Vaccine 38 (2020) 2800–2807

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Field challenges to measles elimination in the Democratic Republic of the Congo

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ARTICLE INFO

Article history:
Received 16 October 2019
Received in revised form 6 February 2020
Accepted 7 February 2020
Available online 25 February 2020

Keywords:
Measles vaccination
Mass vaccination
Vaccination coverage
Vaccine effectiveness
Democratic Republic of the Congo

ABSTRACT

Background: During a measles epidemic, the Ministry of Public Health (MOH) of the Democratic Republic of the Congo conducted supplementary immunization activities (2016-SIA) from August 28-September 3, 2016 throughout Maniema Province. From October 29-November 4, 2016, Médecins Sans Frontières and the MOH conducted a reactive measles vaccination campaign (2016-RVC) targeting children six months to 14 years old in seven health areas with heavy ongoing transmission despite inclusion in the 2016-SIA, and a post-vaccination survey. We report the measles vaccine coverage (VC) and effectiveness (VE) of the 2016-SIA and VC of the 2016-RVC.

Methods: A cross-sectional VC cluster survey stratified by semi-urban/rural health area and age was conducted. A retrospective cohort analysis of measles reported by the parent/guardian allowed calculation of the cumulative measles incidence according to vaccination status after the 2016-SIA for an estimation of crude and adjusted VE.

Results: In November 2016, 1145 children (6–59 months old) in the semi-urban and 1158 in the rural areas were surveyed. Post-2016-SIA VC (documentation/declaration) was 81.6% (95%CI: 76.5–85.7) in the semi-urban and 91.0% (95%CI: 84.9–94.7) in the rural areas. The reported measles incidence in October among children less than 5 years old was 5.0% for 2016-SIA-vaccinated and 11.2% for 2016-SIA-non-vaccinated in the semi-urban area, and 0.7% for 2016-SIA-vaccinated and 4.0% for 2016-SIA-non-vaccinated in the rural area. Post-2016-SIA VE (adjusted for age, sex) was 53.9% (95%CI: 2.9–78.8) in the semi-urban and 78.7% (95%CI: 0–97.1) in the rural areas. Post 2016-RVC VC (documentation/declaration) was 99.1% (95%CI: 98.2–99.6) in the semi-urban and 98.8% (95%CI: 96.5–99.6) in the rural areas.

Conclusions: Although our VE estimates could be underestimated due to misclassification of measles status, the VC and VE point estimates of the 2016-SIA in the semi-urban area appear suboptimal, and in combination, could not limit the epidemic. Further research is needed on vaccination strategies adapted to urban contexts.

1. Introduction

Morbillivirus, responsible for causing measles, is extremely contagious. It constitutes one of the greatest contributors to the vaccine-preventable burden of morbidity and mortality among children. The Democratic Republic of the Congo (DRC) seeks to eliminate measles by 2020 [1]. The current strategy for achieving this ambitious goal includes the administration of two doses of measles vaccine (single antigen). Under the Expanded Program on Immunization (EPI), as part of routine vaccination, the first dose of the measles-containing vaccine (MCV) is given at 9–11 months of age, while the second dose of MCV targets older children (up to 59 months or 14 years) [2]. In 2009, an historic low in reported measles cases was seen in DRC. Unfortunately, from 2010 to present day, DRC has experienced a rebound in measles cases, with epidemics [3–5].

A vast country, DRC is divided into 26 provinces [6]. Maniema Province, located in southeast DRC, comprises 18 health zones,

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https://doi.org/10.1016/j.vaccine.2020.02.029
0264-410X/

including Kunda, which is partitioned into 30 health areas. With approximately one quarter of a million inhabitants, Kunda consists of rural and semi-urban terrain, spread across 6,073 km^2 with poor road infrastructure and limited access to healthcare. Considerable population displacement—related to a history of wars and instability, current armed militia movements, and mining activities—exist, further complicating the fragile health system. Kunda is also prone to measles epidemics [7].

In recent years, the administrative measles vaccine coverages of SIA reported for Maniema Province reached or exceeded 100%: 100.7% in 2013 (six months to 14 years) [8]; 107.8% in 2014 (6 months to 10 years) [8]; and 99.9% in 2016 (6–59 months) [9]. Nevertheless, from epidemiological weeks 11–34, 2016 (March 14-August 28), nearly 400 suspected measles cases were reported from eight health areas of Kunda. Blood samples collected in epidemiological week 34, 2016 from 10 suspected cases all tested IgM-positive for measles by the National Institute of Biomedical Research in Kinshasa. In the following weeks, through epidemiological week 47, 2016 (November 27), more than 1,800 suspected measles cases were reported in 13 health areas of Kunda. From 28 August-03 September 2016, the Ministry of Public Health (MOH) of DRC conducted their previously planned SIA (hereafter referred to as the "2016-SIA"), targeting children from 6 to 59 months of age across all 30 health areas of Kunda. Despite these efforts, the epidemic continued. Approximately six weeks after the start of the 2016-SIA, 20 additional blood samples collected in epidemiological week 40, 2016 from suspected measles cases tested positive for measles. Samples were collected from children ranging in age and severity of illness – all meeting the clinical case definition for measles; half were from children vaccinated 37 days prior to sample collection and half were from children not vaccinated during the 2016-SIA. From October 29-November 4, 2016, in collaboration with the MOH, MSF conducted a reactive measles vaccination campaign (hereafter referred to as the "2016-RVC") targeting children six months to 14 years of age in seven heavily-impacted health areas of Kunda, initially covered by the 2016-SIA, with ongoing measles transmission. To describe this epidemic, we analyzed surveillance data. We also conducted a post-vaccination survey to assess the measles VC of the 2016-RVC in Kunda (primary objective) and the measles VC and the measles vaccine effectiveness (VE) of the 2016-SIA (secondary objectives).

