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Impact of rubella vaccination on elimination of congenital rubella syndrome in Sri Lanka: progress and challenges

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ABSTRACT

Rubella infection in pregnancy can lead to pathologies, including miscarriage, stillbirth and congenital rubella syndrome (CRS) in the neonate. Rubella vaccination can prevent all occurrences of CRS. In Sri Lanka, significant outbreaks of CRS occurred in 1994 and 1995, with 275 and 212 reported cases. In 1996, Sri Lanka introduced rubella vaccination for women aged 16–44 years, to stop CRS. Measles–rubella vaccine was introduced into the routine immunization schedule in 2001 and additional campaigns were carried out in 2003 (all 11–15 year olds) and 2004 (all 16–20 year olds). Reported immunization coverage with a single dose of a rubella-containing vaccine has been more than 95% since 2000. Laboratory-supported surveillance for rubella and CRS was started in 1992. Reported rubella cases fell from 364 (incidence 19/million population) in 1999 to 96 cases (incidence 5/million population) in 2002 and further to 12 cases (incidence 0.6/million population) in 2014. Laboratory-supported CRS surveillance was started in 1990 and the highest number of CRS cases, 275 (incidence 77/100 000 live births), was diagnosed in 1994. Reported CRS cases fell from 22 cases (incidence 7/100 000 live births) in 2002 to 3 cases (incidence <1/100 000 live births) in 2014. Almost 20 years of routine rubella vaccination has resulted in >96% reduction in reported rubella cases and a corresponding >98% reduction in CRS cases. Despite this great achievement, work remains to eliminate rubella and CRS from Sri Lanka.

Key words: congenital rubella syndrome, elimination, rubella-containing vaccine, rubella vaccination, Sri Lanka

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BACKGROUND

Rubella infection in pregnancy can lead to pathologies, including miscarriage, stillbirth and congenital rubella syndrome (CRS) in the neonate, particularly during the first trimester of pregnancy. Widespread epidemics are still experienced in some low- and middle-income countries, despite extensive worldwide vaccination efforts.[1,2]

Evolution and identification of disease entities and descriptions of CRS began in 1752 and intensified with the experience of a major pandemic in 1963. Global attention on epidemiological studies describing correlates and identification of the rubella virus in CRS led to the development of a preventive vaccine during the late 1960s. By 1996, only 83 Member States of the World Health Organization (WHO) had introduced a rubella-containing vaccine (RCV) aiming at CRS control; however, there has subsequently been a steady increase in the number of countries introducing rubella vaccination.[2,3]

Rubella has been described as a periodic disease with epidemics occuring every 5–9 years, and the incidence of surveillance-detected cases varying from 0.8 to 4/1000 live births during epidemics to 0.1–0.2/1000 live births during non-epidemic periods.[3] By the end of 2009, 130 WHO Member States had introduced RCV into their national immunization schedule, including four of the 11 Member States in the WHO South-East Asia Region.[3]

CRS was estimated to have affected 22 000 babies in 1996 in Africa, 46 000 in South-East Asia and nearly 13 000 in the Western Pacific. Very few countries in these regions introduced RCV between 1996 and 2008, so a significant reduction of the disease burden of rubella and CRS was not expected over this time.[4]

In September 2013, the WHO Regional Committee for South-East Asia adopted resolution SEA/RC66/R5, with the goal of eliminating measles and achieving control of rubella/CRS by

2020.[5] In 2014, the South-East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG) reported that they were encouraged by the commitment of countries to this regional goal and by their efforts to put in place the necessary programme components to achieve this goal, including building laboratory capacity, developing systems to conduct case-based reporting, and implementing data-feedback mechanisms.[6]

Substantial progress in control of CRS has been achieved in Sri Lanka, with the introduction of rubella vaccination into the national immunization programme since 1996, leading to a marked decline of CRS-related morbidity and mortality. The national elimination plan was revised in September 2015 and sets elimination targets of <1 rubella case/million population and zero CRS cases/100 000 live births by 2020. Rubella and CRS surveillance have been intensified to achieve the revised targets by 2020.[7] Against this background, the country is working towards elimination of rubella and CRS; detailed guidance will be published in January 2016. This paper summarizes country activities in Sri Lanka to date, the current situation regarding CRS, prospects for elimination of CRS, and the way forward to achieve the goals for elimination of CRS.

