

2nd Edition

GLOBAL ATLAS OF ASTHMA



www.eaaci.org

Published by the European Academy of Allergy and Clinical Immunology

April 2021

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RISK FACTORS FOR ASTHMA: RHINOVIRUSES

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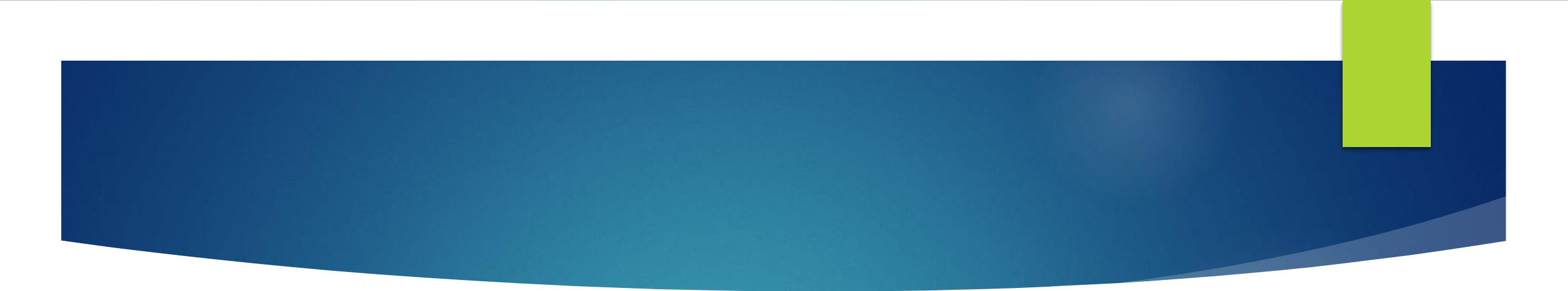
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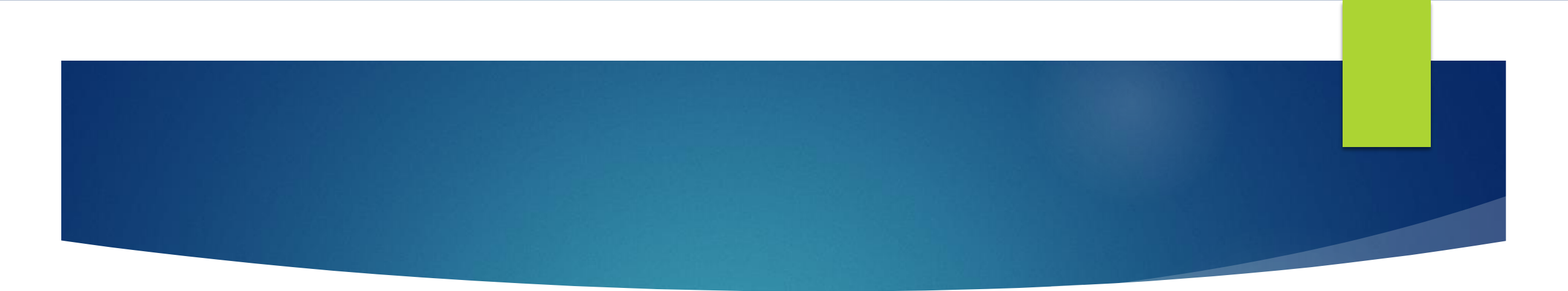
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- ▶ **Rhinoviruses** (RVs) are the most common human infectious agent.
 - ▶ They are responsible for **the large majority of upper respiratory infections**, even during the first years of life.
 - ▶ At the preschool age group, **recurrent wheezing** is usually not diagnosed as asthma, mostly because a large proportion of children who wheeze at that age will not develop persistent disease.
 - ▶ Nevertheless, among children with asthma, the **large majority presents their first episode during that time**.

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- ▶ In several studies, **infection with RV**, rather than syncytial respiratory virus (RSV), has been shown to be *strongly associated with asthma persistence*.
 - ▶ In the COAST trial, **a symptomatic infection with RV during the first year of life** was associated with a highly increased risk for *wheeze persistence at the age of 3 years*.

