The burden of respiratory syncytial virus

Understanding impacts on the NHS, society and economy

Final report annexes

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Abbreviations

ALRI	Acute lower respiratory infections
Can$	Canadian Dollar
CI	Confidence interval
CRPD	Clinical Practice Research Datalink
GBP	British Pound
GP	General Practice
HES	Hospital Episode Statistics
HRG	Health-Related Groups
ICU	Intensive Care Unit
IV	Intravenous
LOS	Length of stay
LRTI	Lower respiratory tract infection
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
ONS	Office for National Statistics
PICU	Paediatric Intensive Care Unit
PL	Productivity loss
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCGP	Royal College of General Practitioners
REA	Rapid Evidence Assessment
RSV	Respiratory syncytial virus
SIMD	Scottish Index of Multiple Deprivation
UK	United Kingdom
US	United States

Annex A. Rapid Evidence Assessment (REA) findings

A.1. Aims of the literature review

This REA aimed to bring together insights from the relevant recent literature to help understand the burden of respiratory syncytial virus (RSV) in the United Kingdom (UK). The focus was on the burden on the National Health Service (NHS) primary and secondary care, society (patient and parent/carers' health and well-being), and the wider economic impact in the UK (through productivity losses to the economy). The insights gained from the literature review informed the methods and variables relevant for modelling and estimating the burden of disease, reported in detail in Annex B.

A.2. Reader's guide

The remainder of this annex provides an overview of the methods used (Section A.3), followed by the REA findings (Section A.4). Section A.4.1 summarises the reviewed literature (e.g. study types, country coverage, and age-group profiles covered in the literature). Sections A.4.2 to A.4.6 summarise the findings from the literature review as they relate to the burden on patients (both short and long term), societal and economic burden on parents/carers and families and the impact on the healthcare system and healthcare resource use. This section ends with a brief overview of possible actions to potentially reduce the burden of RSV, as highlighted in the literature. Throughout Section A.4, we provide boxes overviewing differences in the burden of RSV across various paediatric sub-groups, e.g. by prematurity, comorbidities, ethnicity and deprivation.

This annex focuses primarily on evidence from the UK context. Insights from international studies outside a UK context are included only in cases where UK-based evidence is lacking.

A.3. REA methodology

We conducted the literature review using a Rapid Evidence Assessment (REA) methodology. The REA methodology provides a systematic approach to evidence gathering, placing specific restrictions on the search scope to enable a focused review in a limited timeframe [1]. The REA entailed the following steps: (1) search-strategy development, (2) database searching (e.g. PubMed/Medline), (3) screening of hits to enable paper selection, (4) data extraction from selected papers and (5) evidence analysis and synthesis.

A.3.1. Searches of the published literature

A search was conducted in PubMed for articles published in English and related to humans only. The publication date was restricted to 2011–2021 to capture the most relevant and up-to-date evidence. The search focused on identifying literature from the UK and relevant international literature to fill UK evidence gaps. The search terms are presented in the box below, with the inclusion and exclusion criteria overviewed in Table 1. This search resulted in 3,748 articles to screen.

Box 1: Search terms

Search terms

"respiratory syncytial virus" OR "respiratory syncytial viruses" OR RSV

AND

("United Kingdom" OR British OR England OR English OR Wales OR Welsh OR Scotland OR Scottish OR "northern Ireland" OR "northern Irish" OR NHS OR "National Health Service" OR United Kingdom[MeSH] OR England[MeSH] OR Wales[MeSH] OR Scotland [MeSH] OR "northern Ireland""[MeSH])

AND

Burden OR healthcare OR "health care" OR "primary care" OR "secondary care" OR hospital* OR "general practice" OR communit* OR workforce* OR staff* OR societ* OR econom* OR cost* OR resourc* OR wellbeing OR well-being OR "well being" OR morbidit* OR inequalit* OR sequel* OR "long-term" OR "long term" OR "disability-adjusted life years" OR "disability adjusted life years" OR DALY* OR "quality adjusted life years" OR "quality-adjusted life years" OR QALY* OR labour* OR labor* OR parent* OR carer* OR care giver* OR care-giver* OR caregiver* OR family* OR families OR incidence OR prevalence OR mortalit* OR death* OR fatal* OR "life lost" OR "years lost" OR "life years" OR "life-years" OR impact* OR productivit* OR employ* OR income* OR earning* OR "sick leave" OR absent* OR presenteeism OR wage* OR "workdays lost" OR "lost workdays" OR "work days lost" OR "lost work days" OR "missed work" OR "work missed" OR "quality of life" OR education* OR school* OR academi* OR attend* OR nurser* OR "early years" OR "early year" OR childcare OR "child care"

Table 1: Inclusion/exclusion criteria

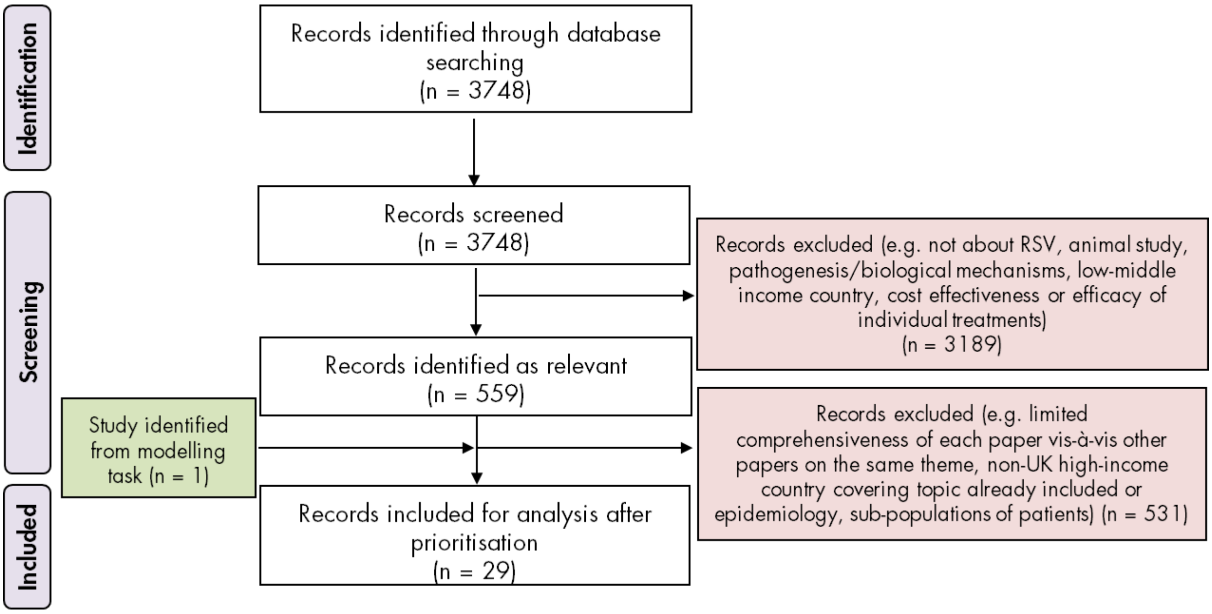
Criteria	Inclusion criteria	Exclusion criteria
Publication date	2011–2021	Pre-2011
Location	High-income countries *Prioritising studies from the UK and complementing with insights from international evidence only when there is a lack of or very sparse evidence on a theme of interest in a UK context*	Low and middle-income countries
Language	English	Not English

Criteria	Inclusion criteria	Exclusion criteria
Study type	Peer-reviewed journal publications presenting empirical evidence, review papers, grey literature with clear authorship, regulations, guidance, position statements	Documents without clear organisational authorship, theoretical work, letters, editorials, comments, or opinion pieces, book reviews, protocol papers, conference proceedings, case reports, book chapter, theses No abstract (unless title appears highly relevant)
Diseases	Respiratory Syncytial Virus only	All other conditions
Topic	Burden of RSV on patients Burden of RSV on family members/carers Burden of RSV on healthcare system (e.g. hospitalisations, impact on workforce) Burden of RSV on economy/costs of RSV Impact on longer term morbidity (e.g. association between RSV and long-term respiratory sequelae) Burden of RSV as a result of RSV contributing to the development of other conditions Impact on inequalities Incidence/prevalence of RSV as the primary focus of the study	RSV is not the main focus of the study (unless relevant aspects relating to burden are mentioned) Biological mechanisms underpinning RSV Cost-effectiveness of individual prevention/treatment strategies Efficacy of individual prevention/treatment strategies Incidence/prevalence of RSV (where this is not the primary focus of the study) Burden caused by RSV alongside other conditions/pathogens If/how burden changes if RSV is prevented/treated Incidence/prevalence in a single setting
Age group	Children with RSV aged 18 and under Parents/carers/siblings/family impacted by a child aged 18 or under with RSV	Adults with RSV (19 years and over) not linked to child (18 or under) with RSV

A.3.2. Citation screening and categorisation

The titles and abstracts of citations from the published literature were screened for inclusion based on pre-specified eligibility criteria, as summarised in Table 1. Initial screening was conducted by two researchers (LH and SS). A pilot of the categorisation process was performed among a random sample of 100 citations by these two team members to ensure that eligibility criteria and categories were appropriate (each team member reviewed all 100 citations for the pilot). The remaining articles were then split between two researchers for independent screening (LH and SS) against the inclusion/exclusion criteria (Table 1). Citations flagged for inclusion were then categorised as to the country of focus (UK, other high-income country or unclear), the article type (e.g. empirical study, review article), age group (child, adult, unclear) and topic (impact on NHS, impact on society, impact on patients and impact on the wider economy) using information available in the title and abstract.

Figure 1: Preferred reporting items for systematic reviews (PRISMA) diagram



A.3.3. Prioritisation of citations

REAs enable the rapid identification of key pieces of literature from the evidence base. Although not intended to be reviews of all available evidence on a topic, they follow a systematic search-and-screening strategy. However, they contain more restrictive inclusion criteria to enable prioritisation within a rapid evidence assessment scope. As such, large volumes of search results need to be prioritised based on the topics they cover to ensure the data to be extracted and interpreted are prioritised based on relevance and diversity of themes of interest whilst also manageable within the timeframe and resources available. To this end, two members of the research team (SM, LH) reviewed titles and abstracts of citations flagged for potential inclusion for topic relevance, scoring articles from '1' (highest priority) to '2' or '3' (lowest priority). The following factors were considered in prioritisation:

- ***Topic***: ensuring a diversity of topics were covered concerning the key study interests/focus areas to understand impacts on the patient (both short and long-term), society (on parents/carers and families), and the healthcare system and wider economy.
- ***The comprehensiveness of each paper***: vis-à-vis other papers on the same theme.
- ***Country of focus***: prioritising UK studies but incorporating studies from other high-income countries to fill gaps in the topic.
- ***The recency of paper***: for articles covering the same or similar topics, we prioritised more recent articles over older ones.

Two research team members (SM, LH) then met to discuss and compare priority scores to arrive at a set of articles for data extraction, interpretation and synthesis. One further study was excluded at the data-extraction stage (see below). Another was added from the modelling task, bringing the total number of papers included in the final analysis to 29.

A.3.4. Data extraction

For the final set of citations, full-text articles were retrieved and information was extracted by three researchers (LH, SS, MB). This stage used an Excel template, with the following data coding categories:

- ***General study details*** (e.g. study aim, methodology, setting, patient population, and geography);
- ***Epidemiology of RSV*** (data on incidence, prevalence, mortality, etc., for RSV);
- ***Understanding the burden of RSV*** (on patients in the short and long term, on society, on the healthcare system and on the wider economy);
- ***Inequalities*** (e.g. differences in health impacts for patients of low income or ethnicity);
- ***Other relevant information*** (impact of Covid-19, challenges related to the burden of disease, approaches to reducing burden).

A detailed assessment of study quality or risk of bias was not conducted within the scope of an REA. However, the following quality-related high-level information was collected to provide context for interpreting the results and conclusions of the reviewed literature: clarity of aims, clarity of population and settings, quality and comprehensiveness, clarity of inclusion/exclusion criteria, and funder and reported/potential conflicts of interest.

A.3.5. Analysis, interpretation and synthesis

The information from the extraction template was analysed thematically, describing and then synthesising the different areas of burden (on patients, the rest of society and the healthcare system). Where studies reported on inequalities in burden (e.g. between term and pre-term infants, ethnic minorities, deprivation levels, comorbidities, and between mothers and fathers), these are highlighted in example boxes throughout.

A.3.6. Strengths, limitations and caveats

The approach to this REA ensured the inclusion of a diversity of papers speaking to the topics of interest. We used a broad set of search terms and a systematic and structured approach to identify relevant UK literature concerning the three areas of RSV burden we were interested in: patients' health and well-being, the well-being and economic impact on parents/carers/family members, and impacts on the healthcare system/resource use. This also enabled us to identify literature on the variety of impacts across sub-groups (e.g. premature vs term infants, children with comorbidities vs otherwise-healthy children, mothers vs fathers). Using a timeframe of the previous ten years as an inclusion criterion ensured we identified the most relevant and up-to-date information.

While the REA search strategy included broad search terms, the nature of this approach meant certain restrictions were put in place to help prioritise the final set of articles to analyse. Therefore, we cannot be certain that we have covered all the potentially relevant literature on the topic.

The methods we adopted enabled a focus on evidence from the UK while also helping tackle some of the gaps in the UK evidence base with insights from international contexts. While our REA primarily focused on understanding the burden of RSV in a UK context, there were some key themes where little or no UK evidence was identified (e.g. parents' out-of-pocket expenses). In these cases, we drew on literature from international studies while recognising the difficulty of comparing across healthcare systems. However, we also found scant international evidence on some of our research themes (e.g. the impact of RSV on siblings), suggesting further research is required.

The literature on this topic is highly diverse. Different estimates concerning key features of interest across studies, geographies, time and age groups make it difficult to draw out clear quantitative patterns or trends on some topics of interest.

Finally, the literature often refers to parents but not to other caregivers. It is plausible that many of the findings would also apply to caregivers who are not biological or adoptive parents.

A.4. Results

A.4.1. Overview of the reviewed literature

Twenty-nine papers were included in the review (see Annex C for the details of each paper). The geographies and study populations covered are described in Table 2 and Table 3, respectively. Most of the papers were original research articles (n=24). The others were review articles, including three systematic reviews, one non-systematic review, and one mixed-methods systematic review plus modelling study. Some papers, including the reviews, drew evidence from multiple studies. Of the UK-based papers, nine focused on England, five on Scotland, one on both England and Wales, and one on the whole UK.

Table 2: Geographical coverage of the included papers

Location	Number of papers
UK	16
United States (US)	3
Unspecified location	2
Global	2
Spain and Italy	1
New Zealand	1
Finland	1
Canada	1
Multi-country: Netherlands, USA, Japan, Spain, Germany, Canada, Poland, Sweden, Israel, Denmark, Brazil, Finland, Norway, UK, South Korea, Qatar, The Gambia, France, Chile, Kenya, Australia.	1
Multi-country: Israel, USA, Brazil, France, Spain, Norway, Netherlands, Bangladesh, Italy, Canada, UK, Malaysia, China and Australia	1
Total	**29**

Table 3: Study population of the included papers

Study population	Number of papers
Children under five	8
Children under two	5
RSV patients of all ages (including information on children)	2
Children aged under one	2
Children up to four	2
Parents or caregivers of infants and young children	2
Pre-term infants 29–35 weeks gestational age	1
Children born less than 36 weeks of gestational age, assessed at a median of seven years	1
Children with RSV before two years, with the infection ending before five years	1
Children who were hospitalised with RSV in their first two years of life were followed until they were 18	1
Children up to three years	1
Children under five years and siblings and parents (aged 5–14 and 15+)	1
Children aged 13 and under	1
Children aged 0–17	1
Total	**29**

Of the included papers, 13 focused on hospital inpatient settings. Three papers focused on primary care and hospital inpatients, and two on primary care only. One paper focused on outpatients, recently-discharged patients and community settings. In eight other papers, the setting was unclear, or multiple settings were included.

The specific age range of participating children varied across papers, as overviewed in Table 3. The majority of papers focused on children younger than five.

As this was an REA, a formal quality assessment was not completed; however, the research team provided comments on the quality of the papers at the extraction stage. The papers' aims were deemed clear in all 29 papers, the population and settings were clear in 27 papers, quality and comprehensiveness were ascertained as 'good' for 27 papers, and the inclusion/exclusion criteria were clear in 28 out of the 29 papers.

The following sections present the REA findings in detail.

A.4.2. Epidemiology of RSV

Prevalence of RSV

Estimates of RSV prevalence for the UK vary across studies, settings, age groups and time

Evidence from English studies suggests some variation in RSV **prevalence estimates** across contexts and age-related subgroups. The Born in Bradford (England) study found that 54% of children had experienced one or more RSV infections by the age of one, and 33% had experienced RSV for the first time when aged between one and two [2]. In total, this study found that 86% of sampled children had evidence of RSV infection by the age of two (n = 422 out of 490 sampled children). In another study in England, 54% of RSV-associated lower respiratory tract infection (LRTI) cases were in infants aged less than six months [3]. It is possible these studies underestimate prevalence: for example, Hodgson et al. [4] estimate that 2.6 million symptomatic RSV infections in England annually are not captured in healthcare surveillance systems because not all patients seek healthcare support [4].

Some studies look at RSV prevalence in specific paediatric sub-groups. In Box 2, we highlight evidence about RSV prevalence, specifically in premature infants and children with underlying conditions. Given the lack of evidence on this issue in a UK context, we highlight insights from international studies.

Box 2: RSV prevalence among premature infants and children with underlying conditions in the UK and elsewhere

A systematic review of the impacts of RSV reported evidence from a UK study noting infection rates of 34.9% among **pre-term births**[1] [5]. This review also highlighted findings from a Spanish study that estimated an RSV infection rate of 22.5% in children under 2 with **severe congenital heart disease**.

A surveillance study conducted in England on 122 children aged under five with RSV (and their parents and older siblings with suspected RSV) found that **illness duration** also varies across age groups [4]. Illness in children aged 5–14 with suspected RSV was shorter, at a median of three days, than in confirmed cases in children under five and suspected cases in family members aged 15 and over (both a median of five days). There is a lack of robust evidence explaining the reasons behind this diversity.

1 The geographical context for this estimate is not clearly specified.

RSV-associated mortality

While mortality figures vary annually, deaths in childhood due to RSV in the UK appear to be relatively rare

In an average season in the UK, RSV was estimated to cause 83 deaths in children under 18[2] [6]. In contrast, another paper focused on England estimated only 25 deaths per year in children under 18 [7]. One paper estimated the annual RSV mortality rate in children under five in Scotland to be 0.49 per 100,000 population [8].

