Journal of Advances and Scholarly Researches in Allied Education
Vol. 16, Issue No. 1, January-2019, ISSN 2230-7540

A Research on Some Challenges and Strategies in Elimination of Measles in South-East Asia

Sudhir Khanal*

PhD-Public Health, AZTECA University, Mexico

Abstract – Measles is a highly infectious viral disease, with complications in over 30% of cases, including deaths. Following successful eradication of small pox and elimination of polio, measles is viewed as the next candidate for global eradication. While the strategies and tools to fight measles elimination drive are available, suboptimal implementation of strategies compounded by lack of resources have been the major challenge to achieve the goal. The global resurgence of the disease in areas that were considered to be free of measles have shown how complacency to the disease can lead to large outbreak.

----------X----------

INTRODUCTION

Measles disease

Aetiology: Measles (khasra or chotimata in Hindi, niang pyriat in Khasi) is a highly transferable disease. MeV (measles virus) is a RNA virus of the Paramyxoviridae group of the variety morbillivirus; it is serologically a monotypic virus, however genetically recognized into 24 genotypes gathered in eight clades (A–H).

Pathogenesis: Measles virus causes systemic infection. The median incubation period is 14 days (range, 7–21 days) from exposure to onset of rash. 2 to 3 days after infection and replication in the respiratory epithelial cells, viruses reach regional lymph nodes and a primary viremia occurs with subsequent spread to the reticuloendothelial system. Following further viral replication in regional and distal reticuloendothelial sites/organs, there is a second wave of viremia, which occurs 5 to 7 days after initial infection. During this secondary viremia, there may be infection of all organs, including the skin, which contributes to the typical rash and the gastrointestinal tract mucosa, which is visible in the oral mucosa as Koplik spots. Measles virus multiplication is more intense now in upper respiratory tract and virus is shed from nasopharynx fluid. Thus, the person is infectious to others from 4 days before rash onset until 4 days after rash onset, the period when the virus spreads into the air as droplets and aerosols). Inhaling such virus results in new hosts getting infected in the community; with the development of immunity, the virus load in the body declines and disappears.

Reservoir: There is no extra human reservoir for measles virus. Infection is self-limited in most individuals, without a chronic carrier state.

Transmission: Measles is a highly infectious (easily transmissible) viral disease spread by direct contact and airborne transmission. If a case of measles is introduced among a group of non-immune subjects, secondary infection may occur in 12 to 18 persons (Ro= 12–18).

Clinical features and complications: Towards the end of the incubation period, patients develop prodromal symptoms of high fever, cough, coryza and conjunctivitis. The typical maculopapular rash appears after another 3–4 days, often accompanied by a fever that peaks at 39–40 °C. At the onset of rash, bluish-white Koplik spots, which are pathognomonic of measles, are seen in the oral mucosa. Patients normally improve by the third day after rash onset and are fully recovered 7–10 days after onset of disease.

The severity of measles varies widely, depending on a number of host and environmental factors. Measles tend to be severe in under 5 children, particularly in those below 3 years. Malnourished (especially with vitamin A deficiency) have risk of severe disease and complications consequent to severe vitamin A depletion. In overcrowded situations and in household transmissions the inoculum dose tends to be high contributing to severity of illness. Children with HIV infection are particularly vulnerable to severe measles. Measles mortality is more common with severe measles. In SEAR countries, case-fatality rates among young children may reach 5–10%.

Relatively common complications of measles include otitis media, laryngo-tracheobronchitis, diarrhoea and pneumonia. In children, otitis media occurs in 5–15% of cases and pneumonia in 5–10%. Diarrhoea and dysentery are also common complications of measles. Persistent diarrhoea with

protein-losing enteropathy may ensue, particularly in infants. Post-infectious measles encephalitis occurs in about 1/1000 cases, and subacute sclerosing pan encephalitis, a slowly progressing infection of the central nervous system, occurs in about 1/5 000–10 000 cases.

Treatment: There is no particular anti-measles treatment; so the fundamental weapon against this potential disease is primary prevention with immunization. The malnourished and the immune compromised are influenced by serious measles infection thus immunizing them with measles containing vaccine (MCV) is basic. In the pre-vaccination period measles was a feared infection influencing over 90% of the children before they attended the age of 15 years

The beneficial impact of two doses of vitamin A during treatment of measles is well established. WHO's current policy advocates administering vitamin A to all acute cases.

Immunity following measles infection: The long-lasting, possibly lifelong, immunological memory of measles virus following natural infection includes both continued production of measles virus-specific antibodies and the circulation of measles virus-specific CD4+ and CD8+ T lymphocytes. Although the levels of anti-measles-virus antibodies may diminish over time, the ability to rapidly mount secondary humoral and cellular immune responses is important in providing protection from infection.

Depending upon the titre of passively acquired maternal antibodies; infants are usually protected against measles for 6–9 months. A large infectious dose may occasionally overcome the protection afforded by maternal antibodies, and measles has also been observed in neonates whose mothers escaped natural infection and had never been vaccinated against measles.

Measles vaccine immunization and immune response: Measles vaccine consists of live, attenuated strains of measles virus and is available, either as monovalent measles vaccine or as measles-containing vaccine (MCV) in combination with rubella, mumps or varicella vaccines. When using the combined measles–rubella vaccine, measles–mumps–rubella (MMR) vaccine or measles–mumps–rubella–varicella (MMRV) vaccine, the protective immune responses to each individual vaccine antigen as well as vaccine-associated adverse events remain largely unchanged. Measles vaccine protects equally well against all wild measles virus genotypes. Although a live vaccine, virus does not spread from vaccinated to the unvaccinated. Measles vaccine induces both humoral and cellular immune responses comparable to those following natural infection, although antibody titres are usually lower. Following vaccination, transient measles-specific immunoglobulin (Ig) M antibodies appear in the blood and IgA antibodies appear in mucosal secretions; IgG antibodies, hence protective immunity, persist for decades. Vaccination also induces measles virus-specific CD4+ and CD8+ T lymphocytes.

Vaccinating infants before or at the age of 6 months often fails to induce seroconversion due to the immaturity of the immune system as well as the presence of neutralizing maternal antibodies. The development of a high avidity antibody response is critical to the development of protective immunity to measles virus. Antibody avidity to measles virus is generally lower in children vaccinated at age 6 to 9 months compared with the avidity obtained in children vaccinated at age 12 months or above. Studies on revaccination in children who failed to respond to their first dose of measles vaccine given at 12 months show that almost all develop immunity after their second dose. Although vaccine-induced antibody concentrations decline over time and may become undetectable, immunological memory persists and, following exposure to measles virus, most people who have been vaccinated produce a protective immune response. Following vaccination, the long-term persistence of neutralizing measles antibodies (26–33 years) and long-lasting protection against measles have been demonstrated by several investigators. No studies yet have identified declining immunity as an important risk factor.

Measles as a global health priority

Measles was a leading global cause of child morbidity and mortality prior to the introduction of measles vaccines in the 1960's and was responsible for more than an estimated two million deaths annually before the increase in global measles vaccine coverage in the 1980's as a consequence of the Expanded Programme on Immunization (EPI). Measles incidence and mortality declined substantially due to the increasingly widespread use of attenuated measles-containing vaccines administered through immunization programmes and, subsequently, through supplementary mass preventive vaccination campaigns. Measles vaccination is estimated to have prevented 21.1 million deaths globally from 2000 to 2017. Despite this enormous progress, measles remains an important vaccine-preventable cause of morbidity and mortality, responsible for more than 100,000 deaths each year, and is a key indicator of the quality of immunization programmes. Due to its high infectiousness, measles serves as the "canary in the coal mine": outbreaks show where children have not been vaccinated and the age distribution of cases identifies age-specific immunity gaps reflecting past programme performance. Importantly, measles anywhere is a risk for measles everywhere, as witnessed by the frequency of measles outbreaks around the world, often a result of importation of cases from other countries.

