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# Malaria transmission blocking vaccines: an ideal public good



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# TABLE OF CONTENTS

<b>MALARIA TRANSMISSION BLOCKING VACCINES: AN IDEAL PUBLIC GOOD.....</b>	<b>1</b>
<b>MEETING PARTICIPANTS/ORGANIZATIONS .....</b>	<b>3</b>
<b>A. TRANSMISSION BLOCKING VACCINES IN THEIR EPIDEMIOLOGICAL SETTINGS .....</b>	<b>4</b>
1. GENERAL FEATURES OF MALARIA TRANSMISSION AND TRANSMISSION BLOCKING VACCINES.....	4
2. USE OF TBV FOR REGIONAL ELIMINATION OF MALARIA.....	6
3. USE OF TBV TO REDUCE MALARIA TRANSMISSION.....	7
4. USE OF TBV TO PREVENT/CONTROL MALARIA EPIDEMICS .....	7
5. USE OF TBV TO PROTECT OTHER VACCINES, AND POSSIBLY ALSO DRUGS, AGAINST THE SPREAD OF VACCINE- OR DRUG-RESISTANT PARASITES.....	7
6. THE ETHICS OF USING TBV.....	8
7. THE ECONOMICS OF TBV.....	8
<b>B. THE SCIENTIFIC AND TECHNICAL BASIS FOR PRODUCTION OF TRANSMISSION BLOCKING VACCINES .....</b>	<b>9</b>
1. THE FEASIBILITY THAT A TRANSMISSION BLOCKING VACCINE COULD BE PRODUCED .....	9
2. PRECLINICAL VACCINE DEVELOPMENT .....	10
3. VACCINE TESTING.....	12
<b>C. INDUSTRIAL ASPECTS OF TRANSMISSION BLOCKING VACCINE DEVELOPMENT.....</b>	<b>13</b>
1. REQUIREMENTS FOR INDUSTRIAL INVOLVEMENT IN TRANSMISSION BLOCKING VACCINES .....	13
2. THE WAY FORWARD – BRIDGING THE GAP.....	14

## **Malaria Transmission Blocking Vaccines: An ideal public good**

Malaria vaccines could be one of the most cost-effective interventions to reduce the enormous burden of disease in the poorest countries of the world. These vaccines are likely to have different components that protect in different ways (see Figure). Liver stage vaccines will reduce the chances of a person becoming infected. Asexual blood stage vaccines will reduce disease severity and risk of death during infection. A transmission blocking vaccine will target the sexual stage of the parasite and prevent the spread of malaria through the community; such a vaccine would have the potential to reduce the burden of disease and death from malaria, including in parts of the world's most malarious continent, Africa. In Asia and Latin America, it could help lead to the elimination of the malaria parasite. The inclusion of a transmission blocking vaccine would also greatly prolong the useful life of vaccines against other stages by preventing the spread of parasites that become resistant to these vaccines.

None of the three types of malaria vaccines is yet available. At present, industry's greatest interest is in liver stage vaccines, with a secondary interest in blood stage vaccines. Both of these, and especially the liver stage vaccines, are of interest for travellers and military and have, therefore, attracted some industrial involvement in their development. There is, however, little commercial interest in a transmission blocking vaccine whose relevance is to poor countries where malaria is endemic. Thus, while a transmission blocking vaccine would be of great public benefit, it lacks industrial support and requires a home in the public sector that can champion its development.

How then should the public sector identify where to place its limited resources in supporting malaria vaccine development? That decision will be based on the potential benefit to public health compared to other existing or new interventions and the likelihood of success in developing particular vaccine components, and on the support needed to reach the identified goal. This report focuses on malaria transmission blocking vaccine (TBV) development. As for any vaccine, industry will be needed to produce the vaccine. Industry, however, is now unwilling to use its resources to this end because the market return is perceived to be minimal.

Through an international effort in basic research, an extensive body of scientific evidence has accumulated that clearly indicates the feasibility of development and eventual deployment of transmission blocking vaccines. In the laboratory, these vaccines can now completely block transmission to mosquitos of the two major human malarias. Vaccine development has, nevertheless, proceeded slowly. Several factors have contributed to this sub-optimal rate of product development. None, however, is as important as the lack of a committed industrial partner. To compensate for this, an adequately resourced, coordinated public sector effort is

now a must. The malaria transmission blocking vaccine needs a home from which to manage and coordinate the programme and to mobilize the funds to support the many international workers who are committed to make this happen. An international group of experts, including scientists, representatives from industry, some major funding agencies and the World Health Organization, met in Bethesda, USA, 3-5 December, 1999, to address the issue of transmission blocking vaccine development. The meeting was funded by the World Health Organization (Tropical Disease Research and Training [TDR] and Roll Back Malaria [RBM]), the Bill and Melinda Gates Foundation and the National Institutes of Health (NIAID and the Fogarty International Center).

