

Original Research Article

Measles occurrence, vaccination coverages and malnutrition in India: correlations, trends, and projections by time series analysis

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ABSTRACT

Background: Measles is a highly infectious viral disease responsible for a considerable morbidity and mortality in childhood. India has committed to achieve measles elimination by 2020. Currently, Sustainable Development Goals (SDG) have placed a lot of emphasis on measles elimination.

Methods: Data on reported measles cases, immunization coverages and malnutrition status of children specific to India for a period from 1980 to 2017 were collected from WHO, UNICEF and related official online web sources. Also, various official measles elimination strategy documents, available literature and experiences from various countries were reviewed. The data were analysed for correlations, trends. Time series model projections were made till 2020 using two different software tools.

Results: The occurrence of measles cases showed a significant downward trend especially since 2000, but continues to exhibit mild cyclical trend of 3-4 years with strong seasonality. Measles vaccine coverages are steadily and significantly increasing more so since 2014. Reduction in measles cases is strongly and significantly correlated with the vaccination coverages; moderate correlation with wasting and mild correlation with stunting was observed. Current progress in India to achieve elimination appears to be well on track with remarkable strides made in strengthening case based surveillance, immunization with 2 doses of measles containing vaccine (MCV) and establishment of high quality laboratory network. MCV1 and MCV 2 coverage forecasts look promising to reach about 95% by 2020 at current rates. Also, the projections of measles case occurrence indicate the reduction in incidence to about 20 per million, which may even be augmented further with concurrent enhancements in nutritional status and socio-economic growth.

Conclusions: India is well on track to achieve measles elimination goal as per the commitment made in 2014, using the established strategies.

Keywords: Measles elimination, India, Measles vaccination, Immunization program, Measles incidence

INTRODUCTION

Measles is a highly contagious disease caused by measles virus, an RNA virus belonging to *Morbillivirus* genus. It is one of the most infectious diseases known to humans.^{1,2} It transmits via droplets from the nose, mouth or throat of infected individuals. Symptoms begin appear

7–18 days after infection which include high fever, coryza, conjunctivitis and Koplik spots on the buccal mucosa. A maculopapular rash develops a few days later, starting on the face and at nape of the neck and then spreading downwards. The most serious complications include blindness, encephalitis, acute gastroenteritis with dehydration, acute otitis media and severe pneumonia.¹⁻³

Measles is one of the main causes of childhood mortality. Every year measles caused millions of deaths globally before the introduction of the measles vaccines. The availability of attenuated measles vaccine since 1963 has made it possible for several western countries to achieve control over measles morbidity, mortality and also reach elimination goals. Measles mortality reduced by 84% from 2000 to 2016 (estimated 550100 deaths in 2000 to 89780 deaths in 2016).³⁻⁵

Factors contributing for measles endemicity include malnutrition, floods, famine, high risk settings with low socioeconomic conditions, overcrowding, displaced populations, occasions when there are natural disasters, conflict ridden areas, and other humanitarian emergencies.^{1,6-12} Measles outbreak size and duration depend on transmissibility which in turn is decided by susceptibility in the population due to non-immune status, frequency of contacts in the population and also the agent factors such as replication speed.^{1,13}

Basic reproduction number (R_0) is estimated for measles to be around 12-18, which is a measure of secondary cases generated from each primary case in a completely susceptible population. The effective reproduction number (R_e) is dependent on the proportion of susceptible individuals in the population. When R_e falls below 1, the transmission of measles stops and secondary cases no longer occur and hence the epidemic dies down. The goal of all elimination strategies is to bring down the value of R_e to less than 1 and maintain it at that level. Studies have shown that by immunizing about 95% of the population with measles containing vaccines (MCV) it is possible to bring down R_e to below 1. There are many methods to estimate R_e when appropriate data is available on epidemic curves and outbreak size, duration, distribution etc.¹³⁻¹⁵

Vaccine efficacy depends on the age of vaccination and other epidemiological contexts. Some studies have shown that the efficacy of measles vaccine administered at 9-11 months of age is of the order of 85-90% in the Indian context.¹⁶ Recently studies have shown, measles containing vaccines (MCV) such as MR vaccine have similar efficacy.^{17,18}