PRACTICES AND PERSPECTIVES IN ELIMINATION OF CONGENITAL RUBELLA SYNDROME

Rubella vaccination policy

Vaccination of women of reproductive age (16–44 years) against rubella has been started as a national policy and has been included in the National Expanded Programme on Immunization (EPI) in Sri Lanka since 1996, based on the evident CRS epidemics in 1994–1995 (see Tables 1 and 2). Through the National EPI, one dose of monovalent measles vaccine had been given routinely at the age of 9 months since 1984, but a requirement to introduce a second dose was identified after a measles outbreak in 1999–2000. This gave an opportunity to introduce a combined measles–rubella (MR) vaccine into the National EPI, and in 2001 MR vaccine was introduced for all children at the age of 3 years, through the National EPI.[8]

In 2011, a National EPI policy decision was taken to introduce measles–mumps–rubella (MMR) vaccine to the EPI. The MR vaccine given at the age of 3 years and measles monovalent vaccine given at the age of 9 months were replaced with MMR vaccine given at 1 year of age, but this was rescheduled in 2015 to be given at 9 months. Currently, all children aged 9 months (birth cohort of around 350 000) and 3 years receive MMR vaccination.[8,9]

Supplementary immunization through catch-up vaccination campaigns conducted in 2003 among individuals aged 10–15-years (coverage of 95%) and in 2004 among those aged 16–20 years (coverage 72%) with MR vaccine further contributed to the development of population immunity to rubella.[8,10]

In addition, school-based adolescent rubella vaccination has been given at the age of 14 years since 2002, initially for girls only. Boys aged 14 years were included in 2004 and this strategy continued until 2012, then stopped once all children who had received MR vaccine at the age of 3 years in 2001 had reached 14 years.[8]

Since 2000, field health-care staff ask all women of reproductive age for their history of rubella vaccination at community level, when a new couple starts their family life and is registered onto the "Eligible Couple Register". If the field health-care staff find anyone who has not been vaccinated, they ensure they are vaccinated for rubella at that time.

Standards for surveillance of rubella/ congenital rubella syndrome

Rubella and CRS have been identified as notifiable diseases by the Government of Sri Lanka and notification has been mandatory since 1996.[11] Rubella antibody testing was continued during the 1990s and specific rubella immunoglobulin (IgM) testing, with follow-up of individuals with elevated titres, was established at the Virology Laboratory after 1990. During the period 1994–1995, an increased number of CRS cases were detected at the laboratory and by clinicians, following an outbreak of rubella; the College of Paediatricians was involved in a special survey (combined retrospective and prospective)

Table 1: Rubella vaccination policy in Sri Lanka, 1996 to present

Year	Vaccine	Target group(s)
1996 EPI	Rubella	Women aged 16–44 years
2001 EPI	MR	All children aged 3 years
2002 (EPI)	MR	14 years (girls first and all after 2 years)
2003 Catch-up campaign	MR	10–15 years (95% coverage)
2004 Catch-up campaign	MR	16–20 years (72% coverage)
2011 EPI	MMR (replacing Measles at 9 months and MR at 3 years)	
	MMR1 advanced to 1 year of age in 2011 and re-scheduled to 9 months in 2015; MMR2 at 3 years of age	

EPI: Expanded Programme on Immunization; MMR: measles–mumps–rubella combined vaccine; MR: measles–rubella combined vaccine.

