

ORIGINAL ARTICLE

Clinical Mechanisms in Allergic Disease

Nasal IgE production in allergic rhinitis: Impact of rhinovirus infection

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Summary

Background: Rhinovirus (RV) infections exacerbate asthma in part by enhancing an allergic state, and these exacerbations can be mitigated via administration of anti-IgE.

Objective: We investigated the presence of local IgE production in the nose of allergic and non-allergic subjects and assessed whether this was enhanced by RV.

Methods: Local production of specific IgE was determined by comparing ratios of specific to total IgE concentrations between nasal and serum samples. Our initial studies were performed in subjects presenting to the emergency department for allergic and non-allergic respiratory complaints. Subsequently, we investigated influences of experimental RV infection on nasal sIgE production in an allergic cohort.

Results: We found evidence of local sIgE production to *Dermatophagoides pteronyssinus* in 30.3% and to *Blomia tropicalis* in 14.6% of allergic subjects. None of the non-allergic subjects demonstrated local IgE. Subjects with active RV infection were more than twice as likely to have local sIgE (45% vs 14%), and subjects with local sIgE being produced were ~3 times more likely to be having an asthma exacerbation. Experimental RV infection was able to induce local sIgE production.

Conclusion: These studies confirm local IgE production in a large subset of allergic subjects and demonstrate that allergic asthmatics with local IgE are more likely to develop an asthma exacerbation when infected with RV. Our RV challenge studies demonstrate that at least some allergic asthmatics can be induced to secrete locally generated IgE in their nasal airway after RV infection.

1 | INTRODUCTION

Most asthma exacerbations in children and adolescents are associated with an upper respiratory tract viral infection,¹ and rhinovirus (RV) is detected in 60%–70% of these exacerbations.^{2–9} While less frequent an occurrence, RV infections remain a common cause of asthma exacerbations throughout adulthood.¹⁰ In our studies, RV infections were identified in 61% of children receiving urgent care

for an asthma exacerbation.^{11,12} These emergency department (ED) visits and hospitalizations for asthma exacerbation consistently spike in the fall with a similar, but smaller increase in the spring.^{4,13} Although RV infections occur year-round, they are more likely to cause asthma exacerbations when aeroallergens are more abundant. In our studies, the likelihood of having an asthma exacerbation in association with RV infection strongly correlated with the presence of a highly atopic state including both high total serum IgE

concentration¹⁴ and high titre of IgE specific to allergens present in the environment.^{12,15,16} For example, in our Costa Rica study, subjects who had a mite allergen-specific serum IgE titre of ≥ 100 IU/mL had a ~95% chance of having an asthma exacerbation if they became infected with RV.¹² Further support for an allergic component driving the seasonal increases in asthma exacerbations was provided from studies demonstrating the ability of anti-IgE to decrease these fall and spring exacerbation rates.^{13,17} We therefore speculated that RV infection may act, at least in part, to exacerbate an ongoing IgE-mediated allergic response to seasonal aeroallergens¹⁸ and that this would be manifested as increased expression of specific IgE to those aeroallergens.

In recent decades, research has explored whether IgE specific (sIgE) to aeroallergen that is expressed in the nasal tissue of allergic rhinitis (AR) patients might partly originate locally in the nasal mucosa, rather than solely ingress from the serum¹⁹⁻²¹ and contribute to patients' symptoms. Although controversial, it has been argued that local IgE production may also occur in a subset of non-allergic rhinitis (NAR) patients and explain their symptoms.²²⁻²⁴ This subset of rhinitis patients would be diagnosed with NAR based on their negative skin-prick test (SPT) and negative sIgE serology.

The observations that RV infections appear to act to enhance an ongoing allergic inflammatory response and that the subsequent asthma exacerbation could be mitigated via administration of anti-IgE led us to speculate that asthmatics having an asthma exacerbation would demonstrate increased local sIgE production in their nasal tissue. We therefore conducted investigations to substantiate the presence of local IgE production in the nasal secretions of allergic as well as non-allergic subjects and to determine whether this was enhanced by the presence of RV.