Some studies also look at RSV-associated mortality in specific paediatric sub-groups. In Box 3, we highlight evidence on RSV mortality in premature infants and children with underlying conditions.

Box 3: RSV-associated mortality rates among premature infants and children with underlying conditions in the UK and elsewhere

Mortality due to RSV may be higher in those with existing comorbidities, although pre-term infants do not appear to be at significantly greater risk of death than infants born at term. Díez-Domingo et al. [5] identify a UK-based study that suggests mortality may be greater than 25% when RSV is present in children with **serious comorbidities**.

Some cohort studies covered in the same review demonstrate none or a very small number of deaths in **pre-term infants** due to RSV [5]. For example, a systematic review and meta-analysis reported in the Díez-Domingo et al. [5] review highlighted that pre-term infant mortality from RSV is likely to be 0.04%, and higher for those pre-term infants with comorbidity (bronchopulmonary dysplasia) at 0.62%. Another paper found that children aged below five in Scotland who died with a history of RSV were more likely to be pre-term than those who died without a history of RSV (47% vs 30%). However, this was not statistically significant [8].

According to one paper focusing on Scotland, pre-term children and those with chronic conditions may have a **longer risk period for death** (up to three months) after RSV infection [8]. The authors suggest reasons for this may include: children without risk factors present at the hospital and get tested for RSV later; RSV may progress more rapidly in children without risk factors (although there is a lack of evidence to support this); and RSV may be associated with a higher risk of secondary bacterial infection in children without risk factors (which may expedite the illness) [8].

2 Since the paper does not provide information about the total number of infections, we could not deduce the mortality rate.

The risk of death for all children with RSV appears to reduce over time, in terms of duration of illness. For example, one case-series study of 162 children in Scotland found that over 90% of respiratory and circulatory deaths in these children that happened within one week of the RSV episode were linked to RSV. For deaths occurring between one week and one month after the RSV episode, 80% of deaths due to respiratory/circulatory issues were attributed to RSV [8].

It is also important to note that RSV can cause death indirectly, e.g. through secondary bacterial infection, when RSV may not be detectable post-mortem – potentially leading to underestimates of RSV-associated mortality [8].

A.4.3. The burden of RSV on patients

Short-term impact on patients' health and day-care and school attendance

Children diagnosed with RSV experience a range of respiratory-related symptoms

A systematic review and meta-analysis estimated that, globally, approximately 20% of all children admitted to hospital with RSV associated acute lower respiratory infections (ALRI) have **hypoxaemia** (low blood oxygen levels) globally [9]. In a Finnish study, 10% of the participating children with RSV presented with asthma exacerbation or wheezing symptoms.

In relation to **allergies**, a review by Díez-Domingo et al. [5] reported data from Sweden, noting that children under one admitted to hospital for RSV had a significantly greater risk of developing allergic rhino-conjunctivitis than the control group (39% vs 15% respectively). In a cohort study of 111 Polish children with RSV, 11% of children aged under 22 months developed rhino-conjunctivitis [10].

While respiratory symptoms may not always be severe, some children can develop **lung failure, acute bronchiolitis or pneumonia** due to RSV [5], with acute bronchiolitis appearing particularly common. Díez-Domingo et al. [5] found that it occurs in 85% of children under one and 31% aged 2–5 hospitalised for RSV, based on US data. Estimates of pneumonia vary across studies and geographies. For example, 3% of children participating in a Finnish study across multiple community settings developed pneumonia as a result of their RSV infection [11]. In another study of 111 children from Poland aged up to 22 months with RSV, a much larger proportion (33%) were reported to experience pneumonia complications [10][3].

A small number of children can suffer from **multiple respiratory symptoms at the same time**. In the population for a cohort study of 111 children from Poland aged up to 22 months, 22.5% had acute otitis media and pneumonia, 3.6% had acute otitis media and conjunctivitis, and 2.7% had pneumonia and conjunctivitis [10]. In another paper, 3% of the 287 Finnish children aged 13 and under with RSV developed both sinusitis and pneumonia [11].

In Box 4, we provide evidence on respiratory symptoms amongst premature infants, children with underlying conditions and different ethnic groups.

3 Details on geography were unclear in this paper.

Box 4: Respiratory symptoms among premature infants, children with underlying conditions and different ethnic groups

A systematic review included in the Díez-Domingo et al. [5] review reported that the rates of **apnoea** varied in acute bronchiolitis episodes among infants depending on **pre-term birth and comorbidity**. Rates in premature infants were higher than for infants born at term (4.9–37.5% vs 0.5–12.4%, respectively), and rates in infants with serious comorbidities were higher than those with no comorbidities (10.0–20.4% vs 1.2–4.3%, respectively).

Iwane et al. [12] conducted a study of nearly 5,000 US children under five hospitalised for acute respiratory illness, including RSV, to explore whether hospital admission rates varied between **black and white children**. The authors found that black children were significantly less likely to receive a diagnosis of pneumonia or bronchiolitis [12]. The authors were unclear about the reason(s) behind these differences.

Otitis media is a common occurrence in children with RSV

Acute otitis media is another common complication with RSV [10], likely due to RSV invading the middle ear [11]. A modelling study estimated that RSV caused 125,487 otitis media cases per RSV season in children aged 0–17 in the UK, but that the majority of cases (63.5%) were in those aged six months to four years [6].

Children can face a range of other RSV-associated symptoms, although evidence on this from the UK is limited

Díez-Domingo et al. [5] also highlighted several symptoms that can occur in children with RSV other than respiratory issues and otitis media. One US-based paper included in their review found that 9% of infants under one admitted to hospital for RSV-induced acute bronchiolitis or community-acquired pneumonia experienced **cardiovascular complications**. Cardiovascular issues may be more likely in children who are very unwell with RSV. A systematic review by Díez-Domingo et al. [5] reported that 35–54% of infants with RSV on ventilators in the paediatric intensive care unit (ICU) showed signs of heart muscle damage (although the authors note that this damage was also seen in some non-ventilated infants).

Diez-Domingo et al. also reported findings from a US-based study that found that 11–19% of children under one with RSV also **suffered electrolyte imbalances.** [5]

Finally, Díez-Domingo et al. [5] reported the results of a systematic review that found that 39% of children with RSV admitted to the paediatric ICU had acute **neurological symptoms**. In contrast, patients with milder RSV only had these symptoms in 1.2% of cases.

A time-series regression model of UK children aged 0–17 years found no link between RSV and urinary tract infections or accidents [6].

Children may need to miss day-care and school days due to their RSV infection, although we identified no studies reporting on this issue in the UK

One prospective cohort study that included 287 children with RSV in Finland reported that 65% of children under three missed one or more day-care days for a mean duration of three days [11]. The same paper found that younger children were significantly more likely to miss more days; those aged less than three (195 missed days of day-care per 100 children) and 3–6 years (162 missed day-care and school days per 100 children) missed more days than children aged 7–13 (58 missed days per 100 children) [11].

Longer-term health and quality-of-life impacts on patients

Respiratory issues can persist for a sustained period after the RSV infection has resolved, although the risk of developing longer-term issues is unclear

Diez-Domingo's review indicated that the risk of **recurrent wheezing** is up to three times higher for children with a history of RSV infection than for children with no RSV history [5].[4] The authors report evidence that wheezing can lead to issues with sleep and the gastrointestinal tract. However, it is unclear whether these symptoms are present for the duration of the illness or immediately after or if these occurred for a more extended post-infection period.

Estimates of the risk for developing **asthma later in life** due to RSV earlier in childhood vary across studies. For example, in a cohort study of nearly 750,000 Scottish children, RSV-related hospitalisation before the age of two was an independent risk factor for asthma through to age 18, with a 2–3 times higher risk for children who were hospitalised with RSV than children who were not [13]. According to this study, the most significant risk for asthma admission was at age seven [13]. Swedish studies in the Díez-Domingo et al. [5] review suggest a link between RSV in early years and childhood **asthma**, indicating that the risk is nearly 22 times higher at 13 months follow-up, five times higher at 13 years follow-up, and four times higher at 18 years follow-up. A systematic review by Brunwasser et al.[5] indicates a 2.64 times higher risk of asthma outcomes for children with a history of RSV than children without [14].

A study in Finland covered in the Díez-Domingo et al. [5] review found that RSV infection in infancy is also an independent risk factor for **poorer lung function** for up to 20 years post-RSV infection compared to controls, with a five-times higher risk. However, a study of 51 pre-term children in England showed no significant difference between lung-function tests at school age for children with a history of RSV related LTRI in infancy and children without a history of LRTI [15].

Evidence from a Swedish study reported in the Díez-Domingo et al. [5] review also suggests a link between RSV in early years and a significant increase in **sensitivity to environmental allergens**. In addition, Wrotek et al. [10] conducted a cohort study of 111 Polish children aged up to 22 months hospitalised with RSV. They found that RSV-associated conjunctivitis may predict future allergic rhino-conjunctivitis, possibly due to inflammation around the eye after RSV infection.

Evidence from England suggests that children with RSV face quality-adjusted life-year (QALY) losses due to their infection, although few studies explore this impact

A surveillance study based on a questionnaire conducted in England on 122 children aged under five with RSV (and their parents and older siblings with suspected RSV) estimated the QALY loss (measured using EQ-5D-3L/EQ-5D-3L-Y) for patients who sought healthcare and those who did not. For healthcare-seeking patients, the authors estimated that RSV leads to a QALY loss per healthcare-seeking RSV episode in children under five of 3.823×10^{-3}. This equals around twice the QALY loss for patients aged five and over. For patients who did not seek healthcare in the same study, the estimated QALY loss per RSV episode was 3.024×10^{-3} for children under five years and 1.543×10^{-3} for those five and older [4].

4 Drawing on data from literature reviews (no geography specified), England and Qatar.

5 Covering Netherlands, USA, Japan, Spain, Germany, Canada, Poland, Sweden, Israel, Denmark, Brazil, Finland, Norway, UK, South Korea, Qatar, The Gambia, France, Chile, Kenya and Australia.

The authors also found that the impact on quality of life varied by infection duration, reducing during the first half of the illness and returning to baseline in the second half [4].

A.4.4. The societal and economic burden on parents, carers and families

Economic impacts on parents, carers and families

Parents in Canada pay approximately Can$737 in out-of-pocket expenses when their child is hospitalised with RSV

Mitchell et al. [16] conducted a descriptive study of 67 Canadian infants aged below one hospitalised with RSV. The study found that the mean out-of-pocket expenses for parents for a child's RSV hospitalisation was Can$736.69 (£560 in 2011 GBP), comprising Can$151.50 for transport costs, Can$273.33 for childcare/home help and Can$311.86 for other costs (such as over the counter medications/medical equipment, food, accommodation) [16]. These costs may well apply to other geographies but we lack evidence on the extent and nature of their impact in the UK.

Parents/carers of children hospitalised with RSV may need to miss work and suffer productivity losses when at work. Older siblings may also miss school due to contracting RSV from their younger siblings

Multiple studies explored the number of missed workdays for parents of children hospitalised with RSV. The exact number of missed days appears to vary across countries and the child's age, but generally amounts to less than two weeks. Carbonell-Estrany et al. [17] conducted an observational, non-interventional study in Spain and Italy of 161 infants under two hospitalised with RSV and their parents. This paper reported that the most important financial burden for parents was having to re-arrange work schedules or take time off work: 34% of parents reported having to take time off work in total, 40% for less than one week, 53% for 1–2 weeks and 7% for more than two weeks. In a prospective cohort study of Finnish children aged 13 and under with RSV, 52% of parents reported they had to miss one or more workdays, with an average time off work of 2.6 days [11]. Work absenteeism also differed depending on the child's age in this study, being significantly greater for parents of children under three years (136 days per 100 children) than for parents of children aged 3–6 years (92 days per 100 children) or 7–13 years (29 days per 100 children) [11].

A study in Canada of 67 infants aged under one reported an average parental absenteeism from work of 49%, with both parents spending an average amount of nearly seven days in the hospital. This suggests that each parent missed over three workdays while their child was in hospital [16]. A small qualitative study of six Alaskan mothers of children hospitalised with RSV noted that mothers reported needing to miss work, although the number of missed days was not specified [18].

Parents and older siblings may also need to take time off work or school due to contracting RSV from their child/younger sibling. Hodgson et al. [4] conducted a surveillance study of 122 children under five in England with confirmed RSV and their siblings and parents with suspected cases of RSV. The authors found that 16.6% of siblings and parents (aged 15+) took time off work or school due to suspected RSV infection (median of two days) after sharing a household with a confirmed RSV case [4].

As well as lost workdays, RSV in children can impact parental work productivity. A study conducted in Spain and Italy with 161 infants under two hospitalised with RSV found that 19% of parents reported a severe impact, 18% moderate impact and 63% mild impact on their work productivity [17]. In another paper, the average presenteeism[6] for both parents with an infant under one hospitalised with RSV in Canada was 51.4%, and overall work impairment was 77.8% [16].

Box 5 considers the differential impact on mothers compared to fathers in terms of workdays lost and highlights the scarce and inconclusive evidence on this theme, drawing on evidence from Canadian and US contexts.

Box 5: Impact on workdays lost on mothers compared to fathers due to children's hospitalisation for RSV (from evidence outside the UK)

Two studies explored the differences in **lost workdays between mothers and fathers** of children hospitalised with RSV but reached different conclusions. Mitchell et al. [16] conducted a Canadian study of 67 infants aged under one. They highlighted that compared to working mothers, working fathers experienced higher levels of absenteeism (51.3% vs 27.8%), presenteeism (62.7% vs 21.4%), and overall work impairment (78.4% vs 73.0%) [16]. The second study investigated absenteeism in working mothers and fathers of pre-term infants aged under one in the US. From discharge to one-month post-discharge, absenteeism went from 73% to 15% amongst mothers and declined from 58% to 4% for fathers. These findings highlight that although lost workdays decline over time, the impact of RSV is still present among all caregivers one-month post-discharge. Contrary to Mitchell et al., this study suggests a more significant impact on mothers [19]. The study also found that, compared to fathers, mothers had higher overall work-and-daily-activity impairment and absenteeism from hospital discharge to one-month post-discharge.

Wider societal impact on parents, carers and families

The families of children hospitalised with RSV may lose time they would otherwise devote to alternative activities due to hospital visits and face disruptions to their normal day-to-day routines

Very little evidence for this impact focuses specifically on a UK context. However, a study in Canada of 67 infants aged under one hospitalised with RSV found that each patients' family spent an average of 10.6 hours travelling to and from the hospital per admission [16]. Time spent travelling is likely to differ across geographies and depending on the vicinity of healthcare settings to patients' homes and the number of independent hospital visits associated with any one case. A systematic review of studies exploring the experiences of parents of children with bronchiolitis and building on evidence from multiple country contexts (one of which includes the UK)[7] also showed that parents experience negative time-related impacts [20].

Families of children hospitalised with RSV may also face disruptions to their usual day-to-day routines. For example, the Mitchell et al. [16] study in Canada found that 82% of regular activities were prevented for each parent, on average. Pokrzywinski et al. [19] found that one of the most frequently raised issues persisting up to one month after the child's discharge from hospital (for children hospitalised for RSV in the US) was disruption to the family routine (e.g. due to travelling to medical appointments).

Box 6 highlights the differential impacts on mothers vs fathers regarding disruption to their regular routines, drawing on evidence from Canadian and US contexts.

6 Attending work but being less productive when there.

7 Australia, Bangladesh, Brazil, Canada, China, France, Israel, Italy, Malaysia, Netherlands, Norway, Spain, the UK and the US.

Box 6: Disruptions to regular routines – the differential impact on mothers vs fathers (from evidence outside the UK)

Mitchell et al. [16] conducted a Canadian study of 67 infants aged under one and found that activity impairment (disruption to regular activities) was greater among working **mothers than fathers** (80% vs 74.2%, respectively). Pokrzywinski et al. found that the **parents of pre-term infants** (born at 29–32 weeks) reported greater disruption to family routines than parents of children born at other gestational ages among US infants aged under one hospitalised with RSV [19].

The quality of life and emotional well-being of siblings and parents of children with RSV who contract RSV can be impaired, and children may miss days from school, although evidence on this is limited

Siblings of children with RSV can also contract the infection, which creates additional challenges for parents having to care for multiple unwell children [18]. Hodgson et al. [4] conducted a surveillance study of 122 children under five in England with confirmed RSV and their siblings and parents with suspected cases of RSV. The authors found that 84% of siblings aged 5–14 with suspected RSV reported anxiety or depression, 76% had their usual activities impacted by RSV symptoms, and 72% reported pain or discomfort. For siblings or parents aged 15+ with suspected RSV, 36% reported anxiety or depression, 54% had their usual activities impacted by RSV symptoms, and 36% reported pain or discomfort. Based on this, the authors estimated a median health-related quality of life loss of 0.456 for siblings aged 5–14 years and 0.358 for siblings/parents aged 15+. When pooling the results of all parents and siblings aged five years and older together, the authors estimated the QALY loss for this age group to be 1.950×10^{-3} per RSV episode for those who did not seek healthcare and 1.543×10^{-3} QALYs for those who did access healthcare [4].

In the same study, 51.5% of the siblings aged 5–14 with suspected RSV were reported missing school due to their infection (with a median of two days off) [4]. The lost school and workdays for older siblings and parents from this study are reported in an earlier section.

Hospitalisation of children with RSV can lead to poor emotional health for parents through stress, anxiety, distress and feelings of helplessness, which can last beyond discharge. However, evidence on this from the UK is limited

Multiple studies identified that having a child hospitalised with RSV takes an emotional toll on parents/carers and families, often presenting as stress, anxiety and distress. Yael Kopacz et al. [18] and Gates et al. [20] found that mothers of hospitalised children reported feeling guilty for not noticing their child's illness earlier, concerns about infection transmission, and fears around how quickly a child's state can decline (in studies in the US and multiple countries,[8] respectively). Other factors contributing to anxiety and stress included worries over recovery/survival, re-infection and readmission, delays accessing care due to living in a rural area, sleep deprivation, keeping family informed, missing work, feeling stuck at the hospital, eating at the hospital, witnessing painful/invasive procedures, and concerns over providing care at home [17, 18, 20]. Gates et al. [20] also identified feelings of helplessness among mothers of hospitalised children. For

8 Israel, the US, Brazil, France, Spain, Norway, Netherlands, Bangladesh, Italy, Canada, the UK, Malaysia, China and Australia.

example, being unable to fulfil their role as a caregiver (e.g. hold their child or breastfeed) or comfort their child led to feelings of helplessness and questioning their ability to be a 'good' mother. These authors also reported evidence suggesting that longer hospital stays for children resulted in increased parental distress [20].

