

**2<sup>nd</sup> Edition**

# **GLOBAL ATLAS OF ASTHMA**



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# RISK FACTORS FOR ASTHMA – RESPIRATORY SYNCYTIAL VIRUS AND OTHER VIRAL INFECTIONS

*Jürgen Schwarze*  
The University of Edinburgh  
Edinburgh, UK

Slides by:

Babak Ghalehbaghi, M.D.  
Allergist and Clinical Immunologist

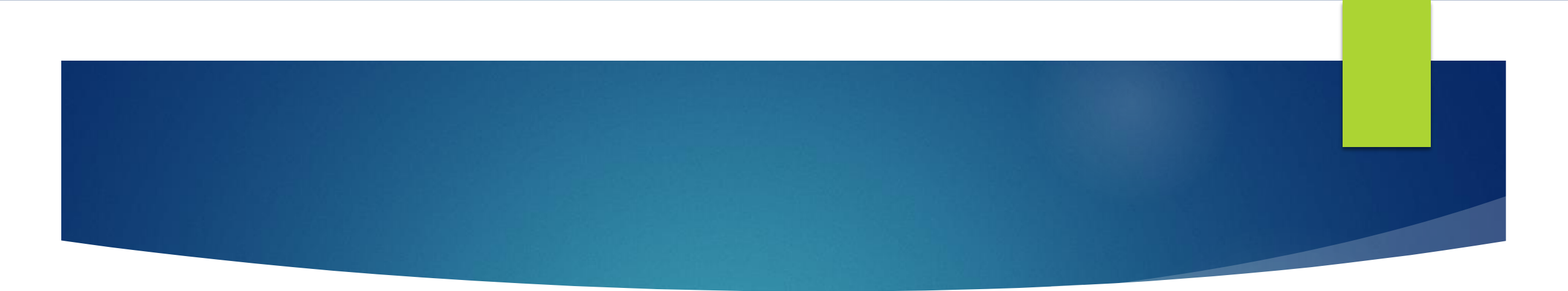


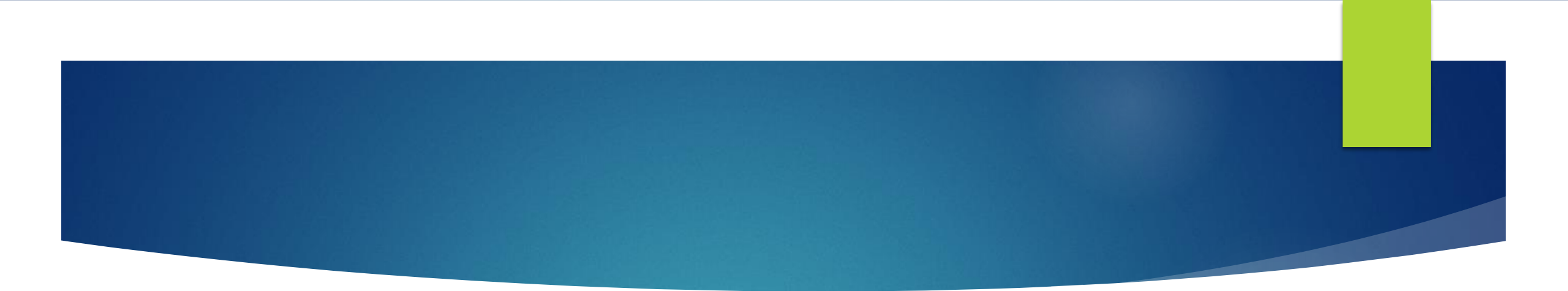
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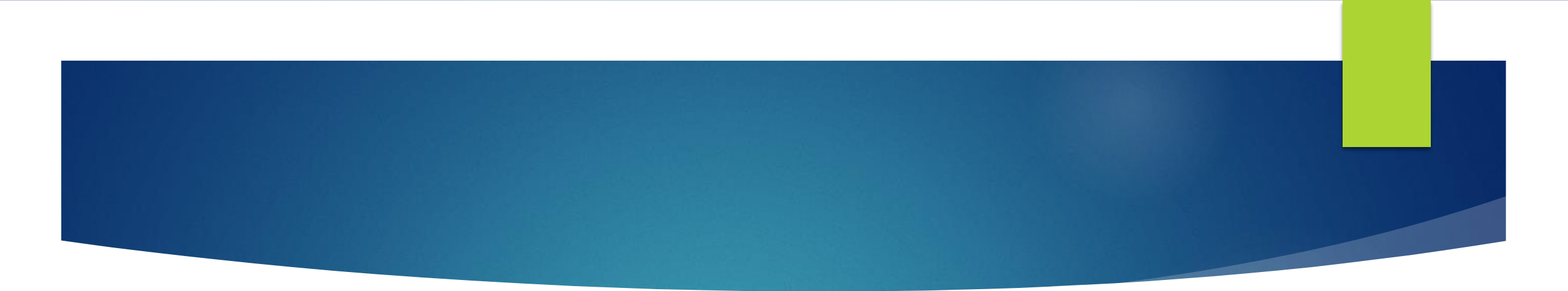


