

# Strength of evidence for a causal effect of RSV-LRTI on subsequent wheezing illness

A critical evaluation of data from human studies

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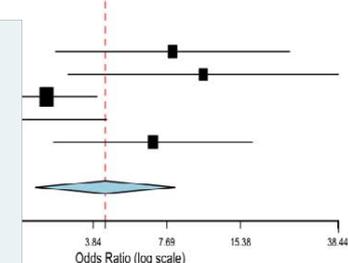
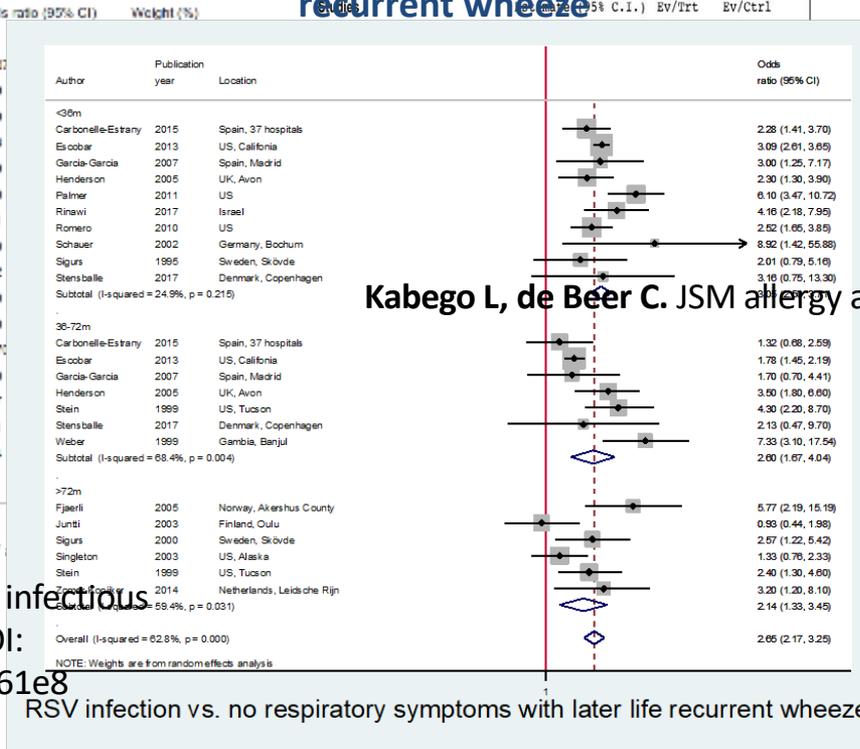
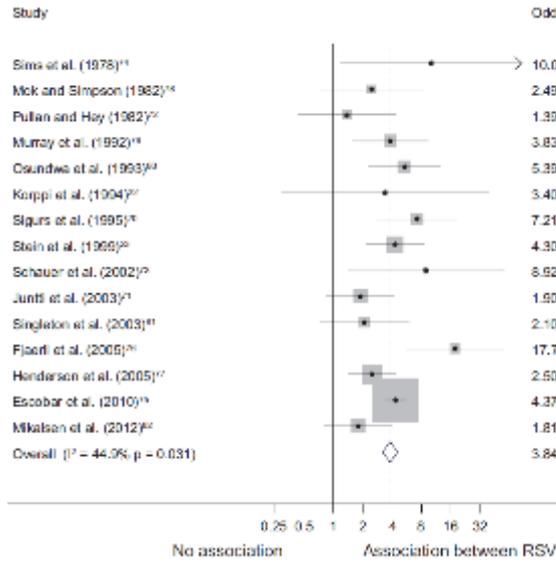


I have nothing to disclose.

