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Measles Vaccination Coverage and Protective Effectiveness in the Amhara Regional State, Ethiopia, 2019-2024

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Research Article

Keywords: Measles, Vaccination Coverage, Protective Effectiveness, Amhara Regional State, Ethiopia

Posted Date: March 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8981443/v1

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Additional Declarations: No competing interests reported.

Abstract

Background: Despite the availability of an effective vaccine, measles remains a major public health problem in Ethiopia, with recurrent outbreaks reported in several areas in Amhara Regional State. Understanding measles vaccination coverage and real-world protective effectiveness is critical for assessing immunization program performance and guiding elimination strategies. Therefore, this study was conducted to determine the regional measles vaccine coverage and the vaccine protective effectiveness level in the region.

Methods: A retrospective test-negative case-control analysis of measles surveillance data and retrospective analysis of district health information system 2 (DHIS2) data from 2019-2024 was employed to determine vaccine effectiveness and vaccine coverage respectively. Measles vaccine coverage was determined by dividing the number of children vaccinated as numerator to the expected number of children legible for vaccination as denominator. Measles vaccine effectiveness level was determined using field evaluation approaches of vaccine effectiveness. The adjusted vaccine effectiveness was calculated using the multivariable logistic regression after adjustment of potential confounders, including age, sex, residence, and outbreak year.

Results: Measles vaccination coverage for both vaccine doses showed variation across geographic locations, time periods with clear seasonal and monthly differences. A total of 3417 participants comprising 2528 cases and 889 controls were enrolled in the analysis of measles vaccine effectiveness. A cumulative vaccine effectiveness estimates was 67% in the region with a clear variation across different years. The subgroup analysis showed comparable level of measles vaccine effectiveness (66.6% vs 66.9%) between males and females. The higher level of measles vaccine effectiveness estimates, 76.2%, among children aged 9 months-2 years while lower vaccine effectiveness estimates, 41.1%, was demonstrated among individuals aged ≥15 years.

Conclusion: It was identified a high and increasing administrative measles vaccine coverage with geographical disparities. The estimated overall vaccine effectiveness level was low far apart from the expected level of protection against the vaccine coverage. Two vaccine doses administered individuals had a higher protection level than a single dose received individuals. There was a better vaccine protection level during the recent periods of vaccination compared to earlier periods. Therefore, it is important to increase the access of vaccines to the most unreachable areas maintaining vaccine integrity during delivery. Vaccine coverage should be monitored based on the head count of legible children in each district in the region. It is also important to strengthen the routine measles vaccination practices in any situations and booster dose should also be administered for those older age children.

Background

Measles is a highly contagious and a vaccine preventable infectious disease characterized by high fever, cough, coryza, conjunctivitis and the appearance of a maculopapular rash (1). It is caused by measles virus that has a high attack rate of over 90% among susceptible close contacts (2) causing serious

illness, lifelong complications and death (3). Measles virus is a single-stranded, negative-sense RNA virus in the family Paramyxoviridae and genus Morbillivirus with a typical genome size of 15,894 nucleotides which encodes six structural and two non-structural proteins (2, 4-7).

Measles affects all population groups and can lead to lifelong complications including blindness, encephalitis, long-lasting immune suppression, or even death (8, 9). Every year, between 15,000-60,000 cases of blindness are reported globally due to measles (2, 10). Pregnant women infected with the virus are also at risk of severe complications, and the pregnancy may end in miscarriage or preterm delivery (11). Once the disease progresses, the immunosuppression caused by measles virus exposes infected individuals to bacterial superinfections that can lead to otitis media, pneumonia, or gastrointestinal infections (11, 12).

Measles is primarily prevented through global immunization program with widely accessible, safe, and highly effective live attenuated vaccines administered in two doses routine vaccination program (8, 13, 14). The first dose, measles containing vaccine dose 1 (MCV1), is given at nine months of age or before the child turns 12 months old upon visiting a health facility (8, 11, 13). The second dose, measles containing vaccine (MCV2), is administered at 15 months of age if MCV1 was given at 9 months or if MCV1 was administered at or after 15 months, there should be a minimum four-week interval between the two doses until the child reaches 23 months old (13).

Globally, effective measles epidemic prevention and control strategy was employed through global immunization program that require a high vaccination coverage with two doses of the measles vaccine aiming for coverage above 95% (15). In this regard, there has been a global progress with the coverage for the first dose of measles-containing vaccine (MCV1) increasing from 72% to 85%(16).

Ethiopia also took a significant improvements in the coverage measles vaccine and incorporation of the second dose of the measles vaccine (MCV2) in the routine immunization program in February 2019 (17). According to measles national and regional annual reports, there has been a notable improvement in the coverage for both MCV1 and MCV2. In 2019, the MCV1 and MCV2 coverage was 91% and 47%, increased to 96% and 84% in 2022 respectively. Similarly, in the Amhara region, the coverage for MCV1 and MCV2 has increased from 84% and 56% in 2019 to 86% and 82% in 2022 respectively.

Implementation of measles prevention and control strategies and increasing trend of measles vaccine coverage expected to brought significant reduction of measles outbreaks. However, the burden of the diseases is still increasing (16). In African continent, an estimated 52,600 people died from measles and most cases were contributed from sub-Saharan countries in 2018 (17). More recently, between January-March 2022, almost 17,500 cases of measles from twenty countries were reported in the African region, marking a 400% case increasement and eight more countries reported compared to the same period in 2021 (18). Several countries in Africa also reported measles epidemics in the year 2019, more than 310,00 measles cases and 6,000 deaths in Democratic Republic of Congo; 5,724 measles cases 83 deaths in the Central African Republic and 26,623 measles cases 259 deaths in Chad were recorded (19).

In Ethiopia, measles diseases which is also called as "*kufugn (ኩፍኝ)*" or "*ankelis (አንቀሊስ)*" or "*alemoche (አለሞች)*" in the local language caused frequent outbreaks as indicated the 157% increments of confirmed cases in 2023 compared to 2022 (20) and 230 deaths, with a case fatality rate of 0.77% during the 2024 (21). Its incidence and the number of affected woreda with measles outbreaks increased from time to time as indicated in different earlier evidences (22, 23). Persistent and recurrent measles outbreaks reported from 52 Woredas in 2021 and 125 Woredas in 2022. In the same year, the nationwide measles incidence rate was increased to 82 cases per one million population (22). Regional surveillance data also revealed that the incidence of measles cases has raised from year to year in Oromia region (24), in West Arsi, 3.4/100,000 during 2011-2014 to 14/100,000 in 2015(25), in Tigray 39/100,000 in 2012 to 77/100,000 in 2015 (26).

Similarly, Amhara region also faced similar trend of measles cases that the number of confirmed measles cases rose dramatically from seven cases in 2004 to 611 cases in 2014, affecting all administrative zones of the region (27). The burden of measles still remained high in the region documenting over 152 measles cases affecting 112 districts and all administrative zones within the region according to the regional report. This situation in Amhara region is exacerbated by local conflicts causing internally displacement of populations (IDPs) that coupled with overcrowded living conditions, creates an environment conducive to frequent measles outbreaks.

The frequent measles outbreaks could be associated with low herd immunity within the population due to low vaccine coverage and its protective effectiveness. The reduced vaccine effectiveness particularly in developing countries, is often linked to inadequate cold chain maintenance, improper vaccine handling in the field, improper route of vaccine delivery, coverage, vaccine dosage (28), and malnutrition (29).

Previous researchers has reported in Ethiopia on level of measles vaccine effectiveness for a single dose reported as 75.3% (30), far apart from the target. This report lacks disaggregation by sex, age category and lasted decades which couldn't indicate the current situation. However, in Amhara region, there was no report on measles vaccine coverage and its level of effectiveness.

