

Effect of large-scale mass drug administration for malaria on mortality and morbidity in Angumu health zone, Ituri, Democratic Republic of Congo

Lise Grout (✉ lise.grout@epicentre.msf.org)

Epicentre

Yves Katuala Givo

Médecins Sans Frontières

Trish Newport

Médecins Sans Frontières

Tom Adoum Mahamat

Médecins Sans Frontières

Priscillah Gitahi

Médecins Sans Frontières

Jean Jacques Mandagot

Médecins Sans Frontières

Michel Quere

Médecins Sans Frontières

Sophie Wodon

Médecins Sans Frontières

Iza Ciglenecki

Médecins Sans Frontières

Mathieu Bastard

Epicentre

Francis Baelongandi

Ministry of Health

Louis Tshulo

Ministry of Health

Herman Jakisa Uluba

Ministry of Health

Esther Sterk

Médecins Sans Frontières

Etienne Gignoux

Epicentre

Keywords: Malaria, Mass drug administration (MDA), Prevention, Mortality, Democratic Republic of Congo

Posted Date: September 28th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-2094309/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Angumu health zone in Ituri, Democratic Republic of Congo) is a highly malaria-endemic area with an overburdened health system and hosting internally displaced persons (IDP). The World Health Organization recommends mass drug administration (MDA) for malaria in complex emergencies. Therefore, three MDA rounds with high coverage were implemented in four health areas by Ministry of Public Health and Médecins sans Frontières from September 2020 to January 2021. We compared reported mortality and morbidity in locations where MDA has been performed and locations where it has not.

A population-based retrospective mortality survey was conducted in March 2021. Two-stage cluster sampling was used in villages; all IDP sites were surveyed with systematic random sampling.

Data was collected for 2554 households and 15470 individuals, of whom 721 died in the 18-month recall period. The under-five mortality rate (U5MR) decreased in the locations where MDA had been implemented from 2.32[1.48–3.16] “before” the MDA to 1.10[0.5–1.71] deaths/10,000 children under 5 years/day “after”, whereas it remained stable from 2.74 [2.08–3.40] to 2.67 [1.84–3.50] deaths/10,000 children/day in the same time periods in locations where MDA had not been implemented. The U5MR and malaria-specific mortality was significantly higher in non-MDA locations after MDA was implemented (aRR = 2.17[1.36–3.49] and 2.60[1.56–4.33] respectively for all-cause and malaria-specific mortality among children < 5 years). Morbidity (all age and < 5 years, all cause or malaria-specific) appeared lower in MDA locations 2.5 months after last round: reported malaria-specific morbidity was 14.7%[11–18] and 25.0%[19–31] in villages and IDP sites where MDA had been implemented, while it was 30.4%[27–33] and 49.3%[45–54] in villages and IDP sites with no MDA.

The documented sharp decrease of under-5 mortality and morbidity confirms that MDA has the potential to become an important malaria-control tool in emergency settings. Based on these results, new MDA rounds, along with Indoor residual spraying campaigns, have been planned in the health zone in 2022. A set of surveys will be conducted before, during and after these rounds to confirm the effect observed in 2021 and assess its duration.

Background

Since December 2017, the province of Ituri in the Democratic Republic of Congo (DRC) has once again been plunged into violence, causing waves of massive population movements towards the safe villages of the Angumu health zone, on the shore of Lake Albert and left bank of the Kakoy River. In February 2019, the emergency team of Médecins Sans Frontières – Operational Center Geneva (MSF-OCG) in DRC carried out an assessment of the humanitarian situation in Angumu health zone and estimated that there were around 29,000 displaced people scattered among host families in the villages and in Internally displaced People (IDP) camps. The under-five mortality rate (U5MR) among IDPs over a 7-month recall period was above the emergency threshold (3.2 deaths per 10,000 persons per day; 95% CI: 2.8–3.6) and the main causes of mortality were respectively malaria (36.6%), anaemia (16.2%) and diarrhoeal diseases (14.9%) (1). To respond to this medical-humanitarian emergency, MSF-OCG has been running the Angumu project since May 2019.

In January 2020, a mortality survey carried out by MSF-OCG showed a crude mortality rate (CMR) above the emergency threshold in the villages and in the IDP camps (respectively 1.53 (95%CI: 1.23–1.82, design effect 4.0) and 1.17 (IC 95% :1.03–1.32, design effect 1.2) deaths/10,000 population/day). The U5MR was also above the emergency threshold in villages with 3.7 (95% CI: 2.61–4.79, design effect 4.4) deaths per 10,000 children per day, and in IDP camps, 3.27 (95% CI: 2.67–3.86, design effect 1.1) deaths per 10,000 children per day. The survey showed that malaria was the main cause of death, particularly among children under 5 years old (2).