2. Methods

2.1. Surveillance data

The MOH epidemiological surveillance system in Kunda Province is based on the national integrated disease surveillance system organized by the Programme Elargi de Vaccination, Ministère de la Santé Publique, Service des Maladies Transmissibles et Non Transmissibles, Direction de la Lutte Contre la Maladie. Health officers in charge of public and private health centers report the aggregated number of cases and deaths attributed to measles weekly to the Health Zone Central Office; information is then relayed to the provincial and national levels. A suspected measles case—as defined by the WHO and validated at the DRC country level—is any person presenting with a fever, and a generalized maculopapular rash, and cough, coryza (runny nose), and/or conjunctivitis (red eyes); or any person whom a health professional suspects as having measles. From August 22-November 27, 2016, MSF strengthened the surveillance system in the health areas of Kunda Province reporting suspected measles cases by introducing individual data reporting, ensuring regular supervisory visits to health centers, engaging the community, and conducting active case finding. Data were entered and analyzed in Excel (Redmond, WA, USA). Attack rates (ARs) were defined as the number of measles cases divided by the population at risk. Population figures were estimated based on a census conducted in early 2016 by the Health Zone Central Office.

2.2. Survey design, population, and sample size

This was a cross-sectional survey using two-stage cluster sampling, stratified by age (6–59 months and 5–14 years) and type of health area (the semi-urban health area of Bikenge and six rural health areas [Kabonga, Kapuri, Kasubi, Mbutu, Mwema and Mingana]). The target population included children six months to 14 years of age at the time of vaccination, residing in the seven health areas of Kunda included in the 2016-RVC. With an expected VC of 90% from the 2016-RVC, aiming for a precision of 5% and assuming a design effect of four (alpha 5%), an estimated minimum sample size of 602 children per age and geographic stratum was calculated. Given an average household size of five [7], with 18% of the population 6–59 months and 50% less than 15 years of age, considering a non-response rate of 10%, 30 clusters of 27 households (810 households) per geographic stratum were needed. Clusters were randomly selected from the list of villages and neighborhoods of the targeted health zones, with the probability of selection proportional to the population size. In each cluster, the first house/compound was randomly selected following a random direction from a central location in the cluster (for areas organized in a non-linear fashion), or by segmentation (for areas organized in a linear fashion). For non-linear villages, this entailed walking to the edge of the village in a random direction, then walking in a new random direction to the village boundary while numbering all houses/concession on the right side, and then choosing the first house or concession using a random number table. For linear villages, this involved dividing the village into four segments, numbering all houses/concessions in the randomly selected segment, and then choosing the first house or concession using a random number table. After the selection of the initial house/compound, each subsequent house/compound was selected by proximity, irrespective of the initial segment. Only one household was randomly selected within each house/compound to limit intra-compound clustering. All children 6 months to 14 years of age, residing—at minimum—in a selected household since the 2016-SIA, and for whom informed consent was obtained, were included.

2.3. Data collection

Trained interviewers, from MSF and the MOH, collected the data using a standardized questionnaire in Swahili. Information was collected on age (with the assistance of a local events calendar in the absence of documentation) and sex, vaccination status against measles (based on documentation or self-report by the parent/guardian), source of vaccination (2016-SIA; and/or 2016-RVC; and/or outside of 2016 campaigns: routine EPI, and/or a previous mass vaccination campaign [SIA or other]), reason for non-vaccination, any deaths among children in the household in 2016, and previous measles episodes (signs, symptoms, date, hospitalization). The parent/guardian was asked whether the child had ever had measles and if so, when. (Of note, the inability of parents/guardians to distinguish between routine EPI and previous campaigns led to the decision to collect this information as a combined variable. Furthermore, information on measles vaccination outside of the 2016 campaigns was limited to "no" or "at least one dose".)

2.4. Data analyses

Data were entered into EpiData v3.1 (Odense, Denmark), with at least 10% of all entries re-entered for quality control. Data were analyzed with Stata v13 (College Station, TX, USA). All analyses

accounted for the sampling design (including weighting on the number of households per compound, though not on the probability of each household being selected [10]) and considered the age groups targeted by the respective vaccination campaigns (i.e., while questionnaires were administered to all children six months to 14 years of age at the time of the survey, the analyses accounted for age at time of vaccination). The analyses assumed that the selection of clusters was self-weighting with the exception of the number of households per compound [10]. VC are presented as percentages with 95% confidence intervals (95%CI).