Parents' emotional distress can last for an extended period after the child's discharge, but evidence differs on the duration of this impact. A study covered in the Gates et al. [20] systematic review of studies from multiple countries[9] identified that stress and anxiety could last weeks after a child is discharged.

However, two other studies indicated this was not always the case. A study in the US on pre-term infants aged under one showed that the infants' caregivers had declining stress levels from discharge to one-month post-discharge, but stress was still prevalent at this time point [19]. Medical concerns (e.g. monitoring the child's breathing) were among the most frequently raised issues that persisted through to one-month post-discharge [19].

Box 7 highlights evidence related to differences in emotional impacts for specific population sub-groups, drawing on insights from US and Canadian studies. However, evidence on this is scarce and should be interpreted with caution.

Box 7: Diversity in emotional impacts related to caregivers and gestational age of the child (from evidence outside the UK)

Levels of stress and anxiety among parents appear to differ between **mothers and fathers**; one study in Canada found that working mothers tended to have higher stress levels and a higher anxiety score than working fathers [16].

Pokrzywinski et al. [19] reported greater emotional impacts on US caregivers of infants born at **33–34 weeks gestational age** than those born at 29–32 weeks gestational age or 35 weeks gestational age.

9 Israel, the US, Brazil, France, Spain, Norway, Netherlands, Bangladesh, Italy, Canada, the UK, Malaysia, China and Australia.

Parent/carer perceptions of suboptimal interactions with healthcare professionals and insufficient information provided to parents/carers can contribute to feelings of stress, anxiety and helplessness

Parents/carers of children hospitalised for RSV can suffer from negative emotional impacts if they feel their experience of engaging with healthcare professionals is suboptimal [17, 20]. However, evidence on the frequency and scale of this challenge is limited. Two studies (one from Italy and Spain, the other focusing on ten countries, including the UK) flagged multiple concerns. These included concerns about staff competence, feeling excluded from their child's care, lacking trust in healthcare professionals (particularly when not informed of their child's progress, or doubting that staff can look after or comfort the child in the same way they could), concerns about post-discharge support, and a poor paediatric ICU experience [17, 20]. Gates et al. found in their systematic review that a lack of information for mothers can contribute to feelings of fear and helplessness, and some mothers can find it difficult to absorb information because they find their situation so overwhelming [20].

A.4.5. Impacts on the healthcare system and healthcare resource use

Impact on primary and community care

Children with RSV place a significant burden on primary and community care, accounting for a significant percentage of calls to NHS 111 related to respiratory conditions and GP visits

Morbey et al. [21] analysed data on 2 million calls to NHS 111[10] in England relating to respiratory issues (out of 18.2 million total calls made to NHS 111). They found that 43% of all respiratory calls per week during two winter seasons were associated with RSV (408 out of 948 respiratory calls, the highest proportion of any respiratory pathogen analysed for the study). Nearly half of these RSV calls were for children aged five and under [21]. Harcourt et al. [22] also explored the impact of RSV on NHS 111 calls in England, focusing on children under five years. The authors found that the NHS 111 medium-intensity threshold for cough-related calls was exceeded in weeks 46 and 47 of the 2017–2018 season, suggesting increased RSV activity (although the increased calls could also have been due to other pathogens) [22].

10 A non-emergency medical telephone helpline.

Studies also consider the number of GP visits in the UK associated with RSV. Although many used modelling to estimate this impact on health-service utilisation, they arrived at relatively consistent estimates. To illustrate[11]:

- Taylor et al. [6] conducted a time-series regression model estimating that 450,158 children under 18 consulted a GP for an episode of respiratory disease per RSV season in the UK from 1995 to 2009. GP episodes were highest for children under six months [6]. GP episodes for RSV accounted for 11–14% of all GP episodes for respiratory diseases in children under five [6].
- Similar results were seen in a study by Cromer [7], who conducted a multivariate regression analysis to model the burden of RSV in children under five in England, estimating that 16% of all acute respiratory GP consultations were associated with RSV in this group. The authors estimated that 12 primary care consultations per 100 children under five are associated with RSV per year, mainly in children under six months.
- In terms of studies that provide data based on observed occurrences (as opposed to modelling estimates), Hodgson et al. [4] conducted a surveillance study using Public Health England data. They found that the total number of GP consultations and hospital admissions for RSV per year for children aged under five was 375,000–383,000 (855,000 for people aged five and over) but did not distinguish data on GP visits from hospital admissions [4].
- Harcourt et al. [22] reviewed the impact on GPs' out-of-hours consultations relating to bronchitis. As with NHS 111 calls, GPs' out-of-hours activity breached the medium intensity threshold for one week in week 47 of the 2017–2018 season, again suggesting increased intensity in RSV activity (although other pathogens can also cause bronchitis).
- Díez-Domingo et al. [5] highlight findings from a study in a UK context that identified that pre-term children with RSV require an average of 12.4 doctor visits (for any cause) in the first two years of life and five visits for respiratory causes, compared to 9.4 and 2.9 respectively for children without RSV [5].

The number of RSV-related GP visits varies seasonally, which may mean that infants born in certain months are at higher risk of needing to visit a GP. Cromer [7] estimated that the GP consultation rate for RSV is 27.4 per 100 births for children born in November compared to 13.9 for children born in March.

Finally, a paper by Zylbersztejn et al. (2021) found that by the end of their first year of life, 38% of children with RSV in the study had contact with healthcare professionals during the peak RSV season. However, this paper did not separate data on primary and secondary care contacts.

11 MacBean et al. (2018) also conducted a prospective cohort study in England of 51 prematurely born children who had symptoms of lower respiratory tract infections and were followed up when they were 5–7 years old. Given this study's small sample size (51 children were included in the study, but only 10 had RSV), we did not profile it in this document's main narrative. In addition, the study did not include an analysis for the first year of life, which is responsible for most of the healthcare burden associated with RSV. This study found an average of 0.49 respiratory GP visits per year and 1.32 non-respiratory GP visits per year among study participants.

Impact on hospital admission, length of stay and readmission

Although the individual hospitalisation rate for children with RSV is not high, the overall prevalence rates mean that the scale of the burden is significant. However, estimates of this burden vary substantially across different studies, geographical contexts and age groups in the UK.

Numerous studies consider hospital admission rates. For example, a 2019 birth cohort study of over 169,000 Scottish children aged up to three with RSV identifies an admission rate for RSV in Scotland of 21.9 per 1,000 children aged up to one, 7.0 per 1,000 children aged up to two and 2.0 per 1,000 children aged up to three [23]. Data from Thwaites et al. (2020) suggest a maximum RSV hospitalisation rate of 45.9 per 1,000 in children under two in Scotland, while Reeves et al. (2017) note that the admission rate for RSV reasons was 35.1 per 1,000 children under one and 5.31 per 1,000 children aged 1–4 years in England [3]. A more recent paper by Reeves looking specifically at children under six months of age in England estimated the annual rate of RSV hospital admissions to be 29.63 per 1,000 [24], suggesting higher hospitalisation rates than for somewhat older children.

Further detail on key studies considering hospital admissions is provided in Box 8.

Multiple studies also explored the difference in hospital admission rates for children by prematurity, comorbidity, ethnicity, socioeconomic background or wider social factors (see Box 9).

Box 8: The burden of RSV hospital admission in the UK – estimates from key studies

Taylor et al. [6] modelled and estimated an average of 29,160 hospitalisations for RSV in children under 18 in the UK, with 92% of these cases being in children under two. In addition, hospitalisations for RSV were estimated to be highest in children aged under six months (at least three times higher than for children aged 6–23 months) for each RSV season [6]. In infants under six months, an estimated 3.8% were hospitalised for RSV-attributed acute bronchitis or bronchiolitis, accounting for 79.3% of all hospitalisations for bronchitis or bronchiolitis in children under six months in the average RSV season [6].

Cromer [7] conducted a multivariate regression analysis to model the burden of RSV in children under five in England, estimating that 22% of all acute respiratory hospital admissions were associated with RSV in this group. The authors estimated that 0.9 hospital admissions per 100 children under five are associated with RSV per year, primarily in children under six months (with this age group accounting for over half of admissions).

Reeves et al. [3] explored hospitalisation rates in children up to four years of age in England from 2007 to 2012. Of the 121,968 children hospitalised for a respiratory infection, an estimated 28% were associated with RSV. Exploring the admission rate by age range, 48% were in children under six months, 21% in ages 6–11 months, and 31% in ages 1–4 years [3]. Per epidemiological year, the admission rate for RSV reasons was 35.1 per 1,000 children under one and 5.31 per 1,000 children aged 1–4 years [3].

A later study conducted by Reeves et al. [24] modelled children under one in England hospitalised with a respiratory infection. The study estimated an average of 20,359 RSV-associated hospital admission per year, accounting for 30% of all hospital admissions for any respiratory diagnosis in infants under one in England during the study period. Of the hospital admissions of children under one, 74% were infants under six months old (49% under three months and 24% aged 3–5 months), with admission peaking at six weeks and reducing with age. The annual rate of RSV hospital admissions of those under six months was estimated at 29.63 per 1,000 [24].

Thwaites et al. [25] studied admission rates for over 623,000 Scottish children under two hospitalised with RSV. The authors found that the hospitalisation rate for definite RSV was 27.2 per 1,000 children, totalling 16,946 admissions. Per year, this equated to 1,410 RSV admissions for the study period. Most admissions (84.3%) occurred in children aged up to one year. The authors also explored hospitalisation rates when including 'possible', 'probable' and 'definite' RSV hospitalisation, estimating the maximum RSV hospitalisation rate in children aged two and under to be 45.9 per 1,000 [25].

Hardelid et al. [23] conducted a birth cohort study of over 169,000 Scottish children aged up to three years with RSV. Of 6,158 children in the cohort with RSV, 87.4% were linked to a hospital admission within two weeks of being tested for RSV (equating to 5,185 admissions in 5,033 children). Of the RSV admissions, 19.1% occurred in children under two months, 48.5% in those under six months old and 29.6% in ages 1–3 years [23]. This equates to an RSV admission rate for children in the first year of life in Scotland of 21.9 per 1,000 aged up to one, 7 per 1,000 aged up to two and 2 per 1,000 up to three [23].

In an analysis of over 740,000 records of children hospitalised in Scotland in their first two years of life, 2.1% were hospitalised with RSV (equating to 17,271 admissions in total) [13]. Of these RSV admissions, 85.5% were in children under one and 59.3% in their first six months [13].

Box 9: Differences in hospitalisation rates by prematurity, comorbidity, ethnicity, deprivation level and other social factors in the UK and elsewhere

Prematurity and comorbidities

Reeves et al. [24] conducted a data linkage modelling study of over 6,700 hospitalised children under one in England. Of the RSV admissions (2,947 in total), only 5% were considered high-risk (due to **prematurity or comorbidities**). However, this group of children accounted for 21% of total bed days.

A cohort study of nearly 624,000 children under two in Scotland found that **pre-term children** were significantly more likely to require RSV hospitalisation than children born at term (5.2% vs 1.9%) [25]. **Comorbidities** were found in 7.1% of children hospitalised for RSV compared to 1.2% of those not hospitalised with RSV, a statistically significant difference. Comorbidities included congenital heart disease/pulmonary hypertension, congenital lung disease/bronchopulmonary dysplasia, Down syndrome, cerebral palsy, cystic fibrosis and neuromuscular disorders [25].

In a study of children aged under three years in Scotland, 19.4% of the 4,966 RSV admissions in children with known gestational age were among those who were **premature or had an underlying chronic condition** [23].

In Canada, one study of 67 infants aged less than one year found that **pre-term infants** were more likely to have an ICU admission than full-term infants (15.4% vs 13.0%) and had a longer average length of stay in the ICU (8.1 days vs 6.2 days) [16].

Deprivation

The risk of hospitalisation due to RSV may be higher in patients from a lower socioeconomic background. Hardelid et al. [23] conducted a study in Scotland of over 5,000 patients aged up to three hospitalised with RSV. This study found that patients who were premature or of lower gestational age, with younger mothers or with delayed or incomplete vaccine schedules (all of which are associated with lower socioeconomic status) were more likely to be hospitalised with RSV [23].

Ethnicity

Although we did not identify any UK studies exploring differences in hospitalisation rates by ethnicity, we identified one from the US. Iwane et al. [12] conducted a study of nearly 5,000 US children aged under five hospitalised for acute respiratory illness, including RSV, to explore whether hospital admission rates varied between black and white children. Across all children in the study, the percentage of RSV-positive admissions was 19% for black children and 29% for white children, suggesting that black children in these age groups are at higher risk of hospitalisation for RSV than their white counterparts. This difference was significant for children aged 12–23 months and 24–59 months, with relative rates of 1.7 and 2.2. However, it was not significant for children aged under 12 months, 0-2 months or 3-5 months, respectively [12]. The authors suggest that the difference in older children in this study may be due to poorer access to healthcare; black children hospitalised with RSV were significantly less likely than white children to have private insurance or receive care from a private physician's office. Black children were also significantly more likely than white children to have a history of a high-risk condition (such as asthma and wheezing) and to have been born prematurely, which may also influence the severity of RSV infection [12].

Other social factors

Díez-Domingo et al. [5] and Hardelid et al. [23] reported several wider risk factors that increased the risk of hospitalisation for RSV in an international context and England, respectively. These included low birth weight/ small size for gestational age, being ten weeks or younger at the start of the RSV season, co-infection with another virus, having been breastfed for less than two months, having school-age siblings, going to day-care, living with four or more adults, exposure to environmental pollution/smoking, maternal tobacco use during pregnancy, younger maternal age, delayed infant vaccination and a family history of asthma. The authors concluded that the risk of hospitalisation increases substantially if two or more of these risk factors are present [5].

A cohort study of nearly 624,000 children under two years in Scotland found that children of multiple births were significantly more likely to require RSV hospitalisation than those born singly (40.6 vs 20.8 per 1,000, respectively) [25].

Hospital admission rates vary by season

Multiple studies highlight RSV peaks during the winter months [3, 7, 24-26], with the highest hospital admissions between October and January. For example, Thwaites et al. [25] found that 91.7% of RSV hospitalisations in children under two in Scotland occurred from October to March, representing 8.5% of all admissions in this age group. In England, Reeves et al. [3] reported that 80–90% of bronchiolitis admissions in children aged 0–4 years were in from November to January, with admission peaking in early December [24]. In addition, Cromer [7] estimated that 70% of all hospital admissions for acute respiratory reasons from October to January in England were in children under six months with RSV.

The seasonality of RSV infections may also lead to a higher risk of hospitalisation for babies born during the autumn/winter months [23, 24] [7, 23, 25]. For example, Cromer [7] estimated the hospital admission rate for RSV at 6.47 per 100 births for children born in November compared to 1.55 for children born in March.

According to most studies, the median length of stay for children admitted to hospital for RSV in the UK is between 2–4 days, with longer stays for those with more severe infections

Most studies exploring hospital stay duration in the UK found that the median stay was around 2–4 days, although globally [9, 13, 25, 26], this could be up to 13–15 days for most severe cases [5]. Paul et al. [26] found that children with more severe RSV infections (i.e. requiring a chest x-ray and/or antibiotics) required 4.5 days in hospital, whereas children with RSV who did not need these interventions only required 2.5 days.

Reeves et al. [24] conducted a data linkage study using lab surveillance and hospital-admission data of children under one in England to explore the number of bed days associated with RSV. The authors estimated that almost 60,000 bed days are required per year for children under one admitted for RSV in England. Of these, 31% were for less than one day, accounting for 5% of all RSV-associated bed days. In addition, the authors estimated that 74% of RSV admissions in children under one were for children under six months, accounting for 80% of annual RSV-associated bed days [24]. Children under three months accounted for 55% of RSV-associated bed days [24].

Box 10 details the duration of RSV-related hospital stays among premature infants, children with underlying conditions and different ethnic groups.

Box 10: Duration of RSV-related hospital stays among premature infants, children with underlying conditions and different ethnic groups in the UK and elsewhere

Hardelid et al. [23] conducted a birth cohort study of over 5,000 Scottish children under three years hospitalised for RSV. The authors found that the median length of stay was significantly longer for **premature infants** and children with underlying chronic conditions: three days vs an overall median of two days. Children with **chronic conditions** made up only 11.1% of RSV-associated admissions but 20.4% of bed days [23].

Iwane et al. [12] conducted a study of nearly 5,000 US children aged under five hospitalised for acute respiratory illness, including RSV, to explore whether hospital admission rates varied between **black and white children**. Black children were significantly less likely to stay in hospital for longer than three days and had a shorter length of stay overall than white. Reasons for this are not provided.

Readmissions for children with RSV add a burden to the health system in terms of bed days and cost, with estimates suggesting costs of £1,515 per readmission in England and Wales. Research in Scotland suggests that just under a fifth of hospitalised cases in children result in readmissions.

In some cases, children may require hospital readmission due to RSV after their initial discharge. Thwaites et al. [25] analysed Scottish inpatient administrative data in children under two, reviewing the records of nearly 624,000 children. This paper found that readmissions occurred in 19.1% of children under two, totalling 2,547 readmissions. Hardelid et al. [23] also explored readmission rates in Scottish children under three via a birth cohort study. Among the 5,033 children studied, 3% had two or more admissions in the first three years of life. Pockett et al. [27]

analysed hospital admission data for children aged 0–4 years in England and Wales. Half of the patients re-admitted for RSV were re-admitted within nine days of their initial discharge. The average length of stay after readmission was 2.6 days, with significant increases (of 0.4%) in the length of stay for each day until readmission. The authors conducted a regression analysis to explore the costs associated with readmission for RSV, estimating it at £1,515 per readmission. This cost increased by 0.2% for each day between discharge and readmission [27].

Box 11 considers RSV-related readmission rates for children with underlying conditions.

Box 11: RSV-related readmission rates among children with underlying conditions/multiple diagnoses in England and Wales

Pockett et al. [27] analysed hospital admission data for children aged 0–4 in England and Wales. The authors found that the average length of stay after readmission significantly increased for patients with **multiple diagnoses** (55.9%). The authors conducted a regression analysis to explore the costs associated with readmission for RSV, which increased by 31.8% for children with multiple diagnoses [27].

In a UK context, data from Scotland suggests that ICU admission may be required for 3.8–4.3% of children under two admitted to hospital with RSV

Data on ICU admissions varies significantly across studies and geographical contexts. Two studies conducted in Scotland found that 3.8–4.3% of children under two admitted to hospital with RSV for a median of five days required ICU admission [13, 25]. Thwaites et al. [25] found that RSV accounted for 6.9% of all ICU bed days for children aged two and under in Scotland. Paul et al. [26] reviewed the testing and intervention requirements of 162 children under two and admitted to one hospital with RSV in England, finding that 2% required paediatric ICU management.

