

Challenges to Achieving Measles Elimination, Georgia, 2013–2018

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Controlling measles outbreaks in the country of Georgia and throughout Europe is crucial for achieving the measles elimination goal for the World Health Organization's European Region. However, large-scale measles outbreaks occurred in Georgia during 2013–2015 and 2017–2018. The epidemiology of these outbreaks indicates widespread circulation and genetic diversity of measles viruses and reveals persistent gaps in population immunity across a wide age range that have not been sufficiently addressed thus far. Historic problems and recent challenges with the immunization program contributed to outbreaks. Addressing population susceptibility across all age groups is needed urgently. However, conducting large-scale mass immunization campaigns under the current health system is not feasible, so more selective response strategies are being implemented. Lessons from the measles outbreaks in Georgia could be useful for other countries that have immunization programs facing challenges related to health-system transitions and the presence of age cohorts with historically low immunization coverage.

The country of Georgia, along with the other member states of the European Region (EUR) of the World Health Organization (WHO), is committed to achieving the goal of eliminating measles and rubella (1,2). However, the resurgence of measles in EUR

since 2018 resulted in record-high numbers of cases and reestablished endemic transmission in some countries that had previously eliminated measles (3,4). Georgia is among the 12 EUR countries that have endemic transmission of measles and continues to experience periodic outbreaks (4,5).

Routine childhood immunization against measles was introduced in Georgia in 1966, resulting in reduction of incidence (Figure 1) (5,6). However, the excessive expansion of the list of contraindications to vaccination in the Soviet Union during the 1980s resulted in substantial immunity gaps (7,8). The immunization program deteriorated dramatically in the 1990s, during the first years after Georgia regained independence, but improved in the 2000s. Combined measles-mumps-rubella (MMR) vaccine (recommended at 12 months and 5 years of age) was successfully introduced in 2004. However, the accumulation of susceptible persons in cohorts born during the mid-1980s through the 1990s led to a series of measles outbreaks. A large-scale outbreak during 2004–2005 affected a wide age range, including older children and young adults (5). A nationwide measles-rubella supplementary immunization activity (SIA) in 2008, targeting the population 6–27 years of age, achieved only 50% coverage because of unjustified vaccine safety concerns (9). Another large-scale outbreak of measles occurred during 2013–2015 and was followed by the outbreak that began in 2017. Here, we review the status of measles in Georgia during 2013–2018, highlight challenges to achieving the elimination goal, and discuss approaches to address these problems.

Methods

We reviewed measles surveillance data from the Georgia national surveillance system. National guidelines for measles surveillance, revised in 2017 (10; Appendix, <https://wwwnc.cdc.gov/EID/article/26/11/20-0259-App1.pdf>), follow WHO regional recommendations. Healthcare providers report suspected measles

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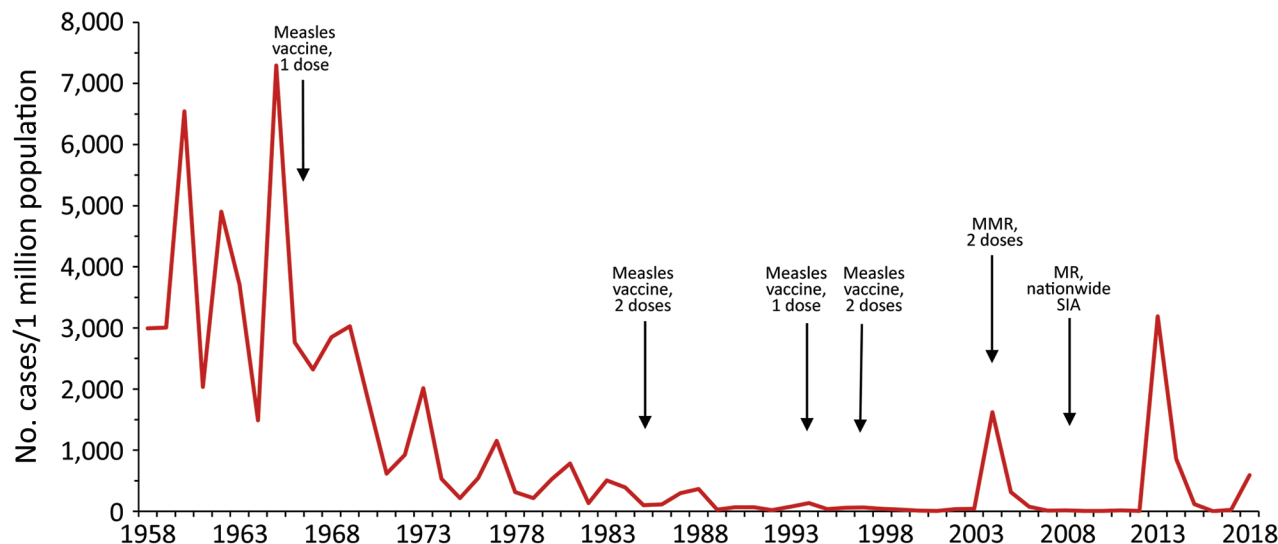


Figure 1. Incidence of measles (reported cases/1 million population), Georgia, 1958–2018. Second dose of measles vaccine was in the national immunization schedule during 1985–1993 but only 1982, 1983, and 1987 birth cohorts were vaccinated because of a lack of vaccine; the second dose was reintroduced in 1997 (5). MMR, measles-mumps-rubella vaccine; MR, measles-rubella vaccine; SIA, supplementary immunization activity.

cases to district public health centers, which report the cases to the national Electronic Infectious Disease Surveillance System and conduct case investigation and response. The National Center for Disease Control and Public Health (NCDC) is responsible for the national level analysis and provides overall guidance. Case-based data on suspected measles cases are reported electronically each month to EUR. Laboratory testing is conducted by the National Measles and Rubella Laboratory at NCDC or, in rare cases, by private laboratories. Virus characterization is performed at the Regional Reference Laboratory in Luxembourg Institute of Health and at the National Measles and Rubella Laboratory. Measles virus sequences are reported to WHO through the Measles Nucleotide Surveillance (MeaNS) database (11,12).

We reviewed basic epidemiologic data for cases reported during 2013–2018 and conducted a detailed analysis of cases reported during 2013–2014, including descriptive epidemiology, occupational status, patterns of transmission, and costs to the public health system. An analysis of measles transmission across age groups was performed for a subset of cases for which the age group of the source (adult vs. child) could be determined from the Electronic Infectious Disease Surveillance System. We obtained information on expenses associated with outbreak response (costs of vaccine and personnel) from NCDC and population data from Georgia's National Statistics Agency.

We obtained information on administrative MMR vaccine coverage from NCDC, supplemented

by independent estimates from a coverage survey that we conducted in 2015–2016 (13; Appendix). In this survey, we estimated immunization coverage (nationwide and in 3 largest cities [Tbilisi, Batumi, and Kutaisi]) for the first MMR vaccine dose (MMR1) and the second MMR vaccine dose (MMR2) among children age-eligible to receive routine vaccinations in 2014 (2009 and 2013 birth cohorts). We estimated both coverage at the time of the survey and timely coverage by standard ages (MMR1 by age 24 months and MMR2 by age 72 months). We obtained additional information on the state of the immunization program in Georgia from WHO and GAVI (<https://www.gavi.org>) assessment reports. Additional details on epidemiologic methods are given in the Appendix.

The activities described in this report were determined by CDC to represent nonresearch. Therefore, institutional review board review was not applicable.

Results

Measles Epidemiology, 2013–2015

Descriptive Epidemiology

A total of 11,495 measles cases were reported in Georgia during 2013–2015 (7,872 in 2013, 3,192 in 2014, and 431 in 2015) (Table 1; Figure 1; Appendix Figure), compared with 30 cases in 2012. The outbreak began in early 2013, and cases occurred predominantly among adults in Tbilisi, the capital city. The outbreak

Table 1. Epidemiologic characteristics of reported measles case-patients, Georgia, 2013–2018*

