Bronchiolitis: Clinical and Aetiological Considerations

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy

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I would like to dedicate this work to my grandfather who always inspired me.

Abstract

Introduction: Bronchiolitis is the most common lower respiratory condition affecting children under two years old. It has a wide range of clinical presentations ranging from a mild cough to respiratory failure. Severity scores are beneficial in the assessment of bronchiolitis as the allow a standardised assessment and aide clinical decision making. More severe disease has previously been associated with younger age, male gender, increased deprivation, and high pollution levels. Many of these risk factors vary greatly by geographical area. The objectives within this thesis are to identify and evaluate scores currently available for the assessment of bronchiolitis. To further assess demographic, clinical, and temporal trends in bronchiolitis attendances to AHCH and to explore the impacts of deprivation and air pollution on admissions.

Methods: To systematically review novel or modified tools available in bronchiolitis assessment before November 30th, 2020, by searching the databases Medline, CINAHL, PubMed and EMCARE. To then evaluate the items used in the scores as well as further investigation into the three most frequently measured items.

To obtain the bronchiolitis coded hospital attendances to Alder Hey Children's Hospital from Liverpool City Region from 1st September 2015 to 31st August 2020 and extract key information such as sex, postcode, age, length of stay, admission to critical care and supplemental oxygen use, and was assessed in relation to each other as well as the index of multiple deprivation and pollution data available from the local council.

Results: The systematic review identified 52 studies including a bronchiolitis severity score. These assessed 51 different items across 9 domains. Scores most commonly assessed respiratory rate (assessed in 46/52), wheeze (43/52) and retractions (37/52). Varying definitions as to what constituted normal and abnormal respiratory rates were used. Similarly, wheeze and retractions were evaluated in multiple ways. Little validity and reliability data were available for the scores. There were 3559 bronchiolitis attendances to AHCH across the period. 2153 (60%) were male, the median age was 120 days, and the median length of stay was 18.18 hours. Of these attendances, 65% had a length of stay greater than 6 hours, 28% (n=996) required supplemental oxygen and 5.51% (n=196) were admitted to critical care. Most attendances happened in November, on Mondays and during the afternoons and evenings. The majority of patients (58.67%) were from the lowest decile of deprivation. The average monthly NO_2 level was 43 µg/m^3, compared to the DEFRA target level of 40 µg/m^3. 66% of attendances occurring when levels exceeded 40 µg/m^3

Conclusion: Multiple bronchiolitis severity scores have been published. Most included respiratory rate, wheeze, and retractions as part of their assessments but there was significant variation in the evaluation of these items. The scores lack validation data. Most attendances to Alder Hey Children's hospital for bronchiolitis were male infants under two months of age. Males were affected more severely. Peak attendances for bronchiolitis at Alder Hey were in November, on Mondays and in the afternoon and evenings. Average monthly NO_2 levels are in breach of the Department for Environment, Food and Rural Affairs recommended levels.

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Abbreviations

A&E	Accident and Emergency
AAP	American Academy of Pediatrics
Abbreviation	Actual
AHCH	Alder Hey Children's Hospital
AUROC	Area under a receiver operating characteristic curve
AURN	Automatic Urban and Rural Networks
CC	Critical Care
DEFRA	Department for Environment, Food and Rural Affairs
ED	Emergency Department
FeNO	Fractional Exhaled Nitric Oxide
GP	General Practitioner
HDU	High dependency unit
HMPV	Human metapneumovirus
hRV	human Rhinovirus
ICAM-1	Intracellular Adhesion Molecule-1
ICC	Intra-class-correlation coefficient
ICU	Intensive care unit
IGF1R	Insulin-like growth factor 1 receptor
IL	Interleukin
IMD	Index of Multiple Deprivation
JBI	Joanna Briggs Institute
LCC	Liverpool City Council
LCR	Liverpool City Region
LoS	Length of Stay
LRTI	Lower Respiratory Tract infection
LSOA	Lower-Layer Super Output Areas
MTS	Modified Tal Score
NHS	National Health Service
NICE	National Institute
NO_2	Nitrogen Dioxide
PCR	Polymerase Chain Reaction
PEWS	Paediatric Early Warning Score
PICU	Paediatric intensive care unit
PM_{10}	Particulate matter (diameter less than 10μm)
$PM_{2.5}$	Particulate matter (diameter less than 2.5μm)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Respiratory rate
RSV	Respiratory Syncytial Virus
SIGN	Scottish Intercollegiate Guidelines Network
SO_2	Sulphur Dioxide

SP	Surfactant Protein
TLR	Toll-like receptor
UK	United Kingdom
UNICEF	United Nations Children's Fund
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Definition

The definition of bronchiolitis used in this thesis is that stated in the National Institute of Health and Care Excellence (NICE) which defines bronchiolitis as a disease of the lower respiratory tract with a coryzal prodrome one to three days before the onset of a persistent cough, respiratory distress and auscultatory findings in children under two years of age (NICE, 2015).

