LETTER

WILEY

Can measles attenuate previous allergic sensitization in children?

To the Editor,

Measles is a highly contagious disease that is characterized by fever, cough, and a maculopapular skin rash. The causative agent, measles virus (MV), targets myeloid, lymphoid, and epithelial cells. Infection and depletion of memory B- and T lymphocytes expressing CD150 results in transient immune suppression, referred to as "immune amnesia".[1,2] At the same time, MV infection also elicits a strong virus-specific immune response, conferring lifelong immunity to measles. This apparent contradiction is also known as the *measles paradox*.[3,4]

In an observational cohort study during a measles outbreak among unvaccinated children in the Dutch Orthodox Protestant community in 2013, paired blood samples were collected before and after natural MV infection. The first blood samples were taken in July 2013, and the follow-up samples were taken 2–3 months later in September–October 2013 with an average of 70 days between the sampling time points (Table S1; Figure S1). All children included in the study were seronegative for measles at sampling 1, and 77 of 82 children seroconverted during the study period. It was previously reported that measles resulted in depletion of memory lymphocytes and a decrease of pre-existing virus-specific antibody levels.[5–7] These observations raised the question whether MV could also infect and deplete allergen-specific memory B- and T lymphocytes and reduce IgE antibody levels, potentially attenuating a previous allergic sensitization.

We have tested this hypothesis using biobanked plasma samples from a total of 81 children collected in the aforementioned study (Figure S2; Tables S1 and S2). Seventy-six children had a laboratory-confirmed MV infection, whereas five children remained seronegative. Of one child in the original cohort, there was not enough biobanked material to perform the analyses for this study. First, samples were screened for total IgE and IgE-specific for mixed food and inhalant allergens using ImmunoCAP total IgE and Phadiatop Infant-specific IgE (sIgE), respectively (both from Thermo Fisher Scientific/Phadia). Subsequent extended sIgE analysis on selected individuals with allergic sensitization was performed using the Allergy Xplorer 2 IgE multiplex test, including up to 300 allergen extracts and components (ALEX®2; MacroArray Diagnostics).

Statistical analysis and data visualization were performed using IBM SPSS v28.0.1.0. Outcomes were adjusted for age, disease severity, time between sampling, and time between the development of skin rash and the second sampling time point. The threshold value for all IgE assays was ≥0.35 kU/L.[8] IgE results below the threshold in both pre- and post-MV infection samples were excluded. With ImmunoCap and Phadiatop Infant, we found decreases in total IgE and sIgE, respectively (Figure 1A,B; Tables S3 and S4). However, it should be noted that a similar decrease in IgE levels was also observed in paired plasma samples from the children that had not experienced measles during the study period, suggesting that these changes were related to seasonal or environmental factors.

From the 76 MV-infected children, 26 were identified as sensitized based on Phadiatop Infant sIgE ≥0.35 kU/L and/or total IgE ≥100 kU/L at the time of first and/or the second blood collection. These 26 children and the five uninfected children were included for subsequent extended sIgE analysis using ALEX®2 (Table S5). Sensitization detected by ALEX®2 was consolidated according to allergen families when possible; for example, house dust mite allergen components Der p1, Der p 2, and Der p 5 were evaluated as one group. A one-sample Wilcoxon signed-rank test was performed on the sIgE levels of each allergen family before and after MV infection (Table 1). In ALEX®2, total IgE was significantly decreased, but the only allergen-specific IgE antibodies to show a significant decrease over time were directed against grass pollen (Figures S3 and S4).

There are several limitations to this retrospective study. The initial study and data collection in 2013 were not designed for the current research question.[5] Additionally, a control group of sufficient size was lacking, making it difficult to correct for seasonal changes in sIgE levels. When examining ImmunoCap total IgE, Phadiatop Infant sIgE, and ALEX®2 sIgE results, it cannot be excluded that the decrease in grass pollen sIgE was related to the decline of regional grass pollen during the months July–October, instead of to MV infection and depletion of allergen-specific lymphocytes. Moreover, no changes in sIgE levels of nonseasonal allergens such as house dust and storage mites were detected in this cohort. A final limitation of this study is the semiquantitative nature of ALEX®2, as opposed to ImmunoCap/Phadiatop, which are fully quantitative and therefore less prone to intertest variability.