Measles vaccine was introduced in India in 1985 as a part of Universal Immunization Programme (UIP) at 9 completed months of age. The coverages steadily increased over last 3 decades (from 56% in 2000 to 87% in 2015) with consequent reductions in reported measles cases and accompanying morbidity and mortality. Measles deaths have declined by 51% in India (estimated 100000 in 2000 to 49000 in 2015). The 2nd dose was introduced into UIP in 2010 which gradually expanded to the whole country. Measles catch up campaigns were held in phases from 2010 to 2013 in select low coverage states and nearly 118 million immunized.¹⁹⁻²⁴ Measles-Rubella (MR) vaccine is being introduced in phased

manner in the country since early 2017 in a campaign mode for the age group of 9 months to 15 years.²⁵

The surveillance system had been of a major concern in India since early days and was one of the main drawbacks. Learning from the success of AFP surveillance under polio eradication initiative, measles surveillance is being gradually strengthened in the country over the last decade. Initially aggregate (outbreak-based) surveillance was established in the morbidity and mortality reduction phase, which was later converted into case-based surveillance system supported by a network of high quality laboratories accredited by WHO.²⁶⁻²⁸

On 13 September 2013 in New Delhi, countries of WHO South-East Asia Region (SEAR) including India committed to eliminate measles and control rubella/congenital rubella syndrome (CRS) by 2020. The resolution was approved during the Sixty-sixth Regional Committee.²⁶ The goals and objectives for measles elimination were set.

Measles elimination: The absence of endemic measles or rubella cases in a defined geographical area for a period of at least 12 months, in the presence of a well-performing surveillance system. Regional elimination can be declared after 36 or more months of the absence of endemic measles or rubella in all Member States.

Endemic transmission: Continuous transmission of indigenous or imported measles or rubella virus that persists for a period of 12 months or more in a defined geographical area.

A strategic plan for measles elimination in WHO SEAR (2014-2020) has been developed and adopted by countries in the Region including India.²⁶ The strategies focus on: “

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.”²⁶

Though the progress is impressive till now, India still continues to have higher incidence of measles cases along

with higher morbidity and mortality.²⁹ Many immunization strengthening efforts such as 'Mission Indradhanush' are being undertaken on the lines of polio eradication success.³⁰ Immunization coverages are steadily increasing for MCV1 and MCV 2 doses; focussed approach targeting vulnerable population groups and low coverage geographical areas are yielding results.^{29,31}

This study is intended to track the trends in measles occurrence, vaccination coverages, and relationship with nutritional status so as to make projections till 2020 to get a preliminary understanding on whether any additional efforts are needed to reach the elimination goals.

METHODS

Data sources

The data on reported measles cases, MCV1 and MCV2 vaccination coverages were obtained from the WHO website for a period from 1980 onwards. The data on month wise confirmed measles cases was obtained from WHO surveillance data source available online.²⁹⁻³¹ The data on prevalence of stunting and wasting was collected from UNICEF joint child malnutrition assessment website which compiles data from various official nutritional surveys from member countries.³²

These data were analysed using MS Excel 2013 (Microsoft®) and SPSS 24.0 (IBM®) for correlation between MCV vaccination coverages, stunting, and wasting with measles case occurrence. Also, analysis was done to create time series models from the available confirmed measles case data from 2014. The occurrence of measles cases were projected using time series analysis models for the future months up to the end of 2020. Correlation analyses were done using SPSS 24.0 and MS Excel. Figures and graphs were prepared using MS Excel.

Time series analysis in MS Excel done by first calculating moving averages for 3 year data considering 12 month cycles. Centralized moving averages were calculated followed by monthly indices and seasonality components. Then the data was deseasonalized and regressed with time component to get intercept and regression coefficient (slope). These parameters were used to get the values to check the match with raw data and also to make forecasts till 2020. Using the measles case raw data and the forecasted data, the incidence estimates were made and inferences drawn.

Time series analysis in SPSS 24.0 was done using the month wise measles case data from January 2014 till July 2017. ARIMA method was used to get the best model which fits the available data and also forecasts the reliable measles case occurrence numbers till December 2020.

RESULTS

Table 1 shows the established measles elimination criteria and lines of evidence in the Western Pacific Region of WHO.³³ The criteria though not explicitly spelt out in the strategic plan document of the SEAR of WHO, the broad principles remain the same.^{26,33} The table also shows the actions needed to meet the criteria and generate required evidence. The last column depicts the current status in India with suggested measures that need to be taken.

In Figure 1, we can see that the reported measles cases have started to decline as the measles vaccine coverages increased especially since last two decades. We can also see that measles follows a pattern of cycles of 3-4 years, when cases tend to increase over preceding years.

