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Research Article

Measles-Rubella Positivity Rate and Associated Factors in Pre-Mass and Post-Mass Vaccination Periods: Analysis of Uganda Routine Surveillance Laboratory Data

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Toward 2019, Uganda experienced an extensive outbreak of measles and rubella. The Uganda National Expanded Programme on Immunization implemented a mass measles-rubella vaccination campaign aimed at halting the ongoing transmission. This study determined the changes in the disease burden thereafter. We conducted a retrospective cross-sectional study on measles-rubella positivity and its associated factors in Uganda using 1697 case-based surveillance data for 2019 and 2020 stratified into two dispensations: prevaccination and postvaccination campaigns. Statistical tests employed in STATA 15 included chi-square, Fisher's exact, and binomial tests. Measles positivity rates in the period before and after the mass immunization campaign were 41.88% (95% CI: 39.30–44.51) and 37.96% (95% CI: 32.81–43.40), respectively. For rubella, the positivity rate in the precampaign season was 21.73% (95% CI: 19.61–23.99) and in the postvaccination season was 6.65% (95% CI: 4.36–10.00). Binomial tests indicated that postcampaign positivity rates were significantly lower than the precampaign rate for measles ($p = 0.003$) and rubella ($p < 0.001$). Generally, age ($\chi 2 = 58.94$, $p = 0.001/\chi 2 = 51.91$, $p < 0.001$) and vaccination status ($\chi 2 = 60.48$, $p = 0.001/\chi 2 = 16.90$, $p = 0.001$) were associated with the measles positivity rate in both pre/postcampaign periods. Rubella positivity rate was associated with vaccination status ($\chi 2 = 32.97$, $p < 0.001/p = 0.001$) in both periods and age in the precampaign season ($p < 0.001$). The measles-rubella mass campaign lessened rubella burden remarkably, but barely adequate change was observed in the extent of spread of measles. Children aged less than 9 months are at higher chances of testing positive amidst low vaccination levels among the eligible. The immunization programme must attain and maintain routine immunization coverage at 95% or more and roll out a second-dose measles-rubella vaccination to sustain the reduced disease burden.

1. Background

Measles and rubella are airborne viruses, and they remain one of the commonest and highly infectious diseases [1]. Although the disease can infect any person regardless of age, the frequency of cases is highest among children below five years of age [2]. Measles presents with fever, cough, coryza, conjunctivitis, and maculopapular rash [3]. Underlying conditions such as malnutrition or immunosuppression of affected persons influence the severity of the disease [4]. Severe measles can result in complications such as blindness, pneumonia, and encephalitis [2]. Rubella, however, presents with milder symptoms [5], and approximately 50% of infections are subclinical [6]. Africa has an alarming measles-rubella situation resulting from ailing immunization programme performance due to inadequate health resources and lack of well-trained manpower [7]. It is estimated that only 25% of countries in Sub-Saharan Africa reached the Global Vaccine Action Plan target of 90% for first-dose measles vaccination in 2019 [8]. The burden is further deepened by poor political commitment, competing national projects, and dotted humanitarian and security crises [9]. Experts have painted a gloomy measles-rubella future due to the ripple effects of COVID-19 [10]. An estimated 19.8 million eligible children did not receive the measles-rubella vaccine in 2020 [11]. From the 2016 Uganda

Demographic and Health Survey, only 55% of children were fully immunized against vaccine-preventable diseases, including measles and rubella [12]. Again, from 2015 to 2018, an estimated 524128 eligible children were unimmunized against measles and rubella [13]. The excessive accumulation of unimmunized children resulted in severe measles and rubella outbreaks in approximately 50% of districts in 2019 [14]. In response to this substantial public health risk, the government of Uganda with support from partners, GAVI (the Vaccine Alliance), the United Nations Children's Fund (UNICEF), and the World Health Organization (WHO), implemented a nationwide first and largest measles-rubella vaccination campaign targeting 18.1 million children (43% of the national population) from the 16th to 20th of October 2019. It was purposed to interrupt the ongoing measles and rubella disease outbreaks through heightened population immunity [15] and introduce rubella vaccination into routine immunization.