Box 12 considers ICU admissions for premature infants, children with underlying conditions and ethnic groups.

Box 12: Differences in ICU admission among premature infants, children with underlying conditions and ethnic groups

A non-systematic review found that RSV-related ICU admission and length of stay vary depending on **prematurity and comorbidities** [5]. The study found that prematurity is a high-risk factor for ICU admission (ranging from 17.8–48.4%), particularly for infants born at 33–35 weeks. The review also highlighted the findings of studies exploring ICU admission rates for children with acute bronchitis and congenital heart disease and found the admission rate was 1.5–17.5% and 30.5%, respectively. This review also reported the length of ICU stay, finding that ICU stays could last ten days for children under two for patients with congenital heart disease (compared to four days for children without this condition). For premature infants, ICU stay was an average of 7.7 days for infants born at 33–35 weeks and six days for those born at 32 weeks or less [5].

In Canada, one study of 67 infants (aged less than one) found that **pre-term infants** were more likely to be admitted to the ICU than full-term infants (15.4% vs 13.0%) and had a longer average length of stay there than full-term infants (8.1 days vs 6.2 days) [16].

Iwane et al. [12] conducted a study of nearly 5,000 US children aged under five hospitalised for acute respiratory illness, including RSV, to explore whether hospital admission rates varied between **black and white children**. There were no significant differences between black and white children hospitalised for RSV requiring ICU admission.

The need for medical interventions and treatment (antibiotics, oxygen supplementation and assisted ventilation)

Antibiotic prescriptions are common for children with RSV in primary and secondary care in the UK, often for bacterial co-infections

Antibiotic prescriptions are common for children with RSV in primary and secondary care in the UK and elsewhere, usually for bacterial co-infections [28]. A time-series regression model of around 3.7 million children aged 0–17 in the UK found that over 416,000 prescriptions for antibiotics were written in primary care per RSV season. Roughly 8.3% of children under six months and 11.9% aged 6–23 months received antibiotics for RSV-associated infection in an average RSV season [6]. Fitzpatrick et al. [29] also conducted a time-series model focused on over 452,000 children under five presenting to primary care in Scotland. The authors estimated that almost 105,000 antibiotic prescriptions were associated with RSV from 2009 to 2017, accounting for 6.9% of all antibiotics prescribed to children under five in Scotland. When exploring antibiotic prescription rates across age groups, 5.2% of prescriptions were associated with RSV for children under one and 5.8% for children aged 1–4 years [29]. Paul et al. [26] reviewed the testing and intervention requirements of 162 children under two years admitted to one hospital with RSV in England, Finding that 49 children required intravenous (IV) antibiotics.

Box 13 highlights medical-intervention and treatment-related evidence for children with underlying conditions.

Box 13: Antibiotic prescribing for children with underlying conditions in Scotland

Fitzpatrick et al. [29] conducted a time-series model using primary care data from almost 453,000 Scottish children under five. The study found that 4.3% of antibiotic prescriptions were associated with RSV among children with a high-risk chronic condition, compared to 7.1% among children without chronic conditions. The authors suggest this may be because children with high-risk conditions are more likely to follow antibiotic-prescription adherence guidance or use them for extended periods.

Evidence suggests that children hospitalised with RSV are highly likely to require supplemental oxygen, and some may require other respiratory support. However, UK data on these issues are limited.

Paul et al. (2017) reviewed the testing and intervention requirements of 162 children under two admitted to one hospital with RSV in England and found that 36 (22%) required respiratory support (although the type was not specified) [26].

A Canadian study on the burden of RSV of 67 children under one hospitalised with RSV found that almost all infants in the study required supplemental oxygen (95.5%) [16].

A non-systematic review conducted by Díez-Domingo et al. [5] reported evidence from a Spanish study showing that 22.1% of children under two who were hospitalised with acute bronchiolitis required oxygen, and oxygen was used more frequently in the presence of RSV infection than in its absence [5]. The same review reported evidence from Spain and the US that found that 6–18% of children hospitalised with RSV required ventilation support for a median of six days.

Box 14: Supplemental oxygen and other respiratory support requirements by prematurity, underlying conditions and ethnic groups

A Canadian study of 67 infants aged less than one found that **pre-term infants** were less likely than full-term infants to use supplemental oxygen (92.3% vs 96.3%, no significance test conducted) [16].

Iwane et al. [12] studied nearly 5,000 US children aged under five hospitalised for acute respiratory illness, including RSV, exploring whether hospital admission rates varied between **black and white children**. They found that black children were significantly less likely to receive supplemental oxygen than white children [12]. However, there was no significant difference in the need for mechanical ventilation between black and white children hospitalised for RSV.

Díez-Domingo et al. [5] explored the need for intubation in **premature infants and those with co-infections**. In acute bronchiolitis or RSV pneumonia cases, intubation was required in 21.4% of infants born at or below 32 weeks, 8.7% of infants born at 33–35 weeks, and 12.1% of infants born at or after 37 weeks. For children aged under two with co-infection, the risk of intubation due to RSV-induced acute bronchiolitis was 10%, compared to 7.5% for children without co-infection Díez-Domingo et al. [5].

Children with RSV may require a range of other interventions, such as chest x-rays, admission to high dependency care units, IV fluids, inhalers and antipyretics

Paul et al. [26] reviewed the testing and intervention requirements of 162 children under two admitted to one hospital with RSV in England and found that 36 children required a chest x-ray, 27 required high-dependency unit care and 26 required IV fluids.

A non-systematic review conducted by Díez-Domingo et al. [5] found that 64.7% of patients under two with acute bronchiolitis were treated with short-acting inhalers of β-2 adrenergic agonist. In addition, 27.6% of acute bronchiolitis paediatric cases required antipyretics.

Box 15: Other treatment interventions – ethnic-group considerations from outside the UK

Iwane et al. [12] studied nearly 5,000 US children under five hospitalised for acute respiratory illness, including RSV. They found that the requirement for chest radiography did not differ significantly **between black and white children hospitalised for RSV** [12].

Inpatient and outpatient RSV costs place a significant burden on healthcare systems. One study estimated the UK financial burden at £54 million per year.

Although multiple studies report overall healthcare costs associated with RSV in children, similar studies in a UK context are rare. Cromer [7] conducted a multivariate regression analysis estimating the burden of RSV in children under five in England. The authors estimated that the healthcare costs associated with RSV in this age group total £54 million per year, equating to £87.58 per child. They estimated that the majority of this cost (£37 million) was due to hospital admission, including ICU admission. Hospital admissions for children under six months were comparable to those aged six months to five years. The costs associated with GP consultations were estimated at £16 million per year, unequally split across the same age groups (£3 million for children under six months and £13 million for children aged six months to five years) [7].

Healthcare costs for treating RSV may vary by patient sub-groups. Box 16 considers RSV-related healthcare costs for premature children and those with comorbidities.

Box 16: RSV healthcare costs for premature children and those with comorbidities in England and elsewhere

Three studies explored how healthcare costs differed when treating premature children with RSV or those with comorbidities:

- MacBean et al. [15] conducted a prospective cohort study in England of 51 children born prematurely with symptoms of lower respiratory tract infections, following up when they were aged 5–7. However, although 51 children were included in the study, only 10 had RSV. In addition, the study did not include costs for the first year of life, estimated to be responsible for most of the healthcare costs associated with RSV [15]. Bearing these limitations in mind, the authors found that children born moderately **prematurely** did not represent a higher burden in terms of respiratory healthcare costs after infancy [15].
- Zhang et al. [30] conducted a systematic review and meta-analyses into the cost of RSV acute lower respiratory infections in children under five years globally. This study found higher RSV-management healthcare costs among children with **comorbidities**, including congenital heart disease, chronic lung disease and bronchopulmonary dysplasia. Total healthcare costs increased by €9,825, €10,879 and €5,516 for each comorbidity, respectively. They estimated that healthcare for children with RSV born **prematurely** costs an additional €4,695 more than full-term children.
- Díez-Domingo et al. [5] found that RSV-related healthcare costs increased as gestational age decreased, although the exact figure varied across studies.

Longer-term respiratory impacts of RSV in children on the healthcare system

The longer-term respiratory impacts of RSV in children create additional resource and cost burdens for the healthcare system

An analysis of over 740,000 hospital records of children hospitalised in Scotland in their first two years of life found that significantly more patients with RSV than controls without RSV were hospitalised for asthma during childhood (8.4% vs 2.4%) [13]. The mean number of asthma admissions per hospitalised child was significantly higher for RSV cases, at 2.3 compared to 1.9 for controls. Overall, the asthma admission rate was 193.2/1000 for RSV cases compared with 46.0/1000 for controls. A significantly higher proportion of RSV cases required more than one hospital admission for asthma than controls (43.7% compared to 35.2%), suggesting that children with a history of RSV face more severe asthma than those without. The difference between RSV cases and controls was highest for children with more than two asthma admissions (23.2% vs 17.1%). Although RSV patients only made up 2.1% of the total study population, they comprised 7% of all children with an asthma hospitalisation and 8.4% of all recorded asthma admissions. Asthma medication use was also higher among cases than controls across all age groups. For those aged 14–18 years, 18% of cases had taken asthma medication compared to 13% of controls [13].

A.4.6. Improvement opportunities to help tackle the burden of RSV

While this study did not aim to identify specific strategies for reducing the burden of RSV, it is important to broadly understand the options when considering burden. Therefore, we briefly summarise opportunities for reducing the burden of RSV mentioned in the literature we reviewed.

Vaccines

Improving RSV vaccine programmes could reduce virus transmission, hospitalisations, illness severity and antibiotic prescriptions

Multiple studies commented on the importance of vaccinations in preventing the transmission of RSV (for pregnant women, children and older siblings) [7, 9, 11, 22, 23, 29]. The development of a maternal vaccine may be beneficial in protecting very young infants, particularly from hospitalisation and death. However, careful consideration of the appropriate pregnancy stage for administering the vaccine will be necessary to protect premature infants [7, 9, 23]. Shi et al. [9] estimate that a successful maternal vaccine (or a newborn antibody immunisation) programme could provide up to 80% protection in infants under six months, potentially preventing up to 1.1 million RSV-associated hospital admission and 22,000 inpatient deaths globally.

Vaccination programmes could also be widened to offer protection for older at-risk children until at least age three to reduce hospital admissions and the risk of subsequent future health issues, such as otitis media [11, 23]. Programmes could be broadened to include healthy older siblings, which might help reduce hospital admissions in their younger siblings, particularly those under three [7, 11, 23].

Fitzpatrick et al. [29] highlighted that future RSV-vaccine programme developments could reduce unnecessary antibiotic prescriptions, particularly among healthy children.

Antivirals

Innovation in the antiviral space

Two studies highlighted how the development of antivirals targeted at RSV could reduce the incidence, length and severity of the infection, including subsequent health impacts such as otitis media and bacterial complications requiring antibiotics [11, 31]

Other improvement prospects

Efforts to reduce RSV transmission (other than vaccination) can help prevent RSV infections, reducing hospitalisation, morbidity and mortality

Díez-Domingo et al. [5] highlighted the importance of prophylactic treatment (specifically Palivizumab) to prevent the contraction of an RSV infection and prevent complications. These authors also recommended informing and educating parents on hygiene measures to prevent RSV transmission, such as hand washing and self-isolation, particularly for parents with premature babies. Finally, the authors noted the importance of addressing the social determinants of health to reduce the risk of hospital admissions, such as overcrowding, tobacco smoke exposure and short breastfeeding duration [5]. Providing parents/carers with information about how to recognise early symptoms of RSV and support affected children could help them manage childcare and reduce stress and anxiety.

Yael Kopacz et al. (2013) highlighted the need for parental RSV education to help them recognise the early signs and symptoms of infection in their children [18].

Multiple studies noted the importance of healthcare professionals answering questions, providing families (primarily parents) with timely and understandable updates on their hospitalised child and advising them on how to care for their child after discharge in reducing anxiety and providing reassurance [17, 18, 20]. Gates et al. [20] highlighted findings from a systematic review demonstrating that implementing coping-support interventions for parents of hospitalised children is feasible and helps reduce parents/carers' anxiety and stress. Providing information to parents can also help develop a trusting relationship with the healthcare team [20]. These authors also note that encouraging a family-centred approach – involving parents in decision-making and allowing them to parent and comfort their child – can improve care and parent satisfaction [20].

Annex B. Modelling the UK economic burden of RSV in children

B.1. Aim, basic approach and assumptions

Our analysis aimed to assess the economic burden of the Respiratory Syncytial Virus (RSV) in children aged five or younger in the United Kingdom (UK). In particular, we aimed to quantify the cost incurred by all parts of the NHS alongside parents' productivity losses due to their children's RSV infections. We investigated the economic burden by predefined subgroup based on age, gestational age and socioeconomic status. We selected 2019 (the most recent year before the COVID-19 pandemic) as our projection year.

Our rapid evidence assessment (REA) identified numerous papers reporting relevant information on the economic impact of the RSV on children younger than five in the UK [2, 3, 6-8, 15, 23-26, 29, 32, 33]. However, only two manuscripts enclosed all the key information for our analysis [6, 7]. We chose to obtain the key data from a single publication to preserve the internal validity of our data and avoid any discrepancies due to methodological differences. While both Taylor [6] and Cromer's [7] analyses attempted to link healthcare resources and RSV laboratory reports using regression methods, these publications used different datasets and methods to attribute the healthcare contacts to RSV infections.

Taylor and colleagues used the Clinical Practice Research Datalink (CPRD), which employs READ codes to summarise the details of the RSV diagnoses. READ codes could be used individually or in combination to describe International Classification of Diseases (ICD) codes. Taylor and colleagues employed expert elicitation to convert the READ codes into ICD codes. The authors focused on acute respiratory infections and limited the pathogens to either RSV or influenza during this process.

Similarly, Cromer and colleagues calculated the number of healthcare contacts attributable to RSV infections using regression techniques accounting for laboratory reports. However, Cromer and colleagues' statistical model used all respiratory pathogens instead of focusing on RSV and influenza, as Taylor and colleagues did. Although the lack of a direct link between administrative and laboratory datasets limits both analyses, we preferred the data generated by Cromer and colleagues since it did not rely on expert elicitation and included all respiratory pathogens. In addition, Cromer and colleagues' data fit better with our subgroup analysis. While Taylor and colleagues reported data for individuals younger than 18, Cromer and colleagues focused on children under five. Likewise, although Taylor and colleagues did not stratify their results by gestation age, this information is available in Cromer and colleagues' study.

Table 4: Key assumptions

	Assumption
1	RSV incidence in 2019 was comparable to the incidence observed by Cromer and colleagues (2001/7).
2	Healthcare resource use per child associated with RSV in 2019 is not different from 2001/7 estimates.
3	Healthcare resource use per case associated with RSV is constant across deprivation groups.
4	Deprivation distribution in the UK RSV population is comparable to the Scottish RSV population.
5	Travelling time due to GP visits is 63 minutes per round trip [7].
6	Hospitalisations lead to eight hours of productivity loss per day spent in hospital.

Our analysis was performed in four steps. First, we extracted the data on resource use (e.g. GP visits, hospitalisations) and events (e.g. deaths) used by Cromer and colleagues, which focused on the English population [7]. Second, we extrapolated Cromer and colleagues' data to the UK population. Third, we performed a Monte Carlo simulation to synthesise the parameters used in our model and, thus, obtain an estimate of the burden of RSV in the UK. Fourth, we tested the robustness of our results by varying key parameter and assumption values, as summarised in Table 4.

B.1.1. Step 1: Cromer and colleagues' study features and data extraction

Cromer and colleagues' approach relied on the weekly count of pathogens obtained from Public Health England's LabBase2 database, including influenza A, influenza B, RSV, parainfluenza, adenovirus, rhinovirus, Streptococcus pneumoniae, Mycoplasma pneumoniae and Haemophilus influenzae. The weekly counts of these pathogens were used as an independent variable to assess the proportion of healthcare consumption attributable to RSV patients.

Cromer and colleagues described the overall number of healthcare outcomes and their annual incidence rate per 100 individuals. Outcomes included GP visits, hospital admissions and hospital deaths due to acute respiratory diseases. Data on primary care access was limited to GP visits and obtained from the Royal College of General Practitioners' (RCGPs') Weekly Returns Service, limiting the data to lower or upper respiratory tract infections. Data on hospitalisations and deaths within 30 days of discharge were obtained from the Hospital Episode Statistics (HES) database using the ICD-10 codes J0*, J1*, J2*, J3*, J40*, J41*, J42*, J43*, J44*, J47*. These hospitalisations were further divided by care intensity, namely intensive care unit (ICU) vs non-ICU stays. Full details on Cromer et al.'s data and statistical methods are available online [7].

Besides the data collected and presented by Cromer and colleagues, we included other items of resource consumption: (a) number of calls to NHS 111, (b) outpatient visits, and (c) out-of-pocket costs.

We obtained data on the number of calls to NHS 111 (by call reason) from the manuscript authored by Morbey and colleagues [21] and tested their association with RSV laboratory reports. Our analysis focused on cough (number of calls, n=637,552), difficulty breathing (n=590,065) and cold/flu (n=107,844) since these were the only reasons significantly associated with RSV. Our model calculated the proportion of these calls attributable to RSV: 21%, 15% and 12% for cough, difficulty breathing and cold/flu, respectively.

Our REA (see Annex A) did not identify relevant publications for modelling the number of RSV-related outpatient visits. Therefore, we consulted a panel of experts to model the number of outpatients visits in our study population. Based on this expert elicitation exercise, we assumed that a proportion of patients accessing the intensive care units (i.e. NICU and PICU) required specialist visits for post-discharge follow-up. To estimate the number of outpatient visits, we calculated the ratio between the number of outpatient attendances due to paediatric respiratory medicine (service code: 258) and non-elective stays (long- and short-term) for those HRG codes plausibly linked to paediatric respiratory medicine. Given that the outpatient visits falling within the paediatric respiratory medicine code could involve numerous reasons beyond acute bronchiolitis, we considered non-elective hospitalisations for the following reasons:

- Paediatric - Acute Upper Respiratory Tract Infection or Common Cold
- Paediatric - Asthma or Wheezing
- Paediatric - Lower Respiratory Tract Disorders without Acute Bronchiolitis
- Paediatric - Acute Bronchiolitis
- Paediatric - Upper Respiratory Tract Disorders
- Paediatric - Cystic Fibrosis.