Table 2: Cases of rubella and congenital rubella syndrome from 1991 to 2014

	Rubella			CRS				
Year	Clinical cases of rubella	Laboratory-confirmed rubella	Birth cohort	Suspected cases of CRS investigated	Laboratory-positive cases	Diagnosed CRS	CRI	Discarded
1991	—	4	—	659	3	3	—	656
1992	—	—	—	12[a]	12	12[a]	—	0
1993	—	35	—	1142	86	10[a]	—	1132
1994	—	221	356 071	2069	89	275[c]	—	1848
1995	87	214	342 224	1632	81	212	—	1418
1996	138	37	340 649	1847	59	143	—	1704
1997	115	63	333 219	2070	17	115	—	1955
1998	132	NA	322 672	NA	26	136	—	—
1999	364	44	328 725	2655	45	155	—	2500
2000	122	14	347 749	2232	25	27	—	2205
2001	146	15	358 583	2258	15	15	—	2243
2002	96	12	367 709	2206	22	22	—	2184
2003	101	42	367 064	1092	6	6	—	1086
2004	54	NA	364 711	NA	19	19	—	—
2005	156	NA	370 731	NA	5	5	—	—
2006	89	NA	373 538	1630	1	1	—	1629
2007	55	NA	386 513	1495	4	4	—	1491
2008	35	94	379 912	1827	2	2	—	1825
2009	27	26	376 843	871	3	0	3	868
2010	65	22	364 565	1037	5	3	2	1032
2011	438[b]	142	363 492	907	4	4	—	903
2012	61	19	355 900	1366	18	12	2 (2 remained untraceable)	1352
2013	24	20	365 524	1181	5	5	—	1176
2014	12	10	349 715	1168	4	3	1	1164

CRI: congenital rubella infection; CRS: congenital rubella syndrome; NA: could not identify exact numbers from available information.

[a] Laboratory-confirmed cases only.

[b] Since this was during an outbreak, only five cases from each locality were laboratory confirmed.

[c] Paediatricians' survey data.

and identified 275 clinical cases of CRS (103 were laboratory confirmed) in 1994, and 169 cases of CRS in the first 4 months of 1995, with a total of 212 for the whole of 1995.[8]

Since 1996, a routine system has been used to notify all suspected cases of rubella and CRS, from all health-care institutions, to the medical officer of health of the patient's residential area, who is responsible for community-level health care of the people. Any infant with a history that is compatible with the specified case definition for CRS surveillance, which is "maternal history of rubella infection and/or with signs and symptoms from any of cataract/congenital glaucoma,

pigmentary retinopathy, congenital heart disease, loss of hearing or purpura, splenomegaly, jaundice, meningo-encephalitis, microcephaly, mental retardation, radiolucent bone disease or laboratory rubella IgM-positive result", is notified and a detailed case-based investigation is conducted. Details of CRS cases investigated in the field are compiled weekly and reported to the Epidemiology Unit, Ministry of Health, together with case-based field-investigation reports. Rubella notification also follows the same routine surveillance system but notifications are based on surveillance case definitions given in the national *Surveillance case definitions for notifiable diseases in Sri Lanka* for rubella and for measles.[11]

Further, the field-level medical officers of health have developed good working relationships with the private health sectors and receive their notifications of rubella and CRS. All reported cases are compiled and reported to the Epidemiology Unit surveillance system on a weekly basis, and the completeness and timeliness of the information reported is regularly monitored.

In addition, if the field-level public health midwife who provides house-to-house domicillary care identifies any suspected cases of rubella or CRS at household level, they report them to their relevant field-level medical officer of health for further investigations, reporting, preventive measures and follow-up. It is expected that all suspected cases of rubella and CRS are tested at the laboratory for rubella IgM for case confirmation.

In Sri Lanka, nearly 100% of births occur in health institutions, and over 90% take place in institutions with specialists available. More than 90% of patients attend conventional (rather than traditional) health facilities,[12] where the majority of CRS cases are notified. Active surveillance and zero reporting has been added since 2004, including all these health-care institutions as sentinel sites in which medical specialists are available. These sentinel-site hospitals have identified surveillance in-charge officers who actively look for cases and report weekly to the Epidemiology Unit, Ministry of Health. In the abscence of cases, essential zero reporting ensures the comprehensiveness of reporting. The completeness and timeliness of weekly reporting from sentinel sites is closely monitored.

A blood sample is collected from patients on obstetric wards, for TORCH (toxoplasma, rubella, cytomegalovirus and herpes) screening, if the maternal history is suggestive of a risk of exposure to possible rubella infection or babies are born with congenital abnormalities. These samples are sent to the Virology Laboratory at the Medical Research Institute, Ministry of Health, where they are tested for specific antibodies. Babies who are positive for rubella IgM are identified and reported to the National Surveillance System at the Epidemiology Unit, Ministry of Health and followed up for rising antibody titres. The Epidemiology Unit is the main unit that is nationally responsible for surveillance of rubella/CRS and compiles information received, compares the compatibility of observations and test results, and finally classifies cases for CRS, congenital rubella infection (CRI) or discard.