The measles-rubella immunization campaign was planned and executed under the theme "Protect Your Child Against Measles and Rubella; Vaccinate Now." It used a district-led approach with extensive involvement of local opinion leaders, village health teams (VHTs), and school teachers at the operational level. Prior to vaccination, VHTs conducted a thorough house-to-house registration of eligible children (9 months to 15 years). This activity provided vital information for microplanning. Subcounty officials supervised the trained health workers during implementation. The campaign spanned five days, three of which were dedicated to vaccinating children in schools. The quality of the programme was enhanced by the deployment of central/national supervisors to support districts in readiness assessment, microplanning, training, and sensitization of teachers, communities, and VHTs. The campaign successfully ended with an administrative coverage of 108% [16].

However, for decades, limited data have always hindered the determination of the impacts of measles campaigns in developing countries [17]. Beyond confirmation of suspected measles and rubella cases by laboratories to support elimination efforts [6], exploration laboratory results in terms of positivity rate or percent positive provide a clue on the extent of spread of disease in particular geographic zones [18, 19]. Again, characterization of sociodemographic variables as captured by laboratory-investigated cases on case-based surveillance forms aids epidemiological monitoring of measles and understanding the reasons for its occurrence and transmission [20]. Hence, this study determined the positivity rate and associated demographic factors stratified into two (2) dispensations, before and after measles-rubella campaigns, to determine changes in measles-rubella burden and evaluate the effectiveness of the measles-rubella campaign to inform operational planning and decision making. This is in line with the "data-enabled" core principle of the 2021–2030 measles-rubella strategic framework [21].

2. Materials and Methods

2.1. Background to the Study Area. The Republic of Uganda is a landlocked country in East-Central Africa with an estimated population of 41, 737, 156, 50.9% of which are females. The country is classified as a least developed country (LDC). A greater part of the population (72%) is reliant on the farming sector as an occupation and for income. That notwithstanding, Uganda is observing rapid development, and it is forecasted that the country will be among the most urbanized countries on the continent by 2050 [22].

In accordance with the WHO's 2002–2006 measles control strategy, Uganda established nationwide case-based laboratory measles surveillance in October 2003. This system provides continuous epidemiological monitoring of measles cases [20]. The Uganda Virus Research Institute (UVRI) receives serum specimens from all facilities through the laboratory transport hub system or, in some cases, in person for examination (delivered by health workers).

2.2. Study Design. An observational, retrospective, cross-sectional study was carried out. A key feature of the study is the stratification of two-year data by pre-mass and post-mass campaign periods of measles-rubella vaccination.

2.3. Study Population. The September 2012 Working Guide for Health Workers on Integrated Disease Surveillance and Response (IDSR) by the Uganda Ministry of Health defines suspected measles as "any person with fever and maculopapular generalized rash and cough, coryza or conjunctivitis (red eyes) or any person in whom a clinician suspects measles."

The study participants therefore included health care seekers of all ages and genders classified by health workers for samples to be taken for measles and rubella investigations at the laboratory from all parts of the country. The participants also involved community members who were identified by surveillance officers through community-based surveillance as measles or rubella suspects and were investigated.

2.4. Data Sources and Variables. Measles cases investigated by health workers for laboratory confirmation are accompanied by a case-based form or a line list. The forms are completed by persons investigating the suspected case. The form is composed of 5 sections as follows: demographic details, clinical history, specimens, investigator(s), and results. The first 4 sections are completed by the investigator. Upon testing at the designated lab, the results section is completed. The entire information is then entered into an Excel sheet template. The compiled data from the lab are shared with various stakeholders, including the WHO, for operational use. This study uses the compiled data for 2019 and 2020. Purposively, the test result was considered the dependent or outcome variable for the two separate tests that are performed on each sample for measles IgM and rubella IgM. The independent variables considered were age, sex, vaccination, and vitamin "A" status. Age was categorized into underage noneligible (UANE; 0–8 months), routine immunization and campaign eligible (RICE; 9–180 months), and overage noneligible (OANE; 181 and above).