Measles disease is unswervingly linked to the health target 3.2 on child mortality as well as to target 3.8 on universal access to safe, effective, quality and affordable vaccines for all under Sustainable Development Goal (SDG) 3 for health. This goal has an overall impact on child survival and development and thus has an indirect impact on SDG 1 for poverty, SGD 2 for food security and nutrition, SDG 4 for education, SDG 5 for gender equality and SDG 8 for economic growth and employment. It is also a continuation of the unfinished agenda of Millennium Development Goal (MDG) 4.

By reducing the economic burden of infectious diseases, vaccination helps eliminate poverty (SDG1) and promotes sustainable economic growth and productive employment (SDG8). Measles vaccination was shown to have the greatest return on investment, with US$ 58 dollars saved in future costs for every US$ 1 dollar spent, among 10 diseases in 73 Gavi-supported low- and middle-income countries from 2001-2020[33].

GVAP, endorsed in 2012 by the WHA to create a framework for immunization activities through 2020, set target dates for regional measles and rubella elimination. By 2015, four WHO Regions were to have eliminated measles and two to have eliminated rubella. By 2020, five WHO Regions were to have eliminated measles and rubella. Given the high priority to deliver measles and rubella vaccines through essential immunization services, achieving measles and rubella elimination goals will require higher coverage with measles-containing vaccine first (MCV1) and second (MCV2) doses than currently achieved (86% and 69% in 2018). A focus on measles and rubella elimination could promote both universal health care and primary health care by strengthening essential immunization services, addressing inequities in vaccine coverage, protecting zero-dose and under-immunized children, enhancing subnational disease surveillance systems, identifying new approaches to reduce critical immunization gaps, and building national ownership of immunization programmes.

Feasibility of measles elimination and eradication

Measles eradication is defined as worldwide interruption of measles or rubella virus transmission in the presence of a surveillance system that has been verified to be performing well. While measles elimination is defined as the absence of endemic measles transmission in a defined geographical area, e.g. region or country for ≥12 months in the presence of a well-performing surveillance system. However, verification of measles elimination takes place after 36 months of interrupted endemic measles virus transmission. Elimination is the pathway towards eradication.

Measles fulfills every criteria to be considered as eradicable, which were set up at the Dahlem Conference on Disease Eradication in the year 1997: (1) humans must be critical to looking after transmission, (2) precise diagnostic tests must be accessible, (3) a successful intercession (for this situation vaccine) must be accessible and (4) it must be conceivable to interfere with transmission for a delayed period in an enormous geographic territory.

Measles eradication is biologically feasible due to specific properties of the virus and the disease: humans are the main hosts for measles and no vectors are included, deep rooted resistance happens after normal infection, MeV has only one serotype and is a genetically steady virus, just wellspring of infection is an instance of measles which are for the most part obvious and the disease has no long haul bearer state. Notwithstanding, subclinical infection might be there in recently immunized people however they are probably not going to be infectious. MeV is quickly inactivated by warmth, light, acidic pH, ether and trypsin and has a short survival time (<2 hours) in air or fomites. Confinement of the patient for seven days from the beginning of rash covers the time of coherence and limits the odds of secondary infection among potential contacts.

Measles eradication is technically feasible due to availability of a very safe and effective vaccine that gives long term immunity (in any event 20 years) against every single known genotype, and the accessibility of exact diagnostic tests. Measles vaccine effectiveness is 85% with single dose when given at 9 months and 99% when given at >12 months of age. Likewise, MCV can be utilized during acute infection, and vaccination within two days of acute infection may alter the clinical course of measles and have milder disease. There are also easily available diagnostic tools that can be used to identify measles infection that makes the surveillance more effective and help in evidence-based planning for disease eradication.

The programmatic and operational feasibility of measles eradication, has been demonstrated in the region of Americas where all countries have eliminated measles and sustained the elimination using a set of strategies which are now time tested.

While biologic, technical and operational feasibility are necessary to achieve measles and rubella eradication, they are not sufficient. The feasibility of measles and rubella eradication requires broad public support and political will as well as sufficient financial resources to stop measles virus transmission everywhere. And it requires access to children in conflict settings and areas controlled by

[33] Ozawa S, Clark S, Portnoy A, Grewal S, Stack ML, Sinha A, Mirelman A, Franklin H, Friberg IK, Tam Y, Walker N, Clark A, Ferrari M, Suraratdecha C, Sweet S, Goldie SJ, Garske T, Li M, Hansen PM, Johnson HL, Walker D. Estimated

anti-government elements. In addition, an eradication programme requires strong governance, oversight and accountability as well as long-term commitment from all stakeholders. The ITFDE, established at The Carter Center in 1988 and currently supported by The Bill & Melinda Gates Foundation (BMGF), listed the following criteria for assessing whether a disease can be eradicated, highlighting the importance of both scientific feasibility and the need for political will and public support:

Scientific Feasibility

- Epidemiologic characteristics, including the potential existence of nonhuman reservoirs; ease of spread; induction of natural immunity; and ease of diagnosis
- Availability of an intervention, such as a vaccine, that ideally should be effective, safe, inexpensive, long-lasting, and easily deployed
- Demonstrated feasibility of elimination, such as documented elimination from a defined country or region

Political Will/Popular Support

- Perceived burden of disease
- Expected cost of eradication
- Synergy of eradication efforts with other interventions
- Necessity for eradication rather than control

Measles and rubella meet the criteria for scientific feasibility of eradication. The ITFDE report did not fully address programmatic feasibility. The real challenge concerns political will, public support, financial resources, and commitment to an eradication goal.

Since the introduction of measles vaccine in the early 1960's, there have been several rigorous assessments of the feasibility of measles eradication. More recently, the Executive Board of the WHO requested in May 2008 that an ad hoc group of experts assess the feasibility of measles eradication. The Global Technical Consultation to Assess the Feasibility of Measles Eradication concluded that "measles can and should be eradicated" and "recommended that the World Health Assembly consider establishing a target date for measles eradication once the South-East Asia Region established an elimination target", which it set in September 2013. The assessment considered the feasibility of measles elimination in each World Health Organization Region as well as the biological, technical, programmatic, and economic feasibility of measles eradication. Also considered were the impact of measles eradication on health systems and the implications for vaccine supply. The Advisory Group recognized that building the required political, social, and economic platforms for measles eradication would be both a disease control opportunity and an important developmental opportunity, requiring a broad multidisciplinary partnership, and stressed that the success of measles eradication would depend on strong management, accountability, communication, advocacy, and resource mobilization at all levels. Thus, the Advisory Group acknowledged the biological and technical feasibility of measles eradication but recognized the challenges in garnering the public support, political will, and financial resources that will be required to eradicate measles.

International Task Force for Disease Eradication. A decade ago, in 2009, the ITFDE concluded that "measles eradication is biologically possible, using tools that are currently available…. [but that] the delay in eradication of polio is a special obstacle to global measles eradication." The ITFDE reassessed measles eradication in 2015. The ITFDE restated the belief that measles and rubella eradication are technically feasible and recognized that efforts to control and eliminate measles and rubella accelerated since 2000. However, measles eradication "will require a much more demanding enterprise than the current effort, which has suffered from insufficient resources and wavering political commitment."