Because of its climate, and in particular its rainfall, Angumu is extremely exposed to malaria, which remains present throughout the year. The years 2019 and 2020 have seen the heaviest rainfall for more than a decade. Faced with this dramatic situation, MSF, in collaboration with Ministry of Health (MoH), has increased the population's access to healthcare by supporting eight health centres and setting up 13 community care sites in IDP camps. In addition, impregnated mosquito nets were distributed. However, despite these malaria control interventions, the incidence of malaria remained very high.

In this context of a complex humanitarian crisis, population movement, very high mortality caused by malaria, limited access to care and prevention measures, potentially overcrowded health structures and in the context of the COVID-19 pandemic, the use of mass drug administration (MDA) against malaria was justified in accordance with the recommendations of the World Health Organization (3). The implementation of MDA aims to rapidly reduce malaria mortality and morbidity and has an initial short-term impact. Moreover, by reducing the prevalence of the parasite in the community and among vectors, MDA, if it has good coverage and is carried out synchronously, can, in conjunction with preventive and curative actions, have a longer-term impact due to reduction in transmission level (4).

MDA campaign was launched in September 2020 by MSF and MoH. The whole population living in the villages and IDP camps of 4 health areas (HA), namely Ugudo-Zii, Lanyi and Panyandong and Anzika (Fig. 1), were targeted by three MDA rounds (2 rounds of Artesunate-Amodiaquine (ASAQ) and 1 round of Artesunate-Pyronaridine (Pyramax®)). The door-to-door distribution started in September and ended in December for 3 HA and in January in Anzika HA. All people in the targeted areas were eligible for MDA except children under 2 months of age, pregnant women in the first trimester of pregnancy, severely ill people and those who had taken malaria treatment in the 15 days prior to the distribution.

This was the first MDA for malaria conducted in high malaria prevalence area outside of an Ebola context, in a context of complex emergency and in the midst of Covid-19 pandemic. To document feasibility of the implementation and potential impact, the implementational teams collected routine mass campaign indicators, including monitoring of adverse events; routinely collected malaria morbidity data from the health facilities in areas targeted and not-targeted by MDA were analysed, and a retrospective population-based survey was conducted (Fig. 2). This paper focuses on the survey, for which the main objective was to describe the short-term effect of MDA in Angumu health zone by comparing mortality and morbidity between HAs targeted or not for the MDA, and before and after the MDA took place.

Methods

Study setting

There were 20 HAs in the Agumu health zone in 2020, but 7 were not accessible due to insecurity. The survey was conducted in 13 accessible HA in Angumu: the 4 HAs which received MDA (called “MDA locations”), and 9 HAs which had not received MDA (called “non-MDA locations”), from 13 to 27 March 2021.

The target population for the survey was the entire population of the 13 HAs (estimated at 150,000 people), regardless of their status (resident or IDP). A person was included in the study if s/he live in the selected household and informed consent was given by the head of the family. A person was excluded from the study if s/he refused to participate or was not located after two attempts to find him/her.

Outcomes

The main outcome was crude and under-five mortality rates (CMR and U5MR). The secondary outcomes were malaria-specific mortality rate, crude, under-five morbidity and malaria-specific morbidity two weeks prior to the survey. We also used the survey to estimate the MDA coverage for the different rounds.

The recall period was chosen to allow comparison of mortality rate before and since the start of MDA activity. Given the seasonal nature of malaria, it is necessary to have the same months of the year in both sub-periods. The recall period therefore started on 2 September 2019 (back to school day) and ended on the day of the survey, which corresponds to 557 days. It was divided into two periods: “before” from 2 September 2019 to 30 September 2020 and “after” from 1st October 2020 to the day of the survey. The “before” period was sub-divided into two equal periods for the calculation of the mortality rates.

Sample size and sampling strategy

The situation in IDP camps and villages is different in many aspects that could affect the study outcomes (e.g. population density assistance received, access to health care, vulnerabilities). We therefore stratified our sample by location, i.e. villages *versus* IDP camps.

All IDP camps were included in the survey and a random systematic sampling was conducted.

For the villages, we further stratified the sampling strategy between HAs where MDA was conducted versus those where MDA was not. Two-stage proportional to size random sampling was then conducted in each stratum.