Understanding the combined insight on vaccine coverage and level of measles vaccine effectiveness provides evidence on vaccine vulnerabilities remained to further address the gaps and determine whether population is truly protected with administered vaccines in the region. Besides, it provides evidence to correlate vaccine coverage against its effectiveness in the measles prevention and control efforts in the region. Therefore, this study was conducted to determine measles vaccine administrative coverage and estimate the level of protective effectiveness in the Amhara region.

Materials and Methods

Study Design and period

We have conducted a retrospective analysis of regional DHIS2 data to determine the regional administrative coverage and its trend of two doses of measles vaccines from 2019-2024 in the Amhara

region. Besides, we analyzed the measles retrospective regional measles laboratory surveillance data to estimate the effectiveness of the measles vaccine against laboratory-confirmed measles infection and its annual trend using test negative case-control study design. We have used the regional measles laboratory surveillance retrospectively from January 1, 2019 to December 31, 2024.

A test-negative case–control design (TND) involves comparing the odds in vaccine receipt among symptomatic persons who test positive compared to those who test negative (31). Participants who have tested positive for measles virus infection with positive ELISA test using serum/plasma samples was considered as cases whereas participants who had tested negative for measles ELISA test were considered as controls. The exposure of this test negative case control study design was considered as the vaccination status of individuals enrolled in the analysis for at least one doses of measles vaccine (Fig. 1).

Figure 1: Test-negative case control study design for assessment of measles vaccine effectiveness

Study Area

The study was conducted in the Amhara Regional State, the second most populous region in Ethiopia with over 22 million people and an area of 170,752 square kilometres (32). The region has 13 administrative zones, 8 administration towns, 238 *Woredas*, and 3966 *Kebeles* (Fig. 2**)**. The region has 98 hospitals, 917 health centres, and 3725 health posts in the government system, along with 11 private hospitals and over 2595 private clinics (33). The region's altitude ranges from 500 m to 4543 m above sea level. It is bordered by Tigray, Afar, Oromia, Benishangul-Gumuz regions in Ethiopia, and neighbouring country Sudan to the west and north west direction (34).

Figure 2: Geographical maps of zones in Amhara region

Source Population

All individuals in Amhara Regional State were the source population. All measles suspected individuals meeting WHO case definition of measles, with rash persisting for three days, high temperature, and cough, or coryza, or conjunctivitis, were included in the study.

Study Population

To determine the measles vaccine coverage, we extracted the DHS2 data base for those children reported to vaccination of MCV1 and MCV2 during the study period to determine measles vaccine coverage. Similarly, to estimate the level of measles vaccine effectiveness, we extracted the regional measles surveillance database for those tested for IgM antibody with aged nine months and above during the study period in the region.

Case definitions

We utilized the following definitions of cases based on National Measles/Rubella surveillance guideline, adopted based on the WHO/AFRO Measles and Rubella surveillance guideline:

A Measles Outbreak: The occurrence of three or more laboratory confirmed measles cases in a defined community or geographical area such as kebele, woreda, or health facility catchment area within a period of one month with epidemiological linkage between cases.

Suspected Case: Any person with generalized maculopapular (non-vesicular) rash lasting for ≥3 days and fever (≥38.3°C/101°F) and one of cough, coryza (runny nose), or conjunctivitis (red eyes) OR any person in whom a clinician suspects measles.

Clinically Compatible/Confirmed Case: A suspected case that has not been laboratory-confirmed but meets all clinical criteria without epidemiological linkage.

Laboratory-Confirmed Case: A suspected case which has a laboratory result with positive measles-specific IgM antibody test or isolation of measles virus in culture or detection of measles virus RNA by real time polymerase chain reaction indicating infection.

Epidemiologically Linked (Epi-linked) Case: A suspected measles case without sample collection that has linked with laboratory confirmed cases in place, person, and time living in the same or in an adjacent district with confirmed case and the onset of rash of the two cases being within 30 days each other.

Discarded cases: A suspected case which, upon adequate investigation that includes a blood specimen collected in the appropriate time frame, lacks measles-specific IgM antibody test with the absence of epidemiological linkage to a confirmed case.

Vaccination Status: The persons with a documented history of receiving measles containing vaccine, and it is classified as unvaccinated for those with no documented history of vaccination; vaccinated one dose for those with a history of receiving measles vaccine for a single dose; vaccinated two doses for those with a history of receiving two vaccine doses; and vaccinated unknown dose for those who had a history of receiving vaccine but unknown vaccine doses

Inclusion and exclusion criteria

All measles cases with IgM result with age of nine months and above were recruited to the analysis of measles vaccine effectiveness evaluation. Measles cases aged less than nine months were excluded from analysis.

Study Variables

Vaccination coverage, vaccine effectiveness level, and measles IgM status were independent variable. Age, sex, residence, vaccination status, and vaccination dose administered were the independent variables

Sampling technique and recruitment

Since 2014, Ethiopia has initiated efforts to control measles by implementing a measles surveillance system to detect and monitor disease outbreaks, following the recommendation of the World Health Organization (35). This system involves the surveillance and reporting of suspected measles cases in all healthcare facilities, including hospitals, health centers, clinics and in the community. As part of this surveillance program, blood specimens were collected from suspected measles cases for identification of the pathogen that causes the illness within the facility and or community The collected specimen is then sent to the reference laboratory for measles immunoglobulin M (IgM) ELISA testing. As a routine measles surveillance program in the Amhara region, all samples from measles suspected cases sent to Amhara Public Health Institute virology reference laboratory, Measles/rubella laboratory. At the regional level, the results of the measles samples were collected, analyzed, and results were reported back to the corresponding surveillance officers at the zone, woreda, and facility levels for appropriate case management.

As part of this effort, all individuals suspected for measles cases who seek care at health facilities and suspected cases in the community in the Amhara region, regardless of age and gender, were included in the study using the surveillance system. Sampling of study participants in all health facilities and community was performed using purposive sampling technique recruiting all measles suspected individuals identified by the surveillance system, regardless of age and sex. Every individual who met the WHO measles case definition during the study period was included in the study.

Data source and data collection mechanism

Ethiopia has implemented a measles surveillance system to detect and manage outbreaks nationwide, following WHO guidance and recommendations since 2014. As part of this system, any suspected cases identified within healthcare facilities and the community were investigated for appropriate case management that assist also to prevent further spread of the disease. In this context, demographic, clinical, and vaccination-related information was collected by health professionals through a measles case-based form, along with blood and nasopharyngeal swab samples from any measles suspected cases.

Data were collected by trained health professionals working in different health facilities in different zones in the region. Vaccination histories were collected by reviewing all available records such as vaccination cards, medical records, or immunization registries and by asking the individual, guardians/parents (in case of children) for details about their vaccination history like the dates and

dosages of vaccination. The collected samples, along with the case-based forms, were sent to the laboratory for measles serological confirmation as soon as possible. In the Amhara region, as part of the national measles surveillance program, five milliliters blood samples along with completed measles case-based data, were received by Amhara Public Health Institute (APHI), Bahir Dar, from anywhere in the region where measles suspected cases have been identified. The received measles case-based data were entered into the regional measles surveillance database using Epi Info version 7 and is used for further analysis.

Sample collection and Transport

Blood samples together with measles case-based data were collected from measles suspected cases. The blood was collected approximately 5ml from measles suspected individuals within the first few days after onset of rash. This was performed using any test tube labeled with a unique patient identifying code. The optimum time-point for collection of serum was three days after the onset of symptoms (fever and rash) during which more than 90% of cases become measles IgM positive. IgM antibody levels peak after about 7-10 days and then decline rapidly. These samples were used to test for measles virus-specific IgM antibodies. After 30 minutes of collection, the blood samples were centrifuged to separate the serum or plasma. The serum/plasma then transferred to nunc tube and stored at temperatures between 2-8°C for a maximum of 2 days at collection sites.