CURRENT GLOBAL MEASLES SITUATION

The WHA in 2010 established three milestones for measles control by 2015 that reflect the immunization strategies: 1) increase routine vaccination coverage with MCV1 to at least 90% nationally and at least 80% in every district; 2) reduce global annual measles incidence to less than 5 cases per million population; and 3) reduce global measles mortality by 95% from the 2000 estimate. Although the dates for these passed, progress is still assessed against these milestones as well as the GVAP regional elimination targets. Globally, these milestones and goals remain elusive, with variable progress among and within regions.

Measles and rubella vaccination coverage: Global overage with MCV1 was estimated at 86% in 2018 according to WHO and UNICEF (WUENIC) estimates. Regional MCV1 coverage was 74% for AFR, 90% for AMR, 82% for EMR, 95% for EUR, 89% for SEAR, and 95% for WPR. In 2018, 118 (61%) Member States achieved 90% MCV1 coverage and 55 (28%) Member States achieved at least 80% MCV1 coverage in all districts. In addition, as of July 2019, 173 (89%) Member States had introduced MCV2, with 69% coverage globally, and 168 (87%) Member States had introduced rubella vaccine into their national programmes.

Global coverage for rubella vaccine was 69%, with 32% coverage in AFR, 90% in AMR, 45% in EMR, 95% in EUR, 83% in SEAR, and 94% WPR.

Measles incidence: Annual measles incidence for reported cases was 49 cases/million population in 2018, with 353,236 cases reported through annual reporting. However, fewer than 5% of measles cases are reported globally, making a measles incidence milestone difficult to accurately measure. Of 179 countries, 96 had a measles incidence less than 5 cases per million population in 2018, and 66 countries had fewer than 1 case per million population. Every region had an increase in reported cases in 2018 relative to 2017, and major outbreaks have occurred in all regions, garnering global attention. While the proximate causes of the ongoing outbreaks are variable, ranging from political conflict, repeated importations, historical gaps in immunization coverage, weak immunization systems, and insufficient vaccination demand, all outbreaks are characterized by the predominance of cases among unvaccinated persons, reflecting programme failure to administer MCV over multiple birth cohorts. Thus, the current measles epidemiological situation in some settings reflects a predictable consequence of inadequate implementation of current strategies, with the build-up of susceptible individuals, endemic transmission, and imported measles cases sparking outbreaks.

Measles mortality: The 2017 estimate of measles-related mortality was approximately 110,000 deaths globally, with wide confidence intervals. This reflects an 80% decline in estimated measles mortality since 2000 and over 21 million lives saved due to measles vaccination during that time. While impressive, this number falls short of the 95% mortality reduction goal. 2018 mortality estimates will be released in November 2019.

Molecular surveillance: Monitoring progress toward measles and rubella elimination requires high-quality case-based surveillance with laboratory confirmation and supported with genetic characterization of measles and rubella viruses. In 2000, WHO established the Global Measles and Rubella Laboratory Network (GMRLN) to provide high-quality laboratory support for surveillance for measles, rubella, and congenital rubella syndrome. GMRLN is the largest globally coordinated laboratory network, with 704 laboratories supporting surveillance in 191 countries. These laboratories support the confirmation of measles and rubella cases, and molecular surveillance provides a means of tracking progress toward elimination and potential sources of imported cases. However, sequence data and geographic representativeness of reported measles and rubella sequences is not complete, with the African Region particularly underrepresented. During 2016–2018, only six of the 24 recognized measles virus genotypes were detected, and only four in 2018. Two genotypes (B3 and D8) accounted for 95% of reported sequences. During 2016–2018, the diversity index of each measles virus genotype reported to the Measles Nucleotide Surveillance (MeaNS) system, defined as the number of distinct measles sequences divided by the total number of records in the database, decreased overall. Of the 13 known rubella virus genotypes, reported genotypes declined from five to two. Overall, the genetic diversity of detected measles and rubella strains has decreased globally, consistent with progress toward elimination.

Regional measles and rubella elimination goals: Member States in all WHO Regions adopted measles elimination goals to be reached by or before 2020. The regional elimination dates are AMRO (2000), WPRO (2012), EURO (2015), EMRO (2015), AFRO (2020) and SEARO (2023). In addition, four of the Regions (AMRO, EURO, SEARO and WPRO) have rubella elimination goals.

While progress has been made by several metrics, including the number of Member States achieving verified elimination status and the number of Regional Verification Commissions (RVCs) and National Verification Committees (NVCs) established, the Regional elimination goals have not been achieved. All Regions have established RVCs, and 148 of 194 (76%) countries established NVCs. RVCs review all NVC reports and determine measles and rubella elimination status, following the WHO framework for verifying elimination. As of June 2019, 84 of 194 (43%) Member States were verified as having eliminated measles and 79 as having eliminated rubella. The overall status of elimination verification progress by Region is summarized in Table 1.

Table 1: Measles elimination verification by Region, July 2019

WHO Region (number of countries)	Regional Verification Commission Established	Elimination Achieved, Number (%) of Member States (n=194)
		Measles
Americas (35)	**Yes**	33 (94)
Europe (53)	**Yes**	33 (62)
Western Pacific (27)	**Yes**	7 (26)
Eastern Mediterranean (21)	**Yes**	2 (10)
South-East Asia (11)	**Yes**	5 (45)
Africa (47)	**Yes**	-
TOTAL		**84 (43%)**

The Region of the Americas was verified as having eliminated measles in 2016, although most countries were verified by their NVCs many years earlier. Unfortunately, this regional elimination status was lost in 2018 due to circulation of measles virus in Venezuela following a decrease in vaccination coverage and exportation to neighboring countries such as Brazil and Columbia. The Region of the

Americas is the only region to have eliminated measles, and thus demonstrates the feasibility of measles elimination. Many Member States have eliminated measles for decades and the last endemic case of measles in the Americas was in 2002. However, the reversal of this situation in 2018 also demonstrates the fragility of elimination status. Seven countries re-established measles virus transmission after having been declared eliminated, and similar loss of elimination status threatens other countries. In the Americas, Venezuela and Brazil lost their measles elimination status as did Mongolia in the Western Pacific Region. In the European Region, Albania, Britain, the Czech Republic, and Greece lost their elimination status. The recent reversals in measles control and elimination are fundamentally linked to the challenges of achieving and sustaining the high level of population immunity (approximately 92 to 94%) required to interrupt transmission, associated in many countries with insufficient political will, conflict, migration, humanitarian emergencies, and national financial investment. The precariousness of elimination status is also due to the extreme infectiousness of measles virus and more importations in an increasingly interconnected world.

STRATEGIES FOR MEASLES ELIMINATION IN WHO SOUTH-EAST ASIA REGION

The WHO South East Asia Region comprises of eleven countries -Bangladesh, Bhutan, DPR Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka , Thailand and Timor-Leste. These countries comprise of a birth cohort of almost 38 million.

All eleven countries of the WHO South-East Asia Region in the Sixty-Sixth Session of the Regional Committee, in 2013, adopted the goal of measles elimination and rubella control by 2020. To ensure adequate technical guidance to accelerate progress towards the goal, the Regional Strategic Plan for measles elimination and rubella control in the South-East Asia Region, 2014-20, was developed. The strategies adopted by WHO South-East Asia Region were:

1. Achieve and maintain at least 95% population immunity with two doses against measles and rubella within each district of each country in the Region through routine and/or supplementary immunization.

2. Develop and sustain a sensitive and timely case-based measles and rubella and CRS surveillance system in each country in the Region that fulfils recommended surveillance performance indicators.

