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Author/s:

Do, LAH;Tsedenbal, N;Von Mollendorf, C;Mungun, T;Bardach, D;Mulholland, K

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Exploring the Possible Cause of the Dramatic Increase in Measles Mortality During the 2015–2016 Mongolian Outbreak

Keywords. measles virus; measles mortality; respiratory syncytial virus; influenza; immunosuppression.

To the Editor—Measles case fatality rates vary greatly between outbreaks for reasons that are not well understood [1]. In Mongolia, measles returned dramatically as a bimodal epidemic during 2015 and 2016 [2, 3]. The infant measles mortality rate during the 2016 wave, was 10 times higher than during the 2015 wave [2, 3]. Coinfection with influenza B was suggested by Lee and colleagues to be the likely cause of the increase [2, 3], yet from 132 measles deaths only 6 lung tissue samples were

tested for pathogens, of which 2 were positive for influenza B [2, 3].

Since April 2015, we have established ongoing childhood pneumonia surveillance in 4 of the 9 districts of Ulaanbaatar, Mongolia, to evaluate the impact of introducing pneumococcal conjugate vaccine [4]. From April 2015 to September 2016, we screened 1431 children <2 years of age who were admitted with severe pneumonia for respiratory syncytial virus (RSV) and influenza, and we made 2 surprising observations: first, an apparently stronger coincidence of measles deaths with the peak of RSV detection among children with pneumonia, and second, an intriguingly dramatic increase in all pneumonia admissions and severe pneumonia cases associated with RSV, but not with influenza A or B, in the year after the measles virus (MeV) outbreak (Figure 1).

These observations and those of Lee and colleagues [3] could be explained by a phenomenon known as “measles amnesia.” This refers to immunosuppression secondary to MeV infection increasing host susceptibility to other nonmeasles pathogens, both during the acute MeV infection phase and during the months after the MeV infection has resolved. The immunosuppression is due to the depletion of preexisting memory T and B cells specific to nonmeasles pathogens, as demonstrated in a macaque model [5].

In a later study, Mina et al [6] were able to profile the immune memory antibody repertoire against a range of viral and bacterial epitopes in plasma collected before and after measles infection in a cohort of 77 unvaccinated children in the Netherlands. After mild and severe MeV