# Well-established association between RSV and wheezing illness

## RSV hospitalization and asthma

## RSV Infection and both RSV pneumonia and recurrent wheeze

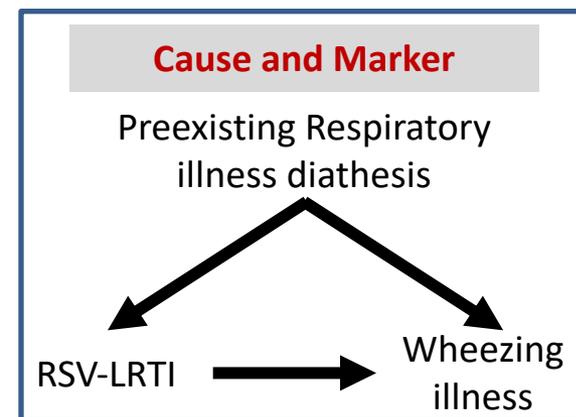
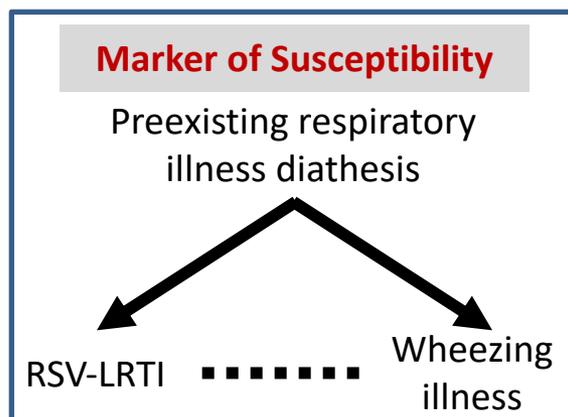
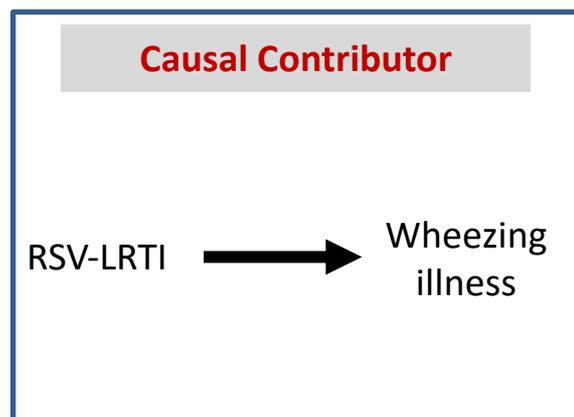


Régnier SA, Huels J. The Pediatric infectious disease journal. 2013. DOI: 10.1097/INF.0b013e31829061e8

Kabego L, de Beer C. JSM allergy and asthma. 2017.

Shi et al. The Journal of infectious diseases. 2019. DOI: 10.1093/infdis/jiz311

It remains unclear whether RSV-LRTI is a:



Is it likely that preventing RSV-LRTI will also prevent chronic pediatric wheezing illnesses?

To determine whether the existing human research provides compelling evidence for a causal effect of RSV-LRTI on subsequent wheezing illness

- **Exposure studies.** Observational studies evaluating associations between early life RSV-LRTI exposure and subsequent wheezing illness
- **Immunoprophylaxis studies.** Randomized controlled trials and observational studies evaluating the association between RSV immunoprophylaxis and subsequent wheezing illness

# Study team

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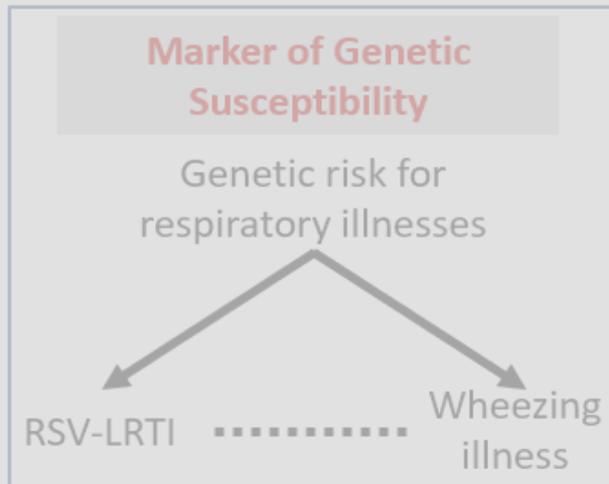
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MLS