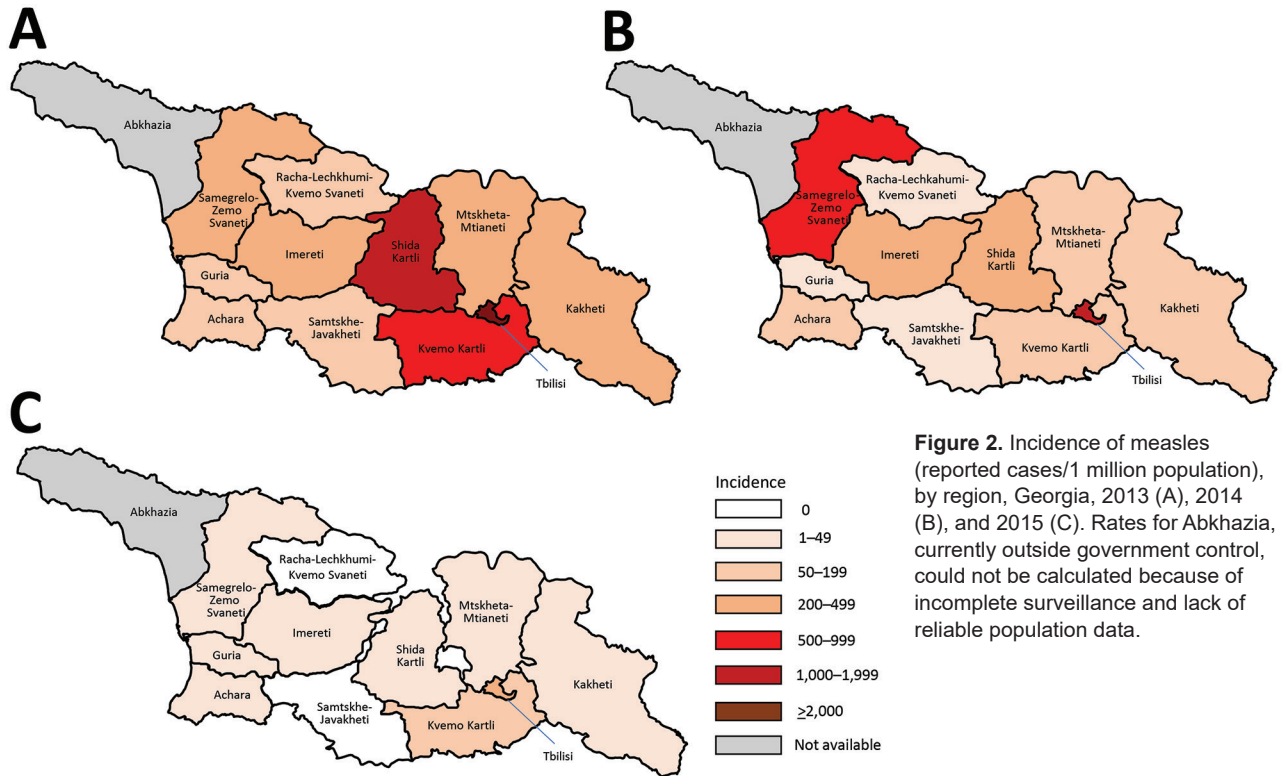
Characteristic	Reported measles cases, no. (%)		
	2013–2015 outbreak	2016	2017–2018 outbreak
Total cases	11,495 (100.0)	14 (100.0)	2,295 (100.0)
Final case classification category			
Laboratory-confirmed	1220 (10.6)	5 (35.7)	1,748 (76.1)
Epidemiologically linked	466 (4.1)	0 (0)	112 (4.9)
Clinically compatible	9,809 (85.3)	9 (64.3)	435 (19.0)
Sex			
M	6,000 (52.4)	8 (57.1)	1133 (49.4)
F	5,457 (47.6)	6 (42.9)	1162 (50.6)
Age group, y			
<1	1,130 (9.8)	4 (28.7)	229 (10.0)
1–4	1,707 (14.9)	6 (42.9)	321 (14.0)
5–9	962 (8.4)	0 (0)	167 (7.3)
10–14	751 (6.5)	1 (7.1)	174 (7.6)
15–19	1,286 (11.2)	0 (0)	164 (7.1)
20–24	1,707 (14.8)	1 (7.1)	302 (13.2)
25–29	1,750 (15.2)	1 (7.1)	304 (13.2)
30–39	1,546 (13.5)	0 (0)	441 (19.2)
40–49	477 (4.1)	0 (0)	143 (6.2)
≥50	179 (1.6)	1 (7.1)	50 (2.2)
No. doses of measles-containing vaccine received			
0	3,972 (34.6)	7 (50.0)	981 (42.7)
≥1	1,346 (11.7)	4 (28.7)	183 (8.0)
1	1,020 (8.9)	4 (28.7)	123 (5.4)
2	326 (2.8)	0 (0)	60 (2.6)
Unknown	6,177 (53.7)	3 (21.3)	1131 (49.3)
Region			
Tbilisi	5,364 (47.0)	7 (50.0)	864 (37.6)
Achara	270 (2.4)	4 (28.7)	380 (16.6)
Guria	87 (0.8)	0 (0)	50 (2.2)
Imereti	742 (6.5)	0 (0)	469 (20.4)
Kakheti	610 (5.3)	1 (7.1)	36 (1.6)
Kvemo Kartli	1,159 (10.2)	0 (0)	87 (3.8)
Mtskheta-Mtianeti	286 (2.5)	1 (7.1)	29 (1.2)
Racha-Lechkhumi-Kvemo Svaneti	83 (0.7)	0 (0)	13 (0.6)
Samegrelo-Zemo-Svaneti	1,200 (10.5)	1 (7.1)	289 (12.6)
Samtskhe-Javakheti	83 (0.7)	0 (0)	28 (1.2)
Shida Kartli	1,509 (13.2)	0 (0)	36 (1.6)
Abkhazia	27 (0.2)	0 (0)	14 (0.6)

*Sex was not reported for 34 cases during 2013–2015. Region was not specified for 75 cases during 2013–2015. For Abkhazia, currently outside Georgia Government control, only cases treated in healthcare facilities in the government-controlled areas are reported.

spread rapidly, affecting all regions by April and continued until mid-2015 (Figure 2). Tbilisi accounted for 47.0% of reported cases. The regions with the highest cumulative incidence per 1 million population during 2013–2015 were Shida Kartli (5,725) and Tbilisi (4,863), whereas Samtskhe-Javakheti (513) and Guria (763) had the lowest incidence.

Cases occurred across a wide age range (0–73 years; median 19 years), but most cases (60.4%) were among those ≥15 years of age (Table 1). The incidence was highest among children <1 year of age, followed by the 1–4-year- and 15–29-year age groups (Figures 3, 4). Almost 90% of the cases were in unvaccinated persons (34.6%) or those who had an unknown immunization status (53.7%); 8.9% had received 1 dose of measles-containing vaccine, and 2.8% had received 2 doses (Table 1). Distribution of cases by age group and immunization status by case-classification category are given in Figures 5–7.

Approximately one third (3,930 [34.3%]) of the 11,477 case-patients with hospitalization status reported were hospitalized. Hospitalizations were most common among unvaccinated persons (40.9% were hospitalized), followed by persons with unknown immunization status (33.5%), and were least common (18.6%) among recipients of ≥1 dose of measles-containing vaccine ($p < 0.001$ by χ^2 test). Complications were reported for 1,883 (16.4%) cases, most commonly pneumonia (1,328 cases [11.6%]) and diarrhea (587 cases [5.1%]). Encephalitis was reported in 9 (0.1%) cases. Adverse outcomes of pregnancy occurred in 5 cases (premature delivery in 3 cases and miscarriage in 2 cases). Four measles-related deaths occurred (case-fatality ratio 0.3/1,000 cases). Three of the fatal cases (in persons 11 months, 4 years, and 19 years of age) were in unvaccinated persons, and 1 was in a 36-year-old person with unknown immunization status.



Molecular Epidemiology

Molecular characterization of 93 measles viruses detected during 2013–2015, mostly in eastern Georgia, identified a single genotype (D8) with 9 different sequence variants (8 belonged to the Frankfurt-Main lineage, and 1 was identical to the Villupuram named strain) (Figure 8). The Frankfurt-Main variant (cluster 1) was the predominant strain associated with the outbreak (n = 74). This strain, first detected in Tbilisi in February 2013, became widespread during 2013–2014 but was not seen in 2015. Cluster 2 was represented by 5 strains from the Frankfurt-Main lineage (4 identical ones and 1 with 1 nucleotide difference) de-

tected during February–April 2014. Another cluster of 4 sequences from March 2014 also differed from the Frankfurt-Main variant by 1 nucleotide (cluster 3). The July 2013 strain from Gagra (cluster 4) (in Abkhazia, currently outside Georgia government control) was clearly distinct from all other strains in the Frankfurt-Main lineage and most likely represents a separate introduction. Three other sequences, which differed from the Frankfurt-Main variant by 1 nucleotide each, were also identified (clusters 5–7). The lack of identical sequences from elsewhere in GenBank suggests that these strains could have evolved locally from the main Frankfurt-Main variant. Six sequences (1 from

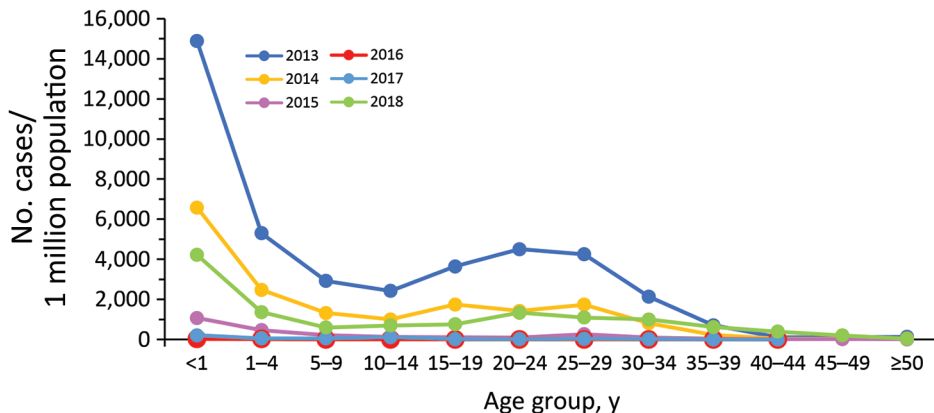
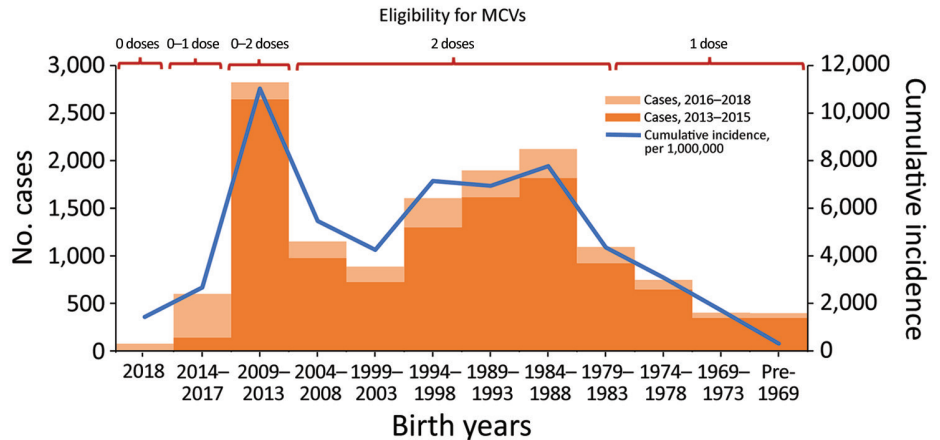


Figure 3. Incidence of measles (reported cases/1 million population), by age group and year, Georgia, 2013–2018.

