supplementation have been inconsistent *(41–47)* and some impairment may be irreversible *(29)*. Conversely, there are concerns that iron may produce adverse effects, including increased susceptibility to infections such as malaria *(48–50)* and impaired physical growth *(51, 52).*

Anaemia in infants and children

The risks for anaemia in children start during gestation. Anaemia in the child's mother during pregnancy is associated with increased risk of low birth weight and maternal and child mortality *(53).* Children born to mothers with anaemia may be more likely to be iron deficient and anaemic early in life. This may irreversibly affect the cognitive development and physical growth of infants *(17, 23, 54, 55).*

Iron is required by infants to produce red blood cells in the first months after birth. Infants commonly use iron stored during the last months of gestation. When the infant is 4–6 months of age, the stores can become low or depleted. This is exacerbated when there are inadequate iron stores due to low birth weight and prematurity *(56);* increased requirements from rapid growth and erythropoiesis; inadequate iron from the diet, such as in cases of early introduction of cereal-based complementary food, from which iron absorption can be as low as 5% *(57)*, or with prolonged milk feeding *(10, 58)*; and blood loss due to intestinal parasitic infections *(59).*

In the preschool years, children undergo rapid growth, with an increase in red blood cells and high iron requirements *(60).* As children reach their third year, growth velocity decreases and daily iron requirements may decline. They are becoming ambulant and, if sanitation is poor, are more likely to acquire intestinal parasitic infections that cause iron deficiency *(61)*. Young children are being weaned from breastfeeding but foods being given may be inadequate for their iron needs *(53).*

Among school-age children, iron deficiency has been associated with impaired cognitive and physical development *(20, 28)*, and provision of iron showed a positive effect *(44, 62, 63)*. However, a causal relation between iron deficiency and cognitive impairment has not been confirmed *(64)*. Assurance of cognitive and physical development though optimal nutrition in school-age children could have benefits beyond school performance *(24).*

No increase in the incidence of respiratory infections has been found as a result of iron supplementation among children *(37–39, 65)*, although, in systematic review, there is evidence of a very slight increase in the risk of developing diarrhoea (at an estimated incidence rate difference of 0.05 episodes per child-year) *(65).*

Iron supplementation in malaria-endemic areas

Malaria is a leading cause of morbidity and mortality in children in sub-Saharan Africa, with most infections caused by *Plasmodium falciparum (66).* The effect of malaria on anaemia in areas of high transmission has been observed to be less after 36 months of age *(67, 68)*. At a very young age, children are somewhat less vulnerable to malaria, owing to immunity passively acquired from their mothers, as well as lower exposure to transmission *(69, 70).* Malaria infection is an important contributor to anaemia in endemic regions, through direct haemolysis of infected red blood cells, the body's immune destruction of both parasitized and uninfected red blood cells, and temporary dysfunction of the bone marrow *(71, 72).*

Iron is required for both regulation of immunity against infections and the survival and virulence of many pathogens *(17, 73).* One study reported a small decrease in the risk for mild clinical malaria in a cohort of children in Kenya *(74),* while others have shown increased risk of malaria with iron interventions *(49, 50).*

In 2006, the results of an evaluation of iron and folate supplements in a malaria-endemic area of Zanzibar (Pemba Island) were published *(48).* This study was terminated prematurely, based on a higher proportion of hospitalization or death among participants randomized to the iron and folic acid treatment group, particularly among those who were iron replete at baseline.

Previous recommendations on daily iron supplementation as a public health measure for infants and children have not differentiated between malaria-endemic or non-endemic areas. A 2007 technical consultation convened by WHO considered iron supplementation among children in malaria-endemic settings, and suggested that, in malaria-endemic areas, screening to identify iron deficiency in children aged less than 2 years, prior to treatment with iron, would need to be in place *(75).*

Concerns have been expressed about the implementation of the conclusions of this consultation in a public health setting *(76–79).* Given the importance and magnitude of anaemia globally, an assessment of all available evidence has been carried out, to examine the positive and adverse effects of daily iron supplementation in children, including in malaria-endemic areas.

OBJECTIVES

The recommendations in this guideline supersede those of previous WHO guidelines on iron supplementation in children such as *Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers (23)* and the Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas *(80)*, as they pertain specifically to daily oral iron supplementation among infants and children.

SUMMARY OF AVAILABLE EVIDENCE

Three systematic reviews that followed the procedures of the *Cochrane handbook for systematic reviews of interventions (6)* were prepared on the use of iron supplementation among children aged 4–23 months *(81)*, 2–5 years *(46)* and 5–12 years *(82)*. A further review was done on iron supplementation in children in malaria-endemic areas, based on an update of previous systematic reviews *(79, 84).* In all the reviews, iron was administered orally (excluding parenteral administration). All reviews searched the Cochrane Central Register of Controlled Trials, Medline and Embase. Some also searched through the WHO regional databases (African Index Medicus, WHO Regional Office for Africa Health Sciences Library, Latin American and Caribbean Health Science Literature Database, Index Medicus for the South-East Asia Region, the Western Pacific Region, and the Eastern Mediterranean Region *(46, 81, 82)*, the WHO International Clinical Trials Registry Platform *(81, 83)*, the Proquest Digital Thesis *(46, 81, 82),* the Australian Digital Theses Database *(46, 81, 82),* OpenSIG*LE (46, 81)* and OpenGrey *(82)*.

The reviews that limited the analysis to specific age ranges (4–23 month*s (81),* 2–5 years *(46)* or 5–12 years *(82)*) considered studies that specifically recruited children from the specified age range but also included studies if the mean or median fell within the age range, if at least 75% of the subjects fell within the designated age range, or if the majority of the study's recruitment age range overlapped with the review's designated age range. These reviews included studies that recruited otherwise healthy children, excluding studies that recruited only children with severe anaemia, those with developmental disability, or those with conditions that affect iron metabolism. Studies were included if they administered iron daily *(81)* or at least 5 days a week *(46, 82)*. Studies were excluded if they provided iron through point-of-use (home) fortification or fortified food and condiments. Outcomes included haemoglobin concentration, anaemia prevalence, iron deficiency, iron deficiency anaemia, cognitive performance, physical growth and safety (including gastrointestinal adverse events and infections like malaria).

Daily iron supplementation in infants and children aged 6–23 months

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in infants and children aged 6–23 months is based on a systematic review of trials involving infants and children aged 4–23 months *(81)*. The systematic review on daily iron supplementation in infants and young children aged 4–23 months included 33 trials (*n* = 42 015 children). Two of the 33 trials were cluster-randomized trials that involved 32 976 infants and young children. Excluding these two large studies would result in inclusion of 31 trials (9039 infants and young children) *(81)*.

Infants and young children aged 4–23 months who received daily iron supplementation had a lower risk for the critical outcomes of anaemia (risk ratio [RR]: 0.61; 95% confidence interval [CI]: 0.50 to 0.74; 17 trials, *n* = 4825), iron deficiency (RR: 0.30; 95% CI: 0.15 to 0.60; 9 trials, *n* = 2464) and iron deficiency anaemia (RR: 0.14; 95% CI: 0.10 to 0.22; 6 trials, *n* = 2145), compared to children receiving placebo or supplementation without iron.

There was no difference in growth measures between those receiving daily iron supplementation and those receiving placebo or supplementation without iron: stunting (RR: 1.10; 95% CI: 0.92 to 1.32; 3 trials, *n* = 1504) and wasting (RR: 1.03; 95% CI: 0.65 to 1.64; 3 trials, *n* = 1504).

The quality of evidence for the critical outcomes varied from high for iron deficiency anaemia; moderate for anaemia and stunting; and low for wasting and mortality, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(5, 85, 86)*. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in infants and young children aged 6–23 months is shown in Annex 1A.

Recommendation

- Daily iron supplementation is recommended as a public health intervention in infants and young children aged 6–23 months, living in settings where anaemia is highly prevalent,[1] for preventing iron deficiency and anaemia (*strong recommendation, moderate quality of evidence*).

The suggested scheme for daily iron supplementation in infants and young children (6–23 months of age) is presented in Table A.

Table A. Suggested scheme for daily iron supplementation in infants and young children aged 6–23 months

TARGET GROUP	**Infants and young children (6–23 months of age)**
SUPPLEMENT COMPOSITION	10–12.5 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 10–12.5 mg of elemental iron equals 50–62.5 mg of ferrous sulfate heptahydrate, 30–37.5 mg of ferrous fumarate or 83.3–104.2 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

[1] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) (*7*).

Rationale

The guideline development group took into consideration the following factors during the deliberations:

- The outcome of iron deficiency anaemia had high-quality evidence. Heterogeneity in results was noted for the outcomes of anaemia and iron deficiency but was related to different beneficial effect sizes rather than different effects. The effect sizes of the intervention on the outcomes were large. The evidence for morbidity and developmental outcomes is weak but the recommendation does not directly address these outcomes.

- In cases where the population prevalence of anaemia is greater than 40%, the causes of anaemia are multifactorial and unlikely to be exclusively caused by iron deficiency. Even taking this into account, most children in most cases will benefit from iron supplementation in settings of high anaemia prevalence.

- Not enough data are available on long-term harm, for instance on overdose, specifically for children who are iron replete.

Daily iron supplementation in children aged 24–59 months

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in children aged 24–59 months is based on a systematic review of trials involving children aged 2–5 years *(46)*. The systematic review on the effects of daily iron supplementation in preschool-age children aged 2–5 years included 15 trials (*n* =4212 children) *(46)*.

Only one trial reported on anaemia and none of the included trials reported on the other critical outcomes of iron deficiency or iron deficiency anaemia specifically. However, ferritin, an indicator of iron stores and a biomarker for iron deficiency, was reported in five trials. Children receiving daily iron supplementation had higher ferritin concentrations compared to children receiving placebo or supplementation without iron (mean difference [MD]: 11.64 ng/mL; 95% CI: 6.02 to 17.25; 5 trials, *n* = 944). Additionally, haemoglobin, a biomarker used to diagnose anaemia using age- and sex-specific cut-off values, was reported in nine trials. Children receiving daily iron supplementation had a higher mean haemoglobin concentration than those receiving placebo or supplementation without iron (MD: 6.97 g/L; 95% CI: 4.21 to 9.72; 9 trials, *n* = 2154).

There were no differences between children receiving daily iron supplementation and those receiving a placebo or supplementation without iron, in terms of final height (MD: –0.1 *Z*-score; 95% CI: –1.14 to 0.12; 3 trials, *n* = 634) and final weight (MD: –0.04 *Z*-score; 95% CI: –0.12 to 0.05; 2 trials, *n* = 634).

The quality of evidence for the critical outcomes was very low for anaemia and low for measures of physical growth, using GRADE methodology *(5, 85, 86)*. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in children aged 24–59 months is shown in Annex 1B.

Recommendation

- Daily iron supplementation is recommended as a public health intervention in preschool-age children aged 24–59 months, living in settings where anaemia is highly prevalent,[1] for increasing haemoglobin concentrations and improving iron status (*strong recommendation, very low quality of evidence*).

[1] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

The suggested scheme for daily iron supplementation in preschool-age children (24–59 months of age) is presented in Table B.

Table B. Suggested scheme for daily iron supplementation in children aged 24–59 months

TARGET GROUP	**Preschool-age children (24–59 months of age)**
SUPPLEMENT COMPOSITION	30 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups/tablets
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

Rationale

The guideline development group took into consideration the following factors during the deliberations:

- Only one study reported on anaemia; none of the studies reported on iron deficiency or iron deficiency anaemia. However, synthesis of evidence from studies that reported on ferritin concentrations and haemoglobin levels had high quality.
- There is no clear evidence regarding harms at proposed doses for diarrhoea and other gastrointestinal effects, liver damage, insulin resistance or iron overload.
- In well-established and well-functioning health-systems settings, the additional costs of distributing iron supplementation may be low. This may not be the case in low-resource settings. Therefore, reaching the children in need and ensuring a high coverage, taking into account the operational costs, merits consideration.

Daily iron supplementation in children aged 60 months and older

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in children aged 60 months and older is based on a systematic review of trials involving children aged 5–12 years. The systematic review on daily iron supplementation in school-age children aged 5–12 years included 32 trials (*n* = 7089 children) *(82)*.

Children receiving daily oral iron supplements had a lower risk of the critical outcomes of anaemia (RR: 0.50; 95% CI: 0.39 to 0.64; 7 trials, *n* = 1763), iron deficiency (RR: 0.21; 95% CI: 0.07 to 0.63; 4 trials, *n* = 1020) and iron deficiency anaemia (RR: 0.12; 95% CI: 0.02 to 0.66; 2 trials, *n* = 334).

There was a small but statistically significant difference in final height between children receiving daily iron supplementation and those receiving a placebo or supplementation without iron (MD: 0.09 *Z*-score; 95% CI: 0.01 to 0.17; 5 trials, *n* = 1318) but not in final weight (MD: 0.10 *Z*-score; 95% CI: –0.03 to 0.23; 5 trials, *n* = 1318).

The quality of evidence varied between high (for the critical outcomes of anaemia, iron deficiency and iron deficiency anaemia) and low (for growth measures), using the GRADE methodology *(5, 85, 86)*. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in children aged 60 months and older is shown in Annex 1C.

Recommendation

- Daily iron supplementation is recommended as a public health intervention in school-age children aged 60 months and older, living in settings where anaemia is highly prevalent[1], for preventing iron deficiency and anaemia (*strong recommendation, high quality of evidence*).

The suggested scheme for daily iron supplementation in school-age children (5–12 years of age) is presented in *Table C.*

Table C. Suggested scheme for daily iron supplementation in school-age children (5–12 years of age)

TARGET GROUP	**School-age children (5–12 years of age)**
SUPPLEMENT COMPOSITION	30–60 mg elemental iron[a]
SUPPLEMENT FORM	Tablets or capsules
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate or 250–500 mg of ferrous gluconate.

[b] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

Rationale

The guideline development group took into consideration the following factors during the deliberations:

- The evidence is of high quality for priority outcomes (anaemia, iron deficiency, iron deficiency anaemia). Cognition and growth may be as important as haemoglobin and anaemia in this age group and the quality of evidence for these outcomes is moderate.

- The main challenge may be in reaching this age group. They can be reached through school-based programmes but success may then depend on the school systems and the attendance rates. Some consideration will need to be made for reaching children outside of the school system.

- No major harms were identified in this age group, though there is not enough evidence on gastrointestinal effects, potential toxic endpoints and the impact of iron overload.

Daily iron supplementation in infants and children in malaria-endemic areas

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in infants and children in malaria-endemic areas is based on a systematic review of trials involving children living in malaria hyper- or

[1] In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS) *(7)*.

holo-endemic areas *(83).* The systematic review on daily iron supplementation in children in malaria hyper- or holo-endemic areas included 39 trials (*n* = 32 759 children). The majority (*n* = 30) of the trials were individually randomized and nine trials were cluster randomized *(83)*. This is an update of previously published Cochrane reviews *(78, 84)*. The review included children aged less than 18 years, with or without anaemia at baseline. Pregnant women were excluded. The review included studies that gave oral iron through any form, including fortification of food or drink, as long as they provided at least 80% of the recommended daily allowance by age for the prevention of anaemia *(36).* Studies were included if they administered iron for any duration or interval.

There was no difference in the risk of clinical malaria between the iron-supplementation group and those receiving placebo or supplementation without iron (RR: 0.93; 95% CI: 0.87 to 1.00; 14 trials, *n* = 7168). The risk for clinical malaria among children receiving iron supplementation was lower, specifically among those younger than 2 years of age (RR: 0.89; 95% CI: 0.82 to 0.97; 5 trials), though there was no significant statistical difference between age groups (test for subgroup difference χ^2 = 3.56; *P* = 0.17). In the subgroup of children who did not have anaemia at baseline in particular, there was no difference in the risk for clinical malaria between those in the iron-supplementation or in the control group (RR: 0.97; 95% CI: 0.86 to 1.09; 5 trials, *n* = 4986).

In the studies where malaria-prevention and treatment programmes were being implemented, the risk of clinical malaria was lower for children randomized to receive iron supplementation (RR: 0.91; 95% CI: 0.84 to 0.97; 7 trials, *n* = 5586). However, in the subgroup of studies in which there was no malaria-prevention or treatment programme being implemented during the study, the risk for malaria among children receiving iron supplementation was higher (RR: 1.16; 95% CI: 1.02 to 1.31; 9 trials, *n* = 19 086; test for subgroup difference χ^2 = 15.70; *P* < 0.01).

The risk for clinical malaria among children receiving iron supplementation was lower when clinical malaria was accompanied by high-grade parasitaemia (RR: 0.90; 95% CI: 0.81 to 0.98; 6 trials). There was no difference in risk between the children receiving iron versus those receiving placebo or no treatment in terms of all-cause mortality (risk difference: 0.00; 95% CI: 0.00 to 0.01; 18 trials, *n* = 7576).

The quality of evidence was moderate for clinical malaria and high for severe malaria and all-cause mortality, using the GRADE methodology *(5, 85, 86).* The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in malaria-endemic areas is shown in Annex 1D.

Recommendation

- In malaria–endemic areas, the provision of iron supplementation in infants and children should be done in conjunction with public health measures to prevent, diagnose and treat malaria *(strong recommendation, high quality of evidence).*

Rationale

The guideline development group took into consideration the following factors during the deliberations:

- The evidence that iron supplementation does not increase the risk of clinical malaria is of moderate quality, owing to publication bias (no small studies in favour of iron supplementation have been published). The quality of evidence that iron supplementation in malaria-endemic areas decreases the risk of severe malaria and does not increase the risk of death is high.

- In malaria-endemic settings with limited malaria prevention and clinical care, universal iron supplementation may be associated with an increased risk of malaria.

- The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas. The cost and logistics that would otherwise be used to screen for anaemia prior to universal iron supplementation in settings where anaemia is highly prevalent can be channelled to other priority health interventions.

Remarks

The remarks in this section are intended to give some considerations for implementation of the recommendations, based on the discussion of the guideline development group.

- Daily iron supplementation is a preventive strategy for implementation at the population level. If a child is diagnosed with anaemia, national guidelines for the treatment of anaemia should be followed.

- If the prevalence of anaemia is 20–40%, intermittent regimens of iron supplementation can be considered *(87)*.

- The selection of the most appropriate delivery platform should be context specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements.

- In malaria-endemic areas, iron supplementation does not increase the risk of clinical malaria or death when regular malaria-surveillance and treatment services are provided. Oral iron interventions should not be given to children who do not have access to malaria-prevention strategies (e.g. provision of insecticide-treated bednets and vector-control programmes), prompt diagnosis of malaria illness, and treatment with effective antimalarial drug therapy.

- The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas. There is no need to screen for anaemia prior to iron supplementation in settings where anaemia is highly prevalent.

- In the presence of comprehensive surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation. Insufficient and inequitable health-care services are associated with an increase in risks in general.