The corresponding HRG codes describing these hospitalisation reasons were PD11A, PD11B, PD11C, PD12A, PD12B, PD12C, PD14A, PD14B, PD14C, PD14D, PD14E, PD14F, PD15A, PD15B, PD15C, PD15D, PD65A, PD65B, PD65C, PD65D, PD13A, PD13B, PD13C and PD13D. As a result, the ratio between the number of paediatric respiratory medicine outpatient visits (100,414) and the number of non-elective hospitalisations mentioned above (192,170) was 0.52. Therefore, our model assumed that half of the hospitalisations requiring intensive care led to one outpatient visit.

As with outpatient attendances, our REA did not identify a suitable publication reporting the size of out-of-pocket costs in the UK population associated with RSV in children aged less than five years. Therefore, we used the data reported in a recent systematic review authored by Zhang and colleagues [30]. In particular, we used out-of-pocket costs in Germany and the Netherlands, assuming that their relative impact on direct cost approximates the out-of-pocket cost for UK children affected by RSV [30].

We extracted the averages and standard errors (SEs) from Cromer and colleagues' study and, where the SEs were not available, used the 95% confidence intervals (95% CI) to back-calculate them [7].

B.1.2. Step 2: Extrapolating to the UK population and costing

One of the key differences between our analysis and Cromer and colleagues' study is the population of interest. While Cromer and colleagues focused on England, our analysis considered the whole of the UK. To extrapolate Cromer's data to the UK population, we first calculated the overall number of patients included in their analysis (calculation A), which refers to the English population from 2000 to 2008. Then, we used Office of National Statistics (ONS) data to calculate the ratio between the UK and English population in 2019 and between 2000 and 2008 (calculation B). We performed these calculations for the two age categories Cromer and colleagues used: less than six months and six months to less than five years. We then applied these ratios (calculation B) to the overall number of children used in Cromer's analysis (calculation A) to extrapolate the data on the UK population, assuming constant RSV incidence over time. We performed our analysis using the 2019 population due to concerns that the social distancing measures used during the COVID-19 pandemic post-2019 could undermine our assumption about RSV incidence.

Once we extrapolated healthcare-resource use to UK levels, we calculated the costs from a societal perspective.

We obtained direct NHS costs by multiplying the number of resources used by unit costs reflecting the NHS tariffs (measured in GBP 2020/21), listed in Table 7. The cost of non-ICU hospitalisations was obtained by calculating the weighted average across the Health-Related Groups (HRG) codes for paediatric Acute Bronchiolitis, namely PD15A, PD15B, PD15C and PD15D. The cost of ICU hospitalisation was calculated by age group. For infants aged less than six months, we used the codes for stays in a Neonatal Intensive Care Unit (NICU), namely XA01Z, XA02Z, XA03Z and XA04Z. For children aged between six months and five years, we used the codes for stays in a Paediatric Intensive Care Unit (PICU), namely XB01Z, XB02Z, XB03Z, XB04Z and XB05Z. We obtained the cost of outpatient visits using the service code 258.

In addition to the direct NHS cost, we considered the out-of-pocket costs as a percentage of the healthcare cost by applying the average between German (0.7% and 3.8% of total healthcare cost) and Dutch (2.3% of total healthcare cost) estimates, i.e. 2.27%.

Our estimates of productivity loss were obtained from the duration of each contact (i.e. GP visits, hospital stays and outpatient visits) and the relative travelling time involved. For GP visits, the travelling time was assumed to be comparable to the time spent by parents attending antenatal tests in the UK [34]. Therefore, the overall time spent by a parent for each GP visit was 72 minutes, comprising 9 minutes for the visit and 63 minutes travelling there and back. For hospitalisations, we assumed that each day spent by children in the hospital corresponded to eight hours of productivity loss for one parent. Hospitalisation durations were assumed to equal those observed by Pockett and colleagues, who reported the length of hospitalisation in vulnerable and non-vulnerable children infected by RSV [35]. Thus, we calculated the hospital length of stay (LOS) for pre-term and at term infants assuming they were comparable to vulnerable or non-vulnerable children, respectively. We calculated the LOS by child's age: LOS for children aged between six months and five years were 1.97 and 8.92 days for at-term and pre-term children, respectively. We multiplied the overall time needed per contact by the average UK salary in 2021. It was assumed that parents of infants aged less than six months did not occur any productivity loss on the assumption that one of them would be on parental leave when the child was that young.

The impact of RSV on quality of life was calculated using the data reported by Hodgson and colleagues, who captured the loss of Quality Adjusted Life Years (QALYs) per RSV episode that needed a contact with healthcare services [4]. Therefore, Hodgson and colleagues' estimates were applied to those children making a contact with NHS regardless of the level of care needed (e.g. primary, secondary care).

Table 5: Unit costs (£ in 2020/21 price terms)

	Unit cost	Source
GP visit (per visit)	£34	PSSRU
NHS 111 call	£2.80	PSSRU
Outpatient visit	£229	NHS Reference cost
Hospitalisation (per stay)		
NICU	£2,289	NHS Reference cost
Non-NICU	£1,356	NHS Reference cost
PICU	£4,274	NHS Reference cost
Non-PICU	£1,356	NHS Reference cost
Average UK salary (per minute)	£0.26	ONS

Sources: [36-38]

B.1.3. Step 3: Statistical analysis

We performed a Monte Carlo simulation to account for the uncertainty around all parameters used in our analysis and the model's non-linearity (due to data sampling).

A thousand simulations were drawn to calculate the mean values and 95% confidence intervals (CI). The complete list of parameters and associated distribution functions are reported in Table 6.

Table 6: List of parameters

	Mean	Standard Error	Distribution	Source
Age of child less than six months				
Direct costs				
GP visits – annual rate	0.214	0.001	Normal	Cromer and colleagues 2017[7]
Hospitalisations - annual rate	0.044	0.0001	Normal	Cromer 2017[7]
Deaths - annual rate	0.00002	0.000001	Normal	Cromer 2017[7]
Proportion of hospitalisations requiring ICU among infants born pre-term	0.090	0.029	Beta	Cromer 2017[7]

	Mean	Standard Error	Distribution	Source
Proportion of hospitalisations requiring ICU among infants born at term	0.018	0.006	Beta	Cromer 2017[7]
Proportion of NHS 111 calls due to cough	0.21	0.0005	Beta	Morbey 2017
Proportion of NHS 111 calls due to difficulty breathing	0.15	0.0005	Beta	Morbey 2017
Proportion of NHS 111 calls due to cold/flu	0.12	0.0010	Beta	Morbey 2017
Age of child between six months and five years				
Direct costs				
GP visits - annual rate	0.109	0.001	Normal	Cromer 2017[7]
Hospitalisations - annual rate	0.005	0.00003	Normal	Cromer 2017[7]
Deaths - annual rate	0.00001	0.0000001	Normal	Cromer 2017[7]
Proportion of hospitalisations requiring ICU – pre-term infants	0.018	0.006	Beta	Cromer 2017[7]
Proportion of hospitalisation requiring ICU – at term infants	0.018	0.006	Beta	Cromer 2017[7]
Indirect costs				
Time (minutes) per GP visit (including travelling time)	72.330	28.9322	Gamma	Verhoef 2016; PSSRU
Time (minutes) per hospitalisation pre-term	4283.02	NA1	NA1	Pockett 2013
Time (minutes) per hospitalisation at term	947.02	NA1	NA1	Pockett 2013
Proportion of NHS 111 calls due to cough	0.21	0.0005	Beta	Morbey 2017
Proportion of NHS 111 calls due to difficulty breathing	0.15	0.0005	Beta	Morbey 2017
Proportion of NHS 111 calls due to cold/flu	0.12	0.0010	Beta	Morbey 2017
QALY loss for RSV episode	0.00382	0.0034	Beta	Hodgson 2020

[1] The uncertainty surrounding the length of hospitalisation was computed considering the regression parameters reported by Pockett and colleagues. Thus, we modelled the uncertainty for each regression coefficient using a normal distribution.

[2] We calculated the standard deviation by assuming a variation coefficient equal to 40%.

B.1.4. Step 4: Subgroups and sensitivity analysis

The subgroups considered in our analysis included age (i.e. less than six months vs six months to five years), gestational age (i.e. born pre-term vs at term) and socioeconomic status (i.e. deprivation index). While the data on age and gestational age were available in Cromer and colleagues' study, the data on socioeconomic status were obtained from a Scottish study using administrative data [25]. Thwaites and colleagues determined the socioeconomic status categorised using quintiles of the Scottish Index of Multiple Deprivation (SIMD), where '1' represents the most deprived and '5' the least deprived quintile.

We tested the most important assumptions and parameters using a one-way sensitivity analysis. Each sensitivity analysis was performed by sampling 1,000 simulations per the base case. The assumptions and parameters tested in our sensitivity analyses included: (i) the number of GP visits attributable to RSV, (ii) death rate, (iii) RSV incidence, (iv) parents of infants aged less than six months were on parental leave, and (v) cost for children between zero months and one year. Given the absence of a direct link between healthcare resource use and pathogen reports datasets, we tested the impact of using a different approach to link these datasets than our base case. To do this, we used the data reported by Taylor and colleagues. Similarly, we ran our analyses using the death rate reported by Taylor and colleagues. We assumed a constant RSV incidence across the years equal to Cromer and colleagues' estimates. To test the impact of alternative RSV incidence rates, we updated our model to reflect RSV incidence observed in the Bradford cohort study [2]. Our base case assumed that parents of children aged under six months were on parental leave. To test this assumption, we simulated a scenario where parents of infants aged less than six months were not on parent leave and, thus, experienced productivity loss.

Our base case focused on two age subgroups, less than six months and between six months and five years, which reflect the available data in the literature. This sensitivity analysis considered a different age subgroup, namely children aged between zero months and one year. To do so, we made assumptions on (a) the number of infants between six months and one year and (b) their healthcare resource use. For (a), it was assumed that the number of infants aged between six months and one year is comparable to the number of infants aged less than six months. This assumption relies on the low mortality due to RSV in the subgroup aged less than six months. To model the resource consumption for infants aged between six months and one year, we used the data from Taylor and colleagues' publication [6]. The data showed in Taylor and colleagues' publication stratified the numbers of GP visits and hospitalisations for age groups including (b.i) less than six months, (b.ii) 6–24 months. In our sensitivity analysis, we assumed that the resource use of infants aged 6–12 months is comparable to those aged 6–24 months. Then, we calculated the ratio between the numbers of GP visits and hospitalisations for (b.ii) and (b.i), which was then applied to the numbers of GP visits and hospitalisations simulated in our base case for infants aged less than six months.

B.2. Results

B.2.1. Overall

The overall annual number of GP visits, NHS 111 calls, hospitalisations and outpatient visits due to RSV in UK children aged less than five years were 467,230 (95% CI: 461,539 to 472,538), 235,344 (95% CI: 234,523 to 236,204), 33,937 (33,752 to 34,132) and 409 (95% CI: 281 to 577), respectively. See Table 7.

We estimate that the overall annual number of deaths attributable to RSV in this age group was 32.59 (95% CI: 31.80 to 33.36) (Table 7).

A breakdown of the resources used and deaths by age and gestational age is presented in Table 7. The monetisation of these healthcare resources corresponded to an annual total cost of RSV to the NHS in the UK in children aged less than five years of **£66,021,274** (95% CI: £65,223,446 to £66,985,880).

When the parents' productivity loss was added to this figure, the overall burden of RSV increased to **£80,218,822** (95% CI: £75,476,062 to £86,871,417). The mean total cost per child was **£97** (95% CI: £91.56 to £105.00).

The overall QALYs loss per year estimated by our model was 3,137 (95% CI: 1,334 to 6,047).

Table 7: Overall annual resource use per age group and gestational age

	Resource used [Average (95% Confidence Intervals)]		
	Less than six months	Six months to less than five years	Less than five years
GP visits	78,513 (77,446 to 79,601)	388,716 (383,085 to 393,856)	467,230 (461,539 to 472,538)
birth at term	65,778 (63,205 to 68,245)	325,665 (312,658 to 338,332)	391,443 (375,989 to 406,312)
birth pre-term	12,736 (10,447 to 15,202)	63,051 (51,837 to 75,218)	75,787 (62,368 to 90,428)
NHS 111 calls	24,139 (24,018 to 24,261)	211,205 (210,436 to 211,975)	235,344 (234,523 to 236,204)
birth at term	20,224 (19,463 to 20,927)	176,946 (170,311 to 183,055)	197,170 (189,732 to 203,918)
birth pre-term	3,916 (3,215 to 4,685)	34,258 (28,149 to 40,952)	38,174 (31,369 to 45,637)
Hospitalisations	16,128 (16,052 to 16,197)	17,809 (17,636 to 17,994)	33,937 (33,752 to 34,132)
ICU	467 (275 to 720)	315 (170 to 513)	783 (538 to 1,104)
Non-ICU	15,661 (15,404 to 15,873)	17,494 (17,237 to 17,725)	33,154 (32,822 to 33,480)
birth at term	13,512 (13,013 to 13,980)	14,920 (14,348 to 15,468)	28,432 (27,356 to 29,429)
ICU	236 (111 to 419)	264 (125 to 467)	500 (300 to 774)
Non-ICU	13,276 (12,740 to 13,771)	14,656 (14,049 to 15,197)	27,932 (26,873 to 28,942)
birth pre-term	2,616 (2,150 to 3,125)	2,889 (2,371 to 3,455)	5,505 (4,528 to 6,571)
ICU	231 (111 to 407)	50.98 (23.09 to 91.58)	282 (155 to 475)
Non-ICU	2,385 (1,912 to 2,884)	2,838 (2,326 to 3,389)	5,223 (4,260 to 6,262)

	Resource used [Average (95% Confidence Intervals)]		
	Less than six months	Six months to less than five years	Less than five years
Outpatient visits	244 (144 to 376)	165 (88.84 to 268)	409 (281 to 577)
birth at term	204 (122 to 313)	138 (75.10 to 223)	342 (235 to 481)
birth pre-term	39.77 (21.53 to 65.12)	26.72 (13.91 to 44.50)	66.49 (42.14 to 100)
Deaths due to RSV	9.08 (8.69 to 9.46)	23.51 (22.83 to 24.17)	32.59 (31.80 to 33.36)
birth at term	7.61 (7.20 to 8.02)	19.70 (18.76 to 20.62)	27.30 (26.06 to 28.51)
birth pre-term	1.47 (1.20 to 1.77)	3.81 (3.11 to 4.54)	5.29 (4.33 to 6.30)

A breakdown of the resources used, costs and QALYs lost by age group, gestational age group and socioeconomic status quintile is presented in Table 8 and Annex D-Annex I and Annex K, respectively.

B.2.2. By age

Children aged between six months and five years used 60% of the healthcare resources used in children younger than five years old. While the number of hospitalisations was distributed evenly across the age groups, children six months to less than five years accounted for more than 80% of the overall number of GP visits. The proportions of hospitalisations requiring intensive care were 3% and 2% for infants aged less than six months and children aged six months to less than five years, respectively. Only a tenth of the NHS 111 calls and 60% of the outpatient visits were simulated in the subgroup including children aged less than six months.

Overall, the annual total cost of RSV to the UK in children aged less than six months and between six months and five years was £26,420,276 (95% CI: £25,876,844 to £27,121,150) and £53,798,546 (95% CI: £49,148,055 to £60,448,944), respectively. Thus, the mean cost per child for these subgroups were £344 (95% CI: £336 to £353) per child aged up to six months and £72 (95% CI: £66 to £81) per child aged between six months and five years. See Table 8. While the QALYs loss for infants aged less than six months was 295 QALYs (95% CI: 107 to 565), children aged six months to less than five years accounted for the majority of QALY loss (91%), namely 2,842 QALYs (95% CI: 1,053 to 5,782)

Table 8: Overall annual cost per age group and gestational age

	Cost (£) [Average (95% Confidence Intervals)]		
	Less than six months	Six months to less than five years	Less than five years
Overall cost	26,420,276 (25,876,844 to 27,121,150)	53,798,546 (49,148,055 to 60,448,944)	80,218,822 (75,476,062 to 86,871,417)
birth at term	21,723,369 (20,851,639 to 22,609,316)	42,974,987 (38,607,422 to 48,844,822)	64,698,356 (59,864,931 to 70,928,275)
birth pre-term	4,696,907 (3,826,324 to 5,752,087)	10,823,559 (8,700,480 to 13,255,954)	15,520,466 (12,674,258 to 18,880,593)
Healthcare costs	26,420,276 (25,876,844 to 27,121,150)	39,600,998 (39,031,419 to 40,272,426)	66,021,274 (65,223,446 to 66,985,880)
birth at term	21,723,369 (20,851,639 to 22,609,316)	33,178,016 (31,891,040 to 34,561,244)	54,901,385 (52,841,676 to 57,019,504)
birth pre-term	4,696,907 (3,826,324 to 5,752,087)	6,422,981 (5,271,775 to 7,682,691)	11,119,888 (9,116,343 to 13,255,889)
GP visits	2,630,197 (2,594,434 to 2,666,620)	13,021,994 (12,833,337 to 13,194,185)	15,652,190 (15,461,570 to 15,830,007)
birth at term	2,203,555 (2,117,357 to 2,286,202)	10,909,775 (10,474,058 to 11,334,137)	13,113,330 (12,595,643 to 13,611,451)
birth pre-term	426,641 (349,969 to 509,263)	2,112,219 (1,736,538 to 2,519,797)	2,538,860 (2,089,337 to 3,029,354)
NHS 111 calls	67,590 (67,249 to 67,931)	591,373 (589,221 to 593,530)	658,963 (656,664 to 661,372)
birth at term	56,627 (54,496 to 58,595)	495,449 (476,870 to 512,554)	552,076 (531,250 to 570,970)
birth pre-term	10,964 (9,002 to 13,119)	95,924 (78,818 to 114,666)	106,887 (87,834 to 127,784)
Hospitalisations	23,080,964 (22,573,785 to 23,725,988)	25,072,154 (24,561,303 to 25,684,381)	48,153,118 (47,409,626 to 49,042,530)
ICU	1,842,484 (1,085,933 to 2,839,395)	1,347,731 (726,566 to 2,194,305)	3,190,216 (2,179,585 to 4,503,382)
Non-ICU	21,238,480 (20,890,531 to 21,526,400)	23,724,422 (23,376,836 to 24,038,113)	44,962,902 (44,511,807 to 45,404,081)
birth at term	18,934,877 (18,144,380 to 19,730,720)	21,005,798 (20,128,258 to 21,975,701)	39,940,674 (38,353,913 to 41,591,548)