Case classification

Case classification is conducted in accordance with the regional guidelines for case classification of CRS,[13] which are described as list A (cataract, congenital glaucoma, congenital heart disease, loss of hearing and pigmentary retinopathy) and list B signs (purpura, splenomegaly, microcephaly, mental retardation, meningo-encephalitis, radiolucent bone disease and jaundice within 24 h of delivery). A clinically compatible CRS case that has at least two symptoms from list A or one from list A and one from list B is considered as a CRS case. If such a case has an IgM-positive laboratory report, it is considered as a laboratory-confirmed CRS case. All other infants with no clinical signs of CRS but who have a positive rubella-specific IgM test, will be classified as CRI. Cases suspected but not compatible with CRS or CRI are discarded as non-CRS or non-CRI cases.

THE SITUATION OF CONGENITAL RUBELLA SYNDROME IN SRI LANKA 2002–2012

Data sources

As it is the national focal point for routine surveillance of communicable disease, the Epidemiology Unit received all compiled data on notified rubella and CRS on a weekly basis through the "Weekly Return of Communicable Diseases" (WRCD), which were entered into the national database.

Weekly reporting from sentinel sites of rubella and CRS cases were maintained on separate databases and the data entered were used to assess the compatibility of numbers reported, to identify individual cases and to exclude duplicates.

Case-based special surveillance was done routinely at the field level for all clinically compatible rubella and CRS cases, and forms that were received were analysed for case identifications and final classifications. All CRS cases identified and tested at the laboratory were used to identify the final results.

Clinicians, including those from specialized units (ophthalmology and cardiology), identified around 1000–1500 suspected cases per annum (including samples for TORCH screening) and tested these for rubella at the National Virology Laboratory. All babies who tested positive for rubella antibody (IgM) have been routinely traced back since 2008, to identify CRS cases and ensure detailed case-based investigations for final case classification.

In the preparation of this paper, the authors were permitted to extract reported information on rubella and CRS cases, as well as laboratory test results from the Ministry of Health's national databases.

Observations

The completeness of reporting of weekly reports of rubella and CRS has been regularly monitored and maintained at around 90–100% for more than a decade by the National

Communicable Disease Surveillance Programme of the Epidemiology Unit.

Data collected from the National Virology Laboratory and the National Communicable Disease Surveillance Programme were compiled. Population data on birth cohorts, which were obtained from the Medical Statistics Unit and from the Department of Census and Statistics are presented in Table 2. Continued surveillance information has shown that the incidence of CRS in the country has been maintained at below 1 per 100 000 live births for the last 15 years (see Figs. 1 and 2).