- Infants and children under 5 years of age are at considerably higher risk of contracting malaria *(66)*. The WHO *Global technical strategy for malaria 2016–2030* provides a technical framework to guide and support malaria-endemic countries as they work towards malaria control and elimination *(89)*.

Iron supplementation is the customary intervention that comes to mind to address anaemia but it should ideally form only a part of a comprehensive, integrated programme for anaemia reduction, antenatal and neonatal care, and improved infant and young child nutrition. Interventions for decreasing iron deficiency or iron deficiency anaemia should include nutrition counselling that promotes diet diversity and food combinations that improve iron absorption; malaria-control programmes including intermittent preventive treatment of malaria in pregnancy and in children, as well as use of insecticide-treated bednets; control of parasitic infections; and improvement in sanitation. Antenatal programmes should promote adequate gestational weight gain and other complementary measures for monitoring, prevention and control of anaemia, such as screening for anaemia, deworming treatment and a referral system for the management of cases of severe anaemia. Delayed umbilical cord clamping is effective in preventing iron deficiency in infants and young children. Other options for children include fortification of staple foods and provision of micronutrient powders, including iron.

RESEARCH PRIORITIES

Discussions between the members of the WHO guideline development group and the external review group highlighted the limited evidence available in some areas, meriting further research on iron supplementation in infants and children, particularly in the following areas:

- the optimal dose, schedule and duration of iron supplementation; the effect of different doses and durations of iron supplementation on different severity, prevalence and causes of anaemia in all WHO regions;
- additional data on the safety of iron supplementation (liver damage; iron overload after continuing the supplementation programme for a number of years; iron supplementation given in conjunction with other interventions; insulin resistance; effects in non-anaemic or non-iron-deficient children);
- the effect of adding other micronutrients to the iron supplement on haemoglobin concentrations and the prevalence of anaemia;
- implementation research on effective behaviour-change strategies for sustained adherence and alternative delivery mechanisms for iron supplements;
- additional long-term studies on functional outcomes (e.g. cognitive and motor development).

DISSEMINATION, IMPLEMENTATION AND ETHICAL CONSIDERATIONS

Dissemination

The current guideline will be disseminated through electronic media, such as slide presentations and the World Wide Web, through either the WHO Nutrition mailing lists *(89)*, social media, the WHO nutrition website *(89)* or the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(89)*. eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines; biological and behavioural rationales; and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. Derivative products such as summaries and collation of recommendations related to iron supplementation will be developed for a more tailored product that is useful for end-users.

Particular attention will be given to improving access to these guidelines for stakeholders that face more, or specific, barriers in access to information, or to those who play a crucial role in the implementation of the guideline recommendations, for example, policy-makers and decision-makers at subnational level that disseminate the contents of the guideline, and health workers and education staff that contribute to the delivery of the intervention. Disseminated information may emphasize the benefits of iron supplementation for infants and children in populations or regions presenting an important risk of anaemia and iron deficiency. In addition, these guidelines and the information contained therein should be accessible to the nongovernmental organizations working in coordination with national authorities on the implementation of nutrition interventions, especially those related to the prevention and control of anaemia in infants and children.

Implementation

As this is a global guideline, it should be adapted to the context of each Member State. Prior to implementation, a public health programme that includes the provision of iron supplements to children should have

well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels, and potential stakeholders. Ideally, iron supplementation should be implemented as part of an integrated programme on child health, which includes addressing micronutrient deficiencies.

Considering the actual experience of children and their caregivers with the intervention is also a relevant implementation consideration: ongoing assessment of the accessibility and acceptability of the intervention can inform programme design and development, in order to increase therapeutic adherence and better assess the impact of the programme. This is particularly relevant in settings where the prevailing social norms and determinants may set unequal conditions and opportunities for different groups. For instance, in some settings, gender norms may create unequal opportunities for girls and boys at any age, within and outside of school; in other settings, social perceptions around ethnicity and race intervene in how certain population groups access and use an intervention.

Furthermore, intersectoral action is fundamental in those settings where the intervention is delivered in coordination with the education sector. The education sector is an important partner in the implementation of the recommendation referring to school-age children. Appropriate coordination mechanisms and proper training of health workers and education staff is necessary for delivery of the intervention and also for collection of data needed for programme monitoring and surveillance, including information on factors related to health inequities.

Specific efforts to increase the acceptability of the intervention to children and their caregivers are also important. Greater acceptability and adoption are better achieved if they are accompanied by simple and easy-to-access information that can be understood by different population groups, in a way that is culturally appropriate and understandable.

Accessing hard-to-reach population groups is extremely important during implementation stages, as it contributes to preventing or tackling health inequities and to furthering the realization of children's rights to health. Appropriate surveillance and monitoring systems can thus provide information on the impact of the disseminated guidelines and their implementation (including information on the adequacy of funding and the effectiveness of the supply chain and distribution channels).

Regulatory considerations

The development of norms, standards and guidelines to promote quality assurance and quality control is a responsibility enshrined in WHO's Constitution. Their development involves consultation with and input from regulatory authorities in the country, including its national drug quality-control laboratories *(91)*.

The WHO Essential Medicines List (EML) compiles medicines that satisfy the priority health-care needs of populations and are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness *(92)*. Hence, the WHO EML is used by countries for the development of their own national essential medicines lists. The quality criteria for vitamins and minerals included in the WHO EML should take into account WHO/Food and Agriculture Organization of the United Nations standards *(93)*.

Universal access to essential medicines is part of the approach of universal health coverage and is used to assess national commitment and progress towards the highest attainable standard of health. Three basic criteria contribute to promoting access to essential medicines: quality, pricing and supply. WHO's regulatory capacity guidance can assist Members States in need of support, in terms of availability, quality and safety of essential medical products, decrease of prices, and improvement of financing, health insurance and social-protection coverage mechanisms *(94).*

Ethical considerations

Ethics refers to standards of what is right or wrong and fair or unfair, which can advise people on what to do and not do in terms of rights, obligations and benefits to society and individuals. Ethics is central to science, research, policy-making and implementation. Every field of human action, including public health nutrition, is subject to facing ethical challenges.

Four principles constitute the most widely accepted framework for ethics in medicine, and are used in other health-related fields: (i) respect for individual autonomy; (ii) beneficence; (iii) non-maleficence; and (iv) justice. These principles assist health workers in identifying whether an intervention is producing benefits to individuals and communities; preventing harms, also at the individual and societal levels; distributing health benefits across social groups, i.e. how much an intervention is contributing to health equity; and respecting and promoting the exercise of human rights.

The delivery of micronutrients to infants and children with micronutrient deficiency is in line with the right to health of children and with the aforementioned ethical principles. For this reason, an assessment of the ethical implications of implementing this intervention is pertinent in malaria-endemic settings, owing to the possible interactions and potential adverse effects of increased iron intake by children affected by malaria. Children who live in malaria-endemic settings should indeed receive adequate iron. However, the provision of iron supplementation should be done in conjunction with public health measures to prevent, diagnose and treat malaria. Otherwise, a nutrition programme working in isolation and not coordinated with a malaria-prevention and treatment programme may lead to unintentional harm, absence of benefit and increased health inequities.

Coordination with public health measures to prevent, diagnose and treat malaria is not just a sound implementation decision, but also an ethics-informed decision. Such coordination should comprise appropriate training for health workers in public health nutrition, so they are knowledgeable of the particular requirements of an iron-supplementation programme for infants and children that should be observed in malaria-endemic areas. Such training should also be provided to education staff co-working in the implementation of this intervention in school-age children and educational settings.

These considerations by no means imply that iron supplementation should not be provided to children in malaria-endemic settings. On the contrary, children in these settings should receive iron supplementation, inasmuch as they suffer greater vulnerability to ill-health, including malnutrition. It requires, however, that appropriate coordination between nutrition and malaria programmes is in place, so the intervention can actually produce health benefits.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages *(95)*. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Evidence and Programme Guidance Unit, jointly with the United States Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has developed a generic logic model for micronutrient interventions in public health *(96)*, to depict the plausible relationships between inputs and expected SDGs, by applying the micronutrient programme evaluation theory. Member States can adjust the model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful escalation of nutrition actions in public health programmes. Additionally, the WHO/CDC *eCatalogue of indicators for micronutrient programmes (97)*, which utilizes the logic model, has been developed as a user-friendly and non-comprehensive web resource for those actively engaged in providing technical assistance in monitoring,

evaluation and surveillance of public health programmes implementing micronutrient interventions. Indicators for iron supplementation are currently being developed and, once complete, will provide a list of potential indicators with standard definitions that can be selected, downloaded and adapted to a local programme context. The eCatalogue will serve as a repository of indicators to monitor and evaluate micronutrient interventions. While it does not provide guidance for designing or implementing a monitoring or evaluation system in public health, some key indicators may include useful references for that purpose.

Since 1991, WHO has hosted the VMNIS micronutrients database *(7)*. Part of WHO's mandate is to assess the micronutrient status of populations, monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition, and track related trends over time. The Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development manages the VMNIS micronutrient database, through a network of regional and country offices, and in close collaboration with national health authorities.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into actions. The Global database on the Implementation of Nutrition Action (GINA) *(98)* provides valuable information on the implementation of numerous nutrition policies and interventions. The use of GINA has grown steadily since its launch in November 2012.

An efficient system for the routine collection of relevant data, including relevant determinants of health, therapeutic adherence, and measures of programme performance, is critical to ensure supplementation programmes are effective and sustained, and drivers to the achievement of the right to health for all population groups. Monitoring differences across groups in terms of accessibility, availability, acceptability and quality of the interventions contributes to the design of better public health programmes. The creation of indicators for monitoring can be informed by the approaches of social determinants of health *(98)*, so inequities can be identified and tackled. It is particularly important to design sound implementation strategies to serve as the base for scaling up efforts. Appropriate monitoring requires suitable data, so efforts to collect and organize information on the implementation are also fundamental.

GUIDELINE DEVELOPMENT PROCESS

This guideline was developed in accordance with the WHO evidence-informed guideline-development procedures, as outlined in the *WHO handbook for guideline development (4).*

Advisory groups

The WHO Steering Committee for Nutrition Guidelines Development (see Annex 6), led by the Department of Nutrition for Health and Development, was established in 2009 with representatives from all WHO departments with an interest in the provision of scientific nutrition advice. The WHO Steering Committee for Nutrition Guidelines Development meets twice yearly and both guided and provided overall supervision of the guideline development process. Two additional groups were formed: a guideline development group and an external review group.

Two guideline development groups participated in the development of this guideline (see Annex 7). Their role was to advise WHO on the choice of important outcomes for decision-making and on interpretation of the evidence. The WHO guideline development group – nutrition actions includes experts from various WHO expert advisory panels and those identified through open calls for specialists, taking into consideration

a balanced gender mix, multiple disciplinary areas of expertise, and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process), and technical staff from WHO and ministries of health from Member States. Representatives of commercial organizations may not be members of a WHO guideline group.

The final draft guideline was peer-reviewed by three content experts, who provided technical feedback. These peer-reviewers (see Annex 8) were identified through various expert panels within and outside WHO *(5, 85, 86, 101)*.

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions (and the components of the questions) to be addressed in the guideline formed the critical starting point for formulating the recommendation. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, based on the policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (see Annex 11). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development and the guideline development group – nutrition actions, and were modified as needed.

A meeting of the guideline development group – nutrition actions was held on 14–16 March 2010, in Geneva, Switzerland, to finalize the scope of the questions and rank the outcomes and populations of interest for the recommendations on iron supplementation. The guideline development group discussed the relevance of the questions and modified them as needed. The group scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key questions on this intervention, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 11.

Four systematic reviews *(46, 81, 82, 83)* were used to summarize and appraise the evidence, using the Cochrane methodology *(6)* for randomized controlled trials and observational studies. Evidence summaries were prepared according to the GRADE approach to assess the overall quality of the evidence *(5, 85, 86, 101)*. GRADE considers the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic review and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. The draft recommendation was discussed by the WHO Steering Committee for Nutrition Guidelines Development and in consultations with the WHO guideline development group – nutrition actions, held on 14–18 March 2011 and 23–26 June 2014 in Geneva, Switzerland.

The procedures for decision-making are established at the beginning of the meetings, including a minimal set of rules for agreement and decision-making documentation. At least two thirds of the guideline development group should be present for an initial discussion of the evidence and proposed recommendation and remarks. The members of the guideline development group secretly noted the direction and strength of the recommendation using a form designed for this purpose, which also included a section for documenting their views on (i) the desirable and undesirable effects of the intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (see Annex 2). Each member used one form, if not advised otherwise after managing any potential conflict of interests. Abstentions were not allowed. The process was improved with the availability of a predefined link to an online form prepared using survey

software. Subsequent deliberations among the members of the guideline development group were of private character. The WHO Secretariat collected the forms and disclosed a summary of the results to the guideline development group. If there was no unanimous consensus (primary decision rule), more time was given for deliberations and a second round of online voting took place. If no unanimous agreement was reached, a two-thirds vote of the guideline development group was required for approval of the proposed recommendation (secondary decision rule). Divergent opinions could be recorded in the guideline. The results from voting forms are kept on file by WHO for up to 5 years. Although there was no unanimous consensus, more than 80% of the guideline development group members decided that each recommendation was strong.

WHO staff present at the meeting, as well as other external technical experts involved in the collection and grading of the evidence, were not allowed to participate in the decision-making process. Two co-chairs with expertise in managing group processes and interpreting evidence were nominated at the opening of the consultation, and the guideline development group approved the nomination. Members of the WHO Secretariat were available at all times, to help guide the overall meeting process, but did not vote and did not have veto power.

MANAGEMENT OF COMPETING INTERESTS

According to the rules in the WHO *Basic documents (102)* and the processes recommended in the *WHO handbook for guideline development (4)*, all experts participating in WHO meetings must declare any interest relevant to the meeting, prior to their participation. The responsible technical officer and the relevant departments reviewed the declarations-of-interest statements for all guideline development group members before finalization of the group composition and invitation to attend a guideline development group meeting. All members of the guideline development group, and participants of the guideline development meetings, submitted a declaration of interests form, along with their curriculum vitae, before each meeting. Participants of the guideline development group meetings participated in their individual capacity and not as institutional representatives. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of competing interests strictly followed the WHO guidelines for declaration of interests. The management of the perceived or real conflicts of interest declared by themembers of the guideline group is summarized next.[1]

Dr Beverley-Ann Biggs declared that the University of Melbourne received funding from the National Health and Medical Research Council and Australian Research Council for research on intermittent iron and folic acid supplementation in pregnancy, conducted in collaboration with the Research and Training Center for Community Development, the Key Centre for Women's Health and the Murdoch Children's Research Institute. It was agreed that she could participate fully in the deliberations and decision-making on this guideline.

Dr Luz Maria De-Regil declared that her present employer is an international nongovernmental organization devoted to the improvement of micronutrient status among infants, children and women. These activities are primarily financed by the government of Canada. The Micronutrient Initiative (MI) is a leading organization working exclusively to eliminate vitamin and mineral deficiencies in the world's most vulnerable populations. It was decided that Dr De-Regil could be a member of the guideline development group and would disclose her interests and the interests of her organization in the relevant guidelines related to micronutrient interventions. She participated in the deliberations related to recommendations for iron supplementation but recused herself from voting on this guideline.

[1] A conflict-of-interest analysis must be performed whenever WHO relies on the independent advice of an expert in order to take a decision or to provide recommendations to Member States or other stakeholders. The term "conflict of interest" means any interest declared by an expert that may affect, or be reasonably perceived to affect, the expert's objectivity and independence in providing advice to WHO. WHO's conflict-of-interest rules are designed to avoid potentially compromising situations that could undermine or otherwise affect the work of the expert, the committee or the activity in which the expert is involved, or WHO as a whole. Consequently, the scope of the inquiry is any interest that could reasonably be perceived to affect the functions that the expert is performing.

Dr Lynnette Neufeld declared that her current employer has received funding in the past 4 years for research and programming related to iron supplementation. At the moment she is not leading any of these initiatives. In a prior position she held with MI, she commissioned research related to iron supplementation. It was decided that Dr Neufeld could be a member of the guideline development group and had to disclose her and her organization's interests in the relevant guidelines related to micronutrient interventions. She could participate in the deliberations but she recused herself from the decision-making (voting) on recommendations related to iron supplementation.

Dr Héctor Bourges Rodriguez declared being chair of the Board of Directors of the Danone Institute in Mexico (DIM), a non-profit organization promoting research and dissemination of scientific knowledge in nutrition, and receiving funds as chair honorarium from DIM. DIM is funded by Danone Mexico, a food company and subsidiary of The Danone Company, Inc. The main products of Danone group worldwide are dairy, bottled water and baby products. Because Danone does not manufacture products nor make claims related to anaemia or iron supplementation, it was agreed that he could participate fully in the deliberations and decision-making on this guideline.

External experts also declared their interest but did not participate in the deliberations or decision-making process.

PLANS FOR UPDATING THE GUIDELINE

The WHO Secretariat will continue to follow the research development in the area of oral iron supplementation in infants and children in malaria-endemic and non-malaria endemic settings, particularly for questions in which the quality of evidence was found to be low or very low. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development (4).*

As the guideline nears the 10-year review period agreed by the guideline development group, the Department of Nutrition for Health and Development at the WHO headquarters in Geneva, Switzerland, along with its internal partners, will be responsible for conducting a search for new evidence.

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ANNEX 1. GRADE SUMMARY OF FINDINGS TABLES

A. Daily iron supplementation in infants and young children aged 6–23 months

Daily oral iron supplementation compared to placebo or control in infants and young children aged 6–23 months

Patient or population: infants and young children aged 6–23 months
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of Pparticipants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.61** (0.50 to 0.74)	4825 (17 RCTs)	⨁⨁⨁⨀ MODERATE [1]	
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	**RR 0.30** (0.15 to 0.60)	2464 (9 RCTs)	⨁⨁⨁⨀ MODERATE [2]	
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	**RR 0.14** (0.10 to 0.22)	2145 (6 RCTs)	⨁⨁⨁⨁ HIGH [3]	
Growth measures (stunting)	**RR 1.10** (0.92 to 1.32)	1504 (3 RCTs)	⨁⨁⨁⨀ MODERATE [4]	
Growth measures (wasting)	**RR 1.03** (0.65 to 1.64)	1504 (3 RCTs)	⨁⨁⨀⨀ LOW [5]	
Mortality (all cause, acute respiratory infections, diarrhoea, malaria)	**Rate ratio 1.10** (0.91 to 1.34)	(3 RCTs)	⨁⨁⨀⨀ LOW [6]	Reported as rate ratio using generic inverse variance method.