Bronchiolitis is a viral respiratory illness occurring in epidemics worldwide. It can lead to an array of symptoms depending on severity. Common symptoms include a persistent cough, increased work of breathing demonstrated by tachypnoea with or without chest recession and auscultatory findings of wheeze or crackles, or a combination of both (NICE, 2015). Younger children, particularly those under the age of six weeks, may present with apnoea (NICE, 2015).

Internationally, there exists debate over the definition of bronchiolitis, particularly regarding the age of the child. Most guidelines cite an age of less than 12 or 24 months, yet studies investigating bronchiolitis have used definitions such as less than six, nine or 18 months, even extending age ranges to 30, 36 or 42 months (Hancock et al., 2017). In the United Kingdom (UK), bronchiolitis is often viewed by paediatricians as being an illness of infancy i.e. affecting children less than one year old (Stewart, 2015).

A questionnaire sent to Portuguese physicians found that although there was some consensus regarding age range (less than 24 months being the most common) there was disagreement between paediatricians and general practitioners (GP) (***Figure 1.1B)*** (Fernandes et al., 2016). Age is an important determinant of bronchiolitis severity as it predicts differences in virus specificity and immune response (Hancock et al., 2017).

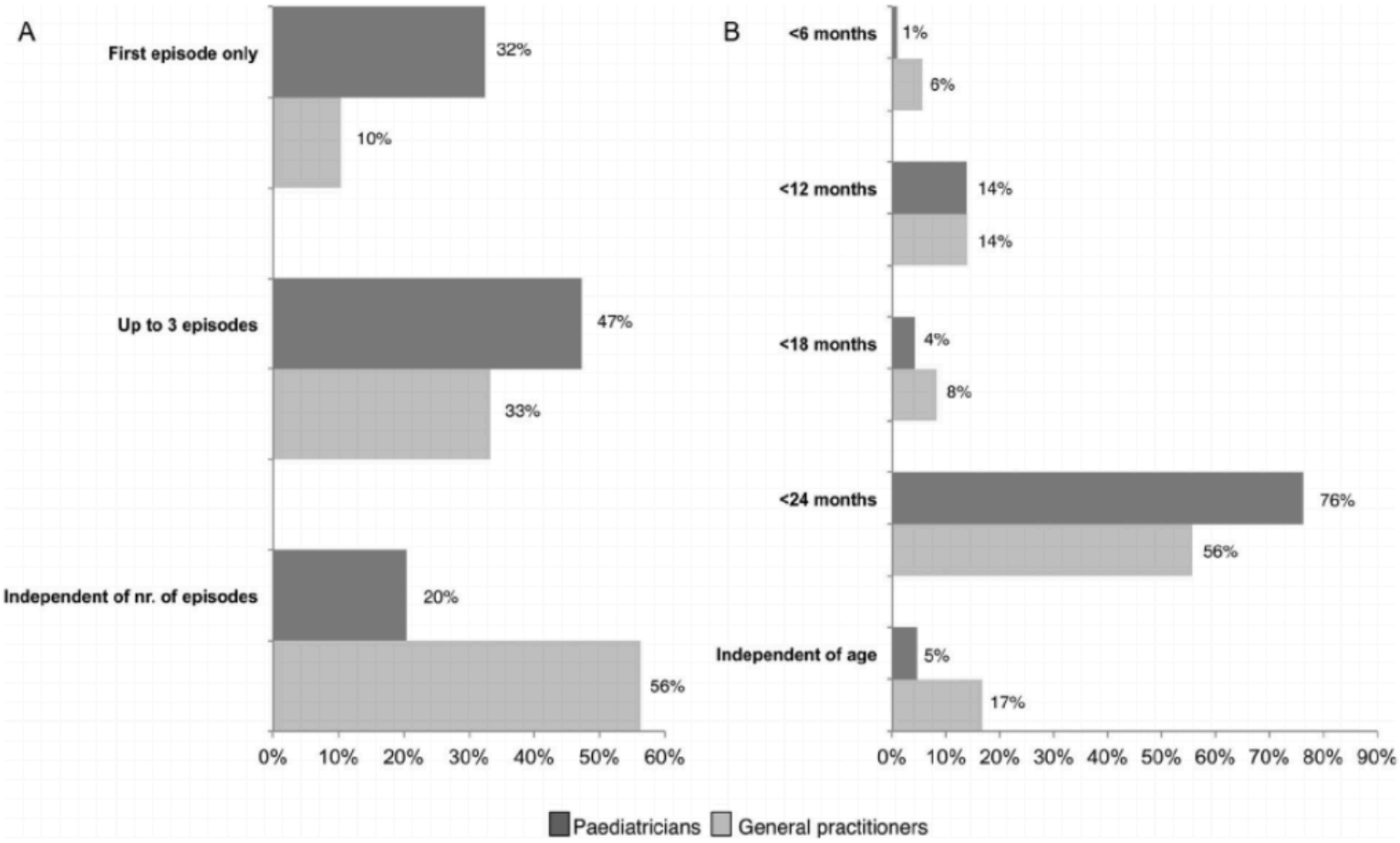


Figure 1. 1 Bar chart demonstrating paediatricians and general practitioner's perceptions of bronchiolitis.

Taken from Fernandes et al. demonstrating varying perspectives of physicians (Fernandes et al., 2016). (A) illustrates the findings for the perspectives regarding the number of presentations that can be bronchiolitis and the lack of consensus found. (B) shows that most physicians perceptions of bronchiolitis are that it affects those less than 24 months. Overall, it shows that many doctors have contrasting definitions of bronchiolitis.

Further differences were seen between paediatricians and GPs in the number of episodes of bronchiolitis (***Figure 1.1A***). 56% of GPs thought that a diagnosis of bronchiolitis was independent of the number of episodes, whereas 47% of paediatricians associated a diagnosis of bronchiolitis with up to three presentations (Fernandes et al., 2016, Hancock et al., 2017). The recurrence of the respiratory illness is important, as an alternate diagnosis may alter the management of the child.

