The rise and fall of malaria in a west African rural community, Dielmo, Senegal, from 1990 to 2012: a 22 year longitudinal study


Summary

Background A better understanding of the effect of malaria control interventions on vector and parasite populations, acquired immunity, and burden of the disease is needed to guide strategies to eliminate malaria from highly endemic areas. We monitored and analysed the changes in malaria epidemiology in a village community in Senegal, west Africa, over 22 years.

Methods Between 1990 and 2012, we did a prospective longitudinal study of the inhabitants of Dielmo, Senegal, to identify all episodes of fever and investigate the relation between malaria host, vector, and parasite. Our study included daily medical surveillance with systematic parasite detection in individuals with fever. We measured parasite prevalence four times a year with cross-sectional surveys. We monitored malaria transmission monthly with night collection of mosquitoes. Malaria treatment changed over the years, from quinine (1990–94), to chloroquine (1995–2003), amodiaquine plus sulfadoxine-pyrimethamine (2003–06), and finally artesunate plus amodiaquine (2006–12). Insecticide-treated nets (ITNs) were introduced in 2008.

Findings We monitored 776 villagers aged 0–101 years for 2 378 150 person-days of follow-up. Entomological inoculation rate ranged from 142·5 infected bites per person per year in 1990 to 482·6 in 2000, and 7·6 in 2012. Parasite prevalence in children declined from 87% in 1990 to 0·3 % in 2012. In adults, it declined from 58% to 0·3%. We recorded 23 546 fever episodes during the study, including 8243 clinical attacks caused by Plasmodium falciparum, 290 by Plasmodium malariae, and 219 by Plasmodium ovale. Three deaths were directly attributable to malaria, and two to severe adverse events of antimalarial drugs. The incidence of malaria attacks ranged from 1·50 attacks per person-year in 1990 to 2·63 in 2000, and to only 0·046 in 2012. The greatest changes were associated with the replacement of chloroquine and the introduction of ITNs.

Interpretation Malaria control policies combining prompt treatment of clinical attacks and deployment of ITNs can nearly eliminate parasite carriage and greatly reduce the burden of malaria in populations exposed to intense perennial malaria transmission. The choice of drugs seems crucial. Rapid decline of clinical immunity allows rapid detection and treatment of novel infections and thus has a key role in sustaining effectiveness of combining artemisinin-based combination therapy and ITNs despite increasing pyrethroid resistance.

Funding Pasteur Institutes of Dakar and Paris, Institut de Recherche pour le Développement, and French Ministry of Cooperation.

Introduction Malaria in tropical Africa differs from malaria in all other regions of the world. The difference led WHO to exclude tropical Africa from the Global Malaria Eradication Programme in the 1950s.3,4 The ferocity of afrotropical malaria is a result of the exceptional vectorial capacity of the three anopheline species endemic in the region: Anopheles gambiae sensu stricto, A arabiensis, and A funestus.5 These species have long life expectancy, strong anthropophily, and high abundance, which can lead to several hundred secondary malaria cases from a single infected individual.6,7,8 Large-scale elimination of A gambiae is unlikely, and an important question is to what extent the burden of malaria can be reduced in tropical Africa without removing this vector? In the 1980s, results from studies done before the emergence of chloroquine resistance showed that the widespread use of chloroquine decreased malaria mortality to low levels despite the persistence of high entomological inoculation rates, high parasite rates, and high incidence of clinical malaria attacks in children.9 However, malaria mortality returned to high levels when chloroquine resistance disseminated across the continent.10 When mass distribution of insecticide-treated nets (ITNs) was combined with the deployment of artemisinin-based combination therapy, malaria prevalence, morbidity, and mortality greatly decreased in various countries or settings in tropical Africa.11,12
However, rapidly emerging pyrethroid resistance in *A gambiae* has raised serious concerns about the future of malaria elimination efforts.10–12

In 1990, we began a longitudinal prospective study of malaria infection and the determinants of the disease in a community living in an area of Senegal with intense and perennial malaria transmission.13 Until 2008, when long-lasting insecticidal nets (LLINs) were deployed, our only intervention was to provide prompt and effective treatment for clinical malaria attacks.11,13 We describe and analyse the important changes in malaria prevalence, morbidity, and transmission that occurred in this community over 22 years, analyse the likely causes of these changes, and discuss their implications for malaria control in tropical Africa in a context of increasing pyrethroid resistance of anopheline vector species.