Figure 2 shows the correlation between reported measles cases and estimated MCV1 vaccination coverages from 1980 to 2016. We can see that there is a clear trend which touched zero line for measles cases when vaccination coverage reaches 95%. We also conducted Pearson's correlation test on SPSS and found a strong, inverse correlation of immunization coverage with measles occurrence ($r=0.885$; $n=29$; 95% CI, 0.766–0.900; $p<0.000$).

Figure 3 shows the scatter plot with correlation between reported measles cases and prevalence of stunting and wasting as documented by various surveys conducted for the corresponding years between 1989 and 2015. We had corresponding data for 8 time periods (1989, 1992-93, 1997, 1999, 2006, 2014 and 2015). An analysis of correlation using non parametric methods on SPSS showed Spearman rho (ρ) value of 0.469 for wasting ($p=0.241$) and a value of 0.114 for stunting ($p=0.788$). The Kendall's Tau-B values were 0.322 ($n=8$, $p=0.288$) and 0.161 ($n=8$, $p=0.595$) respectively. It is clear that wasting and stunting do have a role in the occurrence of measles cases through immunological linkages. There was a positive moderate correlation between wasting and measles case occurrence. But, stunting had a weak positive correlation with measles occurrence.

Figure 4 shows the confirmed measles cases from outbreaks and sporadic cases reported through WHO supported surveillance system in India. It is clearly evident that the disease occurrence has seasonal trends with peaks occurring in the first quarter of each year.

Figure 5 shows the estimated MCV1 and MCV2 coverages from 1980 to 2016. It also shows future linear forecasts till 2020. Coverages are expected to rise at a faster rate with ongoing intensification efforts of immunization in India with focused approach campaigns like Intensified Mission Indradhanush (IMI) and Measles-Rubella vaccination campaign.

Figure 6 shows Moving Average (MA) time series modelling on MS Excel 2013, with moving averages and central moving averages (CMA) calculated for a 12 month cycle using MS Excel for confirmed measles cases data since 2014. It also shows the forecasting of cases

with seasonality till 2020. It is evident that the predicted time series model closely fits the observed data for the years 2014-16 and there is a drastic reduction in cases from 2017 to 2020.

Table 1: Established measles elimination verification criteria and lines of evidence.

Domain	Established standards	Action needed	Current status
Criteria	1. Documentation of the interruption of endemic measles virus transmission for a period of at least 36 months from the last known endemic case.	Measles incidence data.	Reporting needs further strengthening.
	2. The presence of verification standard surveillance.	Sensitive case based surveillance.	In place, needs strengthening.
	3. Genotyping evidence that supports the interruption of endemic transmission.	Virus isolation from all districts.	Presently D4, D8 and B3 strains detected frequently. Samples need to be collected and tested from all districts.
Lines of evidence	1. Detailed description of the epidemiology of measles since the introduction of measles vaccine in the national immunization programme.	Needs to calculate R_0 and R_e (basic and effective reproduction numbers).	Presently not analyzed by any study but needs proper analysis of available data.
	2. Quality of epidemiological and laboratory surveillance systems for measles.	WHO accredited high quality lab network established.	Presently WHO accredited lab supported surveillance in place. Needs regular quality checks.
	3. Population immunity presented as a birth cohort analysis with the addition of evidence related to any marginalized and migrant groups.	Needs seroprevalence data by high quality seroprevalence studies.	Currently only estimates of susceptible in cohorts available through tools such as MSP Tool 2.0. Need seroprevalence data in a larger age group band.
	4. Sustainability of the national immunization programme including the resources for mass campaigns, where appropriate, in order to sustain measles elimination.	RI strengthening and campaign mode activity in risk areas.	Currently focus on RI in place with political and administrative commitment through Intensified Mission Indradhanush etc.
	5. Genotyping evidence that supports interruption of measles virus transmission.	Genotype database of prevalent endemic strains.	Currently D4, D8 and B3 are identified as common strains. Needs continuous testing from all districts.