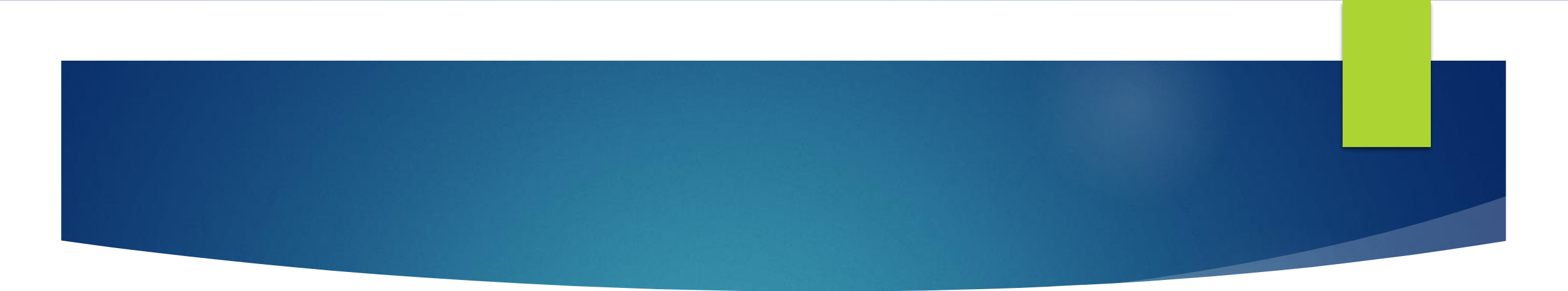
# ASTHMA DEVELOPMENT

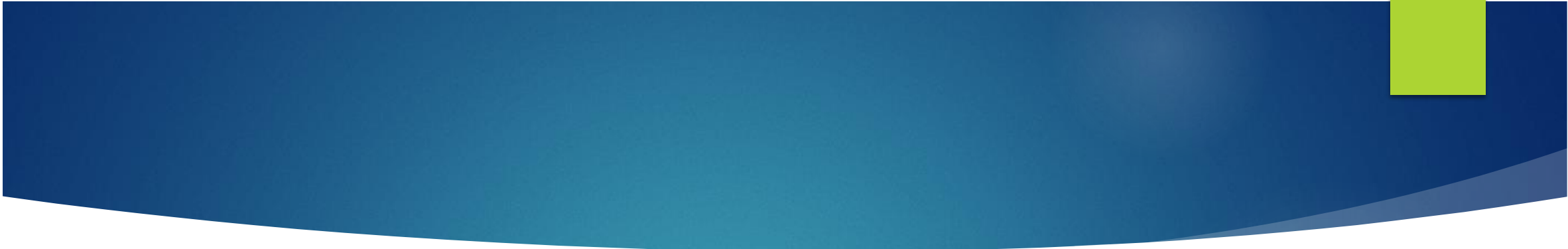
- ▶ Administrative “big” data, epidemiological, clinical, and mechanistic research demonstrates that **viral lower respiratory tract infection** (LRTI), including bronchiolitis and pneumonia, *in infancy is strongly associated with the development of recurrent wheeze of early childhood (RWECC) and childhood asthma*, which is known to frequently continue into adult life.
- ▶ Respiratory syncytial virus (**RSV**) accounts for about 70% of viral bronchiolitis cases.