**Funded by The World Health Organization**

# Assessing the strength of evidence for a causal effect

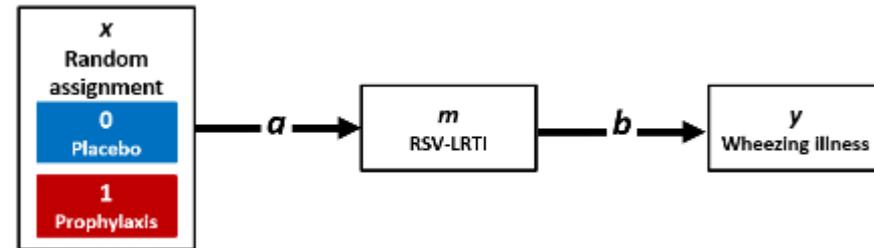
**We could have increased confidence in a causal effect of RSV-LRTI if ...**

a) we could discount the most plausible non-causal explanation: RSV-LRTI is a marker of respiratory illness susceptibility



Effects should be smaller when estimates adjust for genetic risk.

b) RSV immunoprophylaxis reduces risk for wheezing illness

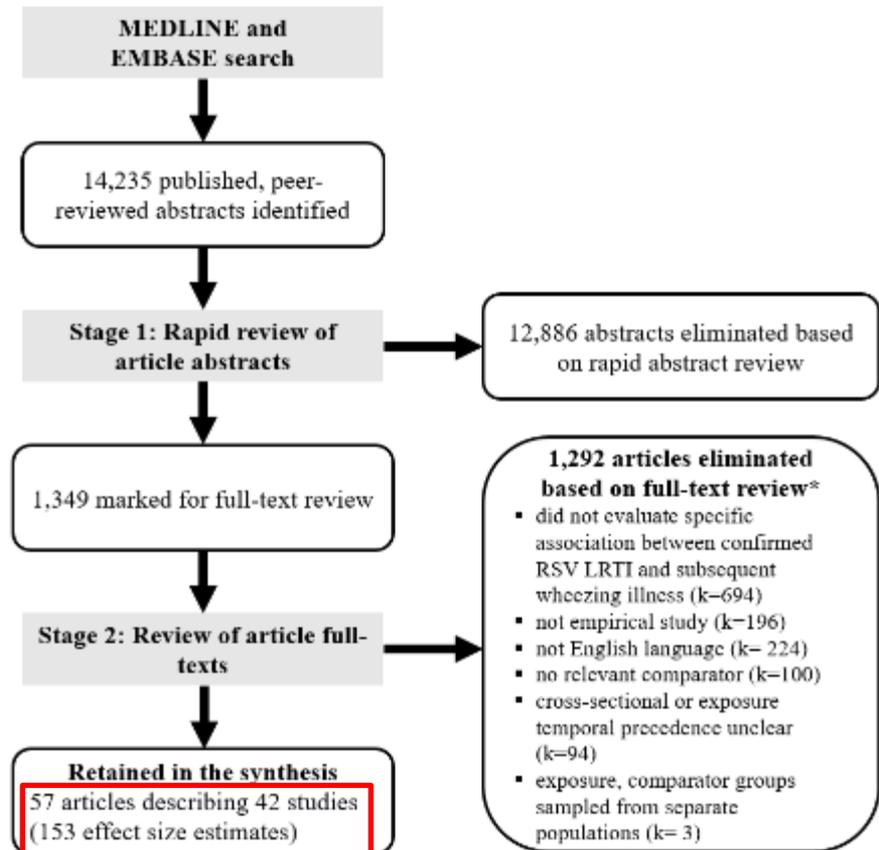


If RSV-LRTI were a cause of wheezing illness, efficacious immunoprophylaxis should prevent wheezing illness.