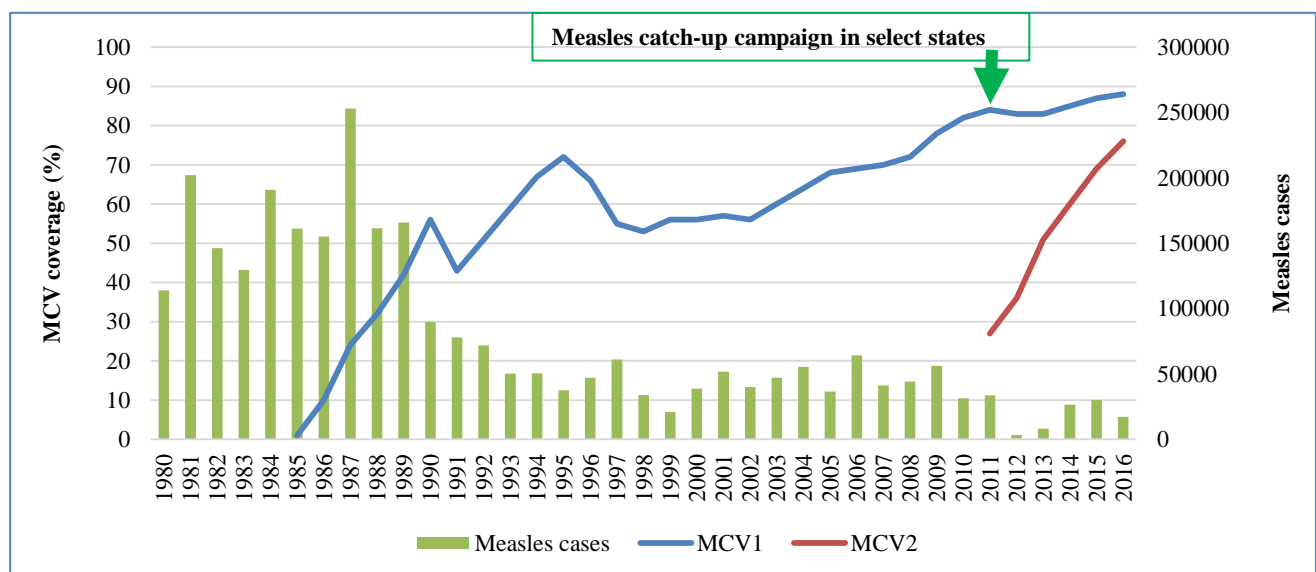


Figure 1: Reported measles cases and estimated MCV coverages, India, 1980-2016.

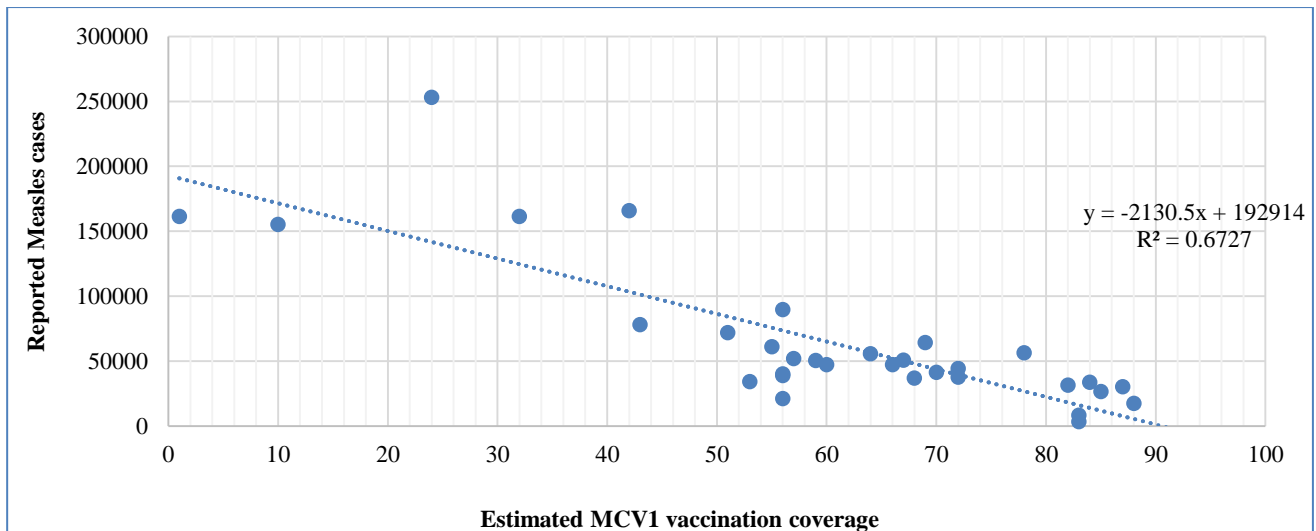


Figure 2: Correlation between MCV1 vaccination coverage and reported measles cases from India, 1980-2016.

