The historical association between measles and pertussis: A case of immune suppression?

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Abstract

Objectives: According to historical medical reports, many children with measles subsequently contracted pertussis, often with fatal results. The likelihood of a child contracting pertussis after a measles infection is increased by its immune-suppressing effects. This research aims to verify the historical reports.

Methods: The analysis examines statistically the historical relationship between average measles and pertussis incidence rates in the United States from 1938 to 1954 at the state level and in average weekly rates. Analysis of incidence rates is cross-sectional at the state level using public health data.

Results: The results show that, on average and over time, states with higher measles rates have higher pertussis rates, and the peaks and nadirs of average weekly incidence rates of pertussis lag measles by a delay of about 3–4 weeks, well within the duration of immune suppression. Measles and pertussis have similar geographical distributions.

Conclusion: The research tentatively supports the hypothesis that because of its immune-suppressing effects, measles causes an increase in pertussis, but other factors may be involved. Epidemic models should give more attention to the possibility of immune suppression for diseases such as measles where that might be a risk factor. The findings reemphasize the importance of measles vaccination for the prevention of other diseases.

Introduction

Historical medical reports and textbooks show that many children with measles subsequently contracted pertussis, often with fatal results. This was described over 150 years ago by Virchow[1] in Germany and later by Osler[2] in the United States, among others.[3,4] (The term "whooping cough," not pertussis, was most commonly used in the period of analysis. Historical research was also done using the terms *hooping cough* and *tussis*, and in German, *Keuchhusten*.) In his history of British epidemics, Creighton[5] writes, "Measles … has undoubtedly been followed by whooping cough in many individual cases and in epidemics as a whole; and it may be that there is a closer association with measles than with any other infectious disease." This analysis examines the historical relationship between measles and pertussis in the United States from 1938 to 1954 to try to verify this reported association.

The possibility of a child contracting pertussis shortly after a measles infection is increased by its immune-suppressing effects. In general, viral infections predispose to secondary microbial infections.[6] Measles, specifically, has been identified as suppressing the immune system, which is the main cause of infant death from measles.[7–9] Immunosuppression begins during infection and can linger for several weeks or more leading to secondary infections. Pneumonia and encephalitis are often cited now as the most important consequences of measles in the West, but in less-developed countries, it is the delayed immune-suppressing effect that causes the most deaths from other diseases.[10] Moreover, new research[11] using historical data from Britain, the United States, and Denmark

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shows that measles vaccination has protective effects against other infectious diseases for 2–3 years and that nonmeasles disease mortality in both the pre- and post-vaccine eras was linked to measles incidence. The authors attribute immunosuppression to depletion of B and T lymphocytes. This study does not, however, break out pertussis data.

Methods

Because historical information on diseases and comorbidity at the individual level is sorely lacking, one must rely on the aggregate data collected by early public health authorities, however limiting this in establishing causal relationships. As it is now, national and state data on measles and pertussis cases were collected historically in the United States through a state-based mandatory public health reporting system. But reporting was not complete and reporting methods were not identical in every state. Both diseases were still common during this period although pertussis cases were in decline. Total reported cases in 1950 were 319,000 for measles and 121,000 for pertussis. Disease incidence in the analysis is reported cases per 100,000 of population.

The analysis relies on state-level data from Project Tycho[12] (Project Tycho data[13] are available at http://www.tycho.pitt. edu/). This project plans to compile and digitize most weekly state and local public health records of reportable disease cases from 1888 to 2011. A subset of these data is now available, and the analysis incorporates the state-level, weekly incidence data for reported measles and pertussis cases from 1938 to 1954. The period of analysis is limited by the availability of pertussis data, which begins in 1938, and it ends at 1954 because of the increasing vaccination rate for pertussis. The analysis aggregates the weekly state data to obtain average weekly and annual incidence rates at the state level. Two states had substantial missing data for both measles and pertussis (Nevada and Mississippi) and are generally missing cases in the analysis, while pertussis data are also missing in some years for Nebraska. Occasionally, weekly data are missing for an arbitrary state and year, but in several years, data are missing for all states in the first week or last 2 weeks of the year. It is unknown whether these data were never reported or whether reporting was delayed, perhaps because of the holidays. Average incidence rates in these weeks may not represent the country as well as other weeks. Cases reported after the 52nd week of the year are included in the first week of the next year. The analysis also incorporates state-level census data on birth rates, household size, average per capita income, population density, and percentage of the population Black.