3. Develop and maintain an accredited measles and rubella laboratory network that supports every country or area in the Region.

4. Strengthen support and linkages to achieve the above three strategic objectives through

a. Advocacy, social mobilization and communication

b. Outbreak preparedness and response

c. Measles immunization in an emergency

d. Research and development

e. Improve management of human resources at all levels; specially at middle level

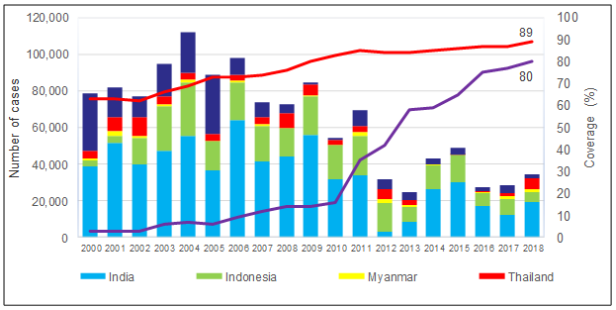
f. Identify and utilize synergistic linkages of integrated programme efforts

g. Programme monitoring and oversight

Progress towards measles elimination in WHO South East Asia Region

Five countries in the Region – Bhutan, Democratic People's Republic of Korea, Maldives, Sri Lanka and Timor-Leste have been verified to have interrupted transmission of endemic measles for more than 12 months and have maintained this status in 2019. Six countries of the Region – Bangladesh, Bhutan, Maldives, Nepal, Sri Lanka and Timor-Leste were verified as having controlled rubella and CRS in 2018.

Figure 1: Coverage of first and second dose of measles containing vaccine in routine immunization and measles cases in SEAR countries, 2000-2018



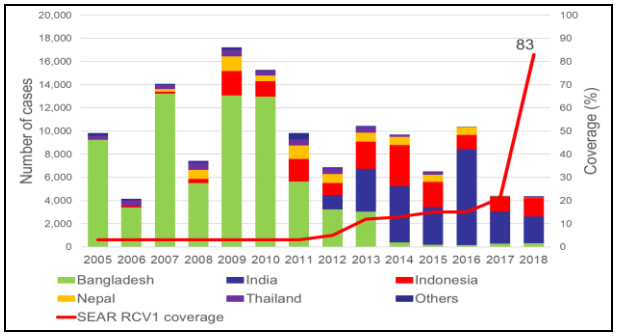
Source: WHO/UNICEF coverage estimates, July 2019 and WHO/UNICEF JRF and EPI/MOHFW

A 75% reduction in mortality due to measles was reported in 2017 as compared to 2000. The reduction in mortality was substantial during the period 2014 to 2017 (23%). As at the end of 2018, all 11 countries were administering two doses of MCV in routine immunization (RI) and 10 countries had already introduced rubella-containing vaccine (RCV). Coverage with the first dose of measles containing vaccine (MCV1) in 2018 was 89% compared to 63% in 2000. Six out of 11 SEA Region countries reported more than 95% coverage for

MRCV1 in 2018. Similarly, the coverage of second dose of measles containing vaccine (MCV2) was reported at 80% as compared to 65% in 2014 and 27% in 2000. Approximately 485 million children were reached through measles and rubella supplementary immunization activities (SIAs) during 2014–2019, mostly in India and Indonesia.

Similarly, coverage of one does of rubella containing vaccine (RVC1) in 2018 was reported at 83% compared to 13% in 2014 and 3% in 2000. This steep rise in coverage of rubella containing vaccine was attributed to nationwide introduction of rubella containing vaccine in routine immunization in two large countries India and Indonesia.

Figure 2: Coverage of one dose of rubella containing vaccine and rubella cases in SEAR countries: 2005-2018



Source: WHO/UNICEF coverage estimates, July 2019 and WHO/UNICEF JRF and EPI/MOHFW

Case-based surveillance for measles and rubella has been initiated in all countries in alignment with the regional guidelines, with India and Indonesia expected to complete the nationwide expansion by end of 2019. Seven out of eleven countries have already met the key surveillance performance indicator of more >2 cases of non-measles non-rubella discarded cases of fever and rash per 100,000 population at national level and only four countries have met this target in all first subnational level. CRS surveillance has been initiated in all 11 countries, either as sentinel surveillance or as part of the case-based surveillance system.

Table 1: Performance on key surveillance indicator of non-measles non-rubella discard rate in SEAR Countries, 2016-2018

Country	Discarded non-measles non-rubella			Percent sub-national units* reporting > 2 non-measles non-rubella cases		
	2018	2017	2016	2018	2017	2016
Bangladesh	2.46	2.37	1.96	70%	75 %	80%
Bhutan	38.98	21.47	8.05	100%*	100 %*	100%*
DPR Korea	2.28	2.10	2.01	83%	83%	83%
India	0.46	0.21	0.55	4%	5%	3%
Indonesia	0.77	0.14	0.95	8%	ND	ND
Maldives	7.42	17.26	3.22	100%*	100%*	100%*
Myanmar	1.03	0.68	0.59	19%	14%	11%
Nepal	3.93	2.60	2.83	69%	55%	56%
Sri Lanka	0.75	0.89	1.09	8%	23%	27%
Thailand	3.30	1.32	0.64	ND	ND	ND
Timor-Leste	11.02	10.07	8.25	100%*	100%*	100%*
SEAR	0.87	0.50	0.77			

*Bhutan, Maldives, Timor-Leste has taken epidemiological blocks to ensure sufficient population size for calculation.
ND: Data not available with WHO SEARO
Source: Volume 22, Week 03, 2019 Weekly reports, IVD SEARO

Surveillance data from all eleven countries has shown that large number of measles cases are unvaccinated or with unknown vaccination status. While most cases are less than 10 years of age, there has been significant increase in measles cases amongst age groups less than one year of age and more than 15 years of age indicating the change in disease epidemiology and need for intervention beyond the conventional age groups to close the immunity gap in the population for measles.

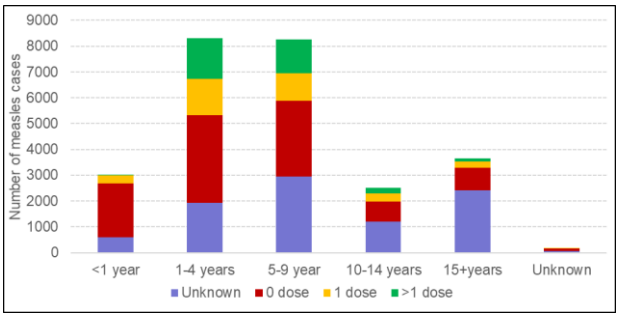


Figure 3: Vaccination of measles cases by age group in SEAR countries, 2018

All countries in the Region now have at least one proficient national laboratory to support measles and rubella case-based surveillance. In 2018, seven countries met the key surveillance performance indicators at national level while only four countries met the same indicators at sub-national level. The measles–rubella (MR) laboratory network has expanded from 23 laboratories in 2013 to 50 in 2018, with 41 laboratories accredited as proficient for measles and rubella testing. Nine new laboratories that were included in the network during 2018 – six in India and three in Indonesia are in the process of capacity-building. Capacity to perform molecular testing (genotyping PCR) has increased from 15 laboratories in 4 countries in 2014 to 25 laboratories in 10 countries in 2018. Similarly, 24 laboratories from 9 countries submitted data in

MeaNS and/or RubeNS compared to 4 labs in 2 countries in 2012. The numbers of nucleotide sequence data submitted in MeaNS have been increased from 41 sequences in year 2012 to 2347 sequences in 2018 which is approximately 15% of the chains of transmissions reported in the Region. The commonly reported genotype for measles in 2018 were B3, D4, D8 and H1 while for rubella 1E and 2B were the reported genotypes.