	Cost (£) [Average (95% Confidence Intervals)]		
	Less than six months	Six months to less than five years	Less than five years
ICU	930,555 (437,469 to 1,652,836)	1,129,845 (534,120 to 1,997,830)	2,060,400 (1,241,123 to 3,168,268)
Non-ICU	18,004,321 (17,277,837 to 18,675,303)	19,875,953 (19,053,027 to 20,609,640)	37,880,274 (36,444,809 to 39,250,220)
birth pre-term	4,146,088 (3,367,394 to 5,089,785)	4,066,356 (3,344,028 to 4,862,164)	8,212,444 (6,714,293 to 9,876,685)
ICU	911,929 (437,984 to 1,604,075)	217,887 (98,684 to 391,360)	1,129,816 (624,819 to 1,881,651)
Non-ICU	3,234,159 (2,593,142 to 3,910,691)	3,848,469 (3,154,293 to 4,595,569)	7,082,628 (5,777,222 to 8,492,636)
Outpatient visits	55,938 (32,969 to 86,204)	37,750 (20,351 to 61,463)	93,688 (64,452 to 132,135)
birth at term	46,827 (27,992 to 71,794)	31,628 (17,205 to 51,056)	78,455 (53,932 to 110,116)
birth pre-term	9,111 (4,933 to 14,918)	6,122 (3,186 to 10,195)	15,233 (9,653 to 22,824)
Out-of-pocket costs	585,586 (573,542 to 601,121)	877,727 (865,103 to 892,609)	1,463,314 (1,445,630 to 1,484,694)
birth at term	481,483 (462,161 to 501,119)	735,367 (706,842 to 766,025)	1,216,849 (1,171,198 to 1,263,796)
birth pre-term	104,104 (84,808 to 127,491)	142,361 (116,845 to 170,281)	246,464 (202,057 to 293,807)
Productivity loss (PL)	-	14,197,549 (9,550,737 to 20,971,838)	14,197,549 (9,550,737 to 20,971,838)
birth at term	-	9,796,971 (5,848,772 to 15,458,481)	9,796,971 (5,848,772 to 15,458,481)
birth pre-term	-	4,400,578 (3,342,383 to 5,855,154)	4,400,578 (3,342,383 to 5,855,154)
PL due to GP and outpatient visits	-	7,297,427 (2,639,776 to 13,932,675)	7,297,427 (2,639,776 to 13,932,675)
birth at term	-	6,114,427 (2,225,988 to 11,516,349)	6,114,427 (2,225,988 to 11,516,349)
birth pre-term	-	1,183,000 (442,543 to 2,299,881)	1,183,000 (442,543 to 2,299,881)

	Cost (£) [Average (95% Confidence Intervals)]		
	Less than six months	Six months to less than five years	Less than five years
PL due to hospitalisations	-	6,900,121 (5,827,008 to 7,940,603)	6,900,121 (5,827,008 to 7,940,603)
ICU	-	122,092 (72,119 to 188,173)	122,092 (72,119 to 188,173)
Non-ICU	-	6,778,029 (5,710,977 to 7,795,371)	6,778,029 (5,710,977 to 7,795,371)
birth at term	-	3,682,543 (2,831,766 to 4,506,515)	3,682,543 (2,831,766 to 4,506,515)
ICU	-	65,297 (29,565 to 119,224)	65,297 (29,565 to 119,224)
Non-ICU	-	3,617,247 (2,781,454 to 4,413,565)	3,617,247 (2,781,454 to 4,413,565)
birth pre-term	-	3,217,578 (2,630,066 to 3,862,087)	3,217,578 (2,630,066 to 3,862,087)
ICU	-	56,795 (25,209 to 101,644)	56,795 (25,209 to 101,644)
Non-ICU	-	3,160,783 (2,580,755 to 3,787,845)	3,160,783 (2,580,755 to 3,787,845)

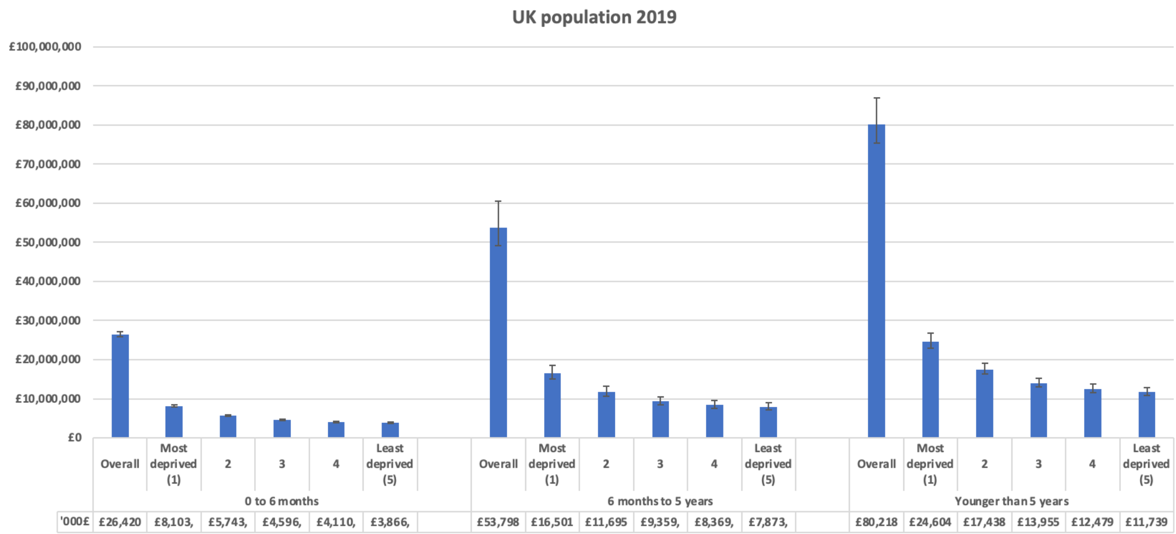
B.2.3. Gestational age

Overall, pre-term children contributed 19% of the burden of RSV, with a similar impact across the age groups (18% for those aged below six months; 20% in those six months to five years). In infants aged less than six months, 50% of the hospitalisations requiring intensive care involved pre-term infants. In children aged between six months and five years, the proportion of hospitalisations requiring intensive care that involved pre-term infants dropped to 16%. Conversely, children aged between six months and five years accounted for 84% of the QALYs loss.

B.2.4. Socioeconomic status

Figure 2 depicts the distribution of the RSV burden according to children's socioeconomic status. Overall, the cost was higher in the most deprived groups (i.e. a deprivation index group equal to or lower than three). However, the statistical significance of these between-group differences depended on children's age. The cost difference in children aged less than six months was statistically significant across all the socioeconomic statuses, except for the least deprived groups (i.e. groups four and five). Across the most deprived groups (i.e. less or equal to group three), all the differences

Figure 2: Societal cost by socioeconomic status (i.e. deprivation index).



registered in children aged between six months and five years were significant. The differences in QALYs lost across the socioeconomic status subgroups were not statistically significant.

A breakdown of the resource use, costs and QALYs per socioeconomic status is shown in Annex D and Annex I and Annex K.

B.2.5. Sensitivity analysis

As a sensitivity test, using the data reported by Taylor and colleagues rather than by Cromer and colleagues simulated a statistically-significant reduction in GP-visit costs but no statistically significant difference in the overall number of deaths compared to our base case. The lower GP-visit costs led to a statistically lower overall cost in infants aged less than six months (average: £24,739,198; 95% CI: £24,160,015 to £25,438,788) compared to our base case. However, Taylor and colleagues' data did not change our conclusions on the burden of RSV in children aged between six months and five years (average: £49,781,969; 95% CI: £45,353,492 to £55,772,175). Likewise, using the death rates reported by Taylor and colleagues did not change our conclusions for infants aged less than six months (average: 7.36; 95% CI: 1.14 to 16.19) or for children aged six months to five years (average: 48.55; 95% CI: 5.00 to 111.00). Further details on these sensitivity analyses results, including the outputs for children younger than five years, are reported in Annex J.

Varying the incidence rate of RSV infections led to statistically significant results. Alternative epidemiological estimates suggested an RSV incidence rate of up to 53% (47% to 59%) and 33% (26% to 41%) in infants aged less than six months and children aged between six months and five years, respectively [2]. Using these incidence rates led to an estimated overall cost of £151,064,486 (95% CI: £130,384,713 to £175,480,451) for children younger than five years. Given the different incidence rates used for age subgroups, the cost for infants aged less than six months and children aged between six months and five years were £66,747,827 (95% CI: £59,357,959 to £74,526,611) and £84,316,658 (95% CI: £64,661,640 to £107,091,823), respectively.

Including productivity losses for parents of infants aged less than six months led to a statistically significant increase in the overall annual cost (NHS costs plus the costs of productivity losses) for that age group (average: £33,867,253; 95% CI: £32,456,236 to £35,545,562) compared to the base case (average: £26,420,276; 95% CI: £25,876,844 to 27,121,150).

Simulating the age subgroup between 6 months to 1 year led us to estimate an overall annual cost of £13,085,029 (95% CI: 11,799,619 to 14,853,799), of which 25% was attributable to productivity losses. As a result, the cost per child aged between 6 months and 1 year was £170 (95% CI: £153 to £193). Therefore, the overall cost and cost per child aged between 0 months and 1 year were £39,515,497 (95% CI: £37,931,636 to £41,396,836) and £257 (95% CI: £247 to £269), respectively.

B.3. Discussion of model results and conclusion

Our analysis estimated the societal RSV burden in British children aged younger than five years, with parental productivity losses exerting a relevant impact. We estimated that in 2019 the total NHS cost plus parents' productivity losses resulting from RSV in children younger than five years in the UK amounted to approximately £80 million, with productivity losses contributing up to 18%. Likewise, our analysis suggests that 3,137 QALYs were lost because of RSV in children younger than five years – of which 91% is experienced by children aged between six months and five years.

Although children aged between six months and five years accounted for 67% of the overall annual cost of RSV in children under five, this result reflects the much larger numbers in this age group than in those aged 0–6 months. Indeed, the cost per child ranges from £72 (95% CI: £66 to £81) for children aged between six months and five years to £344 (95% CI: £336 to £353) for children aged less than six months. RSV is likely to be a disproportionately larger burden for infants during their first six months, particularly since their secondary-care use accounts for almost 87% of their overall annual cost.

Although our analysis' societal perspective is a key strength, it also complicates comparisons with previous research, since most did not consider indirect costs. Excluding the productivity losses from our estimates, the average healthcare cost per child younger than five years (£80.11; 95% CI: £79.12 to £81.30) was £7.47 less than Cromer's estimates (£87.58; 95% CI: £82.00 to £93.00), even though our analysis included calls to NHS 111 and outpatient visits, which Cromer and colleagues study did not. This difference was observed because of the unit costs used in our analysis. In particular, Cromer and colleagues costed hospitalisations requiring intensive care using the 'paediatric advance critical care 5' cost, regardless of children's age. In our analysis, the unit costs for hospitalisations requiring intensive care were age-specific and calculated according to the number of NHS registered activities by different intensity levels [37]. This approach yielded substantially different unit costs (i.e. NICU: £2,289; PICU: £4,274) from those used by Cromer and colleagues (NICU and PICU: £7,920).

As noted above, our REA identified another study that captured UK RSV-related resource consumption in children younger than five: Taylor and colleagues' analysis [6]. Although their analysis did not monetise resource consumption, we used their data in the sensitivity analysis to investigate the impact of a different approach to linking RSV to GP visits and mortality. Using Taylor and colleagues' calculated annual rate of GP visits in our model estimated a lower number of GP visits than our base case, resulting in a small (i.e. less than 7%) but statistically significant reduction of the estimated RSV burden in infants aged less than six months. There are multiple reasons behind this difference, as outlined below.

First, our analysis relies on Cromer and colleagues' data [7], generated using different datasets and methods from Taylor and colleagues' data. While Cromer and colleagues used RCGP data to identify the GP visits related to RSV, Taylor and colleagues employed the CPRD. Another difference between these studies is the method used to calculate the number of GP visits related to RSV infections. Although both studies used laboratory reports and regression analysis to establish a link with RSV, Taylor and colleagues relied on expert elicitation to convert the codes used in the CPRD (i.e. READ codes) into ICD codes. This process probably led to a different classification of the GP visit attributable to RSV and, thus, a different overall number of GP visits due to RSV. Nevertheless, this difference in GP visits was not sufficiently large to change our conclusions on the overall burden of RSV.

Using the death rates reported by Taylor and colleagues did not lead to statistically significant differences. While it doubled the mean number of deaths simulated in children aged between six months and five years, this difference was not statistically significant. This is because the computed confidence intervals around the number of deaths obtained using Taylor and colleagues' data are wider than those obtained using Cromer and colleagues' data. Therefore, this difference is due to the precision employed in reporting the results in these publications.

One source of uncertainty that may limit the reliability of our estimates concerns the RSV incidence rate. Since RSV infections may not present sufficient severity to justify further diagnostic tests, the actual number of RSV cases may be underreported. Although this limitation is common to all RSV research, we tried to mitigate it by using data from studies that attempted to establish a link between the laboratory reports and the administrative databases. We also performed a sensitivity analysis to investigate the implication of varying RSV incidence. Using higher incidence estimates than our base case led to doubling the estimated burden of RSV in children younger than five years.

Likewise, our base case assumed that parents of RSV infants aged less than six months were on parental leave, which does not necessarily reflect the UK parents of children affected by RSV. Thus, we performed a sensitivity analysis where parents of children affected by RSV were back at work and, thus, incurred productivity losses when their child was ill with RSV – resulting in a statistically significant 28% increase in the burden.

Finally, we performed a scenario analysis to simulate the burden in children aged between 0–12 months. Based on our calculations, this age group accounts for 49% of the overall burden of RSV in UK children younger than five.

The burden of RSV is large and unevenly distributed across children younger than five years, with indirect costs playing a role in RSV infections among children older than six months. Nevertheless, secondary care accounts for most of the economic burden, culminating in 90% of the total healthcare cost in infants younger than six months, suggesting a worse prognosis than older children. New healthcare technologies are needed to curb the considerable economic burden of RSV infection, especially in younger infants where RSV infections require more expensive care, such as hospital care.

Annex C. Summary of reviewed literature

Author	Year	Article type	Methodology	Country	Setting	Population age group	Number of participants
Brunwasser et al.	2020	Systematic review and meta-analysis (57 articles describing 42 studies)	Systematic review and meta-analysis	Netherlands, USA, Japan, Spain, Germany, Canada, Poland, Sweden, Israel, Denmark, Brazil, Finland, Norway, UK, South Korea, Qatar, The Gambia, France, Chile, Kenya and Australia.	Unclear	Children with RSV before age two, ending before age five	Unclear
Carbonell-Estrany et al.	2018	Original article	Observational, non-interventional study (parent and healthcare professional meetings and questionnaire)	Spain (Madrid and Bilbao) and Italy (Turin and Verona)	Hospital inpatients	Children under two years with RSV	161 total (105 parents and 56 healthcare professionals)
Cromer et al.	2017	Original article	Multivariate regression analysis and cost-effectiveness analysis	England	Primary care and inpatients	Children under five with RSV	Unclear
Coutts et al.	2020	Original article	Analysis of administrative data	Scotland	Hospital inpatients	Children hospitalised with RSV in their first two years of life and followed until age 18	740,418 children total (15,795 children with RSV)
Díez-Domingo et al.	2014	Non-systematic review article (89 studies)	Literature review	Unclear	Primary care and hospital inpatient predominantly	All RSV patients	Unclear

Author	Year	Article type	Methodology	Country	Setting	Population age group	Number of participants
Fitzpatrick et al.	2021	Original article	Time-series modelling	Scotland	Primary care	Children under five years (with and without RSV)	6,066,492 antibiotic prescriptions among 452,877 children
Foley et al.	2019	Original article	Retrospective case review	New Zealand	Hospital inpatient (one hospital)	Children under two years with bronchiolitis	556 bronchiolitis events corresponding to 434 infants
Gates et al.	2019	Systematic review (29 studies)	Systematic review	Israel, USA, Brazil, France, Spain, Norway, Netherlands, Bangladesh, Italy, Canada, UK, Malaysia, China and Australia	Unclear	Parents or caregivers of infants with bronchiolitis (exact age range not specified)	27,059 parents or caregivers
Harcourt et al.	2019	Original article	Moving Epidemic Method	England	Unclear	Children under five years	Unclear
Hardelid et al.	2019	Original article	Birth cohort study	Scotland	Hospital inpatients	Children up to three years	5,185 RSV admissions among 169,726 children
Heikkinen, Ojala and Waris	2017	Original article	Prospective cohort study	Finland	Outpatients	Children aged 13 and under	6,001 respiratory illnesses (302 RSV cases in 287 children)
Hodgson et al.	2020	Original article	Surveillance study	England	Unclear	Children under five years with confirmed RSV Siblings and parents (aged 5–14 and 15+) with suspected RSV	122 aged 0-4 years with confirmed RSV 33 aged 5-14 with suspected RSV 54 aged 15+ with suspected RSV
Iwane et al.	2013	Original article	Prospective, population-based study (interviews and review of medical records)	USA (Tennessee, New York, and Ohio)	Hospital inpatients	Children aged five and under	4,329 children with RSV total (230 black and 441 white children)

Author	Year	Article type	Methodology	Country	Setting	Population age group	Number of participants
Li, Campbell and Nair	2020	Original article	Self-controlled case study series	Scotland	Unclear	Children aged under five	162 children with respiratory/circulatory deaths total (36 with RSV)
MacBean et al.	2018	Original article	Prospective cohort study	England	Primary Care	Children born at less than 36 weeks gestational age, assessed at a median of seven years	51 children total (10 with RSV)
Mitchell, Defoy and Grubb	2017	Original article	Descriptive study	Canada (Alberta)	Hospital inpatients	Children aged under one	67 infants with RSV
Morbey et al.	2017	Original article	Analysis of administrative data	England	Unclear	All ages	18.2 million NHS 111 calls transferred to PHE (2 million respiratory-related)
Paul et al.	2017	Original article	Epidemiological study	England	Hospital inpatients (one hospital)	Children under two years	319 children total (162 with RSV)
Pockett et al.	2013	Original article	Analysis of administrative data	England and Wales	Hospital (inpatient) readmissions	Children aged 0–4 years	365,693 admissions total for rotavirus, RSV or non-rotaviral gastroenteritis
Pokrzywinski et al.	2019	Original article	Secondary analysis of data collected for the SENTINEL1 study and parental questionnaire	USA	At hospital discharge and one week, two weeks and one-month post-discharge	Pre-term infants at 29–35 weeks gestational age	212 infants with RSV
Reeves et al.	2017	Original article	Ecological time series modelling	England	Hospital inpatients	Children aged up to four	121,968 children total (33,561 with RSV)

