HTA30

Behavioural Structured Expert Elicitation: A Case Study to Inform Hospitalisation Due to Respiratory Syncytial Virus in the UK

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BACKGROUND

- Respiratory syncytial virus (RSV) is a seasonal virus that carries a high clinical and economic burden. It is estimated to cause approximately 21.6–50.3 million episodes of lower respiratory tract infection (LRTI) in children under 5 years old globally each year. RSV is the leading cause of such infections and result in 48,000–74,500 deaths annually in this population[1]
- Given > 80% of infants hospitalised for RSV are otherwise healthy[2], and standard of care for RSV-LRTI is purely supportive (i.e. provision of fluids and oxygen), there is a need to increase access to prophylactic interventions such as vaccines and monoclonal antibodies for infants and young children[3, 4]
  - Currently only palivizumab is available as prophylaxis against RSV in the UK, but its use is restricted to a very small (< 1% of all infants) population of young children with a high risk of serious complications resulting from RSV infection (see Table 1)
- The Joint Committee on Vaccination and Immunisation (JCVI) has recently considered several other options for prophylaxis for all infants, and various programmes to implement either a vaccine (the bivalent prefusion F protein vaccine RSVpreF) or a long-acting monoclonal antibody (nirsevimab) have been debated[5]
- Reimbursement decisions on new therapeutics against RSV require accurate estimates of the current number of RSV-driven hospitalisations and associated deaths, which are key drivers of cost-effectiveness. However, obtaining these numbers is challenging, due to coding practices, a lack of routine testing, and the impact of the COVID-19 pandemic
- As a general rule, the JCVI follows the methods laid out by the National Institute for Health and Care Excellence (NICE).[6] In such cases where empirical evidence is lacking and/or unfeasible to attain, NICE recommends structured expert elicitation (SEE) to address this uncertainty[6]

Table 1: Palivizumab eligibility criteria

- Pre-term infants with chronic lung disease (defined as oxygen dependency for at least 28 days from birth)
- Pre-term haemodynamically significant acyanotic chronic heart disease
- Children < 24 months who have severe combined immunodeficiency syndrome until immune reconstituted
- Children with long term ventilation (LTV) < 12 months at the start of RSV season and LTV children aged < 24 months with additional co-pathology (heart disease/pulmonary hypertension, intrinsic lung disease)
- Infants at particular risk of RSV-related complications for whom the clinical judgement of individual circumstances strongly suggests that palivizumab would prevent serious RSV infection

Key: LTV, long-term ventilation; RSV, respiratory syncytial virus.
Source: Joint Committee of Vaccination and Immunisation, 2010.[8]

OBJECTIVES

- We sought to elicit the views of clinical experts using SEE methodology to reduce uncertainty around estimates of RSV-related hospitalisation and Delphi methodology to achieve a consensus on mortality rates of infants in the UK. These are key drivers of cost-effectiveness, and we have subsequently used the results to support cost-effectiveness analyses and other economic modelling of prophylactic interventions

METHODS

- Several SEE frameworks exist, using different approaches to the elicitation and aggregation (e.g. behavioural and mathematical) of expert judgements. We used the Sheffield Elicitation Framework (SHELF), given its focus on expert discussion and consensus building, to elicit judgements from five clinical experts from different backgrounds regarding the number of annual UK RSV-related hospitalisations across several subgroups of interest
- The aim of the SEE was to elicit:
  - The experts' subjective uncertainty around the number of annual UK hospitalisations caused by RSV in infants born ≥ 35 weeks gestational age (wGA) and ineligible for palivizumab. These are stratified into four age categories based on trials for nirsevimab[7]: < 3 months old (referred to as Term Group 1, or TG1); ≥ 3 and < 6 months old (TG2); ≥ 6 and < 9 months old (TG3); and ≥ 9 and < 12 months old (TG4)
- An online survey was used to obtain from experts their individual judgements using the quartiles method[9] with a 5-point Likert scale and using a level of ≥ 70% agreement as consensus. The experts' judgements were used to generate individual-level probability distributions, using the R package 'SHELF'
- These individual judgements were discussed with each expert via one-on-one interviews to discuss and understand the rationales behind their responses, and to ensure the generated distributions accurately represented their beliefs
- All five experts attended a group workshop, where they were presented with the anonymised individual probability distributions. Group consensus judgements were elicited based on these, with a view to using a rational and impartial observer's perspective (behavioural aggregation)
- In addition, a Delphi approach was used to look for consensus on the following topics:
  - The experts' agreement with estimates of the UK's annual number of RSV-related hospital admissions of: (i) infants born at < 35 wGA, who are ineligible for palivizumab (pre-term group); and (ii) palivizumab-eligible infants infected with RSV
  - The experts' agreement with estimates of the UK's annual number of deaths from RSV in the UK in infants in TGs 1–4; in infants born < 35 wGA who are ineligible for palivizumab (referred to as the pre-term group); and in infants eligible for palivizumab (see Table 1 for criteria about palivizumab eligibility)