# Inclusion criteria and search

Table 2. Summary of inclusion/exclusion criteria and PICOS literature search framework.

	RSV-LRTI Exposure Studies	RSV Immunoprophylaxis Studies
<b>Population characteristics</b>	Human subjects	
<b>Intervention/ Exposure<sup>a</sup></b>	RSV-LRTI during a period beginning before age 2 years and fully contained within ages 0-5 years (operationalized as an exposure or mediator variable)	RSV immunoprophylaxis with established efficacy (either from the trial in question or past RCTs) in preventing/mitigating early life RSV-LRTI
<b>Comparator</b>	LRTI absent or undetected during the exposure period	RSV immunoprophylaxis not received during the exposure period
<b>Outcome</b>	Wheezing illness measured subsequent <sup>b</sup> to the index RSV-LRTI illness that defines membership in the exposure vs. comparator groups	Wheezing illness subsequent to study intervention protection period
<b>Study design</b>	<ul style="list-style-type: none"> <li>• Empirical study published (including Epub-ahead-of- print) in English in a peer-reviewed journal prior to final search date</li> <li>• Exposure/comparator groups sampled from the same population</li> <li>• Method of ascertaining exposure and outcomes were the same for exposure and comparator groups</li> </ul>	



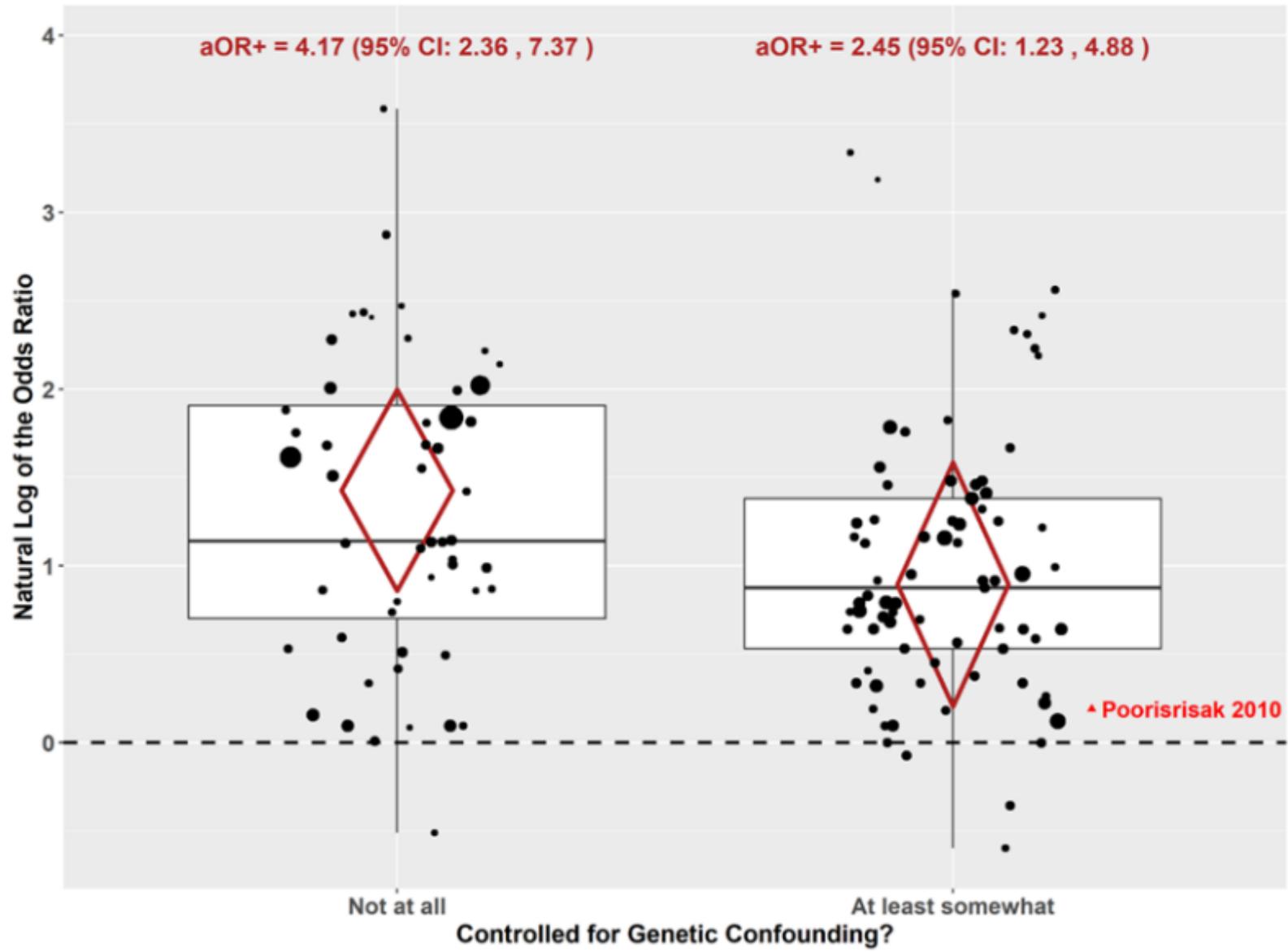
- 35 exposure studies
- 8 immunoprophylaxis studies (2 RCTs)