As a major outcome of this international meeting of experts, an immediate need was identified for a multinational consortium with an independent strategic management structure. The goal of the consortium is to develop safe and effective transmission blocking vaccine candidates to the point of "proof of principle" to induce industrial commitment to vaccine production.

There is urgency to achieve this goal. With adequate support, the necessary field testing of candidate TBVs could be achieved within 5-10 years. Thereafter, licensing and deployment of TBVs could be achieved within 10-15 years.

These trials should be conducted independently of trials of vaccine components against other stages of malaria parasites (see Figure). The final goal, however, should be to join successfully tested malaria vaccine components into combinations which give the maximum individual protection, community protection, and protection of the vaccine itself against the emergence and spread of vaccine-resistant parasites.

***Initial objectives of the consortium:***

1. Identify and gain commitment from a funding organization to sponsor a Consortium Secretariat to plan and manage the development of a Transmission Blocking Malaria Vaccine. The Secretariat would consist of an Executive Director together with support staff and funds necessary to achieve the management of the mission.
2. The Executive Director, in consultation with the Consortium, would establish intermediate-term goals and time-lines and set up mechanisms to achieve them. This would include coordination between the efforts of the different partners in the Consortium, mobilization of funds to support their operations and negotiation with organizations outside the Consortium (e.g. governments where trials would take place) whose involvement would be necessary to reach the goal.

**The analysis that follows reflects the considered views of the meeting participants. It defines the need and demonstrates the potential for the development of a transmission blocking vaccine that justifies the creation of a comprehensive strategic plan to reach this goal.**

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## **A. Transmission blocking vaccines in their epidemiological settings**

### **1. General features of malaria transmission and transmission blocking vaccines**

*Two measures of intensity of malaria transmission are used:*

- i) ***Basal Reproductive Number (R)***, which is defined as the number of new cases of malaria expected to arise in an infinite non-immune and susceptible human population from a single untreated case of malaria in a non-immune individual. ***Ro can range from zero to the order of 1,000.*** Below the critical value of  $R_0 = 1$ , transmission is not sustainable.
- ii) ***The malaria inoculation rates from infected mosquitos (Entomological Inoculation Rates, EIR) vary from zero to several hundred per person per year.***

*TBV immunization would be by:*

- i) ***Periodic vaccination of a population or community.***
- ii) ***Delivery of vaccination through EPI*** (Expanded Programme for Immunization), which is targeted at children.

***The effect of TBV-induced immunity is to prevent the fertilization or the subsequent development of malaria parasites in the mosquito midgut*** (see Figure). As a consequence, the formation of oocysts, and ultimately of infective sporozoites in the mosquito salivary glands is prevented or reduced. This leads to a fall in EIR and  $R_0$  within a community.

***The efficacy of a TBV is defined at the following levels of evaluation:***

- i) Reduction in the proportion of mosquitos that become infected when fed through a membrane upon gametocytes in the presence of sera taken from TBV-vaccinated individuals.

- ii) Reduction in the proportion of mosquitos that become infected when fed directly upon TBV-vaccinated individuals following natural infection.
- iii) Reduction in the incidence of malarial infections – e.g. incidence of clinical cases or parasite prevalence in a TBV-vaccinated community.

***In a TBV- vaccinated population:***

***The basic reproductive number (Ro) will be reduced in proportion to the effective coverage by the vaccine.***

Thus, if  $Ro_{TBV}$  is the Ro under a particular TBV coverage, and  $Ro_I$  is the initial Ro in a community before TBV deployment and  $c$  is the proportion of the community with effective vaccine coverage, then

$$Ro_{TBV} = Ro_I (1 - c)$$

From this equation the relationship between some specific values for TBV vaccine coverage ( $c$ ), initial Ro in a community ( $Ro_I$ ), and the resulting Ro following TBV deployment ( $Ro_{TBV}$ ) are presented in Table 1. ***Note that when  $Ro_{TBV}$  falls permanently below 1, malaria transmission eventually ceases.***

***Reasonable expectations for reductions by TBV of the basic reproduction number (Ro) in a community would be between 2 and 10 fold***, corresponding to effective TBV coverages of a target community of 50% to 90% (Table 1). The level of coverage achievable in a given situation would obviously depend upon the logistics affecting the target population or community. Stability of the human population, with little immigration of unvaccinated individuals into the vaccinated population, would be important for successful TBV vaccination.