2 | MATERIALS AND METHODS

2.1 | Local production of sIgE in subjects undergoing an asthma exacerbation

In our initial studies, we examined local IgE production in a cohort of subjects recruited to the Emergency Department (ED) at the Hospital Nacional de Niños in San José, Costa Rica.¹² This cohort consisted of 134 children (ages 7-12) who presented for either an asthma exacerbation ($n = 47$) or controls who presented with some other urgent condition ($n = 87$). Control subjects included children who had been hospitalized or treated in the ED for asthma or who had been using medications prescribed by a physician for asthma during the previous 12 months ($n = 19$). Data from the latter group were defined as having "stable asthma" and were compared with data obtained from the actively wheezing children and other non-wheezing control subjects.¹² Written-informed consent was obtained from the parents, and informed assent was obtained from the children under protocols approved by the University of Virginia Institutional Review Board (IRB#18795 and #12342). The enrollees were categorized as being allergic ($n = 89$)

or non-allergic ($n = 45$) based on serology studies for sIgE to mites (*Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farinae* (DF), and *Blomia tropicalis* (BT)), animal dander (cat and dog), grass (Bahia), mould (*Aspergillus fumigatus*, *Alternaria alternata*), and cockroach (*Blattella germanica* and *Periplaneta americana*). All of the subjects in the allergic group were sensitized to at least one dust mite species (DP, DF or BT), while all serum sIgE assays were negative in non-atopic subjects. Enrollees in both cohorts were further characterized according to the presence of an RV infection as described below. Clinical features of these subjects are summarized in Table 1.

2.2 | Nasal wash samples

Secreted nasal fluid was collected by nasal irrigation as previously described.¹² Briefly, phosphate-buffered saline (PBS) was instilled into each nostril using a Mucosal Atomizing Device (Wolfe Tory Medical, Inc., Salt Lake City, UT) and wash fluid was aspirated immediately using a BBG Nasal Aspirator (Codan US Corp, Santa Ana, CA). Samples were stabilized with 0.25% gelatin and frozen at -80°C for subsequent analyses, which included assays for tIgE and sIgE via ImmunoCAP®. As previously noted, since dust mite-sIgE was present in all children who fell into the atopic group, testing was performed for sIgE to DP and BT in their nasal secretions. We limited these studies to two allergens (and total IgE (tIgE)) to avoid having to over-dilute the samples and generate a false-negative result. The same procedures were applied to children in the non-atopic group.

2.3 | Virology

RV infection was determined by quantitative RT-PCR performed on the nasal wash samples.²⁵ RNA extractions were done using Qiamp RNA isolation kits (Qiagen, Crawley, UK), and cDNA was generated as previously described.²⁶ The cDNA was amplified using primers and probes specific for conserved regions of RV and detected by qPCR (RV forward 5'-GGCCCTGAATGTGGCTAA-3'; RV reverse 5'-ATCCCCGCAATTGCTCGTTAC-3'; probe 5'-FAM-CTTGCAGCCAATGCA-BHQ-3'; Integrated DNA Technologies, Coralville, IA). The PCR mix consisted of iQ 2 $\times$ supermix (BioRad, Uppsala, Sweden), cDNA and 200 $\mu\text{mol/L}$ of each primer.