To estimate the VE of the 2016-SIA, we used a retrospective cohort analysis. The cumulative measles incidence (%, weighted on the number of households per compound) was calculated by age group and vaccination status for all children 6–59 months of age and residing in the survey area during the 2016-SIA. Only measles cases reported between the end of the 2016-SIA (03 September) and the start of the 2016-RVC (29 October) were meant to be considered for this analysis. However, to account for the period of incubation, time to seroconversion, and given the difficulty of obtaining a precise date for the start of a measles episode, only children reported by the parent/guardian to have had measles in October 2016 were ultimately included in the analysis. The VE was estimated using Poisson regression according to the following formula: 100*(1-[incidence vaccinated / incidence non-vaccinated]). Crude and adjusted (age and sex) estimates were calculated and presented with 95%CIs using Poisson regression and Taylor linearized standard error. Surveillance data suggested an attack rate of 11% among children aged 6–59 months in the semi-urban health area between the two vaccination campaigns. Hence, we expected to find approximately 66 (0.11*602) cases of measles among the children aged 6–59 months included in the survey in the semi-urban health area. This number of cases permits the estimation of a VE of 60%, with a 95%CI from 27 to 78% (Pass v13, Kaysville, Utah, USA).

2.5. Ethics

Conducted during the emergency context of a measles epidemic, this research received approval from the Ministry of Public Health of the DRC and the health authorities of Maniema Province (Reference 5702/07/Rte/17/BUR-SECT/ML/2016). Oral, informed consent was obtained from all study participants prior to participation.

3. Results

3.1. Description of the epidemic

In total, considering all ages, 1818 measles cases were reported from epidemiological weeks 30–47, 2016 (25 July-27 November) as individual data, and approximately 393 cases were reported from epidemiological weeks 11–34 (14 March-28 August), as aggregate data (Fig. 1).

Based on the individual surveillance data, children in the semi-urban area and those less than five years of age were most affected. In the semi-urban stratum, the measles attack rate (AR) among children six months to 14 years of age was 10.4% overall, among children 6–59 months 25.4%, and among children 5–14 years 1.7%. In the rural stratum, the measles AR was 0.6% overall, 1.4% among children 6–59 months, and 0.1% among children 5–14 years (Table 1).

3.2. Description of the survey participants

The survey was conducted November 16–25, 2016.

In the semi-urban stratum, 804 households were included and in the rural stratum, 791 households were included (Table 2). The median number of households per compound was one in both strata (range: urban 1–9, rural 1–5). No households refused participation. During the survey, seven households were absent in the semi-urban and one in the rural strata. In total, 2464 children in the semi-urban and 2771 children in the rural strata participated (Table 2).

3.3. Vaccine coverage

When assessing vaccine coverage of the two campaigns, documentation of vaccine status was readily available for the 2016-RVC, while information on the 2016-SIA relied heavily on parent/guardian recall (Table 3). Of note, study interviewers reported that the paper cards documenting vaccination status that were handed out during the 2016-SIA were subject to stock ruptures, small in size, and distributed without an envelope or other protection; in contrast, the paper cards from the 2016-RVC were large, consistently issued in a plastic envelope, and more recently distributed. Considering written and oral reported vaccination status, the VC of the 2016-RVC reached 99% in all age groups and both geographical strata. VC of the 2016-SIA was around 81% in the semi-urban stratum and about 10% higher in the rural stratum.

No evidence exists of a difference of VC, with or without card, according to sex in the 2016-RVC; the VC reached 99% in both sexes and geographic strata (Table 3). In the 2016-SIA, VC was consistent across sex within each stratum and approximately 10% different between strata; the semi-urban stratum was around 81% while the rural stratum reached 91%, with a slight overlap of the confidence intervals.

For both the 2016-SIA and 2016-RVC, considering the age group 6–59 targeted by both campaigns, the main reasons for non-vaccination were absence of the child from the household during the campaign (2016-SIA: 70/210, 35.0% in the semi-urban and 33/103, 31.1% in the rural strata; 2016-RVC: 8/23, 32.0% in the semi-urban and 5/22, 21.7% in the rural strata) and the parent/guardian of the child not having time to participate (2016-SIA: 43/210, 25.1% in the semi-urban and 17/103, 18.9% in the rural strata; 2016-RVC: 5/23, 20.0% in the semi-urban and 11/22, 52.2% in the rural strata).

In the semi-urban stratum, 62.4% of the children (9 months to 14 years) received at least one dose of MCV outside of the 2016 campaigns (Table 4), via either the routine EPI or previous campaigns, while 12.5% of the population received their first MCV during the 2016-SIA and 24.9% during the 2016-RVC. In the rural stratum, 84.7% of children (9 months to 14 years) received at least one dose of MCV outside of the 2016 campaigns, while 5.1% of the population received their first MCV during the 2016-SIA and 10.1% for the first time during the 2016-RVC. In both the semi-urban and rural strata, less than 1% of the population remained unvaccinated following both campaigns. Among children 9–59 months of age, 88.6% in the semi-urban and 95.2% in the rural areas had received at least two doses of MCV on the date of the survey.