Figure 4. Reported measles cases during 2013–2015 and 2016–2018 and cumulative incidence (cases/1 million population) for 2013–2018, by birth year and eligibility to MCVs, Georgia. Children born during 2014–2017 gradually became eligible for the first dose of measles-mumps-rubella vaccine (MMR) by 2018 as the respective birth cohorts turned 1 year old. Children born during 2009–2013 were <5 years of age in 2013, at the start of 2013–2015 outbreak, and were either too young to be vaccinated (2013 cohort) or were eligible for the first dose of MMR vaccine only (2009–2012 cohorts), but gradually became eligible for the second dose of MMR vaccine by 2018, as the respective birth cohorts turned 5 years old. The 1981–2008 birth cohorts were eligible to 2 doses of MCV (measles vaccine, measles-rubella vaccine or MMR) through routine program, several supplementary immunization activities, or both. The 1959–1980 cohorts were eligible for 1 dose of measles vaccine through routine vaccination or catch-up immunizations conducted at the time of vaccine introduction. MCV, measles-containing vaccine.



April 2014 and all 5 sequences from March–December 2015) were identical to the Villupuram variant (cluster 8), representing ≥ 1 separate introduction.

Virus Transmission across Age Groups

Among the 1,157 cases during 2013–2014 for which the age group of measles source was determined, the source of transmission in most cases (67.2%) was an adult (defined as ≥ 15 years of age) (Table 2), but the distribution of adult and child sources varied by the age of cases ($p < 0.001$). Cases in adults were significantly more likely than those in children to have another adult as the source of infection (81.5% vs. 51.7%; odds ratio 4.0, 95% CI 3.0–5.2; $p < 0.001$). Adult sources accounted for $> 50\%$ of the cases among adults, infants < 1 year of age, and older children (10–14 years of age), whereas young children (1–9 years of age) contracted measles primarily from other children (Table 2).

Population Groups Affected

Information on patient occupation was reported for 6,441 (58.2%) cases during 2013–2014. Almost half (48.1%) of them occurred among children not attending daycare (21.6%) or adults not working regularly outside the home (26.5%) (Table 3). Schoolchildren accounted for 17.5%, college students for 5.2%, and children attending daycare for 4.2% of the cases. Persons involved in direct customer service accounted for 7.5% of the cases. Healthcare facility (HCF) employees and medical or nursing students accounted for 3.9% of the cases, whereas 5.7% of the cases occurred among military or police.

Transmission associated with HCFs was observed in 123 cases linked to 30 different clusters, which also involved an additional 53 cases for which transmission occurred outside an HCF. The settings for HCF-associated transmission included major

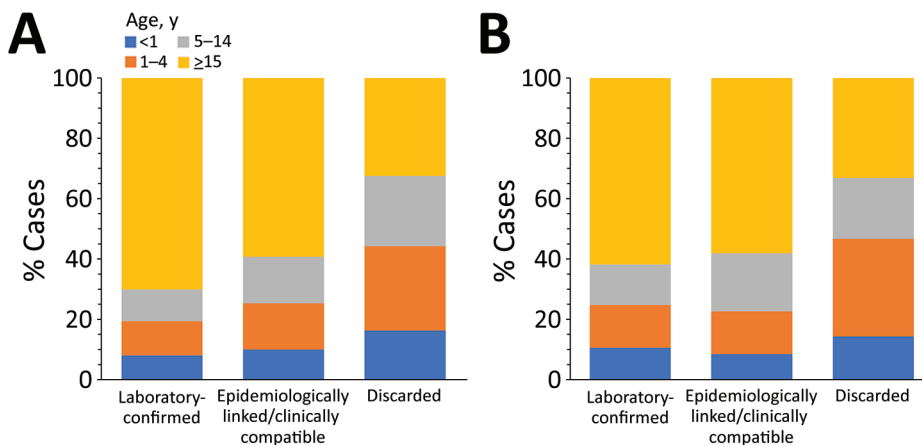


Figure 5. Age distribution of suspected measles case-patients, by final case classification category, Georgia, 2013–2018. A) Cases reported during 2013–2015. B) Cases reported during 2016–2018.

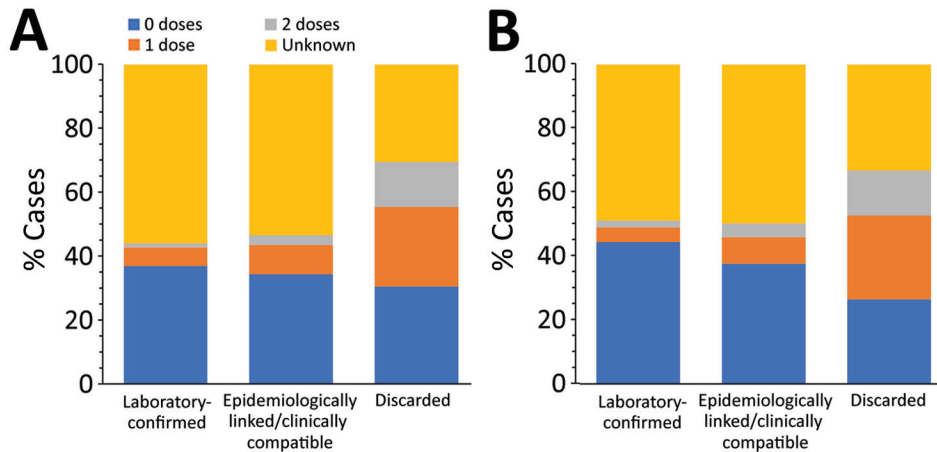


Figure 6. Vaccination status of suspected measles case-patients, by final case classification category, Georgia, 2013–2018. A) Cases reported during 2013–2015. B) Cases reported during 2016–2018.

pediatric hospitals in Tbilisi, ambulance services, a cardiology clinic, infectious disease hospitals, a military hospital, and dental clinics.

Outbreak Response and Cost

The outbreak response activities and additional funds were mandated by the Prime Minister and the Minister of Health of Georgia. During 2013–2015, a total of

272,000 additional doses of MMR vaccine were procured. The immunization response included contact vaccination and offering MMR vaccine free of charge for all unvaccinated children <7 years of age, initially in Tbilisi, then nationwide. Subsequently, the eligible age group was expanded to those ≥30 years of age. Targeted special groups included healthcare workers and military personnel. Vaccine uptake was generally

