Back-to-back meetings

Meeting 1: Comparative assessment of IRS and LLINs and their combination

Meeting 2: A review of the status and future of durable wall linings (DL)

Hold under the work stream "Optimal choice of vector control methods" of the RBM Vector Control Working Group (VCGW)

22-23 June 2010, Geneva, Switzerland

Convenors: **Christian Lengeler, Swiss TPH**
Michael Macdonald, USAID
Jonathan Lines, GMP/WHO

Administrative support: Konstantina Boutsika, Swiss TPH

1. Introduction

The health impact of ITNs/LLINs and IRS

Primary prevention of malaria is essentially achieved through two main vector control interventions: indoor (house) residual insecticide spraying (**IRS**); and insecticide-treated (mosquito) nets (**ITNs**). The health effects of ITNs have been comprehensively summarized for the general population in a Cochrane review (Lengeler 2004). Recently, the development of Long-Lasting Insecticidal Nets (**LLINs**) with the same protective properties as ITNs but with a much longer uselife has made programme implementation significantly easier. Here we use ITNs and LLINs interchangeably.

IRS has a long and distinguished history in malaria control. Using mainly dichloro-diphenyl-trichlorethane (DDT), malaria was eliminated or greatly reduced as a public health problem in Asia, Russia, Europe, and Latin America (Shiff 2002; Lengeler and Sharp 2003; Roberts *et al.* 2004). IRS continues to be used in many parts of the world, with the services provided by the public health system or by a commercial company (usually for the benefit of its employees).

Recently, a Cochrane systematic review on IRS was completed by Pluess *et al.* (2010). Of 134 identified studies, only 6 (4 randomized controlled trials (RCT) and 2 other types of studies) could be included. **None of the studies complied with modern standards of epidemiological investigation**. In addition, 2/4 RCTs were carried out in areas with long-standing IRS implementation (India and South Africa), one study was too short and too small to provide meaningful results (Tanzania), while the last one was done in a refugee population rather than the general population (Pakistan).

As a result, the main conclusions of the review were the following:

"Historical and programme documentation has clearly established the impact of IRS. However, the number of high-quality trials is too few to quantify the size of effect in different transmission settings. The evidence from randomized comparisons of IRS versus no IRS confirms that IRS reduces malaria incidence in unstable malaria settings, but randomized trial data from stable malaria settings is very limited. Some limited data suggest that ITN give better protection than IRS in unstable areas, but more trials are needed to compare the effects of ITNs with IRS, as well as to quantify their combined effects".

Hence, while there is no doubt that IRS reduces malaria transmission and improves health outcomes, current assessments do not allow us to quantify the health effects, neither for IRS alone, nor for the comparison IRS-LLINs. In addition, we totally lack evidence on the health impact of the combination of IRS and LLINs.

Lack of evidence on the comparison of IRS versus ITNs/LLINs

Lacking evidence on the absolute health impact of IRS is not a major problem since the historical documentation is so strong. However, lacking good comparative data on the respective health impact of IRS versus ITNs is much more serious, because it prevents a meaningful comparison between these two strategies. As a result, although we know enough about the comparative operational requirements and the relative cost of the strategies, we can not calculate their relative cost-effectiveness. Given the current heavy investment in vector control (well over USD 500 million per year) this is not an acceptable situation. One consequence has been that the choice of doing an IRS or a LLIN programme in a given setting has mostly been driven by considerations unrelated to

impact and cost. It is in the interest of public health and efficient use of resources to improve this situation.

Lack of evidence on the combination of IRS or ITNs/LLINs

The new ambitious plan of eliminating regionally and ultimately eradicating malaria is now reflected in RBM's Global Malaria Action Plan (GMAP) (RBM 2008). In view of eliminating malaria in highly endemic areas it is clearly attractive to consider the possibility of combining both IRS and LLINs in the same setting in order to maximize chances to interrupt completely transmission. So far, our evidence on the value of this combination is limited to two small descriptive studies from Bioko Island and Mozambique (Kleinschmidt *et al*. 2009) and we do not know whether adding a second intervention in an area having already good vector control coverage with another intervention will have any marginal benefits.

A new vector control technology: Durable Wall Lining (DL)

IRS was developed over 60 years ago, following the invention of DDT, which was the first insecticide with a sufficient residual activity to be used for this purpose. Over that time period, hardly anything has changed in the way IRS is implemented. A greater range of insecticides is now available (12 different products in 4 chemical classes) with some of the newer products being longer lasting formulations (up to 6 months). But basically the technology is still the same. On the basis of how conventional ITNs with an insecticidal effect of maximum 12 months moved on to become LLINs that do not need to be re-treated for 3-5 years, there is a great rationale for making IRS also much longer lasting. This is especially important in areas that are difficult to reach, or where the weakness of the health system is such that repeated applications are difficult.