Because the relationship between measles and pertussis was so often observed historically by medical authorities who had no knowledge of modern statistics and no access to large databases, it should be possible to detect the same relationship in this analysis, if it exists, with fairly basic statistical methods. The analysis is in two stages. First, it is necessary to establish that to a significant degree pertussis epidemics closely follow measles epidemics, as described historically. To test this, measles and pertussis epidemics are compared as to the timing of their peaks and nadirs for each year from 1938 to 1954. Then, the statistical distributions of weeks with the highest incidence rates for measles and pertussis are estimated and compared.

The second phase of the research focuses on the relationship between measles and pertussis incidence at the state level each year and over multi-year periods. Because of the large amplitude of multi-year and seasonal cycles in pertussis and measles, the analysis uses averaging over time to bring out the relationships across states that are relatively persistent. The analysis averages annual incidence rates for equal 5-year intervals from 1940 to 1954 and for the entire period from 1940 to 1954; yearly correlations are examined from 1938 to 1954. The distributions are skewed because of some very high state incidence rates, so the variables are transformed logarithmically for regression analysis. Exogenous factors that might cause a spurious association between measles and pertussis are considered in this part of the analysis.

The third element of this research is a comparison of the geographical distributions of measles and pertussis at the state level in the United States. A regression model for each is developed as a function of state longitude and latitude at the centroid for average state incidence rates in the period 1940–1954. The centroid is the geometrical center of gravity of a state. To find locations of the state centroids, the research uses the geographical software GeoDa 0.9.5.[14] GeoDa[15] follows the ArcView standard for geometric area data files from ESRI, Inc. GeoDa calculates the centroids from the polygons used to map the states according to a shapefile. This analysis uses a geometric shapefile for the United States from Idaho State University's open-source MapWindow (http://www.mapwindow.org). Only the contiguous 48 states are included in this analysis.

In a spatial regression analysis, the regression coefficients are likely to be biased if there is a strong correlation among units.[16] This could result, for example, from the spread of an epidemic from one or more states to their neighbors. In this analysis, correlation among neighboring states is measured as correlation of state incidence rates with their spatial lags, which for each state is the average incidence rate in bordering states (rook contiguity). The possibility that the spatial lag is statistically significant is tested by a Lagrange multiplier (LM) test, that is, the spatial analysis checks whether the regression model captures the entire spatial lag. This test was done for all the regression models. Because the test cannot be done with missing values, the two or three missing state values were replaced by their spatial lags. No problems were found with any of the regression models.

Results

Time series comparison between measles and pertussis

The average weekly state incidence rates from 1938 to 1954 for measles and pertussis are shown in Figure 1 with LOWESS
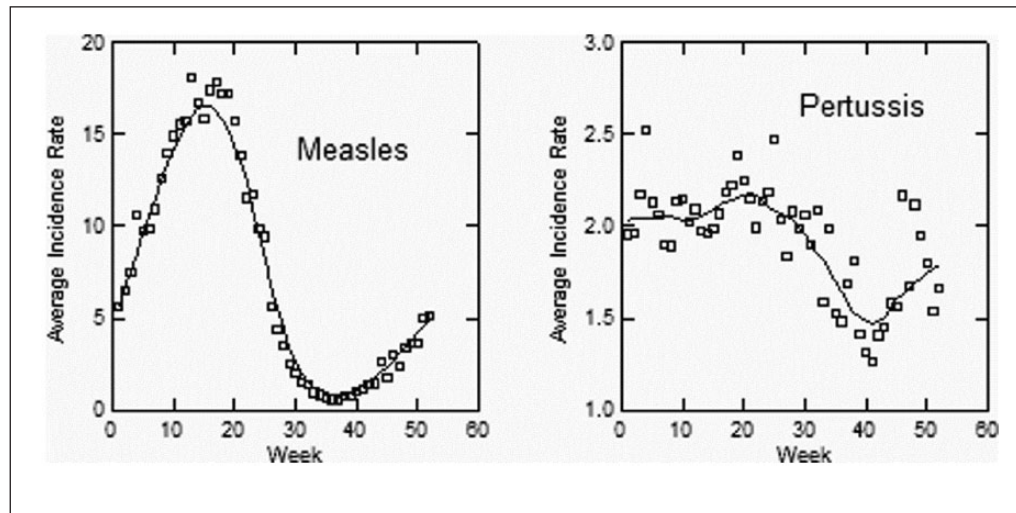
Figure 1. Average weekly state incidence rates for measles and pertussis, 1938–1954, with LOWESS smoothing.