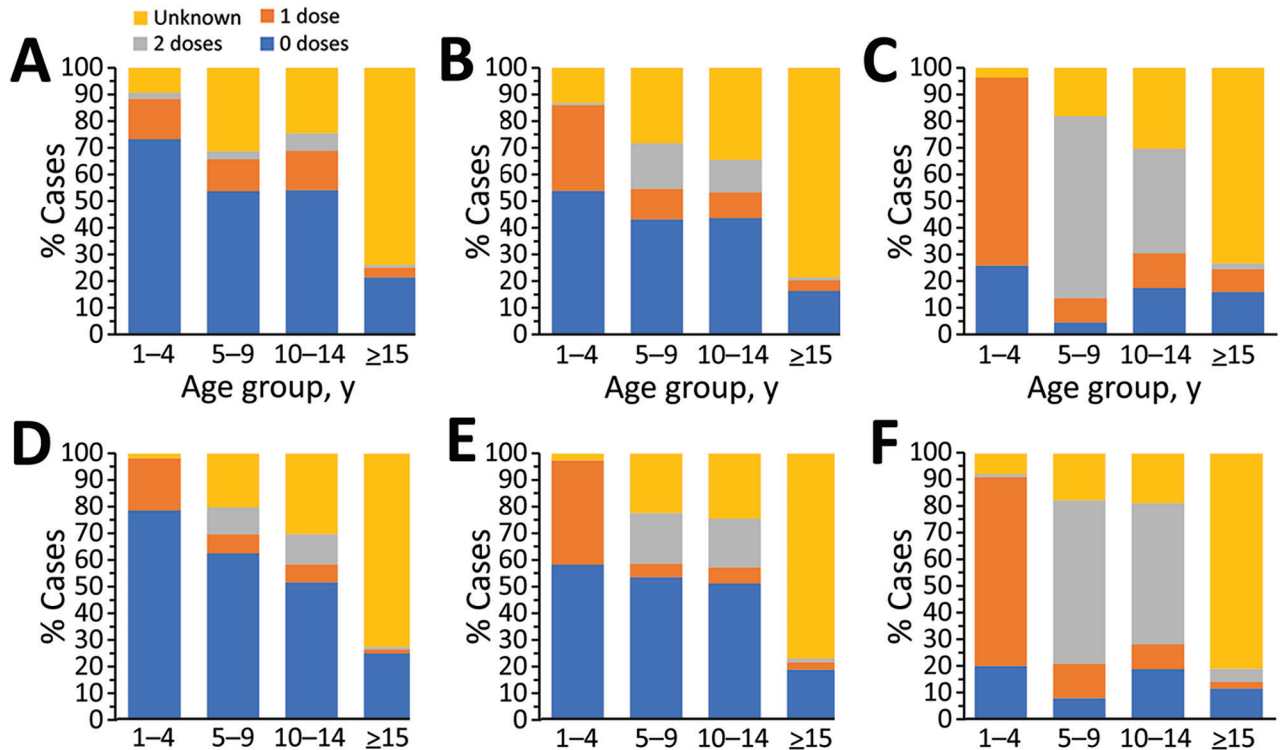


Figure 7. Vaccination status of suspected measles cases, by age group and final case classification category, Georgia, 2013–2015 and 2016–2018. A) Laboratory-confirmed cases reported during 2013–2015 (n = 1,220). B) Epidemiologically linked or clinically compatible cases reported during 2013–2015 (n = 10,275). C) Discarded cases during 2013–2015 (n = 289). D) Laboratory-confirmed cases reported during 2016–2018 (n = 1,753). E) Epidemiologically linked or clinically compatible cases reported during 2016–2018 (n = 556). F) Discarded cases during 2016–2018 (n = 608). Children <1 year of age, too young to be eligible for measles-mumps-rubella vaccination, are excluded.

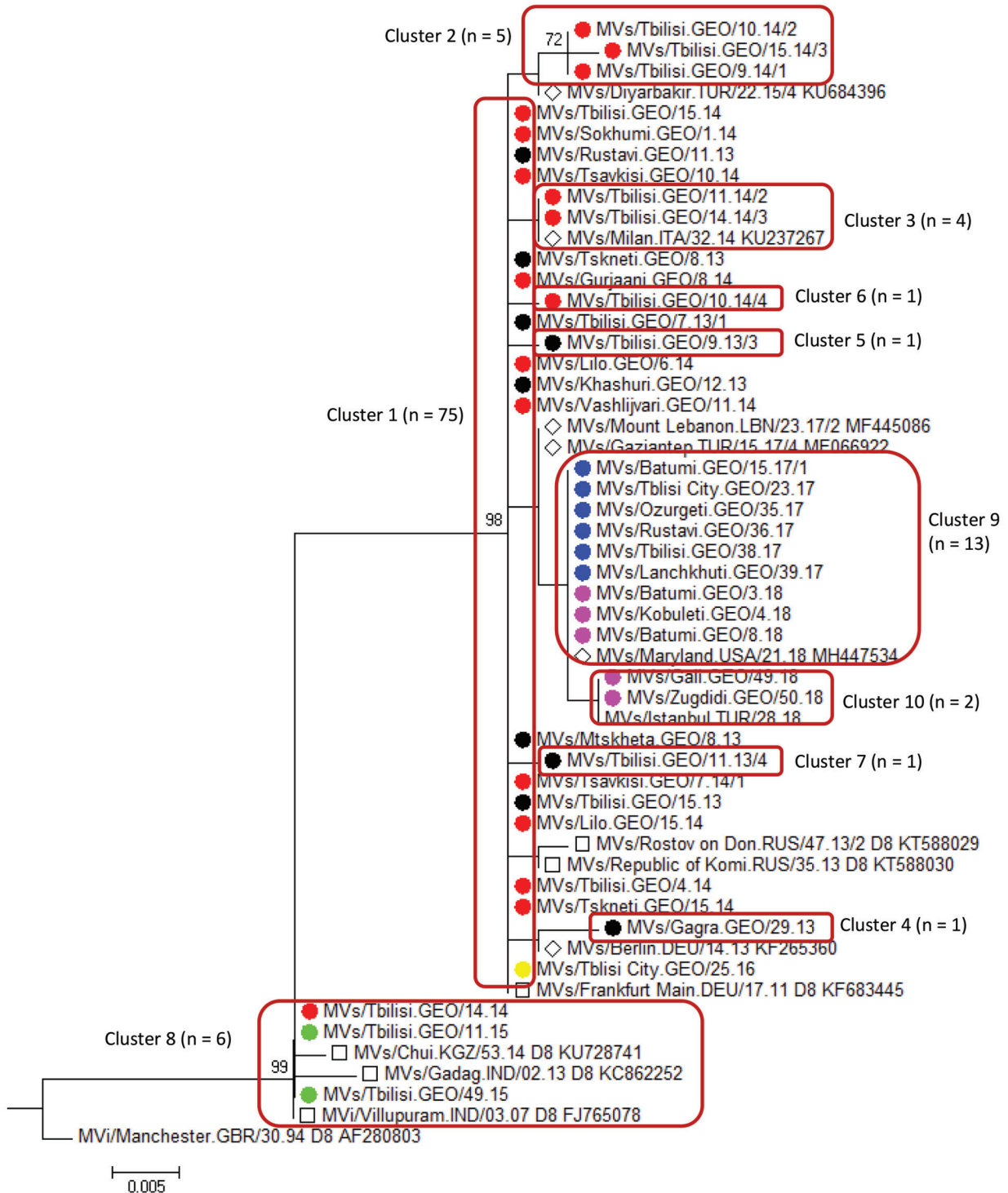


Figure 8. Genetic diversity of measles virus strains identified in Georgia, 2013–2018. Genotype D8 cluster of a phylogenetic tree is based on 450 nt of the measles virus nucleoprotein gene. The Kimura 2-parameter model and the neighbor-joining method in MEGA7 (14) were used, and only bootstrap values >70 are shown. The closest matches of the Georgia sequence variants identified by BLAST (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) are marked with a diamond; named strains of genotype D8 are marked with a square. For identical sequences, only the oldest and the most recent strains found in a certain location in a certain year are shown. The total number of sequences identified in each cluster are included in parentheses. Year of virus detection is indicated by colored circles: black for 2013, red for 2014, green for 2015, yellow for 2016, blue for 2017, pink for 2018. Scale bar indicates genetic distance, calculated based on the Kimura 2-parameter model, measured in nucleotide substitutions per site.

Table 2. Measles transmission sources for adult and child case-patients, by age group of measles case-patients, Georgia, 2013–2014*

Age of measles case-patients	Age group of measles source, no. (%)	
	Adult (≥15 y)	Child (<15 y)
All ages, n = 1,157	778 (67.2)	379 (32.8)
Children <15 y, n = 545	282 (51.7)	263 (48.3)
<1 y, n = 151	118 (78.2)	33 (21.8)
<6 mo, n = 48	43 (89.6)	5 (10.4)
1–14 y, n = 394	164 (41.6)	230 (58.4)
1–4 y, n = 168	69 (41.1)	99 (58.9)
5–9 y, n = 112	35 (31.3)	77 (68.7)
10–14 y, n = 114	60 (52.6)	54 (47.4)
Adults ≥15 y, n = 612	496 (81.1)	116 (18.9)
15–19 y, n = 158	117 (74.1)	41 (25.9)
20–24 y, n = 145	128 (88.3)	17 (11.7)
25–29 y, n = 127	108 (85.0)	19 (15.0)
>30 y, n = 182	143 (78.6)	39 (21.4)

*Includes 1,157 cases reported during 2013–2014 for which the age group of the measles transmission source (adults age ≥15 y vs. children age <15 y) could be established from the available surveillance data.

low (except among the military); 170,000 doses (62.5% of the available doses) were administered (85,000 doses to children 2–14 years of age, 41,000 doses to adults 15–29 years of age, 7,000 doses to healthcare workers, and 37,000 doses to contacts of measles case-patients and military personnel). Because of the substantial numbers of cases among the military, military personnel were considered potentially exposed or at high risk for exposure and vaccinated under the contacts category.

The total direct cost of additional vaccines and salaries for public health personnel during 2013–2015 was \$720,000 (USD), of which \$663,000 (92%), including \$245,000 provided by the US government, was used for purchasing vaccines. The average direct cost per measles case for the public health system during this outbreak was \$63.

Measles Epidemiology, 2016–2018

Only 14 cases were reported in 2016 (Table 1), including a 3-case cluster in Tbilisi in June. The measles virus

identified from that cluster was Frankfurt-Main, identical to the main outbreak strain circulating during 2013–2014 (cluster 1) (Figure 8). The 26-month interval since the last detection of this strain (in 2014) suggests a new introduction rather than continued transmission.

Ninety-six measles cases were reported in 2017 (Table 1), 92 (95.8%) of which occurred during August–December. The first 2 laboratory-confirmed cases occurred in April, 7 months after the previous laboratory-confirmed case. An outbreak of 16 cases during August–September began in Guria and was notable for its very high proportion of cases linked to HCF-associated transmission (13 cases [81.3%]), including 3 cases among healthcare workers. Measles activity further increased in late 2017, starting with school-based outbreaks in 2 districts of Achara and subsequently spreading to the regional capital Batumi. In 2017, Achara (65 cases) and neighboring region Guria (13 cases) accounted for 78 (81.3%) of cases in Georgia.