A solution to this problem has been found with Durable (Wall) Lining (DL). So far, the most advanced product is a woven shade cloth made of polyethylene with 50% shading and treated with 4.4 gm deltamethrin a.i./kg material. The type of treatment is similar to Type 2 LLINs (the insecticide being included in the fiber itself). This product is developed and manufactured by Durable Activated Residual Textiles S.A. (DART), a consortium of three partners: Vestergaard Frandsen®, Acumen Fund and Richard Allan. DL is potentially a durable substitute for IRS with reduced program complexity and higher user acceptability. A number of Phase 1 (laboratory) and Phase 2 (experimental huts) trials have confirmed the feasibility, acceptability and impact of DL.

Phase 3 testing of DL

Phase 3 trials of this product are now required to produce two distinct but complementary forms of evidence:

1. **Basic epidemiological evidence** based on standard malariological outcomes that DL as a new form of malaria control, is protective. This assessment needs to be comparative, i.e. DL is compared to LLINs and to conventional IRS.

2. **Basic evidence required by WHOPES** to decide on the merits and long-lasting nature of the product. Presumably, this will be based on a set of criteria very similar to the one used for testing Phase 3 LLINs. Current guidelines emphasize the regular testing of the materials, both entomologically and chemically, to ascertain that the product is really long-lasting.

Phase 3 trials should be conducted in accordance with the standards of Good Clinical Practice (GCP) as applied to epidemiological studies.

WHOPES Guidelines to test DL do not yet exist but it is to be expected that a full epidemiological assessment will be required, at least initially. Furthermore, this requirement is especially important considering the poor design of all IRS studies to-date.

2. Meeting format

This two-day meeting held in the Geneva area, on 22-23 June, will cover two separate but strongly related components:

Component 1 (1.5 days): The planning of new, large-scale and high quality field trials to compare quantitatively IRS against LLINs and against their combination.

Industry representatives are not invited for that meeting, because of obvious conflicts of interest.

Component 2 (0.5 day): A review of the development path of DL as a new mainstream vector control technology.

For this meeting the representatives of all major vector control companies have been invited.

In order to ensure efficiency, the number of participants will be limited to around 20.

3. Meeting objectives

Component 1: LLIN-IRS combination

1. To initiate and support the coordination of the testing of LLINs versus IRS and their combination in multiple highly endemic settings in sub-Saharan Africa in terms of design, outcomes (epidemiological and entomological), timing, coordinated reporting, and standard economic evaluation.

2. To identify gaps in the ongoing and planned testing in order to support prospectively further essential research initiatives.

3. To provide a preliminary advice to countries with regard to the combination of LLINs and IRS, especially in view of the upcoming GF Round 10 application.

Component 2: DL development path

1. To outline a testing programme leading to epidemiological and entomological proof-of-principle of DL as large-scale vector control tool through full-scale comparative field trials.

2. To prepare and submit to WHOPES a recommendation with regard to the testing of DL (Phases 1-3).

3. To outline how a potential investment of CDC and USAID in DL research could be most effective.

4. To discuss and draft plans for the future development of DL with alternative (non-pyrethroid) insecticides (including fungi and Insect Growth Regulators (IGRs)).

Both meetings will be held back-to-back because they are linked by **two key assumptions**:

1. DL is effectively equivalent to long-lasting IRS; hence testing DL will in effect also be testing the effect of IRS.

2. The conduct of high quality randomized trials will require substantial resources and Phase 3 requirements of the development of DL can be integrated into the work required by component 1.

4. Meeting outputs

1. A comprehensive strategic, coordinated and standardized study plan to investigate comparatively LLINs against IRS and their combination, which also identifies current gaps in the testing plans, as well as outlines mechanisms for overall coordination.

2. A strategic, coordinated study plan to investigate the benefit of DL as a large-scale, mainstream vector control tool.

3. A written proposal to WHOPES for a possible DL registration process, with required study phases and their basic content.

5. References

Kleinschmidt I., Schwabe C., Shiva M., Segura JL., Sima V., Mabunda SJA. and Coleman M. (2009). Combining indoor residual spraying and insecticide-treated net interventions. *Am J Trop Med Hyg* 3, p 519-524.

Lengeler C. (2004). Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database Syst Rev* 2, p 1-56.

Lengeler C. and Sharp B. (2003). Indoor Residual Spraying and Insecticide-Treated Nets. *In*: Reducing Malaria's burden. Evidence of effectiveness for decision makers. Global Health Council, Washington D.C. 2003. Available under: www.globalhealth.org

Pluess B., Tanser F.C., Lengeler C. and Sharp B.L. (2010). Indoor residual spraying for preventing malaria. *Cochrane Database Syst Rev* 4, p 1-48.

RBM (2008). Key facts, figures and strategies. The Global Malaria Action Plan, p 1-24.

Roberts D., Curtis C., Tren R., Sharp B., Shiff C. and Bate R. (2004). Malaria control and public health. *Emerg Infect Dis* 6, p 1170-1171.

Shiff C. (2002). Integrated approach to malaria control. *Clin Microbiol Rev* 2, p 278-293.