***Because of the localized nature of the breeding sources of the mosquito vectors and their limited dispersal range - generally a few hundred metres to one or two kilometres - malaria transmission is very focal. Each TBV-vaccinated individual would, therefore, reduce malaria inoculation rates primarily to members of his or her household and nearby houses.***

***Transmission blocking vaccines would synergise with other antimalarial measures, including other malaria vaccines, towards the reduction of transmission and of morbidity and mortality due to malaria.***

Table 1. Numerical values for  $Ro_{TBV}$ , the malaria Basal Reproductive Number in a community under TBV coverage, from the equation  $Ro_{TBV} = Ro_I (1 - c)$

c	$Ro_{TBV}$												
	$Ro_I$	2	3	5	8	10	15	20	30	50	100	200	500
0.3		1.4	2.1	3.5	5.6	7	10.5	14	21	35	70	140	350
0.4		1.2	1.8	3.0	4.8	6	9.0	12	18	30	60	120	300
0.5		1.0	1.5	2.5	4.0	5	7.5	10	15	25	50	100	250
0.6		0.8	1.2	2.0	3.2	4	6.0	8	12	20	40	80	200
0.7		0.6	0.9	1.5	2.4	3	4.5	6	9	15	30	60	150
0.8		0.4	0.6	1.0	1.6	2	3.0	4	6	10	20	40	100
0.9		0.2	0.3	0.5	0.8	1	1.5	2	3	5	10	20	50
0.95		0.1	0.15	0.25	0.4	0.5	0.75	1	1.5	2.5	5	10	25
0.98		0.04	0.06	0.10	0.16	0.2	0.30	0.4	0.6	1.0	2	4	10
0.99		0.02	0.03	0.05	0.08	0.1	0.15	0.2	0.3	0.5	1	2	5

Values of  $Ro_{TBV}$  below the zig-zag across the Table are less than or equal to 1 and malaria transmission ceases.

## 2. Use of TBV for regional elimination of malaria (the reduction of $Ro_{TBV}$ to below 1)

***Under low endemic transmission conditions*** (annual sporozoite inoculation rates, EIR, generally less than 5;  $Ro$  less than 10), ***a TBV could eliminate malaria within a locality.*** For example, an effective TBV coverage of 70% (as defined above) would eliminate malaria transmission with an  $Ro_I$  of 3; a coverage of 90% would eliminate malaria at an  $Ro_I$  of 10 (see Table 1).

***In high endemic areas*** (annual sporozoite inoculation rates, EIR, and  $Ro$  generally much greater than 10) ***TBV could move malaria transmission rates towards the range in which eradication could be possible with the deployment of other interventions.*** For example, at an  $Ro$  of between about 10 and 30, other interventions such as mosquito control or personal protection, which could reduce the  $Ro$  by 3 to 5 fold, would bring the  $Ro$  down to a level at which TBV could lead to the elimination of malaria transmission. Large populations in Africa and most malaria endemic regions outside Africa are believed to be exposed to malaria transmission rates within or below this range of  $Ro$ .

### 3. Use of TBV to reduce malaria transmission

*In low endemic situations* (as defined above), reducing malaria inoculation rates with *a TBV* would be clearly beneficial, because it *would reduce incidence of disease in proportion to effective TBV coverage*. This would reduce the burden on the health services to a corresponding extent. The risks resulting from lowering immunity would be minimal in these situations.

*In most high endemic areas* (as defined above), *the effects of reducing malaria inoculation rates by TBV would probably be an overall reduction in disease and mortality*. This would tend to move the risk of disease and death from malaria into higher age groups due to a delay to the achievement of protective immunity. The possibility of an increased risk of disease and death in the older age groups should, therefore, be considered. However, TBV would not be deployed in the absence of other health services which would therefore be available to cover any such need.

### 4. Use of TBV to prevent/control malaria epidemics

*TBV-induced immunity could*, even at relatively low coverage, significantly retard the build up of a malaria epidemic. Since the vectorial capacity (the power of the prevailing mosquito populations to transmit malaria) that drives an epidemic is usually time-limited, this could *completely abort a potential epidemic or prevent it from reaching a high level*.

There are two types of epidemic situation in which control by TBV could be considered:

- i) Regions at known risk of malaria epidemics. Keeping populations under long-term TBV coverage would avert such risk.
- ii) Unpredictable situations, such as hurricane-induced flooding, which put an area at imminent risk of a malaria epidemic. Rapidly deploying a TBV could avert such risk.

Mathematical simulations are needed to quantify the effects of TBV, particularly in epidemic control.

### 5. Use of TBV to protect other vaccines, and possibly also drugs, against the spread of vaccine- or drug-resistant parasites

*A TBV, when deployed in combination with other types of malaria vaccine or antimalarial drugs, could be effective in preventing the escape and spread of mutants resistant to those vaccines or drugs*. This would apply particularly to asexual blood stage vaccines and antimalarial drugs to which the chances of resistant mutants arising would be high.