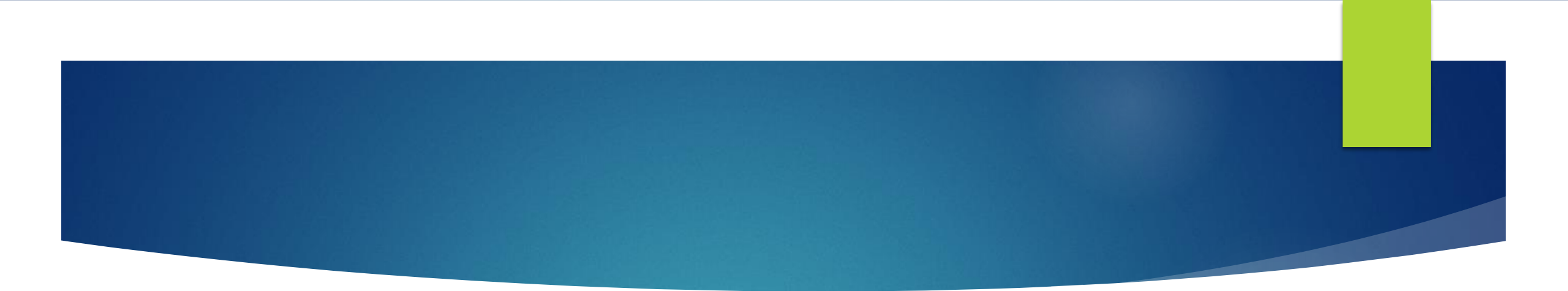
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- ▶ However, the strongest evidence in regards to the risk of RVs in asthma comes from **studies of acute asthma exacerbations.**
 - ▶ The epidemiological association between **a common cold**, induced by **RV in more than 50% of cases**, and the development of an acute asthma exacerbation has been shown more than 30 years ago (Table 1).

TABLE 1

Prevalence of respiratory viruses in asthma exacerbations in children across the continents (average(range))*

	Europe	Americas	Australasia
Rhinovirus	40 (17-82)	57 (26-77)	42 (33-78)
RSV	12 (1.5-61)	40 (8-68)	16 (7.5-17)
Influenza	3 (0-7)	10 (0-20)	6.5 (1-12)
Corona	2.5 (0-13)	1.5 (0-3)	2 (1.5-2)
Parainfluenza	4 (0-7)	4 (2-6)	8 (7.5-8)

*data from Papadopoulos NG, Christodoulou I, Rohde G, et al. Viruses and bacteria in acute asthma exacerbations – A GA2LEN-DARE systematic review. *Allergy* 2011;66:458-468

- ▶ **RVs** can reach the lower respiratory tract, infect the bronchial epithelium, replicate locally and induce local inflammation.
- ▶ **In asthma patients the bronchial epithelium** appears to be **often**, although not always, deficient in production of type-1 and type-3 interferons (IFN), allowing high virus replication, slower clearance and increased virus-induced cytotoxicity.
- ▶ The **immune response against RV in atopic individuals** is **defective** with reduced IFN and increased IL4 production, resembling an 'allergic' response.

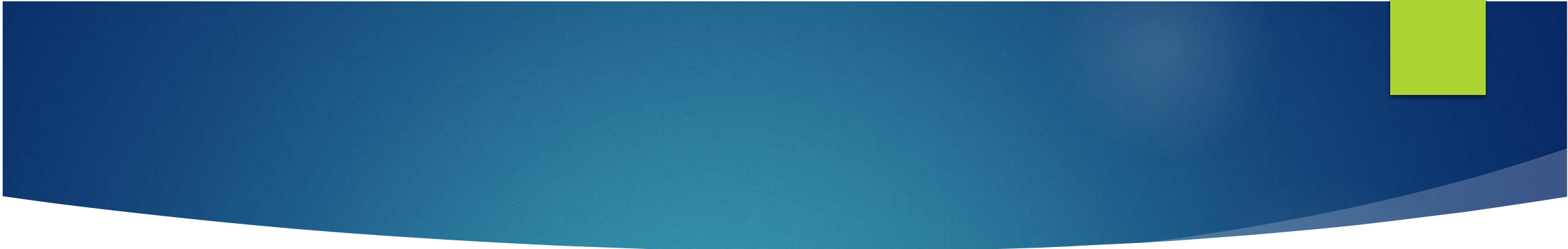
- ▶ At the same time the **epithelium produces cytokines** such as IL25 and IL33, capable of activating type-2 immunity.
- ▶ **Following RV epithelial infection growth factors** such as TGF-beta, FGF-2 and VEGF are *upregulated*, promoting airway remodeling.
- ▶ This physiological response is *augmented in an atopic environment*.
- ▶ Thus, **increased susceptibility to RV infection** and a **cumulative effect of these on airway pathophysiology** may explain **why repeated infections during early childhood** promote the development of persistent asthma (Figure 1).