*The **risk in the intervention** group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. Thus, the quality of evidence was downgraded owing to inconsistency.
2. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. Thus, the quality of evidence was downgraded owing to inconsistency. The magnitude of effect was large, with the RR is between 0.5 and 0.2 (the quality of evidence was not upgraded for the large effect size seen).
3. There was no serious risk of bias among the studies that included this outcome. The magnitude of effect was very large, with the RR less than 0.2 (the quality of evidence was not upgraded for this).
4. The effect size has a wide confidence interval that range from large benefit to small harm. The quality of evidence for this outcome was downgraded for imprecision.
5. The effect size has a wide confidence interval that range from large benefit to large harm. There was low total number of events. The quality of evidence for this outcome was downgraded for very serious concerns on imprecision.
6. The effect size has a wide confidence interval that range from small benefit to large harm. Only two studies reported on this outcome with a few total number of events. The quality of evidence for this outcome was downgraded for serious concerns on imprecision and possible publication bias.

For details of studies included in the review, see reference *(81)*.

B. Daily iron supplementation in children aged 24–59 months

Daily oral iron supplementation compared to placebo or control in children aged 24–59 months

Patient or population: children aged 24–59 months
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.98** (0.88 to 1.08)	359 (1 RCT)	⨁⊖⊖⊖ VERY LOW [1]	
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	Not estimable	None of the studies reported on this outcome.		
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	Not estimable	None of the studies reported on this outcome.		
Growth measures (height *Z*-score)	The mean growth measures (height *Z*-score) in the intervention group was **0.01 *Z*-score lower** (1.14 lower to 0.12 higher)	634 (3 RCTs)	⨁⨁⊖⊖ LOW [2]	
Growth measures (weight *Z*-score)	The mean growth measures (weight *Z*-score) in the intervention group was **0.04 *Z*-score lower** (0.12 lower to 0.05 higher)	634 (3 RCTs)	⨁⨁⊖⊖ LOW [3]	
Mortality	Not estimable	None of the studies reported on this outcome.		

***The risk in the intervention** group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention **(and its 95% CI).**
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Only one cross-over design study reported on this outcome. The quality of evidence was downgraded for serious risk of bias (incomplete outcome data and selective reporting), indirectness (the age of the participants ranged from 12 to 48 months) and suspected publication bias.
2. The studies synthesized for this outcome had uncertain random sequence generation and allocation concealment. The quality of evidence was downgraded for serious risk of bias and strongly suspected publication bias.
3. The studies synthesized for this outcome had uncertain random sequence generation and allocation concealment. The quality of evidence was downgraded for serious risk of bias and strongly suspected publication bias.

For details of studies included in the review, see reference *(46)*.

C. Daily iron supplementation in children aged 60 months and older

Daily oral iron supplementation compared to placebo or control in children aged 60 months and older

Patient or population: children aged 60 months and older
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.50** (0.39 to 0.64)	1763 (7 RCTs)	⨁⨁⨁⨀ MODERATE[1]	
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	**RR 0.21** (0.07 to 0.63)	1020 (5 RCTs)	⨁⨁⨀⨀ LOW[2]	
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	**RR 0.12** (0.02 to 0.66)	334 (2 RCTs)	⨁⨁⨁⨀ MODERATE[3]	
Growth measures (height *Z*-score)	The mean growth measures (height *Z*-score) in the intervention group was **0.09 *Z*-score higher** (0.01 higher to 0.17 higher)	1318 (5 RCTs)	⨁⨁⨁⨀ MODERATE[4]	
Growth measures (weight *Z*-score)	The mean growth measures (weight *Z*-score) in the intervention group was **0.1 *Z*-score higher** (0.03 lower to 0.23 higher)	1318 (5 RCTs)	⨁⨁⨀⨀ LOW [5]	
Mortality (all cause, acute respiratory infections, diarrhoea, malaria)	not estimable			None of the studies reported on this outcome.

*The **risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. Thus, the quality of evidence was downgraded owing to inconsistency. The magnitude of effect was large, with the RR is between 0.5 and 0.2 (the quality of evidence was not upgraded for the large effect size seen).
2. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. There were no small studies with negative results. Thus, the quality of evidence was downgraded owing to inconsistency and strongly suspected publication bias. The magnitude of effect was large, with the RR is between 0.5 and 0.2 (the quality of evidence was not upgraded for this).
3. Only two studies reported on this outcome with a low total number of events. Neither study had serious risk of bias. The quality of evidence was downgraded for strongly suspected publication bias. The magnitude of effect was very large, with the RR less than 0.2 (the quality of evidence was not upgraded for this).
4. Most of the studies had risk of bias (unknown random sequence generation or allocation concealment or selective reporting).
5. Most of the studies had risk of bias (unknown random sequence generation or allocation concealment or selective reporting). There was significant heterogeneity in studies. The quality of evidence was thus downgraded for serious risk of bias and inconsistency.

For details of studies included in the review, see reference *(82)*.

D. Daily iron supplementation in infants and children in malaria-endemic areas

Daily oral iron supplementation compared to placebo or control in infants and children in malaria-endemic settings

Patient or population: infants and children (aged 6 months to 18 years)
Intervention: iron supplementation1
Comparison: placebo or control
Setting: malaria-endemic areas

Outcomes		Relative effect* (95% CI)	Number of articipants (studies)	Quality of the evidence (GRADE)	Comments
Clinical malaria (fever >37.5 °C and any parasitaemia), all		**RR 0.93** (0.87 to 1.00)	7168 (14 RCTs)	⨁⨁⨁⨀ MODERATE[2]	
Clinical malaria by age:[3]	6–23 months	**RR 0.89** (0.82 to 0.97)	3720 (5 RCTs)		
	24–59 months	**RR 0.97** (0.75 to 1.26)	1415 (3 RCTs)		
	60 months or older	**RR 1.04** (0.91 to 1.20)	2033 (6 RCTs)		
Clinical malaria by baseline anaemia:[4]	Anaemic at baseline	**RR 0.92** (0.84 to 1.00)	2112 (9 RCTs)		
	Non-anaemic at baseline	**RR 0.97** (0.86 to 1.09)	4986 (5 RCTs)		
Clinical malaria by availability of malaria-prevention and treatment programme:[5]	Yes (malaria-prevention and treatment programme available)	**RR 0.91** (0.84 to 0.97)	5586 (7 RCTs)		
	No (malaria-prevention and treatment programme not available or unclear)	**RR 1.16** (1.02 to 1.31)	19 086 (9 RCTs)		
Severe malaria (clinical malaria with high-grade parasitaemia)		**RR 0.90** (0.81 to 0.98)	3421 (6 RCTs)	⨁⨁⨁⨁ HIGH	
All-cause mortality		**Risk difference 0.00** (0.00 to 0.01)	7576 (18 RCTs)	⨁⨁⨁⨀ MODERATE[6]	

*The risk in **the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Both arms might include antimalarial treatment as long as both arms receive the same antimalarial treatment.
2. The quality of evidence was downgraded for possible publication bias. There were no small positive studies in favour of iron.
3. Test for subgroup difference for clinical malaria by age: $\chi^2 = 3.56$; $P = 0.17$
4. Test for subgroup difference for clinical malaria by baseline anaemia: $\chi^2 = 0.61$; $P = 0.43$
5. Test for subgroup difference for clinical malaria by availability of malaria prevention and treatment programme: $\chi^2 = 15.70$; $P<0.01$
6. The quality of evidence was downgrade for possible publication bias.

For details of studies included in the review, see reference (*83*).

ANNEX 2. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN CHILDREN AGED 6–23 MONTHS

QUALITY OF EVIDENCE:	Iron deficiency anaemia had high-quality evidence. The recommendation addresses the outcomes targeted for improvement and for these outcomes the evidence is high, based on several randomized controlled trials. Heterogeneity was noted but was related to different beneficial effect sizes rather than different effects. The effect sizes of the intervention on the outcomes were large. The evidence for morbidity and developmental outcomes is weak but the recommendation does not directly address these outcomes.
VALUES AND PREFERENCES:	In cases where the population prevalence of anaemia is greater than 40%, the causes of anaemia are multifactorial and unlikely to be exclusively caused by iron deficiency. Even taking this into account, most children in most cases will benefit from intermittent iron supplementation or daily supplementation. Iron-replete children might not gain from the intervention. Acceptability might be an issue given associated side-effects (gastrointestinal) and compliance may be difficult. Where access to health facilities is limited, as in many rural areas, the problem may be more prevalent. Inequities in access may thus negatively affect successful implementation.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	Benefits include improved haemoglobin and lower risk of anaemia, which have functional consequences. Potential harms include diarrhoea, but evidence is low or very low or not thoroughly evaluated for potential harms. Not enough data are available on long-term harm, for instance on overdose, specifically for children who are iron replete.
COSTS AND FEASIBILITY:	Cost information was not presented but the cost of iron supplements is generally minor compared to the cost of the delivery platform and the need for strong behaviour change and monitoring. Supplements are generally cheaper lipid-based nutrient supplements.

ANNEX 3. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN CHILDREN AGED 24–59 MONTHS

QUALITY OF EVIDENCE:	The evidence provided is based on studies from different time periods, with small sample sizes and where allocation concealment and random selection were not always evident. Studies varied in terms of dose and duration of treatment. Only one study reported on anaemia; none of the studies reported on iron deficiency or iron deficiency anaemia. Studies that reported on ferritin and haemoglobin had high or moderate quality.
VALUES AND PREFERENCES:	It is important to consider the ability to reach children in need, a child's acceptance of supplementation, family adherence and health-systems issues in the implementation.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	The intervention improves haemoglobin and ferritin concentrations and prevents anaemia. There is no clear evidence regarding harms at proposed doses for diarrhoea and other gastrointestinal effects, liver damage, insulin resistance or iron overload
COSTS AND FEASIBILITY:	In well-established and well-functioning health-systems settings, the costs may be low. This may not be the case in low-resource settings. Therefore, reaching the children in need and ensuring a high coverage merits consideration. The drug cost might be acceptable, but operational costs need to be accounted for, in order to ensure a continuous supply, proper supervision and optimal monitoring, as the target group is very large.

ANNEX 4. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN CHILDREN AGED 60 MONTHS AND OLDER

QUALITY OF EVIDENCE:	The evidence is of high quality for priority outcomes (anaemia, iron deficiency, iron deficiency anaemia). Cognition and growth may be as important as haemoglobin and anaemia in this age group and the quality of evidence for these outcomes is moderate.
VALUES AND PREFERENCES:	The main challenge may be in reaching this age group. Lack of awareness on the importance of prevention and treatment of anaemia may reduce acceptability and compliance.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	The intervention improves anaemia, iron deficiency anaemia and iron deficiency. No major harms were identified in this age group, though there is not enough evidence on gastrointestinal effects, potential toxic endpoints and the impact of iron overload.
COSTS AND FEASIBILITY:	Schools may be an appropriate delivery platform for this age group and thus should be considered. The school infrastructure is usually conducive for implementing this intervention. However, success may then depend on the school systems and the attendance rates. Some consideration might need to be made for children outside of school.

ANNEX 5. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN MALARIA– ENDEMIC AREAS

QUALITY OF EVIDENCE:	The quality of evidence that iron supplementation does not increase the risk of clinical malaria is moderate overall. It was noted that the questions for which the quality of evidence was low or very low may not necessarily be of high priority, for various reasons. Research questions that may be considered as high priority were discussed and listed in this guideline.
VALUES AND PREFERENCES:	Since malaria infection occurs in early infancy and is especially dangerous at this age, in malaria-endemic areas, iron supplements should only be given to infants who sleep under insecticide-treated bednets, and where all episodes of malaria illness can be promptly treated with effective antimalarial drug therapy according to national guidelines.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	In malaria-endemic areas, where there is limited malaria prevention and clinical care, universal iron supplementation may be associated with an increased risk of malaria. Control of infectious diseases and malaria with insecticide-treated bednets and vector control, and treatment of malaria episodes with effective antimalarial therapy, are critical components of health care and should be instituted, together with promotion of exclusive breastfeeding up to the age of 6 months, followed by high-quality complementary feeding.
COSTS AND FEASIBILITY:	In the presence of comprehensive surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation. Insufficient and inequitable health-care services are associated with an increase in risks in general.

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ANNEX 11. QUESTIONS IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

A. Effects and safety of daily iron supplementation in infants and young children aged 6–23 months

Could iron supplements given to infants and young children aged 6–23 months improve health outcomes? If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

POPULATION:	Children aged 6–23 months Subpopulations: – By early exposure to iron: infants who regularly received an iron supplement within the first 6 months of life versus no iron – By feeding practices: exclusively breastfed versus iron-fortified formula versus mixed (breast milk plus iron-fortified formula with or without complementary food, multiple micronutrient powders) – By malaria (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission; with consideration of *Plasmodium falciparum* and/or *Plasmodium vivax*) – By use of concurrent antimalarial measures introduced in the study: yes versus no – By antimalarial measures implemented by the health system: yes versus no – By infant's anaemia status: anaemic versus non-anaemic
INTERVENTION:	Iron supplementation Subgroup analyses: – By dose: 2 mg/kg/day versus other – By frequency: daily versus weekly versus flexible – By duration: 3 months or less versus >3 months – By additional nutrient: in combination with other micronutrients or not – By targeting: universal versus prescribed
CONTROL:	No iron supplementation Placebo Same supplement without iron
OUTCOMES:	Short-term outcomes (age 6–23 months) – Anaemia – Iron deficiency anaemia – Iron deficiency – Morbidity – Malaria incidence and severity (parasitaemia with or without symptoms) – Growth measures: underweight, stunting status, head circumference – Mortality – All cause – Acute respiratory infections – Diarrhoea – Malaria
SETTING:	All countries

B. Effects and safety of daily iron supplementation in children aged 24–59 months

Could iron supplements given to children aged 24–59 months improve health outcomes? If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

POPULATION:	Children aged 24–59 months Subpopulations: – By previous exposure to iron: infants who regularly received an iron supplement within the first 23 months of life versus no iron – By malaria (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission; with consideration of Plasmodium falciparum and/or Plasmodium vivax) – By use of concurrent antimalarial measures introduced in the study: yes versus no – By antimalarial measures implemented by the health system: yes versus no – By anaemia status of population: >40% versus 40% or less
INTERVENTION:	Iron supplementation Subgroup analyses: – By dose: 2 mg/kg/day versus other – By frequency: daily versus weekly versus flexible – By duration: 3 months or less versus >3 months – By additional nutrient: in combination with other micronutrients or not – By targeting: universal versus prescribed
CONTROL:	No iron supplementation Placebo Same supplement without iron
OUTCOMES:	Short-term outcomes (age 24–59 months) – Anaemia – Iron deficiency anaemia – Iron deficiency – Morbidity – Malaria incidence and severity (parasitaemia with or without symptoms) – Growth measures: underweight, stunting status, head circumference – Mortality – All cause – Malaria
SETTING:	All countries

C. Effects and safety of daily iron supplementation in children aged 60 months and older

Could iron supplements given to children aged 60 months and older improve health outcomes? If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

POPULATION:	Children aged 60 months and older Subpopulations: – By previous exposure to iron: infants who regularly received an iron supplement within the first 59 months of life versus no iron – By malaria (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission; with consideration of Plasmodium falciparum and/or Plasmodium vivax) – By use of concurrent antimalarial measures introduced in the study: yes versus no – By antimalarial measures implemented by the health system: yes versus no – By anaemia status of population: >40% versus 40% or less – By individual's anaemia status: anaemic versus non anaemic
INTERVENTION:	Iron supplementation Subgroup analyses: – By dose: 2 mg/kg/day versus other – By frequency: daily versus weekly versus flexible – By duration: 3 months or less versus > 3 months – By additional nutrient: in combination with other micronutrients or not – By targeting: universal versus prescribed
CONTROL:	No iron supplementation Placebo Same supplement without iron
OUTCOMES:	Short-term outcomes (age 6–18 years) – Anaemia – Iron deficiency anaemia – Iron deficiency – Morbidity – Malaria incidence and severity (parasitaemia with or without symptoms) – Mortality – All cause – Acute respiratory infections – Diarrhoea – Malaria
SETTING:	All countries

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Malaria Policy Advisory Committee Meeting

16–17 March 2016, Geneva, Switzerland
Background document for Session 3

Minutes of the Technical Expert Group (TEG) on Drug Efficacy and Response

Crowne Plaza Hotel, Geneva, Switzerland – 10–11 December 2015

Contents

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Acknowledgements

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Abbreviations

ACT	artemisinin-based combination therapy
AL	artemether–lumefantrine
AQ+SP	amodiaquine + sulfadoxine–pyrimethamine
ASAQ	artesunate–amodiaquine
ASMQ	artesunate–mefloquine
ASPY	artesunate–pyronaridine
AS+SP	artesunate + sulfadoxine–pyrimethamine
DER	Drug Efficacy and Response Unit (part of GMP)
DP	dihydroartemisinin–piperaquine
ERG	evidence review group
GMP	Global Malaria Programme
GMS	Greater Mekong subregion
IPTp	intermittent preventive treatment in pregnancy
iRBC	infected red blood cell
K13	*P. falciparum Kelch 13*
KARMA	*K13* Artemisinin Resistance Multicenter Assessment
LBW	low birth weight
MDA	mass drug administration
MDR	multidrug resistant
MFLT	multiple first-line treatments
NMCP	national malaria control programme
NS	non-synonymous
OUCRU	Oxford University Clinical Research Unit
PCR	polymerase chain reaction
Pfcrt	P. falciparum *chloroquine resistance transporter*
Pfdhfr	P. falciparum *dihydrofolate reductase*
Pfdhps	P. falciparum *dihydropteroate synthase*
Pfmdr1	P. falciparum *multidrug resistance protein 1*
qPCR	quantitative PCR
$RSA_{0–3h}$	ring-stage survival assay
SEA	South-East Asia
SMC	seasonal malaria chemoprevention
SP	sulfadoxine–pyrimethamine
TEG	Technical Expert Group
WHO	World Health Organization

Summary and recommendations

The format of the summary and recommendations are similar to those of the previous Technical Expert Group (TEG) (*1*). The TEG's recommendations are made specifically in response to questions directed to the TEG from WHO (Annex 3).

Session 1 Update on artemisinin resistance

Definitions of *confirmed* and *associated K13* mutations are required. The criteria for determining whether a *K13* propeller mutation is confirmed or associated still follow the criteria suggested by the ERG on *K13* 2014; that is, one of the following:

- a statistically significant association ($p < 0.05$) between a *K13* mutation and either a half-life of the parasite clearance slope of ≥5 hours or positive parasitaemia at 72 hours (±2 hours) via a chi-squared test or appropriate multivariable regression model on a sample of at least 20 clinical cases; or
- >1% survival using the $RSA_{0–3h}$ (or >2 standard deviations above the mean value for *K13* wild-type parasites from the same area) in at least five individual isolates with a given mutation; or a statistically significant difference ($p < 0.05$) in the $RSA_{0–3h}$ assay between culture-adapted recombinant isogenic parasite lines, produced using transfection and gene-editing techniques, which express a variant allele of *K13* as compared to the wild-type allele.

A *K13* mutation is *confirmed* when both of these requirements are met, and *associated* when only one of these requirements is met. However, the $RSA_{0–3h}$ and thresholds for in vivo tests are currently only validated for South-East Asian parasites and patients.