2.5. Exclusion and Inclusion Criteria. The study used data for laboratory-examined measles and rubella cases for 2019 (precampaign season) and 2020 (postcampaign season). Given that the measles-rubella mass campaign was conducted in the last quarter of 2019, the study excluded entries from October to December in both periods. In addition, the study excluded tests for measles and rubella IgM that yielded indeterminate results.

2.6. Study Size. All cases that met the inclusion criteria were incorporated, and a random sample was not obtained. A total of 1697 cases were involved in the study.

2.7. Statistical Methods. Data from the laboratory on measles-rubella routine surveillance were imported into Stata version 15 (64 bit) for cleaning and analysis. Descriptive statistics such as frequency and proportion were used to analyze the demographic factors and outcome.We employed binomial test to extablish any significant changes in positivity rates. Chi-square test and Fisher's exact test were used to test for the association between demographic factors and test outcomes for the precampaign and postcampaign seasons based on 95% statistical significance. A p value <0.05 was considered statistically significant.

2.8. Ethical Approval and Consent to Participate. The study used secondary data entirely from routine surveillance, a legitimate function sanctioned by the Ministry of Health. The need for informed consent was waived. However, a justifiable request was made for the use of data. The World Health Organization Uganda Country Office granted approval.

3. Results

3.1. Background Characteristics of the Study Participants. From Table 1, a total of 1697 individuals were involved in the study. These were laboratory-examined measles and rubella cases for the study periods from January to September 2019 and 2020. The ages range from 1 to 804 months. The modal age was 60 months (5 years), with 81 (4.77%) of all cases. The mean age was 78.31 months with a standard deviation of 85.43 months. Individuals within the routine immunization and campaign eligible (RICE) age category formed the majority of cases (78.90%). Less-predominant suspected cases were among those underage noneligible (UANE) and overage noneligible (OANE), which accounted for up to 21.09% (Table 1). The suspected cases were fairly distributed between males (52.33%) and females (47.67%) but disproportionally distributed between rural (88.82%) and urban (0.18%) people. Disease outcome as indicated on case-based forms and line lists points to a case fatality rate (CFR) of 0.12 per 100 suspected cases. Close to half of the cases investigated did not receive any dose of measles or measles-rubella vaccine (Table 1).

3.2. Measles-Rubella Positivity Rate. In the case of measles, the positivity rates in the period preceding and following the mass immunization campaign were 41.88% (575/1373, 95% CI: 39.30–44.51) and 37.96% (123/324, 95% CI: 32.81–43.40), respectively (Figure 1). A two-sided binomial test ($n = 1373$, assumed proportion = 0.3796, observed proportion = 0.4188) at the 95% confidence interval indicates that the precampaign positivity rate differs significantly from the postcampaign rate ($p = 0.003$). For rubella, the positivity rate in the precampaign season was 21.73% (297/1367, 95% CI: 19.61–23.99). The positivity rate in the postvaccination season was 6.65% (21/316, 95% CI: 4.36–10.00) (Figure 1). A two-sided binomial test ($n = 1367$, assumed proportion = 0.067, observed proportion = 0.217) showed that the two positivity rates were significantly different ($p < 0.001$).