TABLE 1 Subject characteristics

Cohort	Allergic		Non-Allergic	
	Virus	No Virus	Virus	No Virus
Acute wheeze ($n = 47$)	41 (87%)	6 (13%)	0 (0%)	0 (0%)
Stable asthma ($n = 19$)	3 (23%)	10 (77%)	0 (0%)	6 (100%)
Non-asthmatic ($n = 68$)	3 (10%)	26 (90%)	1 (3%)	38 (97%)

2.4 | Demonstration of local production of specific IgE

In the allergic cohort, because of the presence of sIgE in their serum, the identification of local production of IgE in the nasal tissue necessitated correcting for transudation, exudation, transcytosis, or other processes driving a systemic origin for any measured nasal sIgE. In addition, we had to correct for the dilutions involved in our collection technique. We reasoned that any movement of IgE from the circulation through the nares would be stochastic and not be specific for any relevant allergen-targeted IgE. We therefore calculated the specific to total IgE ratio in the circulation and in the nasal samples and posited that a higher ratio in the nasal samples would signify local IgE production. For non-atopic subjects (who by definition lacked sIgE in their serum) and for skin test positive ImmunoCAP® negative AR subjects, any detection of nasal sIgE would be sufficient to define local production. Local IgE production was compared between RV infected and non-infected subjects.

2.5 | Challenges

To investigate influences of RV infection on presence and extent of local IgE production, we investigated the induction of local IgE production in subjects who were involved in a research study involving experimental RV inoculations in allergic asthma (UVA IRB#14427 and 12673).¹⁴ These subjects all had mild intermittent asthma as defined by physician diagnosis of asthma, presence of normal lung function managed with rescue inhalers only, and a positive methacholine challenge. Briefly, on day 0, subjects were challenged with an inoculum containing 300 TCID₅₀ of RV16. Specific and total IgE was determined in blood samples and nasal secretions on day 0 and again on day 4. Based upon subject history and skin test results, RV challenges were performed either in the spring or fall and local IgE in nasal secretions was evaluated for timothy grass and DP.

2.6 | Statistical Analysis

For comparison of local IgE production in AR and NAR subjects, 2-sided Fisher's exact test was performed (GraphPad Prism 6 software; La Jolla, CA). Influences of RV infection on local IgE production were performed via 2-tailed Z-tests (www.socscistatistics.com). P-values <0.05 were considered significant.

3 | RESULTS

3.1 | Nasal sIgE in subjects presenting to the ED with asthma exacerbations or acute rhinitis

We initially evaluated allergic and non-allergic subjects presenting to the ED in Costa Rica and quantified DP-specific IgE in their nasal secretions. This included 89 subjects determined to have systemic allergic sensitization to DP based upon ImmunoCAP testing and 45 subjects without systemic sensitization to DP. As displayed in Figure 1 47/89 subjects

with serum sIgE to DP also had nasal sIgE to DP. None of the subjects without serum sIgE to DP demonstrated nasal sIgE to DP (0/45).

3.2 | Local IgE production in asthma exacerbation and acute rhinitis subjects

For atopic subjects, nasal sIgE concentrations were generally ~10-fold lower than their serum sIgE concentrations. To distinguish whether this represented local production of sIgE (in the nasal mucosa) rather than transudation or other process driving a systemic origin for the nasal sIgE, we compared the ratio of specific to total IgE concentrations in the serum and nasal compartments. Local IgE production was implied by a ratio of nasal sIgE/tIgE to serum sIgE/tIgE >1.2. Evidence for local IgE production was demonstrated to DP in 30.3% and to BT in 14.6% of the atopic subjects (Table S1).

3.3 | Influence of RV infection on local IgE production

Nasal samples were next evaluated for RV infection, which was confirmed by PCR to be present in 36% of the subjects, including 87% of the subjects presenting with asthma exacerbations, 16% with stable asthma, and 6% in the non-asthmatic controls (Table 1). We found evidence for local sIgE production to DP in 14% and to BT in 7% of uninfected allergic subjects (Figure 2A). Approximately twice as many allergic subjects with acute RV infection had evidence of specific IgE production in their