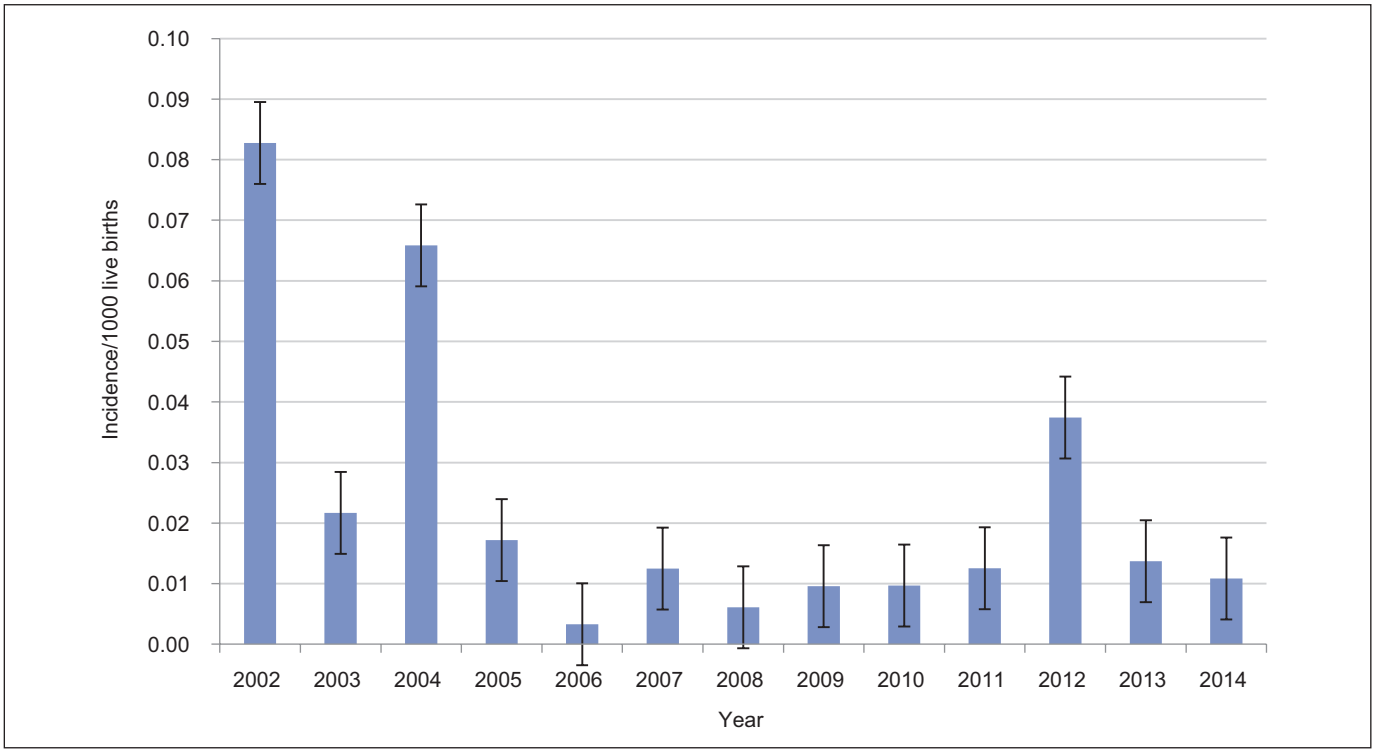

Figure 1: Incidence of congenital rubella syndrome cases by year with 95% confidence intervals