3.4. Cumulative measles incidence and vaccine effectiveness

In the semi-urban area, the 2016 measles attack rate (AR) was 16.0% (186/1146) in children aged 6–59 months at the time of the survey and 2.0% (31/1315) in children aged 5–14 years. In the rural area, the 2016 measles AR was 3.0% (37/1159) in children aged 6–59 months at the time of the survey and 0.8% (13/1611) in children aged 5–14 years. A history of measles before October 2016 was reported for 116 (semi-urban stratum) and 25 (rural stratum) children aged less than 5 years who were excluded from the vaccine effectiveness analysis (Table 5). In the semi-urban stratum, the cumulative measles incidence (CMI) in October 2016 was more than double in the group unvaccinated during the 2016-SIA (11.2%)

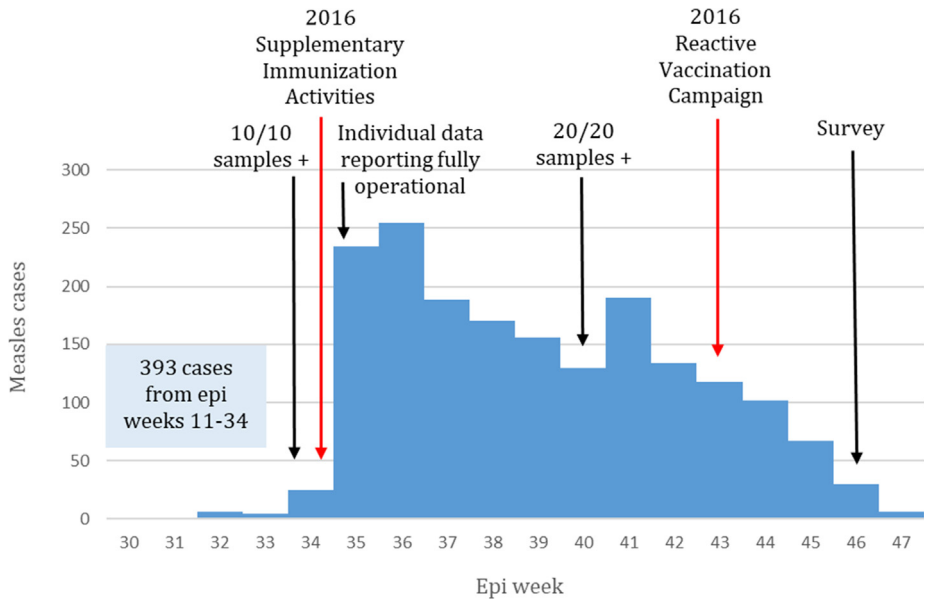

Fig. 1. Epidemiological curve of measles cases, Kunda, 2016. Given the inability to compare aggregate to individual data for the assessment of potential double reporting, aggregate data from week 11–34 are featured in a box separate from the epidemiological curve. Individual data reporting, initiated in epidemiological week 34, was expected to be fully operational by the beginning of epidemiological week 35.

Table 1
Attack rate according to stratum and age group, Kunda, 2016.

Stratum	Age group[a,b]	Population	Reported cases (W30 - W47)	AR (%)
Semi-urban	6–59 months	5408	1371	25.4
	5–14 years	9380	161	1.7
	Total	14,787	1532	10.4
Rural	6–59 months	10,501	151	1.4
	5–14 years	18,215	20	0.1
	Total	28,716	171	0.6

[a] 30 values missing for age group.
[b] Proportion of the population by age group based on "United Nations, Department of Economic and Social Affairs, Population Division, World Population Prospects, the 2015 Revision"; Proportion of the population 6–59 months extrapolated (9/10 of the population 0–59 months).

Table 2
Age and sex of survey participants, Kunda 2016.

Stratum	Males		Females		Total	
	n	%	n	%	N	%
Semi-urban[a] (30 clusters, 804 households)						
6–59 months	561	48	584	46	1145	47
5–14 years	609	52	710	54	1319	53
Total	1170	100	1294	100	2464	100
Rural[a,b] (30 clusters, 791 households)						
6–59 months	573	42	585	41	1158	42
5–14 years	780	58	833	59	1613	58
Total	1353	100	1418	100	2771	100

[a] Age at time of survey; age missing for five children.
[b] Gender missing for five children.

than in the vaccinated group (5.0%) (Table 5). The CMI in October 2016 was similar among children with a written MCV history (5.1%) and children with a verbally reported MCV history (4.9%). Adjusting for age (among children aged 9–59 months on the date of the survey, that is aged 6–56 months at the time of the 2016-SIA) and sex, the point estimate of VE of the 2016-SIA was lower than 80% with wide confidence intervals. In the rural stratum, cumulative incidence was lower and VE tended to be higher, but 95%CIs were very wide.

4. Discussion

Given its high infectivity, disrupting measles virus transmission requires high population immunity, with thresholds ranging from 89 to 94% (according to the setting) [11]. However, in 2015, the estimated coverage of the first dose of MCV in the African Region was 74% and the worldwide coverage of the second dose of MCV only 61% [12]. A review of field-based studies found a median VE from the first dose of MCV of 84% (interquartile range (IQR),

Table 3
Vaccine coverage according to age and sex of the 2016-RVC and the 2016-SIA, Kunda.