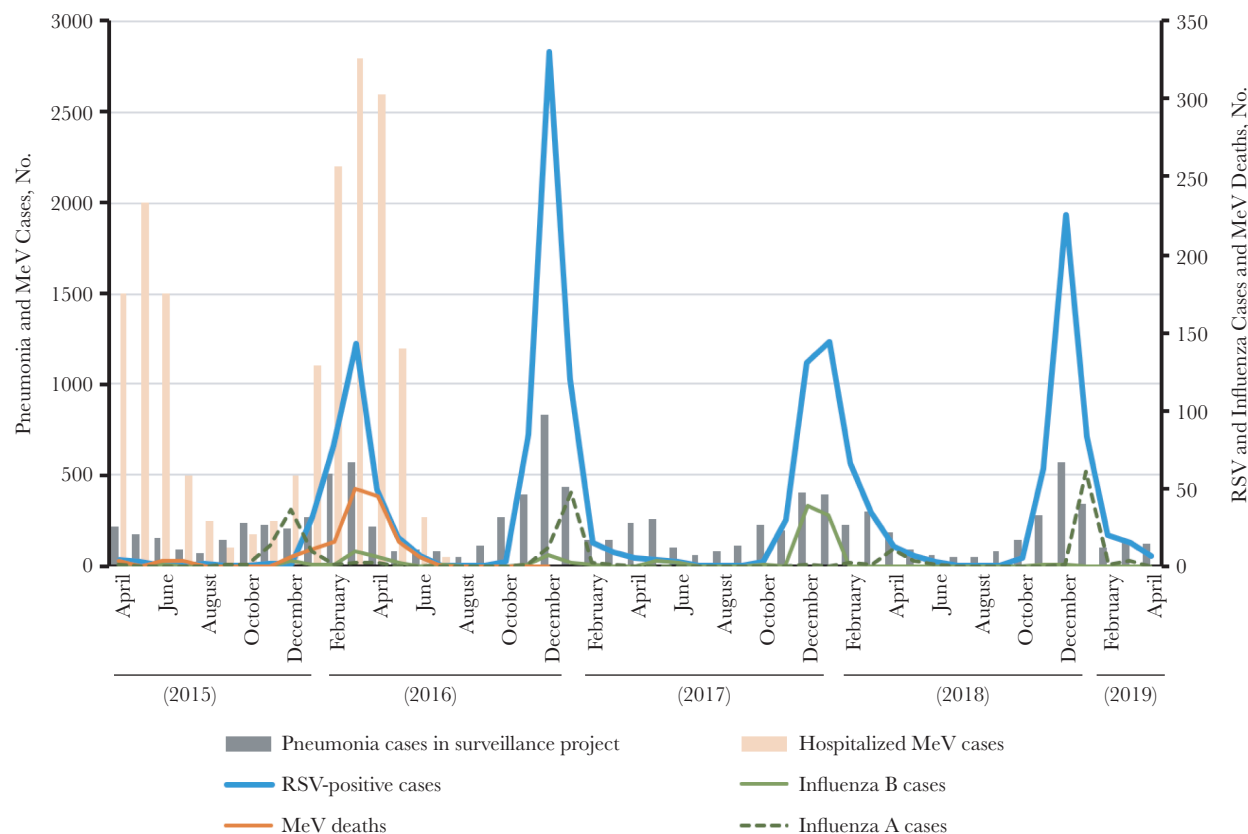


Figure 1. Measles cases and measles deaths during pneumonia, respiratory syncytial virus (RSV) and influenza surveillance (measles data from Orsoo et al [2]).

infections, children lost a median of 20% and 40%, respectively of their total preexisting pathogen-specific antibody repertoire. This loss varied among children and specific pathogens. It was observed across nearly all subjects for their antibody repertoires for *Streptococcus pneumoniae*, influenza B, enterovirus, rhinovirus and RSV. A significant reduction in the avidity of antibody binding to the important palivizumab binding site of RSV was also observed in 22 of the 77 children.

These findings were confirmed again by similar findings from the macaque model, where MeV infection led to variable reductions in RSV and influenza B antibody repertoires of 45% and 60%, respectively [6]. This loss of antibody repertoire in macaques persisted for at least 5 months, and epidemiological evidence in humans suggests there is increased susceptibility to deaths from nonmeasles infectious disease for up to 5 years after a measles outbreak [6]. In applying these findings to the Mongolian outbreak, it seems that the excess measles mortality rate may be due to RSV or influenza B infection leading to a fatal outcome among children recovering from measles. This may also partly explain the excess of RSV-associated pneumonia admissions the following winter.

Another side of the interplay between MeV and RSV is the potential heterologous protection between the 2 viruses, because they belong to the same Paramyxoviridae family. T-cell cross reactive responses between RSV and MeV have been reported for in vitro and in vivo mice models [7]. Better immunoglobulin G responses to measles vaccine were shown in patients previously exposed to RSV than in those never infected by RSV [8]. In addition, MeV vaccine has been shown to have unexpected beneficial (nonspecific) effects on general morbidity and mortality rates associated with infectious diseases, including RSV infection specifically [9].

In conclusion, measles mortality rates vary greatly between epidemics and regions, but few studies have

interrogated the causes of measles-associated deaths, mainly because of complex logistic, administrative and research capacity limitations during MeV epidemics. The potential link between RSV and MeV warrants further investigation with the goal of better controlling both diseases.

Notes

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Lien Anh Ha Do,^{1,2} Naranzul Tsendbal,³
Claire von Mollendorf,^{1,2} Tuya Mungun,³
Darmaa Bardach,³ and Kim Mulholland^{1,2,4}

¹New Vaccines Group, Murdoch Children's Research Institute, Melbourne, Australia, ²Department of Paediatrics, The University of Melbourne, Melbourne, Australia, ³National Center of Communicable Diseases, Ulaanbaatar, Mongolia, and ⁴London School of Hygiene and Tropical Medicine, London, United Kingdom

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Association Between the Use of Statins and Risk of Tuberculosis: A Real-World Analysis

TO THE EDITOR—We read with great interest the recent study by Dutta et al [1], which demonstrated that pravastatin could exhibit potent anti-tuberculosis (TB) activity in 2 mouse models of TB chemotherapy and human-like necrotic TB lung granulomas. These findings suggest a potential role for pravastatin as an adjunctive host-directed therapy in the management of TB and support the need for further randomized clinical trials. In addition, we previously showed that statin therapy could be associated with a decreased risk of TB and suggested a role for the use of statins in preventing TB [2]. However, we did not assess the protective effect of individual statins, such as pravastatin. Thus, we conducted a real-world study using a national health insurance claims database to examine whether pravastatin and other statins exhibit protective effects against active TB.