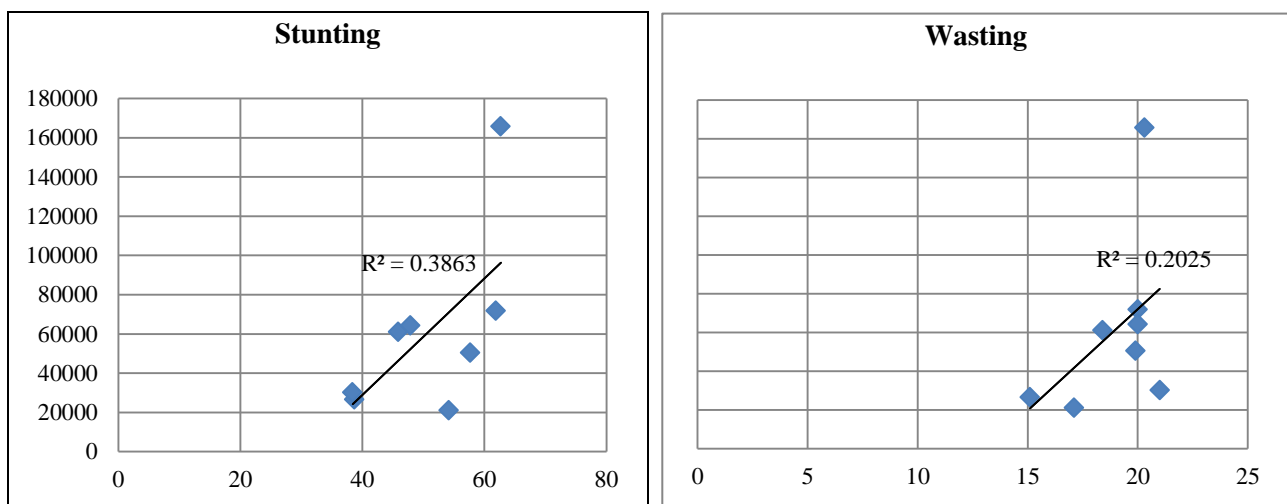


Figure 3: Correlation between stunting and wasting prevalence with reported measles cases from India, 1989-2015.

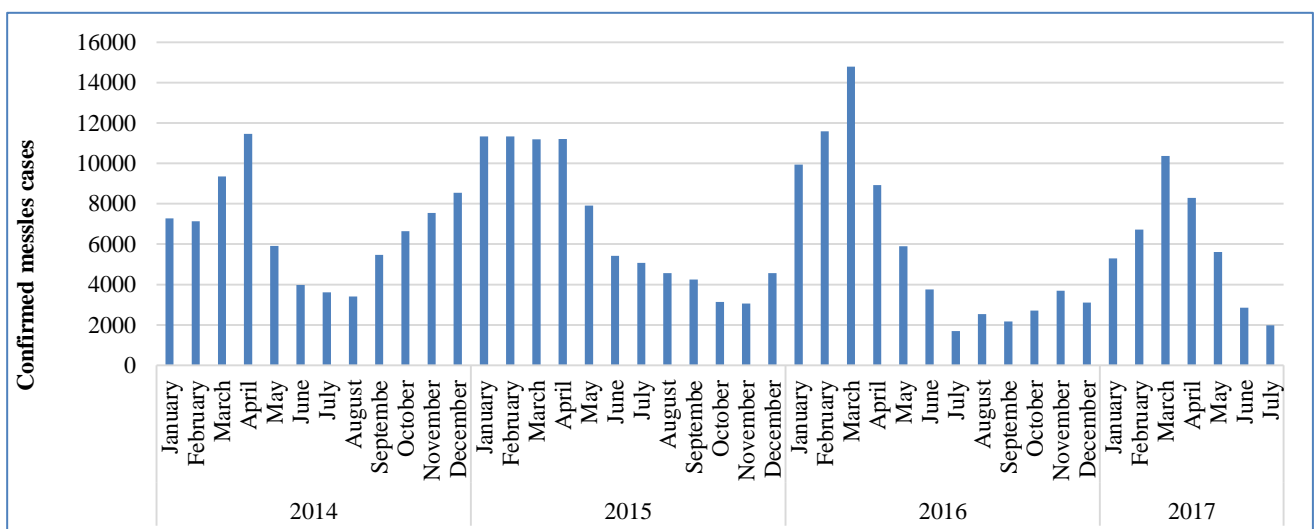


Figure 4: Confirmed measles cases through surveillance (lab, epi link, clinical), India, 2014-17.