The sample size was calculated to detect a significant difference in terms of U5MR between the period “before” and “after” MDA in targeted villages, and between targeted and non-targeted villages “after” the MDA. The same reasoning applies in the sites. In total, 786 and 731 households were needed in each stratum of the villages and in the IDP camps respectively; 31 clusters of 26 households were randomly selected in each stratum of the villages, and a sampling interval of 15 households was used in the IDP camps.

Data collection

All interviewers and supervisors were recruited locally and received theoretical and practical training before conducting the interviews. Selected households (defined as a group of people who live together under the responsibility of one person, and share their meals at least 3 times a week, whether or not they have a family relationship), and were revisited later in the day if the head of the household or an adult was absent, and not replaced if absent at second visit.

Interviewers used a standardized pre-tested questionnaire to collect information on the household, the people living in the household (age, sex, MDA receipt for the 3 rounds, compliance with 3 days treatment for the last round, morbidity and health care use in the two weeks prior to the survey) and the people who left the household (date of departure) or died (date of death, cause of death, health care use prior to the death) in the recall period. Data were collected using Kobo collect.

Data analysis

Descriptive analysis of the studied population was first conducted, in terms of size and demographic characteristics. Then, the main and secondary outcomes were estimated, comparing villages and IDP camps, locations where MDA was conducted versus locations where it was not, and “before” and “after” periods.

The departure date for people who left the household during the recall period was not collected. In calculating mortality rates, these departed individuals counted for half the recall period. Since the explanatory data analysis was split into “before” and “after” MDA, we randomly assigned a departure date during the recall period to all persons who left.

After pooling villages and IDP camps together, a weighted Kaplan-Meier estimates was used to draw survival curves and log-rank test was run to compare the mortality in the two groups (MDA and non-MDA locations). The explanatory analysis used a mixed poisson regression to estimate adjusted mortality rate ratio (aMRR) and a mixed binomial regression to estimate adjusted relative risks (aRR) of being sick in the two weeks prior to the survey.

R and Stata v16 were used for the statistical analysis.

Ethical considerations

This study was sponsored by MSF. The authors assume full responsibility for the analyses and interpretation of the data.

This study was conducted according to the ethical principles for research on human subjects, described in the Helsinki Declaration, and in accordance with international principles and guidelines for biomedical research involving human subjects, published by the Council for International Organizations of Medical Sciences (5). The study protocol was approved by the MSF Ethics Review Board and the Kisangani University of DRC.

MDA was provided free of charge. Participation in the study was voluntary and oral informed consent was obtained from the head of the household or another adult in charge.

Results

From 13 to 27 March 2021, 1603 and 951 households were visited respectively in selected villages and IDP camps, with 9954 and 5440 individuals included respectively. No household refused to participate to the survey. In the camps, 98.2% of the households were internally displaced, while they were 22% in the villages. The size of the surveyed households was 5.5 in the villages and 5.0 in the camps. The age pyramid was slightly different between camps and villages, but comparable between MDA and non-MDA sites (S1 Fig).

MDA coverage

The coverage of the three rounds of MDA was > 95% in the IDP camps and > 90% in the villages (Table 1). It was > 90% in IDP camps and > 85% in villages when considering only the vaccination cards.

Table 1
Coverage of the different rounds of mass drug administration against malaria in 2020 in Angumu health zone, Ituri province, Democratic Republic of Congo

Villages				IDP camps		
	% (N)	95% IC	Design effect	% (N)	95% IC	Design effect
ASAQ1						
Documented	85% (3443)	[81–89]	16.7	92.9% (1238)	[91–95]	2.9
Orally reported	6.8% (274)	[4–10]	13.6	3.8% (50)	[2–6]	3.6
<i>Missing</i>	38			0		
Overall coverage	90.5% (3717)	[88–94]	11.8	96.6% (1288)	[95–98]	1.9
ASAQ2						
Documented	85.1% (3448)	[81–89]	15.7	93.1% (1240)	[91–95]	2.9
Orally reported	7% (282)	[4–10]	13.2	3.8% (50)	[2–6]	3.6
<i>Missing</i>	34			0		
Overall coverage	90.9% (3730)	[88–94]	11.8	96.7% (1290)	[95–98]	1.9
PYRAMAX						
Documented	84.7% (34343225)	[80–89]	15.3	93.3% (1243)	[91–96]	3
Orally reported	7.6% (296)	[4–10]	12.6	3.8% (50)	[2–6]	3.6
<i>Missing</i>	33			0		
Overall coverage	90.9% (3724)	[88–94]	11.8	96.7% (1293)	[95–98]	1.9