Table 3. Occupations of reported measles case-patients, Georgia, 2013–2014

Occupation of case-patients	No. (%)
Adult not working outside the home	1,704 (26.5)
Unemployed	1,011 (15.7)
Housewife	693 (10.8)
Child not attending daycare	1,392 (21.6)
School student (all grades)	1,127 (17.5)
Customer services (e.g., employees of banks, stores, casinos, restaurants)	484 (7.5)
Military or law enforcement	369 (5.7)
Military	239 (3.7)
Law enforcement	130 (2.0)
College or vocational school student	334 (5.2)
Child attending daycare	271 (4.2)
Healthcare facility employee or medical student	250 (3.9)
Healthcare facility employee	209 (3.2)
Medical student	41 (0.6)
Government or office worker	141 (2.2)
Other	369 (5.7)
Total with occupation information reported	6,441 (100)

The outbreak expanded in 2018, resulting in 2,199 reported cases (Table 1; Figures 1, 3, 9; Appendix Figure). During 2017–2018, the 4 regions with the highest cumulative incidence (cases/1 million population), Achara (1,119), Imereti (911), Samegrelo-Zemo Svaneti (894), and Tbilisi (760), accounted for 2,002 (87.3%) cases. Two unvaccinated case-patients (ages 11 months and 16 years) died in 2018. The age distribution and immunization status of case-patients during 2017–2018 was comparable to the 2013–2015 period (Table 1; Figures 5–7). As seen during 2013–2015, most affected groups in 2016–2018 included birth cohorts too young to be vaccinated or age-eligible for MMR1 only, as well as young adults born during the 1980s and 1990s (Figure 4).

Measles virus sequences from 2017–2018 (n = 15) were detected across 8 regions and belonged to genotype D8. Thirteen identical strains (cluster 9) (Figure 8) detected during April 2017–February 2018 differed by 2 nucleotides from cluster 1, the predominant strain during 2013–2014. The other 2 identical sequences from December 2018 (cluster 10) were 1 nucleotide different from the rest of the 2018 strains and were identical to a virus identified earlier (July 2018) in Turkey (Figure 8).

Outbreak response activities included intensifying contact tracing and case-finding, enhancing surveillance and testing, reviewing immunization

records of children in affected areas, and offering MMR vaccine free of charge to contacts and unvaccinated and undervaccinated persons <40 years of age. During 2017–2018, approximately 60,000 additional doses of vaccine were procured, and 47,000 doses were administered as part of the outbreak response. In November 2018, Georgia’s healthcare law was amended to make routine childhood immunizations mandatory (15). In early 2019, the policy of mandatory MMR vaccination for certain occupational groups, including healthcare workers, was introduced (16). The National Strategic Plan for Measles and Rubella Elimination was developed and is pending government approval.

Immunization Coverage

The administrative coverage fluctuated over time and mostly remained below the national target (95%) (Figure 10). However, in 2015 and 2017, reported MMR1 coverage reached 95%–96% and MMR2 coverage reached 90%–91%. In 2018, coverage for both doses exceeded 95% for the first time (98% for MMR1 and 96% for MMR2).

A coverage survey conducted during 2015–2016 demonstrated that by the time of the survey, 89% of children born in 2013 and 93% of children born in 2009 had received MMR1; and 76% of children born in 2009 had received MMR2 (Figure 11). Timely coverage was lower, particularly in the 2009 cohort,

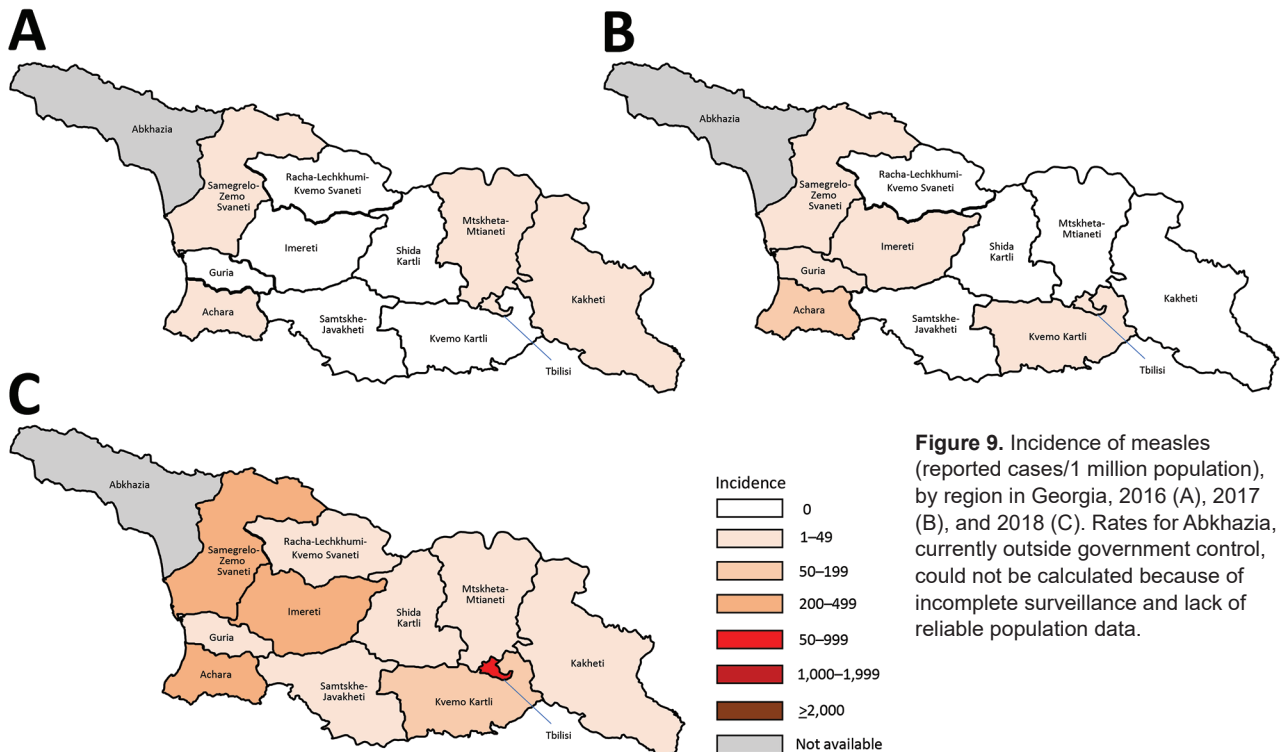


Figure 9. Incidence of measles (reported cases/1 million population), by region in Georgia, 2016 (A), 2017 (B), and 2018 (C). Rates for Abkhazia, currently outside government control, could not be calculated because of incomplete surveillance and lack of reliable population data.

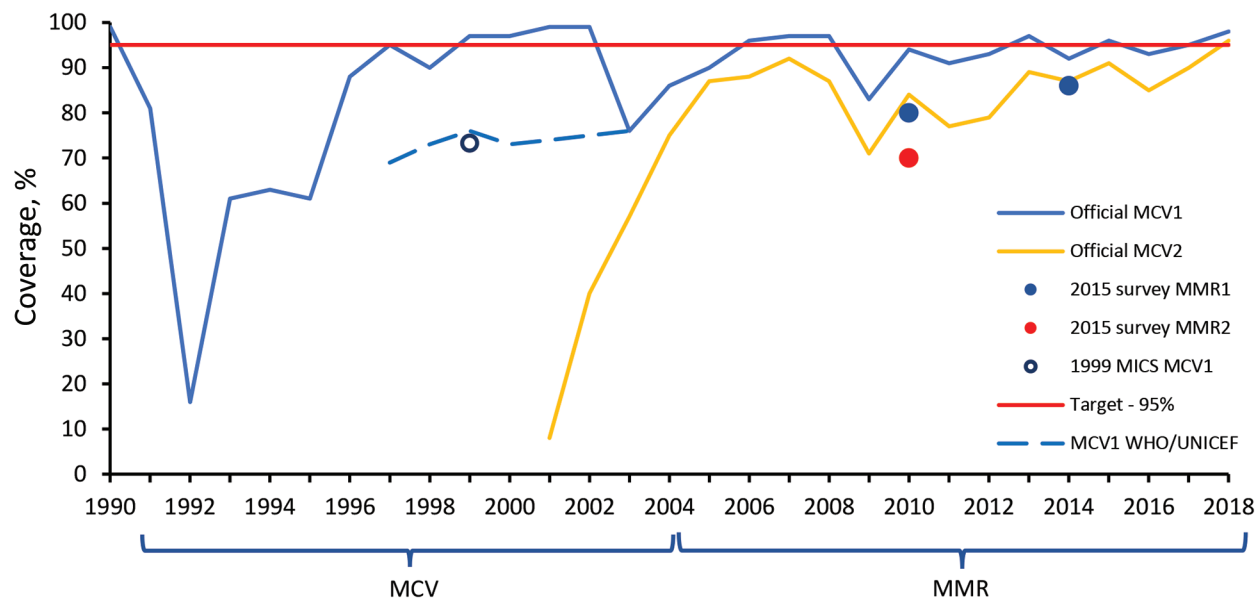


Figure 10. Immunization coverage with measles-containing vaccines in Georgia, 1990–2018. WHO/UNICEF estimates are included for 1997–2003, when official estimates were unreliable because of uncertainty in population numbers. WHO/UNICEF estimates are in agreement with the official estimates from 2003 to present. MCV, measles-containing vaccine; MCV1, first dose of MCV; MCV2, second dose of MCV; MICS, Multiple Indicator Cluster Survey; MMR, measles-mumps-rubella vaccine; MMR1, first dose of MMR; MMR2, second dose of MMR; WHO/UNICEF, World Health Organization/United Nations Children's Fund.

highlighting the problem with delayed vaccinations, although MMR1 coverage by age 24 months improved from 80% in the 2009 cohort to 86% in the 2013 cohort. Timely MMR2 coverage in the 2009 cohort was 70%. Geographic variations were particularly notable for the 2009 cohort, with substantially higher coverage in Batumi than in other sites. MMR1 coverage in the 2013 cohort was lowest in Kutaisi. MMR2 coverage was low in all sites except Batumi (Figure 11).