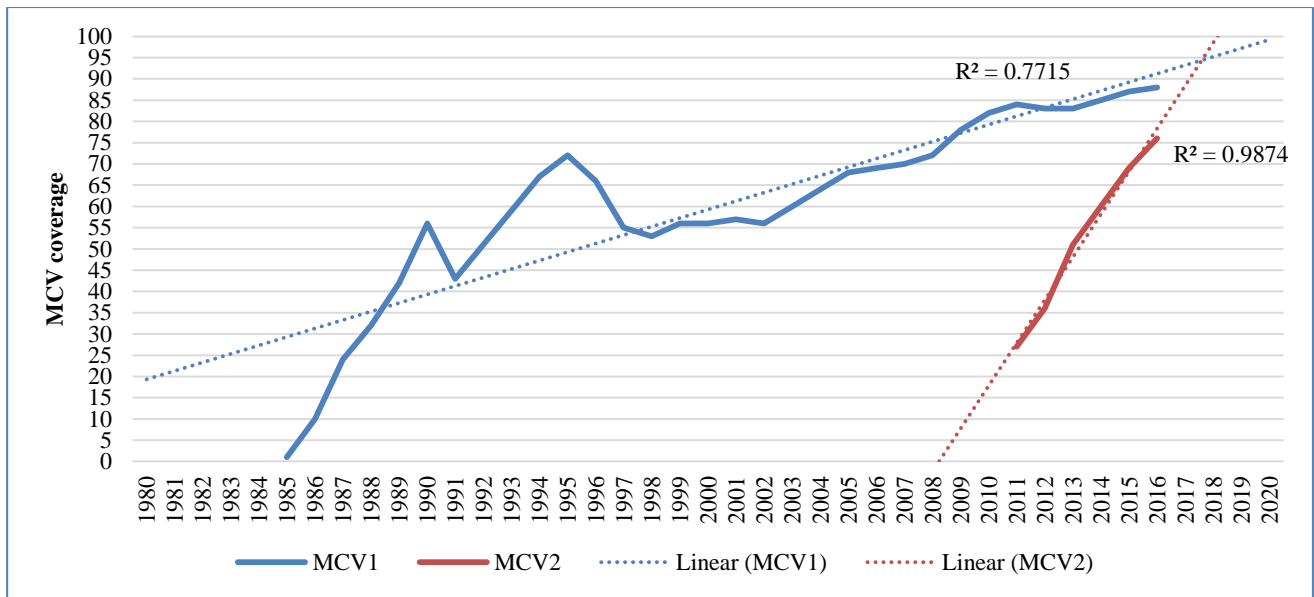


Figure 5: Estimated MCV 1 and MCV2 coverage trends and projections till 2020.

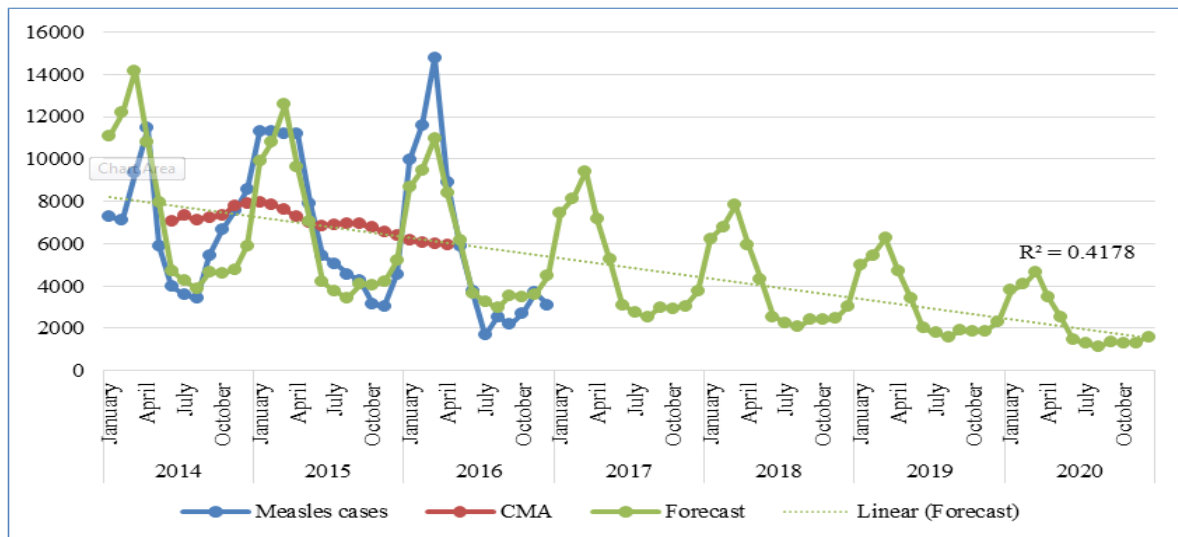


Figure 6: Time series trend and projections for measles cases, India, 2014-20 (MS Excel).