95% CI = 95% confidence interval; IDP = Internally Displaced People

ASAQ1 = 1st round of Artesunate Amodiaquine; ASAQ2 = 2nd round of Artesunate Amodiaquine

PYRAMAX = Round of Artesunate Pyronaridine

Mortality

For the whole recall period, 645 deaths were reported, 426 in the “Non-MDA locations” and 229 in the “MDA locations”. The overall CMR was 1.23 [1.05;1.41] deaths/10,000 population/day (deff = 2.74), while the U5MR was 2.23 [1.75;2.71] deaths/10,000 children under 5 years of age/day (deff = 2.11) (S2 Fig).

The CMR was very similar in “non-MDA” and “MDA locations” before the MDA campaign (respectively 1.07 [0.84–1.30] and 0.99 [0.68–1.29] deaths/10,000 population/day) and remained very similar after the MDA campaign started (respectively 0.92 [0.78–1.06] and 0.80 [0.51–1.08] deaths/10,000 population/day) (Table 2).

Table 2

Mortality rates (crude, under-five and malaria-specific) in locations where mass drug administration has been implemented (MDA locations) and where it has not (Non MDA locations), before and after the first round of MDA - Angumu health zone, Ituri province, Democratic Republic of Congo, March 2021.

	Non MDA locations			MDA locations		
	Deaths/ 10,000/ day	95%CI	Cluster effect	Deaths/ 10,000/ day	95%CI	Cluster effect
All causes						
All ages						
Before MDA 1	0.67	[0.46– 0.88]	2.55	0.54	[0.35– 0.72]	1.54
Before MDA 2 Avril 2020- Sept 2020	1.07	[0.84– 1.30]	2.08	0.99	[0.68– 1.29]	2.49
After MDA	0.92	[0.78– 1.06]	0.89	0.80	[0.51– 1.08]	2.58
Children under 5 years						
Before MDA 1	2.78	[1.79– 3.77]	2.07	1.63	[0.89– 2.36]	1,27
Before MDA 2	2.74	[2.08– 3.4]	1.09	2.32	[1.48– 3.16]	1.36
After MDA	2.67	[1.84– 3.5]	1.76	1.10	[0.5– 1.71]	1.55
Malaria-specific mortality						
All ages						
Before MDA 1	0.36	[0.21– 0.51]	2.47	0.33	[0.18– 0.47]	1.50
Before MDA 2	0.56	[0.43– 0.69]	1.33	0.44	[0.25– 0.63]	2.15
After MDA	0.39	[0.27– 0.5]	1.38	0.28	[0.14– 0.42]	1.85
Children under 5 years						
Before MDA 1	2.07	[1.31– 2.82]	1.63	1.47	[0.8– 2.15]	1.17
Before MDA 2	2.05	[1.42– 2.67]	1.31	1.72	[0.89– 2.55]	1.79

95% CI = 95% confidence interval; MDA = Mass drug administration; Before MDA 1: October 2019-March 2020; Before MDA 2: April-September 2020; After MDA: October 2020-March 2021; After MDA: October 2020- March 2021

	Non MDA locations			MDA locations		
After MDA	1.71	[1.16– 2.26]	1.23	0.78	[0.21– 1.36]	1.96
<i>95% CI = 95% confidence interval; MDA = Mass drug administration; Before MDA 1: October 2019-March 2020; Before MDA 2: April-September 2020; After MDA: October 2020-March 2021; After MDA: October 2020- March 2021</i>						

The U5MR was above emergency threshold in “non-MDA” and “MDA locations” before the MDA campaign (2.74 [2.08–3.40] and 2.32 [1.48–3.16] deaths/10 000 children/day respectively). It remained above the emergency threshold in “non-MDA locations” after October (2.67 [1.84–3.50]) while it decreased sharply below the emergency threshold in “MDA locations” (1.10 [0.50–1.71]).

The malaria-specific mortality was very similar in the whole population in “non-MDA” and “MDA locations” before the MDA campaign (0.56 [0.43–0.69] and 0.44 [0.25–0.63] malaria-related deaths/10 000 population/day respectively) and remained very similar after the MDA campaign started (0.39 [0.27–0.50] and 0.28 [0.14–0.42] respectively). Among children under 5 years of age, the malaria-specific mortality was very similar in the “non-MDA” and “MDA locations” before the MDA campaign (2.05 [1.42–2.67] and 1.72 [0.89–2.55] malaria-related deaths/10 000 children/day respectively). It decreased in both strata, but slightly more in “MDA locations” (0.78 [0.21–1.36]) than in “non-MDA locations” (1.71 [1.16–2.26]).