		Vaccinated with card			Vaccinated with or without card		
	N	% (n)	95%CI	Deff	% (n)	95%CI	Deff
2016-RVC[a,b,c]							
Semi-urban							
6–8 months	71	95.7 (68)	84.4 – 98.9	1.5	100.0 (71)	/	/
9–59 months	1074	94.0 (994)	90.7 – 96.1	3.2	98.7 (1050)	97.3 – 99.4	1.7
5–14 years	1318	94.4 (1224)	89.7 – 97.1	7.3	99.5 (1306)	98.4 – 99.8	1.9
Male	1172	94.2 (1090)	90.2 – 96.7	5.2	99.3 (1158)	98.5 – 99.7	1.2
Female	1296	94.2 (1200)	20.4 – 96.6	4.9	99.0 (1274)	97.7 – 99.5	2.1
Total	2468	94.2 (2290)	90.7 – 96.5	11.5	99.1 (2432)	98.2 – 99.6	3.7
Rural[d]							
6–8 months	54	96.4 (52)	85.6 – 99.2	1.0	96.4 (52)	85.6 – 99.2	1.0
9–59 months	1106	96.1 (1064)	91.9 – 98.2	6.0	98.3 (1086)	94.3 – 99.5	6.8
5–14 years	1615	98.4 (1590)	95.6 – 99.4	6.6	99.2 (1604)	97.0 – 99.8	5.5
Male	1356	98.0 (1327)	95.7 – 99.1	3.8	98.9 (1340)	97.0 – 99.6	3.6
Female	1419	97.2 (1380)	93.4 – 98.8	7.5	98.7 (1402)	95.8 – 99.6	6.5
Total	2775	97.6 (2707)	94.7 – 98.9	10.3	98.8 (2742)	96.5 – 99.6	7.2
2016-SIA[b,e,f]							
Semi-urban							
6–8 months	76	37.2 (23)	19.9 – 58.6	3.3	88.3 (61)	79.4 – 93.6	1.0
9–59 months	977	33.8 (258)	23.6 – 45.8	13.2	81.0 (781)	75.8 – 85.4	3.5
Male	523	35.8 (155)	25.2 – 48.1	7.4	81.2 (418)	75.3 – 86.1	2.4
Female	535	32.4 (128)	20.9 – 46.3	9.6	81.9 (428)	75.8 – 86.6	2.5
Total	1058	34.1 (283)	23.9 – 46.1	18.8	81.6 (846)	76.5 – 85.7	4.7
Rural[g]							
6–8 months	53	42.6 (22)	25.7 – 61.4	1.7	81.5 (43)	60.1 – 92.8	2.0
9–59 months	1028	43.2 (444)	30.8 – 56.5	17.3	91.4 (933)	85.0 – 95.2	7.7
Male	534	41.3 (219)	29.7 – 54.2	8.1	90.6 (479)	84.8 – 94.3	3.2
Female	549	44.9 (246)	31.9 – 59.0	10.3	91.1 (498)	82.9 – 95.6	6.0
Total	1083	43.1 (465)	31.1 – 56.1	13.3	90.9 (977)	84.9 – 94.6	5.5

Totals presented correspond to the analyses by gender.
Results weighted according to the number of households in each compound.
95%CI : 95% confidence interval; DEFF : Design effect.
[a] Age at the time of the survey.
[b] Five children missing age in each stratum excluded from analysis.
[c] One child missing vaccination status in each stratum excluded from analysis.
[d] Five children missing sex in the rural stratum excluded from analysis.
[e] Age at the time of the 2016-SIA.
[f] 21 children in the semi-urban stratum and 25 children in the rural stratum with missing or unknown vaccination status excluded from analysis.
[g] Two children missing sex in the rural stratum excluded from analysis.

Table 4
Vaccination opportunity and number of vaccinations with measles-containing vaccine, Kunda.

	N[a]	%			
		Vaccination opportunity			
		≥ One dose outside of 2016 campaigns	First dose 2016-SIA	First dose 2016-RVC	Not vaccinated
Semi-urban					
9–59 months*	974	62.2	26.8	10.6	0.4
5–14 years*	1103	62.5	0.0	37.4	0.1
Rural					
9–59 months*	1029	83.3	12.2	4.5	0.1
5–14 years*	1413	85.9	0.0	14.1	0.0
		Vaccinated at all 3 opportunities	**Vaccinated at 2 out of 3 opportunities**	**Vaccinated at 1 out of 3 opportunities**	**Not vaccinated**
Semi-urban					
9–59 months*	974	55.2	33.4	10.9	0.4
5–14 years*	1103	0.0	62.3	37.6	0.1
Rural					
9–59 months*	1029	78.8	16.4	4.7	0.1
5–14 years*	1413	0.0	85.2	14.8	0.0

308 in semi-urban and 272 in rural strata "did not know" if MCV had been administered outside of the 2016 campaigns; 21 in semi-urban and 25 in rural strata "did not know" if MCV had been administered during the 2016-SIA. These children were excluded from analysis; they were not classified as "not vaccinated".
* *Age at the time of the survey.*

72–95%) when administered at 9–11 months of age and 92.5% (IQR, 84.8–97%) when given at more than 12 months of age [13]. In DRC, ongoing measles transmission and the high risk of measles mortality drive down the recommended age for the first dose of MCV to nine months for EPI (to as low as six months during campaigns), ultimately augmenting the importance of the second dose of MCV, after which approximately 95% of children develop protective immunity [12]. To limit measles transmission and ultimately

Table 5
Cumulative measles incidence (CMI) in October 2016 and VE of 2016-SIA, Kunda.