Further debate in the definition of bronchiolitis exists surrounding the auscultatory findings. Within English-speaking national guidelines, findings related to diagnosis commonly state wheeze, crepitations or a combination of both. However, some fail to mention any significant auscultatory sign, with others citing more nuanced possible findings such as rales or rhonchi (Hancock et al., 2017). With regards to auscultatory findings, there is a relative consensus between physicians for the expected findings in relation to the presence of wheeze, but this is not found with crepitations (Fernandes et al., 2016).

Having an internationally accepted definition of bronchiolitis is important as it helps in the development of guidelines, thereby ensuring the uniform treatment and management of infants and children with bronchiolitis.

1.2 Epidemiology

In temperate climates, like the UK, peaks occur over the winter months, and in tropical areas they generally occur in rainy seasons (Smyth and Brearey, 2006). Bronchiolitis accounts for 18% of all hospitalisations in those under one year of age (Green et al., 2016). Respiratory syncytial virus (RSV) is responsible for approximately 80% of hospitalised cases of bronchiolitis, with 70% of children experiencing RSV infection within the first year of life. This figure rises closer to 100% of children being infected by the time they have turned two years (Glezen et al., 1986). The second most common virus responsible for bronchiolitis is human rhinovirus (hRV) (Miller et al., 2013). Of those diagnosed with bronchiolitis, approximately 3% will require hospital admission with 2-6% of those requiring further admission to a paediatric intensive care unit (PICU) (Green et al., 2016).

There is geographical variation in admission rates for bronchiolitis. In the UK, admission rates range 5.3-fold across the 352 Local Government Areas (Green et al., 2016). This variation may be due to differences in socioeconomic deprivation. It may also reflect to local outbreaks of respiratory viral infection in more populous areas.