The survival curves for “MDA” and “non-MDA locations”, drawn through the weighted Kaplan-Meier (S3 Fig) and compared with the log-rank test, were not different “before” the MDA, neither for all-cause mortality not for malaria-specific mortality. However, for the period “after MDA” (from October 1st to study date), if the survival curves were not different for all-cause mortality among whole population ($p = 0.510$), they were significantly different among children under 5 years of age ($p = 0.003$). Malaria-specific survival curves were significantly different among children under 5 ($p = 0.007$) and tended to be different for the whole population ($p = 0.063$).

Finally, based on the results of the Poisson regression, there was no difference in the mortality indicators (CMR, U5MR and malaria-specific mortality) between “MDA” and “non-MDA locations” before the MDA campaign (Table 3). After the MDA campaign started, there was still no difference in the all-cause mortality. However, the U5MR was 2.17 [1.36–3.49] higher in “non-MDA locations” than in “MDA locations”, malaria-specific mortality was 2.60 [1.56–4.33] higher in “non-MDA locations” among children under 5 years of age and 1.78 [1.12–2.82] higher in “non-MDA locations” among whole population.

Table 3

Adjusted mortality rate ratio in non-MDA locations compared to MDA locations, “Before” and “After” the MDA campaign– Angumu health zone, Ituri, DRC, 2021

	« Before » (01/10/2019 to 01/10/2020)		« After » (01/10/2020 to 26/03/2021)	
	aMRR	[IC 95%]	aMRR	[IC 95%]
Mortality (all causes)	1.09	[0.78–1.53]	1.32	[0.93–1.88]
Under 5 mortality (all causes)	1.15	[0.76–1.74]	2.17	[1.36–3.49]
Malaria-specific mortality	1.12	[0.74–1.70]	1.78	[1.12–2.82]
Malaria-specific mortality in < 5 years	1.15	[0.75–1.78]	2.60	[1.56–4.33]
<i>aMMR = mortality rate ratio, adjusted on age, sex, status (autochthonous/displaced) and mortality “before”; 95% CI = 95% confidence interval; MDA = Mass drug administration.</i>				
<i>Reference = MDA locations (locations where three rounds of MDA have been implemented between September 2020 and January 2021)</i>				

Malaria or anaemia was the main cause of death reported by the heads of households, both in children under 5 years of age (66.0% in villages and 72.3% in IDP camps) and in the rest of the population (31.4% in villages and 31.7% in IDP camps) (Table 4).

Table 4
Details of the deaths that occurred between September 2019 and March 2021 in Angumu health zone, Ituri province, DRC.

	Village		IDP camps	
	< 5 years	>=5 years	< 5 years	>=5 years
Total number of deaths	191 (100%)	210 (100%)	83 (100%)	161 (100%)
By status				
Autochthonous	137 (71.7%)	150 (71.4%)	2 (2.4%)	4 (2.5%)
Displaced	54 (28.3%)	60 (28.6%)	81 (97.6%)	157 (97.5%)
By age				
< 1 month	38 (19.9%)		8 (9.6%)	
< 1 an	105 (55%)		29 (34.9%)	
5–9 years		26 (12.4%)		18 (11.2%)
By cause				
Malaria or anemia	126 (66.0%)	66 (31.4%)	60 (72.3%)	51 (31.7%)
Respiratory issue	4 (2.1%)	20 (9.5%)	3 (3.6%)	16 (9.9%)
Diarrhea/Vomiting	6 (3.1%)	7 (3.3%)	7 (8.4%)	14 (8.7%)
Accident	2 (1%)	15 (7.1%)	1 (1.2%)	12 (7.5%)
Violence	0 (0%)	4 (1.9%)	1 (1.2%)	18 (11.2%)
Delivery complication	20 (10.5%)	2 (1%)	1 (1.2%)	4 (2.5%)
Other	31 (16.2%)	91 (43.4%)	7 (8.4%)	45 (27.9%)
Unknown	2 (1%)	5 (2.4%)	3 (3.6%)	1 (0.6%)
Access to health care before death				
Hospital	74 (38.7%)	98 (46.7%)	28 (33.7%)	64 (39.8%)
Health center	92 (48.2%)	88 (41.9%)	61 (73.5%)	77 (47.8%)
Health post	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Community care sites (IDP camps)	2 (1%)	3 (1.4%)	16 (19.3%)	11 (6.8%)
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Morbidity