	Vaccination status	N[a]	CMI October 2016		VE of SIA		
			n	CMI[b]%	Crude[b]	Adjusted[b] (age[c] and sex)	
					VE%	VE%	95% CI
Semi-urban[e]	Vaccinated[d] at 2016-SIA	745	36	5.0	55.5	53.9	2.9 – 78.1
	with card	*254*	*12*	*5.1*			
	without card	*491*	*24*	*4.9*			
	Not vaccinated at 2016-SIA	192	19	11.2			
	1st MCV[d] at 2016-SIA	230	12	6.4	67.7	66.6	14.3 – 87.0
	Additional MCV[d,f] at 2016-SIA	469	19	4.0	78.8	78.5	46.2 – 91.4
	≥1 MCV[d,f] prior but not at 2016-SIA	57	1	0.8	95.7	95.6	59.2 – 99.5
	No MCV before or at 2016-SIA	105	18	18.7			
Rural[g]	Vaccinated[d] at 2016-SIA	959	8	0.7	81.5	78.7	0 – 97.1
	Not vaccinated at 2016-SIA	97	4	4.0			

[a] Among children aged 9–59 months on the date of the survey, that is aged 6–56 months at the time of the 2016-SIA.
[b] All results are weighted on the number of households per compound
[c] Adjusted for age in months according to the following categories: 9–11 months on the date of the survey (i.e. 6–8 at 2016-SIA), 12–14 (9–11 at 2016-SIA), 15–26 (12–23 at 2016-SIA), 27–38 (24–35 at 2016-SIA), 39–50 (36–47 at 2016-SIA), 51–59 (48–56 at 2016-SIA).
[d] With or without card.
[e] 21 missing values for vaccination status, among which five children had measles in October 2016; one unknown episode of measles in 2016.
[f] Unknown vaccination status prior to 2016-SIA for 76 children – including five with a measles episode reported in October 2016 and one unknown episode of measles in 2016.
[g] 23 missing values for vaccination status, none of which had measles in October 2016; one unknown episode of measles in 2016.

eliminate measles, the WHO recommends 95% or higher coverage with two doses of MCV.

This study found that while the VC of the 2016-RVC was high in both strata, the VC of the 2016-SIA differed between the semi-urban and rural strata, with coverage in the semi-urban area appearing suboptimal for preventing the epidemic. Other researchers have similarly described suboptimal VC in urban/semi-urban areas. A study in Burkina Faso found urban children less likely than rural children to obtain all but the BCG vaccine as scheduled [14]. Findings from Iran showed that while no differences were observed among children less than 1 year old, among 1–6 year olds, urban children were much more likely than rural children to have missed vaccines [15]. A study in China noted significantly lower vaccination rates in urban children compared to rural children [16]. Nevertheless, other studies have found contradictory results [17,18]. Differences in context may explain the divergent findings.

Our study found that among children aged 5–14 years, 14.1% in the rural and 37.4% in the semi-urban health areas did not receive their first dose of MCV until the 2016-RVC; this suggests a history of poor performance of vaccination activities and strategies resulting in immunization deficiencies. This finding is supported by the fact that despite initiating an approach in 2004 to bolster EPI, SIA, and epidemiological surveillance activities, since 2010 DRC has experienced a resurgence of measles and large-scale outbreaks across the country [3–5]. According to our data, while a large proportion of children had been vaccinated at two to three different opportunities, there were still some children not reached through routine immunization nor through both 2016 campaigns. A study from Malawi [19] reported that SIAs are biased towards children for whom access to care is already high. Conversely, a study from Kenya [20], as well as an analysis of multiple low-/middle-income countries [21], found that SIAs provide an effective opportunity for receiving a second dose of MCV and promote greater equity by reaching children from lower socio-economic status. Various factors may explain the differences, including characteristics unique to each campaign. Importantly, these findings underscore the necessity of routinely conducting post-SIA coverage surveys rather than relying on administrative coverage estimates. A study of seven countries in southern Africa that experienced a resurgence in measles cases in SIA-targeted age groups suggested that the outbreaks were due to suboptimal SIA coverage related to overestimation of administrative coverage in the absence of post-SIA coverage surveys [22].

While wide confidence intervals preclude drawing conclusions about the VE in the rural area, in the semi-urban area, the VE point estimates of the 2016-SIA tended to be below standard. VE constitutes a valuable quality control measure of immunization programs. Concerns regarding a possible loss of VE arise when measles outbreaks follow vaccination campaigns, especially in areas where the economic and logistical burden of vaccine stockpiling, handling, and distribution in observance of cold chain requirements present challenges [23]. The DRC suffers from inadequate infrastructure, insufficient human resources, fuel shortages, and insecurity [2]; these factors may compromise the cold chain, resulting in exposure to heat and light, leading to loss of potency of the MCV [24] and providing a possible explanation for the suboptimal VE point estimate observed.

A limitation of our study is that the sample size did not allow for enough precision to assess VE, resulting in wide confidence intervals; this is because the study was originally powered to assess VC, with the VE analysis added subsequently. Second, the sampling design may not have resulted in a strict probability sample; the effect of this on the estimates and confidence intervals is not known [10]. Third, the definition of a measles case was based on clinical signs/symptoms reported by the parent/guardian for which non-differential misclassification bias is possible. In a seroepidemiologic study of 600 children aged 12–47 months conducted in Mozambique in 1986, low specificity of measles diagnosis based on caregiver recall of the last two to three years introduced significant bias; VE estimates informed by serology were nearly double the estimates obtained from maternal reporting [25]. Although recall bias is likely limited in our study given that VE was assessed based on measles cases reported in the past two months, the inclusion of suspects that were not true measles cases could result in an underestimation of VE. The lack of investigation of MCV history prior to 2016 (i.e., the number of doses received as a component of EPI, SIA or another campaign) constitutes another study limitation. In addition, data on nutritional status and malaria infection, important confounders associated with measles severity and vaccine uptake, were not collected [26–35].