All samples were transported in a triple packaging system, following national and international regulations for sample packaging and transportation ensuring samples packaging with sufficient volume, with no leakage of the container, and protected from possible external contamination. Samples were transported at 2-8°C using ice packs in triple packaging and transported and delivered to testing site within 3 days of collection. To reduce or avoid the number of freezing and thawing, samples were stored at the same shipping temperature, 2-8^{O}c, at the sample collection health facility before transportation to testing laboratory. Serum/ plasma samples were then tested for measles ELISA test immediately within 2 days of receival unless stored at -20^{O}c if anticipated to delay testing.

Measles laboratory analysis

Measles-specific IgM antibodies were detected using EUROIMMUN Ant-Measles Virus ELISA (IgM) ELISA kits, Lubeck, Germany with a 100% sensitivity, 98% specificity at APHI's WHO-standardized virology laboratory. The Amhara Public Health Institute Measles/Rubella laboratory in Virology Reference laboratory adheres to the standards and protocols set forth by the World Health Organization (WHO) revised in 2015 (36) and operates as a sub-national measles laboratory in the Amhara Regional State, Ethiopia. Annually, the laboratory receives external quality assessment (EQA) panel samples from WHO, achieving a perfect score of 100% in all evaluations. Furthermore, on a quarterly basis, it dispatches 10% of its samples to the Ethiopian national measles laboratory for inter-laboratory comparison, consistently

attaining a 100% concordance rate with the national laboratory result for all samples. Since 2018, the laboratory has been accredited with the ISO 15189 standard by the Ethiopian Accreditation Service (EAS) and has successfully maintained its accreditation through four consecutive assessments until 2024.

To detect measles IgM antibodies in a sample, microtiter wells of plates coated with measles antigen. The serum sample then added to the well and any specific IgM antibodies to measles virus in the test sample bind to the bound antigen. After the removal of unbound material, measles reactive IgM antibodies in the samples then detected using a commercial peroxidase enzyme-labelled anti-human IgM (goat). After washing to remove unbound conjugate, a colorless TMB/H2O2 chromogen/substrate is added. This reacts with the conjugate to produce a color change. Then, sulfuric acid, 0.5M, stop solution was added to stop reaction between substrate enzyme. The optical density (OD) of this colored product then read at 450 wavelengths after 650 wavelengths reference reading using Gene5 reading software in ELISA reader (ELx800). The color product intensity quantified photometrically and is proportional to the level of IgM antibody bound.

Quality Control

The reliability of the study findings was guaranteed by implementing Quality Control (QC) measures throughout the whole process of data collection and the laboratory work. Socio-demographic, clinical data related to the study and vaccination data were collected using the semi-structured questionnaire customized from measles case-based form used in the routine measles surveillance. The socio-demographic, clinical data related to the study and vaccination data were collected by well-trained health professionals who were involved in the measles surveillance program.

All materials, equipment and procedures and job aids were adequately followed. Pre-analytical, analytical and post-analytical stages of quality assurance activities and standard operating procedures (SOPs) were strictly followed. In measles ELISA testing, negative, positive, inhouse positive controls and calibrators were used in each run with the following acceptance criteria for Controls and calibrators: OD of the calibrator must be in the range given on the quality control certificate of the manufacturer leaflet; positive control ratio must fall within the range in quality control certificate; and negative control ratio must fall within the range given on the quality control certificate.

Data organization, processing, and analysis

All data collected were entered into EPI-info version 7 and were exported to SPSS version 26 for statistical analysis after performing a rigorous data cleaning procedure. Our analytical approach included descriptive statistics, such as frequencies and incidence rates, annual trends, monthly variations. To determine the incidence of measles per 100,000 population at risk, we used the annual projected population estimated from the Central Statistical Agency (CSA) of Ethiopia for each woreda,

zone, and region population as the denominator and the number of confirmed measles cases were used as the numerator in a yearly basis.

We determined the measles vaccine administrative coverage for two doses of measles vaccine by using the number of children who have received the measles vaccine for a specific measles dose as the numerator and the estimate of eligible children expected to be vaccinated at the specified period and place as denominator. The administrative coverage was expressed in terms of percentage. The estimate of eligible children population expected to receive a specific does of measles vaccine was determined by estimating the target population in each year from preceding year target population using the population estimation factor obtained from the CSA for Amhara region.

Univariate and multivariate binary logistic regression was conducted to determine the crude and adjusted odds of vaccinated against unvaccinated measles suspected cases for acquiring measles infection which was used to determine the level of measles vaccine effectiveness. The crude and adjusted level of measles vaccine effectiveness among vaccinated individuals in comparison with unvaccinated individuals was derived from the crude and adjusted odd ratio values based on the formula of (1-crude/adjusted odd ratio) x100. Measles vaccine effectiveness adjustment was performed based on age, sex, year of diagnosis and residence.

The results were presented in the form of tables and figures and the results like the incidences, temporal pattern, spatial distribution of measles cases, and the adjusted level of measles vaccine effectiveness was compared to findings from previous studies conducted in Ethiopia and other countries to provide context at different situations. Additionally, the genetic diversity, circulating genotypes, the mutation rate, selection pressure types, and significant neutralizing H gene epitope alterations of the measles virus were compared to other earlier studies in the global context.

Vaccine Effectiveness Determination

Under ideal circumstances, measles vaccine expected to protect up to 85% populations when administered to children at nine months of age (37). Similarly, if the MCV administered at 12 months, studies have found that up to 93% protection and would be increased more if the second dose measles vaccine is administered (38). To determine the level of vaccine effectiveness in the Amhara region situation, we conducted a vaccine effectiveness analysis using the methods described by Walter a. Orenstein et.al. (37) for field evaluation of vaccine effectiveness in large populations. First, the odd of vaccinated individuals was determined by dividing the number of cases in vaccinated individuals to the total number of vaccinated individuals. Similarly, the odd of unvaccinated individuals was determined by dividing the number of cases in unvaccinated individuals to the total number of unvaccinated individuals. The odd ratio was then obtained by dividing the odd in vaccinated to the odds in unvaccinated individuals. Then the vaccine effectiveness was determined based on the formula of 1-odd ratio, i.e., one minus odds ratio. These odds of vaccinated and unvaccinated individuals were determined using logistic regression analysis through SPSS version 26.

Results

Measles vaccinee administrative coverage

The measles vaccine administrative coverage for the first dose measles containing vaccine (MCV1) in the Amhara region has varied from 76% to 100%. The coverage progressed from 89% in 2019 to 90% in 2020 and declined to 76% by the year 2021. In the later periods, it raised to 96%, 97%, and 100% in years 2022, 2023, and 2024 respectively. The cumulative vaccine effectiveness estimates in the Amhara region from 2019-2024 was 67% (56.4-75%) after adjustment with age, sex and Figure 3: Yearly measles vaccination administrative coverage in the Amhara region, Ethiopia, 2019-2024

Measles vaccination coverage monthly trend

The highest vaccination coverage for both doses, MCV1 and MCV2, reported during the months of February-June during the study periods from 2019-2024. The highest peak of MCV2 coverage was reported during the report periods of 2019 and 2022 compared to other reporting periods (Fig. 4).

Figure 4: Monthly measles vaccination administrative coverage in the Amhara region, Ethiopia, 2019-2024

Measles vaccination coverage seasonal analysis

During the report years of 2019, 2020, and 2021, the highest vaccine administrative coverage for MCV1 and MCV2 was reported during the summer season. In 2022, and 2023, the highest MCV1 and MCV2 coverage were reported within the spring seasons while in 2014, it was during winter seasons. In contrast to this, the lower MCV1 and MCV2 coverage was reported during various seasons within the study periods. During the years 2019, the lowest MCV2 coverage was achieved during winter season. Similarly, during the years of 2020 and 2021, the lowest MCV1 and MCV2 coverage was reported during spring, and autumn seasons (Fig. 5).