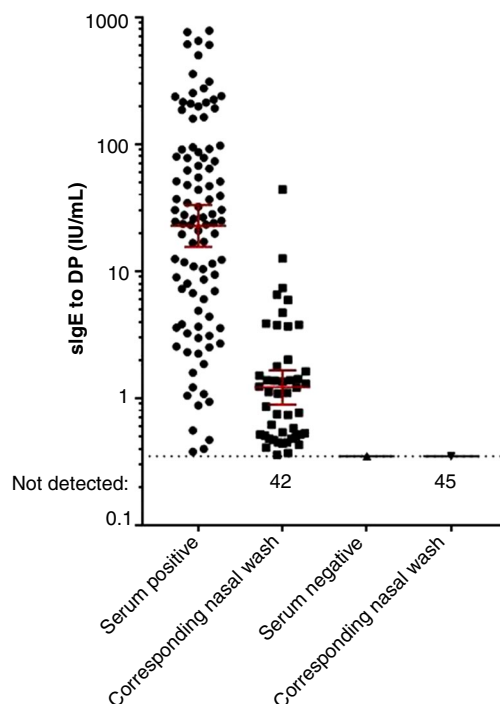


FIGURE 1 Prevalence of sIgE to *Dermatophagoides pteronyssinus* (DP) in nasal secretions of children in a Costa Rican emergency department. Specific IgE was assayed in the serum and nasal secretions and are displayed comparing those with and without serum sIgE

nares compared to those without RV (45% for DP and 21% for BT) and this achieved statistical significance for DP ($P < 0.002$). And, again, none of the non-allergic subjects demonstrated local IgE production, regardless of whether or not they were RV infected.

3.4 | Association of nasal local IgE production with RV-induced asthma exacerbation

In support of the concept that local IgE production could be associated with worse clinical outcomes in the setting of RV infection, allergic subjects presenting to the ED with an asthma exacerbation were ~3-times more likely to demonstrate local IgE in their nares in comparison with those allergic subjects who were infected but not demonstrating an asthma exacerbation (Figure 2B).

3.5 | Rhinovirus challenge

RV challenge studies were performed on allergic subjects with mild intermittent asthma. This cohort of allergic asthmatics ($n = 33$) was selected on the basis of having symptomatic AR with positive

slgE testing for grass (timothy; $n = 27$ and/or dust mite (DP; $n = 28$). Volunteers were infected with RV-16 and local IgE production evaluated at baseline (day 0) and again at the peak of symptoms on day 4. In this highly atopic asthmatic cohort, a higher rate of local nasal IgE production was observed at baseline than in our previous Costa Rica study or University of Virginia studies (65.6% for Timothy and 53% for DP) (Table S2). However, supporting the concept that RV could promote or exacerbate local IgE production, 4 of 11 subjects without local allergy to timothy at baseline and 1 of 16 subjects without local allergy to DP at baseline converted to local production at day 4.

4 | DISCUSSION

Studies have associated RV-mediated asthma exacerbations to the presence of a highly allergic phenotype and high titre IgE to allergens present in the environment at the time of the infection.^{12,14-16} Support for the ability of RV to exacerbate asthma by enhancing an ongoing IgE-mediated allergic inflammatory response is provided by the ability of anti-IgE to prevent or attenuate these RV-mediated exacerbations.^{13,17} Although anti-IgE could influence numerous factors including mast cell and basophil activation or IgE-facilitated antigen uptake by dendritic and other cells, we speculated that RV infection might act, at least in part, to increase expression of specific IgE to seasonal- or exposure-relevant aeroallergens. Numerous studies have demonstrated the production of allergen-specific IgE within the upper and lower airways.¹⁹⁻²¹ We speculated that RV infection could enhance (or induce) local IgE generation and that blockade of this pathway could explain at least a component of the beneficial effects of anti-IgE.