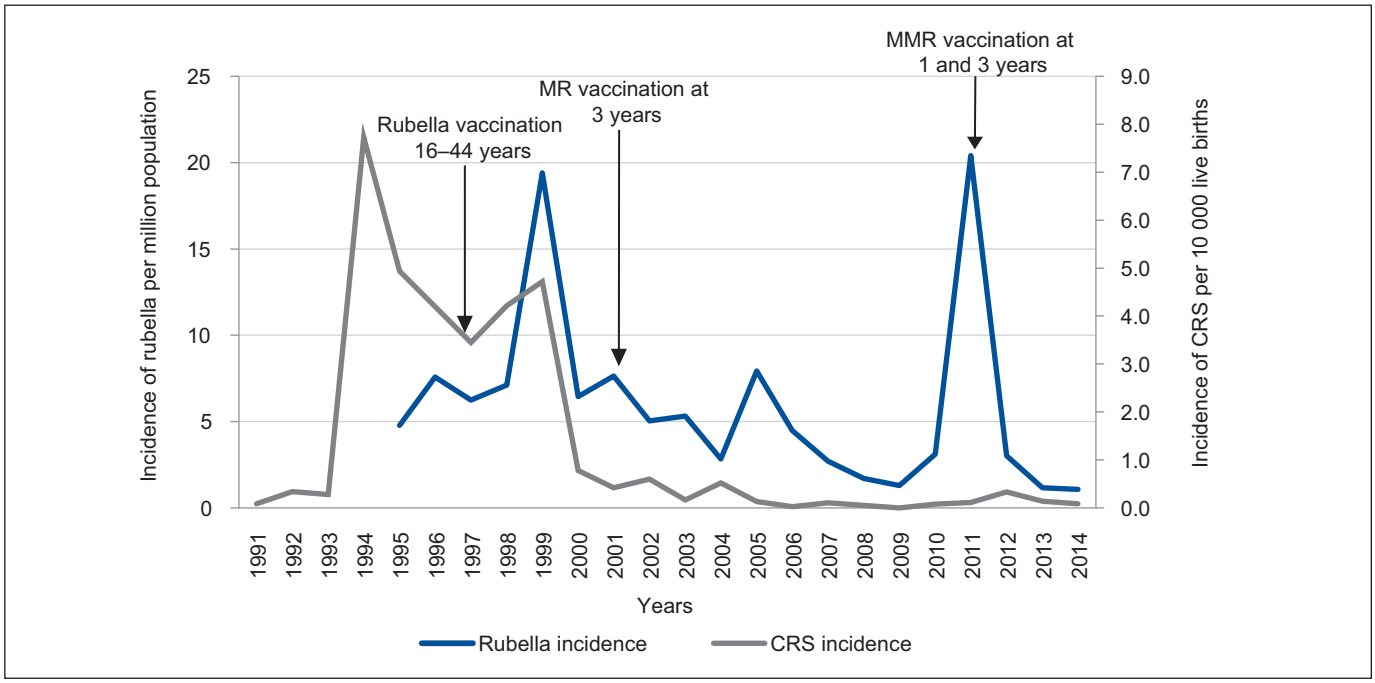

Figure 2: Trend of rubella and congenital rubella syndrome cases

CRS: congenital rubella syndrome; MMR: measles–mumps–rubella vaccination; MR: measles–rubella vaccination.

National coverage of MR (during 2001–2011)/MMR (during 2011–present), as shown in Figure 3, contributes to maintenance of high population-level immunity among children under 15 years of age. High transmission of rubella experienced among adult males during 2011 was probably due to the number of adult males who were still susceptible to rubella, but were expected to be protected by herd immunity at the population level. Adult males still remain susceptible because the first rubella vaccination was introduced only to females of reproductive age (16–44 years) in 1996, and the first exposure of males to rubella vaccination was in 2001 (through EPI at 3 years) and during 2003–2004 (measles catch-up campaign with MR).

All pregnant mothers (367 528 in 2014) were asked for their history of rubella vaccination status at antenatal clinics and routine reporting to the National Maternal and Child Health Programme detected that 98% of pregnant mothers were protected against rubella disease in 2014 (personal communication). A gradual increase in the coverage of rubella protection has been observed over the last 5-year period reported, from 93% in 2008 to 97% in 2013.[14]

A sero-survey conducted in 1999 showed a range of 75–92% susceptibility to rubella in children aged 3–13 years, providing research-based evidence for the decision in 2001 to vaccinate all children aged 3 years with RCV, as the best strategy in Sri Lanka to reduce the risk of CRS in the long term.[13,15]

Case-based CRS investigation of all suspected cases at institutional and field level has been strengthened. If a pregnant mother is found not to have been vaccinated against rubella (without a proper history of documented rubella dose), adequate investigation and follow-up of the baby is done to exclude possible CRS, and post-partum rubella vaccination is administered to the mother. Close monitoring of the sentinel-site zero-reporting system, CRS surveillance, and laboratory surveillance of rubella infection (IgM) of neonates with any congenital abnormalities is further strengthened by close vigilance that is expected to halt endogenous transmission of rubella.

Recent outbreaks of rubella and congenital rubella syndrome

Sri Lanka experienced sporadic isolated small outbreaks of rubella in 2011. A total of 410 of 438 cases of rubella reported in 2011 were outbreak related (see Table 3); the remaining 28 cases were identified via routine surveillance, and case-based investigations could not identify any relationship with outbreak cases. The majority of reported outbreak cases were adult males and locations were mainly military camps or factories where adult males were in close proximity to each other, making those who had not been immunized through the National EPI more susceptible to infection. Detailed analysis revealed that even though obvious rubella disease was not seen in females, 12 cases of CRS were diagnosed following outbreaks experienced during this period (see Table 3).

STRENGTHENING STRATEGIES FOR ELIMINATION OF CONGENITAL RUBELLA SYNDROME – LESSONS LEARNT

Sri Lanka has already achieved the regional CRS control target of <1 CRS case per 100 000 live births and is progressing well