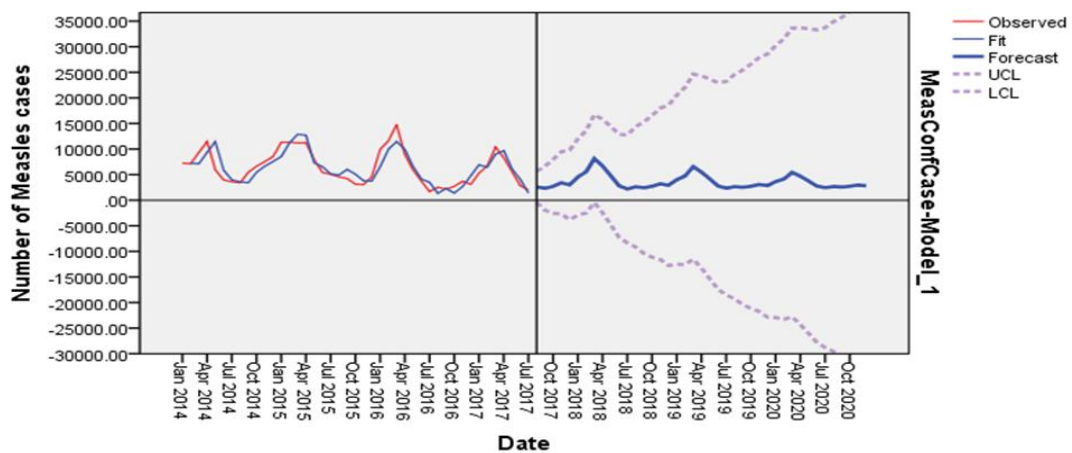


Figure 7: Time series trend and projection for measles cases, India, 2014-20 (SPSS).

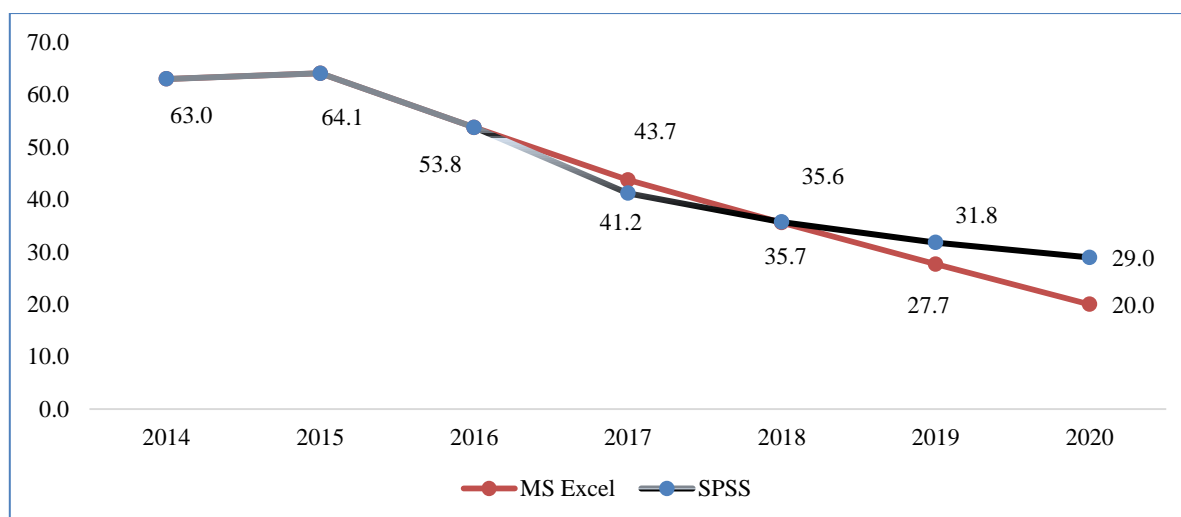


Figure 8: Measles incidence trends and projections per million population, India 2014-20.