We therefore investigated the expression of relevant allergen-specific IgE in nasal secretions in allergic asthmatics subjects with and without an asthma exacerbation. To support that nasal IgE was being produced locally and did not comprise serum slgE that appeared in the nasal secretions as a result of transudation, exudation, transcytosis or other non-specific inflammatory or stochastic processes, we corrected for these mechanisms by comparing the ratio of specific to total IgE in nasal secretions with that observed in the serum. Nasal IgE production in the context of an RV infection could reflect local B-cell maturation into IgE-producing cells or the activation of previously expressed IgE⁺ B cells or plasma cells being stimulated to secrete IgE. By whichever mechanism, we concluded that an elevated slgE/tIgE ratio in the nasal compared to the serum samples implies local production of the slgE. Proof of local IgE production would require demonstrating slgE egressing from B or plasma cells, something not feasible in human research given the requirement for accessing nasal-associated lymphatic tissue. However, our studies compellingly support nasal-derived specific IgE in a large subset of subjects in each of the allergic asthmatic cohorts included in these studies. What was particularly striking, however, was that the prevalence of local IgE production was approximately twofold

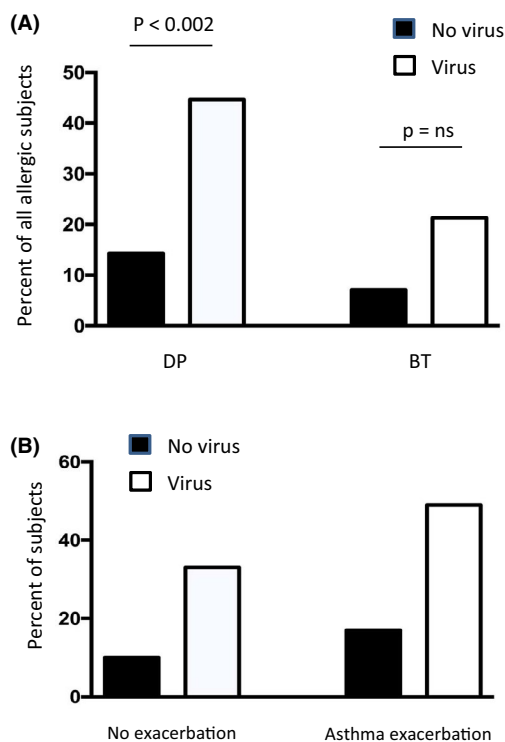


FIGURE 2 Local production of slgE to *Dermatophagoides pteronyssinus* (DP) or *blomia tropicalis* (BT) in nasal secretions. Specific IgE and total IgE were each assayed in the serum and nasal secretions of allergic children. slgE/tIgE was calculated for the serum and the nasal secretions and a higher ratio (>1.2) in the nasal secretions was used to define local production. A, Per cent of atopic subjects with local IgE production to either DP or BT based upon presence of RV infection as determined by quantitative RT-PCR. B, Per cent of atopic subjects with local IgE production to DP distinguished by presence of RV infection and presentation with an asthma exacerbation

higher in allergic asthmatics infected with RV (Figure 2A). More impressively, subjects presenting to the ED with an RV-associated asthma exacerbation were ~threefold more likely to demonstrate nasally produced specific IgE (49%) in comparison with subjects demonstrating an exacerbation in the absence of an acute RV infection (17%)(Figure 2B).

By themselves, these data cannot determine whether RV infection induces local IgE production or alternatively whether those with established local IgE production were just more likely to present to the ED when infected with RV. However, the concept that RV could produce an environment conducive to IgE generation is supported by our demonstrating that 5 subjects only began to produce allergen-specific IgE in their nasal airway after the infection. This observation does not distinguish whether Costa Rica subjects demonstrating local IgE production in the setting of an asthma exacerbation had local IgE production established before the infection or alternatively only developed this phenomenon with the infection (or comprised a combination of both phenomena). That RV can induce local IgE production is a potentially important observation suggesting previously unconsidered cellular mechanisms driving RV-associated asthma exacerbations.

