A Comparison of Frequentist and Bayesian Meta-analyses of Risk Factors for Respiratory Syncytial Virus Hospitalization in Preterm Infants

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BACKGROUND

- Typically, direct meta-analyses (DMAs) are performed using frequentist methods; however, these methods are generally considered to be less robust than Bayesian techniques at accounting for trial heterogeneity.[1,2]
- The statistical heterogeneity that characterizes meta-analyses is driven by within-study and between-study variance.
- Fixed-effects models account only for within-study variation while, in principle, random-effects models recognize both types of heterogeneity.
- Bayesian random-effects models are superior to frequentist random-effects models with respect to estimating between-study variance, because they do not ignore the imprecision of the variance estimates.[1]
- Acute lower respiratory tract infection caused by the respiratory syncytial virus (RSV) is a major cause of childhood morbidity throughout the world.[3]
- A frequentist DMA indicated that in otherwise healthy preterm infants (32-35 weeks' gestation age [WGA]) there are two important risk factors for an RSV hospitalization:
  - Birth immediately prior to, or soon after, the start of the RSV season (age)
  - Presence of school-age siblings (siblings)

OBJECTIVE

- The objective of this study was to perform a Bayesian sensitivity analysis to assess the robustness of a conventional frequentist DMA that assessed age and siblings as risk factors for RSV infection requiring hospitalization in preterm infants.

METHODS

- A systematic literature review was conducted to identify clinical studies reporting risk factors for RSV hospitalizations in otherwise healthy preterm infants (32-35 WGA) who had not received RSV prophylaxis.[4]
- A frequentist DMA of odds ratios for age and siblings was conducted using fixed- and random-effects models.
- To assess the reliability of the frequentist results, a Bayesian meta-analysis was performed.
- Trial heterogeneity was investigated using forest plots, Cochrane Q heterogeneity tests, and Higgins' I^2.

RESULTS

- Five observational studies included data suitable for meta-analysis for age or sibling risk factors (or both). Four were cohort studies,[5-8] and one was a case-control study (Table 1).[9]
- Trial heterogeneity was low for all risk factors (Q *P* value > 0.05 and I^2 < 20%) (Table 2).
- Age and sibling frequentist fixed- and random-effects model estimates were significant at the 95% level (95% confidence interval [CI] > 1) (Figure 1, Table 2).
- Bayesian model estimates for these risk factors were also significant (Figure 1, Table 2).
- Although frequentist and Bayesian estimates were highly consistent for fixed effects, they were not consistent for random effects; the Bayesian 95% CIs were wider (Figure 1, Table 2).

Table 1. Study Characteristics and Data for Age and Siblings Risk Factors

Reference Trial Acronym Country	Study Design RSV Seasons ROB Score[a] No. of Preterm Infants in Target Population	RSV Hospital Cases/ Nonhospital Controls	Odds Ratio (95% CI)	
			Age[b]	Siblings[c]
Ambrose et al., 2014 REPORT United States	Prospective cohort 2009-2011 ROB score: 1.9 N = 1,642 (< 36 WGA)	57/1,585	Not available	1.91 (1.13-3.24)[d]
Blanken et al., 2013 RISK The Netherlands	Prospective cohort 2008-2011 ROB score: 1.6 N = 2,421 (32 to < 36 WGA)	129/2,292	2.60 (1.61-4.21)	4.70 (1.69-13.05)[e]
Figueras-Aloy et al., 2004 FLIP Spain	Case control 2002-2003 ROB score: 1.9 N = 557 (33-35 WGA)	186/371	3.95 (2.65-5.89)	2.85 (1.88-4.33)
Figueras-Aloy et al., 2009 FLIP-2 Spain	Prospective cohort 2005-2007 ROB score: 1.6 N = 4,761 (32-35 WGA)	193/4,568	2.95 (2.19-3.97)	2.07 (1.54-2.79)[e]
Law et al., 2004 No trial acronym Canada	Prospective cohort 2000-2002 ROB score: 2.0 N = 1,758 (33-35 WGA)	66/1,692	4.88 (2.57-9.28)	2.76 (1.51-5.04)

ROB = risk of bias.

[a] Average score over 11 questions using RTI item bank scale, where 0 indicates maximum ROB and 2 indicates no ROB for each question; ROB characterized as low (1.6-2.0), medium (1.0-1.5), and high (0.0-0.9).

[b] Birth immediately prior to, or soon after, the start of the RSV season.

[c] Presence of school-age siblings.

[d] Result reported as a hazard ratio.

[e] Siblings reported as a composite risk factor combining presence of school-age siblings with index infant attendance at day care.