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- ▶ Recent systematic reviews and meta-analyses demonstrate an **association between RSV LRTI** and RWEC, childhood asthma, reduced lung function and increased airway reactivity with a **3-fold** increased risk compared to children without infant viral LRTI.
  - ▶ Interestingly, comparisons between **children with non-RSV, non-rhinovirus LRTI** (e.g. due to human metapneumo virus, parainfluenza, human coronaviruses) and RSV LRTI, did *not find a difference in the risk* of RWEC/asthma development, suggesting that this may be linked with viral LRTI rather than RSV infection specifically.

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- ▶ Several studies indicate that **high RSV load** and **severity of RSV bronchiolitis** are associated with *increased RWEC/ asthma risk*.
  - ▶ **Potential biological factors leading to high RSV load and severe RSV LRTI** include infection with a particularly virulent RSV strain, an aberrant respiratory microbiome, inadequate antiviral immune and excessive inflammatory responses to RSV, environmental exposure (e.g. air pollution, smoke exposure) and reduced lung function.
  - ▶ **Potentially**, these factors also confer an *increased RWEC/asthma risk independently of RSV LRTI*.

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- ▶ While still a topic of debate, some observations suggest that **RSV and/or other respiratory viruses** make a causal *contribution to asthma development*.
  - ▶ An insurance data study from the US found the **highest risk of asthma at 5 years of age in children** who were 4 months old before the peak winter virus season, the *age of highest risk for severe RSV bronchiolitis*.
  - ▶ This suggests **a period of particular susceptibility** for virus-induced RWE/C/asthma development.

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- ▶ Furthermore, a randomised placebo controlled trial (RCT) of **RSV prophylaxis with palivizumab**, an anti-RSV antibody, *for late premature infants* demonstrated reduction in wheezing days (by 73%) and RWEC (by 46%) during *10 months of follow-up* after the intervention.
  - ▶ When this study cohort was *reassessed at 6 years of age* parents reported a 41% reduction in wheeze/ use of asthma medication in those children who had received RSV prophylaxis, however without any difference in doctor diagnosed asthma, lung function or FeNo levels.

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- ▶ **Future studies** of quasi-random RSV exposure, adequately powered RCTs and post-introduction studies (cluster randomised trials) of novel RSV prophylaxis or vaccination and mechanistic studies are needed to determine *if RSV (and non-RSV) LRTI make a causal contribution to RWEC/asthma development.*