The list of associated, confirmed and not associated mutations has been updated as shown in the table below.[1]

***K13* mutation**	**Classification**
E252Q	Not associated
P441L	Associated
F446I	Associated
G449A	Associated
N458Y	Associated
Y493H	**Confirmed**
R539T	**Confirmed**
I543T	**Confirmed**
P553L	Associated
R561H	**Confirmed**
V568G	Associated
P574L	Associated
A578S	Not associated
C580Y	**Confirmed**
A675V	Associated

1. Other rare variants were reported associated with in vivo or in vitro tests, or both: M476I; C469Y; A481V; S522C; N537I; N537D; G538V; M579I; D584V; H719N.

Investigation of associated mutations should be prioritized based on their prevalence, clinical evidence of resistance and the results of the $RSA_{0–3h}$, triggering subsequent transfection studies, if feasible.

A confirmed single *K13* propeller mutation at a threshold prevalence of ≥5% probably signifies selection of the genotype in the parasite population, which is an appropriate indirect measure of the partial artemisinin resistance phenotype. Current research focuses on identifying other possible parasite genetic variants that may facilitate the successful selection of *K13* mutants; however, at present, these possible permissive or compensatory background mutations are insufficiently defined or established.

Currently available tools are sufficient for the detection of artemisinin resistance in an area. The percentage of patients with positive parasitaemia at day 3 is a relevant and practical measure for routine surveillance. Blood filter papers should be routinely collected at day 0 in all studies for identification of *K13* mutations. In the research setting, the parasite clearance slope is currently most appropriate, but other tool including lag phase and tail should not be ruled out. In the context of potential drug resistance, tools to evaluate residual parasitaemia should be considered.

The definition of partial artemisinin resistance has not been amended from TEG 2014 except for the specification of day 3 being 72 hours (±2 hours) after the start of a full artemisinin-based treatment course. At this time, there should be a single global definition of artemisinin resistance.

Suspected endemic artemisinin resistance is defined as:

- ≥5% of patients carrying *K13* resistance-confirmed mutations; or
- ≥10% of patients with persistent parasitaemia by microscopy at 72 hours (±2 hours; i.e. day 3) after treatment with ACT or artesunate monotherapy; or
- ≥10% of patients with a half-life of the parasite clearance slope ≥5 hours after treatment with ACT or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:

- ≥ 5% of patients carrying K13 resistance-confirmed mutations, all of whom have been found, after treatment with ACT or artesunate monotherapy, to have either persistent parasitaemia by microscopy on day 3, or a half-life of the parasite clearance slope ≥ 5 hours.

The detection of artemisinin resistance signifies an epidemiological threat, but does not necessarily signify reduced ACT efficacy as a manifest public health problem. The immediate consequences should be the investigation of possible causes, such as irrational drug use, substandard antimalarial drugs or the importation of resistant genotypes. Detection of resistance must also prompt surveillance and evaluation of ACT efficacy, to assess potential concomitant partner drug resistance (for some partner drugs, molecular markers are available). The priority in such areas is to ensure that antimalarial treatment is based on a definitive diagnosis, that drugs are of good quality, and that there is a good clinical provider and patient adherence. Based on the local epidemiological situation, capacity for intensifying vector-control efforts to interrupt transmission should be investigated, including the potential for malaria elimination. In countries where targeting of malaria control and treatment interventions is directed by risk stratification, the presence of artemisinin resistance is clearly a criterion for upgrading risk.

Session 2 Intermittent preventive treatment in pregnancy (IPTp-SP)

At a population level, IPTp-SP is associated with improved birth outcomes (fewer LBW), irrespective of SP's failure to clear or prevent parasitaemia, in all settings where the prevalence of sextuple mutant haplotype containing *Pfdhps* A581G is below 5%. The presence of parasites bearing the sextuple mutant haplotype containing *Pfdhps* A581G at a prevalence of >35% appears to negate the benefits of IPTp-SP on birth outcomes. Overall, the evidence suggests that IPTp-SP given to women with the sextuple mutant is not harmful. This concern was suggested in a single study, but was not confirmed by later studies. There are no data at present on the effectiveness of IPTp-SP at the prevalence of sextuple mutant haplotype containing *Pfdhps* A581G of 5–35%.

For national malaria control programme (NMCP) settings, molecular surveillance should be used to guide routine assessment of IPTp-SP effectiveness. IPTp-SP should be continued or implemented in areas of unknown, low or moderate SP resistance. In areas of high SP resistance, IPTp-SP may be of more limited benefit, and this benefit is primarily associated with the specific prevalence of the *Pfdhps* A581G sextuple mutation. The threshold of A581G prevalence at which IPTp-SP is no longer of benefit is unclear, but the evidence suggests that there will be no benefit of IPTp-SP at >35% A581G prevalence. However, IPTp in areas with a high prevalence of A581G is not thought to cause harm. Therefore, even in settings of high SP resistance, molecular monitoring of the prevalence of A581G mutations can be used as a proxy for IPTp-SP effectiveness. Molecular surveillance should focus on the *Pfdhps* gene, and in particular on the mutations occurring at codons S436A/F, A437G, K540E, A581G and A613S/T. Methods include aggregate genotyping by sequencing of pooled samples (frequency) or individual-level genotyping by polymerase chain reaction (PCR) and sequencing, or through allele-specific assays such as PCR-RFLP (restriction fragment length polymorphism), PCR-SSOP (sequence specific oligonucleotide probe) and real-time PCR (prevalence). Genotyping may be carried out on parasite samples if collected from a population that has not recently (i.e. in the previous 6 weeks) been treated with antifolates. Sampling should take place every 3 years in areas of low SP resistance, every 2 years in moderate areas, and every year in high areas. Quality control of genotyping should be implemented whether molecular data are generated in-country, in regional laboratories or with international partners.

In research settings, additional considerations are mutations in *Pfdhfr* and the sequencing of each locus, which may identify new mutations in the gene targets of interest. The impact of I431V, which is emerging in Nigeria, needs to be investigated. Although there are sufficient data from areas with low, moderate and high SP resistance, more information is needed from areas with the highest levels of SP resistance, defined by the presence of *Pfdhps* A581G mutants; when these data become available, they will help to define the thresholds at which alternative strategies are needed. In these areas with the highest levels of SP resistance, priority research themes include:

- ecological studies of the impact of IPTp-SP on birth outcome (birth weight), maternal anaemia, and maternal and placental malaria measured at the time of delivery;
- individual-level studies of the impact of *Pfdhps* A581G-bearing parasites on birth outcomes, and of whether this relationship is modified by IPT-SP; and
- effective, well-tolerated, feasible alternatives for prevention.

Session 2 Seasonal malaria chemoprevention (SMC)

The ongoing ACCESS-SMC study will provide more robust information about which SMC measures will be most appropriate – an issue that will need to be revisited by the TEG once the data are available. Both molecular markers and efficacy evaluation are required and, ideally,

some measure of transmission intensity. In addition to the protocol for monitoring drug resistance of the ACCESS-SMC study presented at the TEG meeting, the following parameters should be explored:

- Efficacy evaluation – the ratio of malaria cases in children aged under 5 years versus those aged over 10 years; the occurrence of clinical malaria relative to the time of the previous SMC dose; the incidence of severe malaria at sentinel sites; case–control sampling before each dose for microscopy, gametocytaemia and PCR positivity relative to the time of previous SMC dose.
- Molecular markers – at least Pfcrt K76T and Pfmdr1 N86Y, Y184F and D1246Y (still rare in west Africa) should be determined routinely to track any changes in their prevalence, as an indicator of changes in amodiaquine efficacy. In particular, the prevalence of the Pfcrt codon 72 to 76 haplotype SVMNT (Ser-Val-Met-Asn-Thr) should be determined. Also Pfdhfr and Pfdhps should be included in the molecular markers to be tested.
- Capacity-building – local capacity-building for the monitoring of molecular markers is needed.
- Impact on transmission – assessed through standard membrane feeding assay, if feasible, and parasite genetic indicators of complexity of infection and overall changes in parasite diversity levels, where possible.
- Drug policy effects – the impact of SMC on first-line ACT diversity (and thus drug pressure) should be monitored.

Session 3 Safe and effective treatment in areas of confirmed multidrug resistance (MDR) malaria

Rotational first-line treatment (where the first-line treatment is changed based on updated surveillance data, which can include molecular markers) is already being implemented in Cambodia. However, operational issues in switching therapies are challenging. At present, there is no alternative in Cambodia other than to be flexible, and use rotational first-line treatment.

Information is limited on the efficacy and safety of prolonged treatment with an ACT, triple combination treatment containing an artemisinin and two partner drugs, or sequential ACTs. Once more data are available, it is recommended that the DER TEG should hold a joint session with the Chemotherapy TEG to evaluate the information emerging from these studies.

ASAQ may have a role to play in Cambodia. As a first step, resistance markers for amodiaquine (single nucleotide polymorphism alleles *Pfcrt* 72-76, *Pfmdr1* N86Y, Y184F and D1246Y) and in vitro susceptibility should be examined in GMS isolates. This should be followed by a therapeutic efficacy study of a fixed-dose ASAQ combination in Cambodia in 2016, if molecular marker data suggest reasonable amodiaquine efficacy.

Session 3 Prevention or delay of MDR where it has not been identified

In areas where there is no established MDR, simultaneous deployment of multiple effective ACT first-line treatments (MFLT) is unlikely to hasten, and may actually delay, the emergence of drug resistance, according to modelling studies. Therefore:

- countries that presently have multiple approved ACT first-line treatments should continue to use them; and
- countries that rely on a single ACT first-line treatment are encouraged to add additional effective ACT treatments to the national treatment guidelines, both to potentially delay

the onset of resistance and to be better prepared to respond to failure (or stock-outs) of the current first-line treatment.

Because modelling is the only means of evaluating the impact of MFLT on delaying resistance, the TEG recommends that the Malaria Modelling Consortium be asked to further develop these modelling approaches. Implementation issues should also be considered. The DER TEG is ready to examine outputs from the Malaria Modelling Consortium and any supporting clinical data.

1 Welcome and introduction of guest speakers

The list of participants is provided in Annex 1. All members except J. Thwing and N. Q. Thieu attended the meeting. Organizations invited as observers were the Bill & Melinda Gates Foundation; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the United Kingdom of Great Britain and Northern Ireland (United Kingdom) Department for International Development; the Medicines for Malaria Venture; and the United States (US) Agency for International Development. The meeting agenda is provided in Annex 2.

Membership of the Technical Expert Group (TEG) is rotated every 3 years. Thanks were extended to L. Conteh, C. Karema, C. Rogier and S. Vreden, who have left the TEG; D. Ménard and S. Volkman were welcomed as new members. A further five TEG members will rotate out next year, to maintain a core membership of 15.

The remit of this TEG has changed from "drug resistance and containment" to "drug efficacy and response", to reflect reorganization within the Global Malaria Programme (GMP). The role of this TEG is to advise the GMP's Drug Efficacy and Response Unit (DER) on policy and recommendations regarding drug efficacy and response. Questions directed to the TEG from DER are listed in Annex 3.

2 Declarations of interest

All TEG members participating in the meeting submitted a declaration of interest, which was assessed by DER at GMP and by the Legal department at WHO. WHO policy on how to report conflicts of interest has changed. In the future, TEG member biographies and conflict of interest forms will be placed on the GMP website 2 weeks before the meeting, to comply with the public notice and comment requirements set by WHO.

3 Minutes and action points of TEG 2014

The minutes of the TEG 2014 were accepted (*1*). The chair also summarized the key recommendations of the evidence review group (ERG) on *K13* held in September 2015 in Geneva (Annex 4).

4 Update on drug resistance and new WHO policies

4.1 WHO policies

Presentation

The *Global technical strategy for malaria 2016–2030* (*2*) was adopted by the World Health Assembly in May 2015.

The *Strategy for malaria elimination in the Greater Mekong subregion (2015–2030)* (*3*) was developed in collaboration with six countries, WHO and multiple development partners, and was launched during a side event at the World Health Assembly in May 2015.

Based on available clinical trial data and input from the Malaria Modelling Consortium, the Malaria Policy Advisory Committee (MPAC) made recommendations on mass drug administration (MDA). A policy brief is available on the GMP website (*4*).

Discussion

The highlighting of the Greater Mekong subregion (GMS) as a special situation where MDA is warranted was welcomed; WHO is meeting with GMS partners to reinforce the recommendations for MDA in the region. The implications for MDA of the rapid emergence of resistance to dihydroartemisinin–piperaquine (DP) in Cambodia need to be considered. The TEG commented that MDA should not be used as a general tool to reduce malaria prevalence, and that the focus on areas approaching elimination, epidemics and complex emergencies is appropriate, although "approaching elimination" requires more specific guidance.

4.2 Drug resistance

Presentation

Following detection of the *Plasmodium falciparum Kelch 13* (*K13*) C580Y mutant in Guyana in 2010, a 7-day artesunate and single-dose primaquine clinical trial found no evidence of artemisinin resistance. The next step is a survey comprising 800 samples. No C580Y has been reported from elsewhere in the region.

Artemether–lumefantrine (AL) and artesunate–amodiaquine (ASAQ) remain efficacious in Africa.

Currently, nine countries in the Middle East, eastern Africa and India have recommended artesunate+sulfadoxine–pyrimethamine (AS+SP) as their first-line treatment. However, studies with elevated treatment failure rates have been observed in Somalia, Sudan and north-east India near the Myanmar border, leading to a treatment policy change to AL in this region of India. AS+SP treatment failures are associated with *Pfdhfr* and *Pfdhps* quadruple and quintuple mutants, in the absence of artemisinin resistance. In India, only four isolates with *K13* mutations have been identified so far.

In the GMS, high rates of treatment failure have been reported for DP in western, northern and eastern Cambodia. Artesunate–mefloquine (ASMQ) is 100% efficacious in areas where DP treatment failure is common. Artesunate–pyronaridine (ASPY) failure rates are about 10–15% in western Cambodia. Preliminary results report treatment failures with AL in southern Laos and with DP in Binh Phuoc province of Viet Nam. Investigations are ongoing.

5 Session 1: Update on artemisinin resistance

5.1 Current definition of artemisinin resistance and tools to monitor

Presentation

The current definition of partial artemisinin resistance developed from the TEG 2014 and ERG *K13* 2014 is complex. The list of associated and confirmed *K13* resistance mutations may require expansion, and additional mutations outside *K13* may also be relevant. On average, the parasitaemia at day 3 represents 1–2% of the initial parasitaemia, and the trend does not vary

over time. There is no evidence for the recent emergence of a higher level of artemisinin resistance. The phenotype is confined to a delay in parasite clearance that results from a reduction in ring-stage sensitivity, which seems to be associated with decelerated parasite ring-stage development. Slow parasite clearance in patients treated with an artemisinin-based combination therapy (ACT) causes more parasites to be exposed to the partner medicine alone, increasing the risk of de novo resistance to the partner medicine. Selection of resistance to the partner drug is correlated with the half-life of the partner drug, prolonging the period of subtherapeutic drug levels. In two comparative studies (one in Democratic Republic of Congo and one in Viet Nam), the ACT partner did not affect the clearance time compared to the artesunate monotherapy. The tools used to define artemisinin resistance all have strengths and limitations. Day-3 parasitaemia is highly dependent on the initial parasitaemia, immunity of the patient, skill of the microscopist and method used for slide reading. Although the half-life of the parasite clearance slope is not influenced by the initial parasitaemia, it does not take into consideration the lag phase and the tail, cannot be used for low parasitaemia levels (i.e. it requires at least 1000 parasites/µL) and is difficult to implement in a routine surveillance. In addition, the half-life of the parasite clearance slope also depends on the skill of the microscopist and the method used for slide reading.

Discussion

There should be a single global definition of artemisinin resistance; it should not depend on the region. Although the ring-stage survival assay ($RSA_{0–3h}$) and thresholds for in vivo tests are currently only validated for parasites and patients in South-East Asia (SEA), there are not enough data from other regions to justify the additional complexity of regional definitions of artemisinin resistance.

By focusing the criteria for confirmed artemisinin resistance on *K13* mutations, there was concern that *K13*-independent resistance mutations may be overlooked. It was also noted that the $RSA_{0–3h}$ will only detect changes in drug susceptibility in ring-stage parasites, and that additional in vitro testing may be needed if there are discrepancies between $RSA_{0–3h}$ findings, molecular data and clinical observations. However, these two tools remain fully effective to detect the spread of South-East Asian parasites outside SEA.

As a general recommendation, sample sizes should be sufficient to reliably determine the prevalence of *K13* mutations in a population. However, there may be cases where the identification of a *K13* mutation at a low frequency will require further investigation.

It needs to be explicit that parasite positivity at day 3 means at 72 hours post-treatment (±2 hours). If sampling at this time is not feasible, then the actual sampling time should be recorded. The positivity at day 3 should be corrected for parasitaemia of >1000 to <100 000 parasites/µL if patients with lower or higher parasitaemia levels are included in a study.

5.2 KARMA project

Presentation

The *K13* Artemisinin Resistance Multicenter Assessment (KARMA) project aims to construct a global map of *K13* propeller sequence polymorphisms. Over 14 000 samples from 59 countries (163 sites) have been analysed, yielding 108 non-synonymous (NS) mutations, among which 70 had never been described before and nine had been reported with >1% frequency. In SEA and China, *K13* mutants have reached intermediate frequency to fixation. There was no overlap between the sets of mutations and haplotypes in the Cambodia–Viet Nam region versus the China–Myanmar region. Eight NS mutations observed in SEA and China were associated with day-3 positivity cases (F446I, N458Y, N537D, R539T, I543T, P553L, P574L and C580Y).

South America, Oceania, the Philippines and central and south Asia are free of NS mutations. In Africa, NS mutations are generally uncommon, except in the Central African Republic, Chad, Comoros, Gambia, Guinea, Kenya and Zambia (>3%), where the mutation is mainly A578S. However, the A578S allele does not spread and does not confer in vitro artemisinin resistance; there is no evidence of resistance-conferring alleles in Africa.

Discussion

Not all *K13* mutations are relevant to artemisinin resistance; a signal for selection (e.g. frequency or evidence of spreading) is also required. A prevalence of at least 5% can be considered evidence of selection for a confirmed *K13* mutation. The inclusion of additional data in KARMA from areas of low transmission in Africa would be desirable.

The *K13* F446I mutation has been much more refractory to gene editing. This mutation was engineered into a *K13* donor plasmids for gene editing, and two to three independent transfections were attempted with different parasite strains; no edited parasites were observed. This mutation may carry a fitness cost that precludes it from being readily introduced into a wild-type parasite. $RSA_{0–3h}$ will be conducted by Institut Pasteur and the University of Maryland on culture-adapted strains carrying this specific mutation.