3.3. Factors Associated with the Test Outcome for Measles and Rubella in Pre-Mass and Post-Mass Campaign Periods. From Table 2, there was no significant association between sex, place of residence, and specimen condition with outcomes in either season for measles. However, age, vaccination status, and vitamin "A" dosage were associated with test outcomes in the precampaign season for measles. In the postcampaign period, age ($\chi 2 = 51.91$, $p < 0.001$) and vaccination status ($\chi 2 = 16.90$, $p = 0.001$) were associated with measles outcome. It is noted that 71.30% and 64.04% of the participants in the UANE age category tested positive for measles in precampaign and postcampaign seasons, respectively. Following the mass immunization exercise, 65.57% of individuals in the OANE age category tested positive for measles compared with 23.94% in the RICE category. The majority of the individuals who received a dose (66.23%) or two (80.95%) tested negative in the postcampaign season.

In the case of rubella (Table 3), sex ($\chi 2 = 1.10$, $p = 0.295$) was associated with test outcome in the postcampaign period as well as age ($p < 0.001$) in the precampaign period only. Vaccination status was significantly associated with the rubella outcome in both periods of the study. The level of positivity was reduced across all vaccination statuses. While 34.33% of the persons who received 2 doses of vaccines tested positive in the precampaign period, only 1.67 of such people tested positive in the postcampaign period.

4. Discussion

Traditionally, mass campaigns have been applied in measles and rubella elimination efforts to interrupt ongoing transitions and rife outbreaks [23]. We explored routine surveillance case-based data to study changes in measles-rubella burden after a mass campaign in Uganda. We also assessed factors associated with measles-rubella positivity. The study demonstrated a reduced disease burden, particularly for rubella.

Just as a study that modeled the impact of measles-rubella vaccination in Vietnam showed a sustained decrease in the incidence of the disease [24], we observed that a year after the mass campaign, the number of suspected measles and rubella cases decreased tremendously and subsequently the number of laboratory-examined cases. This drop in the

Table 1: Background characteristics of the study participants.

Variable/category	Frequency ($N = 1697$)	Percentage
Data type/source		
Case-based data	942	55.51
Line list data	755	44.49
Sex		
Male	888	52.33
Female	809	47.67
Age		
Underage noneligible (0–8 months)	165	9.72
RI and campaign eligible (9–180 months)	1339	78.90
Overage noneligible (181 months and above)	193	11.37
Place of residence		
Urban	3	0.18
Rural	1694	88.82
Department of care		
Inpatient care	250	14.73
Outpatient care	1447	85.27
Disease outcome		
Alive	1695	99.88
Dead	2	0.12
Vaccination status		
Not vaccinated	812	47.88
1 dose	576	33.96
2+ doses	129	7.61
Unknown	179	10.55

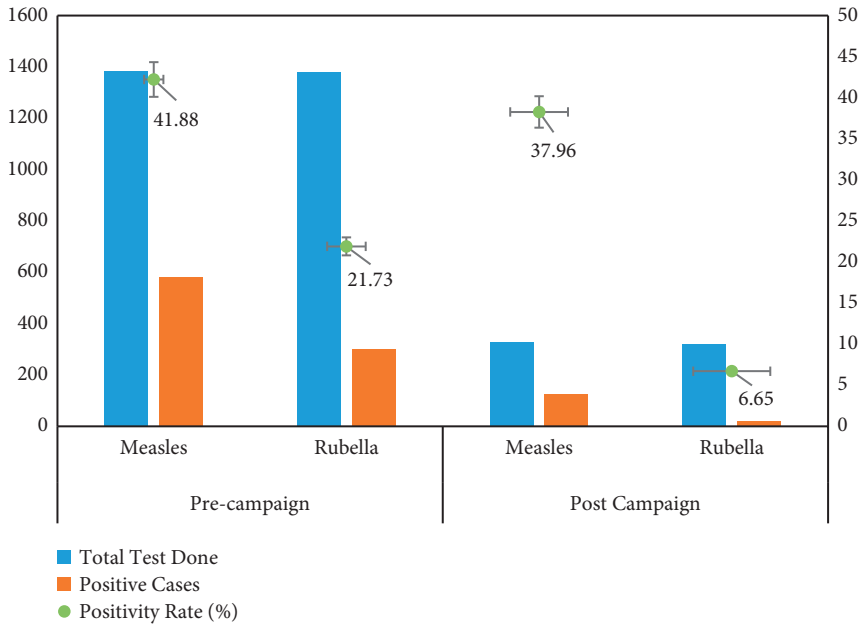

Figure 1: Measles-rubella percent positives in pre-mass and post-mass vaccination periods.