**Methods**

**Study area and participants**

Dielmo village (13°45’N, 16°25’W), Senegal, is located on the marshy bank of a permanent stream (the Nema) in an area of Sudan-type savanna, 280 km southeast of Dakar and about 15 km north of the Gambian border (figure 1). Most of the houses are built in the traditional style with mud walls and thatched roofs (appendix). The inhabitants of the village are settled agricultural workers. Millet and peanut crops are cultivated during the wet season. Market gardening is the main activity during the dry season. Mangos and cashew trees provide some additional income. Small herds of domestic animals live in close contact with the houses. A detailed description of the study area and the origin of the project were reported previously.13

Between 1990 and 2012, we did a prospective longitudinal study of the population of this village to identify all episodes of fever and investigate the relation between malaria host, vector, and parasite. Our study included daily medical surveillance with systematic parasite detection in individuals with fever, cross-sectional surveys of malaria prevalence, and monitoring of malaria transmission.13

Our project was initially approved by the Ministry of Health of Senegal and the assembled village population. Approval was then renewed on a yearly basis with written informed consent from individuals enrolled in the project and parents or guardians of children enrolled. National Ethics Committee of Senegal and ad-hoc committees of the Ministry of Health, The Pasteur Institutes (Dakar and Paris), and the Institut de Recherche pour le Développement (IRD, formerly ORSTOM) did audits regularly.

**Procedures**

We visited all households daily, and recorded nominative information every day except Sunday including the presence of fever or other symptoms, and the presence or absence in the village of every individual we had enrolled and their location when absent. We systematically recorded body temperature at home three times a week (every second day) in children younger than 5 years of age, and in older children and adults in cases of history of fever or fever-related symptoms (hot body, asthenia, headache, vomiting, diarrhoea, abdominal pain, and cough). We did some blood testing for all suspected or confirmed cases of fever, and we provided detailed medical examination, prompt diagnosis and specific treatment for malaria and other diseases. We applied the national guidelines of the expanded programme of immunisation (EPI). The dispensary created for our project within the village was open 24 h a day, 7 days a week, to allow both active and passive case detection.

We successively used four first-line drugs regimens for treatment of malaria attacks: oral quinine (June, 1990–December, 1994), chloroquine (January, 1995–October, 2003), sulfadoxine-pyrimethamine plus amodiaquine (November, 2003–May, 2006), and artesunate plus amodiaquine (June, 2006–December, 2012, and from January, 2013, onwards). We initially selected oral quinine because chloroquine resistance was emerging in Senegal in 1990. However, we decided to abandon this drug when we recorded a fatal case of blackwater fever in December, 1994.14 The use of chloroquine (with sulfadoxine-pyrimethamine for second-line treatment in case of clinical failure),

Figure 1: Satellite view of Dielmo village, Senegal (Google Earth, 2013)
(1) The Nema River. (2) Dispensary and field station. (3) Primary school. (4) Santhe Mouride hamlet.
efforts to limit malaria transmission, and artesunate plus amodiaquine was systematically given to all patients with fever associated with malaria parasites independent of age and parasite density.

From April, 1990, to December, 2012, we measured vector density by collections of human-landing mosquitoes at two indoor and two outdoor sites in typical households of the central part of the village. Captures were done weekly or during three consecutive nights the first week of every month (average: 12·8 person-nights of capture per month). The households selected for captures remained unchanged during the whole study. We measured the entomological inoculation rate of *P falciparum* (ie, the potential number of bites by malaria infected mosquitoes per person per year) from the monthly values of human biting rates (ie, the number of landing mosquitoes per person) for *A gambiae* sensu lato and *A funestus* and the proportion of infected mosquitoes identified by dissection of the salivary glands (from April, 1990, to March, 1992) or by testing the circumsporozoite protein rate by ELISA (from April, 1992, to December,
2012) as previously described.14,15 At the beginning of the project, 49% of the villagers used traditional mosquito nets, which were untreated, and this proportion remained almost unchanged until July, 2008, when we offered LLINs (Permanet 2.0, Lausanne, Switzerland) to all villagers. There were no ITNs in Dielmo before July 2008, and the LLINs of all villagers were renewed in July 2011, after we documented a rebound in malaria morbidity.15