Table 1. Average timing of the peaks and nadirs of annual measles and pertussis epidemics, 1938–1954.

| Year	Measles peak week	Pertussis peak week	Measles nadir week	Pertussis nadir week
1938	25	25	37	41
1939	4	4	36	51
1940	17	21	36	41
1941	14	20	35	42
1942	16	3	36	40
1943	12	24	35	43
1944	11	18	38	41
1945	13	12	38	41
1946	17	26	38	41
1947	19	20	37	52
1948	17	3	37	52
1949	12	31	37	37
1950	18	12	36	35
1951	16	19	36	40
1952	17	19	38	40
1953	17	4	38	8
1954	13	12	37	17

smoothing. Note that the incidence of pertussis is relatively flat in the first few months of the year.

The timing of the peaks and nadirs for measles and pertussis for each year from 1938 to 1954 is given in Table 1. The mean of the measles nadir is at week 36.8 and for pertussis at week 38.9. The mean peak for measles is at week 15.2 and for pertussis at week 16.0. A nonparametric sign test confirms that measles leads pertussis at the nadir (p = 0.02). At their peaks, measles leads pertussis in 9 weeks of 17 with their peaks twice in the same week, which is not statistically significant in a sign test. This again reflects the relatively flat distribution of pertussis rates early in the year.

Determination of the timing of pertussis peaks, as in Table 1, has a margin of error. The incidence rate is so flat in the first part of the year that the rate may hardly change over an interval of several weeks, and small, random variations in incidence can change the timing of the peak. (For the same reason, it is not worthwhile to do a cross-correlation analysis between measles and pertussis or to consider lagged relationships.) To get a better handle on statistical variation in the timing of the peaks for measles and pertussis, the 10% of weeks with the highest incidence rates for measles and pertussis were analyzed and compared, that is, for 88 of 884 weeks from 1938 to 1954. For measles, the median of the peaks is in week 14.5, average 14.6, 95% confidence interval CI (13.4, 15.8); corresponding values for pertussis are median week 18, average 18.1, 95% CI (15.7, 20.5). The delay from measles to pertussis peaks is about 4 weeks, and the difference in means is statistically significant (p < 0.001). One can compare this lag with the time it would likely take for a child to be infected with pertussis after a case of measles and for the pertussis infection to be reported. The incubation period of pertussis is typically 7–10 days, and if pertussis is not reported until the telltale cough appears, which is another week or two later, the gap at the peak from an active measles case to pertussis infection is about 1 or 2 weeks, on average.

Correlation and regression models

Correlations between average annual state measles and pertussis rates over equal 5-year intervals from 1940 to 1954 are 0.90 for 1940–1944, 0.84 for 1945–1949, and 0.69 for 1950–1954 (for all, p < 0.001). The decrease in correlation over time likely reflects increasing vaccination rates for pertussis that may vary across states. Taking each year individually, one finds that the correlation between measles and pertussis is positive and statistically significant (p < 0.05) in every year from 1938 to 1954 except 1950 and 1953, but the correlations are not as strong as for the 5-year averages.
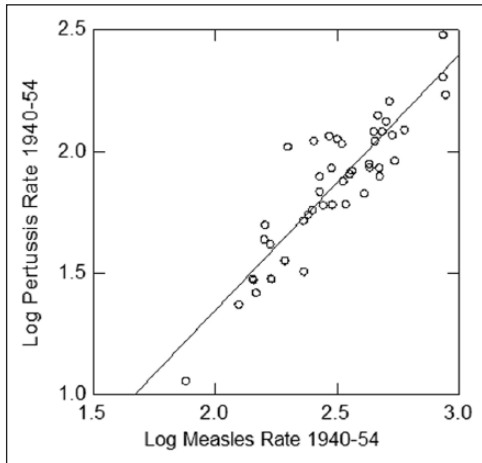
Figure 2. Average state pertussis rates, 1940–1954, in relation to average measles rates expressed logarithmically.