number of cases is attributable to the measles-rubella vaccination campaign. A decrease in the number of measles and rubella cases comes with tremendous economic benefit for families in terms of time and cost of treatment. The health care services will also count gains in terms and reduce facility visits, resources used to sample the specimen, transportation, and cost of the laboratory tests.

From the study, 47.88% of the suspected cases were not vaccinated. This is concurrent with the report of the Uganda 2016 Demographic and Health Survey and a similar study in

Table 2: Factors associated with the measles outcome among laboratory-examined cases before and after the 2019 measles-rubella mass vaccination campaign.

Variable	Precampaign season ($n = 1373$)				Postcampaign season ($n = 324$)			
	Positive	Negative	$\chi 2$	p value	Positive	Negative	$\chi 2$	p value
Sex								
Male	297 (41.77)	414 (58.23)	0.010	0.934	68 (38.42)	109 (61.58)	0.030	0.853
Female	278 (41.99)	384 (58.01)			55 (37.41)	92 (62.59)		
Age								
UANE	82 (71.30)	33 (28.70)			32 (64.00)	18 (36.00)		
RICE	421 (37.39)	705 (62.61)	58.94	0.001	51 (23.94)	162 (76.06)	51.91	<0.001
OANE	72 (54.55)	60 (45.45)			40 (65.57)	21 (34.43)		
Place of residence								
Urban	1 (100)	0 (0.00)		0.419*	0 (0.00)	2 (100)		0.528*
Rural	574 (41.84)	798 (58.16)			123 (38.20)	199 (61.80)		
Vaccination status								
Not vaccinated	336 (49.48)	343 (50.52)			65 (48.87)	68 (51.13)		
1 dose	152 (30.46)	347 (69.54)	60.48	<0.001	26 (33.77)	51 (66.23)	16.90	0.001
2+ doses	16 (24.24)	50 (75.76)			12 (19.05)	51 (80.95)		
Unknown	71 (55.04)	58 (44.96)			20 (39.22)	31 (60.78)		
Vitamin A doses								
1 dose	134 (36.71)	231 (63.29)			28 (41.18)	40 (58.82)		
2+ doses	223 (45.79)	264 (54.21)	7.06	0.029	43 (35.25)	78 (64.75)	0.72	0.697
Unknown	218 (41.84)	303 (58.16)			52 (38.81)	82 (61.19)		
Specimen condition								
Good	575 (42.06)	792 (57.94)		0.078*	122 (37.77)	201 (62.23)	**	**
Bad	0 (0.00)	5 (100)			0 (0.00)	0 (0.00)		

*Fisher's exact test; **not applicable.

Table 3: Factors associated with the rubella outcome among laboratory-examined cases before and after the 2019 measles-rubella mass vaccination campaign.