We measured malaria prevalence and density for each Plasmodium species at least quarterly from 1990 to 2012 in all villagers enrolled in the project. Blood was taken using a finger prick and we examined 200 oil-immersion fields (about 0·5 μL of blood). We applied similar procedures when examining thick blood films from patients.

We monitored the presence of each person in the village daily, and we measured the incidence of malaria attacks and other causes of fevers as the ratio of the number of fever episodes recorded during a given period divided by the number of followed up person-days under survey during the corresponding period. We counted separately two episodes of fever (including history of fever) if they occurred 15 days or more apart. We attributed fever to malaria when parasite density was higher than an age-dependent threshold calculated for each Plasmodium species during the corresponding period according to methods described elsewhere.18,19 Maximum threshold values in young children for P ovale and P malariae ranged from 3800 per μL to 2000 per μL according to study periods and decreased to 350–300 per μL in older adults.20 For P falciparum, maximum threshold values for parasite density in young children ranged from 21 500 parasites per μL to 10 000 parasites per μL and minimum values in older adults from 2000 to 500 parasites per μL.20 For infants thick blood films were taken twice a month up to 6 months and we attributed fever episodes to malaria when the onset of fever corresponded either to the onset of patent parasitaemia or to peaks of high parasitaemia, or both. We measured rainfall with a rain gauge located in the dispensary and the presence of water in the Nema meteorological service for this area of Senegal.21

Statistical analysis
We did the analyses with R software. We used binomial negative regression to measure the relation between the quarterly incidence rate and the different covariates (age, treatment period, entomological variables, rainfall). All covariates with a p value lower than 0·20 were included in the multivariable model. Multivariable backward step-by-step binomial negative regressions were done to take into account confounders, bias, and interactions linked to the dependent variable. We deemed statistical differences to be significant for p values lower than 0·05.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results
We invited all villagers to enrol in our project. In June 1990, all villagers had accepted (254 individuals aged from 1 day to 83 years), but between October and December, 1990, 26 left the study. Over the following years, the study population increased progressively to 499 people aged between 24 days and 101 years by Dec 31, 2012 (table I).

Reasons for this increase were births (264 neonates between 2008 and 2011, after we documented a rebound in malaria morbidity.11 153 migrated, and 60 withdrew). During the whole study period according to methods described elsewhere.18,19 297 villagers left the project after enrolment (64 died, 173 migrated, and 60 withdrew). During the whole study

![Figure 2: Mean monthly human biting rate, entomological inoculation rate, and mean monthly rainfall and temperature, Dielmo, April, 1990-December, 2012](image-url)

(A) Human biting rate is number of Anopheles gambiae and Anopheles funestus bites per person per night. (B) Entomological inoculation rate is number of infected A gambiae and A funestus bites per person per month. Error bars are standard errors of the mean.
Figure 3: Treatment periods and annual trends in Anopheles species human biting rates, entomological inoculation rates, malaria prevalence, mean numbers of non-malaria fever and clinical attacks per person, Dielmo, Senegal, 1990–2012.

(A) Anopheles species human biting rates, entomological inoculation rates. (B) Malaria and Plasmodium falciparum gametocytes prevalence during cross sectional surveys. (C) Mean numbers of non-malaria fever and clinical attacks due to P. falciparum, Plasmodium malariae, and Plasmodium ovale per person. AQ+SP=amodiaquine plus sulfadoxine-pyrimethamine. AQ+AS=amodiaquine plus artemunate. LLINs=long-lasting insecticide-treated nets.
period, we enrolled 802 villagers in the project, but only 776 of these were followed up for at least 4 months consecutively and included in the analysis; this choice of minimum surveillance period corresponded to the initial 4 months of the project (June–September, 1990) when all villagers participated in the study. The number of permanent residents in the village among the enrolled population, as defined every year by at least 75% of days of

![Figure 4:](image-url)

*Figure 4: Annual incidence density of all causes fever episodes, malaria parasites associated fever episodes, and Plasmodium falciparum clinical malaria attacks in young children, older children, and adults, Dielmo, Senegal, 1990–2012*
presence in the village during follow-up, ranged from 225 individuals in 1992 to 352 in 2010 and 2012 (table 1).

