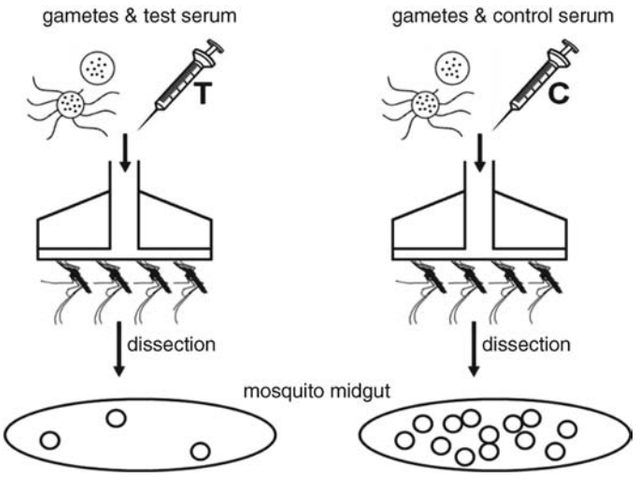

Figure 3 Standard Membrane Feeding Assay. Laboratory reared *Anopheles* mosquitoes are allowed to take a blood meal from membrane-covered glass devices that contain cultured gametocyte-infected red blood cell suspensions mixed with test or control serum (T or C). After feeding, the mosquitoes are maintained for six to eight days, and then are dissected to determine oocyst counts in mercurochrome-stained midguts. Transmission blockade is calculated by comparing oocyst numbers in a series of mosquitoes that are fed in the presence of test serum versus those fed with control serum.

detection of transmission-reducing activity in test sera (286). Another shortcoming of this time-consuming and laborious bioassay is the current limited capacity for large-scale testing of sera. Good correlations between antibody levels (as determined by ELISA) and transmission-reducing activity in the SMFA were shown for some of the major TBMV antigens (287; van de Kolk unpublished). This relationship will greatly aid in prescreening and down selection of TBMV during early development, since the ELISA is much easier to perform.

Control of Malaria Transmission

Malaria parasites spread in populations by *Plasmodium*-infected *Anopheles* mosquitoes. The intensity of malaria transmission is determined by the prevalence of gametocytes in endemic populations and the number of *Anopheles* mosquitoes in the area. Depending on the transmission pattern, malaria can be (*i*) present throughout the year in areas where transmission is perennial, (*ii*) seasonal following the onset of the rainy season and associated increase in mosquito breeding, and (*iii*) present as epidemics in areas where transmission occurs occasionally as a function of climatological fluctuations.

Transmission intensity can be defined by either the Entomological Inoculation Rate (EIR) or Basic Reproduction number (Ro). EIR is the number of infectious bites per person/year which can vary even within the same country in endemic areas of Africa from <1 to >1000 infectious bites/yr. Ro is the number of nonimmune individuals that can be infected from a single untreated and nonimmune malaria case and ranges from 1 to >3000 (288). Ro is directly related to vectorial capacity and malaria transmission is sustainable when Ro >1. Although the wet and warm parts of sub-Saharan Africa show perennial intense transmission, sustainable levels of transmission may be unpredictable or generally absent in large parts of the continent that are dry or cool at altitudes >1600 to 1800 m where malaria transmission drops to Ro <10.

In many parts of sub-Saharan Africa more than half of the population carries malaria parasites in the blood without becoming ill because of the acquisition of clinical immunity in childhood. These persons form an important reservoir for malaria transmission by mosquitoes. Large *Anopheles* mosquito populations often live near human habitats and regularly need blood meals for egg production. In fact, the principal malaria vector in Africa (*Anopheles gambiae*) only feeds on humans and is very efficient in transmitting malaria. The combination of abundant numbers of efficient mosquito vectors and a large reservoir of infected persons results in a high turn-over of parasites and intense infection pressure. Although the mechanism is not understood, there is a relationship between the incidence of (severe) malaria and transmission intensity. Obviously low transmission associates with low attack rates of disease but also a slow induction of clinical immunity and therefore a relatively high proportion of casualties.

The objective of malaria control is to find a package of control measures that will reduce the risk for (severe) disease with minimal impact on NAI. Not every infection leads to disease and it is a challenge to separate both phenomena to allow for the built up of immunity. In the past there have been concerns that reduction of transmission per se would harm the acquisition of immunity and worsen or only shift the age of severe malaria (289). When transmission is very low, as is the case in most countries outside Africa, malaria can be quite effectively contained by residual household spraying with insecticides. In addition, with the introduction of long-lasting insecticide-impregnated bed nets and combination therapy, which includes artemisinin-based preparations that kill gametocytes and reduce transmission from men to mosquito, there is accumulating evidence showing that the incidence of clinical (severe) disease is significantly reduced over time (290–292). The long-term impact of these control measures and the impact in areas of intense malaria transmission is unpredictable since there are fewer examples of successful large-scale vector control programs in high-intensity areas. Coverage of artemisinin combination therapy and compliance may be lower in semi-immune individuals, because a substantial proportion of infections in these individuals are asymptomatic and any symptoms present are more likely to resolve with incomplete treatment than in nonimmunes (291). Thus it may be hard to achieve substantial reductions in transmission intensity, and the addition of an effective transmission-blocking vaccine could be of great benefit.

Reduction of transmission intensity in a particular area has not been directly studied together with markers of malaria immunity in the population, so it is difficult to gauge the potential effect of a transmission-blocking vaccine on hindering the development of NAI. Serological markers have recently been shown to correlate with transmission intensity and may serve as an important tool to study changes in transmission intensity (293). For a rational epidemiological control strategy it remains important to determine the relationship between transmission reduction under a given intensity, presentation of clinical disease and effect on immune responses in longitudinal studies. There are clear indications, however, that transmission reduction possibly alone but more obviously as part of a larger control package, has a positive impact on malaria control.