MEASLES	2014	2015	2016	2017	2018
Bangladesh	B3	B3	**D8**	B3, D8	B3, D8
Bhutan		D8, B3	D8	D8	D8
DPRK	H1				
India	B3, D4, D8	B3, D4, D8	B3, D4, D8	D4, D8	D4, D8
Indonesia	D8, D9, G3	D8, D9	D8, D9	D8	D8
Maldives					D8
Myanmar			H1, D8	H1	D8, H1
Nepal		D4, D8	D8		D8
Sri Lanka	B3		B3		D8, H1
Thailand	B3	H1	H1, B3, D8	H1, B3, D8	B3, D8, H1
Timor-Leste					
RUBELLA					
Bangladesh	2B				
India			2B	2B	2B
Thailand		2B		2B	1E
Source –MeaNS and RubNS database as of May 2019					

All 11 countries have well-functioning national verification committees that are independently assessing the programme's progress and reporting annually to the WHO South-East Asia Regional Verification Commission (SEA-RVC) for measles elimination and rubella/CRS control. The Regional Verification Commission (SEA-RVC) for measles elimination and rubella/CRS control was established in 2016 and meets annually to review and verify status of countries for measles elimination and rubella/CRS control.

Risk in Delaying measles elimainiton and eradicaiton

The changing epidemiology of measles could make eradication even more challenging in the future, thus creating urgency in accelerating progress toward regional elimination goals. First, as more women of child bearing age have vaccine-induced immunity and are not exposed to wild-type measles virus, lower levels of maternal antibodies are transferred to their infants, who then become susceptible to measles at a younger age. This has led to discussions as to whether the age of administration of MCV should be reduced from nine to six months of age and a change to the EPI schedule. The WHO currently recommends a supplementary dose of measles vaccine at six months of age in some circumstances, including during outbreaks, for refugees or internally displaced persons, and to HIV infected or exposed infants. However, measles vaccination at six months of age results in reduced immunogenicity and effectiveness compared to nine months of age. Second, there remains the possibility that vaccine-derived measles immunity may wane in older individuals, particularly those vaccinated below 12 months of age who were not subsequently exposed to wild-type virus, expanding the age range of susceptibility and need for vaccination. The experience thus far in the United States suggest this is not a public health problem but more data from other settings are needed, particularly in countries where MCV1 was administered at nine months of age. Third, increasing urbanization, resulting in increased contact rates and thus measles virus transmission, could lead to higher levels of population immunity needed to interrupt measles virus transmission, hindering eradication efforts. Finally, increasing globalization, travel, and population movement greatly amplify the risk of re-importations into countries that have eliminated measles. The constant threat of measles outbreaks creates an unsustainable burden even on the countries with strong programmes.

The GVAP documents mentions that every 1000 children vaccinated with first dose of measles containing vaccine will avert 16.4 deaths and with second dose 1.9 deaths per 1000 child vaccinated. Similarly, every 1000 children vaccinated with measles vaccine in vaccination campaign will avert 3.5 deaths due to measles.

CHALLENGES TOWARDS MEASLES ELIMINATION IN WHO SOUTH-EAST ASIA REGION

A comprehensive review of the Global Measles and Rubella Strategic Plan, 2012-2020 was conducted in 2016, assessing the global strategy for measles and rubella elimination. The Measles and Rubella Midterm Review acknowledged that tremendous progress had been made towards measles and rubella elimination since 2001 and identified ten key points regarding the global strategy for measles and rubella elimination: 1) measles eradication is the ultimate goal but regional elimination goals should be pursued to enable a decision by 2020 as to whether or not a target be set for measles eradication; 2) the basic strategic approaches articulated in the Global Measles and Rubella Strategic Plan 2012–2020 are valid to achieve the goals but have not been fully implemented; 3) reliance on SIAs should be changed to primary reliance on well-performing essential immunization services to assure administration of two doses of MCV; 4) reliance on vaccine coverage to measure progress should be changed to measurement of measles and rubella incidence as the metric to track progress toward elimination; 5) measles and rubella vaccination programmes should be considered an indicator of the quality of the overall immunization programme, and incidence and vaccination coverage should be considered primary indicators of immunization programme performance; 6) polio transition presents risks and opportunities for measles and rubella eradication, and the opportunities should be maximized; 7) school entry immunization checks could contribute to strengthening overall immunization services; 8)

programme decisions should increasingly be based on high quality data and appropriate analysis; 9) incorporation of rubella vaccination into the immunization programme should be accelerated; and 10) outbreak investigation and response are critical but most important is the prevention of measles and rubella outbreaks. The Measles and Rubella Midterm Review emphasized the need to achieve and sustain elimination by strengthening health systems. Specifically, the report recommended "focusing on improving ongoing immunization systems – although this may delay reaching measles and rubella elimination goals – in order to ensure that gains in measles and rubella control can be sustained. Reorienting the measles and rubella elimination program to increase emphasis on surveillance so that programmatic and strategic decisions can be guided by data is critical."

A midterm review of progress towards achieving the measles elimination goal in WHO South-East Asia Region by 2020 was conducted in 2017, which conferred to the findings of the Global Measles and Rubella midterm review and noted with cautious optimism that significant progress had been made. The regional review made the following conclusions- "the basic strategies articulated in the strategic plan for measles elimination in the South-East Asia Region are sound but the measles elimination programme is off-track in the Region. robust and effective implementation of the specific strategies have been limited by country-level governance, national political will and global impetus, all of which are reflected in insufficient allocation of resources. The overall financial envelope for the MR elimination programme was much lower than proposed and is likely to be a major challenge in achieving the 2020 target. The programme has gathered momentum but the challenge is particularly substantial for two of the largest member countries – India and Indonesia. Measuring true disease incidence, in the presence of an effective surveillance system, is the most important indicator of progress (canary in the coal mine). The presence or absence of measles is also one of the best indicators of the overall performance of an immunization programme (accountability framework). In fact, the burden of MR in the largest countries is still not accurately known."

Operational challenges

Several operational challenges will need to be addressed to achieve measles elimination, including: 1) the high vaccine coverage required to achieve and sustain 92-94% population immunity to measles virus and delivered through strong essential immunization programmes; 2) the need for high quality data on vaccine coverage and measles and rubella incidence at the subnational level (e.g. district or health center catchment area); 3) the need for logistically and financially feasible methods to identify immunity gaps, including zero-dose and under-immunized children; 4) the potential for increased susceptibility among young infants from decreased levels of maternal antibody as a result of maternal vaccination and limited boosting; 5) the possibility of significant waning immunity in vaccinated persons no longer boosted by exposure to wild-type virus; 6) and the risk of measles virus re-introduction from laboratories and from neighboring countries after elimination.

Most importantly, region and country-specific challenges will continue to hinder progress: 1) insufficient vaccination demand (vaccine hesitancy); 2) access to children in regions of conflict, insecurity, and humanitarian emergency; and 3) weak health infrastructure and immunization programmes. These latter issues are likely to be major challenges to measles elimination and eradication and were identified as three of the ten threats to global health in 2019.