The duration of the TBV immunity would have to be at least as long as that of the vaccine it protects. The chances of resistant mutants emerging to the TBV would be minimal compared to the rate at which they would arise to asexual blood stage malaria vaccines and antimalarial drugs. This is because sexual stages do not multiply, and are present in relatively very low numbers, when they are under TBV-induced immune pressure.

Mathematical simulations are needed in order to quantify the protective effects of TBV on other vaccines and drugs.

## 6. The ethics of using TBV

*In situations which call for the deployment of TBV, there will, as described above, be benefits to all individuals in the community in which the vaccinee resides. Because of the focal nature of malaria transmission, the benefit will be greatest to members of a vaccinee's household. Thus, the potential benefits of TBV use would justify a degree of risk to the individual associated with vaccination.*

In deploying TBV, the nature of action of these vaccines will have to be explained in community education and in obtaining informed consent of the individuals to be vaccinated.

## 7. The economics of TBV

The group reviewed the available cost-effectiveness analyses on existing antimalarial interventions, including an analysis carried out on malaria vaccines.

This is an area of fundamental importance, not only for TBV, but for all interventions against malaria, and it is one in which very little research has been done for any malaria intervention. Several general points can be made, however.

- In spite of the poverty of the countries involved or, indeed, because of it, the economic gains from reducing or eliminating malaria from the huge populations affected are potentially enormous.
- The proportion of the national budgets (both government and private/individual) currently dedicated to dealing with malaria is generally very high in the area of health expenditure, and would almost certainly increase in response to improved returns on expenditure i.e. greater reduction in the malaria burden per \$ spent.
- The economic value of any individual intervention will be determined both by its cost-effectiveness relative to other interventions available and by the added value of using it in combination with other interventions with which it has a synergistic effect.
- A general survey of the cost effectiveness of vaccines in public health use indicates that they lead to a very efficient return in improved health per \$ spent.

Thus, from the perspective of the user community, the specific issues that need to be addressed with respect to TBV were identified as the following:

- i) What is the maximum cost at which a TBV would be an attractive intervention in endemic situations?
- ii) What would be the cost-effectiveness of TBV relative to, or in combination with, other measures to reduce the burden of malaria?

Approaches to estimating cost-effectiveness of TBV could include:

- i) Cost per DALY saved.
- ii) The value represented by the protection that TBV offers to other malaria vaccines.

***Studies to estimate the cost-effectiveness of TBVs should be conducted.***

## **B. The scientific and technical basis for production of transmission blocking vaccines**

### **1. The feasibility that a transmission blocking vaccine could be produced**

*There is strong evidence that the leading candidates already identified and characterized could form the basis of a transmission blocking vaccine.* The group considered the range of antigens available, and their relative strengths and weaknesses as potential vaccine candidates (Table 2). In addition, a number of less well characterized antigens (e.g. chitinase, gametocyte surface antigens) were identified as having potential.

*Immune effector mechanisms: The data on the immune mechanisms of transmission blocking are sufficient to conclude that a vaccine is feasible.* The major component is antibody mediated, and vaccine development can initially be optimized for level and specificity of antibody, especially using membrane feeding assays to determine the quality of antibody response. Participants emphasized that these assays will provide the basis for milestones during vaccine development and testing phases.

*There is no conclusive evidence of immune enhancement of infectivity which would prevent vaccine development.* There have been some reports of enhancement, but the group felt that at the levels of transmission blocking activity being targeted, enhancement would not be a major issue. The possibility of enhancement needs to be taken into account in trial design.

*There is no evidence that antigenic diversity in the leading candidates would be an impediment to the development of a vaccine.* Limited sequence diversity does exist in some candidates. Further research in this area would be useful to extend the range of isolates typed and to test the effects of sequence polymorphism in functional assays.

*There is no overwhelming evidence that host immunoresponsiveness is a theoretical problem for key antigens.* For certain target antigens of natural transmission blocking antibodies e.g. Pfs230 and Pfs48/45, the level of immune response varies between individuals. Additional information will be obtained in the course of further studies. The group felt that the ultimate test will be in human Phase I trials and that there is ample evidence to proceed to this stage.

#### ***Recommendations for further strategic research***

- Vaccine formulation studies for the leading candidates to optimize the balance between immunogenicity and reactogenicity.
- Assay standardization including the membrane feeding assay, and the creation of repositories of standard reagents, e.g. within the MR4 (Malaria Research and Reference Reagent Resource Center).

Other areas were identified, including further transmission blocking target antigen discovery, and immune response mechanisms, which researchers should be encouraged to pursue. It is important to emphasize the ongoing need for good research into the biology of transmission that needs to proceed independent of the decision to take any antigen through clinical development.