5.3 Slope versus day-3 positivity rate

Presentation

The log-linear section of the parasite clearance slope is the most robust part of the curve for measuring changes in the pharmacodynamic properties of the artemisinins. However, there is significant variation and confounders, such as immunity and splenic clearance rates for infected red blood cells (iRBCs). The half-life cut-off of at least 5 hours performs well for SEA, but it is somewhat arbitrary and depends on the underlying proportions of resistant versus sensitive parasite strains. Immunity can affect the half-life of the parasite clearance slope (by 0.3–1.0 hour).

It was reiterated that the parasite positivity rate at day 3 is a useful screening tool, although it is dependent upon the initial parasitaemia. Hence, a better phenotype for artemisinin resistance (or partial resistance) is needed.

Discussion

In areas of high transmission, demonstrating phenotypic artemisinin resistance using a day-3 positivity rate or the parasite clearance slope may be confounded by high levels of immunity, justifying screening in nonimmune populations, as with the therapeutic efficacy assessments. Also, the impact of artemisinin resistance on the dynamics of parasite clearance outside SEA is unknown. Thus, thresholds for defining the in vivo phenotype for artemisinin resistance may require amendment for other regions.

It is important to include a measure describing residual parasitaemia (the tail end of the parasite clearance curve), because this is relevant for the development and spread of resistance. The day-3 parasite positivity is a pragmatic approach to this. In addition, the log-linear portion of the parasite clearance slope provides robust information for evaluating the delay in parasite clearance caused by artemisinin resistance. Thus, the two measures are complementary.

5.4 Slope and artemisinin resistance

Presentation

The presented model of parasite clearance rates suggests that host immunity dominates the dynamics of parasite clearance unless drug resistance is high. Hence, the model indicates that parasite clearance rates have a poor sensitivity for detecting decreases in drug efficacy. Declining immunity is also predicted to increase parasite clearance times in the absence of resistance. The same model indicates that twice-daily dosing of artemisinin may be more appropriate than once-daily dosing, and has the potential to increase drug efficacy.

Discussion

There is no straightforward method in clinical studies for differentiating between dead and live parasites in iRBCs. Thus, the parasite clearance rate is a "noisy" measure of parasite killing. The log-linear section of the parasite clearance slope is the most robust, and has been shown to correlate closely with the in vitro artemisinin resistant phenotype ($RSA_{0–3h}$), and the *K13* genetically defined resistant parasites. Quantification of the effect of immunity (measured as the presence of *P. falciparum* antibodies) shows that the effect on parasite half-life is about 0.5 hours (up to 1 hour).

The fact that a flattening of the parasite clearance slope can be observed for parasites harbouring *K13* propeller mutations indicates that these mutations have a highly significant effect on the survival of ring-stage parasites following artemisinin therapy. However, this may not result in treatment failure if efficacy of the partner drug is maintained.

Confirmation of artemisinin resistance requires an artesunate monotherapy study. Artesunate for 3 days followed by ACT will provide the parasite clearance slope and day-3 positivity rate, but is no longer recommended as a standard design. A 7-day artesunate monotherapy study will provide additional information on changes in treatment efficacy (recrudescence); this is better aligned with the conventional definitions of antimalarial drug resistance and will detect emergence of higher level of artemisinin resistance.

On its own, the parasite clearance slope is not an appropriate metric for the development of new drugs. Efficacy at day 28 or day 42 remains the gold standard for evaluating the efficacy of new therapies. New combinations should contain active ingredients at dosage regimens that provide high efficacy for each compound if given alone.

Recommendations: Session 1

Definitions of *confirmed* and *associated K13* mutations are required. The criteria for determining whether a *K13* propeller mutation is confirmed or associated still follow the criteria suggested by the ERG on *K13* 2014; that is, one of the following:

- a statistically significant association ($p < 0.05$) between a *K13* mutation and either a half-life of the parasite clearance slope of ≥5 hours or positive parasitaemia at 72 hours (±2 hours) via a chi-squared test or appropriate multivariable regression model on a sample of at least 20 clinical cases; or
- >1% survival using the $RSA_{0–3h}$ (or >2 standard deviations above the mean value for *K13* wild-type parasites from the same area) in at least five individual isolates with a given mutation; or a statistically significant difference ($p < 0.05$) in the $RSA_{0–3h}$ assay between culture-adapted recombinant isogenic parasite lines, produced using transfection and gene-editing techniques, which express a variant allele of *K13* as compared to the wild-type allele.

A *K13* mutation is *confirmed* when both of these requirements are met, and *associated* when only one of these requirements is met. However, the $RSA_{0–3h}$ and thresholds for in vivo tests are currently only validated for South-East Asian parasites and patients.

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A578S	Not associated
C580Y	**Confirmed**
A675V	Associated

Investigation of associated mutations should be prioritized based on their prevalence, clinical evidence of resistance and the results of the $RSA_{0–3h}$, triggering subsequent transfection studies, if feasible.

A confirmed single *K13* propeller mutation at a threshold prevalence of ≥5% probably signifies selection of the genotype in the parasite population, which is an appropriate indirect measure of the partial artemisinin resistance phenotype. Current research focuses on identifying other possible parasite genetic variants that may facilitate the successful selection of *K13* mutants; however, at present, these possible permissive or compensatory background mutations are insufficiently defined or established.

Currently available tools are sufficient for the detection of artemisinin resistance in an area. The percentage of patients with positive parasitaemia at day 3 is a relevant and practical measure for routine surveillance. Blood filter papers should be routinely collected at day 0 in all studies for identification of *K13* mutations. In the research setting, the parasite clearance slope is currently most appropriate, but other tool including lag phase and tail should not be ruled out. In the context of potential drug resistance, tools to evaluate residual parasitaemia should be considered.

The definition of partial artemisinin resistance has not been amended from TEG 2014 except for the specification of day 3 being 72 hours (±2 hours) after the start of a full artemisinin-based treatment course. At this time, there should be a single global definition of artemisinin resistance.

Suspected endemic artemisinin resistance is defined as:

2. Other rare variants were reported associated with in vivo or in vitro tests, or both: M476I; C469Y; A481V; S522C; N537I; N537D; G538V; M579I; D584V; H719N.

- ≥5% of patients carrying *K13* resistance-confirmed mutations; or
- ≥10% of patients with persistent parasitaemia by microscopy at 72 hours (±2 hours; i.e. day 3) after treatment with ACT or artesunate monotherapy; or
- ≥10% of patients with a half-life of the parasite clearance slope ≥5 hours after treatment with ACT or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:

- ≥ 5% of patients carrying K13 resistance-confirmed mutations, all of whom have been found, after treatment with ACT or artesunate monotherapy, to have either persistent parasitaemia by microscopy on day 3, or a half-life of the parasite clearance slope ≥ 5 hours.

The detection of artemisinin resistance signifies an epidemiological threat, but does not necessarily signify reduced ACT efficacy as a manifest public health problem. The immediate consequences should be the investigation of possible causes, such as irrational drug use, substandard antimalarial drugs or the importation of resistant genotypes. Detection of resistance must also prompt surveillance and evaluation of ACT efficacy, to assess potential concomitant partner drug resistance (for some partner drugs, molecular markers are available). The priority in such areas is to ensure that antimalarial treatment is based on a definitive diagnosis, that drugs are of good quality, and that there is a good clinical provider and patient adherence. Based on the local epidemiological situation, capacity for intensifying vector-control efforts to interrupt transmission should be investigated, including the potential for malaria elimination. In countries where targeting of malaria control and treatment interventions is directed by risk stratification, the presence of artemisinin resistance is clearly a criterion for upgrading risk.

6 Session 2: Monitoring efficacy and effectiveness of preventive treatment

6.1 Intermittent preventive treatment in pregnancy

6.1.1 IPTp-SP efficacy and molecular marker for SP resistance

The quadruple mutant (*Pfdhfr* S108N, C59R, N51I; *Pfdhps* A437G) is present in >50% of isolates in central and west Africa. The quintuple mutant (+ *Pfdhps* K540E) is present in >50% of isolates from east Africa. The sextuple mutant (+ *Pfdhps* A581G) is mainly confined to a few areas of east Africa and does not appear to be accelerating towards fixation. Although the impact of SP resistance on the efficacy of intermittent preventive treatment in pregnancy (IPTp)-SP is of concern, there are currently no approved alternatives in Africa.

Low birth weight (LBW) is influenced by many factors. Hence, determining the effect of molecular resistance markers on this outcome in small clinical studies is problematic.

A meta-analysis of individual-level participant data derived from observational studies, including >200 000 pregnancies, indicated that even in areas with >95% prevalence of *Pfdhps* K540E, there was a statistically significant dose–response for a lower risk for LBW associated with each incremental dose of SP, provided the additional (sextuple) *Pfdhps* A581G mutation was still rare (<5% prevalence). There was no association between the administration of SP and a lower risk of LBW in areas where *Pfdhps* A581G was prevalent at >35%, suggesting that the effectiveness of IPTp-SP to reduce LBW is nearly fully compromised in these areas. However, data are lacking for birth outcomes associated with *Pfdhps* A581G sextuple mutation prevalence of 5–35%.

Efficacy is probably not compromised by the presence of the A581G mutation where K540E is absent.

Although one study suggested that IPTp-SP in women with the sextuple mutant was harmful, this has not been confirmed in five additional studies (two of quintuple, three of sextuple mutants). However, *Pfdhps* A581G does appear to be associated with higher parasite densities and malaria-associated reduction in birth weights, possibly reflecting the lack of protective efficacy in women infected with these highly resistant parasites.

Discussion

In the individual-level meta-analysis, the prevalence of *Pfdhps* A581G as sextuple mutation was either <5% or >35%. Although data are lacking and more information is needed to understand the impact at prevalence of *Pfdhps* A581G sextuple mutations between 5% and 35%, the current analysis indicates that at >35% prevalence the impact of IPTp-SP on reduction of LBW is lost.

The positive effect of IPTp-SP on birth weight, despite failure to prevent parasitaemia and reduced efficacy at clearing antenatal parasites, could be due to a combination of its antimicrobial effects, the provision of partial antimalarial protection through suppression of parasite densities in the placenta (rather than clearance) reducing placental pathology, or other off-target effects of SP.

6.1.2 Draft protocol to monitor efficacy of IPTp-SP

Presentation

Three observational protocol modules were considered:

- *Molecular module* – this is a temporal and spatial distribution of molecular markers of SP resistance. In a meta-analysis of aggregated data from 48 published studies reporting more than 54 000 births, the relative risk reduction of LBW associated with IPTp-SP was stratified based on molecular markers in *Pfdhps* with:
    - *low* defined as A437G <50%;
    - *moderate* defined as A437G ≥50% plus K540E <10%, or K540E ≥10% plus <1% A581G; and
    - *high* defined as K540E ≥10% plus A581G ≥1%.

  The relative risk reduction of LBW associated with the receipt of antenatal SP was 28% in low resistance settings, 20% in moderate settings, and 9% in high settings.
- *In vivo module* – this includes the efficacy of SP to clear peripheral parasitaemia in asymptomatic pregnant women and the assessment of post-treatment prophylaxis. Although there is a strong correlation at population level between SP parasite resistance and the efficacy of IPTp with SP to clear existing infections or prevent new infections from occurring, the correlation between the parasite clearance and maternal anaemia, birth weight or other outcomes is weak. These studies are also labour intensive and difficult to conduct, and follow-up is limited to 28 days.
- *Delivery module* – determination of the effects of varying doses of IPTp-SP on malaria infection, maternal anaemia, placental malaria and birth outcomes (LBW). These studies require large sample sizes to detect effects on birth outcomes. They are subject to selection bias because the participant, not the investigator, determines exposure to SP, and pregnant women taking multiple doses of IPTp-SP are different from those

taking one or a few doses. Previous studies have shown only a weak correlation between the level of SP parasite resistance in the population and pregnancy outcomes, and there is considerable variation in the SP protective efficacy in areas of high resistance.

Discussion

Clinical studies are difficult to conduct and interpret, and in vivo studies may lead to premature withdrawing of IPTp-SP, because IPTp-SP continues to be associated with a reduced prevalence of LBW, despite poor efficacy in clearing antenatal parasites.

There is now evidence that molecular markers for SP resistance can be used to evaluate the effectiveness of IPTp-SP.

In the consideration of potential alternative drugs for IPTp, such as DP, the risk of jeopardizing first-line antimalarial drug treatment should also be taken into account.

Recommendations: Session 2 IPTp-SP

At a population level, IPTp-SP is associated with improved birth outcomes (fewer LBW), irrespective of SP's failure to clear or prevent parasitaemia, in all settings where the prevalence of sextuple mutant haplotype containing *Pfdhps* A581G is below 5%. The presence of parasites bearing the sextuple mutant haplotype containing *Pfdhps* A581G at a prevalence of >35% appears to negate the benefits of IPTp-SP on birth outcomes. Overall, the evidence suggests that IPTp-SP given to women with the sextuple mutant is not harmful. This concern was suggested in a single study, but was not confirmed by later studies. There are no data at present on the effectiveness of IPTp-SP at the prevalence of sextuple mutant haplotype containing *Pfdhps* A581G of 5–35%.

For national malaria control programme (NMCP) settings, molecular surveillance should be used to guide routine assessment of IPTp-SP effectiveness. IPTp-SP should be continued or implemented in areas of unknown, low or moderate SP resistance. In areas of high SP resistance, IPTp-SP may be of more limited benefit, and this benefit is primarily associated with the specific prevalence of the *Pfdhps* A581G sextuple mutation. The threshold of A581G prevalence at which IPTp-SP is no longer of benefit is unclear, but the evidence suggests that there will be no benefit of IPTp-SP at >35% A581G prevalence. However, IPTp in areas with a high prevalence of A581G is not thought to cause harm. Therefore, even in settings of high SP resistance, molecular monitoring of the prevalence of A581G mutations can be used as a proxy for IPTp-SP effectiveness. Molecular surveillance should focus on the *Pfdhps* gene, and in particular on the mutations occurring at codons S436A/F, A437G, K540E, A581G and A613S/T. Methods include aggregate genotyping by sequencing of pooled samples (frequency) or individual-level genotyping by polymerase chain reaction (PCR) and sequencing, or through allele-specific assays such as PCR-RFLP (restriction fragment length polymorphism), PCR-SSOP (sequence specific oligonucleotide probe) and real-time PCR (prevalence). Genotyping may be carried out on parasite samples if collected from a population that has not recently (i.e. in the previous 6 weeks) been treated with antifolates. Sampling should take place every 3 years in areas of low SP resistance, every 2 years in moderate areas, and every year in high areas. Quality control of genotyping should be implemented whether molecular data are generated in-country, in regional laboratories or with international partners.

In research settings, additional considerations are mutations in *Pfdhfr* and the sequencing of each locus, which may identify new mutations in the gene targets of interest. The impact of I431V, which is emerging in Nigeria, needs to be investigated. Although there are sufficient data from areas with low, moderate and high SP resistance, more information is needed from areas with the highest levels of SP resistance, defined by the presence of *Pfdhps* A581G mutants;

when these data become available, they will help to define the thresholds at which alternative strategies are needed. In these areas with the highest levels of SP resistance, priority research themes include:

- ecological studies of the impact of IPTp-SP on birth outcome (birth weight), maternal anaemia, and maternal and placental malaria measured at the time of delivery;
- individual-level studies of the impact of *Pfdhps* A581G-bearing parasites on birth outcomes, and of whether this relationship is modified by IPT-SP; and
- effective, well-tolerated, feasible alternatives for prevention.

6.2 Seasonal malaria chemoprevention

6.2.1 Monitoring efficacy of SMC

Presentation

The ACCESS-SMC project aims to provide seasonal malaria chemoprevention (SMC) for 8 million children in seven countries in the Sahel over 2 years. The London School of Tropical Medicine and Hygiene is working with research groups in each country to measure SMC coverage and the impact of SMC on malaria, to support pharmacovigilance and to monitor the efficacy of SMC drugs (AQ+SP). Children aged under 5 years are included, except in Senegal where children aged under 10 years are also treated. The study includes 30 sentinel sites, but is limited to 2 years. A system is needed for collecting surveillance and efficacy data in the future.

Monitoring will provide reassurance about efficacy after 2 years, establish a baseline for future monitoring and indicate factors that may limit the selection of resistance.

The objectives of the protocols are to:

- measure the prevalence of molecular markers associated with resistance to SP and amodiaquine before SMC in the community in children aged under 5 years and in age groups that are too old for SMC;
- measure the change in the prevalence of these markers after 2 years of SMC;
- measure the prevalence of markers in samples from clinical cases (children and adults) in selected clinics before and after SMC;
- monitor the prevalence of markers in cases in adjacent non-SMC areas;
- measure the protective efficacy of SMC treatments (using case–control studies);
- assess the utility of the screening method for monitoring efficacy (from dates of any SMC doses in malaria cases in children in sentinel surveillance clinics);
- monitor coverage and adherence through surveys at the end of each cycle and at the end of each season; and
- if possible, measure clearance of parasitaemia after AQ+SP treatment.

There is still an opportunity to make limited amendments to the protocol.

Discussion

Based on the ACCESS-SMC protocol, recommendations are needed as to what studies should be continued following the 2-year scope of the study. The studies need to be practical, affordable and sustainable for implementation within NMCPs. SMC is a new tool, and data upon which to

base recommendations are sparse. However, there is a need for systems that can be activated at the end of the 2-year ACCESS-SMC study. Thus, general recommendations should be made at this time and re-examined once data are available.

Resources for high-throughput molecular evaluation are currently absent in the region. Coordination and standardization between laboratories needs to be established. It may be possible to leverage existing networks in the region to enhance capacity.

Signals for an effect on transmission should be examined, particularly in Senegal where children aged up to 10 years are being treated.

Reserving amodiaquine for SMC may deter the use of ASAQ and drive the increased use of AL in Africa. AL is already heavily used in Africa, whereas greater ACT diversity should be encouraged.

The use of SP in SMC may influence how it is used in IPTp, for example. In turn, this may affect the type of monitoring necessary.

6.2.2 Modelling prophylactic effect of antimalarial medicines

Presentation

Pharmacokinetic and pharmacodynamic modelling can provide information on the prophylactic potential of antimalarial drugs. As parasite susceptibility decreases, the duration of prophylaxis decreases. Models for AL, ASMQ and DP are well developed and published. Models for ASAQ and IPTp-SP require further development.

Modelling indicates that DP efficacy is extremely vulnerable to decreases in parasite susceptibility to piperaquine, because of its long flat terminal elimination. A small increase in piperaquine resistance can also substantially reduce the period of prophylaxis, which could jeopardize its use in MDA.

Discussion

The drug concentration-parasite clearance relationship is poorly defined, particularly for the artemisinins. It is not clear how the period of prophylaxis for long-acting medicines relates to the window of selection of resistance. However, the models can be used to look at this.