Figure 5: Measles vaccination administrative coverage in different seasons in the Amhara region, Ethiopia, 2019-2024

Measles vaccine coverage zonal disparities

The vaccination coverage for MCV1 has shown a variability among different zones. Some zones have reported constantly high above 85% in all years including Bahir Dar town, Oromo zone, Debre Berhan, and Debretabor towns. Some zones including Central Gondar, Dessie town, East Gojjam, North Gondar, and South Gondar zones has also reported above 85% in all periods except during the year 2021 with a coverage of 83.1%, 79.6%, 73.6%, and 83.4% respectively. In contrast to this, a relatively lower MCV1

coverage was reported in West Gojjam, North Shoa, South, and North Wollo zones. In North Shoa, the coverage was 66.3% in 2019 with decrement to 62.9% in 2021 and rebound to 87.6% in 2024. In North Wollo, it was varied from 91% in 2019 to 100% in 2024 with an alarming decrement to 49.6 in 2021. Besides, the MCV1 coverage in South Wollo was least, 72.9% in the year 2021 far apart from the coverage among other periods that range from 84% to 100%. More alarmingly, a persistently low MCV1 vaccination coverage was reported in West Gojjam zone varying from 39.9% in 2019 to 81.3% in 2024 (Table 1)

Table 1: Vaccine administrative coverage of MCV1 at zonal level in the Amhara region, Ethiopia, 2019-2024

Zone/town demonstrations	Vaccination coverage (%) in years					
	2019	2020	2021	2022	2023	2024
Awi	83.1	86.7	85.1	87.3	89.2	80.7
Bahir Dar town	125.1	132.9	132.0	125.8	139.8	161.6
Central Gondar	86.3	88.7	83.1	99.0	101.0	93.8
Debre Berhan town	140.8	131.7	108.7	98.3	101.9	108.2
Debre Markos town	100.3	92.8	103.2	88.9	81.4	79.5
Debre Tabor town	105.6	135.5	119.3	102.4	99.1	105.2
Dessie town	90.4	96.1	79.6	105.5	86.2	87.1
East Gojjam	84.4	85.5	85.5	94.9	79.8	103.1
Gondar town	81.8	75.2	70.6	85.3	92.5	91.4
Kombolcha town	107.7	104.0	81.6	99.0	106.3	107.6
North Gojjam	-	-	-	91.0	85.7	87.5
North Gondar	92.8	88.9	73.6	87.6	103.6	99.5
North Shoa	66.3	68.2	62.9	77.2	83.0	87.6
North Wollo	91.0	94.2	49.6	109.7	103.9	101.8
Oromia special	118.3	115.4	92.8	134.3	125.6	127.9
South Gondar	86.9	87.6	83.4	95.8	93.9	93.7
South Wollo	84.4	85.4	72.9	108.1	98.7	99.4
Waghimra	101.4	101.0	73.0	99.7	96.1	110.7
West Gojjam	39.9	42.2	43.2	71.8	79.0	81.3
West Gondar	84.9	94.3	80.5	110.3	115.0	102.2
Woldiya town	98.0	84.1	96.5	88.0	78.4	107.0

The second dose measles vaccine coverage showed an increasing coverage in all zones in the region. In most town administrations, higher MCV2 coverage was reported compared to other zones. However, a comparatively low MCV2 coverage reported in zones like East Gojjam, Gondar town, Kombolcha town, North Shoa, North Wollo, South Gondar, and West Gondar Zones. In West Gojjam Zone, persistently lowest MCV2 vaccination coverage varying from 31.9% in 2020 to 68.8% in 2024 was reported (Table 2)

Table 2: Vaccine administrative coverage of MCV2 at zonal level in the Amhara region, Ethiopia, 2019-2024

Zone/town administrations	Vaccination coverage (%) in years					
	2029	2020	2021	2022	2023	2024
Awi	102.7	74.5	71.6	77.6	78.9	72.2
Bahir Dar town	63.6	100.6	108.3	107.9	117.1	135.6
Central Gondar	77.3	63.0	63.1	109.0	96.3	88.0
Debre Berhan town	135.2	103.2	85.7	86.0	93.4	99.5
Debre Markos town	96.3	73.5	86.0	82.4	70.4	70.2
Debre Tabor town	62.0	96.2	98.1	88.9	86.6	96.9
Dessie town	69.5	84.2	63.6	83.8	70.7	78.0
East Gojjam	83.3	64.0	73.0	86.0	72.8	92.8
Gondar town	63.1	50.7	52.7	78.1	69.9	80.5
Kombolcha town	60.0	74.4	76.9	83.0	91.1	101.9
North Gojjam	-	-	-	81.9	74.3	80.3
North Gondar	93.1	59.5	54.5	92.8	82.1	89.0
North Shoa	58.4	60.8	53.4	70.7	75.3	81.9
North Wollo	70.2	70.0	39.7	104.3	83.9	90.1
Oromia special	139.8	124.1	73.1	142.7	104.9	121.0
South Gondar	60.0	49.7	60.5	101.1	81.2	82.2
South Wollo	88.6	63.8	63.2	105.3	90.3	94.3
Waghimra	115.1	86.5	63.2	92.3	77.9	96.2
West Gojjam	32.3	31.9	35.9	63.6	67.9	68.8
West Gondar	72.9	48.2	54.6	102.4	90.1	85.3
Woldiya Town	34.0	50.8	73.2	124.3	54.5	80.3

Demographic characteristics of vaccine effectiveness study participants

A total of 3417 participants comprising 2528 cases and 889 controls were enrolled in measles vaccine effectiveness analysis. The distribution of study participants with regard to gender revealed that 1714 (50.2%) were females and 1703 (49.8%) were males. The age distribution also revealed that many of participants, 1307(38.2%) were within the age of 5-14 years followed by 9 months-2 years, 884 (25.8%).

Majority off the participants 2200 (64.4%) were vaccinated for at least one dose of measles vaccine. Among vaccinated participants, large proportion of participants, 936 (42.5%) were vaccinated the first dose followed by vaccinated participants with unknown dose, 795 (36%) (Table 3).

Table 3: Demographic characteristics of cases and control of measles vaccine effectiveness study in symptomatic measles suspected cases in the Amhara region, Ethiopia, 2019-2024

Variable	Category	Cases (n=2528)	Controls (n=889)	Total (n=3417)
Sex	Female	1251	463 (	1714 (
	Male	1277	426	1703
Age	9 months-2 Years	705	179	884
	3-4 years	383	141	524
	5-14 years	880	427	1307
	>=15 years	542	120	662
Vaccination Status	Unvaccinated	1033	184	1217
	Vaccinated	1495	705	2200
Vaccine dose	one dose	846	90	936
	Two doses	425	44	469
	Unknown dose	224	571	795
Zone	Bahir Dar city	5	19	24
	Awi	632	47	679
	Central Gondar	184	39	223
	Debre Berhan town	43	29	72
	Debre Markos town	20	16	36
	Debre Tabor town	0	6	6
	Dessie town	5	19	24
	East Gojjam	358	184	542
	Gondar town	12	40	52
	Kombolcha town	34	3	37
	North Gojjam	60	57	117
	North Gondar	40	15	55
	North Shoa	209	14	223
	North Wollo	261	61	322
	Oromo	223	14	237
	South Gondar	230	137	367
	South Wollo	55	86	141

	Waghimra	58	39	97
	West Gojjam	89	52	141
	West Gondar	10	12	22
Year	2019	94	88	182
	2020	48	56	104
	2021	111	117	228
	2022	661	266	927
	2023	1539	268	1807
	2024	75	94	169

Vaccine effectiveness Analysis

The cumulative vaccine effectiveness estimates in the Amhara region from 2019-2024 was 67% (56.4-75%) after adjustment with age, sex and year. The cumulative measles vaccine effectiveness among those received with one, two, and unknown dose was 16.9, 61.5%, 73.2% respectively (Table 4)

Table 4: Cumulative vaccine effectiveness level and vaccine effectiveness among various vaccine doses in the Amhara region, 2019-2024

Characteristics	Category	COR	AOR	Vaccine effectiveness, % (95%CI)	
				Crude	Adjusted
Vaccination status	Vaccinated	0.321	0.33	67.9 (59.9-74.4)	67 (56.4-75)
	One dose	0.743	0.831	25.7 (-4-47)	16.9 (-20.2-42.5)
	Two doses	0.376	0.385	62.4 (36.8-77.6)	61.5 (30-78.8)
	Dose unknown	0.25	0.268	75 (68.2-80.4)	73.2 (65.1-79.4)

Subgroup analysis of measles vaccine effectiveness by sex, age and year

The subgroup analysis showed comparable level of measles vaccine effectiveness between males and females, with adjusted level of measles vaccine effectiveness estimates of 66.6% and 66.9% respectively. Age-specific analysis revealed the highest level of measles vaccine effectiveness estimate among children aged 9 months-2 years (76.2%) and 5-14 years (73.3%), while vaccine effectiveness estimate was notably lower in individuals aged ≥15 years (41.1%). The age group 3-4 years old subgroup analysis showed vaccine effectiveness estimates of 62.7% (0.6-86%) with wide confidence intervals (Table 5).