In the two weeks prior to the survey (2.5 months after the last round of MDA), 49.8% [47–52] (deff = 5.9) of the population had been sick, and 57.4% [54–61] (deff = 2.4) of the children under 5 years of age. All

morbidity indicators were significantly higher in “non-MDA locations” than in “MDA locations” (Table 5). The all-age morbidity was 1.89 [1.53–2.22] times higher in “non-MDA locations” (marginal morbidity equals to 52.1% [47.2–57.1] in “non-MDA locations” and 27.6% [22.4–32.7] in “MDA locations”. The morbidity among children under 5 years of age was 1.45 [1.27–1.66] times higher in “non-MDA locations”. Finally, the malaria-specific morbidity was 1.93 [1.59–2.34] and 2.13 [1.67–2.72] times higher in “non-MDA locations” among children under 5 years of age and whole population respectively.

Table 5

Marginal morbidity and adjusted risk ratio (aRR) of being sick 2 weeks prior to survey, depending on MDA status, Angumu health zone, Ituri province, DRC, March 2021

Non-MDA locations				MDA locations				
	n	Marginal morbidity*	[95%CI]	n	Marginal morbidity*	[95%CI]	aRR*	[IC 95%]
All causes morbidity								
All ages	4854	52.1%	[47.2–57.1]	1758	27.6%	[22.4–32.7]	1.89	[1.53–2.22]
Children < 5 years	1076	70.0%	[65.9–74.2]	522	48.3%	[42.4–54.1]	1.45	[1.27–1.66]
Malaria-specific morbidity								
All ages	2646	29.3%	[26.5–32.1]	849	13.7%	[10.5–17.0]	2.13	[1.67–2.72]
Children < 5 years	684	44.0%	[40.0–48.0]	239	22.8%	[18.9–26.6]	1.93	[1.59–2.34]
<i>aRR = risk ratio, adjusted on age, sex and status (autochthonous/displaced); 95% CI = 95% confidence interval; MDA = Mass drug administration.</i>								
<i>Reference = MDA locations = locations where three rounds of MDA have been implemented between September 2020 and January 2021.</i>								

Non MDA locations = locations where MDA has not been implemented in 2020

The main reported cause of morbidity was malaria, which was reported as the cause of morbidity for half of the sick people. For children under 5 years, this proportion was slightly higher in non-MDA locations (62% and 65% respectively in villages and IDP camps) than in MDA locations (46% in villages and camps).

Discussion

Key results

The survey carried out in March 2021 in Angumu health zone shows very high coverage and adherence of the population to the MDA carried out at the end of 2020 in four HAs. The door-to-door strategy, even though heavy to implement, most probably contributed to this success. It also shows a very strong reduction in U5MR and malaria-specific mortality (all age and < 5 years), in HAs that have benefited from the MDA campaign, compared to non-targeted HAs, as well as in the morbidity (all age and < 5 years, all cause and malaria-specific) more than two months after the end of the 3rd round of MDA.

Limitations

As for any retrospective survey relying on respondent recall, a potential memory bias could have happened, however is *a priori* similar in MDA and non-MDA locations and would therefore not affect the results.

The main indicators were calculated based on what the head of household reported. No death certificate was consulted, no clinical examination by medical staff or confirmatory biological test was carried out during the investigation. The absolute malaria mortality and morbidity values should therefore be taken with caution. However, this bias would be similar in both strata, not affecting much the comparisons.

The data was analyzed with "health area approach", i.e. by classifying individuals according to their health area of residence and not according to the actual receipt of the drugs. Some people living in MDA locations, may not have received the drugs, but the estimated coverage for the three rounds is very high. Conversely, some people living in non-MDA locations may have received the drugs after traveling to the villages where the activity took place. This is very plausible since the number of people who received the treatment was much higher than the number of people expected in the targeted HAs (3). But in both cases, this bias would lead to underestimating the observable effect when comparing mortality and morbidity in MDA and non-MDA locations.