The PreDicta hypothesis

Figure 1 The PreDicta hypothesis states that following the trigger of a single event, repeated infections on a background of increased susceptibility may condition the immune system towards a continuous hyperreactivity.

- ▶ **While RV is the most frequent virus associated with both initiation and exacerbation of asthma**, it has **not been clear** if this was because of their frequency in relation to upper respiratory infections **or** it is due to specific properties that could make them more predisposed to asthma.
- ▶ **In children of any age hospitalized for flu-like illness**, **RV infection** was associated with **wheeze** (independent of a previous asthma diagnosis), in *contrast to influenza infection*.

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- ▶ In asthmatics, **influenza-associated disease** was *different from a RV-induced exacerbation*, suggesting a different pathophysiological background, coined as '**asthma-augmented influenza**' (Figure 2).

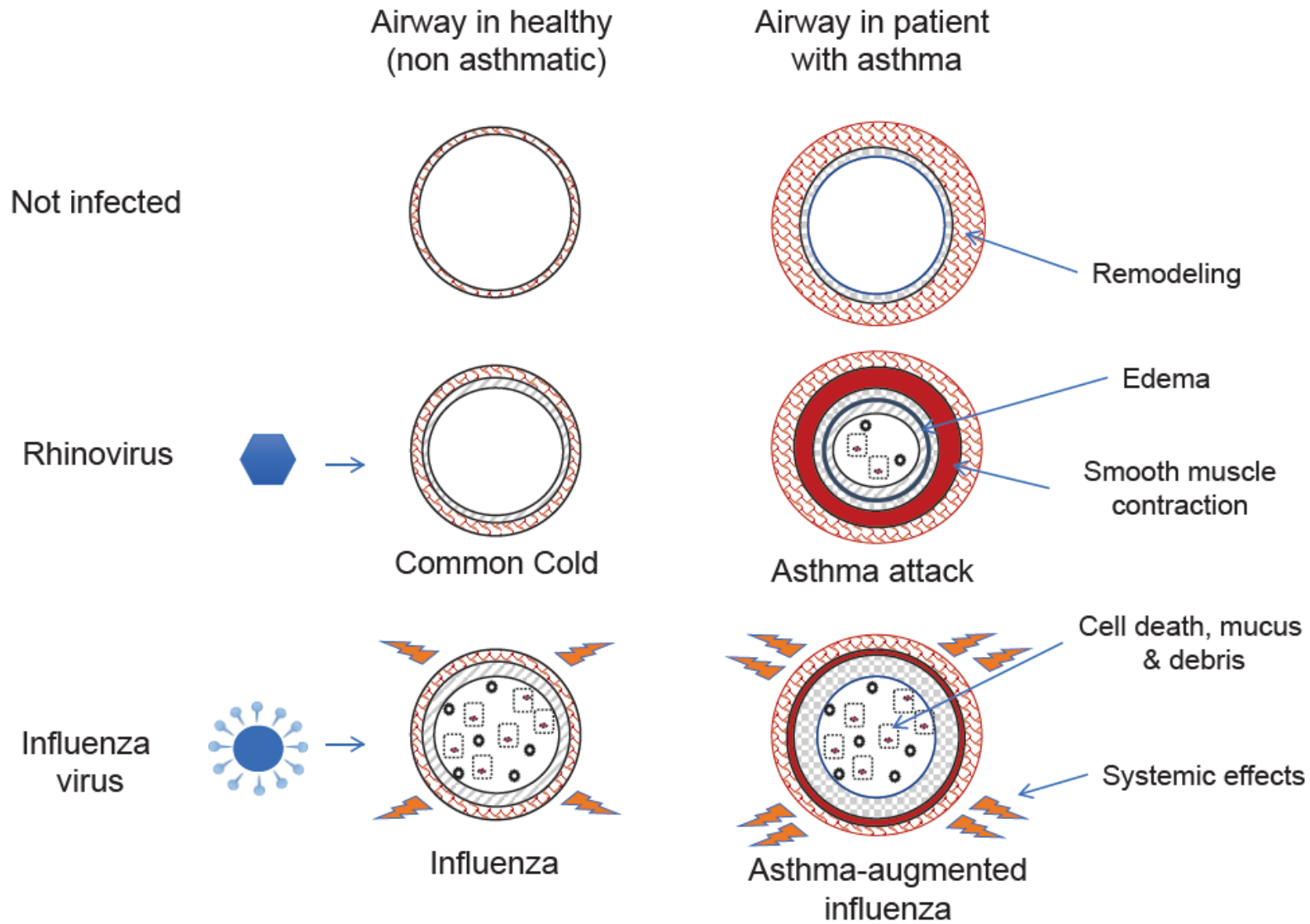
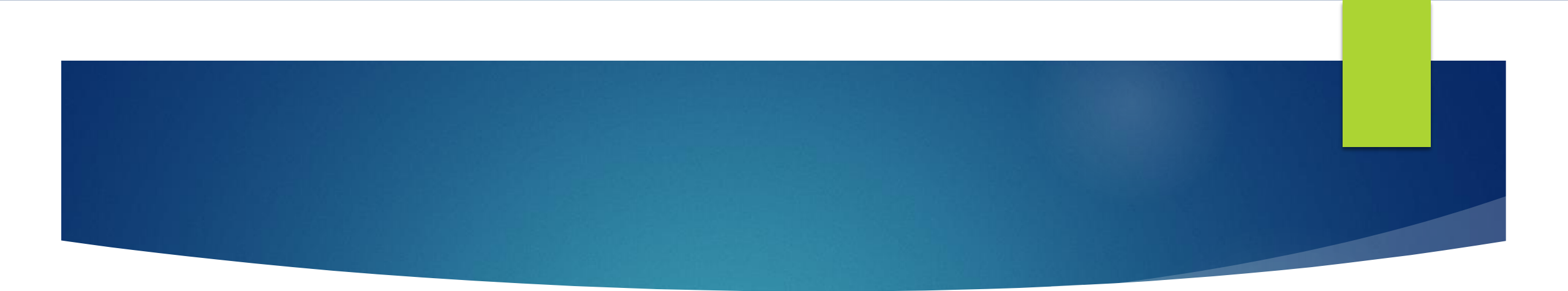


Figure 2 Distinction between RV-induced asthma exacerbation and asthma-augmented influenza: rhinovirus infection is capable of triggering type-2 inflammation and typical symptoms of exacerbation in an asthmatic background, while influenza virus infection in a person with asthma results in a disease has the characteristics of influenza, of increased severity.

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- ▶ **RVs are key pathogens** driving not only symptoms of acute asthma, but also at least part of the disease initiation and persistence.
 - ▶ RV infection is **particularly asthmagenic** and *should be targeted specifically, ideally with a vaccine.*
 - ▶ However, the **design of such a vaccine** needs to consider the pronounced evolutionary capacity of the RV for immune evasion.

KEY MESSAGES

- Rhinoviruses (RVs) are the most frequent virus associated with both initiation and exacerbation of asthma
- The immune response against RV in atopic individuals is defective with reduced IFN and increased IL4 production, resembling an 'allergic' response
- A vaccine against RVs could decrease both the pediatric asthma prevalence and the frequency of asthma exacerbations, both in children and in adults