Despite the efforts undertaken, elimination of measles remains a challenge. The worst measles epidemic in the world and the largest in the DRC in decades, declared in 2018 after the initial writing

of this article, demonstrates this. A combination of suboptimal VC and below standard VE lowers vaccine-induced immunity in the population, exacerbating the risk of epidemics [5,12]. The findings from this study highlight the need for more research to guide the development of vaccination strategies tailored to urban contexts. In addition, more qualitative research is needed to elucidate the perspective of the population towards vaccination in order to understand why some children remain unvaccinated despite multiple opportunities. Finally, greater investigation and documentation of field VE and its determinants is essential to confirm the results from this study and understand reasons why VE may be below standard; it may be beneficial for vaccination campaigns to provide and emphasize to the population the importance of keeping documentation to facilitate the ascertainment of vaccination status and for future research to collect blood samples to assess seroprevalence data.

5. Sources of support

This work was supported by Médecins Sans Frontières-Operational Centre Brussels.

CRediT authorship contribution statement

R.M. Coulborn: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **F. Nackers:** Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision, Project administration. **C. Bachy:** Conceptualization, Writing - original draft, Writing - review & editing, Project administration. **K. Porten:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **H. Vochten:** Investigation, Writing - review & editing, Project administration. **E. Ndele:** Investigation, Writing - review & editing, Project administration. **M. Van Herp:** Conceptualization, Writing - review & editing, Supervision. **E. Bibala-Faray:** Investigation, Writing - review & editing. **S. Cohuet:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **I. Panunzi:** Conceptualization, Validation, Writing - original draft, Writing - review & editing, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Many thanks to the Ministry of Public Health of the Democratic Republic of the Congo for their support and participation in this research as well as to other members of the study team and all study participants. Funding for this study was provided by Médecins Sans Frontières-Operational Centre Brussels.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.02.029.