Variable	Precampaign season ($n = 1367$)				Postcampaign season ($n = 316$)			
	Positive	Negative	$\chi 2$	p value	Positive	Negative	$\chi 2$	p value
Sex								
Male	157 (22.11)	553 (77.89)	0.12	0.719	14 (7.95)	162 (92.05)	1.10	0.295
Female	140 (21.31)	517 (78.69)			7 (5.00)	133 (95.00)		
Age								
UANE	4 (3.54)	109 (96.46)			0 (0.00)	50 (100)		
RICE	278 (24.84)	841 (75.16)		<0.001*	15 (7.21)	193 (92.79)		0.058*
OANE	15 (11.11)	120 (88.89)			6 (10.34)	52 (89.66)		
Place of residence								
Urban	0 (0.00)	1 (100)		1.000*	0 (0.00)	2 (100)		1.000*
Rural	297 (21.74)	1069 (78.26)			21 (6.69)	293 (93.31)		
Vaccination status								
Not vaccinated	119 (17.68)	554 (82.32)			3 (2.29)	128 (97.71)		
1 dose	140 (28.17)	357 (71.83)	32.79	<0.001	11 (14.29)	66 (85.71)		0.001*
2+ doses	23 (34.33)	44 (65.67)			1 (1.67)	59 (98.33)		
Unknown	15 (11.54)	115 (88.46)			6 (12.50)	42 (87.50)		
Vitamin A doses								
1 dose	83 (22.99)	278 (77.01)			9 (13.24)	59 (86.76)		
2+ doses	116 (24.12)	365 (75.88)	4.85	0.089	7 (6.09)	108 (93.91)	6.60	0.037
Zero/unknown	98 (18.67)	427 (81.33)			5 (3.76)	128 (96.24)		
Specimen condition								
Good	296 (21.75)	1065 (78.25)		1.000*	21 (6.65)	295 (93.35)	**	**
Bad	1 (20.00)	4 (80.00)			0 (0.00)	0 (0.00)		

*Fisher's exact test; **not applicable.

Nigeria [25]. Low vaccination rates foster the spread of measles and rubella. To avoid outbreaks in the future, efforts must be made to improve routine immunization. With measles and rubella being the last dose of vaccination on the Ugandan routine immunization schedule given at 9 months, caregivers are most likely to be at default. Defaulter tracing will therefore be of utmost importance to ensure adherence to measles-rubella vaccination to ensure completeness of the routine immunization schedule for eligible children. It is also important to address geographical context inequalities. The immunization programme must reconsider its regular service delivery approaches and equally focus on static and outreach sessions [26]. The measles positivity rate was reduced by 3.92%, and the rubella positivity rate was decreased by 15.08%. The extent of spread of measles in the postcampaign period was just slightly lower than that in the precampaign period. It was expected that the positivity rate would have decreased considerably like an identical study in Iowa students demonstrating that the positivity rates decreased at a much higher rate of 50% after campaign [27]. Similarly, a study that investigated the measles occurrence rate in both immunized and unimmunized children revealed that a substantial number of children tested positive for measles despite measles vaccination [25]. The study therefore recommended the need to find explanations for the low levels of vaccination protection.

The routine immunization schedule recommends administration of measles-rubella vaccine at 9 months. The mass campaign targeted children 9 months to 15 years as usual [28]. The study showed that these groups of children in the RICE age category had reduced chances of testing positive compared with infants who were not eligible (underage) for the vaccine. In the postcampaign era, 64.00% of individuals in the UANE age category tested positive for measles compared with 23.94% in the RICE category. Kanakoudi-Tsakalidou and colleagues reported similar findings in Europe [29]. The worrisome trend of a higher burden of measles and rubella in children of age 0–8 months was also seen in a study in Myanmar [30]. Again, Koudio et al. studied an outbreak of measles and rubella in refugee transit camps in Ivory Coast among Liberian refugees. The highest incidence of measles and rubella was seen in individuals of age less than 9 months [31]. The practice of administering the measles-rubella vaccine at 9 months is premised on the assertion that children are born with a certain level of maternal immunity, but measles and rubella immunity are acquired. Our speculation on this issue is that, in situations where mothers lack adequate immunity, children born may be exposed to the disease, as this study reveals. Uganda has a single-dose measles-rubella schedule, of which administrative coverage has been low, as in many African countries [32]. If mothers have not been exposed to the disease with naturally acquired immunity, we can hypothesize that most mothers did not have adequate immunity and subsequently their offspring. A humoral immunity study in Paris has shown that only 59% of mothers have vaccine-induced immunity and 15% have infection-acquired immunity. The study further revealed that 90% of infants who are four months and above were susceptible to measles and rubella [29]. To cater for routine immunization underage noneligible children, mass campaigns can have lower age limits, as laboratory data may suggest. It is also recommended by some scientists to vaccinate women of childbearing age and adolescents in Italy [33].