Yearly trends demonstrated fluctuating vaccine performance. The highest adjusted level of measles vaccine effectiveness was observed in 2022, 89.5% (77.4-95.1%), followed by 2021, 80.8% (41.7-93.7%) and 2023, 75.6% (58.1-85.8%). In contrast, the vaccine effectiveness estimates during the year 2020 was very low, 6.6% and statistically non-significant, with a wide confidence interval. Besides, the vaccine effectiveness estimates in the year 2024 declined to 55.3% (-16.8-82.9%) with a wide CI, indicating reduced sample size in this category (Table 5).

Table 5: Measles vaccine effectiveness level subgroup analysis by age, sex, and year in the Amhara region, 2019-2024.

Characteristics	Crude OR	Adjusted OR	Vaccine effectiveness, % (95%CI)	
			Crude	Adjusted
Sex				
Female	0.314	0.334	68.6 (56.9-77.1)	66.6 (50.4-77.5)
Male	0.322	0.331	67.8 (55.6-76.7)	66.9 (50.2-78)
Age				
9 months-2 years	0.247	0.238	75.3 (50.1-87.8)	76.2 (42.3-90.2)
3-4 years	0.619	0.373	38.1 (-30-70.7)	62.7 (0.6-86)
5-14 years	0.259	0.267	74.1 (61.7-82.4)	73.3 (58.2-82.9)
>=15 years	0.599	0.589	40.1 (6.1-61.8)	41.1 (0.4-65.2)
Year				
2019	0.357	0.291	64.3 (34.7-80.5)	70.9 (40-85.9)
2020	0.988	0.934	1.2 (-113.8-54.3)	6.6 (-132.8-62.5)
2021	0.273	0.192	72.7 (43.8-86.7)	80.8 (41.7-93.7)
2022	0.222	0.105	77.8 (62.4-86.9)	89.5 (77.4-95.1)
23	0.307	0.244	69.3 (54.1-79.5)	75.6 (58.1-85.8)
2024	0.375	0.447	62.5 (25.8-81.1)	55.3 (-16.8-82.9)

Discussion

The administrative coverage for the first dose of measles vaccine surged from 89% to 100% during the period from 2019 to 2024, with the notable exception of a decline to 76% in 2021. The administrative coverage for the second dose of the measles vaccine (MCV2) also experienced a downturn, falling from 79% in 2019 to 67% in 2021. However, it subsequently rebounded to exceed 85% in the later periods.

The declined MCV1 coverage in the year 2021, coupled with the declining trend of MCV2 coverage between 2019 and 2021 underscores the accumulation of substantial susceptible populations, thereby precipitating recurrent outbreaks within the region. This might be related with the disruption of the health system in relation to the pandemics of COVID-19 and local conflicts in Amhara region. The measles vaccination programs had been disrupted by the pandemics of COVID-19 during these periods as witnessed by different earlier evidences (39, 40).

The highest vaccination coverage for both doses, MCV1 and MCV2, reported during the months of February-June during the study periods from 2019-2024. The high measles vaccine coverage during the months of February to June might reflect the delivery of vaccines for eligible children during the reactive vaccination campaigns carried out in response to increased measles cases and outbreaks as these periods were reported as the peak periods for measles cases and outbreaks in the region (41, 42). Similarly, the measles vaccine administration was boosted in other settings globally during the temperate seasons during which peak reports of the measles cases and outbreaks registered (43, 44)

The MCV1 and MCV2 coverage among town administrations was high above 85% and relatively reduced coverage among zones consisting many rural districts and kebeles. The high coverage of measles vaccine in town administrations might be related to easier access to health facilities for vaccination services in that the towns have a better infrastructure, access to transport and closer proximity of health facilities to vaccination services as supported by earlier evidences in Ethiopia (45, 46), Kenya (47), Senegal (48), and Senegal (49). Measles vaccine coverage at zonal level analysis showed a persistently low measles vaccine coverage in West Gojjam zone among all administrative zones in the Amhara region. The lowest coverage report in west Gojjam zone might be related with weak coordination of immunization programs at the zonal health department and woreda level to immunize all eligible children including children residing in unreachable and pocket areas within the zone. This imposes the accumulation of the high number of susceptible populations within the zone that would also be the source for measles outbreak for adjacent neighbouring zones in the region.

Measles vaccine effectiveness in the region during the last six years was estimated to be 67% (56.4-75%) after adjustment with age, sex and year. This implies that only 67% of vaccinated individuals were protected from the measles infection leaving 33% of vaccinated individuals unprotected regardless of the administered vaccine doses predisposing the accumulation of pool of susceptible individuals in the region. This estimate of measles vaccine effectiveness in the Amhara region is comparable with the earlier studies in Guinea-Bissau (50), Uganda (51), and Ethiopia (52) with measles vaccine effectiveness level of 66%, 74%, and 71.9% respectively. Similarly, a comparable estimate of measles vaccine effectiveness was also reported in earlier meta-analysis of pooled measles vaccine effectiveness estimate of 69.97% among African children (53).

In another hand, the current estimate of measles vaccine effectiveness in this report is much far apart from the expected 85% effectiveness level for a single dose measles vaccination as indicated in evidences from WHO weekly report (54, 55). Besides, it is lower than earlier reports indicated in Nigeria

(56), Egypt (57), Gambia(58), Kenya (59), and Tanzania (60) in African countries and Germany (61), Australia (62), Bosnia and Herzegovina (63), Bangladesh (64) in developed countries. This discrepancy might be associated with the variation in socio-economic, geographical scope, socio-cultural, technological, and health system strengths. The socio-economic status of the population in the current setting is under the living standard imposing for low access to measles vaccine that result a reduced vaccine coverage leaving a high pool of susceptible population. Besides, the current study was limited in specific geographic regions whereas the earlier studies were reported at the wider geographic areas including country level evidences which would

Moreover, the socio-cultural characteristics of the populations especially in the rural areas in the current setting promotes other alternatives like religious prayer healing rather than vaccinations which could underpromote the vaccination coverage. Besides to this, there is limited infrastructure and technology including the cold chain system to assist the transportation and storage of vaccines at the rural clinics and health facilities. The insufficiency in the delivery and storage of vaccines could lead to the loss of the vaccine integrity resulting a diminished measles vaccine potency which intern minimize the effectiveness of vaccine to produce protective antibodies among vaccinated individuals.

The health system in the current setting is also weak compared to the developed settings which lags behind to build technically well-equipped man power and deployment of sufficient number of health professionals especially in the remote health facilities. This phenomenon directly affects the quality of measles vaccination practices in maintaining the integrity of the vaccine as well as good vaccine administration routes which could facilitate in the reduction of vaccine coverage and insufficient vaccine dose administration resulting low level of measles vaccine effectiveness.