Main Performance Indicators for Measles Surveillance

During 2013–2017, the discarded case rates ranged from a high of 4.5/100,000 population in 2013 to a low of 1.2/100,000 population in 2016; the $\geq 2.0/100,000$ population WHO target for this indicator was met only in 2013. Geographic variations were observed, with consistently low discarded case rates in some regions. In 2018, surveillance quality improved substantially, with a discarded case rate of 13.6/100,000 population nationwide and $>2/100,000$ population in all regions. The $\geq 80\%$ target for timeliness of case investigation (1) was consistently met; during 2013–2018, case investigation was initiated within 48 hours of notification for $>95\%$ of suspected measles cases. The rate of laboratory investigation of cases (1) has improved substantially, from 13.3% during 2013–2015 to 79.6% in 2016 and 84.6% during 2017–

2018, resulting in a decline in the proportion of clinically compatible cases among all measles cases from 85.3% during 2013–2015 to 19.0% during 2017–2018. Comparison of age distribution and vaccination status of suspected measles cases by final classification category indicated relatively minor differences between laboratory-confirmed cases and those classified as epidemiologically linked or clinically compatible; however, cases in all these categories differed substantially from discarded cases, which had lower proportions of adults and higher proportions of vaccinated persons (Figures 5–7). The highest proportions of unvaccinated cases were observed in the laboratory-confirmed category among children 1–4 years of age (who were age-eligible for MMR1 only), whereas the highest proportions of vaccinated children were observed among epidemiologically linked or clinically compatible cases in children 5–14 years of age (who were age-eligible for both MMR1 and MMR2) (Figure 7). In contrast, in the discarded category, most case-patients <15 years of age were vaccinated; 1-dose recipients were predominately children 1–4 years of age and 2-dose recipients children 5–14 years of age. The similarities between different categories of measles cases and their clear differences from discarded cases during large-scale outbreaks provide additional reassurance regarding the quality of measles surveillance in Georgia.

Discussion

Measles epidemiology in Georgia during 2013–2018 shows widespread circulation and genetic diversity of measles viruses and points to persistent gaps in population immunity across a wide age range that have not been sufficiently addressed by interventions undertaken so far (5,9). Measles in Georgia is associated with substantial economic costs, disease, and deaths; its effects extend beyond the acute illness, as suggested by the recently demonstrated high risk for subacute sclerosing panencephalitis after measles outbreaks in Georgia (17).

Cases among children highlight challenges with routine immunization services. Previous suboptimal MMR1 coverage and vaccination delays, primarily because of unwarranted contraindications (13), likely contributed to the high incidence of measles among children. Although most children receive MMR vaccine, vaccination often happens years after the recommended ages, widening the window of susceptibility, particularly among those age-eligible to MMR1 only.

High incidence among adults and <1-year-old infants results from continued susceptibility among persons born in the 1980s and 1990s (Figure 4) and is consistent with the results of a serosurvey conducted in Georgia immediately after the 2013–2015 outbreak (18), which demonstrated residual seronegativity to measles above the 7% susceptibility threshold needed for preventing outbreaks (19) among young adults. Seronegativity was 10.1% among persons 18–24 years of age, including 14.5% among college students and 8.0% among those 24–29 years of age (18). Analysis of measles transmission patterns demonstrated the important role of adults in virus circulation, suggesting that the adult population could potentially maintain measles transmission in Georgia. Along with

widespread susceptibility among adults, small birth cohorts and the generally small number of children in households in Georgia (20) could have contributed to this finding.

Our findings highlight the urgent need to address population susceptibility across all age groups in Georgia. To improve immunity among children, ongoing catch-up immunization of unvaccinated and undervaccinated children should be accelerated, along with further strengthening routine immunization services. Educational efforts promoting awareness among parents and healthcare providers should be intensified to address needless delays attributable to unwarranted contraindications. Effective communication and stakeholder coordination will be needed to ensure the successful implementation of legislation endorsing mandatory childhood vaccinations in Georgia (15). Implementing mandatory MMR vaccination of certain occupational groups (16) and expanding this policy to include all college students could considerably reduce measles transmission among adults in high-risk settings, including HCFs, which have been a substantial contributor to outbreaks. However, reaching susceptible persons in the general adult population who account for a large proportion of cases, remains extremely challenging. The unsuccessful measles-rubella SIA conducted in 2008 (9) was a missed opportunity to close historic immunity gaps in Georgia. Conducting large-scale SIAs in Georgia's present healthcare environment is not feasible because of the lack of defined catchment areas or populations, the voluntary nature of patient registration with HCFs, the lack of mechanisms or motivation for providers to identify and offer vaccinations to unregistered persons, and difficulties in locating historic records to ascertain vaccination status of adults. In addition, acceptance of mass

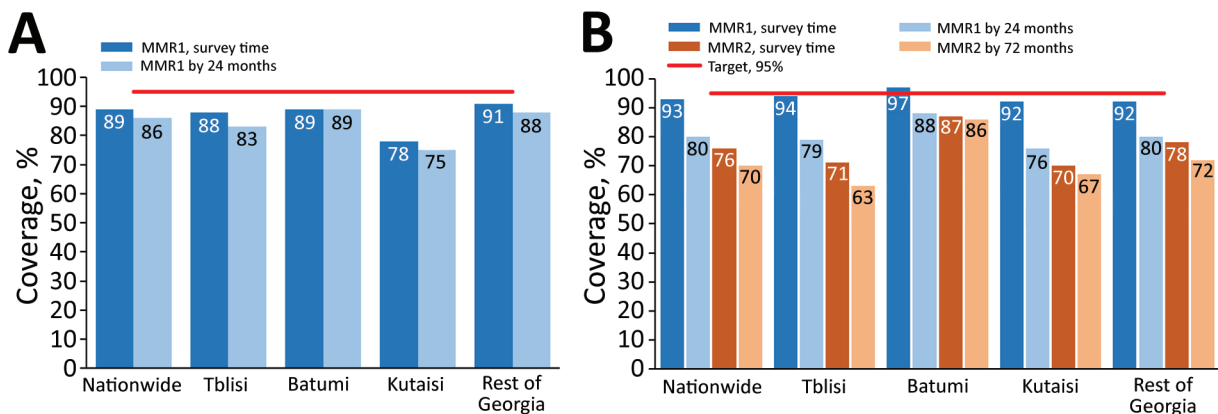


Figure 11. Coverage with the first and the second doses of measles-mumps-rubella vaccine, according to an immunization coverage survey, Georgia, 2015–2016. A) 2013 birth cohort. B). 2009 birth cohort. MMR, measles-mumps-rubella vaccine; MMR1, first dose of MMR; MMR2, second dose of MMR.

immunizations among healthcare providers and public health professionals has been low since the SIA in 2008 (9). Under these circumstances, more selective and targeted efforts to control measles outbreaks are being implemented. The result of these efforts will depend primarily on the level of public acceptance. The suboptimal uptake of MMR vaccine among adults indicates the need for interventions to generate vaccine demand.

Information provided by the measles surveillance system is critical for guiding outbreak responses and documenting virus transmission. Measles surveillance in Georgia currently meets most performance indicators. Further improving the quality of case and outbreak investigations will help ensure that all chains of transmission are promptly identified and followed up.

Improved molecular surveillance, notwithstanding certain temporal and geographic gaps, helped demonstrate that virus introductions and local evolution likely contributed to continued transmission. At least 2 variants of measles virus (the main outbreak strain [cluster 1] and the strain in cluster 8) have likely established long-term (≥ 12 months) transmission in Georgia during the 2013–2015 outbreak, but their circulation has been interrupted since then. Cluster 9, detected during April 2017–February 2018, possibly represents a new introduction. Given the slow rate of measles virus evolution (21) and a very low level of measles activity in 2016, the 2-nucleotide difference from the Frankfurt-Main strain probably would not have emerged over the 9-month period since its last detection in Georgia. Cluster 9 strains also might have circulated for ≥ 12 months, but no virus specimens were collected during March–November 2018 (the peak of the outbreak), preventing definitive conclusion.

Controlling measles outbreaks throughout EUR is crucial for achieving the regional elimination goal. The experience in Georgia demonstrates that without adequate and timely response, substantial susceptibility to measles can persist in settings with historically suboptimal coverage even after large-scale outbreaks, thus leaving room for future outbreaks. A similar pattern was observed in Ukraine and in Bosnia and Herzegovina, where, in the absence of appropriate response, the historically underimmunized birth cohorts were affected by repeated outbreaks of measles (22–27). In contrast, those countries in the former Soviet Union and Eastern Europe that successfully implemented wide-age SIAs, achieved elimination or substantial reduction of measles incidence for prolonged periods (4,28,29). However, implementing

traditional SIAs is not feasible in many middle- and high-income countries of EUR. Lessons learned from Georgia could be useful for other countries with immunization systems facing similar challenges related to health-system transitions and the presence of age cohorts or population groups with historically low coverage.