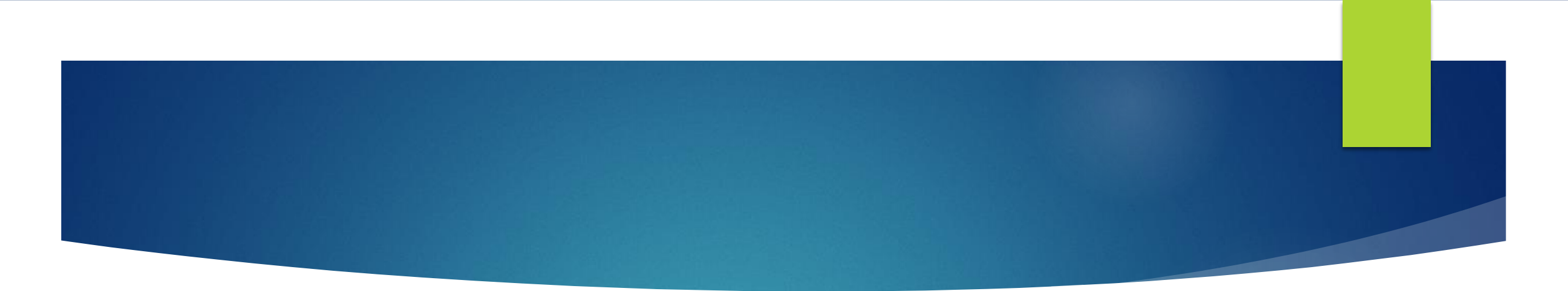


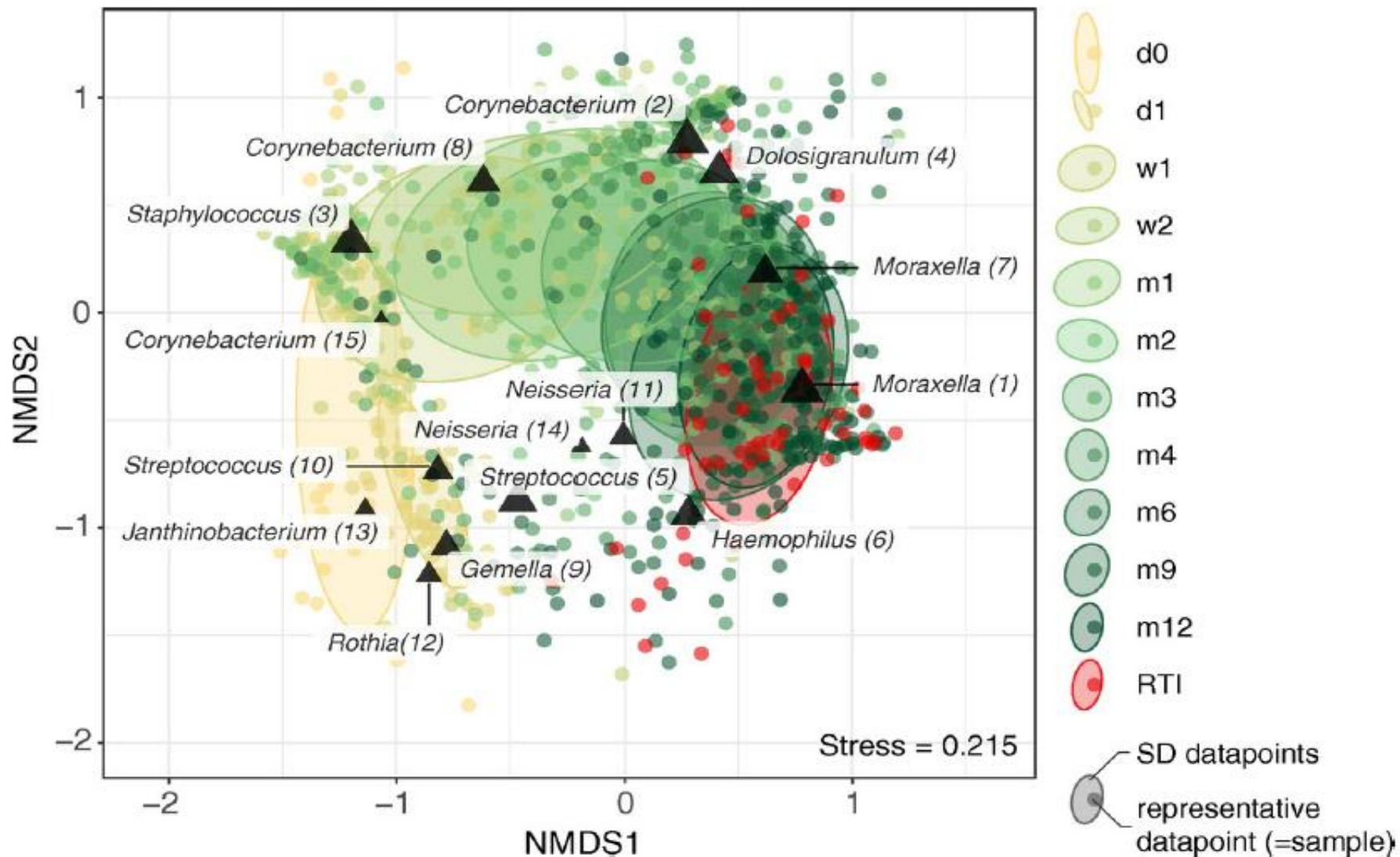
# ASTHMA EXACERBATIONS

- ▶ **Most acute asthma exacerbations (AAEs)** are triggered by respiratory viral infections, mostly by *rhino viruses* and **in allergic asthma, AAEs are most severe if viral infection and allergen exposure coincide.**
- ▶ **Other respiratory viruses** including enteroviruses, RSV, human metapneumoviruses (hMPV), human corona viruses (hCoV), parainfluenza viruses and influenza virus are also associated with AAEs and importantly **influenza vaccination**, which is effective in people with asthma, can contribute to a *reduction in AAEs*.