It is also indicated that the measles vaccine effectiveness varied with administered vaccine doses with estimates of 16.9%, 61.5%, 73.2% among individuals who received one dose, two dose, and unknown doses respectively. The effectiveness estimate increased with the number of vaccine doses administered indicating improved protection with full dose vaccination. The increase of vaccine effectiveness estimates among those who have unknown vaccine dose might be related with the inclusion of vaccinated individuals while they had been actually vaccinated due to the absence of vaccination history. The increase in vaccine effectiveness with additional doses reflects both immunological mechanisms and programmatic factors. The first dose primes the immune system, generating initial antibody responses, while the second dose acts as a booster, consolidating long-term immunity. These findings are consistent with prior evidence indicating that a single dose of measles-containing vaccine (MCV) provides partial protection, whereas two doses significantly enhance immunity, reduce susceptibility to infection, and improve herd immunity (29, 65).

The vaccine effectiveness analysis among males and females showed a comparable (66.6% and 66.9%) effectiveness level. However, the subgroup analysis by age group demonstrated the highest vaccine effectiveness among children aged 9 months-2 years (76.2%) and 5-14 years (73.3%), whereas measles vaccine effectiveness substantially lower among individuals aged ≥15 years (41.1%). This high vaccine

effectiveness level among 9 months to 2 years could be described in association with the effect of measles vaccine administered between 9 months to 1year for the first dose as well as 15 months to 23 months for the second dose that enables production of high concentration of antibodies at early periods of vaccination but waning the immunity during older ages due to long duration after immunization among older aged groups. As the time interval since vaccination increases, the concentration of protective measles specific antibodies gradually declines due to wanning immunity (66, 67). The waning immunity has implications as the gradual reduction in concentration of measles specific antibody increases susceptibility to measles infection among older adolescents and relatively getting older individuals despite their earlier vaccination (66, 68). Similar age specific decline of measles vaccine effectiveness estimate was reported in many earlier evidences in line with our current study (69-71).

The estimated measles vaccine effectiveness in the region also varied substantially across various periods. Lower level of vaccine effectiveness was estimated during the year 2020 followed by 20219 and 2024 with measles vaccine estimate of 6.6%, 70.9%, and 55.3% respectively. On the other hand, the higher estimate of measles vaccine was reported during the year 2022 with effectiveness estimate of 89.5%. Lower effectiveness estimate in these periods could be associated with the disruption of the health system including the surveillance and immunization programs due to movement restriction, health system reallocation, and reduced health care seeking behaviour in relation to COVID-19 pandemics during the 2019 and 2020 and local conflicts in the easter part of the region starting from late 2023 impacting the effectiveness estimate of 2024 (72).

The comparatively higher estimate of measles vaccine effectiveness in the latter periods during post-COVID-19 pandemics especially during the years 2021 and 2022. This might be associated with the reflection of improved service recovery, intensified vaccination campaigns, and outbreak response activities through aggressive implementations in response to the outbreaks during COVID-19 pandemics. The moderate effectiveness estimates during the years 2019 and 2024 suggests the ongoing immunity gaps and residual effects of earlier disruptions underscoring the sensitivity of vaccine effectiveness estimates to programmatic stability and transmission intensity over time (73). In line to this report, globally, the same situations had reported during disruption of health system as a consequence of COVID-19 pandemics (74-76) and local conflicts in Ukraine (77).

Strength and limitation of the study

This current study was conducted on a large sample size, encompassing all reported measles cases in the Amhara regional State over the past six years. It presents pioneering evidence on level of measles vaccine effectiveness in the Amhara region. Moreover, the evidence depicts the estimate of vaccine effectiveness level through sub-group analysis among different age groups, sex, and different years.

However, this analysis has some limitations that needs to consider. The administrative measles vaccine coverage analysis was obtained using the expected number of target children calculated from the total population using the correction factor recommended by the central statistics agency (CSA). The target children population calculated using this factor would underestimate the actual population size resulting

for over estimation of vaccine coverage. Besides, the measles vaccine effectiveness analysis relays on surveillance data which would be biased in the presence of an active surveillance whereas underestimated in the situation of absence of active surveillance. Besides, the analysis was conducted using epidemiological estimation that might not be accurately measured the immune status of the population rather it estimates the vaccine effectiveness level. Therefore, future sero-survey studies should be conducted to determine the immune protection level of measles vaccine using immunological approaches.

Conclusion and recommendation

This study has identified a high level of administrative measles vaccine coverage in the region. The overall estimated level of measles vaccine effectiveness in the Amhara region was very, far apart from the expected level of measles vaccine effectiveness in the Amhara region. The vaccine effectiveness level among those who received two doses of measles vaccine was higher compared to those who received one dose. The vaccine effectiveness level in males was almost comparable with the level in females. Higher level of measles vaccine effectiveness was observed among children aged 9 months-2 years while notably lower in individuals aged ≥15years. Yearly trends of vaccine effectiveness demonstrated fluctuating vaccine performance with highest level of measles vaccine effectiveness observed in 2022 while lowest level reported during the year of 2020.

Therefore, it is important to increase the access of effective measles vaccine to the most unreachable areas with maintaining the integrity of the vaccine during delivery of vaccine to remote areas. The coverage measles vaccine should be monitored based on the head count of legible children in each district in the region. It is also important to improve the transport and storage facilities for measles vaccine at the health facilities after distribution and pharmaceutical warehouses before vaccine distribution to health facilities. Strengthen the routine measles vaccination practices in any health system disruption situations. The booster dose should also be administered for those older age children as the level of measles vaccine effectiveness wanned as the age increased.

Abbreviations

AOR: Adjusted Odd Ratio; APHI: Amhara Public Health Institute; COR: Crude Odd Ratio; COVID-19: Coronavirus Diseases 2019; CSA: Central Statistics Agency; DHIS2: District Health Information System 2; EAS: Ethiopian Accreditation Service; ELISA: Enzyme Linked Immuno-Sorbent Assay; EPI-Info 7: Epidemiological Information version 7; EQA: External Quality Assurance; IDPs: Internally Displaced Populations; IgM: Immunoglobulin M; ISO: International Organization for Standardization; MCV1/2: Measles Containing Vaccine 1/2; RNA: Ribonucleic Acid; OD: Optical Density; QC: Quality Control; SOP: Standard operating procedures; SPSS: Statistical Package for the Social Sciences; TND: Test-Negative case–control Design; WHO/AFRO: World Health Organization/Africa Region Office

Declarations

Ethics approval and consent to participate

The study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical clearance was obtained from the Bahir Dar University Institutional Review Board with protocol number 17/IRB/24. The review board granted waiver for informed consent, as the study utilized anonymized secondary data in compliance with national research regulation. Permission letters were obtained from both Amhara Public health Institute and Amhara Regional State Health Bureau to access and utilize regional measles surveillance data and DHIS2 data base after de-identification.

Clinical Trial

Not applicable

Consent for publication

Not applicable

Availability of data and material

The data used for this research are available at the hands of corresponding author and could be accessed upon reasonable request of the corresponding author.

Competing interests

The authors declare that they have no competing interests

Funding

The authors didn’t receive any specific fund to conduct this research

Authors' contributions

DE: Concept design, Data entry, Data cleaning, Data Analysis or interpretation of data, write up of manuscript, review of the manuscript

DE, EN, AM, and GY: Conceive the manuscript title, review the manuscript, and validated the final manuscript.

EN, AM, GY, FM, ST, TZ, MT, WYG, SDA, KE, DK, BB: Involved in analysis, software work, and reviewing and validating the final manuscript. All authors read and approved the final manuscript.

Acknowledgments

We would like to express our sincere gratitude to Bahir Dar University, the Institute of Biotechnology, and the Health Biotechnology Division for their support in conducting this work. Were also extend our gratitude to the APHI and Amhara region Health Bureau for granting us access to the Amhara Region

measles surveillance data and DHIS2 data base for measles vaccination coverage data. Our heartfelt thanks also goes to the surveillance officers, immunization officers, and healthcare workers across various health facilities in the region for their invaluable efforts in facilitating and collecting the surveillance data.