Rains averaged 702 mm per year during the study period (appendix). We analysed anopheline breeding sites in the marshland all year round. In 3488 person-night of captures during 273 months, we caught 47837 A gambiae sensu lato mosquitoes and 44011 A funestus mosquitoes. The yearly average daily human biting rate ranged from 2.7 (in 2012) to 29.8 (in 1990) for A gambiae sl, and from 0.9 (in 2010) to 28.6 (in 2002) for A funestus (table 1). The number of A gambiae sl mosquitoes substantially increased during the dry season, with A funestus being the dominant species during the dry season (figure 2).

The mean sporozoite or circumsporozoite rate was 2% (889 of 44904 tested mosquitoes) for A gambiae sl and 3% (1271 of 42686) for A funestus. The yearly average sporozoite or circumsporozoite rate ranged from 0.79% (in 2009) to 3.27% (in 1996) for A gambiae sl, and from 0.9 (in 2009–12, with 688 mosquitoes tested) to 4.40% (in 1993) for A funestus (table 1). Malaria transmission was noted year round, with A funestus and A gambiae sl alternating as the main malaria vectors (figure 2).

Figure 3 shows annual values of entomological inoculation rates, and table 1 shows details of sporozoite inoculation rates, and table 1 shows details of sporozoite infections alone or mixed. Malaria transmission averaged 220.5 infected bites per person per year during 1990–2012, with a maximum of 482.6 in 2000 and a minimum of 7.6 in 2012 (figure 2).

We measured malaria prevalence in 31575 blood films collected during cross-sectional surveys. For all age groups and for all surveys, 90–100% of villagers present in the village at the time the surveys were tested. During the first year of the study in 1990, the mean malaria prevalence in villagers was 71.9% (table 1), with prevalence of P falciparum being 69.3%, of P malariae 20.4%, and of P ovale 5.5% alone or mixed. Malaria prevalence started to decrease the second year of the project (figure 3). Strong decreases of malaria prevalence occurred in 2004 in young children only (appendix), then in all age groups in 2005. In 2010, malaria prevalence was only 2·2% in children 0–14 years and 2·5% in adults aged 15 years or older, with almost exclusively P falciparum infections (table 1). In 2012, prevalence continued to decrease and was only 0·3% both in children and adults. The spleen rate of children 2–9 years old was nil in September, 2012, compared with 89% in September, 1990.

We recorded 23546 episodes of fever or fever-related symptoms during 2378150 person-days of active plus passive surveillance among the 776 villagers enrolled in the study. The incidence of fever episodes was highest in 2000, where it reached 5·7 episodes per person per year, and lowest in 2010 and 2012, where it was 1·5 episodes per person per year (figure 3). By age group, the incidence density of fever episodes was maximum in children 2 years old (8·1 episodes per year) and minimum in adults aged 60 years or older (1·0 per year). Up to 10·7 fever episodes per year were noted in children 0–4 years during the chloroquine treatment period (figure 4).

We recorded malaria parasites in 15132 (64%) of the 23546 fever episodes, including 14243 P falciparum, 2415 P malariae, and 716 P ovale infections alone or mixed. On the basis of parasite density measurements, we attributed 8243 (35% of all fever episodes) to P falciparum,
219 (≤1%) to *P. ovale*, and 290 (1%) to *P. malariae*, including ten episodes where *P. falciparum* and *P. ovale* (seven cases) or *P. falciparum* and *P. malariae* (three cases) caused successive fever attacks within less than 15 days of each other. The youngest infant presenting fever with *P. falciparum* parasites was 2 days old (parasitaemia:
240 parasites per μL) and 17 attacks were recorded in infants during their second month of life (maximum parasitaemia 53,320 parasites per μL). The oldest adult presenting a *P. falciparum* attack was a 94-year-old man who had spent all his life in Dielmo (parasitaemia: 2,480 parasites per μL) and eight attacks occurred in adults aged 70 years or more (maximum parasitaemia: 32,960 parasites per μL in a 74-year-old man who had spent all his life in Dielmo).