We conducted a secondary analysis on a previously published population-based nested case-control study using

the national health claims database of Taiwan [2]. In brief, the study cohort was followed longitudinally from January 1999 to December 2011. We identified newly diagnosed active TB cases using the following criteria: at least 1 outpatient visit or 1 hospital admission with *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for TB (010–018, including all subcategories), plus the prescription of >2 anti-TB medications for >28 days. Patients with a subsequent diagnosis of non-TB mycobacterial infection or lung cancer were excluded. For each case, 100 controls were randomly selected using the incidence density sampling method and were matched by index date, 5-year age group, and sex. We analyzed the 5 most commonly used statins in Taiwan, including atorvastatin, simvastatin, rosuvastatin, fluvastatin, and pravastatin. Users with exposure to medications of interest were defined as having a drug prescription record ≥ 7 days. Current user status was defined as patients with a statin prescription filled within 30 days of the index date. We performed conditional logistic regression analysis adjusting for 32 potential confounders (sex, age, site, insurance premiums, the number of outpatient department visits, the number of emergency department visits, the number of hospitalizations, alcohol/drug use, psychiatric disorder, neurologic disorder, obesity, other cancer except metastatic solid tumor, chronic obstructive pulmonary disease, silicosis, gastrointestinal or esophageal hemorrhage, nonsteroidal

anti-inflammatory drugs, aspirin, systemic immunosuppressive agents and biologics, systemic corticosteroids, disease-modifying anti-rheumatic drugs, angiotensin-converting enzyme inhibitors, β -blockers, angiotensin-II antagonists, nitrates, proton pump inhibitors, calcium channel blockers, acetaminophen, congestive heart failure, cerebrovascular disease, myocardial infarction/acute coronary syndromes, stroke or transient ischemic attack, and Charlson score).

Overall, we found that the current use of statins (within 30 days) was associated with a reduced risk of active TB (adjusted rate ratio [aRR], 0.79 [95% confidence interval {CI}, .68–.92]) (Table 1). However, when we investigated individual statins, a significant association was only observed in pravastatin users (aRR, 0.54 [95% CI, .30–.98]). Although other statins, including atorvastatin, simvastatin, rosuvastatin, and fluvastatin were associated with a lower risk of active TB, the difference did not reach statistical significance (Table 1).

In this real-world study, we had 2 significant findings. First, statins may help prevent the development of TB, which was consistent with our previous study [2] in Taiwan. Another study using a propensity score-matched analysis in Korea demonstrated that statin users had a significantly lower risk of TB than non-statin users (hazard ratio, 0.67 [95% CI, .46–.98]) [3] and was corroborated by a meta-analysis [3] in which statin use was related to a considerably lower risk of TB in the general population (pooled RR,

Table 1. Association Between Statin Use and the Risk of Active Tuberculosis

Variables	Current Statin Users Among TB Cases (n = 8164), No. (%)	Current Statin Users Among Controls (n = 816 400), No. (%)	Crude Effect Estimate, RR (95% CI)	Confounder-Adjusted Effect Estimate, Adjusted RR (95% CI)
Overall statin	183 (2.2)	22 286 (2.7)	0.82 (.71–.95) ^a	0.79 (.68–.92) ^a
Atorvastatin	67 (0.82)	7658 (0.94)	0.85 (.66–1.08)	0.81 (.64–1.04)
Simvastatin	36 (0.44)	4086 (0.53)	0.88 (.62–1.24)	0.84 (.61–1.18)
Rosuvastatin	28 (0.34)	2940 (0.36)	0.94 (.64–1.36)	0.90 (.62–1.32)
Fluvastatin	18 (0.22)	2451 (0.30)	0.72 (.45–1.14)	0.68 (.43–1.09)
Pravastatin	11 (0.13)	1972 (0.24)	0.55 (.31–1.00)	0.54 (.30–.98) ^a

Abbreviations: CI, confidence interval; RR, rate ratio; TB tuberculosis.

^a $P < .05$.