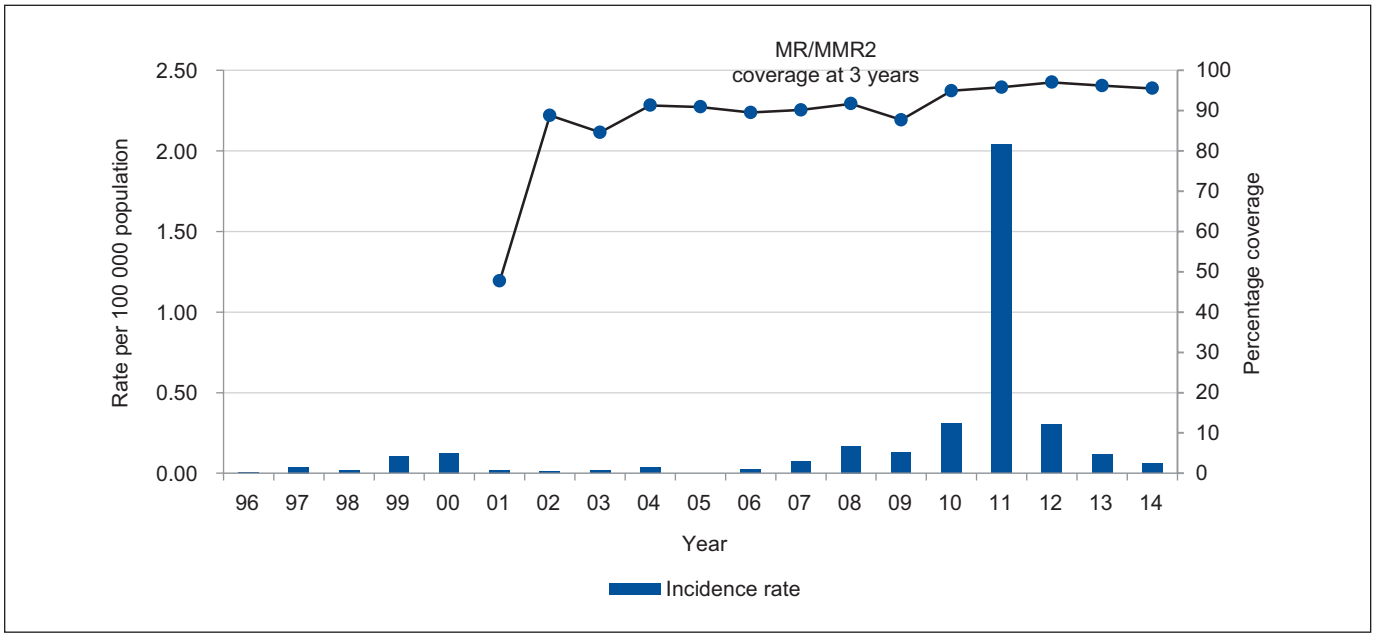

Figure 3: Incidence of rubella cases (1996–2014) and MR/MMR2 vaccination coverage (2001–2014)

MMR2: second measles–mumps–rubella vaccination (from 2011 to present); MR: measles–rubella vaccination (2001–2011).

Table 3: Rubella outbreak situation 2011 and CRS cases in 2012

District	Location	Number of rubella cases 2011	Number of CRS cases 2012
Gampaha	Factory 1	41	2
	Factory 2	31	
Galle	Military camp	12	2
Colombo	Hotel 1	14	2
Moneragala	Military camp	126	—
Polonnaruwa	Military camp	5	—
Badulla	Military camp	97	—
Anuradhapura	Military camp 1	22	—
	Military camp 2	25	—
Badulla	Military camp	37	—
Nuwara Eliya	—	—	2[a]
Kurunegala	—	—	2[a]
Ratnapura	—	—	1[a]
Kalutara	—	—	1[a]

[a] Military personnel were from all over the country. CRS cases in districts that differed from those of military camps were probably due to transmission of rubella to susceptible females through military personnel who were asymptomatic had only mild infections.

to achieving zero endogenous transmission of rubella by 2020. National immunization coverage of RCVs (MR/MMR) at the age of 3 years has continued to be above 95% from 2010 to 2014, as reported through United Nations Children's Fund (UNICEF)–WHO joint reports (author permitted access to national data).

Despite all this, the authors understand the challenges ahead for completeley eliminating CRS. Identification of population-level immunity by serosurveillance and population-susceptibility profiles is essential to ensure success. Community transmission of rubella disease is expected to be at a low level, owing to high coverage of rubella vaccination preventing sustained community transmission, through herd protection. But potential transmission in special situations, such as gatherings of adult males, is identified as a possible factor favouring transmission. Further, importation of rubella virus by international travellers is possibile. However, establishment of transmission in the community is not likely to occur, owing to high rubella immunity among females and children aged up to 15 years.

Sri Lanka serves as a good example of how different combined strategies work to provide one path for success. Such different vaccine-implementation strategies pave the way for success in filling the gaps in population immmunity, while a stregthened surveillance system detects cases early, using case-based investigations.

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