The overarching, long-term relationship between average pertussis and measles rates from 1940 to 1954 is illustrated in Figure 2 with the variables transformed logarithmically. The corresponding linear regression models with standard errors in parentheses are

$$\text{Pertussis rate} = 1.0\ (8.5) + 0.24\ (0.02)\ \text{measles rate},$$
$$R^2 = 0.75, N = 45$$

$$\text{Log pertussis rate} = -0.75\ (0.20)$$
$$+ 1.05\ (0.08)\ \text{log measles rate}, R^2 = 0.80, N = 45$$

The connection between measles and pertussis remains strong if one compares the change in pertussis rates between 1940–1944 and 1945–1949 to change in measles rates between the same two periods. The correlation is $r = 0.71$ ($p < 0.001$). Obviously, location does not change, so the correlation between measles and pertussis, on average, is not simply a coincidence of location or of the two diseases having similar geographic distributions.

An alternative explanation for the strong measles–pertussis association might be that states with disproportionately more children have higher rates of both measles and pertussis. Further analysis, however, calls this supposition into question. In the first place, both diseases had lower average rates in 1945–1949 than 1940–1944, while birth rates increased in most years of the decade. To test the effect of birth rate directly, these data for 1942 were added to the analysis.[17] In 1942, the US birth rate was the highest in history up to that point. All states except New Mexico had an increase in birth rate, and the national birth rate increased by 11% over 1941. The analysis followed this birth cohort in subsequent years as to its effect on measles and pertussis. The first observation is that birth rate in 1942 does not have a correlation with either state latitude or longitude, which is pertinent

to the subsequent geographical analysis. Furthermore, correlations of state birth rates in 1942 with disease incidence in subsequent years are weak and not simultaneous: for pertussis in 1944, $r = 0.30$ ($p = 0.04$, $N = 46$) and for measles in 1945, $r = 0.32$ ($p = .03$, $N = 46$). Next, average household size from the 1940 census was introduced to the analysis. It has no correlation with state measles or pertussis in any year from 1940 to 1945.

Additional analysis was done to check for the possible influence of state per capita average income, population density, and percentage of the population Black using 1950 census data. Low income levels, for example, might have led to poor diets for children and caused a degree of immune suppression, as through lack of vitamin A, while the Black population generally had poorer living conditions than Whites. Population density might affect the geographic spread of disease within a state. Average state pertussis rates from 1945 to 1949, and from 1950 to 1954, were regressed on the 1950 census variables and average measles rates over the respective time periods. The regression analysis shows that population density and income are not statistically significant in either regression. But percentage Black has a modest positive relationship with state pertussis incidence in the 1945–1949 period after controlling for the measles rate, which remains by far the strongest predictor.

Geographical analysis

The spatial relationships for measles and pertussis from 1940 to 1954 are indicated by the regression models in Table 2. Disease incidence is regressed on latitude and longitude of the state centroid. (Note that longitude is a negative quantity in the United States.) The logarithms of both average state measles rates and pertussis rates from 1940 to 1954 have similar parabolic relationships with longitude. Measles and pertussis rates tend to be higher in the East and West and lower in the center of the country. Measles also tends to increase with latitude, but pertussis is weakly related to latitude, at best. (Higher-order polynomial terms are not statistically significant.) One can calculate the locations of the minima of the fitted quadratic curves from the estimated coefficients. The measles curve has a minimum at −90° longitude and, not far away, pertussis is at −94°—both about the same longitude as St. Louis, Missouri, at −90°. The closeness of the two minima to each other is a numerical measure of the strength of association between the two diseases. As stated earlier, a LM test was done and showed that spatial lag need not be included in the model; the coefficient estimates are unbiased.

Further analysis shows that the parabolic geographic distribution for pertussis had already emerged by 1938, if not before. And measles incidence already had the same distribution in the 1930s, as seen in the Tycho data, and perhaps earlier. This testifies to the persistence of these geographic patterns despite strong seasonality and multi-year cycles in the disease rates.

Table 2. Spatial regressions for log average state measles rates and log average state pertussis rates, 1940–1954, with standard errors (SE) and the longitude of the estimated minimum.