Table 2. Relative strengths and weaknesses of the leading transmission blocking antigens

Antigen	Strengths	Weaknesses
<b>Pfs25/Pvs25</b>	Not expressed in the vertebrate host and less likely to be subject to naturally occurring immune selection pressure. <i>P. vivax</i> and <i>P. falciparum</i> antigens both cloned and expressed. Vaccination with both the <i>P. vivax</i> and <i>P. falciparum</i> antigens induces complete transmission-blocking in model systems. Monoclonal antibodies to both antigens block transmission in membrane feeds.	Not expressed in the vertebrate host and so not subject to natural boosting following vaccination (although some T cell reactivity has been observed in field samples to Pfs25).
<b>Pfs28/Pvs28</b>	Similar to Pfs25/Pvs25.	Similar to Pfs25/Pvs28.
<b>Pfs48/45</b>	Monoclonal antibodies to the 48/45 completely block transmission in membrane feeds. A close correlation exists in field samples between transmission blocking activity and antibodies to the 48/45. Expressed on the gametocyte, and so boosting of antibody response a possibility. Essential for fertilization in gene knock-out experiments.	
<b>Pfs230</b>	A close correlation exists in field samples between transmission blocking activity and antibodies to the 230. Monoclonal antibodies to the 230 completely block transmission in membrane feeds. A clear mechanism of antiparasite activity (compliment mediated). Expressed on the gametocyte, and so boosting of antibody response a possibility.	A very large molecule, so unclear which part/s to make.

## 2. Preclinical vaccine development

**Developmental stage of lead candidates.** The group reviewed the progress towards clinical grade material. Clinical grade material is available for Pfs25. Pfs28, Pvs25 and Pvs28 are close, but substantial work is required for Pfs48/45 and Pfs230 (Table 3).

**Isolation and expression of equivalent antigens from *P. vivax* is a high priority.** The group determined that the equivalent antigens from *P. malariae* and *P. ovale* are not considered vital at this stage.

***P. falciparum* and *P. vivax* vaccines should follow parallel development.** For these and other antigens which may ultimately form the basis of a combined vaccine, it was noted that the issues of increased risk of adverse events, difficulties in formulation, interference with immune responses etc, warranted separate development through Phase I and early efficacy testing (Phase II/III). The group noted that this strategy will require repeated testing of mixtures following decisions to combine antigens into a combination vaccine.

***Recommendations for further developmental research.***

- Investigate formulation, including ways of minimizing the risk of hypersensitivity reactions.
- Develop ways of improving longevity of antibody response.
- Further developmental research for Pfs48/45 and Pfs230 is essential.

The group noted the progress in DNA vaccines with Pfs25 and the positive achievements with prime boost strategies.

Table 3. Current product development of leading transmission blocking vaccines

<b>Antigen</b>	<b>Current Development</b>
<b>Pfs25/Pvs25</b>	Yeast expression gives high yields for both Pfs25 and Pvs25. Correctly folded as judged by induction of biologically active transmission-blocking antibodies. TBV25H (yeast-expressed Pfs25) clinical grade material produced. Clinical grade Pvs25 soon to be produced.
<b>Pfs28/Pvs28</b>	Similar to Pfs25.
<b>Pfs48/45</b>	Expressed in <i>E. coli</i> , but without a correct conformation. Combinatorial peptide approach being explored. Other expression strategies being explored.
<b>Pfs230</b>	Similar structure to the 48/45, but very large (360kDa). Fragments have been expressed as <i>E. coli</i> MBP-fusion proteins, with evidence of transmission-blocking activity. Fragments have been expressed as yeast rec. proteins (+/- tetanus toxoid), with evidence of transmission-blocking activity.

**Alternative delivery and adjuvant systems.** While the group noted the value of exploring new and unlicensed adjuvants and delivery systems such as microspheres, the need for caution was also noted, especially where the use of novel technology may impede the ability to form multi-antigen and multi-stage vaccines which include a transmission blocking component.

As the manufacturing costs will be critical for a vaccine with a weak pull, further development research is needed on developing cost effective delivery systems. These may include vector- based vaccines.

**Membrane feeding of gametocytes mixed with serum from immunized volunteers is an adequate surrogate measure of efficacy to form the basis of decisions to proceed to phase III trials.** The group noted that additional information using field isolates of gametocytes would be desirable for *P. falciparum*, and that for *P. vivax*, field isolates would be a major source of gametocytes. Since vaccine trials are likely to make heavy use of membrane feeds, increased capacity will be needed. Further development of other potential surrogate measures, for example validated ELISA assays which correlate with transmission blocking activity, are needed for use in multiple sites.