Although this study does not answer the question whether measles attenuates pre-existing allergic sensitization, we consider this an important hypothesis-generating study. To the best of our knowledge, this is the first study investigating the effects of MV infection

(A)

(B)
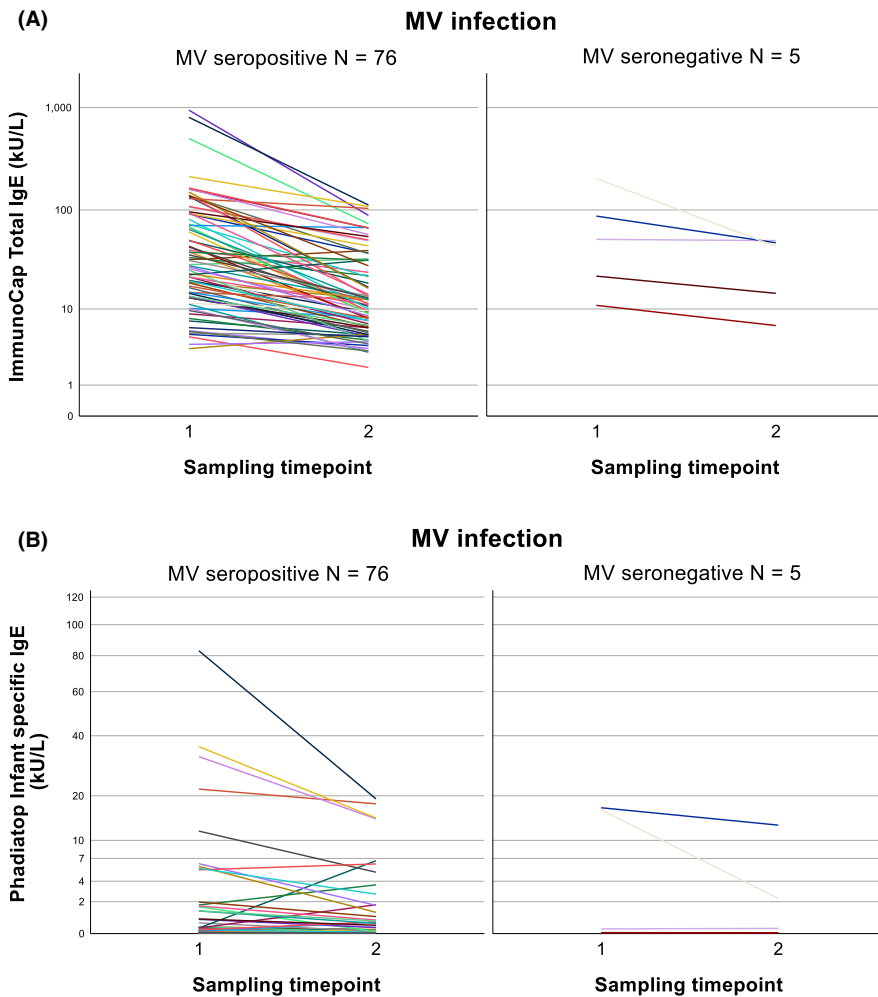
FIGURE 1 Trends in ImmunoCap Total IgE (A) and Phadiatop Infant sIgE (B) in paired plasma samples. Depicted in the left panels are cases with laboratory-confirmed measles in between the measurements. The right panels show cases without intermittent MV infection. No statistics were performed on this set due to small sample size in the control group.

TABLE 1 Changes in ALEX®2 detected specific IgE in children sensitized for different allergens and allergen families before and after MV infection.

	Allergen family	N[a]	Test statistic	Standard error	Sig.[b]
1	Tree pollen	4	.00	2.739	.068
2	Grass pollen	13	.00	14.309	.001
3	Hemp	1	.00	.500	.317
4	Cat and dog	1	.00	.500	.317
5	House dust mite	9	21.00	8.441	.859
6	Storage mite	3	4.00	1.871	.593
7	Peanut	2	1.00	1.118	.655
8	Seafood	5	10.00	3.708	.500
9	Fenugreek	1	.00	.500	.317
10	Insect venom	3	2.00	1.871	.593
11	Latex	1	.00	.500	.317
12	Total IgE	19	5.00	24.850	<.001

Note: ALEX®2 data of allergen-sensitized children were consolidated according to the major allergen families when possible and total IgE (cutoff IgE ≥0.35 kUA/L). One-sample Wilcoxon signed-rank tests were performed to assess whether the differences in sIgE before and after MV infection deviated significantly from 0.

[a]Sensitized children with MV infection. The five noninfected children were excluded from the analysis.

[b]The significance level is .050. Asymptotic significance is displayed.

on allergic sensitization. We propose larger longitudinal observational cohort studies with more sampling time points should be performed, specifically during the acute and convalescent stages of measles.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.14033.

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