Disease	Constant (SE)	Longitude (SE)	Longitude^2 (SE)	Latitude (SE)	Minimum at longitude	R^2	p
Measles (N = 46)	4.82 (1.39)	0.067 (0.028)	0.00037 (0.00015)	0.016 (0.007)	−90°	0.32	0.001
Pertussis (N = 45)	6.51 (1.56)	0.100 (0.033)	0.00053 (0.00018)	0.009 (0.009)	−94°	0.17	0.02

Discussion

The analysis has successfully demonstrated an association between measles and pertussis similar to what historical observers reported, that is, with pertussis following relatively soon after measles. The comparison of peaks and nadirs for average weekly incidence rates shows measles leading pertussis by no more than 3 or 4 weeks, which is well within the period of immunosuppression caused by measles and consistent with historical evidence. And there is a strong correlation between average state measles and pertussis rates. Variation in average measles rates explains over half the variation in average pertussis rates across intervals of 5–15 years. The strength of the measles–pertussis correlation wanes, however, in the 1950s as vaccination for pertussis increases. Immune suppression is a possible cause for the relationship, but the correlation and regression analysis cannot rule out the possibility that exogenous factors may contribute to or cause the observed association. The inference that the population level association between measles and pertussis truly reflects a connection at the individual level is best supported by the solid historical reports of preeminent medical authorities of their time like Virchow[1] and Osler,[2] as with the new research by Mina et al.[11] Alternatives related to birth rate, household size, rates of change, and state geography were tested and rejected as well as population density, income, and percentage Black. Other limitations of this research are that it was not possible to find data on the extent of pertussis vaccination or the frequency of quarantine for these diseases at the state level.

Pertussis and measles have been reported to have a connection with each other that would seem to contradict the finding that measles often leads directly to pertussis, namely, disease interference.[18] Simply put, disease interference is the situation when children who get measles stay home for a time, or possibly die, thereby reducing the likelihood that they would catch and spread pertussis in the same year. The result is that a measles epidemic may delay a pertussis epidemic until the following year. This was reported for some European cities in the late 19th and early 20th centuries,[19] but other cities did not show the pattern. This analysis was not able to find specific evidence of an interference effect or the neat out-of-phase annual cycles of measles and pertussis described in other research; historically, pertussis cycles were a year or two longer than measles cycles in the United States. It is plausible to assume that some children might have temporarily escaped pertussis by staying home when infected with measles, while other children down the street contracted pertussis as a result of measles. If this happened, however, the effect of the delay on a pertussis epidemic and its timing is hard to predict, and a possible interference effect must be weaker than the potential immunosuppressive effect of measles on pertussis or one would expect to see longer delays between measles and pertussis over the course of a year. Nevertheless, this topic deserves more research to disentangle the two phenomena.

The historical association between pertussis and measles contradicts the findings of Smallman-Raynor and Cliff.[20] They study comorbidity of childhood illnesses in the 1930s in English boarding schools using nonmetric, multidimensional scaling to search for associations among about two dozen illnesses. Although their analysis is able to identify clusters of diseases, they conclude that many childhood diseases are immunologically independent of one another including measles and pertussis. Pertussis stands out as the most remote from other childhood diseases in the multidimensional statistical space. The difference in findings is likely caused by the truncated age range of students in their research—pertussis tends to strike younger children and infants before school age.

The geographical distribution of pertussis is about the same as reported by Choisy and Rohani.[21] They analyze the geographical spread of pertussis in the United States in the 1950s using monthly incidence data for the states and state centroids for location. They report finding synchronous foci of the epidemics in the northeastern and northwestern states from which epidemics spread out to the southwest and southeast, respectively. Longitude of the state's centroid is a strong predictor of incidence rate. The result is that pertussis incidence is high in the East and West and low in the center of the country—the same pattern seen here for both pertussis and measles. They speculate that the synchronicity of the regional foci stems from air travel between the coasts in the 1950s, but this is unlikely to be the cause because the spatial pattern had emerged as early as 1938, if not before. Their analysis is problematic in that it does not consider the possible effect of measles on the spread of pertussis.

In general, epidemiological models could give more attention to immune suppression. As in the case of measles, this can have long-term effects on other infectious diseases, their mortality, and their dynamic cycles from one year to the next.[11] The greatest puzzle, however, is why *pertussis* has a special connection with measles—a relationship that has been observed for over 150 years. Immunosuppression may

be a necessary condition, but it does not seem sufficient to account for this association. Immune suppression by measles increases the likelihood of a child contracting other diseases, but none seem to have had the same close connection to measles that pertussis has. Historical observers have commented on several factors that the two diseases have in common to account for the association. These include the fact that both diseases attack the respiratory epithelium and affect children of about the same age; and it is now known that both also cause the immune system to produce interleukin 10[22,23,24], which suppresses the immune response. Whatever the cause, the findings here support the importance of measles vaccination for preventing pertussis. This does not imply, however, that children who are vaccinated for measles can go without vaccination for pertussis or other childhood diseases or that measles vaccination can prevent epidemics of other childhood diseases.