### 3. Vaccine testing

The group noted the following definitions of vaccine trials:

**Phase I:** A test of safety and immunogenicity in naive or target populations. As part of the immunogenicity assessment, the ability of volunteers' antibodies to block infections of mosquitos in a membrane feed, or other surrogate measures of efficacy, would be used.

**Phase II:** A test of the ability of the vaccine to block the transmission of malaria from naturally infected vaccinees to mosquitos by direct feed. The measures of transmission from person to mosquito may include:

- Direct feeds on vaccinated, gametocytemic individuals by laboratory reared mosquitos.
- Investigation of infection rates in wild caught mosquitos on individual vaccinees, e.g. mosquitos collected from bednets covering volunteers.
- Community wide measures of mosquito infection rates following vaccination of a high proportion of community members.

**Phase III:** A test of the ability of the vaccination to prevent people from becoming infected, i.e. to break the human - mosquito - human infection cycle. A Phase III trial may have several endpoints, including:

- The rate at which new infections are detected in humans by active case detection.
- The proportion of people who seroconvert for antimalarial antibodies over the course of the vaccine trial.
- The number of people presenting with disease symptoms (passive case detection). This last measure may be especially applicable in high transmission areas.

The group noted the need for careful selection and preparation of study areas, including social, entomological and parasitological factors. These are detailed in the WHO report TDR/CTD/TBV/92 *Guidelines for community-based trials against the sexual stages of malaria parasites*.

**Conduct of Phase I trials.** A special consideration for the use of TBV will be the need to vaccinate a high proportion of the population. Since Phase III trials will inevitably require relatively large numbers to be vaccinated before there is any measure of efficacy, particular care will be needed to progressively test sufficient adults, adolescents, and children to ensure that the risks of exposing volunteers to serious adverse events are minimized. In this context, the use of communities where infants constitute an insignificant gametocyte reservoir would be desirable.

**Need for Phase II trials.** The group considered that Phase II trials are feasible for both *P. falciparum* and *P. vivax* in hyperendemic areas, and for *P. vivax* alone in low endemic areas. However, these trials may only be required to initially validate membrane feeding assays as a predictor of efficacy. Only if membrane feeding assays were found to be inappropriate would Phase II trials be a routine necessity. In any case, the group did not consider that a Phase II trial conducted in a high transmission area lies on the critical path for taking a vaccine through a Phase III trial in a low endemic region.

**Conduct of Phase III trials.** The group considered that Phase III trials in both hyperendemic areas and areas of low, but stable transmission, were feasible. Issues of test selection are detailed in TDR/CTD/TBV/92. The meeting noted the long lead time for these trials, which, including the necessary Phase I studies in the target population, will be of the order of 4 or 5 years minimum. In addition to the primary outcome, the group noted the need to take into account secondary outcomes which will provide important information on the feasibility of implementing transmission blocking vaccines.

**Need for Phase III studies with separate vaccine.** A Phase III study will be required where it is intended to use a TBV as the only vaccine component of a control programme. However, the availability of surrogate markers of protection (e.g. membrane feeding) may obviate the need for Phase III trials of individual TBV components and extensive efficacy testing would then only occur as a combination of multiple antigens (e.g. *P. falciparum* and *P. vivax*).

## **C. Industrial aspects of transmission blocking vaccine development**

### **1. Requirements for industrial involvement in transmission blocking vaccines**

**Industrial involvement for the production of a TBV is achievable in a suitable economic environment.** The issues that need to be addressed to engage industry in a way that could result in the production and commercialization of a transmission blocking vaccine, either alone or in combination with pre-erythrocytic and erythrocytic vaccine components, were categorized into ‘**Pull**’ and ‘**Push**’ mechanisms (see Table 4).

‘Pull’ refers to downstream incentives to induce companies to invest in R&D, production and commercialization. ‘Push’ refers to front-end investments by the public sector to facilitate industry engagement and reduce industry risk. Transmission blocking vaccines are a special

case where there is low ‘pull’, so there needs to be substantial ‘push’. Because of the public health relevance of transmission blocking vaccines, a strong commitment from the public sector will be needed to provide the resources that can be made available to develop (push) and purchase (pull) the vaccine.

***Transmission blocking vaccines would have an appreciable value to the public sector, and this will impact positively on the market value to the private sector.*** The public sector value of a TBV depends on the goal and end use of the vaccine.