Author	Year	Article type	Methodology	Country	Setting	Population age group	Number of participants
Reeves et al.	2019	Original article	Data linkage modelling study	England	Hospital inpatients	Children aged under one	6,758 children total (2,947 with RSV)
Shi et al.	2017	Mixed methods	Systematic review and modelling study (326 articles, 329 studies)	Global	Multiple – mainly hospital inpatients	Children aged under five	Unknown
Taylor et al.	2016	Original article	Time-series regression modelling	UK	Primary care and inpatients	Children aged 0–17	Unknown
Thwaites et al.	2020	Original article	Analysis of administrative data	Scotland	Hospital inpatients	Children aged below two	623,770 children total (13,362 hospitalised with RSV)
Wrotek et al.	2020	Original article	Cohort study	Unknown	Hospital inpatients	Children aged up to 22 months	111 children with RSV
Yael Kopacz, Predeger and Kelley	2013	Original article	Qualitative descriptive study (interviews)	USA (Alaska)	Hospital inpatients (one hospital)	Mothers of infants and pre-school children (exact age not specified)	Six mothers
Zhang et al.	2020	Systematic review and meta-analysis (41 studies)	Systematic review and meta-analysis	Data from 5 WHO regions (all except African Region).	Unclear	Children aged up to five	365,828 RSV episodes
Zylbersztejn et al.	2021	Original article	Community cohort study	England	Community	Children under five years	477 aged below one 229 aged 1–2

Annex D. Overall annual resource use by deprivation index: 0–6 months

	Resource used [Average (95% Confidence Intervals)]: 0–6 months				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
GP visits	24,082 (23,366 to 24,801)	17,068 (16,516 to 17,662)	13,659 (13,152 to 14,214)	12,214 (11,687 to 12,725)	11,490 (10,998 to 12,021)
birth at term	20,175 (19,271 to 21,083)	14,299 (13,606 to 14,990)	11,444 (10,821 to 12,034)	10,233 (9,650 to 10,788)	9,626 (9,105 to 10,180)
birth pre-term	3,906 (3,220 to 4,674)	2,768 (2,260 to 3,294)	2,216 (1,803 to 2,672)	1,981 (1,635 to 2,364)	1,864 (1,510 to 2,222)
NHS 111 calls	7,404 (7,214 to 7,602)	5,248 (5,084 to 5,416)	4,200 (4,049 to 4,358)	3,755 (3,605 to 3,909)	3,533 (3,390 to 3,691)
birth at term	6,203 (5,929 to 6,470)	4,396 (4,177 to 4,605)	3,518 (3,336 to 3,693)	3,146 (2,969 to 3,315)	2,960 (2,801 to 3,125)
birth pre-term	1,201 (987 to 1,438)	851 (694 to 1,013)	681 (556 to 815)	609 (503 to 727)	573 (465 to 683)
Hospitalisations	4,947 (4,820 to 5,078)	3,506 (3,394 to 3,617)	2,806 (2,704 to 2,914)	2,509 (2,405 to 2,609)	2,360 (2,261 to 2,464)
ICU	143 (84.51 to 221)	102 (59.59 to 156)	81.29 (47.85 to 126)	72.70 (43.68 to 113)	68.40 (40.06 to 104)
Non-ICU	4,803 (4,665 to 4,942)	3,404 (3,281 to 3,526)	2,725 (2,614 to 2,836)	2,436 (2,328 to 2,535)	2,292 (2,191 to 2,396)
birth at term	4,144 (3,966 to 4,322)	2,937 (2,788 to 3,075)	2,351 (2,227 to 2,467)	2,102 (1,983 to 2,212)	1,977 (1,871 to 2,088)
ICU	72.40 (33.98 to 128)	51.29 (24.28 to 90.10)	41.06 (19.16 to 72.83)	36.71 (17.22 to 65.32)	34.55 (16.17 to 61.51)
Non-ICU	4,072 (3,895 to 4,252)	2,886 (2,740 to 3,028)	2,310 (2,179 to 2,425)	2,065 (1,942 to 2,178)	1,943 (1,836 to 2,055)
birth pre-term	802 (661 to 961)	569 (465 to 678)	455 (372 to 544)	407 (336 to 486)	383 (310 to 457)
ICU	70.95 (34.00 to 126)	50.27 (23.88 to 88.70)	40.23 (19.16 to 70.56)	35.98 (17.15 to 63.66)	33.85 (15.99 to 59.67)
Non-ICU	731 (588 to 890)	518 (413 to 625)	415 (331 to 502)	371 (298 to 451)	349 (279 to 424)

	Resource used [Average (95% Confidence Intervals)]: 0–6 months				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
Outpatient visits	74.90 (44.16 to 115)	53.07 (31.14 to 81.30)	42.47 (25.00 to 65.71)	37.99 (22.83 to 58.83)	35.74 (20.93 to 54.41)
birth at term	62.70 (37.44 to 96.14)	44.43 (26.31 to 67.51)	35.56 (21.34 to 54.14)	31.80 (19.15 to 49.03)	29.92 (17.82 to 45.28)
birth pre-term	12.20 (6.59 to 19.95)	8.64 (4.69 to 14.15)	6.92 (3.72 to 11.36)	6.19 (3.37 to 10.14)	5.82 (3.10 to 9.55)
Deaths due to RSV	2.78 (2.65 to 2.92)	1.97 (1.86 to 2.08)	1.58 (1.49 to 1.66)	1.41 (1.33 to 1.49)	1.33 (1.26 to 1.41)
birth at term	2.33 (2.20 to 2.48)	1.65 (1.54 to 1.76)	1.32 (1.24 to 1.41)	1.18 (1.10 to 1.27)	1.11 (1.04 to 1.19)
birth pre-term	0.45 (0.37 to 0.54)	0.32 (0.26 to 0.38)	0.26 (0.21 to 0.31)	0.23 (0.19 to 0.27)	0.22 (0.17 to 0.26)

Annex E. Overall annual resource use by deprivation index: six months to five years

	Resource used [Average (95% Confidence Intervals)] – six months to five years				
	Most deprived (=1)	2	3	4	Least deprived (=5)
GP visits	119,228 (115,832 to 122,694)	84,503 (81,505 to 87,166)	67,627 (64,891 to 70,270)	60,471 (57,812 to 63,054)	56,887 (54,305 to 59,603)
birth at term	99,888 (95,560 to 104,557)	70,797 (67,189 to 74,222)	56,657 (53,709 to 59,635)	50,663 (47,775 to 53,422)	47,660 (45,002 to 50,496)
birth pre-term	19,340 (15,850 to 23,210)	13,706 (11,174 to 16,372)	10,969 (8,951 to 13,107)	9,808 (8,116 to 11,724)	9,228 (7,500 to 11,033)
NHS 111 calls	64,781 (63,098 to 66,522)	45,913 (44,465 to 47,352)	36,744 (35,457 to 38,113)	32,856 (31,491 to 34,206)	30,909 (29,678 to 32,300)
birth at term	54,273 (51,927 to 56,602)	38,466 (36,549 to 40,240)	30,784 (29,150 to 32,319)	27,527 (25,948 to 29,022)	25,895 (24,504 to 27,345)
birth pre-term	10,508 (8,647 to 12,564)	7,447 (6,081 to 8,872)	5,960 (4,880 to 7,116)	5,329 (4,400 to 6,368)	5,014 (4,066 to 5,982)
Hospitalisations	5,462 (5,316 to 5,617)	3,871 (3,747 to 3,998)	3,098 (2,980 to 3,217)	2,770 (2,657 to 2,886)	2,606 (2,496 to 2,721)
ICU	96.74 (52.51 to 155)	68.55 (37.04 to 112)	54.86 (29.66 to 89.76)	49.06 (26.96 to 79.51)	46.15 (24.89 to 74.98)
Non-ICU	5,366 (5,213 to 5,521)	3,803 (3,673 to 3,938)	3,043 (2,925 to 3,162)	2,721 (2,605 to 2,840)	2,560 (2,448 to 2,680)
birth at term	4,576 (4,377 to 4,778)	3,244 (3,084 to 3,399)	2,596 (2,458 to 2,732)	2,321 (2,186 to 2,449)	2,184 (2,064 to 2,309)
ICU	81.10 (38.36 to 142)	57.46 (27.75 to 101)	45.99 (21.81 to 81.39)	41.13 (19.49 to 72.46)	38.69 (18.37 to 67.84)
Non-ICU	4,495 (4,291 to 4,697)	3,186 (3,019 to 3,341)	2,550 (2,413 to 2,687)	2,280 (2,142 to 2,407)	2,145 (2,019 to 2,267)
birth pre-term	886 (728 to 1,060)	628 (513 to 746)	503 (410 to 603)	449 (372 to 538)	423 (343 to 505)
ICU	15.64 (6.94 to 27.96)	11.08 (5.02 to 19.90)	8.87 (4.02 to 15.93)	7.93 (3.55 to 14.41)	7.46 (3.38 to 13.47)
Non-ICU	870 (716 to 1,046)	617 (505 to 735)	494 (402 to 593)	441 (363 to 529)	415 (337 to 496)

	Resource used [Average (95% Confidence Intervals)] – six months to five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
Outpatient visits	50.55 (27.44 to 81.14)	35.82 (19.35 to 58.52)	28.67 (15.50 to 46.90)	25.64 (14.08 to 41.55)	24.12 (13.01 to 39.18)
birth at term	42.35 (23.07 to 68.69)	30.01 (16.28 to 48.67)	24.02 (13.03 to 39.54)	21.48 (11.79 to 35.03)	20.20 (10.99 to 33.19)
birth pre-term	8.20 (4.29 to 13.67)	5.81 (3.05 to 9.72)	4.65 (2.41 to 7.75)	4.16 (2.17 to 6.95)	3.91 (2.05 to 6.53)
Deaths due to RSV	7.21 (6.94 to 7.49)	5.11 (4.89 to 5.34)	4.09 (3.90 to 4.29)	3.66 (3.48 to 3.84)	3.44 (3.26 to 3.62)
birth at term	6.04 (5.72 to 6.37)	4.28 (4.04 to 4.51)	3.43 (3.22 to 3.63)	3.06 (2.87 to 3.26)	2.88 (2.70 to 3.07)
birth pre-term	1.17 (0.96 to 1.40)	0.83 (0.68 to 0.98)	0.66 (0.54 to 0.79)	0.59 (0.49 to 0.71)	0.56 (0.45 to 0.67)

Annex F. Overall annual resource use by deprivation index: younger than five years

	Resource used [Average (95% Confidence Intervals)] – younger than five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
GP visits	143,310 (139,264 to 147,300)	101,571 (98,097 to 104,670)	81,286 (78,123 to 84,452)	72,685 (69,602 to 75,747)	68,378 (65,331 to 71,609)
birth at term	120,063 (114,889 to 125,614)	85,096 (80,877 to 89,185)	68,101 (64,492 to 71,589)	60,896 (57,383 to 64,249)	57,286 (54,139 to 60,726)
birth pre-term	23,247 (19,088 to 27,818)	16,475 (13,436 to 19,644)	13,185 (10,734 to 15,753)	11,789 (9,747 to 14,089)	11,091 (9,011 to 13,259)
NHS 111 calls	72,185 (70,303 to 74,135)	51,161 (49,548 to 52,772)	40,944 (39,502 to 42,469)	36,612 (35,091 to 38,115)	34,442 (33,068 to 35,993)
birth at term	60,476 (57,856 to 63,072)	42,863 (40,727 to 44,851)	34,303 (32,486 to 36,007)	30,674 (28,921 to 32,334)	28,855 (27,302 to 30,478)
birth pre-term	11,709 (9,633 to 14,003)	8,298 (6,775 to 9,885)	6,641 (5,436 to 7,930)	5,938 (4,904 to 7,095)	5,587 (4,532 to 6,667)
Hospitalisations	10,409 (10,142 to 10,692)	7,378 (7,150 to 7,611)	5,904 (5,686 to 6,129)	5,279 (5,064 to 5,493)	4,967 (4,760 to 5,183)
ICU	240 (165 to 338)	170 (117 to 239)	136 (93.20 to 193)	122 (81.97 to 171)	115 (78.15 to 160)
Non-ICU	10,169 (9,892 to 10,452)	7,207 (6,972 to 7,447)	5,768 (5,549 to 5,987)	5,158 (4,939 to 5,368)	4,852 (4,647 to 5,071)
birth at term	8,721 (8,351 to 9,096)	6,181 (5,872 to 6,472)	4,946 (4,684 to 5,193)	4,423 (4,174 to 4,660)	4,161 (3,934 to 4,396)
ICU	153 (92.60 to 238)	109 (64.94 to 168)	87.05 (52.06 to 135)	77.84 (46.37 to 120)	73.24 (43.86 to 111)
Non-ICU	8,567 (8,191 to 8,940)	6,072 (5,767 to 6,366)	4,859 (4,597 to 5,110)	4,345 (4,085 to 4,585)	4,088 (3,861 to 4,320)
birth pre-term	1,689 (1,388 to 2,021)	1,197 (977 to 1,424)	958 (781 to 1,146)	856 (707 to 1,025)	806 (654 to 962)
ICU	86.59 (47.83 to 146)	61.36 (33.71 to 103)	49.09 (26.80 to 81.36)	43.91 (23.97 to 73.71)	41.31 (22.33 to 69.35)
Non-ICU	1,602 (1,302 to 1,919)	1,135 (921 to 1,360)	909 (738 to 1,094)	812 (664 to 970)	764 (620 to 914)

	Resource used [Average (95% Confidence Intervals)] – younger than five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
Outpatient visits	125 (86.28 to 177)	88.89 (60.89 to 125)	71.14 (48.70 to 101)	63.62 (42.83 to 89.48)	59.86 (40.83 to 83.83)
birth at term	105 (72.12 to 147)	74.44 (50.77 to 105)	59.57 (40.56 to 83.50)	53.28 (36.01 to 75.31)	50.12 (34.42 to 69.92)
birth pre-term	20.40 (12.95 to 30.56)	14.45 (9.16 to 21.75)	11.57 (7.27 to 17.55)	10.34 (6.57 to 15.44)	9.73 (6.16 to 14.43)
Deaths due to RSV	10.00 (9.65 to 10.35)	7.08 (6.80 to 7.37)	5.67 (5.42 to 5.92)	5.07 (4.83 to 5.32)	4.77 (4.54 to 5.01)
birth at term	8.37 (7.95 to 8.81)	5.94 (5.60 to 6.24)	4.75 (4.48 to 5.01)	4.25 (3.99 to 4.50)	4.00 (3.76 to 4.24)
birth pre-term	1.62 (1.33 to 1.94)	1.15 (0.94 to 1.37)	0.92 (0.75 to 1.10)	0.82 (0.68 to 0.98)	0.77 (0.63 to 0.92)

Annex G. Overall annual cost by deprivation index: 0–6 months

	Cost (£) [Average (95% Confidence Intervals)]: 0–6 months				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
Overall cost	8,103,751 (7,837,641 to 8,394,265)	5,743,423 (5,526,263 to 5,967,102)	4,596,433 (4,414,929 to 4,798,523)	4,110,119 (3,928,181 to 4,317,991)	3,866,550 (3,673,691 to 4,061,405)
birth at term	6,663,004 (6,355,992 to 6,984,249)	4,722,416 (4,473,876 to 4,952,801)	3,779,310 (3,570,487 to 3,988,277)	3,379,483 (3,179,334 to 3,565,356)	3,179,157 (3,002,761 to 3,368,710)
birth pre-term	1,440,747 (1,164,660 to 1,763,842)	1,021,008 (829,158 to 1,247,127)	817,123 (661,173 to 1,002,720)	730,636 (595,198 to 889,278)	687,393 (550,712 to 838,315)
Healthcare costs	8,103,751 (7,837,641 to 8,394,265)	5,743,423 (5,526,263 to 5,967,102)	4,596,433 (4,414,929 to 4,798,523)	4,110,119 (3,928,181 to 4,317,991)	3,866,550 (3,673,691 to 4,061,405)
birth at term	6,663,004 (6,355,992 to 6,984,249)	4,722,416 (4,473,876 to 4,952,801)	3,779,310 (3,570,487 to 3,988,277)	3,379,483 (3,179,334 to 3,565,356)	3,179,157 (3,002,761 to 3,368,710)
birth pre-term	1,440,747 (1,164,660 to 1,763,842)	1,021,008 (829,158 to 1,247,127)	817,123 (661,173 to 1,002,720)	730,636 (595,198 to 889,278)	687,393 (550,712 to 838,315)
GP visits	806,740 (782,758 to 830,843)	571,777 (553,284 to 591,661)	457,589 (440,596 to 476,168)	409,172 (391,515 to 426,272)	384,919 (368,447 to 402,690)
birth at term	675,873 (645,588 to 706,289)	479,033 (455,795 to 502,167)	383,363 (362,487 to 403,123)	342,806 (323,265 to 361,405)	322,480 (305,016 to 341,034)
birth pre-term	130,868 (107,864 to 156,575)	92,744 (75,722 to 110,347)	74,226 (60,407 to 89,509)	66,366 (54,771 to 79,201)	62,438 (50,586 to 74,437)
NHS 111 calls	20,732 (20,200 to 21,285)	14,693 (14,236 to 15,164)	11,759 (11,336 to 12,202)	10,515 (10,093 to 10,946)	9,892 (9,491 to 10,336)
birth at term	17,369 (16,602 to 18,115)	12,310 (11,697 to 12,895)	9,852 (9,341 to 10,340)	8,809 (8,312 to 9,283)	8,287 (7,842 to 8,749)