Challenges to close immunity gaps for measles in the population

A modeling exercise using the Measles Strategic Planning tool developed by WHO, with the data as of December 2018 shows that for measles elimination in the Region Bangladesh, India, Indonesia, Myanmar, Nepal, and Thailand will have to do a follow-up measles and rubella vaccination campaign in 2021 targeting age group 9 months to five years and Myanmar and Thailand will also have to target age groups 20-40 years all over the country. These campaigns will have to achieve more than 95% coverage as all subnational levels which is unprecedented in WHO South-East Asia Region.

Closing immunity gaps in children through measles vaccination has been difficult because the coverage for first dose has remained at approximately 85% for a decade despite substantial investments. Thus, the continued need for preventive vaccination campaigns are forecast for many years based on projections of the accumulation of susceptible children which are costly and need external support for countries to conduct such massive campaign regularly. Delays in conducting SIAs are common and are often linked to postponing the request submission or delays in approval. School entry vaccination checks are not universally implemented. Although the benefits of catching-up children on missed doses is obvious, implementation of the strategy is complex, requiring legislative policy frameworks and collaboration with Ministries of Education. In addition, policies for school entry vaccination checks generally focus on first entry, such as 5- to 6-year-old children, and not on older children. Where measles surveillance show disease occurring in older school-aged children, school vaccination checks on all age groups may be needed to close susceptibility gaps for children already in school even when a school entry check policy was implemented. Unless effective

campaigns are conducted, and catch-up opportunities utilized, birth cohorts with immunity gaps will age into older cohorts with residual immunity gaps. Although guidance on replacing missing doses exists, there continues to be a gap in effective guidance on how to administer, record and report these doses.

Closing immunity gap in adult population is more challenging. With high coverage, the circulation of virus has been at low level because of which number of people have skipped natural infection and thus remain susceptible up to adult hood. This has resulted in wide age range immunity gap making elimination and eradication efforts complex and costlier.

Vaccine demand and access

Critical to achieving measles elimination, and eradication is ensuring demand for and access to measles vaccines. Vaccine hesitancy, particularly for measles vaccines, is an increasingly prevalent and complex challenge to measles elimination, in part because of misinformation spread through social media platforms, and could be a major impediment to measles elimination and eradication. WHO identified vaccine hesitancy as one of the ten threats to global health in 2019. Much has been written about vaccine hesitancy and demand, and the reasons underlying these views are complex. A vaccines advisory group to the WHO identified complacency, inconvenience in accessing vaccines, and lack of confidence as key reasons underlying hesitancy. Efforts to achieve measles and rubella eradication will need on-going, multi-disciplinary approaches to address vaccine hesitancy and increase vaccine demand to be successful.

Ensuring access to vaccines will be critical to measles elimination and eradication and achieving equity. Limited or poor access to measles and rubella vaccines could also be a major impediment to measles elimination and eradication, particularly in regions affected by prolonged conflict, mass population movement, and humanitarian emergencies. Marginalized populations, who lack recognition and government support, and those controlled by anti-government elements, face particular challenges in accessing vaccines. For example, the major challenge currently faced by the Global Polio Eradication Initiative (GPEI) is gaining access to Taliban-controlled areas of Afghanistan and Pakistan. Efforts to achieve measles elimination and eradication will need to develop strategies to maintain vaccine access in the most challenging countries and settings, with lessons learned from the GPEI.

Vaccine and diagnostic test supply for measles

Measles elimination and eradication efforts require careful planning to ensure the necessary vaccine supply. The shortage of inactivated poliovirus vaccine provides a cautious reminder of the potential risks to an eradication initiative. Vaccine manufacturers should be fully engaged in the planning processes and the use of measles vaccines after eradication should be considered. An assessment of the feasibility of measles eradication by WHO in 2008 concluded that the number of MCV doses estimated at that time to be needed for eradication were within existing and planned MCV-manufacturing capacity, but supply-chain disruptions could reduce supply or increase prices. Proposed mitigation strategies included stockpiling, long-term contracts, and further coordination with manufacturers. The WHO (MI4A) initiative is currently updating a global forecast for measles-containing vaccines supply and demand through 2030 and the analysis is expected by the end of 2019. A risk with the current vaccine supply is the reliance on a single supplier. According to data reported through the WHO MI4A/V3P vaccine purchase database for 2017, the Serum Institute of India supplies as much as 87% and 97% of the global measles and measles-rubella vaccine market, respectively. Having additional manufacturers of pre-qualified measles and measles-rubella vaccines would help keep costs low and secure adequate supplies. Other manufacturers produce measles-mumps-rubella and measles-mumps-rubella-varicella vaccines, which are principally used in middle- and upper-income countries.

Also critical to achieving measles eradication is having an adequate supply of enzyme immunoassay diagnostic test kits to support case-based surveillance with laboratory confirmation. The supply of diagnostic test kits for measles and rubella was exacerbated by the buy-out of the Siemens by Diasorin. Elimination standard surveillance, in which all suspected cases are laboratory confirmed or discarded, requires a robust and diverse supply of pre-qualified and quality-assured test kits.

Data needs for measles eradication

Measles elimination and eradication will require high quality and highly sensitive data on measles incidence and vaccination coverage (MCV1, MCV2 and supplementary doses), as well as from disease burden and risk modeling and mapping and from targeted serological surveys. Importantly, an integrated and open data platform, rather than the current disparate data streams, will be needed for programme management. The *Roadmap to Elimination Standard Measles and Rubella Surveillance* report identified eight key attributes of a measles surveillance system: 1) detection of cases and outbreaks; 2) notification; 3) investigation and confirmation; 4) data collection on cases, potential risk factors for infection, spread, complications and death; 5) data analysis; 6) feed-forward to higher levels; 7) feedback to peripheral levels; and 8) interpretation and use of data. Effective use and interpretation of data applies to

case classification, risk factors, spread, complications and death, vaccine effectiveness, outbreak source, extent and characteristics of the outbreak, monitoring surveillance performance, monitoring immunization programme performance, calculation of the effective reproduction number, actions to prevent further transmission, and evaluation of interventions. At a minimum, these eight elements will need to be in place throughout every country for surveillance to be adequate to verify elimination. For elimination standard surveillance, all suspected cases, defined as fever with rash, need to be reported following rapid investigation within 24 hours, with laboratory testing of all suspected cases and comprehensive contact tracing to target chains of transmission for interruption. Cases should also be classified according to the source of infection as imported, importation-related, endemic or unknown source, and reporting should be weekly rather than monthly.

Management and accountability framework

A strong management and accountability framework will be critical to measles elimination and eradication, building on lessons learned from the GPEI management and accountability structure. The accountability framework for the GPEI is much more extensive than that described for measles and rubella in the Global Vaccine Action Plan and Measles and Rubella Strategic Plan 2012-2020. The Measles and Rubella Midterm Review emphasized that governments have primary responsibility for measles elimination and the need for local accountability. Levels of accountability include parents, families, communities, CSOs, and national governments, as well as M&RI partners.

The global measles and rubella surveillance system necessary to achieve, sustain and verify elimination and eradication will need to improve upon current practices. Currently, fewer than 5% of global measles cases, and many fewer rubella or CRS cases, are reported to the WHO. However, a strengthened measles and rubella surveillance should not constitute a vertical disease surveillance programme but should be part of a broader comprehensive effort to strengthen surveillance for all VPDs. Notwithstanding, for measles elimination and eradication, countries would need to better implement current recommendations everywhere and work to achieve surveillance targets. Epidemiologic and laboratory data need to be better linked so that all cases are accounted for. More granular data, such as data on risk factors, might be requested at regional and global levels, and those levels will need to be staffed properly to handle the increased data demands. Innovation in laboratory methods will be needed to help refine virus tracking, and rapid diagnostic tests that are under development will need to be integrated into disease surveillance. CRS surveillance will need to be expanded. WHO is currently undertaking an exercise to estimate the cost of comprehensive surveillance, which includes measles, rubella, and CRS surveillance, and preliminary data will be available in the second quarter of 2020.