1. ***TBV would have a high value as a component in an integrated control programme to reduce disease globally and to eliminate malaria in many areas.*** A TBV component will be vital to achieving these goals.
2. ***TBV would have a high value in combination with drug treatment or as a component in a multivalent vaccine to prevent the spread of mutant parasites.*** This could dramatically extend the useful life of both existing and new generation drugs and antimalarial vaccines when they are introduced.
3. Because a TBV blocks the malaria – mosquito cycle, ***TBV would have a high value as an attractive alternative to the problems (expense and environmental) associated with the use of insecticides.***

## **2. The way forward – bridging the gap**

***There is a growing recognition that malaria is a major economic and social development issue that demands a global response.*** Resources for purchasing appropriate tools (pull) and undertaking R&D for such tools (push) are becoming available at much higher levels than in the past and a window of opportunity exists to make a major impact in these diseases.

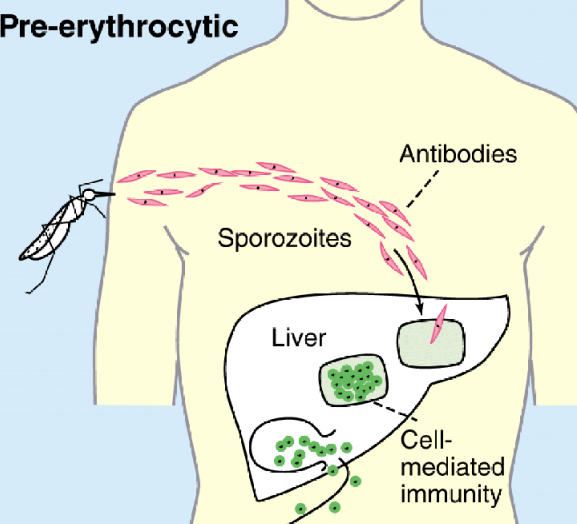
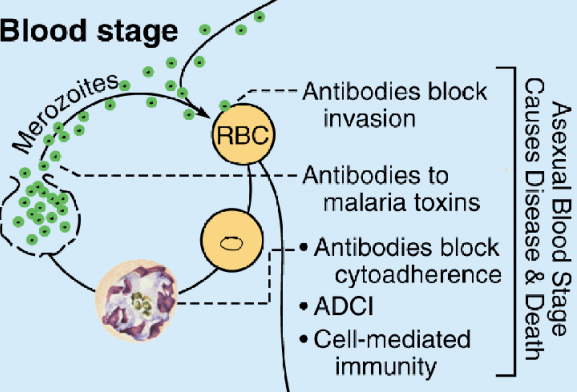
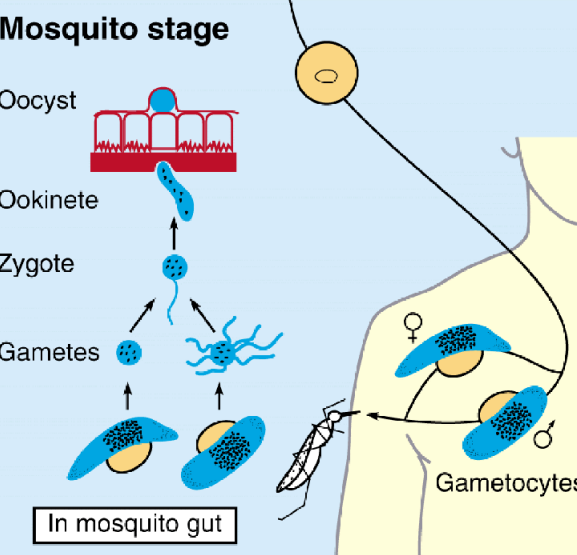
***Malaria transmission blocking vaccines have progressed in their development to the point where a comprehensive development programme is justified.*** To engage industry, the development plan needs to include:

1. ***An assessment of the value of developing a TBV.*** This should include an estimate of the willingness of the public sector to pay for a final product and an approximation of the likely market size. The value of a TBV should be assessed in comparison and in combination with other control measures.
2. ***A comprehensive and globally-integrated, strategic plan for the development of a TBV,*** based on a defined product profile and milestones. As noted in the technical section, a major advantage of TBV over other types of malaria vaccine is the *in vitro* assay of likely efficacy, which will not only enable early optimization of immunogenicity, but also greatly facilitates the development of strategic plans with credible ‘go – no go’ decision points.
3. ***Estimates of the resources required to develop and commercialize a TBV product and the development of a financing strategy that takes into account the substantial value to the public health sector.*** This assessment would need to take into account that new strategies and programmes for delivering vaccines to adult populations may need to be developed.

Table 4. Requirements for the industrial production of a transmission blocking vaccine: public sector investment (push) and inducement for R&D investment in R&D (pull).