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Challenges to Achieving Measles Elimination, Georgia, 2013–2018

Appendix

Measles Epidemiology And Surveillance: Additional Details On Methods

According to Georgia's national guidelines for measles surveillance (1), which follows regional guidance (2) from the European Office of the World Health Organization, all suspected measles cases (i.e., cases which meet clinical case definition for measles) are notifiable within 24 hours. Following the review of clinical, epidemiologic and laboratory data, all suspected cases are classified into one of the following final classification categories: laboratory-confirmed, epidemiologically linked, clinically compatible, and discarded. Cases classified as laboratory-confirmed, epidemiologically linked and clinically compatible are included in the total count of reported measles cases. Discarded cases are excluded from measles case count, but they are still reported as a separate category for the purpose of monitoring measles surveillance quality.

Measles incidence rates were expressed as number of reported measles cases per 1 million population. Population data for calculating rates was obtained from the National Statistics Office of Georgia (3). Population data exclude regions currently not under Georgian government's control (South Ossetia and Autonomous Republic of Abkhazia). Georgia's total population in 2013 was 3.7 million, with the age distribution presented in Appendix Table 1. There were no substantial variations in the population size or age distribution during the period covered in this report. Region-specific rates were not calculated for Abkhazia because of incomplete surveillance (the only reported cases from Abkhazia were those treated at the healthcare facilities in regions under Georgian government control) and the lack of reliable population data. No data were available for South Ossetia.

Patterns for transmission of measles across age groups (adults versus children) was analyzed for cases reported in 2013–2014, for which the age group of the source of transmission could be determined from the Electronic Infectious Disease Surveillance System. Children were

defined as persons aged <15 years, adults, as persons aged ≥ 15 years. We analyzed the proportion of cases of different age groups by the age group of potential sources. X^2 test was used for statistical comparisons. In the analysis of the costs of measles outbreaks, the expenses were converted into USD using exchange rates at the time when they were incurred.

Various indicators are used to assess sensitivity, specificity, timeliness and completeness of measles surveillance (1,2). The main indicators reviewed in this report are included in the Appendix Table 2.

Immunization Coverage Survey: Methods

Below is the summary of the background and methods of the immunization coverage survey conducted in Georgia in 2015–2016 applicable to coverage with measles-mumps-rubella vaccine (MMR). The full report is available online (4).

Participating Institutions

U.S. Centers for Disease Control and Prevention (CDC), Center for Global Health, Global Immunization Division; CDC South Caucasus office, Field Epidemiology and Laboratory Training Program; National Center for Disease Control and Public Health (NCDC), Tbilisi, Georgia

Background

Vaccination against measles has been in place in Georgia since 1966. Since 2004, the national immunization schedule includes MMR vaccine at 12 months and 5 years.

Immunization coverage in Georgia had been high until 1990, but declined in the 1990s, during the immediate period after the regaining of independence and subsequent armed conflicts and economic crisis. Although immunization services have improved in the last decade, challenges remain, as demonstrated by continued occurrence of outbreaks of measles. As of 2015, at the time of planning the survey, national coverage estimates for the first and second doses of measles-containing vaccines (MCV1 and MCV2, respectively) reported by Georgia to WHO (Appendix Table 3) remained largely below the national target of 95% (6).

The accuracy of administrative coverage data was unclear because of difficulties with determining target populations, particularly in the cities where the continuous changes to health

care system had greatest impact on primary health care facilities (HCFs). The abolition of geographic catchment areas for HCFs, intense population movement, and existence of uncertain number of children not registered with HCFs resulted in greater difficulties with assessing coverage in large cities than in smaller towns and rural areas. Administrative coverage data have not been validated for over a decade, as no independent nationwide coverage surveys have been conducted in Georgia since a Multiple Indicator Cluster Survey (MICS) in 1999 (8). Immunization data could not be analyzed for the MICS survey conducted in 2005 because immunization cards for ~85% of households were not stored at home (8).

Because of the lack of independent validation of the coverage data in Georgia and ongoing uncertainty with target populations, we conducted a nationwide immunization coverage survey during 2015–2016 to assess coverage with vaccines included in the routine immunization schedule through 5 years of age.

Survey Design

Survey Population and Vaccine Doses Assessed

Most standard protocols for immunization coverage surveys (MICS, DHS, EPI cluster survey) only include vaccines given during the first year of life and first dose of measles vaccine, but this approach leaves out later doses, such as second dose of measles-containing vaccines, and doses after primary series for diphtheria-tetanus toxoids and polio vaccines. The coverage with vaccine doses recommended after 12 months of age in Georgia has not been independently assessed previously. Therefore, we decided to assess coverage with all vaccines included in the immunization schedule before the age 6 years.

Per NCDC request, and because of greater uncertainties with accuracy of reported coverage data in cities, the survey was designed to allow obtaining separate estimates for three largest cities of Georgia – Tbilisi (2015 population 1,100,000), Batumi (154,000), and Kutaisi (148,000), which together account for 38% of total population of the country (3). Therefore, these three cities and rest of Georgia were surveyed separately and nationwide estimates were obtained by pooling the data from these surveys. The areas currently not under Georgian Government control (South Ossetia and Autonomous Republic of Abkhazia) were excluded because of lack of population data, inaccessibility and security concerns.

We included in the survey children eligible for routine immunizations in 2014, the most recent year with available coverage data at the time of planning and initiation of the survey.

These included three birth cohorts:

- Children born in 2014, eligible to receive vaccines recommended during the first year of life
- Children born in 2013, eligible to receive vaccines recommended during the second year of life, including first dose of MMR vaccine (MMR1), recommended at 12 months of age
- Children born in 2009, eligible to receive vaccines recommended during the sixth year of life, including second dose of MMR vaccine (MMR2), recommended at 5 years of age.

We estimated immunization coverage with age-appropriate vaccines for each birth cohort based on the national immunization schedule. The survey design allowed us to assess coverage for vaccines recommended by 12 months of age for all three birth cohorts, for vaccines recommended between 12 and 23 months for two birth cohorts (2013 and 2009), including MMR1, and for vaccines recommended between 60 and 71 months, including MMR2, for the birth cohort of 2009.

Because of very recent introductions, we did not assess coverage for pneumococcal conjugate vaccine for 2014 birth cohort or for Hib vaccine for 2009 birth cohort. Tetanus-diphtheria (Td) vaccine recommended at 14 years was not included in the survey.

It was not practical to conduct a household survey for the purpose of coverage assessment in three age strata. The small average household size (3.3 persons; range, from 2.5 in Racha-Lechkhumi to 4.0 in Achara) (9) and small birth cohort in Georgia (approximately 50,000-60,000) would have required selecting a very large sample of households to identify sufficient number of households with children from targeted birth cohorts. The existence of the nationwide Civil Registry database linked to the Immunization Management Module provided an opportunity to conduct the survey targeting individual children rather than households.

Since very few families in Georgia keep their children's immunization cards at home (8) and parental recall is not considered a reliable source of a child's immunization history, we

obtained information on immunizations from HCFs where children receive immunization services, in accordance with recently revised WHO guidance on conducting immunization coverage surveys (10).

Sampling Frame

The lists of children born in 2014, 2013, and 2009 obtained from the Civil Registry database and linked to the recently introduced electronic Immunization Management Module of the Health Information Management System were used as a sampling frame for the survey. The availability of a highly accurate sampling frame allowed us to include all children in the survey, not only those registered with HCFs on which officially reported administrative coverage data are based.

The Civil Registry database includes information on all children who are born and receive a birth certificate in Georgia. Based on a UNICEF assessment in 2010, the rate of registration at the time of birth was very high (97%) (11) and has likely increased since then with further substantial improvement of Civil Registry services. The information available included child's name, date of birth, personal ID number, legal address, and, for a subset of children, the actual address and the name of HCF where the child receives health services. Children living outside Georgia were considered ineligible for the survey. Therefore children with foreign address listed in the Civil Registry database were excluded from the survey (301 [0.5%] children in 2014 cohort, 326 [0.6%] in 2013 cohort, and 497 [0.8%] in 2009), as well as children who were initially sampled but were subsequently found to have moved overseas.

Design and Sample Size

A complex, stratified, multi-stage design was used for the survey (Appendix Table 4). The country was divided into four survey domains consisting of the three largest cities (Tbilisi, Kutaisi, and Batumi) and the rest of the country. In the three large city domains, simple random sampling (SRS) was used to select children [primary sampling units (PSU)] from each of the three age groups. The fourth domain, consisting of the populations not residing in one of the three largest cities, was divided into seven strata. In the first stratum, which included Rustavi and Poti, participants within each age group were selected by SRS because the sampling frame had no easily identifiable subdivisions to be used as sampling units for cluster survey. Five strata required a two-stage cluster design. In the first stage, settlements (village/town) were selected by

probability proportionate to population size (PPS), followed by an SRS of children within each age group. The last stratum, representing the remaining 54 districts of Georgia, required a 3-stage cluster design. In the first stage, districts were selected by PPS, followed by selection of settlements (village/town) by PPS, followed by a SRS of children within each of the three age groups. Very small settlements were pooled to create sampling unit with >10 children in it.

A sample size of 750 per birth cohort was allocated to Tbilisi (representing 3.8% of all children), and 600 per birth cohort to Batumi (20.0%) and Kutaisi (22.1%), resulting in 1950 children per birth cohort for the three cities combined. In the rest of Georgia domain, a sample size of 50 per birth cohort was allocated to Gori and combined Rustavi/Poti stratum. A sample size of 25 per birth cohort was allocated to the next four strata (five per PSU). In the last stratum, a sample size of five children per SSU was allocated, resulting in 25 children per PSU. This resulted in 800 children per birth cohort in the fourth domain (2.4% of all children). In total, 2,750 children per birth cohort were selected, which resulted in a total sample size of 8,250 children for all three birth cohorts included in the survey.