Recommendations: Session 2 SMC

The ongoing ACCESS-SMC study will provide more robust information about which SMC measures will be most appropriate – an issue that will need to be revisited by the TEG once the data are available. Both molecular markers and efficacy evaluation are required and, ideally, some measure of transmission intensity. In addition to the protocol for monitoring drug resistance of the ACCESS-SMC study presented at the TEG meeting, the following parameters should be explored:

- Efficacy evaluation – the ratio of malaria cases in children aged under 5 years versus those aged over 10 years; the occurrence of clinical malaria relative to the time of the previous SMC dose; the incidence of severe malaria at sentinel sites; case–control sampling before each dose for microscopy, gametocytaemia and PCR positivity relative to the time of previous SMC dose.
- Molecular markers – at least Pfcrt K76T and Pfmdr1 N86Y, Y184F and D1246Y (still rare in west Africa) should be determined routinely to track any changes in their prevalence, as an indicator of changes in amodiaquine efficacy. In particular, the prevalence of the Pfcrt codon 72 to 76 haplotype SVMNT (Ser-Val-Met-Asn-Thr) should be determined. Also Pfdhfr and Pfdhps should be included in the molecular markers to be tested.

- Capacity-building – local capacity-building for the monitoring of molecular markers is needed.
- Impact on transmission – assessed through standard membrane feeding assay, if feasible, and parasite genetic indicators of complexity of infection and overall changes in parasite diversity levels, where possible.
- Drug policy effects – the impact of SMC on first-line ACT diversity (and thus drug pressure) should be monitored.

7 Session 3: Prevention and treatment of multidrug resistant malaria

7.1 Definition of multidrug resistant malaria and rotational first line: the example of Cambodia

Presentation

In Cambodia, resistance to DP has spread rapidly. In areas of DP resistance, efficacy of ASMQ was restored to 100%, leading to the recommendation that ASMQ be reintroduced as the first-line ACT in these areas. However, switching to ASMQ has been delayed by complications in procuring the medicine and by issues in the supply chain. The efficacy of ASAQ in Cambodia is unknown, but data from Myanmar and Viet Nam suggest that this drug may have efficacy in the region.

Discussion

Artemisinin delayed clearance does not meet the current conventional WHO 1973 definition of antimalarial drug resistance[3], though a limited number of cases were described as potentially fully resistant to artemisinin.

The definition of multidrug resistance (MDR), which is still valid, requires resistance to more than two operational antimalarial compounds of different chemical classes.

In reporting the findings of therapeutic efficacy tests, ACT resistance is imprecise. ACT treatment failure is a more appropriate term that notes the specific ACT and the nature of the resistance (i.e. artemisinin partial resistance or partner drug resistance, or both).

The restoration of ASMQ efficacy in areas of DP resistance is probably a combination of competing resistance mechanisms and the removal of mefloquine drug pressure.

ASAQ may have a role to play in Cambodia. There is no evidence of cross-resistance between piperaquine and amodiaquine in South-East Asian parasites. Although ASPY does not meet WHO criteria to be introduced as a first-line treatment in western Cambodia, it may be an option in other regions of Cambodia and in the GMS. Cross-resistance between piperaquine and pyronaridine needs to be urgently explored.

Until trials on alternative regimes provide results, there is no alternative in Cambodia other than to be flexible and rotate the first-line ACT based on surveillance data. However, the operational issues involved in changing drug regimens are challenging.

3. Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject.

7.2 Prolonged duration of treatment

Presentation

In a study conducted in the Myanmar–Thailand border area comparing 3-day and 5-day AL therapy, efficacy was 100% and 97%, respectively. There was no difference in quantitative PCR (qPCR) positivity between arms; about 40% of patients were qPCR positive at day 21. Both regimens were well tolerated.

Discussion

There is no efficacy argument to extend AL therapy from 3 days to 5 days in Myanmar, where AL is still highly efficacious. However, extended therapy could theoretically reduce the potential for resistance to develop. Extension of the artemisinin dose to 5 days is closer to the fully effective dose of artemisinin (as a single agent).

7.3 Triple combination

Presentation: TRAC II

TRAC II is testing several different drug regimens in regions with failing ACTs:

- triple ACTs: AL versus AL+AQ, and DP versus DP+mefloquine (currently recruiting);
- arterolane–piperaquine;
- extended course AL (see above); and
- extended course DP (planned, no funding).

Presentation: combined ACTs

An additional short-to-medium solution to a decline in ACT efficacy may be to administer sequential courses of two different ACT regimens, giving a full 6 days of artemisinin. A protocol has been developed using AL followed by DP in Kenya and Tanzania, and ASAQ followed by AL in Burkina Faso. The primary outcomes are parasitological cure, incidence of severe adverse events, laboratory assessment, gametocyte clearance, selection of marker of drug resistance, and acceptability of and adherence to the proposed treatment schemes. This study is powered to detect the effect of submicroscopic residual parasitaemia on late recrudescence.

Discussion

Implementing triple combination therapy or a sequential ACT regimen requires drug interaction data and rigorous safety monitoring. Cardiotoxicity must be assessed particularly, but not only, for piperaquine and mefloquine. A study in Cambodia reported that 30% of care-seeking patients have residual levels of piperaquine in their blood. Higher cumulative artemisinin doses can cause bone marrow suppression at 10–14 days post-therapy; thus, monitoring should be included in any protocol evaluating increased dose or duration of artemisinin.

For triple therapy, it is unlikely that pharmaceutical partners will develop a co-formulated triple combination therapy quickly; hence, a co-blister pack would be necessary. However, the 3-day therapy duration is retained, aiding adherence. The TRAC II protocol was developed before the rapid spread of piperaquine resistance in Cambodia. The efficacy of the triple combination thus requires fast and careful evaluation, because all possible options need to be considered in this region.

For sequential ACT regimens, the drug formulations concerned are already available. In Africa, where standard ACTs are still working, there is the benefit of time, meaning that safety can be assessed rigorously in clinical trials including roll-out to large community trials. Adherence may be problematic with 6-day therapy, although education may improve this situation. A 6-day regimen may be more acceptable in areas with high ACT failure rates. If AL is a component, the switch between once-daily to twice-daily ACT is perhaps a more challenging adherence issue. Ensuring adequate stocks of both components may also be problematic.

In addition to addressing the issue of ACT failures, enhanced ACT regimens (e.g. triple, sequential and extended) should be evaluated for their potential to prevent the emergence and spread of resistance; for example, by computer modelling or the effect on submicroscopic residual parasitaemia. Cost implications for using enhanced ACT regimens should also be taken into consideration.

7.4 Multiple first-line treatments

Presentation

Multiple first-line treatments (MFLT) is the simultaneous distribution of multiple, different first-line treatments against uncomplicated malaria. Thus, with MFLT, different patients receive different treatments. The effect of this approach on delaying resistance development cannot be evaluated in clinical trials because resistance may not emerge for many years. Thus, computer modelling is the only method available to predict whether MFLT is a better approach than the alternative (i.e. cycling of first-line therapies). Two modelling groups had previously presented data to address this question but results differed between the two groups.

The results of a revised model from Oxford University Clinical Research Unit (OUCRU) were presented, indicating that MFLT delays the emergence of resistance to a greater extent than cycling first-line therapies. It also indicated that including a non-ACT drug with >85% efficacy plus two ACTs may be preferable to the deployment of three ACTs.

Implementation of MFLT requires consideration. For example, can therapy distribution be achieved by sector, location, age, or type of clinic or pharmacy? Day-of-the-week randomization requires a lot of infrastructure and education, but allows long-term flexibility.

Discussion

MFLT is not analogous to combination therapy at a population level because simultaneous resistance development to all deployed regimens is not required for parasite survival, only resistance to each individual treatment regimen.

The two published models diverge mainly at high MFLT drug coverage levels (>60%), but not greatly, with one showing a 10% increase and the other a 10% decrease in treatment failures. In the OUCRU model presented, this translates into a longer useful therapeutic life, with resistance emerging after 11 years with MFLT versus 7 years with cycling of first-line therapies. The modelling uses conservative assumptions; in particular, it tests scenarios, which are potentially averse to yielding a benefit, and it includes all reasons for treatment failure rather than just drug resistance. Consequently, the benefit of MFLT is probably underestimated in the OUCRU model.

The model does not allow for pre-existing resistance in the population, only de novo mutations. Thus, in areas such as Cambodia, where resistance is already established and drug therapies are limited, MFLT would probably not be appropriate. The model suggests that MFLT is appropriate for areas where resistance mutations are absent or at a prevalence of about 0.1%.

Modelling how drug resistance mutations appear in a population is complex. For some drugs (e.g. chloroquine), the mutations arise rarely and spread, but for others (e.g. mefloquine), resistance may arise much more frequently. Thus, constructing a model based on how mutations arise is contentious.

The current models are not sufficient to make a clear recommendation for MFLT. Multiple models need to be evaluated, and the Malaria Modelling Consortium should be consulted. However, other existing models of drug resistance may be limited and require further development.

An advantage of having MFLT available is that failing therapies can be discontinued without affecting malaria treatment provision. MFLT can also help to limit drug stock-outs.

Recommendations for MFLT should include pragmatic implementation methods (e.g. using paediatric formulations in children and tablets in adults).

In many countries, MFLT is already a reality. Public and private sector prescribing can vary greatly, with data on private sector prescribing being largely ignored, even though it may account for 80% of treatments in some regions.

Recommendations: Session 3

Safe and effective treatment in areas of confirmed MDR malaria

Rotational first-line treatment (where the first-line treatment is changed based on updated surveillance data, which can include molecular markers) is already being implemented in Cambodia. However, operational issues in switching therapies are challenging. At present, there is no alternative in Cambodia other than to be flexible, and use rotational first-line treatment.

Information is limited on the efficacy and safety of prolonged treatment with an ACT, triple combination treatment containing an artemisinin and two partner drugs, or sequential ACTs. Once more data are available, it is recommended that the DER TEG should hold a joint session with the Chemotherapy TEG to evaluate the information emerging from these studies.

ASAQ may have a role to play in Cambodia. As a first step, resistance markers for amodiaquine (single nucleotide polymorphism alleles *Pfcrt* 72-76, *Pfmdr1* N86Y, Y184F and D1246Y) and in vitro susceptibility should be examined in GMS isolates. This should be followed by a therapeutic efficacy study of a fixed-dose ASAQ combination in Cambodia in 2016, if molecular marker data suggest reasonable amodiaquine efficacy.

Prevention or delay of MDR where it has not been identified

In areas where there is no established MDR, simultaneous deployment of multiple effective ACT first-line treatments (MFLT) is unlikely to hasten, and may actually delay, the emergence of drug resistance, according to modelling studies. Therefore:

- countries that presently have multiple approved ACT first-line treatments should continue to use them; and
- countries that rely on a single ACT first-line treatment are encouraged to add additional effective ACT treatments to the national treatment guidelines, both to potentially delay the onset of resistance and to be better prepared to respond to failure (or stock-outs) of the current first-line treatment.

Because modelling is the only means of evaluating the impact of MFLT on delaying resistance, the TEG recommends that the Malaria Modelling Consortium be asked to further develop these modelling approaches. Implementation issues should also be considered. The DER TEG is ready to examine outputs from the Malaria Modelling Consortium and any supporting clinical data.

References

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Annex 2: Meeting agenda

Technical Expert Group on Drug Efficacy and Response, 10–11 December – Crowe Plaza, Geneva, Switzerland

Thursday 10 December 2015		
09:00–09:15	Welcome **P. Alonso – Director GMP** **A. Dondorp – Chair TEG DER**	
09:15–09:20	Declaration of interest **P. Ringwald**	
09:20–10:00	Minutes and action points of the last TEG meeting and ERG on *K13* **A. Dondorp**	→ For information
10:00–10:30	Update on drug resistance and new WHO policies **P. Ringwald**	→ For information
10:30–11:00	Coffee/tea break	
Session 1: Update on artemisinin resistance		
11:00–12:30	i) Current definition of artemisinin resistance and tools to monitor **P. Ringwald 20' + 10'** ii) KARMA project **D. Ménard 20' + 10'** iii) Slope versus day 3 positivity rate **A. Dondorp 20' + 10'**	→ For information and decision
12:30–13:30	Lunch	
13:30–15:30	iv) Slope and artemisinin resistance **I. Hastings 20' + 10'** **Discussion 90'**	
15.30–16.00	Coffee/tea break	
Session 2: Monitoring efficacy/effectiveness of preventive treatment		
16:00–18:00	i) IPTp-SP efficacy and molecular marker for SP resistance **S. Taylor invited speaker 20' + 10'** ii) Draft protocol to monitor efficacy of IPTp-SP **F. ter Kuile invited speaker 20' + 10'** **Discussion 60'**	→ For information and decision
18:30–20:00	Reception	

Friday 11 December 2015		
Session 2: Monitoring prophylactic effect of preventive treatment		
8:00–9:45	iii) Monitoring efficacy of SMC **P. Milligan invited speaker 20' + 10'** iv) Modelling prophylactic effect of antimalarial medicines **I. Hastings 20' + 10'** **Discussion 45'**	→ For information and decision
9:45–10:15	Coffee/tea break	
Session 3: Prevention and treatment of MDR malaria		
10:15–13:15	i) Definition of MDR malaria and rotational first line: the example of Cambodia **P. Ringwald & S. Sovannaroath 15' + 10'** ii) Prolonged duration of treatment **A. Dondorp & F. Smithuis 15' + 10'** iii) Triple combination TRAC 2 **A. Dondorp 15'** Combined ACTs **C. Sutherland invited speaker 15' + 10'** iv) Multiple first-line treatments **M. Boni invited speaker 15' + 10'** **Discussion 60'**	→ For information and decision
13:15–14:00	Lunch	
14:00–17:00	Adoption of TEG recommendations **A. Dondorp**	Closed session
17:00	Closing remarks **A. Dondorp/P. Ringwald**	Closed session

Annex 3: List of questions

Session 1: Update on artemisinin resistance

K13

1. Are both definitions of *confirmed* and *associated K13* mutation necessary and should the list be updated?
2. Are confirmed *K13* mutations necessary and sufficient to determine the presence of artemisinin resistance?

Tools for detection of artemisinin resistance

3. Are the current tools used for the early detection and monitoring of artemisinin resistance (i.e. percentage of patients positive on day 3, parasite clearance slope, presence of *K13* mutation) adequate?
4. Are there additional or better parameters that could ensure timely detection of AR (e.g. PC90, PCT, …)?

Definition of artemisinin resistance

5. Does the current definition of artemisinin resistance require modification? If so, which ones?
6. Based on the modification of the definition, when is action needed to respond to the presence of artemisinin resistance?
7. What type of programmatic action is needed to respond to confirmed artemisinin resistance?

Session 2: Monitoring efficacy/effectiveness of preventive treatment

Intermittent preventive treatment in pregnancy (IPTp-SP)

8. In asymptomatic pregnant women, is SP failure in clearance and prevention of parasitaemia associated with low birth weight (LBW), maternal anaemia at delivery or placental malaria infection?
9. In pregnant women on IPTp-SP, are infections with *P. falciparum* carrying specific sextuple mutations associated with LBW, increased incidence of maternal parasitaemia, maternal anaemia at delivery or placental malaria compared to falciparum infections not carrying these mutations?
10. Propose the outline protocol of a prospective study to monitor IPTp-SP effectiveness, in particular should the protocol be based on SP parasite clearance, molecular markers of resistance, and/or delivery outcomes (LBW, maternal parasitaemia, maternal anaemia and/or placental malaria)?

Seasonal malarial chemoprevention (SMC)

11. Propose an outline protocol of a prospective study to monitor amodiaquine-SP effectiveness in the context of SMC.

Session 3: Prevention and treatment of multidrug resistant (MDR) malaria

Safe and effective treatment in areas of confirmed MDR malaria

12. In areas with high treatment failures to more than one recommended ACTs, should rotational first-line treatment (where the first-line treatment is changed based on updated surveillance data) be implemented and how?
13. Compared to currently recommended 3-day treatment, will patients diagnosed with falciparum malaria in areas with confirmed MDR, be provided with a more efficacious and safe cure?
    a. when given a prolonged treatment with an ACT?
    b. when given a triple combination treatment containing an artemisinin and two partner drugs?
14. Is there a role for artesunate–amodiaquine in the GMS?

Prevention/delay of multidrug resistance where it has not been identified

15. What is the evidence that multiple first-line treatment (MFLT) will delay or prevent the development of MDR?

Annex 4: Minutes of the ERG on K13

Final Report_Expert Review Group (ERG)

Double click on the above icon to open the document.