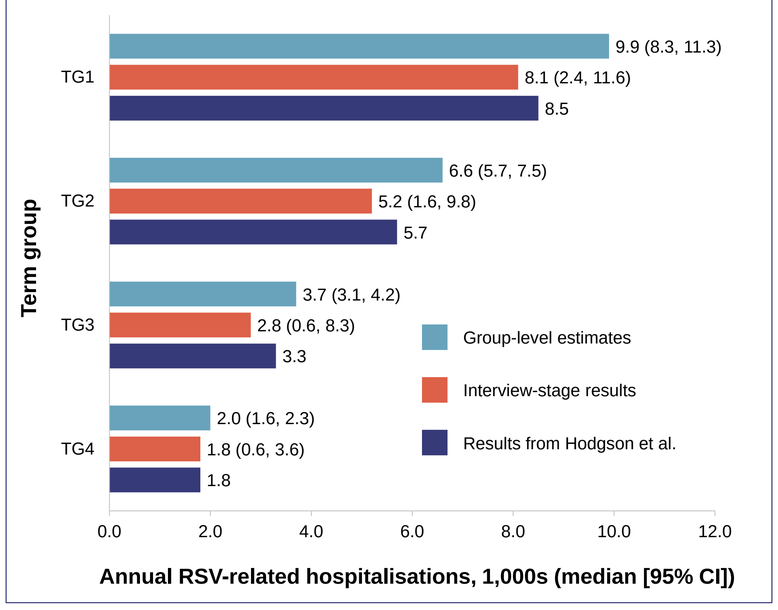
RESULTS

- Individual-level probability distributions were successfully elicited for the subjective uncertainty around RSV-related annual hospitalisations in TGs 1–4, agreement with estimates for RSV-related annual hospitalisations in the pre-term and palivizumab-eligible groups, and agreement with estimates for RSV-related mortality