# Analytic approach

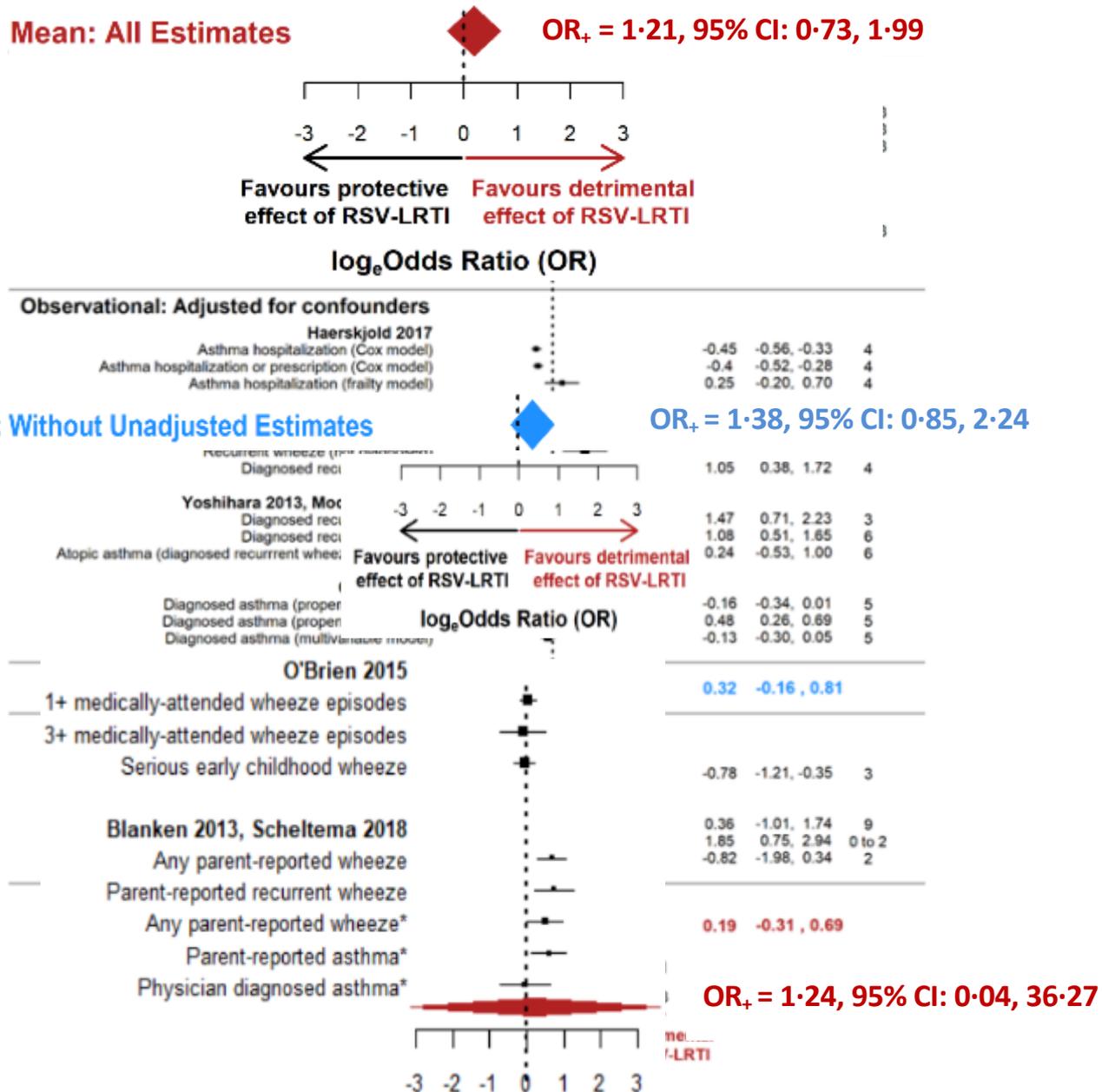
- Definitions for relevant outcomes (asthma, recurrent wheeze) were inconsistent, so all outcomes combined for analysis: **wheezing illness**
- Most studies provide multiple dependent estimates
  - Multiple relevant outcomes, time points, and group comparisons
- Robust variance estimation meta-regressions (Hedges et al. 2010)
  - Accommodates dependent estimates
  - Adjustments for small sample size
  - `robumeta` package in R (Fisher & Tipton, 2015)
- Detailed analytic summary with data and code are available at:  
<https://brunwasser.github.io/whorsv.github.io/index.html>