What was called the "After" period is a mix of "during the three rounds of MDA" and "after the three rounds of MDA". To differentiate the "during" effect from the "after" effect, we conducted a sub-analysis of mortality by starting the "after" period successively on January 25th (4 weeks after the average date of the 3rd round of MDA) and on February 8th (6 weeks after the average date of the 3rd round of MDA). No significant effect on mortality could be demonstrated for these two sub-periods "after the three rounds" through Kaplan-Meier estimates and Poisson regression. However, the recall period for this sub-analysis was very small, and the power insufficient to demonstrate a difference if there was one.

The departure date for people who left the household during the recall period was not collected. This could have introduced a bias in the estimation of mortality rates, in particular an under-estimation of the mortality rate in the MDA locations if the proportion of people who left there had been high. However, the proportion of people who left was low, and even lower in areas where MDA took place.

Comparison with other MDA surveys

The composition of the population studied in March 2021 seems consistent with previous surveys conducted in the health zone (1,2): the age pyramids or the proportion of autochthonous people and IDPs in villages and IDP sites were similar to what had been described previously. The mortality and morbidity indicators estimated in non-MDA locations or prior to MDA are also in similar range than in previous surveys conducted in this health zone.

To our knowledge, there are no similar survey assessing the impact of MDA in a complex context with high malaria prevalence to compare our results with.

In 2014, during the Ebola outbreak, two rounds of MDA with ASAQ were carried out in four neighbourhoods of Monrovia (Liberia) and the districts hardest hit by the outbreak in Sierra Leone. Routine data were analysed to assess the short-term effect of this intervention. In Sierra Leone (6), the number of suspected cases tested with rapid diagnostic test (RDT) decreased significantly by 43% (95% CI 38–48%) at week 1 and remained low at week 2 and 3 post-first MDA and at week 1 and 3 post-second MDA; RDT positive cases decreased significantly by 47% (41–52%) at week 1 post-first and remained lower throughout all post-MDA weeks. The total malaria (clinical + confirmed) cases decreased significantly by 45% (39–52%) at week 1 and were lower at week 2 and 3 post-first MDA; and week 1 post-second MDA. The proportion of confirmed malaria cases (out of all-outpatients) fell by 33% (29–38%) at week 1 post-first MDA and were lower during all post-MDA weeks. On the contrary, the non-malaria outpatient cases (cases due to other health conditions) either remained unchanged or fluctuated insignificantly. In Liberia (7), the incidence of self-reported fever decreased from 4.2% (52/1229) in the month prior to 1st round to 1.5% (18/1229) after ($p < 0.001$) and decrease was larger among household members completing ASAQ (Risk difference = 4.9%) compared to those not initiating ASAQ (Risk difference = 0.6%) ($p < 0.001$).

There have been studies conducted in pre-elimination context. In Zanzibar (8), where a cluster randomised controlled trial of two rounds of MDA in Zanzibar was conducted, no difference in cumulative malaria case incidence was observed between the control and intervention arms 6 months post-MDA (4.2 and 3.9 per 1000 population; $p = 0.94$). Neither was there a difference in PCR-determined parasite prevalences 3 months post-MDA (1.4% and 1.7%; OR = 1.0, $p = 0.94$), although having received at least the first MDA was associated with reduced odds of malaria infection (aOR = 0.35; $p = 0.02$). Conversely, in Zambia (9) where four rounds of MDA or focal MDA using dihydroartemisinin–piperaquine (DHAp) were conducted, infection incidence declined dramatically across all study arms during the period of study, and MDA was associated with reduced risk of first infection (hazards ratio: 0.36; 95% CI: 0.16–0.80) and cumulative infection incidence during the first rainy season (incidence rate ratio: 0.34; 95% CI: 0.12–0.95). However, no significant effect was found for focal MDA or for either arm over the full study period.

Conclusions

The MDA campaign organized in Angumu health zone from September 2020 to January 2021 was a success in several aspects. The coverage of the different rounds and adherence to the treatments taken in the days following the distribution was very high, both in villages and IDP camps. Mortality in children under 5 years of age during and just after MDA was halved in HAs that benefited from MDA. Morbidity, and in particular malaria morbidity, was also divided by two in MDA locations 2.5 months after the last round of

MDA. It therefore appears that implementing MDA was feasible, well accepted, and impactful in complex emergency context in a malaria holo-endemic area. Our findings suggest MDA for malaria can be an important tool for rapidly reducing malaria morbidity and mortality in emergency contexts with high malaria burden. Further evidence is needed to determine the duration of positive effect, the optimal timing and spacing of MDA rounds and best combination package of malaria control interventions. It seems important to repeat this type of survey to determine the duration of the effect on the mortality and morbidity and the frequency at which such activities must be carried out.