Drug Efficacy and Response

Minutes of the TEG on Drug Efficacy and Response

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

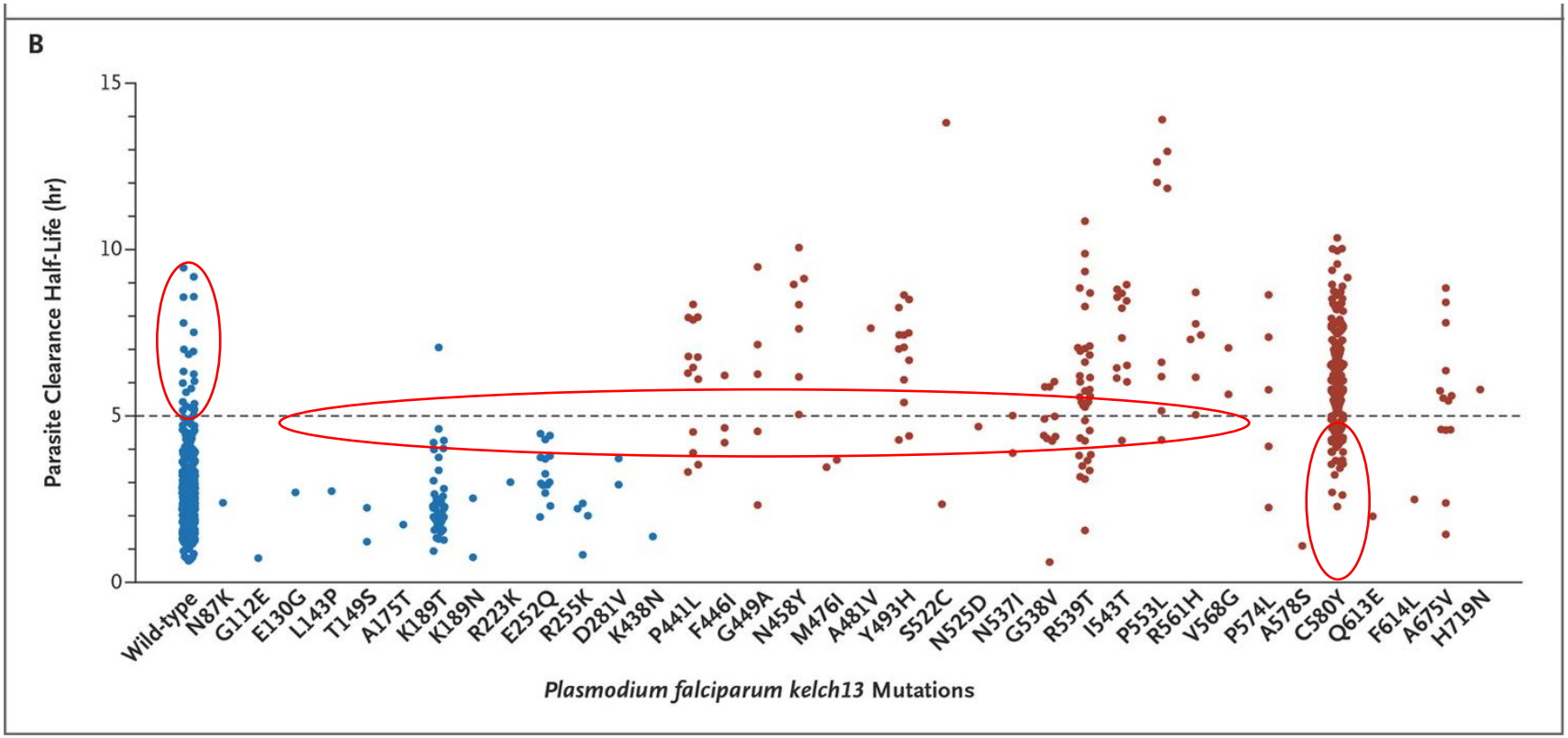
World Health Organization

Outline

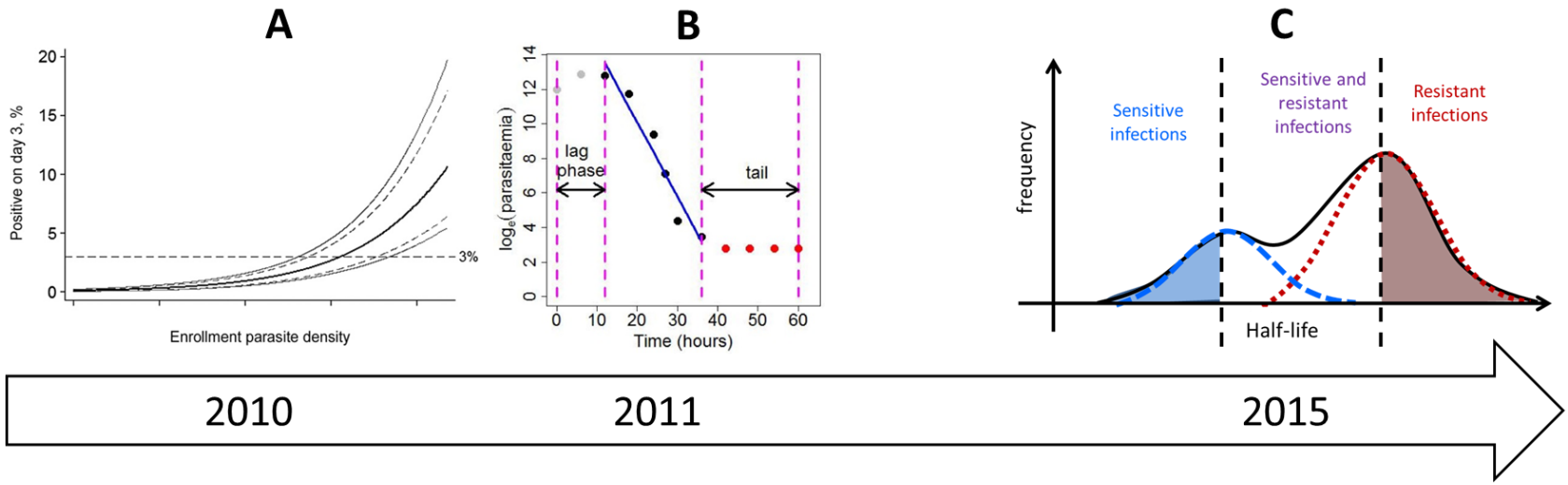
- Update on artemisinin resistance
- Monitoring efficacy and effectiveness of preventive treatment
  - IPTp-SP
  - Seasonal Malaria Chemoprevention
- Prevention and treatment of multidrug resistant malaria
  - Rotational first line
  - Prolonged duration
  - “Triple” combination or sequential ACT
  - Multiple first line treatments

Update on artemisinin resistance

Correlation between K13 mutations and parasite clearance half-lives



Ashley EA et al. (2014) *N Engl J Med*



	2010	2011	2015
RESULT ->	Stepniewska *et al.* (2010) analysis of recrudescence probability leads to the WHO definition of potential artemisinin resistance if >10% of patients are still parasitaemic by microscopy on day-3.	Flegg *et al.* (2011) propose the peripheral blood parasite half-life derived from the log-linear parasite clearance curve which is robust to initial parasitaemia and lag-phase.	White *et al.* (2014) propose a population-level definition of resistance which is robust to uncertainty of resistance status of individual infections.
CAVEAT->	This definition may not be suitable for populations with high or low parasitaemia on admission.	This definition leads to distributions of half-lives which appear to overlap.	Generalisation to a high transmission setting as in regions of Sub-Saharan Africa will need additional evaluation.

Day 3 vs slope

Day 3

- The proportion of patients who are parasitaemic after 3 days of treatment is highly dependent
  - on the initial parasitemia;
  - immunity of the patients;
  - the skills of the microscopists;
  - the methodology used for slide reading;
  - D3 ≠ 72 hours (day 3 overestimates positivity rate).

Slope

- Slope half-life is not influenced by initial parasitemia but still by the skills of the microscopists and the methodology used for slide reading;
- Highly dependent on immunity (variation up to 1 h);
- Limitations of the tool in real life:
  - low parasitemia
  - rapid clearance
- Does not take into consideration the lag phase or the the tail;
- Ideal samplings are too complicated for routine surveillance and 12-hourly sampling overestimates slope half-life.

Recommendations

- Currently available tools are sufficient for the detection of artemisinin resistance in an area;
- The percentage of patients with positive parasitaemia at day 3 is a relevant and practical measure for routine surveillance. Blood filter papers should be routinely collected at day 0 in all studies for identification of *K13* mutations;
- In the research setting, the parasite clearance slope is currently most appropriate, but other tool including lag phase and tail should not be ruled out. In the context of potential drug resistance, tools to evaluate residual parasitaemia should be considered.

Additional recommendations

- The detection of artemisinin resistance signifies an epidemiological threat, but does not necessarily signify reduced ACT efficacy as a manifest public health problem;
- The immediate consequences should be the investigation of possible causes and to to ensure that antimalarial treatment is based on a definitive diagnosis, that drugs are of good quality, and that there is a good clinical provider and patient adherence;
- Based on the local epidemiological situation, capacity for intensifying vector-control efforts to interrupt transmission should be investigated, including the potential for malaria elimination;
- In countries where targeting of malaria control and treatment interventions is directed by risk stratification, the presence of artemisinin resistance is clearly a criterion for upgrading risk.

Artemisinin resistance definition

- *Suspected* endemic artemisinin resistance is defined as:
  - ≥ 5% of patients carrying *K13* resistance-confirmed mutations; or
  - ≥ 10% of patients with persistent parasitaemia by microscopy at 72 hours (± 2 hours, i.e. day 3) after treatment with ACT or artesunate monotherapy; or
  - ≥ 10% of patients with a parasite clearance half-life of ≥ 5 hours after treatment with ACT or artesunate monotherapy.
- *Confirmed* endemic artemisinin resistance is defined as ≥ 5% of patients fulfil both of the following criteria:
  - ≥ 5% of patients carrying K13 resistance-associated mutations, all of whom have been found, after treatment with ACT or artesunate monotherapy, to have either persistent parasitaemia by microscopy on day 3, or a parasite clearance half-life of ≥ 5 hours.

Definitions of ‘confirmed’ and ‘associated’ K13 mutations

- The criteria for determining whether a K13 propeller mutation is ‘confirmed’ or ‘associated’ remain as per the suggestion of the ERG on K13 2014:
  - a statistically significant association ($p < 0.05$) between a K13 mutation and either a parasite clearance half-life ≥ 5 hours or parasitaemia at 72 hours (± 2 hours) via a chi-squared test or appropriate multivariable regression model on a sample of at least 20 clinical cases; or
  - > 1% survival using the $RSA_{0–3h}$ (or > ± 2 standard deviations of the mean value for K13 wild type parasites from the same area) in at least five individual isolates with a given mutation; or a statistically significant difference ($p < 0.05$) in the $RSA_{0–3h}$ assay between culture-adapted recombinant isogenic parasite lines, produced using transfection and gene editing techniques, which express a variant allele of K13 as compared to the wild-type allele.
- A K13 mutation is ‘confirmed’ when both requirements 1 and 2 are met, ‘associated’ when either 1 or 2 are met.

Associated and validated K13 resistance mutations 2014

K13 mutation	Classification
E252Q	*Not associated*
P441L	Associated
F446I	Associated
G449A	Associated
N458Y	Associated
Y493H	**Confirmed**
R539T	**Confirmed**
I543T	**Confirmed**
P553L	Associated
R561H	**Confirmed**
V568G	Associated
P574L	Associated
A578S	*Not associated*
C580Y	**Confirmed**
A675V	Associated

Other rare variants were reported associated with in vivo, in vitro or both:
M476I; C469Y; A481V; S522C; N537I; N537D; G538V; M579I; D584V; H719N.

Monitoring efficacy and effectiveness of preventive treatment

Protocol to monitor efficacy of IPTp-SP

Three observational protocol modules were considered:

- *Molecular module*
  - temporal and spatial distribution of molecular markers of SP resistance;
  - in a meta-analysis of aggregated data from 48 published studies reporting more than 54 000 births, the relative risk reduction of LBW associated with IPTp-SP was stratified based on molecular markers in *Pfdhps* with:

    low defined as A437G <50%;

    moderate defined as A437G ≥50% plus K540E <10%, or K540E ≥10% plus <1% A581G; and

    high defined as K540E ≥10% plus A581G ≥1%;
  - the relative risk reduction of LBW associated with the receipt of antenatal SP was 28% in low resistance settings, 20% in moderate settings, and 9% in high settings.

Protocol to monitor efficacy of IPTp-SP

- *In vivo module*
  - includes the efficacy of SP to clear peripheral parasitaemia in asymptomatic pregnant women and the assessment of post-treatment prophylaxis;
  - although there is a strong correlation at population level between SP parasite resistance and the efficacy of IPTp-SP to clear existing infections or prevent new infections from occurring, the correlation between the parasite clearance and maternal anaemia, birth weight or other outcomes is weak;
  - these studies are also labour intensive and difficult to conduct, and follow-up is limited to 28 days.

Protocol to monitor efficacy of IPTp-SP

- *Delivery module*
  - determination of the effects of varying doses of IPTp-SP on malaria infection, maternal anaemia, placental malaria and birth outcomes (LBW);
  - these studies require large sample sizes to detect effects on birth outcomes. They are subject to selection bias in particular because the participant, not the investigator, determines exposure to SP;
  - previous studies have shown only a weak correlation between the level of SP parasite resistance in the population and pregnancy outcomes, and there is considerable variation in the SP protective efficacy in areas of high resistance.

Important confounders to consider

Module		Potential confounders
Molecular markers		Use of IPTp-SP, CTX, other sulfa drugs
In vivo efficacy		Gravidity, ITN use
Delivery outcomes	Malaria infection	Timing of the last SP dose, age, gravidity, ITN
	Birth weight	Maternal age, gravidity, nutritional status, number of ANC visits, timing of 1st ANC visit, HIV infection, multiple gestations (twins)
	Hemoglobin	Gravidity, nutritional status, number of ANC visits, HIV infection, timing of collection with regards to delivery (pre or post-delivery)

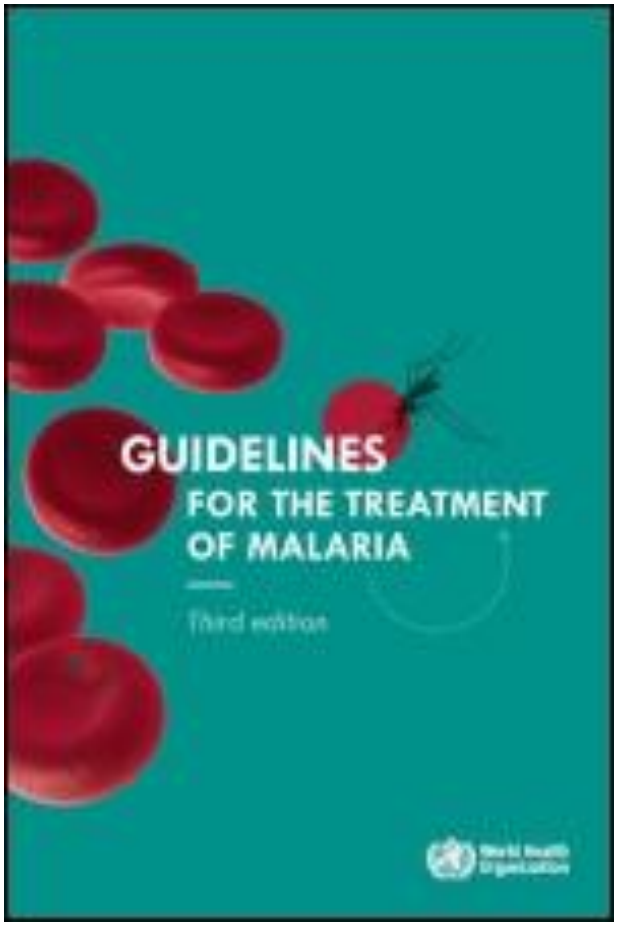
Recommendations

- At a population level, IPTp-SP is associated with improved birth outcomes (fewer LBW), irrespective of SP's failure to clear or prevent parasitaemia, in all settings where the prevalence of sextuple mutant haplotype containing *Pfdhps* A581G is below 5%;
- The presence of parasites bearing the sextuple mutant haplotype containing *Pfdhps* A581G at a prevalence of >35% appears to negate the benefits of IPTp-SP on birth outcomes;
- Overall, the evidence suggests that IPTp-SP given to women with the sextuple mutant is not harmful. This concern was suggested in a single study, but was not confirmed by later studies;
- There are no data at present on the effectiveness of IPTp-SP at the prevalence of sextuple mutant haplotype containing *Pfdhps* A581G of 5–35%.

Recommendations

- For national malaria control programme (NMCP) settings, molecular surveillance should be used to guide routine assessment of IPTp-SP effectiveness.
- The threshold of A581G prevalence at which IPTp-SP is no longer of benefit is unclear, but the evidence suggests that there will be no benefit of IPTp-SP at >35% A581G prevalence;
- Molecular surveillance should focus on the *Pfdhps* gene; genotyping may be carried out on parasite samples if collected from a population that has not recently (i.e. in the previous 6 weeks) been treated with antifolates;
- Sampling should take place every 3 years in areas of low SP resistance, every 2 years in moderate areas, and every year in high areas.

Guidelines for the treatment of malaria



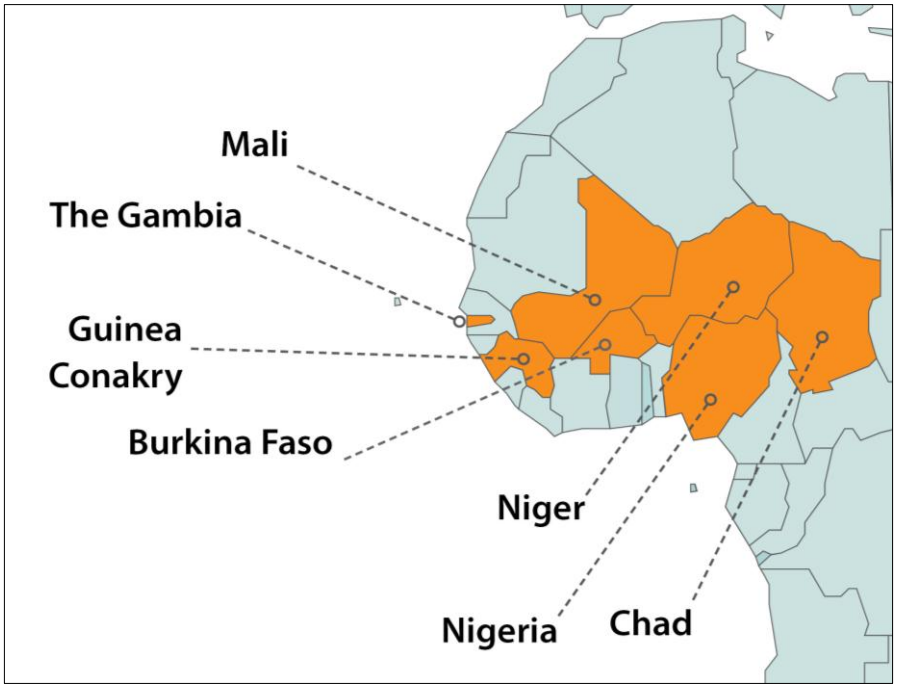
IPTp-SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion (> 90%) of P. falciparum parasites carry these quintuple mutations. Therefore, IPTp-SP should still be administered to women in these areas. In areas where P. falciparum carrying six mutations (either Pfdhfr 164 or Pfdhps 581) are prevalent, the efficacy of IPTp-SP may be compromised. It is unclear by how much.

In summary:

- Threshold of 35% *Pfdhps* 581
- Not necessarily a stopping rule but clearly reduced effectiveness
- In area of high SP resistance, good place to study alternative regimens

ACCESS-SMC

ACCESS-SMC is a UNITAID-supported project, led by Malaria Consortium in partnership with CRS, which is supporting NMCP-led scale-up of SMC across the Sahel to save children's lives. This 3-year project is supported by LSHTM, CSSI, MSH, MMV and SUA. ACCESS-SMC provided more than 14M SMC treatments in 2015 to over 3.2M children aged 3 to 59 months in Burkina Faso, Chad, Guinea, Mali, Niger, Nigeria, and The Gambia, and will provide 30M SMC treatments in 2016 to approximately 6.5M children



Monitoring efficacy of SMC drugs

- Monitoring will provide reassurance about efficacy after 2 years, establish a baseline for future monitoring and indicate factors that may limit the selection of resistance.
- The objectives of the protocols are to:
  - measure the prevalence of molecular markers associated with resistance to SP and amodiaquine before SMC in the community in children aged under 5 years and in age groups that are too old for SMC;
  - measure the change in the prevalence of these markers after 2 years of SMC;
  - measure the prevalence of markers in samples from clinical cases (children and adults) in selected clinics before and after SMC;
  - monitor the prevalence of markers in cases in adjacent non-SMC areas;
  - measure the protective efficacy of SMC treatments (using case–control studies);
  - assess the utility of the screening method for monitoring efficacy (from dates of any SMC doses in malaria cases in children in sentinel surveillance clinics);
  - monitor coverage and adherence through surveys at the end of each cycle and at the end of each season; and
  - if possible, measure clearance of parasitaemia after AQ+SP treatment.