5. Agendas

Meeting 1: Comparative assessment of IRS and LLINs and their combination

Time	Topic	Presenter
Day 1: Tuesday 22nd June 2010		
9.00-9.15	Welcome and introduction	C. Lengeler, M. Macdonald, J. Lines
9.15-10.00	Current evidence on the combination of ITNs and IRS Followed by general discussion	I. Kleinschmidt Chair: C. Lengeler
10.00-10.30	**Tea**	
10.30-12.30	Presentations of funded and planned trials 10 min overview on objectives, design and outcomes followed by 10 min discussion - The Gambia (ongoing – Kalifa Bojang) - New USAID trial (planned - TBD) - Democratic Republic of Congo (planned – A. Tshefu) - Sudan (ongoing - I. Kleinschmidt) - Modelling (N. Chitnis)	One representative per site Chair: J. Lines
12.30-13.45	**Lunch**	
13.45-15.45 Working groups	4 working groups: 1. Study design(s) 2. Outcomes 1 (epidemiological) 3. Outcomes 2 (entomological) 4. Coordination mechanism	Each group with one chair and rapporteur
15.45-16.00	**Tea**	
16.00-17.30	Plenary feedback and discussion of first draft from working groups	Rapporteurs Chair M. Macdonald
Day 2: Wednesday 23rd June 2010		
8.00-9.30	Group work (continued)	Each group with one chair and rapporteur
9.30-10.30	Plenary reports and finalization of recommendations	All. Chair C. Lengeler
10.30-11.15	Planning next steps	All. Chair C. Lengeler
11.15-11.45	**Tea**	
11.45-12.30	Feedback of key results from IRS-LLIN combination meeting to larger group including industry representatives	Selected Rapporteur Chair C. Lengeler
12.30-13.30	**Lunch**	

Meeting 2: A review of the status and future of durable wall linings (DL)

Time	Topic	Presenter
Wednesday 23rd June 2010		
11.45-12.30	Feedback of key results from IRS-LLIN combination meeting to larger group including industry representatives	Selected Rapporteur Chair C. Lengeler
12.30-13.30	**Lunch**	
13.30-13.50	DL: an introduction	DART – R. Allan Chair: C. Lengeler
13.50-14.10	The potential place of DL in large-scale VC and the management of insecticide resistance	J. Lines
14.10-14.30	WHOPES testing rules for LLIN (that could provide a basis for testing DL) and IRS	J. Gimnig
14.30-15.30	Development plan and the generation of epidemiological information for DL (Managed general discussion)	All
15.30-15.45	**Tea**	
15.45-17.15 Working groups	3 working groups: 1. Outline of proposal for Phases 1 and 2 WHOPES assessment of DL 2. Outline of proposal for Phase 3 WHOPES assessment of DL 3. Generating a development plan for DL, with a focus on Phase 3 RCTs	Each group with one chair and rapporteur
17.15-18.15	Plenary and finalization of outline recommendations	Selected Rapporteurs Chair C. Lengeler

6. List of participants

	LLIN / IRS Combination			DL development	
	Name	**Institution**		**Name**	**Institution**
1	Mike Macdonald	USAID		Mike Macdonald	USAID
2	Christian Lengeler	Swiss TPH		Christian Lengeler	Swiss TPH
3	Jo Lines	WHO/GMP		Jo Lines	WHO/GMP
4	Shiva Murugasampillay	WHO/GMP		Jacob Williams	RTI
5	Jacob Williams	RTI		Immo Kleinschmidt	LSHTM
6	Immo Kleinschmidt	LSHTM		Mark Rowland	LSHTM
7	Mark Rowland	LSHTM		Kalifa Bojang	MRC Gambia
8	Kalifa Bojang	MRC Gambia		Antoinette Tshefu	ESP Kinshasa
9	Antoinette Tshefu	ESP Kinshasa		Tom McLean	IVCC
10	Bob Wirtz	CDC		Robert Sloss	IVCC
11	John Gimnig	CDC		Bob Wirtz	CDC
12	Vincent Corbel	IRD		John Gimnig	CDC
13	Kate Aultman	BMGF		Vincent Corbel	IRD
14	Richard Allan	DART		Kate Aultman	BMGF
15	Nakul Chitnis	Swiss TPH		Gary Clark	USDA
16	Mary Hamel	USAID		Richard Allan	DART
17	Gary Clark	USDA		John Thomas	DART
18	Louisa Messenger	LSHTM		Helen Jamet Pates	VF
19	Natacha Protopopoff	Malaria Consortium		John Invest	Sumitomo
20	Tom McLean/R. Sloss	IVCC		Karin Horn	Bayer
22	Steve Lindsay	LSHTM		Egon Weinmueller	BASF
23	Janet Hemingway	LSTM / IVCC		Andy Bywater	Syngenta
24	Albert Kilian	Malaria Consortium		Anuj Shah	A to Z
25	Paul Libiszowski	MACEPA		Bill Jany	Clark
26				Ole Skovmand	Intelligent Insect Control
27				Rajpal Yadav	WHO/WHOPES

Not able to attend

Secretariat: Konstantina Boutsika, Swiss TPH