Local IgE being produced in the airway would directly contribute to an asthma exacerbation by promoting mast cell and basophil activation. However, IgE is likely to also be important via the expression of IgE receptors on other cell types including eosinophils and especially on plasmacytoid dendritic cells, where their expression of high-affinity IgE receptors would lead to facilitated allergen uptake and enhanced Th2 and T follicular helper activation. The concept that RV could promote an environment conducive to IgE generation is supported by studies demonstrating the ability of RV infection to induce expression of cytokines relevant to B-cell activation including, in particular, IL-4 and IL-13.^{27,28}

In summary, these studies suggest local IgE production in a large subset of AR subjects and demonstrate that allergic asthmatics with seasonal- or exposure-relevant local IgE production are much more likely to develop an asthma exacerbation when infected with RV. These observations cannot distinguish whether RV infection induces de novo local IgE production or just that those with pre-existing relevant local IgE production are more likely to exacerbate their asthma when infected. However, our RV challenge studies do demonstrate that at least some allergic asthmatics can be induced to secrete locally generated IgE in their nasal airway after becoming infected with RV. Finally, we failed to identify *any* non-atopic subjects who produced local sIgE whether or not they were infected.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table IS: Local DerP sIgE Production in Uninfected and Infected Costa Rica ED Subjects

Cohort	RV infection	Serum total IgE	Serum Derp1 sIgE	Serum ratio	Nasal total IgE	Nasal Derp1 sIgE	Nasal ratio	Nasal: Serum ratio
Acute asthma	HRV-A	676	15.4	0.02	20.8	0.88	0.04	1.86
Acute asthma	HRV-C	176	64.1	0.36	7.8	2.10	0.27	0.74
Control	--	89.3	9.59	0.11	8.19	1.24	0.15	1.41
Control	--	834	49.3	0.06	3.04	0.00	0.00	0.00
Control	--	390	50.3	0.13	6.49	0.86	0.13	1.03
Control	--	459	3.21	0.01	2.87	0.00	0.00	0.00
Control	--	166	0	0.00	2.82	0.00	0.00	--
Control	--	46.5	2.62	0.06	2.53	0.00	0.00	0.00
Control	--	353	0	0.00	2.83	0.00	0.00	--
Stable asthma	--	527	163	0.31	3.77	0.46	0.12	0.39
Control	--	63	0	0.00	3.34	0.00	0.00	--
Control	--	1313	262	0.20	15.4	5.58	0.36	1.82
Control	--	206	0.45	0.00	3.42	0.00	0.00	0.00
Control	--	208	22.3	0.11	4.98	1.06	0.21	1.99
Acute asthma	HRV-C	1261	355	0.28	34.1	11.10	0.33	1.16
Acute asthma	HRV-C	937	16	0.02	6.52	0.00	0.00	0.00
Acute asthma	HRV-C	249	0	0.00	3.93	0.00	0.00	--
Acute asthma	HRV-C	347	74.2	0.21	8.97	2.56	0.29	1.33
Acute asthma	HRV-C	1941	417	0.21	3.93	0.83	0.21	0.98
Stable asthma	--	171	34.4	0.20	8.36	1.31	0.16	0.78
Acute asthma	HRV-C	2184	818	0.37	43.8	13.40	0.31	0.82
Stable asthma	--	2337	990	0.42	5.88	1.19	0.20	0.48
Acute asthma	--	150	4.89	0.03	2.32	0.00	0.00	0.00
Acute asthma	--	977	376	0.38	17	5.23	0.31	0.80
Stable asthma	--	1577	275	0.17	4.38	0.64	0.15	0.84
Control	--	38.3	0	0.00	2.86	0.00	0.00	--
Stable asthma	--	1309	4.07	0.00	7.93	0.00	0.00	0.00
Acute asthma	HRV-C	1474	29.3	0.02	4.13	0.42	0.10	5.12
Acute asthma	HRV-C	2538	18.9	0.01	24.1	0.38	0.02	2.12