<b>Push</b>	<b>Pull</b>
<ul style="list-style-type: none"> <li>• Risk reduction through providing               <ul style="list-style-type: none"> <li>➤ R&amp;D costs (<i>money at front end</i>)</li> <li>➤ Technical support (see below)</li> <li>➤ Liability (including safety)</li> <li>➤ Manufacturing (including low cost)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Clear market definition               <ul style="list-style-type: none"> <li>➤ Optimized in size and value (<i>money at the back end</i>)</li> <li>➤ Strategy and commitment for purchase and use of TBV</li> <li>➤ Market maintenance</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• Detailed strategic R&amp;D plan which               <ul style="list-style-type: none"> <li>➤ Defines and evaluates goals of TBV vaccine and its use</li> <li>➤ Adopts an industry paradigm (including product profile, Stop / Go criteria etc)</li> <li>➤ Details management infrastructure</li> <li>➤ Provides for the pro-active engagement of industry at                   <ul style="list-style-type: none"> <li>▪ CEO-level</li> <li>▪ R&amp;D level</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Define added value for TBV               <ul style="list-style-type: none"> <li>➤ Immediate and direct saving in treatment costs resulting from reduction in disease incidence (total direct and indirect costs of \$2 billion globally in 1995)</li> <li>➤ Long term reduction in recurrent expenditure on malaria control in areas where malaria is eliminated. (e.g. annual expenditure of \$350 million outside Africa in 1995)</li> <li>➤ As a component to prolong life of a antimalarial drugs and malaria vaccines (\$300 million in development costs per drug or vaccine lost to resistance)</li> <li>➤ Replacement for insecticides such as DDT</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• Technical support for               <ul style="list-style-type: none"> <li>➤ Proof-of-principle</li> <li>➤ Developing low unit cost vaccines</li> <li>➤ Standardizing of surrogate efficacy and analytic assays</li> <li>➤ Developing compatibility with other vaccine components</li> <li>➤ Good clinical testing design, facilities and management</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Public Sector commitment               <ul style="list-style-type: none"> <li>➤ Clear statement of need</li> <li>➤ Mandate for TBV</li> <li>➤ Evidence for commitment to go the distance</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• Public sector investment in TBV specific expertise and facilities               <ul style="list-style-type: none"> <li>➤ Insectaries</li> <li>➤ Entomology</li> <li>➤ Epidemiology</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Other               <ul style="list-style-type: none"> <li>➤ Protection of intellectual property</li> <li>➤ Stratification of market</li> <li>➤ Fast track registration</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• <b>VISIBLE PUBLIC SECTOR COMMITMENT</b> <ul style="list-style-type: none"> <li>➤ Realistic definition of resource requirements</li> <li>➤ Provision of funds for focused R&amp;D milestones</li> <li>➤ Guaranteed commitment to build on achievements / milestones</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>VISIBLE PUBLIC SECTOR COMMITMENT</b> <ul style="list-style-type: none"> <li>➤ Establishment of track record for purchase and global access to current vaccines</li> <li>➤ Good vaccine delivery systems</li> </ul> </li> </ul>

Figure: The action of malaria vaccines

Stages targetted by vaccines	Goals of vaccination	Target population and situation for vaccination
<p><b>Pre-erythrocytic</b></p>  <p>Antibodies</p> <p>Sporozoites</p> <p>Liver</p> <p>Cell-mediated immunity</p>	<p>A. Prevent disease by blocking infection before emergence from liver</p> <p>B. Reduce disease by a vaccine that combines partially effective pre-erythrocytic and blood stage components</p>	<p>A. Non-immune travelers and residents in areas of low transmission (e.g. India)</p> <p>B. Children and pregnant women in areas of high transmission (e.g. Africa)</p>
<p><b>Blood stage</b></p>  <p>Merozoites</p> <p>RBC</p> <p>Antibodies block invasion</p> <p>Antibodies to malaria toxins</p> <ul style="list-style-type: none"> <li>• Antibodies block cytoadherence</li> <li>• ADCI</li> <li>• Cell-mediated immunity</li> </ul> <p>Asexual Blood Stage Causes Disease &amp; Death</p>	<p>A. Reduce disease by reducing blood stage asexual parasite burden</p>	<p>A. Children and pregnant women in areas of high transmission (e.g. Africa)</p>
<p><b>Mosquito stage</b></p>  <p>Oocyst</p> <p>Ookinete</p> <p>Zygote</p> <p>Gametes</p> <p>In mosquito gut</p> <p>Gametocytes</p>	<p><b>Prevention of transmission</b></p> <p>A. Eradication</p> <p>B. Limit spread of parasites resistant to vaccines</p> <p>C. Prevent epidemics in areas of unstable malaria transmission</p>	<p>A. Entire community in isolated areas of low transmission</p> <p>B. In combination with blood stage or pre-erythrocytic vaccines in any situation</p> <p>C. Entire population before high transmission season</p>