RSV-related annual hospitalisations in TGs 1–4

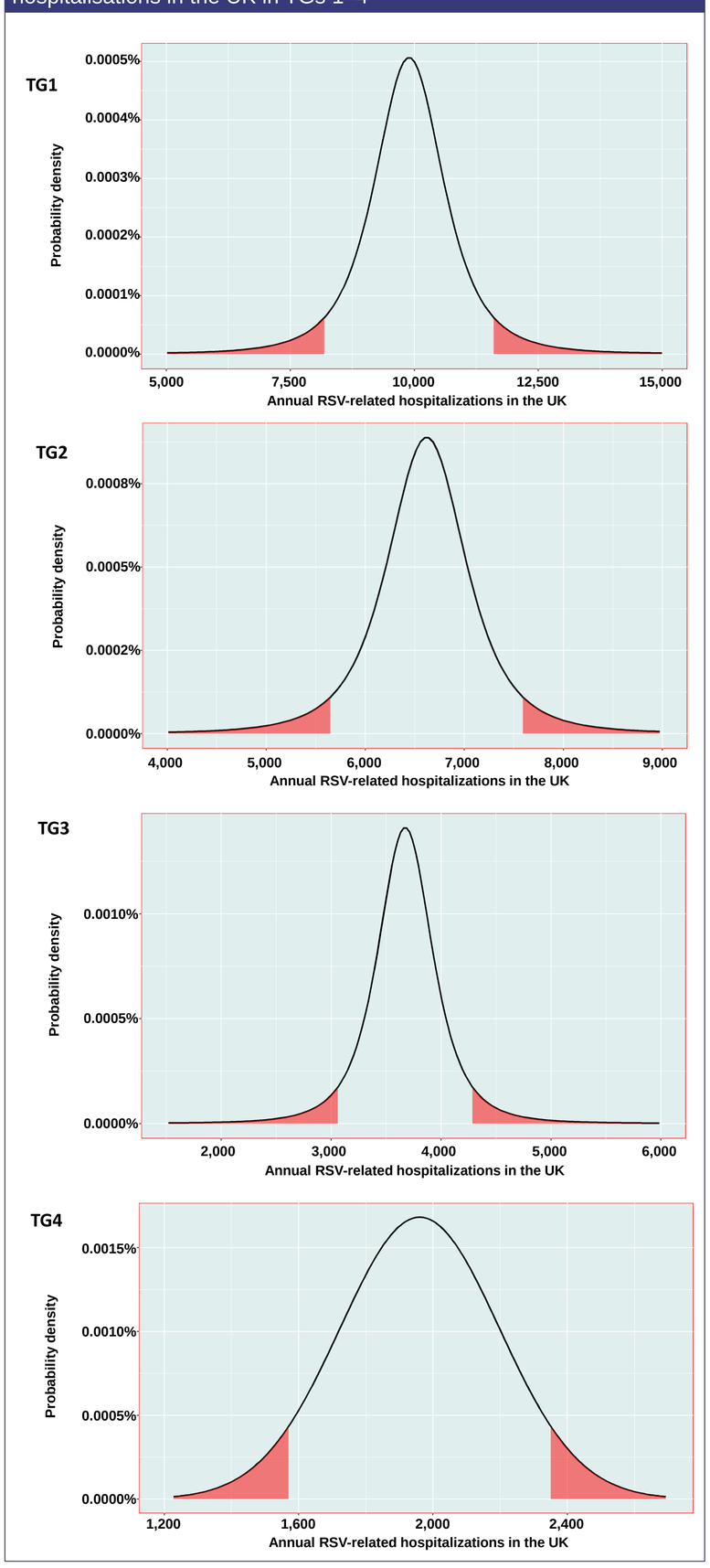
- Key data sources that experts referred to in their rationale were Reeves et al. (2019)[10], Hodgson et al. (2020)[4] and Cromer et al. (2017).[3] Of these, Hodgson et al. was identified as the most relevant to the research question, as it was the only study to stratify the modelling according to the four age categories of interest
- Consensus was reached that the estimates from Hodgson et al. are likely to be underestimates of the actual number of hospitalisations
- Following the workshop, group-level probability distributions were generated considering the collaboratively established multiple facets of uncertainty
- Figure 1 shows the median estimates from the individual- and group-level probability distributions, compared with the estimates from Hodgson et al. Figure 2 presents the group-level probability distributions of annual RSV-related hospitalisations in the UK in TGs 1–4

Figure 1: Estimates of annual RSV-related hospitalisations in the UK from Hodgson et al. compared with SEE results



Key: CI, confidence interval; RSV, respiratory syncytial virus; SEE, structured expert elicitation; TG, term group.

Figure 2: Group-level probability distributions of annual RSV-related hospitalisations in the UK in TGs 1–4



Key: RSV, respiratory syncytial virus; TG, term group; TG1, < 3 months old; TG2, ≥ 3 and < 6 months old; TG,; ≥ 6 and < 9 months old; TG4, ≥ 9 and < 12 months old.

RSV-related annual hospitalisations in the pre-term and palivizumab-eligible groups

- Experts were individually shown annual hospitalisation estimates derived using hospitalisation rates from Narayan et al. (2019)[2] and live birth cohort data from 2019 from the Office for National Statistics (ONS).[11] The estimates are shown in Table 2
- Consensus was reached that the estimates for both the pre-term group and the palivizumab-eligible group were plausible. Four out of five (80%) experts agreed; one expert strongly disagreed, estimating the numbers to be 2,500 for the pre-term group and 1,000 for the palivizumab-eligible group

Table 2: Annual number of RSV-related hospitalisations in the UK per subgroup (model inputs)