The incidence density of malaria attacks varied substantially during the study period, with increasing levels from 1990 to 2000, a decrease from 2004 to 2007, and very low levels from 2008 to 2012 (figure 3, appendix). Only 17 malaria attacks were recorded in 2012, compared with 771 in 2000 (appendix). LLINs use in 2011 and 2012 remained stable compared with 2008–10, with 46–80% of villagers using treated bednets every night depending on year and age group (appendix). The rebound of clinical attacks noted in adults in 2010 was not sustained but the age pattern of malaria attacks clearly changed during the most recent period, with a higher relative proportion of malaria attacks occurring in older children and adults (appendix). During this period, almost all infections with malaria parasites were clinical *P. falciparum* attacks (figure 4). These changes in malaria morbidity (initial increase during the 1990s then great decline after 2003) were clearly related to changes in treatment policies, especially for young children, but also, to a lesser extent, for older children and adults (table 2, figure 5, appendix). The incidence density of malaria attacks was highest in 3-year-old children, in whom it reached 7.3 attacks per child per year during the chloroquine period. It declined in this age group to 3.2 malaria attacks per year during the sulfadoxine–pyrimethamine plus amodiaquine period, to 2.0 attacks during the artesunate plus amodiaquine period, and to only 0.07 attacks per year in 2011–12. Figure 6 shows trends in the monthly incidence rates of *P. falciparum* attacks and non-malaria fevers in each age group.

26 children and 38 adults died during the study. Three children died from *P. falciparum* malaria despite correct clinical monitoring and prompt treatment with oral then intramuscular quinine (one boy aged 11 months, who died in May, 1991) or chloroquine then intramuscular quinine (a boy aged 7 months who died in March, 1998, and a boy aged 16 months who died in July, 2000). These three children from the same family were brothers with the same mother and father. We attributed the death of two other children to severe adverse events of antimalarial treatment: one case of blackwater fever in December, 1994, in a 7-year-old boy who received 40 quinine treatment courses for malaria attacks between 1990 and 1994, and one case of chloroquine toxic effects by overdose resulting from a medical mistake from our team in a 5-month-old girl in July, 1996.

**Discussion**

Malaria epidemiology changed greatly in Dielmo, Senegal, between 1990 and 2012. All classic criteria of holoendemic malaria were met at the beginning of the project: the parasite and spleen rates in children were about 90% and transmission was intense and perennial because of the presence year round of *A. gambiae* s.s. and *A. funestus*, the major African malaria vectors. 22 years later, the parasite rate was only 0.3% both in children and adults, no enlarged spleen was recorded in children, and the WHO malaria pre-elimination criteria were met. Clinical malaria caused 44.0% of fever episodes from 1990 to 2003, but only 2.6% of fever episodes in 2012. The incidence of malaria attacks in the community decreased 57-fold between 2000 and 2012. This decrease was 98-fold among children and 12-fold among adults. The daily monitoring of fever episodes combined with cross-sectional surveys of malaria parasitaemia have made it possible to establish precise criteria for distinguishing clinical malaria from other causes of fever in all age groups. The procedures of medical, parasitological, biological, entomological, and epidemiological monitoring had remained unchanged from 1990 to 2012, allowing a comprehensive integrated analysis of the changes that occurred in this community (panel).