Figure 7 shows the time series modelling using Autoregressive Integrated Moving Average process (ARIMA) method in SPSS with forecasts till 2020. The fitted model matched visually with the observed data and seasonal changes to maximum extent (Model fit statistics: Stationary R^2 , 0.445; R^2 , 0.739; RMSE, 1734.625; MAE, 1329.293). ARIMA model (0,1,0;1,0,0) was highly significant (AR, Seasonal, Lag 1; Estimate, 0.708; SE, 0.110; t, 6.418; $p < 0.000$). Ljung-Box test showed that there was no autocorrelation for residuals with $Q(18) = 14.894$, $df = 17$, $p = 0.603$. It is clear that the cases will gradually decrease over next few years till 2020.

Figure 8 shows the trends and projections of measles incidence per million population using the data of confirmed measles cases, measles case projections by time series models on MS Excel and SPSS analysis software, and census 2011 population projections for the respective years. We can see that the incidence rates will be reduced drastically from more than 60 in 2014 to less than 30 by 2020 given the current rates of increase in immunization coverages.

DISCUSSION

Measles case occurrence is decreasing over the last 3 decades ever since the introduction of measles vaccine in India. It is more so in the present decade where India is catching up with the control and elimination measures with the rest of the world.³⁻⁵ It is clear from the analysis that the measles case occurrence has drastically reduced, along with the reductions in morbidity and mortality.⁵ The reductions are largely attributable to improvements in measles vaccine coverages and hence the reduction in number susceptible individuals in the population.³ In our study, we found highly significant correlations between measles case reduction with MCV coverages. Though there are many other epidemiological factors responsible for measles occurrence such as malnutrition,

overcrowding, poor living conditions etc., measles vaccine appears to play a major role in prevention and control of measles.^{1,8-12}

In our study, even with limited data availability on the trends of nutritional status, we observed a positive correlation of measles case occurrence with wasting and stunting. Many previous studies have also observed similar findings.^{10-12,34} Hence, in addition to vaccination measures, India also needs to step up the nutritional status of children to achieve measles elimination goal and to sustain it subsequently.

The study of trends in MCV coverages reveal that till 2014 the rate of increase in coverages was about 2% per year from 2000-2013. However, since 2014 coverages are increasing at a faster rate with up to 5% a year in poor performing states, and at about 3% for India. Very high rates of increase (10% per year) in MCV2 coverages are observed especially due to immunization intensification efforts with focus on tracking children in their second year of life for booster doses and MCV2. Many studies and publications have documented the dramatic improvements in immunization levels in India recently.^{23,25,30,31}

The analysis of recent confirmed measles case data showed that there was a strong seasonality component and the outbreaks/epidemics lasted for few months in the first part of each year. We also observed that the measles cases appear to have increased post 2013 probably due to the accumulation of susceptibles because of non-sustenance of population immunity, following the measles catch up campaign held from 2010-13, in some states of India. This underlies the importance of sustained efforts needed for measles control and elimination. Many western countries are experiencing measles resurgence due to falling immunization levels.³⁵⁻³⁸

The forecasting of vaccination coverages look good with all possibility of achieving both MCV1 and MCV2 coverages up to 95% by the end of 2020. Sustained system strengthening efforts are needed for this purpose. The forecast looks further attractive and feasible by considering the fact that there is an ongoing MR campaign throughout the country in phased manner which will further rise the population immunity against measles in the age group of 9 months to 15 years especially in high burden states such as Uttar Pradesh and Bihar.²⁵

The time series forecasting of measles cases till 2020 show that there will be a drastic reduction in the occurrence of measles cases over next few years with the incidence rates per million population falling to as low as 20 cases a year. Though it is generally accepted that the measles incidence should fall below 5 cases per million population a year for achieving elimination goal, as evidenced by the incidences in some western countries, there are studies which put forward an alternate criteria for considering the verification of measles elimination.^{13-15,35,39,40}

CONCLUSION

The future of measles elimination programme looks promising with strong commitments at international level through SDGs and also ensuring sustained funding to the Measles-Rubella Initiative. The level of political and administrative commitments in India towards measles elimination also look promising. System strengthening measures are also being undertaken at a rapid pace. Further, enhancing the socio-economic growth and nutritional status of Indian children would augment the speed at which elimination of measles could be achieved and sustained in India. In addition, we need constant monitoring and analysis of epidemiological data to guide mid-course corrections in the implementation of strategies.

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