Pre-term group	1,673
Palivizumab-eligible group	446

Key: RSV, respiratory syncytial virus.
Note: Calculated using Narayan et al. (2019)[2] and Office for National Statistics live birth cohort data.[11]

RSV-related mortality

- Experts were individually shown annual mortality estimates for (i) the all-term group, (ii) the pre-term group, and (iii) the palivizumab-eligible group. A two-step approach was used to derive these:
  - Using the number of confirmed RSV monthly infections from Public Health England and the age of infants entering the season to calculate the number of infants infected with RSV for each age category
  - Multiplying the number of infants derived above by the RSV-related mortality rates from Taylor et al. (2016)[12] to provide the total number of RSV deaths
- The estimates are shown in Table 3
- Consensus was initially not reached during the survey, with two experts stating that the numbers were plausible, two indicating they were underestimates, and one neither agreeing nor disagreeing that the estimates were plausible. The two disagreeing experts provided alternate estimates, summarised as the following mean values (range): 30 (20–40) per year for the all-term group; 25 (20–30) per year for the pre-term palivizumab-ineligible group; and 20 (20–20) for the palivizumab-eligible group
- Following the group workshop, consensus was unanimously reached that: 1) the estimates of annual RSV-related deaths presented to them are likely to be conservative; and 2) for all infants < 1 year of age in the UK, the true number of annual deaths from RSV may be as high as 40

Table 3: Annual number of RSV-related deaths in the UK per subgroup (model inputs)

TGs 1-4 (palivizumab-ineligible)	18.67
Pre-term group (palivizumab-ineligible)	0.62
Palivizumab-eligible group	0.11
Total number of annual RSV-related deaths	**19.40**

Key: RSV, respiratory syncytial virus; TG, term group; wGA, weeks gestational age.
Note: Calculated using mortality rates from Taylor et al. (2016)[12] and infection data from Public Health England.

DISCUSSION

- The consensus workshop was critical for experts to share experiences and rationales for why the rates of RSV-related hospitalisations and mortality may differ from estimates published in and derived from the published literature
- They were able to discuss the uncertainties they had around the estimated hospitalisation rates from Hodgson et al., including the following:
  - The increased likelihood of false negatives over false positives in clinical testing, owing to sample quality (though this likely has a lower impact on infants in TG4)
  - Since the COVID-19 pandemic, more sensitive techniques such as polymerase chain reaction (PCR) tests have become available, and routine diagnostic testing has increased
  - Given that diagnosis of RSV does not alter treatment, many hospitals choose not to test for this – so studies (including Hodgson et al.) that only include laboratory-confirmed cases will omit from analyses the RSV cases that are routinely missed in hospitals
  - Seasonal/annual variation in infection rates (which could affect either way)
- In addition, the workshop provided an opportunity for the experts to discuss the lack of consensus around RSV-related mortality. The experts who had previously disagreed with the estimates (and considered them underestimates) were able to share their rationale – which included the differences between the estimates and their own clinical practices, and the fact that RSV may lead to deaths outside the hospital setting. A final unanimous consensus statement was agreed and supported by new justifications agreed across the group, including:
  - The fact that the all-term group covers infants with other conditions (e.g. neuromuscular and neurological disorders) as well as healthy babies
  - The lack of consideration in studies of deaths that occur outside the hospital setting, which are omitted from the calculated estimates

CONCLUSIONS

- **Our results suggest that the available estimates of RSV-related hospitalisation and mortality rates in the UK may be underestimates. The true number of annual RSV-related deaths among infants < 1 year old in the UK may be as high as 40 across all subgroups of interest**
- **The insights gained from the workshop regarding the issues around the published literature, plus the estimates given by the experts in response to these estimates, can be used to address some of the uncertainty around key economic model inputs used in technology appraisals for upcoming RSV therapeutics. Further empirical research is needed to reduce remaining uncertainty surrounding the clinical burden of RSV**
- **While mathematical aggregation is an efficient method to address uncertainty of a large group of experts, behavioural aggregation using SHELF can be valuable to explore more complex quantities that require between-expert interaction with a smaller group of experts when it is expected that the knowledge of the whole is greater than its sum**

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DISCLOSURES

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