Data analysis suggests that the choice of the antimalarial drug used for first-line treatment and the universal deployment of LLINs were the most important factors governing the great changes in parasite rates and malaria morbidity. Before the beginning of the project, the use of antimalarial drugs by villagers was very scarce and most malaria attacks in children were not treated. Parasite rates decreased progressively after the first months of the project, probably in relation with the high incidence of malaria attacks in children and thus the high number of treatments they received. A second step in the decrease of parasite rates followed the switch from chloroquine to sulfadoxine–pyrimethamine plus amodiaquine treatment. The decrease was much more rapid and greater in young children than in other age groups, as a result of this combination therapy. Finally, a third, very important step was associated with the deployment of LLINs with parasite rates becoming very low in all age groups.

Trends in malaria morbidity presented a quite distinct pattern. First, morbidity (but not parasite rates) increased greatly in children when chloroquine replaced oral quinine. This change was made at a time when chloroquine resistance was spreading in Senegal. Chloroquine resistance spread in Dielmo within a few weeks after we began to use this drug in January, 1995, for first-line treatment, with almost half of *P. falciparum* clinical...
Panel: Research in context

Systematic review
We searched PubMed with the terms “malaria”, “epidemiology”, “morbidity”, “control”, “longitudinal study”, “ITN”, “ACT”, “drug policies”, for articles up to March, 2014, in English, French, Spanish, or Portuguese. We found no cohort study measuring malaria transmission, prevalence, and morbidity over a decade or more in a rural African community, and analysing the trends in the malaria burden on the basis of a daily medical surveillance with both active and passive case detection of all fever episodes for an entire village population. In this unique study, we describe and analyse the changes in malaria epidemiology that occurred in an African village community over a 22 year period, analyse the probable causes of these changes, and discuss their implications for malaria control in tropical Africa.

Interpretation
Daily monitoring during 22 years of 776 inhabitants of a Senegalese village, blood testing of all episodes of fever, quarterly measurements of asymptomatic parasitaemia, and monthly mosquito captures generated a unique dataset, which allowed an integrated analysis of the effect of precisely timed interventions on malaria morbidity and epidemiology. The malaria vectors Anopheles gambiae sl and A funestus were present and often abundant year-round during the whole study. This study provides the first evidence that malaria control policies combining prompt treatment of malaria attacks and deployment of ITNs can nearly eliminate parasite carriage and reduce dramatically the burden of malaria in African populations exposed to intense perennial malaria transmission with A gambiae and A funestus as vectors. The choice of drugs seems crucial.

infections harbouring the chloroquine-resistance associated P falciparum mutation by mid-1995.22 This emergence of resistance caused frequent early and late treatment failures such as persistence of malaria parasites after treatment, including gametocytes, and, much less frequently, clinical relapses. These treatment failures were the probable cause of the strong increase of sporozoite rates of A gambiae sl and A funestus, entomological inoculation rates, and malaria morbidity during the chloroquine period compared with the quinine period.

Second, a striking finding was the size of the decrease in malaria morbidity in young children that followed the switch from chloroquine to combination therapy with sulfadoxine-pyrimethamine plus amodiaquine and then with artesunate plus amodiaquine. The decrease of malaria morbidity was important in all age groups, but only in younger children did incidence rates of malaria attacks substantially decrease during the period of combination treatment compared with the quinine period, despite little difference in entomological inoculation rates between both periods. The mean time intervals between two attacks of P falciparum malaria were 338 days in children aged 0–1 year and 152 days in those aged 2–4 years during the sulfadoxine-pyrimethamine plus amodiaquine and artesunate plus amodiaquine periods, compared with only 98 days in children aged 0–1 years and 68 days in those aged 2–4 years during the quinine period. Although infants and young children are typically much less exposed to mosquito bites than adults,23,24 and the long half-life of amodiaquine (and sulfadoxine-pyrimethamine) was likely to delay time to reinfection since resistance to these drugs was low,25 the mere addition of these two factors seems insufficient to explain such a long interval. A combination of additional factors or mechanisms might be implicated.