A person with at least a dose of measles-rubella vaccine is less likely to test positive for measles and rubella. Increasing the dose increases the negativity of the test results. Approximately half of the suspected cases of measles-rubella have received one or more doses of measle vaccine. In percentage terms, 48.87 of persons who did not receive any dose vaccines tested positive for measles, but only 19.05% of people who received two (2) or more doses tested positive for measles in the postcampaign period. The effect of additional measles-rubella dose administration was established in a meta-analysis. Two or more doses were linked to high seropositivity (antibody), effectiveness of vaccines, and T-cell responses [34]. High immunogenicity is required to avoid outbreaks [35]. This implies that a second-dose schedule in the routine immunization programme will be vital. Aside from the reduction in measles-rubella cases, the intervals between mass campaigns will be prolonged due to the slow accumulation of susceptible individuals. Before the campaign, the routine immunization programme administered measles-containing vaccines (MCVs) only. The measles-rubella vaccine (MRV) was used for the first time in Uganda in the mass campaign and introduced in the routine immunization programme thereafter. Major change observed in rubella burden is the reduction of positivity rate among the mass campaign targets of 9 months to 15 years from 24.84% in the precampaign era to 7.21 in the postcampaign era.

Even though the place of residence was not statistically associated with measles-rubella positivity, the disproportionate rural-urban distribution of cases could point to a systematic disproportionate access and utilization of quality immunization services. It has been proven that geographic vaccination coverage influences the occurrence of measles and rubella [30]. We can assume urban areas may have access to quality immunization services, hence the low occurrence of measles and rubella. On the other hand, subjective classification of place of residence by health workers may lead to disproportionate assignment. Rural-urban classification should therefore be clearly define on the case-based investigation form to ensure objectivity.

5. Conclusion

Health care providers depend on laboratory results to make informed decisions about treatment and case management, but from the measles-rubella epidemiological monitoring perspective, periodic determination of the positivity rate establishes levels of transmission in populations, especially in times before and after major interventions such as mass campaigns. The 2019 measles-rubella campaign suppressed the frequency of suspected measles and rubella cases and showed statistically significant reduction in positivity rates, thereby reducing the disease burden. However, children under the age of nine months and unvaccinated remain at

higher chances of testing positive. To consolidate on this gain and tackle the at-risk group, UNEPI must attain and maintain routine immunization coverage at 95% or more and roll out a second-dose measles-rubella vaccination. Serosurveys can be employed to assess gaps in maternal immunity. Global strategies or models are required to protect underage noneligible children from measles and rubella.

Abbreviations

AOR: Adjusted odds ratio
CFR: Case fatality rate
COVID-19: Coronavirus disease 2019
DHIS -2: District health information system-2
GAVI: The vaccine alliance
IDSR: Integrated disease surveillance and response
LDC: Least developed country
MCV: Measles containing vaccine
MR: Measles-rubella
MRV: Measles-rubella vaccine
OANE: Overage noneligible
RICE: Routine immunization and campaign eligible
UNEPI: Uganda national expanded programme on immunization
UVRI: Uganda Virus Research Institute
UANE: Underage noneligible
UNICEF: United Nations Children's Fund
VHTs: Village health teams
WHO: World Health Organization.

Data Availability

The study data are available from the corresponding authors upon reasonable request and with permission of the immunization cluster Team Lead, World Health Organization Uganda Country Office.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

EAM conceived and designed the study and drafted the initial manuscript. EAM and SOG performed the data extraction, analysis, and interpretation of the results and discussion. They drafted a revised manuscript to enhance intellectual content and agreed to and approved the final manuscript.

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