Stable asthma	--	492	42.4	0.09	3.14	0.00	0.00	0.00
Acute asthma	--	1536	61.3	0.04	11.5	0.75	0.07	1.63
Stable asthma	--	906	91.7	0.10	2.07	0.00	0.00	0.00
Acute asthma	HRV-C	1198	298	0.25	62.5	19.60	0.31	1.26
Acute asthma	HRV-C	109	7.6	0.07	4.23	0.36	0.09	1.22
Control	--	106	8.62	0.08	2.75	0.00	0.00	0.00
Acute asthma	--	46.8	0	0.00	3.82	0.00	0.00	
Acute asthma	HRV-A	667	93.2	0.14	3.43	1.11	0.32	2.32
Acute asthma	--	278	0.84	0.00	2.46	0.00	0.00	0.00
Control	--	145	0.53	0.00	1.87	0.00	0.00	0.00
Control	--	23.7	1.16	0.05	1.86	0.00	0.00	0.00
Acute asthma	HRV-A	1012	41.1	0.04	6.33	0.77	0.12	3.00
Control	--	240	24.9	0.10	3.77	0.48	0.13	1.23
Control	--	28.2	0	0.00	2.64	0.00	0.00	--
Control	--	238	36.5	0.15	4.34	0.48	0.11	0.72
Acute asthma	--	891	364	0.41	8.92	1.47	0.16	0.40
Control	--	436	0.57	0.00	11	0.00	0.00	0.00
Control	--	897	356	0.40	5.04	0.80	0.16	0.40
Stable asthma	HRV-B	41.2	0	0.00	1.71	0.00	0.00	--
Control	--	2152	13.8	0.01	13.3	0.39	0.03	4.57
Control	--	79.9	0	0.00	2.48	0.00	0.00	--
Control	--	230	2.13	0.01	2.54	0.00	0.00	0.00
Control	--	213	37.3	0.18	1.94	0.00	0.00	0.00
Stable asthma	--	663	44.7	0.07	3.2	0.00	0.00	0.00
Control	--	1349	15	0.01	4.01	0.00	0.00	0.00
Acute asthma	HRV-C	112	10.4	0.09	3.92	0.00	0.00	0.00
Acute asthma	HRV-C	333	36.5	0.11	7.67	0.79	0.10	0.94
Stable asthma	--	4194	905	0.22	4.99	7.89	1.58	7.33
Control	HRV-B	53.7	1.01	0.02	2.22	0.00	0.00	0.00
Acute asthma	HRV-A	351	26.4	0.08	9.07	1.19	0.13	1.74
Control	--	350	0	0.00	2.24	0.00	0.00	--
Acute asthma	HRV-A&-B	742	0.42	0.00	3.55	0.00	0.00	0.00
Acute asthma	HRV-C	489	3.57	0.01	0.99	0.00	0.00	0.00

Acute asthma	HRV-C	86.3	19.6	0.23	2.51	0.50	0.20	0.88
Control	HRV-A	161	0	0.00	5.04	0.00	0.00	--
Acute asthma	HRV-C	566	86.5	0.15	4.72	1.24	0.26	1.72
Acute asthma	HRV-C	1119	24	0.02	7.83	0.45	0.06	2.68
Acute asthma	HRV-C	572	198	0.35	9.86	4.71	0.48	1.38
Acute asthma	HRV-C	1735	78.2	0.05	20.1	1.39	0.07	1.53
Stable asthma	--	7330	611	0.08	5.62	0.00	0.00	0.00
Control	HRV-A	207	6.99	0.03	1.86	0.00	0.00	0.00
Stable asthma	HRV-A	251	8.6	0.03	4.21	0.41	0.10	2.84
Acute asthma	HRV-C	2578	25.9	0.01	3.85	0.00	0.00	0.00
Acute asthma	HRV-C	205	28.2	0.14	3.67	0.00	0.00	0.00
Acute asthma	HRV-A	255	27.8	0.11	3.33	0.58	0.17	1.60
Acute asthma	HRV-C	877	30.3	0.03	7.68	0.48	0.06	1.81
Acute asthma	HRV-C	658	97.5	0.15	30.9	12.60	0.41	2.75
Acute asthma	HRV-C	836	30.4	0.04	4.25	0.00	0.00	0.00
Acute asthma	HRV-A	900	50.8	0.06	6.1	0.00	0.00	0.00
Acute asthma	HRV-C	886	62.2	0.07	6.48	0.62	0.10	1.36
Acute asthma	HRV-C	716	239	0.33	16.9	7.39	0.44	1.31
Acute asthma	HRV-C	193	8.01	0.04	2.79	0.00	0.00	0.00
Acute asthma	HRV-C	705	215	0.30	138	44.00	0.32	1.05
Acute asthma	HRV-C	165	0	0.00	5.77	0.00	0.00	--
Acute asthma	HRV-A	704	237	0.34	6.66	1.39	0.21	0.62
Stable asthma	HRV-C	2356	20.9	0.01	7.27	0.00	0.00	0.00
Acute asthma	HRV-C	1083	275	0.25	11	3.78	0.34	1.35
Acute asthma	HRV-C	160	34.5	0.22	6.21	0.77	0.12	0.58
Acute asthma	HRV-A	804	213	0.26	15.1	3.79	0.25	0.95
Acute asthma	HRV-C	413	91.8	0.22	18.5	5.94	0.32	1.44