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Figures

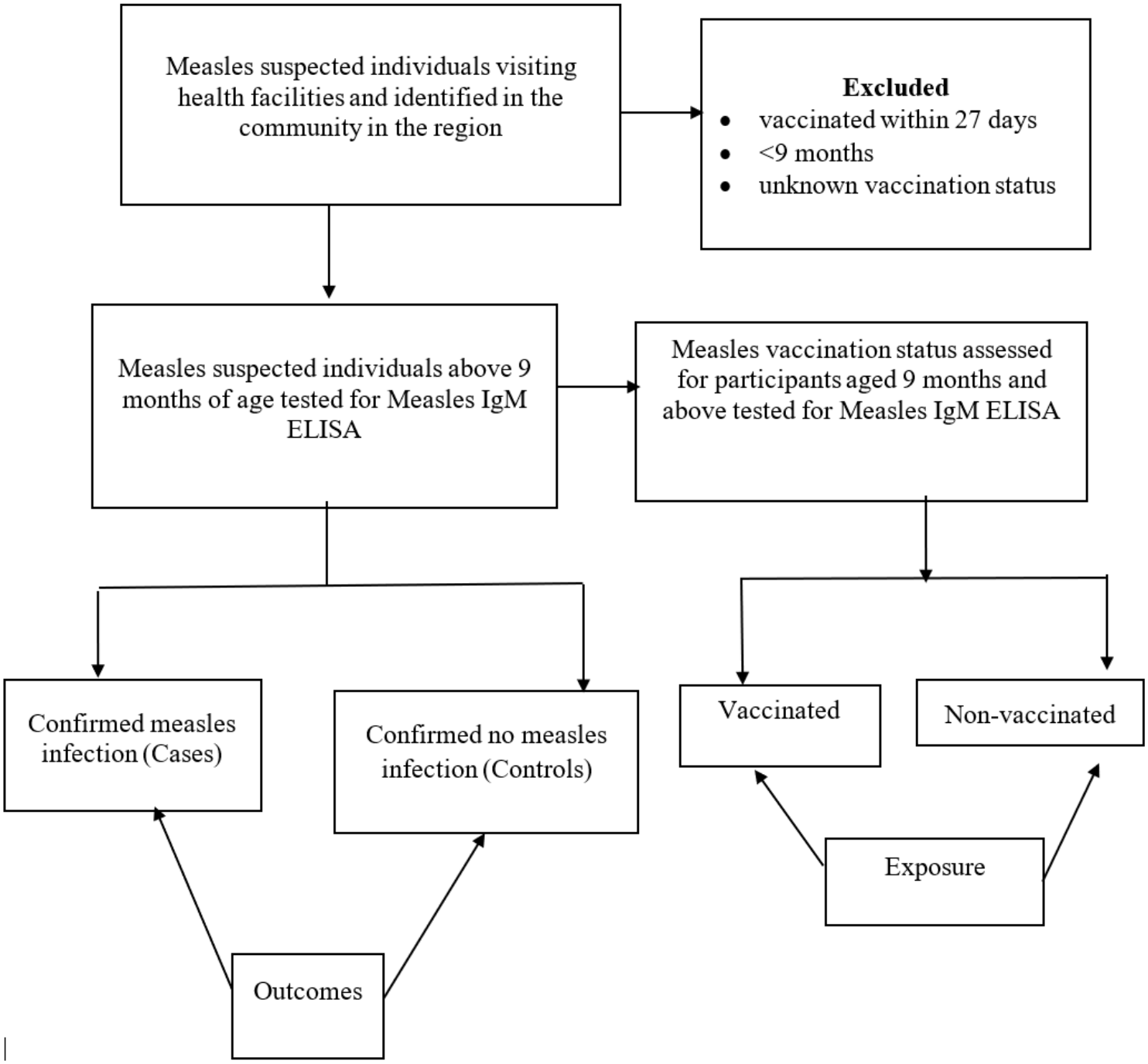


Figure 1

Test-negative case control study design for assessment of measles vaccine effectiveness

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Figure 2

Geographical maps of zones in Amhara region

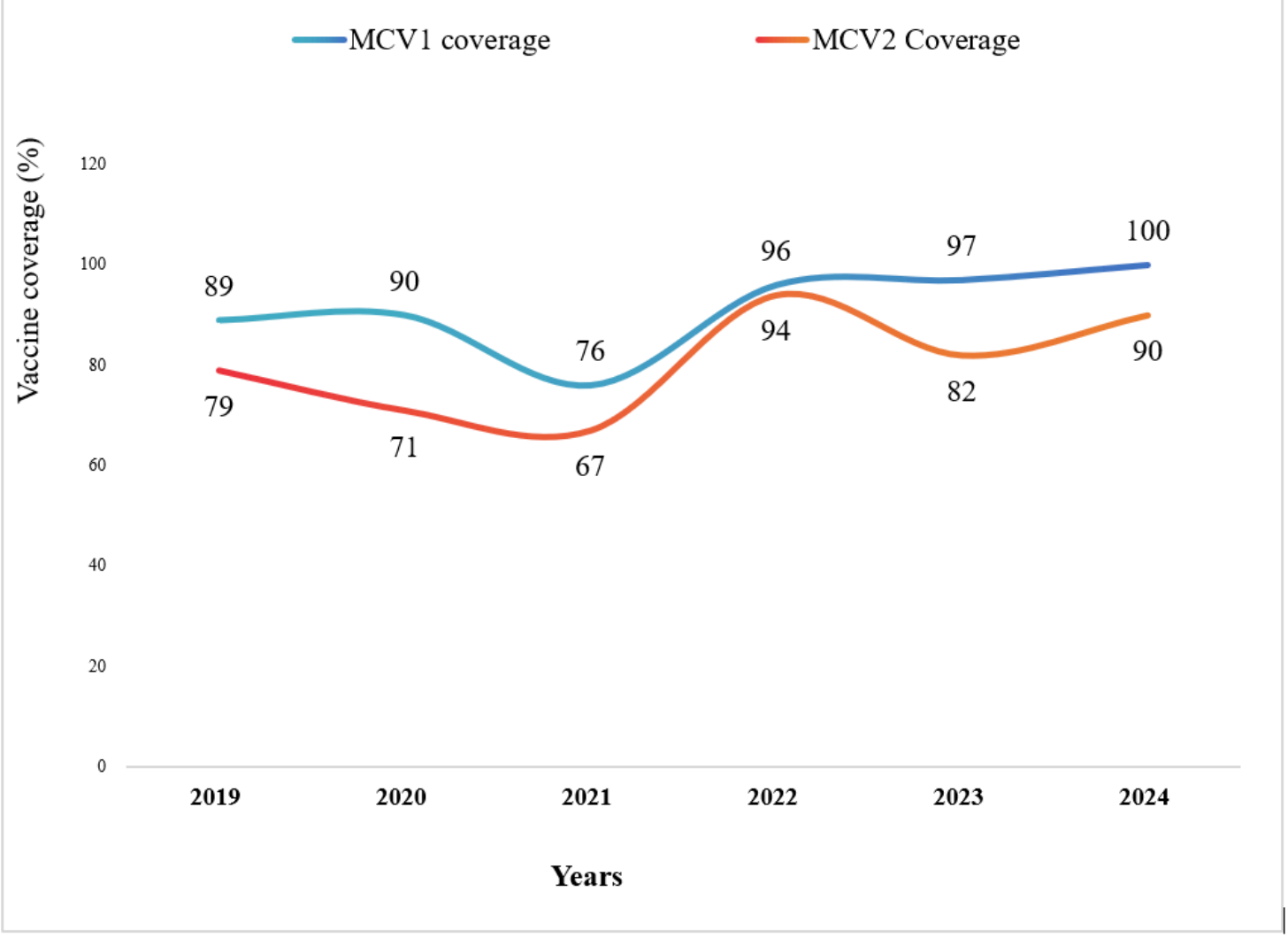


Figure 3

Yearly measles vaccination administrative coverage in the Amhara region, Ethiopia, 2019-2024