Selection of sampling units was performed using the population data for the 2014. Individual children were selected from the sampled units using line-lists for respective birth cohorts.

Upon survey implementation, of 8,250 children selected in the three birth cohorts, 103 (1.2%) were found to have moved to other countries, resulting in 8,147 children eligible for the survey. We obtained immunization information for 7,723 of them for an overall enrollment rate of 94.5%, and 424 (5.2%) children could not be found. In all birth cohorts and domains, >90% of eligible participants were enrolled (range, 90.4%–98.0%).

Survey Procedures

The relevant population subsets were extracted from the Civil Registry birth registration database via the Immunization Management Module link. The residence codes were assigned to each administrative unit based on child's address. If actual address was different from the child's legal address, the actual address was used to assign the child to sampling unit, accounting for some population movement and reducing the proportion of children who could not be located.

Participant selection process was performed by survey coordinators. SRS was applied using an online random number generator (www.random.org). The survey field teams were given lists of selected children with their addresses and, if known, HCF indicated in the Immunization Management Module (the list and contact information of HCF is available through the Health Information Management System). For children with known HCFs, the teams visited HCFs to locate the immunization records of children selected for the survey.

If the child's immunization records could not be located at the listed HCF or no HCF was listed, the teams visited the child's residence and, after providing an information sheet about the survey, asked parents/guardians if the child had received at least one vaccination. If the answer was positive, parents/guardians were asked to provide information about HCF where the child receives immunizations. If the immunization card was available at home, the data were obtained on-site. Otherwise, the team visited the HCF indicated by a parent/guardian to obtain immunization records. If the child was unvaccinated per parent/guardian report, this information was noted in the interview form and no further attempts to locate records for this child were undertaken. Children who could not be found were not replaced by selecting another child.

The information collected on survey participants included date of birth, sex, residence district/city, HCF, vaccine doses received and dates of vaccination. The information was recorded on a survey data collection form.

To accommodate the timeframes of availability of staff and funding, the survey was implemented sequentially in Batumi in August 2015, in Kutaisi in September 2015, in Tbilisi in March 2016, and in the rest of Georgia in August-October 2016. To reduce the impact of sequential timing of survey implementation, immunization records for the children in Batumi and Kutaisi who had not reached full year of the cohort age at the time of initial field work (were born in the late months of year) and had not received all age-eligible vaccines were reviewed again at HCFs or via Immunization Management Module in early 2016, and any additional doses received were noted.

The survey field teams were comprised of personnel from NCDC, CDC/GID, CDC South Caucasus Office, FELTP graduates and from local Public Health Centers of survey areas. Before beginning fieldwork, the survey personnel received comprehensive training on the survey objectives, methodology, and procedures for data collection.

Data Management and Analysis

The statistical software Epi Info 7 was used for data entry. Analysis was conducted using SAS v9.4 and R v3.3. Analyses accounted for the complex survey design and sampling weights. We report Wilson-Score confidence intervals for proportions using survey procedures in SAS 9.4. Main outcome measures included per cent coverage for MMR1 and MMR2. Overall coverage for MMR1 and MMR2 at the time of the survey and the timely coverage at standard time points – by 24 months for MMR1 and by 72 months for MMR2 were calculated.

To account for differences in the time of observation, comparisons across cohorts were made based on the timely coverage. To remove the impact of the sequential implementation of the survey in different domains on the coverage levels, we calculated coverage for each dose by the time of the end of the initial field work in Batumi (the city surveyed first), by excluding any vaccine doses administered after September 1, 2015. Direct comparisons across survey sites were made based on the status as of September 1, 2015.

The estimates of coverage were compared to the national target of 95% coverage for all doses. The target does not specifically refer to timely coverage, therefore, in the analysis we applied it to overall coverage by the time of the survey. The survey results were also compared to corresponding administrative coverage reported through GEOVAC system. GEOVAC, the existing system for administrative reporting of coverage in Georgia, is based on the data provided by HCFs to NCDC and only reflects children registered with HCFs.

Ethical Issues

The coverage survey protocol was reviewed by Human Subject Research Coordinator, GID/CGH/CDC and Ethical Committee, NCDC, and determined to be an evaluation of public health program rather than human subject research.

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Appendix Table 1. Population of Georgia by age group, 2013

Age group, y	Population
<1	49,600
1–4	207,400
5–9	216,000
10–14	210,400
15–19	233,200
20–24	281,100
25–29	280,000
30–39	507,000
40–49	490,600
≥50	1,242,000
Total	3,717,300

Appendix Table 2. Main surveillance indicators for measles reviewed for this report (1,2)

Indicator	Definition	Target
Rate of discarded cases	Number of discarded cases per 100,000 population	≥2.0/100,000
Rate of laboratory investigation of cases	Number of suspected cases of measles tested divided by the number of all suspected cases excluding cases that have not been tested but were confirmed by epidemiologic link to another laboratory confirmed case or discarded based on epidemiologic link to a case of another disease, expressed as percentages	≥80%
Timeliness of case investigation	Percent of suspected cases with investigation initiated within 48 h of reporting	≥80%

Appendix Table 3. Official country estimates of immunization coverage with measles-containing vaccines reported to WHO, Georgia, 1990–2014*

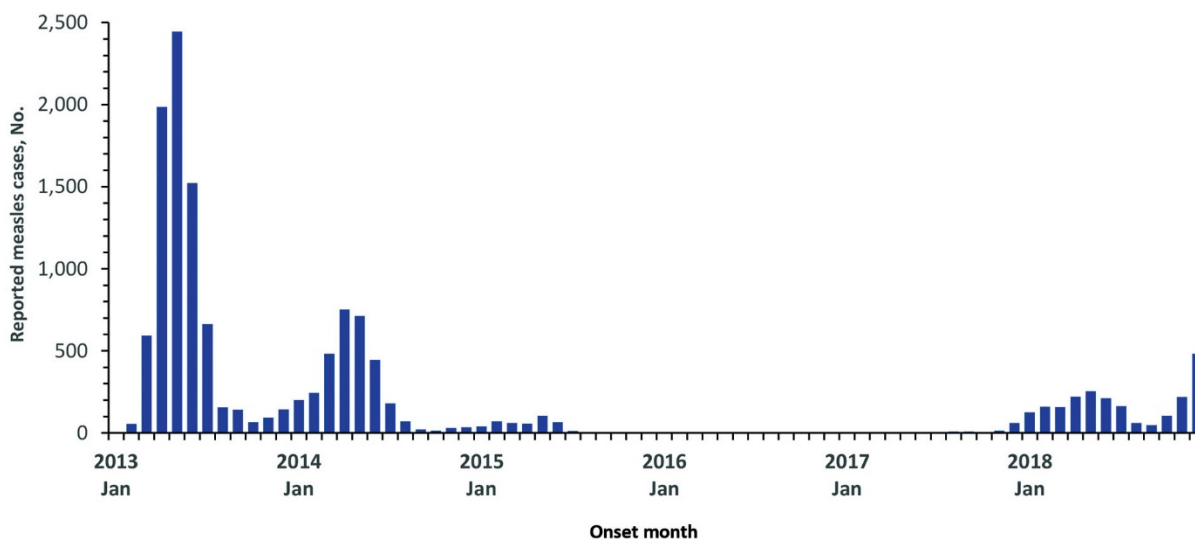
Year	MCV1 coverage, %	MCV2 coverage, %
1990	99	N/A
1991	81	N/A
1992	16	N/A
1993	61	N/A
1994	63	N/A
1995	61	N/A
1996	88	N/A
1997	95	N/A
1998	90	N/A
1999	97	N/A
2000	97	N/A
2001	100	8
2002	99	40
2003	80	57
2004	86	75
2005	92	87
2006	95	88
2007	97	92
2008	96	87
2009	83	71
2010	94	84
2011	94	77
2012	93	84
2013	97	89
2014	92	87

*MCV, measles-containing vaccine; MCV1, first dose of MCV; MCV2, second dose of MCV; measles vaccine was used until 2004; measles-mumps-rubella vaccine was introduced in 2004. N/A, not applicable. Source: Official country estimates reported to WHO (5).

Appendix Table 4. The design of the coverage survey and sample size per birth cohort, Georgia, 2015–2016*

Domain	Strata	PSU	# of PSUs	SSU	# of SSUs per PSU	# of TSUs per SSU	Design	PSU size	Total children
1	Tbilisi (capital city)	Child	750	N/A	N/A	N/A	SRS	1	750
2	Kutaisi (city)	Child	600	N/A	N/A	N/A	SRS	1	600
3	Batumi (city)	Child	600	N/A	N/A	N/A	SRS	1	600
4	Three large cities								1,950
	Rustavi and Poti (cities)	Child	50	N/A	N/A	N/A	SRS	1	50
	Gori (district)	Village	10	Child	5	N/A	2-stage cluster	50	50
	Kobuleti, Marneuli, Zugdidi, and Gardabani (districts)	Village	5	Child	5	N/A	2-stage cluster	25	25 × 4 = 100
	Remaining 54 districts	District	24	Village or town	5	5	3-stage cluster	25	24 × 5 × 5 = 600
	Rest of Georgia								800
	Georgia								2,750

*PSU, primary sampling unit; SSU, secondary sampling unit; TSU, tertiary sampling unit; SRS, simple random sampling; N/A, not applicable. Rustavi and Poti were combined in one unit for sampling purposes.



Appendix Figure. Reported cases of measles by month of onset, Georgia, 2013–2018.