	Cost (£) [Average (95% Confidence Intervals)]: 0–6 months				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
birth pre-term	3,363 (2,764 to 4,027)	2,383 (1,944 to 2,837)	1,907 (1,558 to 2,282)	1,705 (1,409 to 2,035)	1,605 (1,302 to 1,914)
Hospitalisations	7,079,506 (6,836,532 to 7,343,933)	5,017,496 (4,822,818 to 5,215,116)	4,015,478 (3,850,661 to 4,196,632)	3,590,632 (3,427,665 to 3,776,610)	3,377,853 (3,204,729 to 3,550,550)
ICU	565,200 (333,196 to 870,494)	400,460 (234,958 to 613,430)	320,497 (188,655 to 495,853)	286,638 (172,239 to 443,945)	269,690 (157,948 to 410,598)
Non-ICU	6,514,306 (6,326,258 to 6,702,858)	4,617,036 (4,449,275 to 4,781,851)	3,694,982 (3,544,848 to 3,846,256)	3,303,994 (3,157,821 to 3,438,413)	3,108,163 (2,971,992 to 3,249,780)
birth at term	5,807,718 (5,538,158 to 6,092,404)	4,116,226 (3,898,855 to 4,317,182)	3,294,184 (3,112,740 to 3,475,811)	2,945,678 (2,765,404 to 3,109,238)	2,771,072 (2,615,683 to 2,939,326)
ICU	285,448 (133,980 to 505,708)	202,241 (95,725 to 355,257)	161,884 (75,531 to 287,153)	144,758 (67,908 to 257,540)	136,224 (63,754 to 242,520)
Non-ICU	5,522,270 (5,282,936 to 5,765,801)	3,913,985 (3,715,793 to 4,106,959)	3,132,300 (2,954,464 to 3,289,280)	2,800,920 (2,633,900 to 2,953,362)	2,634,847 (2,490,112 to 2,787,162)
birth pre-term	1,271,788 (1,026,414 to 1,566,123)	901,270 (728,026 to 1,108,578)	721,295 (583,001 to 888,429)	644,954 (523,004 to 790,738)	606,781 (485,276 to 742,476)
ICU	279,752 (134,049 to 497,479)	198,219 (94,155 to 349,735)	158,613 (75,525 to 278,194)	141,879 (67,617 to 251,005)	133,465 (63,042 to 235,286)
Non-ICU	992,036 (796,977 to 1,206,455)	703,051 (560,095 to 848,147)	562,682 (449,137 to 680,649)	503,074 (404,503 to 611,222)	473,316 (378,400 to 574,724)
Outpatient visits	17,160 (10,116 to 26,428)	12,158 (7,133 to 18,624)	9,730 (5,728 to 15,054)	8,702 (5,229 to 13,478)	8,188 (4,795 to 12,466)
birth at term	14,364 (8,577 to 22,025)	10,178 (6,027 to 15,466)	8,145 (4,889 to 12,404)	7,285 (4,386 to 11,233)	6,854 (4,082 to 10,373)
birth pre-term	2,795 (1,511 to 4,571)	1,980 (1,075 to 3,242)	1,585 (852 to 2,603)	1,417 (772 to 2,323)	1,334 (710 to 2,189)

Annex H. Overall annual cost by deprivation index: six months to five years

	Cost (£) [Average (95% Confidence Intervals)] – six months to five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
Overall cost	16,501,038 (14,996,265 to 18,588,460)	11,695,096 (10,632,906 to 13,217,225)	9,359,313 (8,468,380 to 10,529,232)	8,369,824 (7,546,284 to 9,535,469)	7,873,275 (7,109,689 to 8,922,814)
birth at term	13,181,063 (11,855,360 to 15,038,104)	9,342,266 (8,344,020 to 10,666,694)	7,476,334 (6,648,839 to 8,497,903)	6,686,091 (5,973,244 to 7,666,625)	6,289,233 (5,600,085 to 7,169,405)
birth pre-term	3,319,975 (2,670,529 to 4,084,683)	2,352,831 (1,884,901 to 2,869,587)	1,882,979 (1,509,776 to 2,299,519)	1,683,733 (1,372,265 to 2,072,601)	1,584,042 (1,271,175 to 1,959,016)
Healthcare costs	12,146,566 (11,795,902 to 12,550,626)	8,608,806 (8,299,168 to 8,907,118)	6,889,560 (6,611,458 to 7,166,580)	6,160,594 (5,890,340 to 6,433,082)	5,795,472 (5,540,012 to 6,073,545)
birth at term	10,176,382 (9,689,682 to 10,669,440)	7,212,564 (6,828,442 to 7,569,653)	5,772,127 (5,449,472 to 6,082,597)	5,161,481 (4,853,980 to 5,452,048)	4,855,462 (4,589,387 to 5,149,086)
birth pre-term	1,970,184 (1,619,814 to 2,367,998)	1,396,242 (1,131,543 to 1,658,001)	1,117,434 (909,856 to 1,336,008)	999,113 (822,702 to 1,196,469)	940,009 (766,250 to 1,123,794)
GP visits	3,994,133 (3,880,357 to 4,110,259)	2,830,841 (2,730,426 to 2,920,068)	2,265,503 (2,173,844 to 2,354,049)	2,025,787 (1,936,718 to 2,112,308)	1,905,730 (1,819,204 to 1,996,710)
birth at term	3,346,233 (3,201,254 to 3,502,671)	2,371,684 (2,250,842 to 2,486,438)	1,898,026 (1,799,246 to 1,997,778)	1,697,225 (1,600,465 to 1,789,651)	1,596,606 (1,507,566 to 1,691,609)
birth pre-term	647,900 (530,971 to 777,549)	459,157 (374,337 to 548,446)	367,477 (299,857 to 439,070)	328,562 (271,886 to 392,749)	309,123 (251,248 to 369,609)
NHS 111 calls	181,388 (176,675 to 186,262)	128,558 (124,501 to 132,585)	102,884 (99,280 to 106,716)	91,998 (88,176 to 95,778)	86,545 (83,098 to 90,440)
birth at term	151,964 (145,395 to 158,486)	107,706 (102,337 to 112,672)	86,195 (81,620 to 90,493)	77,077 (72,654 to 81,261)	72,507 (68,610 to 76,566)

	Cost (£) [Average (95% Confidence Intervals)] – six months to five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
birth pre-term	29,424 (24,211 to 35,180)	20,852 (17,028 to 24,842)	16,688 (13,664 to 19,926)	14,921 (12,321 to 17,831)	14,038 (11,385 to 16,750)
Hospitalisations	7,690,245 (7,441,306 to 7,979,953)	5,450,394 (5,239,724 to 5,661,254)	4,361,904 (4,173,545 to 4,552,437)	3,900,391 (3,725,341 to 4,088,396)	3,669,220 (3,500,735 to 3,853,731)
ICU	413,434 (224,387 to 663,619)	292,945 (158,282 to 478,660)	234,454 (126,752 to 383,618)	209,664 (115,196 to 339,795)	197,234 (106,381 to 320,416)
Non-ICU	7,276,811 (7,070,018 to 7,488,024)	5,157,449 (4,981,047 to 5,340,455)	4,127,450 (3,966,199 to 4,288,398)	3,690,727 (3,532,342 to 3,851,133)	3,471,986 (3,320,560 to 3,634,038)
birth at term	6,442,931 (6,113,098 to 6,783,523)	4,566,438 (4,318,299 to 4,803,366)	3,654,468 (3,443,417 to 3,868,481)	3,267,858 (3,063,856 to 3,463,326)	3,074,102 (2,897,005 to 3,273,920)
ICU	346,599 (163,942 to 607,011)	245,574 (118,577 to 433,056)	196,564 (93,190 to 347,841)	175,774 (83,289 to 309,676)	165,333 (78,527 to 289,925)
Non-ICU	6,096,332 (5,819,938 to 6,370,542)	4,320,865 (4,093,942 to 4,531,599)	3,457,903 (3,272,328 to 3,644,096)	3,092,084 (2,904,507 to 3,264,637)	2,908,769 (2,738,360 to 3,075,008)
birth pre-term	1,247,315 (1,023,180 to 1,493,339)	883,955 (721,736 to 1,049,106)	707,436 (576,630 to 848,102)	632,533 (520,334 to 758,176)	595,117 (484,762 to 708,825)
ICU	66,835 (29,669 to 119,497)	47,371 (21,437 to 85,042)	37,889 (17,171 to 68,090)	33,890 (15,155 to 61,563)	31,901 (14,452 to 57,546)
Non-ICU	1,180,479 (971,546 to 1,418,122)	836,584 (684,743 to 996,723)	669,547 (544,858 to 803,631)	598,642 (492,400 to 717,262)	563,217 (457,090 to 673,164)
Outpatient visits	11,580 (6,285 to 18,588)	8,205 (4,434 to 13,407)	6,567 (3,550 to 10,745)	5,873 (3,227 to 9,518)	5,525 (2,980 to 8,975)
birth at term	9,702 (5,285 to 15,736)	6,875 (3,728 to 11,149)	5,502 (2,985 to 9,059)	4,920 (2,701 to 8,026)	4,629 (2,517 to 7,602)
birth pre-term	1,878 (982 to 3,131)	1,331 (699 to 2,226)	1,065 (553 to 1,776)	952 (498 to 1,593)	896 (470 to 1,495)

Annex I. Overall annual cost by deprivation index: younger than five years

	Cost (£) [Average (95% Confidence Intervals)] – younger than five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
Overall cost	24,604,789 (23,009,965 to 26,737,133)	17,438,520 (16,286,453 to 19,035,240)	13,955,746 (12,948,785 to 15,161,347)	12,479,943 (11,552,572 to 13,731,577)	11,739,825 (10,863,290 to 12,846,957)
birth at term	19,844,067 (18,309,296 to 21,786,061)	14,064,681 (12,908,442 to 15,479,676)	11,255,644 (10,277,454 to 12,346,112)	10,065,574 (9,209,371 to 11,142,682)	9,468,390 (8,664,425 to 10,461,013)
birth pre-term	4,760,722 (3,884,296 to 5,820,528)	3,373,838 (2,713,053 to 4,090,518)	2,700,102 (2,185,815 to 3,284,175)	2,414,369 (1,979,085 to 2,941,296)	2,271,435 (1,842,737 to 2,787,914)
Healthcare costs	20,250,316 (19,671,413 to 20,883,103)	14,352,230 (13,864,072 to 14,840,667)	11,485,993 (11,050,728 to 11,940,407)	10,270,712 (9,837,386 to 10,730,957)	9,662,022 (9,249,224 to 10,108,159)
birth at term	16,839,386 (16,067,876 to 17,627,722)	11,934,980 (11,306,316 to 12,511,211)	9,551,436 (9,034,542 to 10,060,314)	8,540,964 (8,042,435 to 8,995,851)	8,034,619 (7,603,816 to 8,505,843)
birth pre-term	3,410,931 (2,799,231 to 4,085,649)	2,417,250 (1,980,548 to 2,886,542)	1,934,557 (1,577,268 to 2,328,878)	1,729,749 (1,422,428 to 2,073,146)	1,627,403 (1,322,275 to 1,950,125)
GP visits	4,800,873 (4,665,354 to 4,934,548)	3,402,618 (3,286,246 to 3,506,439)	2,723,092 (2,617,111 to 2,829,158)	2,434,959 (2,331,664 to 2,537,529)	2,290,648 (2,188,573 to 2,398,910)
birth at term	4,022,106 (3,848,791 to 4,208,078)	2,850,717 (2,709,382 to 2,987,705)	2,281,389 (2,160,498 to 2,398,240)	2,040,031 (1,922,320 to 2,152,356)	1,919,087 (1,813,655 to 2,034,311)
birth pre-term	778,767 (639,449 to 931,915)	551,901 (450,097 to 658,074)	441,702 (359,599 to 527,726)	394,928 (326,537 to 471,980)	371,562 (301,866 to 444,182)
NHS 111 calls	202,119 (196,850 to 207,579)	143,251 (138,734 to 147,761)	114,643 (110,605 to 118,914)	102,513 (98,255 to 106,721)	96,437 (92,590 to 100,779)
birth at term	169,332 (161,997 to 176,601)	120,016 (114,037 to 125,581)	96,047 (90,960 to 100,819)	85,886 (80,978 to 90,534)	80,794 (76,444 to 85,338)

	Cost (£) [Average (95% Confidence Intervals)] – younger than five years				
	Most deprived (=1)	**2**	**3**	**4**	**Least deprived (=5)**
birth pre-term	32,787 (26,973 to 39,208)	23,235 (18,970 to 27,677)	18,596 (15,220 to 22,205)	16,627 (13,730 to 19,866)	15,643 (12,690 to 18,666)
Hospitalisations	14,769,751 (14,344,723 to 15,260,158)	10,467,890 (10,095,120 to 10,851,515)	8,377,382 (8,056,973 to 8,720,411)	7,491,023 (7,156,929 to 7,835,825)	7,047,072 (6,733,040 to 7,377,033)
ICU	978,634 (670,724 to 1,379,191)	693,405 (478,706 to 979,578)	554,951 (381,125 to 788,152)	496,302 (333,562 to 700,889)	466,923 (318,266 to 653,102)
Non-ICU	13,791,117 (13,415,621 to 14,174,467)	9,774,484 (9,455,811 to 10,099,306)	7,822,432 (7,525,563 to 8,119,026)	6,994,721 (6,697,905 to 7,279,449)	6,580,149 (6,302,685 to 6,877,672)
birth at term	12,250,648 (11,674,249 to 12,850,740)	8,682,664 (8,220,805 to 9,109,631)	6,948,651 (6,572,964 to 7,333,759)	6,213,537 (5,849,204 to 6,556,477)	5,845,174 (5,524,528 to 6,195,444)
ICU	632,047 (380,052 to 977,499)	447,814 (267,600 to 693,823)	358,448 (215,487 to 553,857)	320,532 (190,407 to 498,514)	301,558 (178,950 to 460,245)
Non-ICU	11,618,601 (11,107,945 to 12,123,512)	8,234,850 (7,820,592 to 8,633,445)	6,590,203 (6,234,041 to 6,930,565)	5,893,004 (5,539,742 to 6,217,391)	5,543,616 (5,235,694 to 5,858,304)
birth pre-term	2,519,103 (2,057,149 to 3,031,437)	1,785,226 (1,457,954 to 2,148,216)	1,428,731 (1,161,428 to 1,726,294)	1,277,486 (1,047,322 to 1,534,459)	1,201,898 (972,721 to 1,443,611)
ICU	346,587 (192,677 to 576,818)	245,591 (135,771 to 409,871)	196,502 (107,993 to 324,841)	175,770 (96,608 to 293,638)	165,366 (90,149 to 275,394)
Non-ICU	2,172,515 (1,766,226 to 2,603,013)	1,539,635 (1,249,175 to 1,844,165)	1,232,229 (1,001,129 to 1,483,375)	1,101,717 (900,014 to 1,315,644)	1,036,533 (840,867 to 1,239,862)
Outpatient visits	28,740 (19,765 to 40,463)	20,363 (13,949 to 28,651)	16,297 (11,156 to 23,094)	14,575 (9,812 to 20,499)	13,712 (9,355 to 19,205)
birth at term	24,067 (16,521 to 33,771)	17,053 (11,630 to 24,130)	13,648 (9,291 to 19,128)	12,205 (8,251 to 17,253)	11,483 (7,886 to 16,018)
birth pre-term	4,673 (2,966 to 7,001)	3,311 (2,098 to 4,984)	2,650 (1,665 to 4,020)	2,370 (1,506 to 3,538)	2,230 (1,412 to 3,306)

Annex J. Sensitivity analysis: GP visit and death rates – Taylor 2016 [6]

	0–6 months	Six months to five years	Younger than five years
Base case			
Overall cost - total	26,420,276 (25,876,844 to 27,121,150)	53,798,546 (49,148,055 to 60,448,944)	80,218,822 (75,476,062 to 86,871,417)
Direct costs - total	26,420,276 (25,876,844 to 27,121,150)	39,600,998 (39,031,419 to 40,272,426)	66,021,274 (65,223,446 to 66,985,880)
Number of GP visits	78,513 (77,446 to 79,601)	388,716 (383,085 to 393,856)	467,230 (461,539 to 472,538)
GP visits cost	2,630,197 (2,594,434 to 2,666,620)	13,021,994 (12,833,337 to 13,194,185)	15,652,190 (15,461,570 to 15,830,007)
Deaths due to RSV per infant	9.08 (8.69 to 9.46)	23.51 (22.83 to 24.17)	32.59 (31.80 to 33.36)
Taylor 2016			
Overall cost - total	24,739,198 (24,160,015 to 25,438,788)	49,781,969 (45,353,492 to 55,772,175)	74,521,168 (70,024,561 to 80,516,274)
Direct costs - total	24,739,198 (24,160,015 to 25,438,788)	37,033,078 (35,606,200 to 38,533,417)	61,772,277 (60,208,755 to 63,433,771)
Number of GP visits	29,382 (24,471 to 34,897)	314,155 (275,032 to 352,583)	343,537 (303,384 to 383,906)
GP visits cost	984,294 (819,792 to 1,169,056)	10,524,198 (9,213,583 to 11,811,536)	11,508,492 (10,163,350 to 12,860,858)
Deaths due to RSV per infant	7.36 (1.14 to 16.19)	48.55 (5.00 to 111)	55.91 (12.09 to 116)

Annex K. QALY loss

	Total	Most deprived	2	3	4	Least deprived
Infants aged between 0–6 months	295 (107 to 565)	90.08 (4.21 to 297)	63.80 (3.06 to 215)	52.99 (3.37 to 172)	45.69 (1.87 to 152)	42.61 (2.26 to 146)
Preterm	47.93 (17.16 to 98.44)	14.65 (0.69 to 49.09)	10.39 (0.51 to 36.36)	8.57 (0.56 to 28.92)	7.41 (0.27 to 26.24)	6.91 (0.39 to 24.04)
At term	247 (90.92 to 478)	75.43 (3.53 to 244)	53.41 (2.58 to 180)	44.43 (2.81 to 145)	38.28 (1.57 to 127)	35.71 (1.90 to 122)
Infants aged between six months and five years	2,842 (1,053 to 5,782)	909 (44.45 to 3,069)	607 (32.12 to 2,086)	497 (20.19 to 1,772)	435 (22.83 to 1,455)	394 (16.90 to 1,362)
Preterm	461 (168 to 939)	148 (7.05 to 529)	98.72 (5.05 to 344)	80.42 (3.73 to 278)	70.26 (3.62 to 233)	63.91 (2.67 to 218)
At term	2,381 (872 to 4,933)	761 (35.84 to 2,613)	509 (26.60 to 1,786)	417 (16.75 to 1,500)	364 (19.73 to 1,210)	330 (13.75 to 1,129)
Infants aged less than five years	3,137 (1,334 to 6,047)	999 (106 to 3,210)	671 (73.10 to 2,127)	550 (56.39 to 1,801)	480 (56.23 to 1,489)	437 (50.04 to 1,400)
Preterm	509 (203 to 985)	163 (18.01 to 547)	109 (11.64 to 351)	88.99 (9.06 to 287)	77.67 (8.90 to 240)	70.82 (8.33 to 222)
At term	2,628 (1,118 to 5,128)	836 (88.50 to 2,775)	562 (61.48 to 1,789)	461 (47.36 to 1,525)	403 (46.28 to 1,261)	366 (40.42 to 1,159)

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