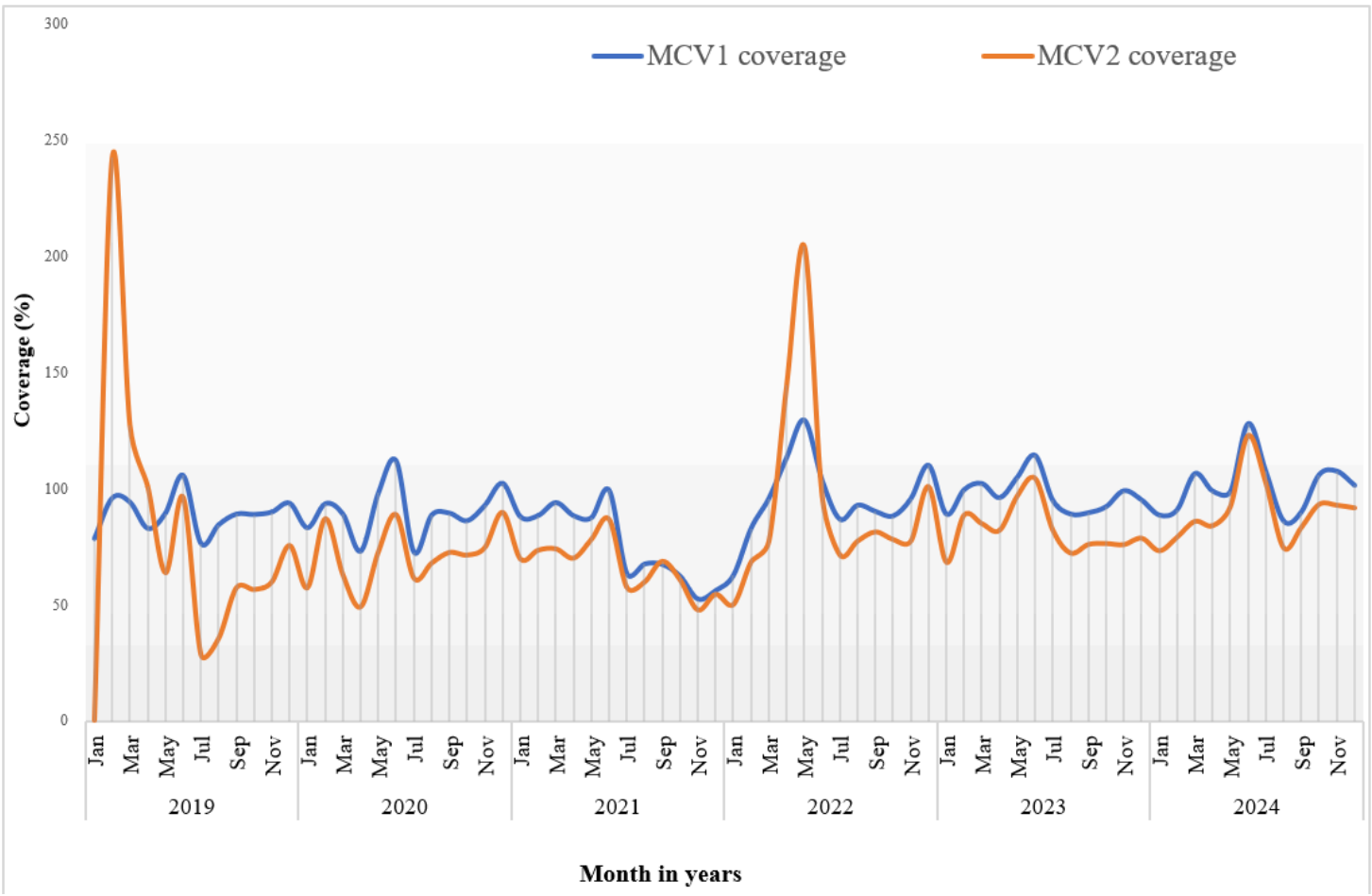


Figure 4

Monthly measles vaccination administrative coverage in the Amhara region, Ethiopia, 2019-2024

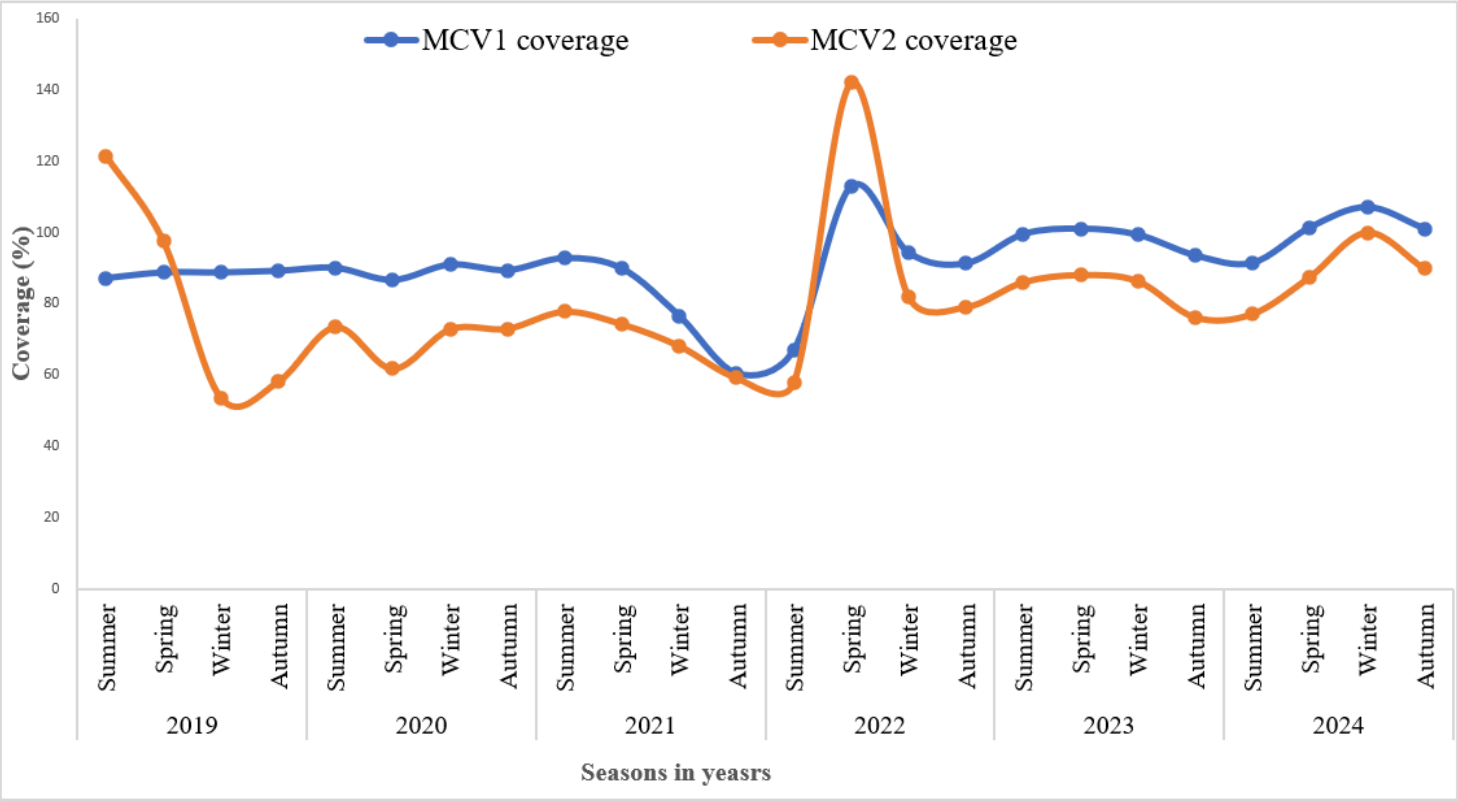


Figure 5

Measles vaccination administrative coverage in different seasons in the Amhara region, Ethiopia, 2019-2024