Additional recommendations

In addition to the protocol for monitoring drug resistance of the ACCESS-SMC study presented at the TEG meeting, the following parameters should be explored:

- Efficacy evaluation – the ratio of malaria cases in children aged under 5 years versus those aged over 10 years; the occurrence of clinical malaria relative to the time of the previous SMC dose; the incidence of severe malaria at sentinel sites; case–control sampling before each dose for microscopy, gametocytaemia and PCR positivity relative to the time of previous SMC dose;
- Impact on transmission – assessed through standard membrane feeding assay, if feasible, and parasite genetic indicators of complexity of infection and overall changes in parasite diversity levels, where possible;
- Drug policy effects – the impact of SMC on first-line ACT diversity (and thus drug pressure) should be monitored.

Prevention and treatment of multidrug resistant malaria

Definitions

- Artemisinin delayed clearance does not meet the current conventional WHO 1973 definition of antimalarial drug resistance, though a limited number of cases were described as potentially fully resistant to artemisinin:
    - *Ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject.*
- The definition of multidrug resistance (MDR), which is still valid, requires resistance to more than two operational antimalarial compounds of different chemical classes.
- In reporting the findings of therapeutic efficacy tests, ACT resistance is imprecise. ACT treatment failure is a more appropriate term that notes the specific ACT and the nature of the resistance (i.e. artemisinin partial resistance or partner drug resistance, or both).

Situation of ACT efficacy/resistance

	Cambodia	Lao PDR	Myanmar	Thailand	Viet Nam
AL	Resistance	Treatment failure ≈ 10%	Effective	Treatment failure ≈ 10%	?
AS-AQ	?	?	Effective	?	Effective
AS-MQ	Effective after reversal of mefloquine R	?	Effective	Resistance most part of the country	Effective
AS-Pyro	Treatment failures in Western	?	?	Effective	Effective
AS-SP	Likely resistance	Likely resistance	Likely resistance	Likely resistance	Likely resistance
DHA-PIP	Resistance	Effective	Effective	Treatment failures?	Treatment failures?

Clinical outcome after ACT treatment according to sensitivity pattern of each component

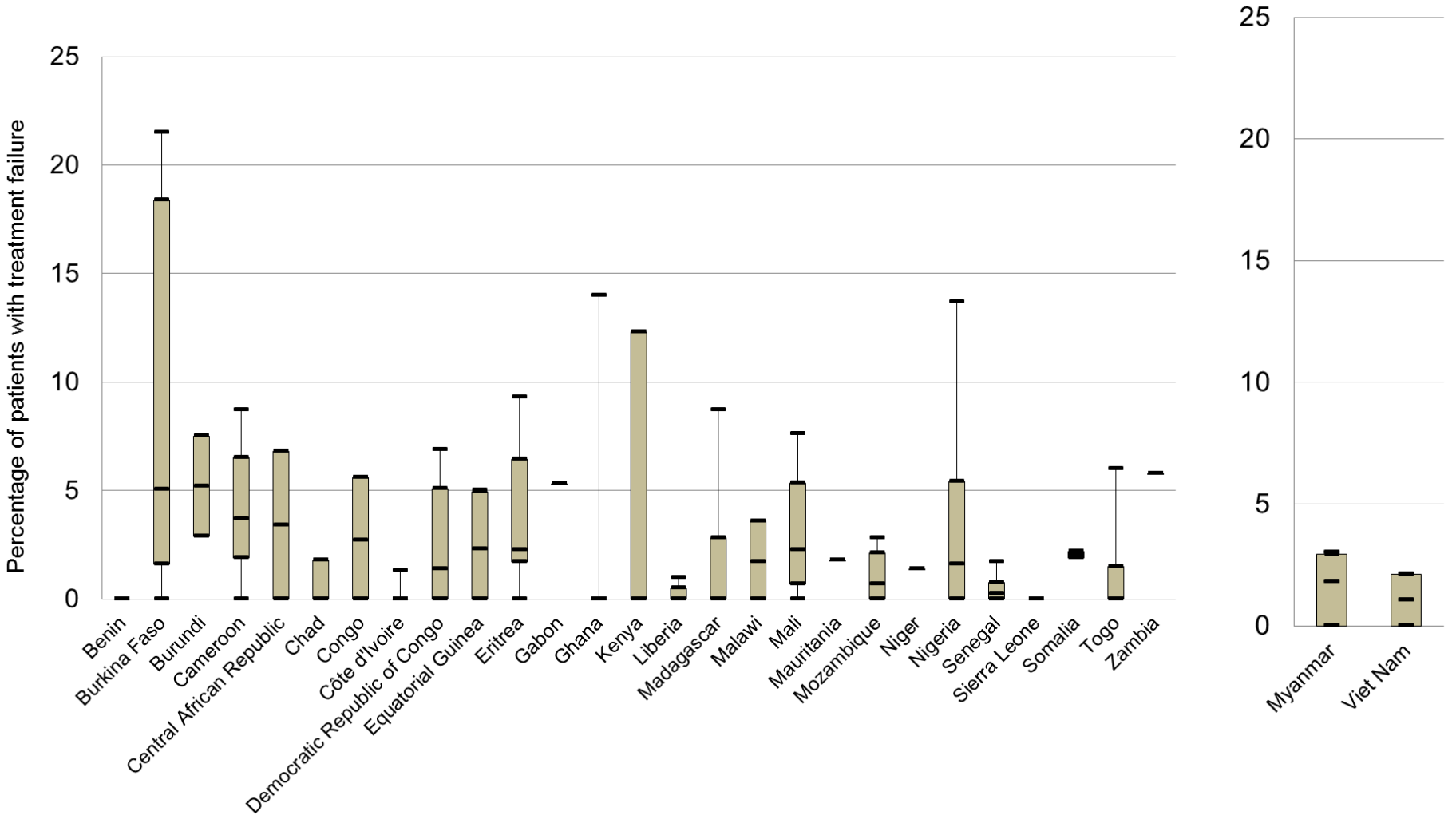
Artemisinin	Partner drug	Treatment outcome
S	S	TS (ACPR)
R (Delayed clearance)	S	TS (ACPR) China, Laos, Myanmar, Viet Nam
S (3-day AS = 50% TS)	R	TS → TF (ASSP, India)*
R	R	TF Cambodia (DP), Thailand (ASMQ)

* If resistance to partner drug increases: > 20-30% for AQ or SP

Safe and effective treatment in areas of confirmed MDR malaria

- Rotational first-line treatment is already being implemented in Cambodia. At present, there is no alternative in Cambodia other than to be flexible, and use rotational first-line treatment.
- Information is limited on the efficacy and safety of:
  - prolonged treatment with an ACT;
  - “triple” combination treatment containing an artemisinin and two partner drugs;
  - or sequential ACTs.
- ASAQ may have a role to play in Cambodia:
  - as a first step, analysis of resistance markers for amodiaquine (single nucleotide polymorphism alleles Pfcrt 72-76, Pfmdr1 N86Y, Y184F and D1246Y);
  - followed by a therapeutic efficacy study of a fixed-dose ASAQ combination in Cambodia in 2016, if molecular marker data suggest reasonable amodiaquine efficacy.

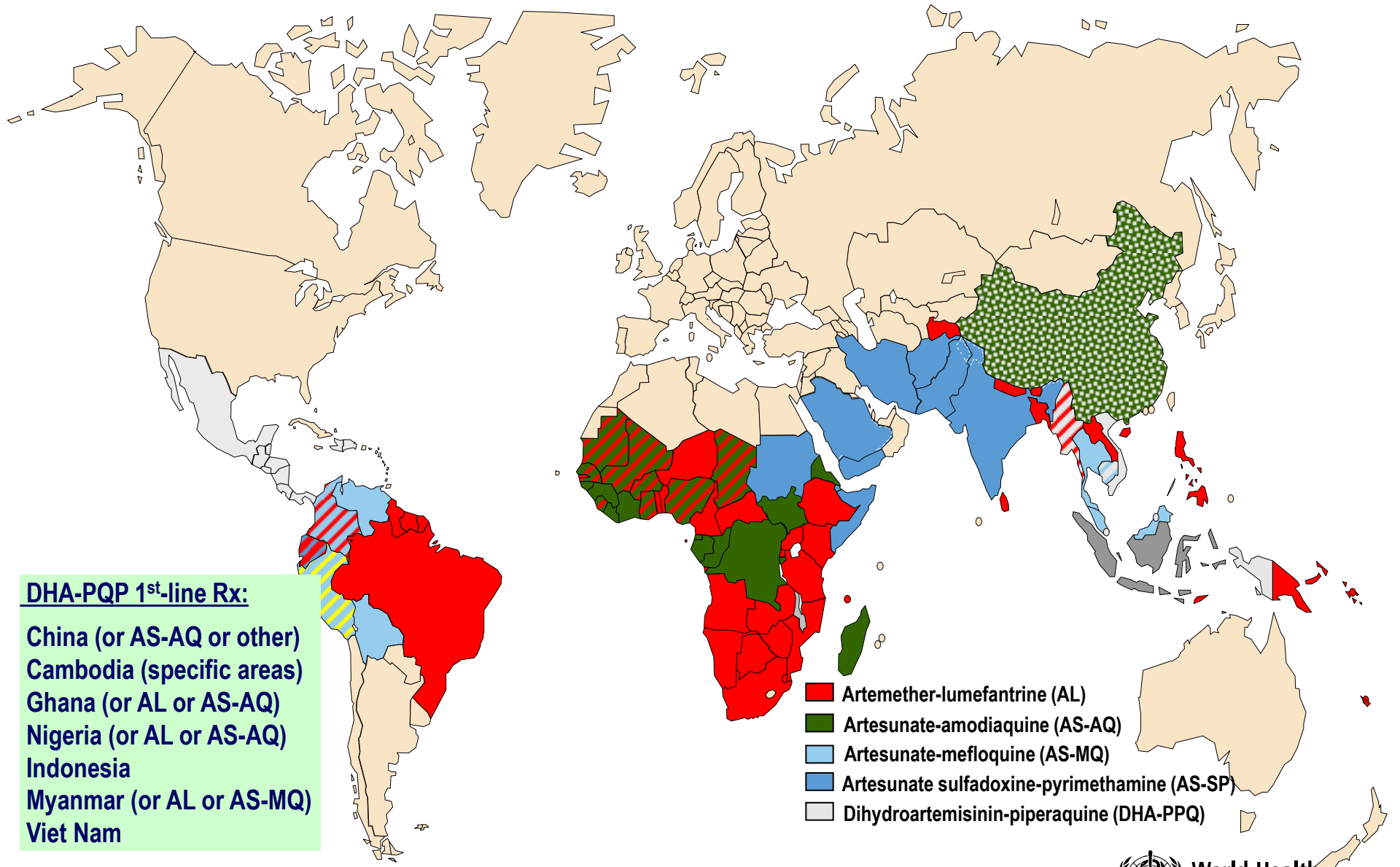
Summary of treatment failure rates with artesunate-amodiaquine



Prevention or delay of MDR where it has not been identified

- In areas where there is no established MDR, simultaneous deployment of multiple effective ACT first-line treatments (MFLT) is unlikely to hasten, and may actually delay, the emergence of drug resistance, according to modelling studies. Therefore:
  - countries that presently have multiple approved ACT first-line treatments should continue to use them; and
  - countries that rely on a single ACT first-line treatment are encouraged to add additional effective ACT treatments to the national treatment guidelines, both to potentially delay the onset of resistance and to be better prepared to respond to failure (or stock-outs) of the current first-line treatment.
- Because modelling is the only means of evaluating the impact of MFLT on delaying resistance, the TEG recommends that the Malaria Modelling Consortium be asked to further develop these modelling approaches. Implementation issues should also be considered.

First-line antimalaria treatment policies in 80 countries with CQ-resistant falciparum malaria



DHA-PQP 1st-line Rx:

China (or AS-AQ or other)
Cambodia (specific areas)
Ghana (or AL or AS-AQ)
Nigeria (or AL or AS-AQ)
Indonesia
Myanmar (or AL or AS-MQ)
Viet Nam

Global **Malaria** Programme

World Health Organization

Strategic Advisory Group on Malaria Eradication

Assessing the feasibility of Malaria Eradication

Dr Pedro L. Alonso, Director

Malaria Policy Advisory Committee, Geneva, Switzerland, 16 March 2016

Global **Malaria** Programme

World Health Organization

Terminology

- **Malaria Control**
  - Reduction of disease incidence, prevalence, morbidity, or mortality to a locally acceptable level as a result of deliberate efforts. Continued intervention efforts are required to sustain control.
- **Malaria elimination**
  - Interruption of local transmission (reduction to zero incidence) of a specified malaria parasite in a defined geographic area as a result of deliberate efforts. Continued measures to prevent re-establishment of transmission are required.
- **Malaria eradication**
  - Permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate efforts. Intervention measures are no longer needed once eradication has been achieved.

Revised "WHO Terminology of Malaria", 2016 A. Bosman and R. Steketee Glossary

Background

- Understand and incorporate lessons from the past
  - First Global Malaria Eradication Programme (GMEP)
  - Smallpox eradication
- Reassess the impact of malaria control interventions (vs. other factors) in burden reduction these past 15 years
- Analyse ongoing eradication efforts: polio and dracunculiasis
- Recognise the multiplicity of factors that impact on the past and future evolution of the distribution and burden of malaria
  - Poverty, economic development, health systems and policies, agricultural patterns, electrification, urbanization, human mobility
  - Malaria specific financing and access to effective prevention and treatment tools and strategies

Strategic Advisory Group on Malaria Eradication: OBJECTIVE

- Perform analysis of future malaria trends taking into consideration the broad and comprehensive set of determinants (exploratory work)
- Deliver a report that advises WHO GMP on feasibility, expected cost and potential strategies of malaria eradication over the next decades.

Functions of WHO Strategic Advisory Group on Malaria Eradication

ANALYSIS

- To commission a set of studies, analyses and position papers that will help define the likely scenarios of the world's malaria situation over the next decades.

  Building on the recognition that a number of determinants impact on malaria trends, e.g. malaria control and elimination activities, policy and finance, socio-economic development, population growth and movement, agricultural patterns, urbanization and potential products of innovation.

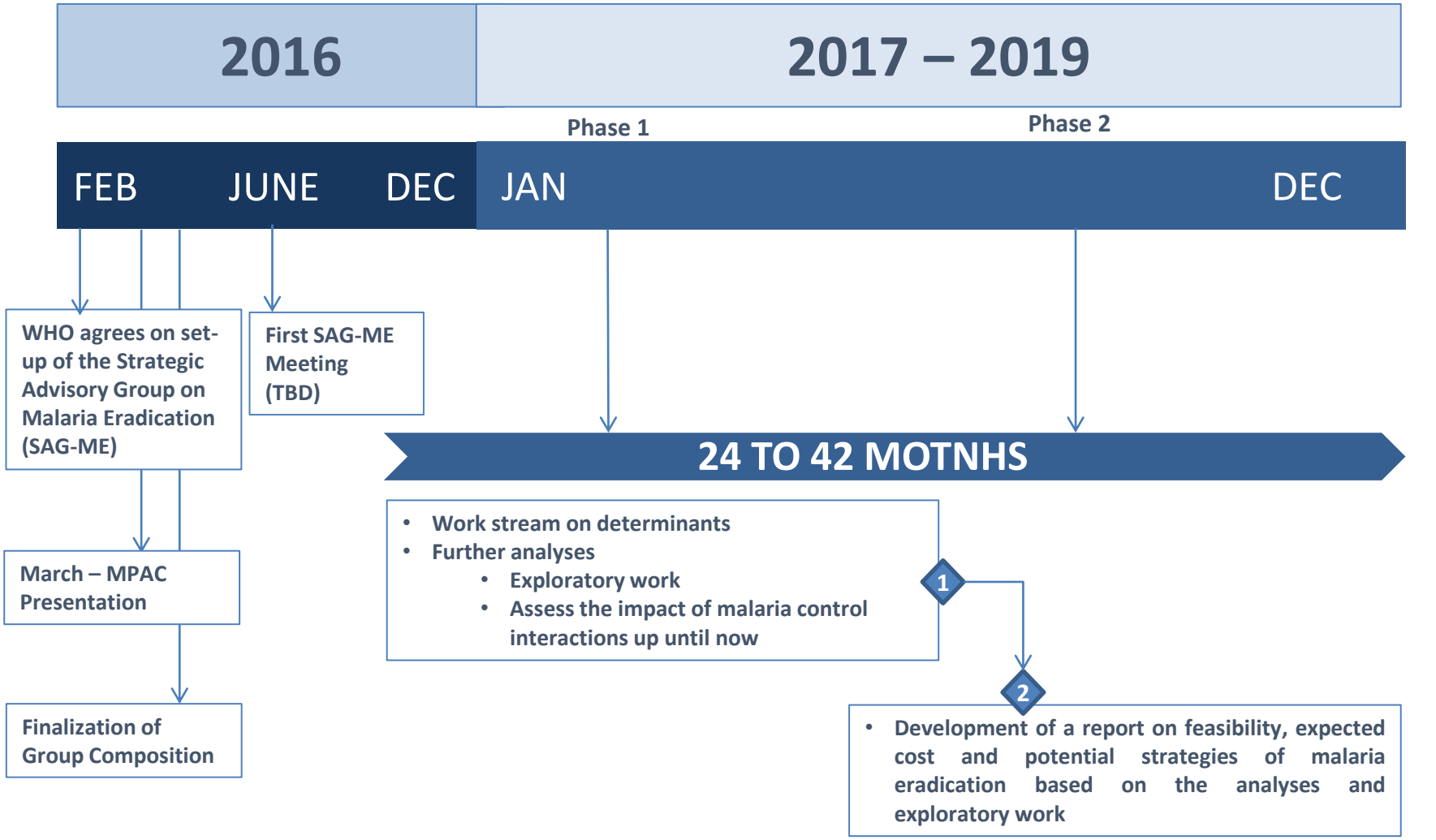
ADVICE

- To provide **advice** to WHO on the **feasibility**, **expected cost**, **potential strategies** and to accelerate regional elimination strategies or launch full eradication efforts.

Composition

- This will be an ad hoc committee convened by the WHO and composed of about 15 members that will represent a wide range of expertise, including:
  - Malariology and public health, including experience in previous or ongoing eradication efforts
  - Development economists
  - Demographers and population movement
  - Health systems and health policy
  - Agricultural planning and land use
- The group will ensure adequate regional representation and gender balance. It will meet not more than twice per year and will be supported by the WHO/GMP Secretariat.
- The group will also draw on support to be provided by WHO collaborating centres, GMP Coordinators and other relevant groups and partners.

Duration


2016
2017 – 2019
Phase 1
Phase 2
FEB
JUNE
DEC
JAN
DEC
WHO agrees on set-up of the Strategic Advisory Group on Malaria Eradication (SAG-ME)
First SAG-ME Meeting (TBD)
24 TO 42 MOTNHS
March – MPAC Presentation
Finalization of Group Composition
• Work stream on determinants
• Further analyses
• Exploratory work
• Assess the impact of malaria control interactions up until now
1
2
• Development of a report on feasibility, expected cost and potential strategies of malaria eradication based on the analyses and exploratory work