# Exposure studies: Modification by adjustment for genetic confounding

Observed Effect Size Distributions and Conditional Mean Effect Sizes by whether Estimates Controlled for Genetic Confounding



# Immunoprophylaxis studies



# Summary and conclusions

## ■ Exposure studies

- RSV-LRTI exposure studies controlling for genetic confounding produced smaller effect estimates.
- We cannot discount the theory that the association is driven by genetic confounding.

## ■ Immunoprophylaxis studies

- We cannot feel confident that RSV immunoprophylaxis reduces risk for subsequent wheezing illness.

- Although we cannot rule out a causal effect of RSV-LRTI on wheezing illness, neither of these findings increase confidence in causality.
- Projections of potential public health benefits of RSV-LRTI prevention should include null & negligible effects on subsequent wheezing illness.

# Limitations

- Not all potentially relevant evidence was included in the synthesis
  - Experimental evidence from animal and human tissue studies
  - Some relevant studies did not meet inclusion criteria
- Combined all wheezing illness outcomes
- Outcomes were generally based on subjective (e.g., parent-reported asthma diagnosis) rather than objective (e.g. lung function) measures
- All but two studies were conducted in high-income countries (World Bank)

## ■ Exposure studies

- Use designs that minimize the influence of genetics (e.g., twin studies)
- Investigate potential gene x RSV interactions
- Evaluate RSV infection separate from severity of RSV infection (LRTI)
- Take advantage of advances in causal modeling (e.g., directed acyclic graphs)

## ■ Immunoprophylaxis studies

- Standardize methods and outcomes for RCTs
- Consider pooling subject-level data to improve precision

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**Thank you!**