References

[1] World Health Organization. Global Measles and Rubella: Strategic Plan 2012-2020. 2012. doi:ISBN 978 92 4 150339 6.
[2] Doshi RH, Mukadi P, Shidi C, Mulumba A, Hoff NA, Gerber S, et al. Field evaluation of measles vaccine effectiveness among children in the Democratic Republic of Congo. Vaccine 2015;33:3407–14. https://doi.org/10.1016/j.vaccine.2015.04.067.
[3] Doshi RH, Shidi C, Mulumba A, Eckhoff P, Nguyen C, Hoff NA, et al. The effect of immunization on measles incidence in the Democratic Republic of Congo: results from a model of surveillance data. Vaccine 2015;33:6786–92. https://doi.org/10.1016/J.VACCINE.2015.10.020.
[4] Mancini S, Coldiron ME, Ronsse A, Ilunga BK, Porten K, Grais RF. Description of a large measles epidemic in Democratic Republic of Congo, 2010–2013. Confl Health 2014. https://doi.org/10.1186/1752-1505-8-9.
[5] Grout L, Minetti A, Hurtado N, François G, Fermon F, Chatelain A, et al. Measles in Democratic Republic of Congo: an outbreak description from Katanga, 2010–2011. BMC Infect Dis 2013. https://doi.org/10.1186/1471-2334-13-232.
[6] Bruneau J-C. Les nouvelles provinces de la République Démocratique du Congo : construction territoriale et ethnicités. L'esp Polit 2009. https://doi.org/10.4000/espacepolitique.1296.
[7] Ministère de la santé publique. République Démocratique du Congo. Deuxième enquête démographique et de santé (EDS-RDC II 2013-2014). 2014.
[8] Ministère de la santé publique. République Démocratique du Congo. Plan Pluri Annuel Complet du Programme Elargi de Vaccination de la République Démocratique du Congo, 2015-2019. 2014.
[9] Ministère de la Santé Publique. République Démocratique du Congo. Rapport technique de la campagne de suivi contre la rougeloe dans la province du Maniema organisée du 30 août au 3 septembre 2016. 2016.
[10] Cutts FT, Izurieta HS, Rhoda DA. Measuring Coverage in MNCH: Design, Implementation, and Interpretation Challenges Associated with Tracking Vaccination Coverage Using Household Surveys. PLoS Med 2013;10. https://doi.org/10.1371/journal.pmed.1001404.
[11] Thompson KM. Evolution and Use of Dynamic Transmission Models for Measles and Rubella Risk and Policy Analysis. Risk Anal 2016. https://doi.org/10.1111/risa.12637.
[12] World Health Organization. Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec 2017;17:205–28.
[13] Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. J Infect Dis 2011. https://doi.org/10.1093/infdis/jir102.
[14] Schoeps A, Ouédraogo N, Kagoné M, Sié A, Müller O, Becher H. Socio-demographic determinants of timely adherence to BCG, Penta3, measles, and complete vaccination schedule in Burkina Faso. Vaccine 2013;32:96–102. https://doi.org/10.1016/j.vaccine.2013.10.063.
[15] Tabatabaei SM, Mokhtari T, Salari M, Mohammdi M. Rural-Urban Differences in Reasons for Incomplete Vaccination in Children Under Six Years, Southeast Iran 2013. Int J Infect 2015. https://doi.org/10.17795/iji28109.
[16] Zhang X, Syeda ZI, Jing Z, Xu Q, Sun L, Xu L, et al. Rural-urban disparity in category II vaccination among children under five years of age: Evidence from a survey in Shandong, China. Int J Equity Health 2018. https://doi.org/10.1186/s12939-018-0802-4.
[17] Ijarotimi IT, Fatiregun AA, Adebiyi OA, Ilesanmi OS, Ajumobi O. Urban–rural differences in immunisation status and associated demographic factors among children 12–59 months in a Southwestern state, Nigeria. PLoS ONE 2018. https://doi.org/10.1371/journal.pone.0206086.
[18] Nair TN, Varughese E. Immunization coverage of infants–rural-urban difference in Kerala. Indian Pediatr 1994.
[19] Minetti A, Hurtado N, Grais RF, Ferrari M. Reaching hard-to-reach individuals: nonselective versus targeted outbreak response vaccination for measles. Am J Epidemiol 2014. https://doi.org/10.1093/aje/kwt236.
[20] Vijayaraghavan M, Martin RM, Sangrujee N, Kimani GN, Oyombe S, Kalu A, et al. Measles supplemental immunization activities improve measles vaccine coverage and equity: evidence from Kenya, 2002. Health Policy (New York) 2007. https://doi.org/10.1016/j.healthpol.2006.11.008.
[21] Portnoy A, Jit M, Helleringer S, Verguet S. Impact of measles supplementary immunization activities on reaching children missed by routine programs. Vaccine 2018;36:170–8. https://doi.org/10.1016/j.vaccine.2017.10.080.
[22] Shibeshi ME, Masresha BG, Smit SB, Biellik RJ, Nicholson JL, Muitherero C, et al. Measles resurgence in southern Africa: Challenges to measles elimination. Vaccine 2014;32:1798–807. https://doi.org/10.1016/j.vaccine.2014.01.089.
[23] Zhang J, Pritchard E, Hu X, Valentin T, Panilaitis B, Omenetto FG, et al. Stabilization of vaccines and antibiotics in silk and eliminating the cold chain. Proc Natl Acad Sci 2012. https://doi.org/10.1073/pnas.1206210109.
[24] Goodson JL, Chu SY, Rota PA, Moss WJ, Featherstone DA, Vijayaraghavan M, et al. Research priorities for global measles and rubella control and eradication. Vaccine 2012;30:4709–16. https://doi.org/10.1016/j.vaccine.2012.04.058.
[25] Cutts FT, Smith PG, Colombo S, Mann G, Ascherio A, Soares AC. Field evaluation of measles vaccine efficacy in mozambique. Am J Epidemiol 1990;131:349–55. https://doi.org/10.1093/oxfordjournals.aje.a115504.
[26] Halsey NA, Boulos R, Mode F, Andre J, Bowman L, Yaeger RG, et al. Response to Measles Vaccine in Haitian Infants 6 to 12 Months Old. N Engl J Med 1985;313:544–9. https://doi.org/10.1056/NEJM198508293130904.
[27] Reddy V, Bhaskaram P, Raghuramulu N, Milton RC, Rao V, Madhusudan J, et al. Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. Am J Clin Nutr 1986;44:924–30. https://doi.org/10.1093/ajcn/44.6.924.
[28] Bhaskaram P. Micronutrient Malnutrition, Infection, and Immunity: an Overview. Nutr Rev 2002;60:S40–5. https://doi.org/10.1301/00296640260130722.

[29] Kizito D, Tweyongyere R, Namatovu A, Webb EL, Muhangi L, Lule SA, et al. Factors affecting the infant antibody response to measles immunisation in Entebbe-Uganda. BMC Public Health 2013;13:619. https://doi.org/10.1186/1471-2458-13-619.
[30] McMurray DN, Loomis SA, Casazza LJ, Rey H. Influence of moderate malnutrition on morbidity and antibody response following vaccination with live, attenuated measles virus vaccine. Bull Pan Am Health Organ 1979;13:52–7.
[31] Rytter MJH, Kolte L, Briend A, Friis H, Christensen VB. The immune system in children with malnutrition–a systematic review. PLoS ONE 2014;9:. https://doi.org/10.1371/journal.pone.0105017e105017.
[32] Idris S, El Seed AM. Measles vaccination in severely malnourished Sudanese children. Ann Trop Paediatr 1983;3:63–7.
[33] Powell GM. Response to live attenuated measles vaccine in children with severe kwashiorkor. Ann Trop Paediatr 1982;2:143–5.
[34] Hafez M, Aref GH, Mehareb SW, Kassem AS, El-Tahhan H, Rizk Z, et al. Antibody production and complement system in protein energy malnutrition. - PubMed - NCBI. J Trop Med Hyg 1977;80:36–9.
[35] Greenwood BM, Bradley-Moore AM, Bryceson AD, Palit A. Immunosuppression in children with malaria. Lancet 1972;1:169–72. https://doi.org/10.1016/s0140-6736(72)90569-7.