Abbreviations

aMRR
adjusted mortality rate ratio
aRR
adjusted risk ratio
ASAQ
Artesunate amodiaquine
CI
Confidence interval
CMR
Crude mortality rate
DHAp
dihydroartemisinin–piperaquine
DRC
Democratic Republic of Congo
HA
Health area
IDP
Internally displaced people
MDA
Mass drug administration
MoH
Ministry of health
MSF
Médecins sans Frontières
U5MR
Under-five mortality rate

Declarations

Ethics approval and consent to participate

This study was conducted according to the ethical principles for research on human subjects, described in the Helsinki Declaration, and in accordance with international principles and guidelines for biomedical research involving human subjects, published by the Council for International Organizations of Medical Sciences. The study protocol was approved by the MSF Ethics Review Board and the Kisangani University of DRC.

MDA was provided free of charge. Participation in the study was voluntary and oral informed consent was obtained from the head of the household or another adult in charge.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was sponsored by MSF.

Authors' contributions

YKG and EG wrote the protocol, which was reviewed by TN, TAM, PG, JJM, IC, FC, FB, LT, HJU and ES. YKG collected the data, with the technical and operational support of EG, TN, TAM, PG, JJM, MQ, SW, FC, FB, LT and HJU. LG, YKG, EG and MB analyzed the data, and interpreted it together with IC, TN and ES. LG drafted the manuscript, which initial version has been reviewed by EG and IC. All authors read and approved the final manuscript.

Acknowledgements

The authors assume full responsibility for the analyses and interpretation of the data.

We would like to thank the field teams from MSF and the MoH for their dedication during the MDA campaign and for their support to prepare and carry out this survey. We thank Andrea Incerti, Jean-Patrick Ouamba and

Patrick Nkemenang for their insight in this work and for the interesting discussions preparing the new MDA campaign in 2022. We thank the surveyors and supervisors for their hard work. We also would like to thank the population living in Angumu health zone for their openness and kindness.

Preliminary results were presented as poster to the annual meeting of the American society of tropical medicine and hygiene, and as oral presentation to the Epicentre scientific day in June 2022.

References

1. MSF-OCG. Traitement médicamenteux de masse contre le paludisme, zone de santé rurale d'Angumu, Province de l'Ituri, République Démocratique du Congo. 2020; Geneva: MSF, 2021.
2. MSF-OCG. Enquête de mortalité rétrospective dans la Zone Sanitaire d'Angumu, Province de l'Ituri, République Démocratique du Congo. 2020; Geneva: MSF, 2020.
3. World Health. Organization Mass drug administration for falciparum malaria: a practical field manual. Geneva, 2017. Licence: CC BY-NC-SA 3.0 IGO.
4. Newby G, Hwang J, Koita K, Chen I, Greenwood B, Von Seidlein L, et al. Review of mass drug administration for malaria and its operational challenges. *Am J Trop Med Hyg.* 2015;93(1):125–34.
5. International Ethical Guidelines for Health-related Research Involving Humans. Fourth Edition. Geneva: Council for International Organizations of Medical Sciences (CIOMS). 2015.
6. Aregawi, et al. Impact of the Mass Drug Administration for malaria in response to the Ebola outbreak in Sierra Leone. *Malar J.* 2016;15:480. doi:10.1186/s12936-016-1493-1.
7. Kuehne A, et al. Impact and Lessons Learned from Mass Drug Administrations of Malaria Chemoprevention during the Ebola Outbreak in Monrovia, Liberia, 2014. *PLoS ONE.* 2016;11(8):e0161311. doi:10.1371/journal.pone.0161311.
8. Morris U, et al. A cluster randomised controlled trial of two rounds of mass drug administration in Zanzibar, a malaria pre-elimination setting - high coverage and safety, but no significant impact on transmission. *BMC Med.* 2018;16:215. doi:10.1186/bmcmed.s12916-018-1202-8.
9. Bennett A, et al. A longitudinal cohort to monitor malaria infection incidence during mass drug administration in Southern province. Zambia *Am J Trop Med Hyg.* 2020;103(Suppl 2):54–65. doi:10.4269/ajtmh.19-0657.

Figures

Figure 2

Timeline of malaria interventions and the different components of the assessment, from February 2019 to March 2021, in Angumu health zone, Ituri province, DRC.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryS1Agepyramid.docx](#)
- [SupplementaryS2MortalityStratifiedv2.docx](#)
- [SupplementaryS3Survivalcurves.docx](#)