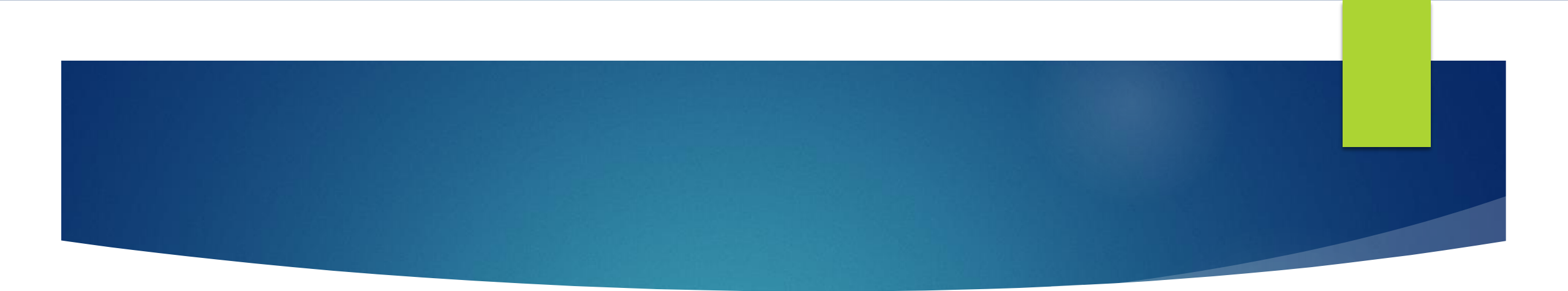
# THE RESPIRATORY MICROBIOME IN VIRUS INDUCED ASTHMA DEVELOPMENT AND EXACERBATIONS

- ▶ **Bacterial culture studies** have implicated the *neonatal carriage of pathobionts*, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moxarella catarrhalis*, in the *development of childhood asthma*.
- ▶ More recently, **next generation sequencing** has enabled *increasing insight into the respiratory microbiome in early childhood* and its role in viral LRTIs and asthma development.

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- ▶ **Breast feeding-associated respiratory microbiome profiles** dominated by *Dolosigranulum* and *Corynebacterium* are *stable and confer a reduced risk of LRTI and RWEC*, **whereas less stable profiles** dominated by *Haemophilus*, *Streptococcus* or initially by *Moraxella* followed by *Neisseria* and *Prevotella* are less stable and *associate with higher numbers of LRTIs* (Figure 1).
  - ▶ **Pathobionts may interact with respiratory viruses** in *promoting RWEC and asthma development*: *Haemophilus*-dominance of the respiratory microbiome has been associated with more severe RSV-LRTI with delayed viral clearance and a heightened CXCL8 (IL- 8) inflammatory response.



**Figure 1** Nonmetric multidimensional scaling (NMDS) plot visualizing the microbiota succession patterns in the first year of life. Each point represents the microbial community composition of one sample. (Reproduced from the *American Journal of Respiratory and Critical Care Medicine* (official journal of the American Thoracic Society), *Maturation of the Infant Respiratory Microbiota, Environmental Drivers, and Health Consequences. A Prospective Cohort Study*, Bosch AATM et al., Volume 196, 1582-1590, 2017 with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved.)

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- ▶ **In established asthma**, airway carriage of *H. influenzae* and *S. pneumoniae* is *more frequent* than in health and commensal bacteria of the Phylum bacteroidetes are *lacking*.
  - ▶ **The abundance of other airway commensals** (*Comamonadaceae*, *phingomonadaceae*, *Oxalobacteraceae*) *correlates with the degree of bronchial hyperresponsiveness*, a marker of disease severity.

## KEY MESSAGES

- Respiratory syncytial virus (RSV) low respiratory tract infection (LRTI) in infancy, especially if severe, is strongly associated with an increased risk of recurrent wheeze of early childhood and asthma development
- RSV-LRTI and non-RSV, non-rhinovirus LRTI confer a similar risk of recurrent wheeze of early childhood and asthma development
- There is evidence of a period of susceptibility to virus induced asthma development around four months of age. An intervention preventing RSV LRTI in infancy significantly reduced recurrent wheeze, however the causal contribution of viral LRTI to asthma development, while likely remains unproven
- Individual development trajectories of the respiratory microbiome in infancy predict the frequency of LRTI and of recurrent wheeze of early childhood, raising the prospect of microbial interventions for asthma prevention
- The respiratory microbiome influences disease activity and exacerbation frequency in established asthma