One of these factors could be a decrease in the transmission of the more pathogenic parasite populations (ie, those that caused most malaria attacks) by the effects of sulfadoxine-pyrimethamine plus amodiaquine and artesunate plus amodiaquine on gametocyte production and infectivity to mosquitoes.26 Another factor could be a decrease in sporozoites succeeding to induce patent parasitaemia or clinical malaria, or both, as a result of decreasing parasite diversity in sporozoite inocula or more efficient immune responses acquired against pre-erythrocytic stages associated with the much longer chemoprophylactic effects of sulfadoxine-pyrimethamine plus amodiaquine or artesunate plus amodiaquine than those of quinine.26–28

The great changes in parasite rates and the burden of malaria between 1990 and 2012 were associated with major changes in several entomological variables. These changes were particularly strong during the most recent period that followed the introduction of LLINs. Before this period, the major change in entomological variables was the two-fold increase in sporozoite rates and entomological inoculation rates that followed the switch from quinine to chloroquine. Only the gametocyte rate of children aged 0–4 years increased during the chloroquine period compared with that in the quinine period. Since these young children received most chloroquine treatments, this finding suggests a direct effect of chloroquine treatment on gametocyte carriage, and a major contribution of these children to the increased sporozoite rates and entomological inoculation rates.

The implementation of LLINs was followed by a substantial decrease of A funestus, but the human biting rate of A gambiae sl and the mean entomological inoculation rates of this period initially remained higher than expected, given the great decrease in malaria prevalence and morbidity that followed the implementation of LLINs. Finally, the entomological inoculation rates decreased to its lowest value in 2012 when parasite carriage almost disappeared in Dielmo villagers. Combining LLINs with artemisinin-based combination therapy was so effective at preventing malaria infections in all age groups that acquired immunity in older children and adults rapidly decreased. Indeed, most patent infections were symptomatic from 2010 onwards whatever the age, and consequently they were rapidly detected and treated. The efficient drug
treatment apparently prevented replenishment of the parasite reservoir despite emerging pyrethroid resistance in *A gambiae* mosquitoes, which increased from 7% in 2007, to 48% in 2010. 13 We believe that this finding is of great importance since it suggests that as long as artemisinin-based combination therapies remain efficacious and infections remain rapidly treated, the emergence and spread of pyrethroid resistance in mosquitoes might not increase the malaria burden in communities in whom parasite rates have been previously reduced to low levels and acquired immunity has consequently decreased.

Only three deaths were directly attributable to malaria although 8252 *P falciparum* attacks occurred in Dielmo villagers between 1990 and 2012. The fact that the three children who died from malaria several years apart had the same mother and father suggests a role for genetic factors, and we eliminated alternative hypotheses regarding health care provided at home to these children. However, given that children aged younger than 5 years (the only age group typically at risk of death under perennial malaria transmission) were monitored during 885 children-years before the deployment of LLINs, the death of three children representing 1.7% of the cohort of young children suggests rapid monitoring and treatment alone might not be sufficient to prevent malaria mortality in a substantial number of children exposed to malaria.

To what extent these findings in one village would be generalisable? Our intervention was to provide easy access to baseline health services, as it should be in Africa as everywhere else. We were unable to reduce the malaria burden for almost 15 years, until we abandoned both quinine (an excellent drug, but with a short half-life) and chloroquine (a former excellent drug that rapidly became ineffective in the 1990s).4 Most houses remained unchanged, and general social and economic development in the village was slow and progressive. The only substantial change was the building of a school in the village by the project; only one person in the village could read and write in 1990 at the beginning of the project; only one person in the village could read and write in 1990 at the beginning of the project; however, many people were able to do so, and the school was well attended. We thank the villagers of Dielmo for their continuous support to the project. We thank all those who participated in field or laboratory work, or both. J-FT did the data analysis with the contribution of ND, CM, VR, JF, and CR. J-FT wrote the paper with the contribution of CM, PD, and OMP. All authors approved the final report.

Declaration of interests

We declare that we have no competing interests.

Acknowledgments

The Pasteur Institutes of Dakar and Paris, the Institut de Recherche pour le Développement, and the French Ministry of Cooperation provided funding. We thank the villagers of Dielmo for their continuous support to the project. We thank all those who participated in field and laboratory work at different stages of the project. We are indebted to everyone who provided support and encouragement, and all those who every year contributed to convince our institutions, donors, and auditors, to let us add another 1 year to the project.

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