Public, political and donor support and responsibility

The global landscape has changed significantly since polio eradication was first declared in 1988, and bold global health goals consisting of top-down, vertical, disease-specific eradication programmes no longer have the public, political and donor support they once had. Early discussions of polio eradication were in the context of the successful smallpox eradication programme, whereas discussions of measles eradication have the prolonged polio eradication efforts as backdrop. Public, political and donor support will be essential to measles elimination and eradication, particularly country commitment. Engagement with key stakeholders, including governments, political leaders, donors, and policy makers, is needed. Heads of state, Ministries of Health and Ministries of Finance must support measles elimination and eradication, in addition to major donors. Planning should begin with an analysis of current political and donor support for measles elimination and eradication and development of a plan to engage such support.

Measles eradication cannot be achieved without public support, community ownership, and committed accountability. Comprehensive communication and stakeholder engagement strategies should be implemented, with monitoring and review of successes and learning. The Measles and Rubella Midterm Review identified multiple strategies to garner and sustain public support for measles elimination and eradication, including: 1) increase resources for communication to raise the visibility and perceived risks of vaccine-preventable diseases, with a focus on measles and rubella; 2) create and promote sustained demand for immunization through tailored and targeted strategies that are informed by local evidence; 3) develop targeted communication and engagement plans for different audiences, including politicians, public health leaders and workers, healthcare providers, caregivers, and non-traditional stakeholders; 4) use data on measles incidence, including complications and deaths, as well as information on the costs associated with outbreaks, to communicate the importance of eradicating measles and rubella and the related investment case; 5) supplement these data with stories of actual cases and deaths, including cases of congenital rubella syndrome; 6) identify the most effective means of communication, including methods to counter misinformation; 7) use the opportunity of measles and rubella outbreaks to promote the importance of vaccination; 8) collect

stories on how a focus on measles and rubella elimination enhanced overall immunization and health systems; and 9) ensure community engagement in planning, implementation and oversight of immunization. Carefully crafted communication and advocacy strategies are particularly important as the disease burden decreases, when there is less public memory of the disease burden and an increased concern for potential risks associated with vaccines.

CONCLUSION

Measles is the most infectious virus known to mankind that can lead to complications in around 30% of cases infected. Safe and effective vaccines are available to prevent measles infection. Number of studies and task force have highlighted that measles elimination and eradication is feasible biologically, technically, programmatically and operationally which is reinforced by the fact that more than 83 countries globally and five countries in WHO South East Asia Region have sustained measles elimination. However, a midterm review conducted in 2016 at global level and in 2017 in WHO South-East Asia Region has highlighted that strategies are sound but suboptimal implementing of strategies compounded by other operational issues, political will and insufficient financial resources have slowed down the progress towards measles elimination and eventually eradication.

REFERENCES

1. Burki T. (2013). Challenges and targets for measles elimination. *Lancet Infect Dis* 2013; 13: pp. 479-80.

2. Centres for Disease Control and Prevention. Progress toward regional measles elimination – worldwide. 2000–2014. *MMWR Morb Mort Wkly Rep* 2015; 64: pp. 1246-51.

3. Christie A.S. & Gay A. (2011). The Measles Initiative: Moving Toward Measles Eradication. *J Infect Dis* 2011; 204 (suppl 1): pp. 14-17.

4. Global eradication of measles. Report by the Secretariat. Sixty third World Health Assembly. March 2010. Available at: http://apps.who.int/gb/ebwha/pdf_files/wha63/a63_18-en.pdf. Last accessed on: 21 Oct, 2013.

5. Griffin D.E. (2013). Measles virus. In: Knipe DM, Howley PM, editors. Fields Virology. Volume 6. Philadelphia, PA, USA: *Wolters Kluwer Lippincott Williams & Wilkins*: pp. 1042-69.

6. Indian Academy of Pediatrics (2014). Advisory Committee on Vaccines and Immunization Practices (ACVIP), Vashishtha VM, Yewale VN, Bansal CP, Mehta PJ. IAP perspectives on measles and rubella elimination strategies. Indian Pediatr; 51: pp. 719-22.

7. Keegan R., Dabbagh A., Strebel P.M., Cochi S.L. (2011). Comparing Measles With Previous Eradication Programs: Enabling and Constraining Factors. *J Infect Dis*; 204 (suppl 1): pp. S54-S61.

8. Measles and Rubella Initiative. *Annual report 2015* http://measlesrubellainitiative.org/annual-report-2015/ (accessed July 29, 2017).

9. Measles. WHO. Updated on 5th July, 2017, Available from: http://www.wpro.who.int/mediacentre/factsheets/fs_20120224/en/ [Last accessed on 13 Aug, 2017]

10. Mina M.J., Metcalf C.J.E., de Swart R.L. et. al. (2015). Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* (New York, NY); 348 (6235): pp. 694-99.

11. Mishra P.P. & Chauhan N.T. (2012). Double outbreak of measles in the Talaja block of Bhavnagar district, Gujarat, India 2011: A need for improving the vaccine coverage and the community participation. J. Clin Diagn Res.; 6: pp. 1713-7.

12. Morris S.K., Awasthi S., Kumar R., Shet A., Khera A., Nakhaee F., *et. al*. (2013). MDS Collaborators. Measles mortality in high and low burden districts of India: Estimates from a nationally representative study of over 12,000 child deaths. Vaccine; 31: pp. 4655-61.

13. National Centre of disease control. New Delhi. *NCDC Newsletter*; 6(1): pp. 8-9.

14. Orenstein W.A., Strebel P.M., Papania M., Sutter R.W., Bellini W.J., Cochi S.L. (2000). Measles eradication: is it in our future? Am J Public Health; 90: pp. 1521–5.

15. Press Information Bureau, Government of India. Prime Minister's Office 03-July-2014 16:31 IST. Available from: http://pib.nic.in/newsite/PrintRelease.aspx?relid= 106055. Accessed September 30, 2014.

16. Shakya A.K., Shukla V., Maan H.S., Dhole T.N. (2012). Identification of different lineages of measles virus strains circulating

in Uttar Pradesh, North India. Virol J.; 9: p. 237.

17. Simons E., Ferrari M., Fricks J., Wannemuehler K., Anand A., Burton A. et. al. (2012). Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *Lancet*; 379: pp. 2173-8

18. Sowers S.B., Rota J.S., Hickman C.J. et. al. (2016). High concentrations of measles neutralizing antibodies and high-avidity measles IgG accurately identify measles reinfection cases. *Clin Vaccine Immunol*; 23: pp. 707-16.

19. Sugerman D.E., Barskey A.E., Delea M.G., et. al. (2010). Measles outbreak in a highly vaccinated population, San Diego, 2008: Role of the intentionally undervaccinated. Pediatrics; 125: pp. 747–55.

20. Thompson K.M. & Odahowski C.L. (2016). Systematic review of health economic analyses of measles and rubella immunization interventions. *Risk Analysis* 2016; 36: pp. 1297-1314.

21. Vaidya S.R., Kumbhar N.S., Bhide V.S. (2014). Detection of measles, mumps and rubella viruses by immuno-colorimetric assay and its application in a focus reduction neutralization tests. Microbiol Immunol.; 58: pp. 666-74.