Table IIS: Change in local IgE production after RV challenge

Derp1				Timothy			
d0 nasal/serum sIgE ratio	d0 local IgE production	d4 nasal/serum sIgE ratio	d4 local IgE production	d0 nasal/serum sIgE ratio	d0 local IgE production	d4 nasal/serum sIgE ratio	d4 local IgE production
1.78	Yes	1.84	Yes	0.75	No	1.17	No
5.74	Yes	5.19	Yes	11.35	Yes	5.54	Yes
45.12	Yes	4.18	Yes	0.31	No	0.14	No
3.70	Yes	1.60	Yes	14.23	Yes	4.34	Yes
0.18	No	0.08	No	9.62	Yes	1.67	Yes
no sample	--	0.92	No	no sample	--	27.53	Yes
11.10	Yes	1.62	Yes	0.73	No	1.13	No
2.60	Yes	2.16	Yes	14.20	Yes	14.84	Yes
109.13	Yes	101.70	Yes	4.32	Yes	6.22	Yes
0.27	No	1.06	No	0.53	No	1.28	Yes
0.16	No	0.59	No	49.00	Yes	18.47	Yes
17.41	Yes	38.18	Yes	1.27	Yes	3.77	Yes
0.13	No	0.23	No	1.34	Yes	1.38	Yes
59.12	Yes	15.94	Yes	0.25	No	0.82	No
19.45	Yes	7.29	Yes	16.99	Yes	4.04	Yes
0.25	No	0.93	No	31.54	Yes	12.75	Yes
5.54	Yes	5.62	Yes	0.46	No	1.02	Yes
1.40	Yes	0.97	No	9.31	Yes	2.75	Yes
0.15	No	0.68	No	33.46	Yes	3.42	Yes
10.73	Yes	8.05	Yes	0.35	No	1.20	Yes
0.08	No	0.11	No	1.78	Yes	1.48	Yes
7.53	Yes	4.68	Yes	60.28	Yes	837.74	Yes
0.07	No	0.43	No	1.59	Yes	1.70	Yes
0.57	No	0.71	No	1.12	No	0.78	No
0.55	No	1.51	Yes	2.91	Yes	0.50	No
0.38	No	0.75	No	4.77	Yes	3.33	Yes
0.24	No	0.70	No	0.49	No	1.02	No

83.15	Yes	17.55	Yes	690.83	Yes	58.44	Yes
0.53	No	0.64	No	5.98	Yes	1.80	Yes
0.42	No	0.49	No	2.44	Yes	3.36	Yes
24.47	Yes	14.84	Yes	0.30	No	1.05	No
0.40	No	0.61	No	468.29	Yes	181.42	Yes
20.47	Yes	35.20	Yes	1.16	No	2.02	Yes