Declaration of conflicting interests

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References

1. Virchow RLK. *Handbuch der speziellen Pathologie und Therapie* [Handbook of Special Pathology and Therapeutics], part 1, vol. 5. Erlangen: Verlag von Ferdinand Enke, 1854, p. 565.
2. Osler W. *Lehrbuch der Internen Medizin* [Textbook on Internal Medicine]. Hamburg: Servus Verlag, 1909, 2012, p. 104.
3. Williams D. Diseases of children: medical, measles and whooping cough. *Practitioner* 1895; 55: 74–78.
4. US Public Health Service. Public health reports: part 2, vol. 32. Report, US Department of Treasury, Washington, DC, July–December 1919.
5. Creighton CA. *History of Epidemics in Britain*, vol. 2. Cambridge: Cambridge University Press, 1894, pp. 674–675.
6. Mills EL. Viral infections predisposing to bacterial infections. *Annu Rev Med* 1984; 35: 469–479.
7. Pelton BK, Hylton W and Denman AM. Selective immunosuppressive effects of measles virus infection. *Clin Exp Immunol* 1982; 47: 19–26.
8. Kerdiles YM, Sellin CI, Druelle J, et al. Immunosuppression caused by measles virus: role of proteins. *Rev Med Virol* 2006; 16: 49–63.
9. Griffin DE, Ward BJ and Esolen LM. Pathogenesis of measles virus infection: a hypothesis of altered immune response. *J Infect Dis* 1994; 170(Suppl. 1): S24–S31.
10. Schneider-Schaulies S and Schneider-Schaulies J. Measles virus-induced immunosuppression. *Curr Top Microbiol Immunol* 2009; 330: 243–269.
11. Mina JM, Metcalf CJ, de Swart RL, et al. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* 2015; 348: 694–699.
12. Van Panhuis WG, Grefenstette J, Jung SY, et al. Contagious diseases in the United States from 1888 to the present. *N Engl J Med* 2013; 369: 2152–2158.
13. Project Tycho database, 2014, http://www.tycho.pitt.edu/ (accessed 19 November 2014).
14. Anselin L, Sybari I and Kho Y. GeoDa: an introduction to spatial data analysis. *Geogr Anal* 2006; 38: 5–22.
15. GeoDa software, http://geodacenter.asu.edu (accessed 19 November 2014).
16. Ward MD and Gleditsch KS. *Spatial Regression Models*. Los Angeles, CA: SAGE, 2008.
17. US Department of Commerce. *Vital statistics—special reports*, vol. 19. Washington, DC: US Department of Commerce, 1943, 1945.
18. Rohani P, Earn DJ, Finkenstaedt B, et al. Population dynamic interference among childhood diseases. *Proc R Soc B Biol Sci* 1998; 265: 2033–2041.
19. Rohani P, Green CJ, Mantilla-Beniers NB, et al. Ecological interference between fatal diseases. *Nature* 2003; 422: 885–888.
20. Smallman-Raynor M and Cliff AD. Epidemics in semi-isolated communities: statistical perspectives on acute childhood diseases in English boarding schools, 1930–1939. *J R Stat Soc Ser A Stat Soc* 2013; 176: 321–346.
21. Choisy M and Rohani P. Changing spatial epidemiology of pertussis in continental USA. *Proc Biol Sci* 2012; 279: 4574–4581.
22. Moss WJ, Ryon JJ, Monze M and Griffin DE. Differential regulation of Interleukin IL-4, IL5, and IL-10 during measles in Zambian children. *J Infect Dis* 2002; 186: 879-887.
23. Moss WJ, Ora MO and Griffin DE. Measles: Immune suppression and immune responses. *Int J Biochem Cell Biol* 2004; 36: 1380–1385.
24. McGuirk P, McCann C and Mills KHG. Pathogen-specific T regulatory 1 cells induced in the respiratory tract by a bacterial molecule that stimulates Interleukin 10 production by dendritic cells: A novel strategy for evasion of T helper type 1 responses by Bordetella pertussis. *J Exp Med* 2002; 195: 221-231.