22. WHO (2012). Measles virus nomenclature update: 2012. *Wkly Epidemiol Rec*; 87: pp. 73-81.

23. WHO. World Health Organization. Regional Office for the Western Pacific. Field Guidelines for Measles Elimination. Available from: http://www.whqlibdoc. who.int/wpro/2004/929061126X.pdf. [Last accessed on July 29, 2017].

24. World Health Organization SEARO. Measles Elimination by 2020. Available from: http://www.searo.who.int/ mediacentre/releases/2013/pr1565. Accessed July 18, 2014.

25. World Health Organization (2009). Measles vaccines: WHO position paper. Wkly Epidemiol Rec.; 84: pp. 349-60.

26. World Health Organization. Resolution WHA 70.14: Strengthening immunization to achieve the goals of the global vaccine action plan. Geneva, World Health Assembly 70, 2017 (http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R14-en.pdf).

27. World Health Organization. Proceedings of the Global Technical Consultation to assess the feasibility of measles eradication, 28-30 July 2010. Journal of Infectious Diseases; 204: pp. S4-S13.

28. World Health Organization (2014). Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010. Summary, conclusions and recommendations. Weekly Epidemiological Record, 86: pp. 1–16.

29. Orenstein W.A., Hinman A., Nkowane B., Olive J.M., Reingold A. (2018). Measles and Rubella Global Strategic Plan 2012-2020 midterm review. Vaccine; 36 Suppl 1: pp. A1-A34.

30. Recommendations of the International Task Force for Disease Eradication. Morbidity and Mortality Weekly Report 1993;42(RR-16): pp. 1-38. (available at https://www.cdc.gov/mmwr/preview/mmwrhtml/00025967.htm).

31. Dabbagh A., Laws R.L., Steulet C., Dumolard L., Mulders M.N., Kretsinger K., Alexander J.P., Rota P.A., Goodson J.L. (2018). Progress Toward Regional Measles Elimination - Worldwide, 2000-2017. Morbidity and Mortality Weekly Report; 67: pp. 1323-29.

32. https://www.who.int/immunization/global_ vaccine_action_plan/GVAP_doc_2011_2020/en/

33. Moss W.J. & Strebel P. (2011). Biological feasibility of measles eradication. Journal of Infectious Diseases; 204 Suppl 1: pp. S47-53.

34. Recommendations of the International Task Force for Disease Eradication. MMWR 1993; 42(RR-16): pp. 1-38. (available at https://www.cdc.gov/mmwr/preview/mmwrhtml/00025967.htm).

35. Nandi A., Shet A., Behrman J.R., Black M.M., Bloom D.E., Laxminarayan R. (2019). Anthropometric, cognitive, and schooling benefits of measles vaccination: Longitudinal cohort analysis in Ethiopia, India, and Vietnam. *Vaccine*

36. http://www.who.int/entity/immunization/monitoring_surveillance/data/coverage_estimates_series.xls

37. Dabbagh A., Laws R.L., Steulet C., Dumolard L., Mulders M.N., Kretsinger K., Alexander J.P., Rota P.A., Goodson J.L. (2018). Progress Toward Regional Measles Elimination - Worldwide, 2000-2017. Morbidity and Mortality Weekly Report; 67: pp. 1323-29.

38. Brown K.E., Rota P.A., Goodson J.L., Williams D., Abernathy E., Takeda M., Mulders M.N. (2019). Genetic characterization of measles and rubella viruses detected through global measles and rubella elimination surveillance, 2016-2018. Morbidity and Mortality Weekly Report; 68: pp. 587-591.

39. World Health Organization. Guidance for evaluating progress towards elimination of measles and rubella. Weekly Epidemiological Record; 93: pp. 544–552.

40. Gay N.J. (2044). The theory of measles elimination: implications for the design of elimination strategies. Journal of Infectious Diseases; 189: Suppl 1: pp. S27-S35.

41. Guerra F.M., Bolotin S., Lim G., Heffernan J., Deeks S.L., Li Y., Crowcroft N.S. (2017). The basic reproduction number (R0) of measles: a systematic review. Lancet Infectious Diseases; 17: pp. e420-e428.

42. World Health Organization (2017). Measles vaccines: WHO position paper – April 2017. Weekly Epidemiological Record; 92: pp. 205-28.

43. Fine P.E.M., Mulholland K., Scott J.A., Edmunds W.J. (2018). Community Protection in Ploktin's Vaccines 7th edition. Plotkin SA, Orenstein WA, Offit PA, Edwards KM eds. Elsevier: pp. 1512-153.

44. Orenstein W.A., Hinman A., Nkowane B., Olive J.M., Reingold A. (2018). Measles and Rubella Global Strategic Plan 2012-2020 midterm review. Vaccine; 36 Suppl 1: pp. A1-A34.

45. Smith G., Michelson J., Singh R., Dabbagh A., Hoekstra E., van den Ent M., Mallya A. (2011). Is there enough vaccine to eradicate measles? An integrated analysis of measles-containing vaccine supply and demand. Journal of Infectious Diseases;204 Suppl 1: pp. S62-70.

46. World Health Organization (2017). Roadmap to elimination standard measles and rubella surveillance. Weekly Epidemiological Record; 92: pp. 97-105.

47. Goodson J.L., Alexander J.P., Linkins R.W., Orenstein W.A. (2017). Measles and rubella elimination: learning from polio eradication and moving forward with a diagonal approach. Expert Review of Vaccines; 16: pp. 1203-1216.

48. Durrheim D.N. & Crowcroft N.S. (2017). The price of delaying measles eradication. Lancet Public Health; 2: pp. e130–e131

49. Graham M., Winter A.K., Ferrari M., Grenfell B., Moss W.J., Azman A.S., C. Jessica E. Metcalf C.J.E., Lessler J. (2019). Measles and the canonical path to elimination. Science; 364: pp. 584-587.

50. Omer S.B., Orenstein W.A., Koplan J.P. (2013). Go big and go fast--vaccine refusal and disease eradication. N. Engl. J. Med; 368: pp. 1374-6.

51. World Health Organization (2009). Measles vaccines. WHO Position Paper. Weekly Epidemiological Record; 84(35): pp. 349–60.

52. Strebel P.M., Papania M.J., Dayan G.H., Hasley N. (2013). Measles vaccines. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 6th ed. Philadelphia, PA: Elsevier Saunders; pp. 352–387.

53. World Health Organization. Global measles and rubella strategic plan: 2012–2020. Geneva, Switzerland: World health Organization; 2012 (https://www.who.int/immunization/sage/meetings/2016/october/1_MTR_Report_Final_Color_Sept_20_v2.pdf, accessed 2 February 2019).

54. Strategic plan for measles elimination and rubella and congenital rubella syndrome in the South-East Asia Region, 2014-2020. New Delhi, India: World Health Organization, Regional Office for South East Asia; 2014 (https://apps.who.int/iris/handle/10665/205923, accessed 2 February 2019).)

55. Mid-term Review of the Strategic Plan for Measles Elimination and Rubella /CRS Control, 2014-2020. New Delhi: World Health Organization Regional Office for South-East Asia; 2017.

56. Resolution of the Sixty-Sixth Session of the Regional Committee for WHO South-East Asia Region on measles elimination and rubella/congenital rubella syndrome control (SEA/RC66/R5). New Delhi, India: World Health Organization, Regional Office for South East Asia; 2013 (http://repository.searo.who.int/bitstream/123456789/16894/1/SEA-RC-66-R5-Rubella.pdf, accessed 2 Feb 2019).

Corresponding Author

Sudhir Khanal*

PhD-Public Health, AZTECA University, Mexico