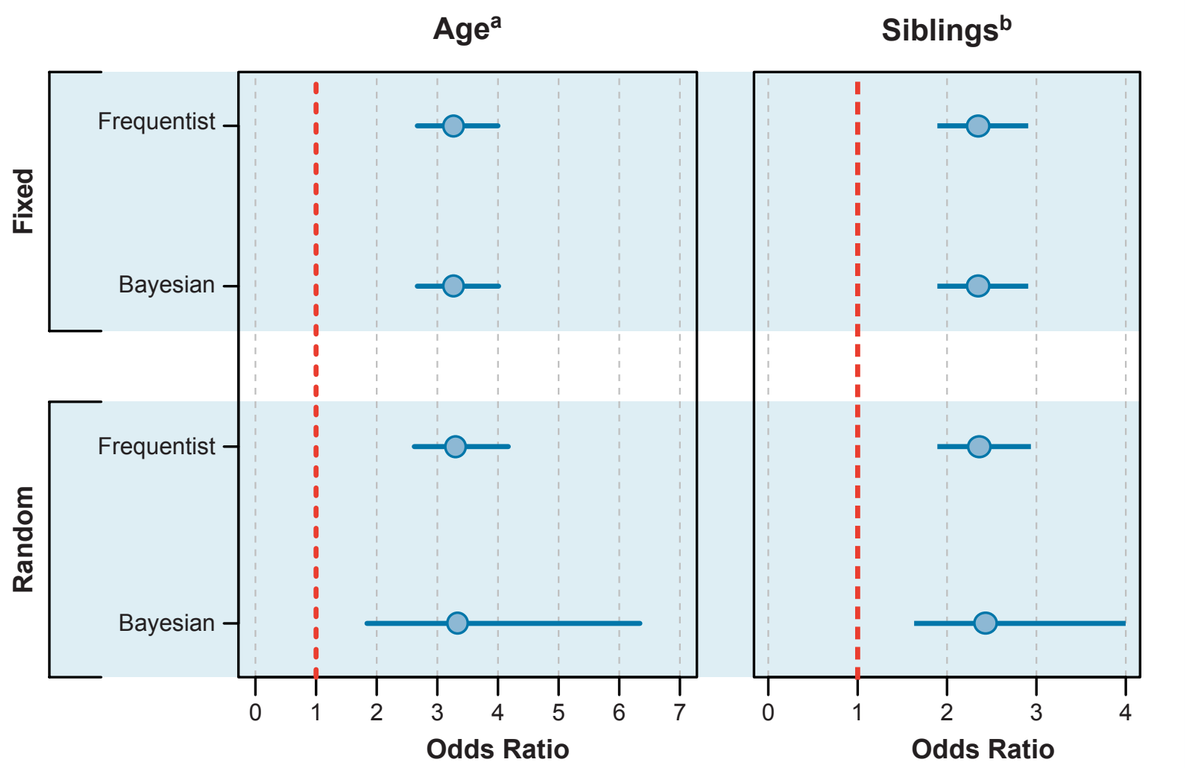
Table 2. Model Estimates and Heterogeneity Tests of Hospitalization Due to RSV Infection: Odds Ratios for Age and Siblings Risk Factors

Risk Factor	Analysis	Fixed-Effects Model	Random-Effects Model	Heterogeneity	
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	I^2 (%)	Cochrane Q *P* Value
Age[a]	Frequentist	3.27 (2.67-4.00)	3.30 (2.62-4.17)	18	0.30
	Bayesian	3.27 (2.67-4.01)	3.33 (1.84-6.34)		
Siblings[b]	Frequentist	2.35 (1.92-2.88)	2.36 (1.92-2.91)	4	0.38
	Bayesian	2.35 (1.92-2.88)	2.43 (1.66-3.97)		

[a] Birth immediately prior to, or soon after, the start of the RSV season.

[b] Presence of school-age siblings.

Figure 1. Forest Plots of Hospitalization Due to RSV Infection: Odds Ratios for Age and Siblings Risk Factors



[a] Birth immediately prior to, or soon after, the start of the RSV season.

[b] Presence of school-age siblings.

LIMITATIONS

- The evidence base comprised only observational study data, rather than randomized controlled trial evidence. Observational data are more likely to be affected by bias due to underlying unknown confounders.
- Higgins' I^2 and Cochrane Q, which were used to assess trial heterogeneity, were unreliable for detecting heterogeneity due to the small number of studies included in the DMA.[10,11]
- Covariate adjustments were not performed to account for clinical and methodological differences between studies. However, there was no evidence of substantial trial heterogeneity for any of the risk factors.
- The composite risk factor combining presence of school-age siblings with index infant attendance at day care reported in Blanken et al., 2013[6] and Figueras-Aloy et al., 2009[7] was assumed to be a proxy for the presence of school-age siblings.
- The hazard ratio reported in Ambrose et al., 2014[5] was assumed to be a proxy for the odds ratio.

CONCLUSIONS

- This study provides additional evidence that birth close to the start of the RSV season and the presence of school-age siblings are risk factors for RSV infection requiring hospitalization for otherwise healthy preterm infants.
- Meta-analyses are typically characterized by considerable between-study variation; consequently, a Bayesian random-effects model is more likely to accurately reflect the true relative effect than a frequentist random-effects model or any type of fixed-effects model.
- The wider CIs of the Bayesian random-effects results indicate that the frequentist approach is likely to be underestimating the variance of the risk factor relative effects.
- Comparison of frequentist and Bayesian random-effects model estimates should be undertaken in other DMA studies to further explore the underestimation of uncertainty by frequentist methods.
- Frequentist DMA, particularly when based on small numbers of trials, should be validated by Bayesian DMA to ensure the robustness of the results.

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