Bronchiolitis is a significant financial burden on healthcare systems. Currently, there is no published data to quantify the cost of bronchiolitis on the National Health System (NHS). However, in the USA, it was estimated that between 1997 to 2000 the cost of bronchiolitis hospitalisation was $2.6billion (Smyth and Brearey, 2006, Leader and Kohlhase, 2003). A more recent American study calculated the national medical costs of bronchiolitis hospitalisation in 2009 to be $545 million, with children under one-year-old accounting for most of these hospitalisations (Hasegawa et al., 2013). Bozzola et al. calculated the mean cost for bronchiolitis hospitalisation for each infant to the Italian healthcare system in 2017 to be 5,753€ for RSV patients compared to 5,395€ for other viruses (Bozzola et al., 2021). Importantly, these figures do not account for the impact of bronchiolitis in primary care and less acute settings. Therefore, it is reasonable to assume that the total costs associated with bronchiolitis to healthcare systems is much greater.

1.3 Clinical Features

RSV can cause a broad spectrum of disease in early childhood. After an incubation period of one to two days, upper respiratory tract infection signs are commonly observed. These include nasal congestion, cough, and low-grade fever typically lasting one to three days. In 30-40% of children infected with RSV, lower respiratory tract signs and symptoms will develop such as tachypnoea, wheeze, retractions, nasal flaring, and other signs of respiratory distress potentially leading to hypoxia (Fretzayas and Moustaki, 2017, Smyth and Brearey, 2006, Erickson et al., 2020).

In approximately 5% of bronchiolitis cases (particularly those less than 6 weeks of age), the child may present with apnoea (Smyth and Brearey, 2006, Ricart et al., 2014). Apnoeic episodes can be defined as respiratory pauses lasting longer than 20 seconds. They may also be shorter but occur in conjunction with signs such as bradycardia, cyanosis, pallor or hypotonia (Blackmon et al., 2003). Inability to maintain oxygen saturations greater than 92% on room air, signs of severe respiratory distress (cyanosis, tachypnoea greater than 70 breaths per minute or grunting), or

inadequate oral intake are clinical features indicating a need for hospital admission (NICE, 2015, Fretzayas and Moustaki, 2017).

A diagnosis of bronchiolitis is reached based on the presenting history, and clinical signs and symptoms.

1.4 Viral Aetiology

1.4.1 Respiratory Syncytial Virus

RSV was first discovered in 1956 in chimpanzees and has subsequently been associated with seasonal infections in humans, mainly children but also the elderly (Morris et al., 1956). RSV is of the Genus *Orthopneumovirus*, Subfamily *Pneumovirinae,* Family *Pneumoviridae* and order *Mononegavirales* (Rima et al., 2017, Salimi et al., 2021). The RSV genome comprises of 10 genes, encoding for 11 proteins as two overlapping frames that are able to produce two distinct matrix proteins making it a relatively complex virus (Borchers et al., 2013).

The most common cause of bronchiolitis is RSV, accounting for 50-80% of acute presentations of bronchiolitis (***Figure 1.2***) (Carroll et al., 2008, Mansbach et al., 2012, Hasegawa et al., 2014). ***Figure 1.2*** displays the different viral aetiologies in different clinical settings. In this review, which included studies from America, Australis and the UK, RSV was found to be the most common viral aetiology in inpatient and emergency department (ED) settings possibly suggesting that RSV is associated with more severe disease.

RSV can be classified into two major groups RSV-A and RSV-B. Both are simultaneously present during epidemics with yearly shifts between the dominant variants (Hasegawa et al., 2014, Peret et al., 1998). RSV-A has previously been demonstrated to relate to more severe illness (Hasegawa et al., 2014, Papadopoulos et al., 2004).

	Outpatient (%)[†]	Emergency department (%)[‡]	Inpatient (%)[§]
Respiratory syncytial virus	11–27	64	73
Rhinovirus	29–49	16	26
Adenovirus	2	NA	8
Coronavirus	6–9	NA	7
Human metapneumovirus	2	9	7
Enterovirus	NA	NA	5
Parainfluenza virus	5–13	NA	3
Influenza virus	1–5	6	1
Coinfections	11–17	14	30

[†]Based on three cohort studies of infants with acute respiratory infections [109,141,142].
[‡]Based on EMNet study of 277 children <2 years of age presenting to 14 emergency departments with bronchiolitis [21].
[§]Based on EMNet study of 2207 children <2 years of age admitted to 16 hospitals with bronchiolitis [20].
NA: Not available.

Figure 1. 2 Table demonstrating the frequency of viral causes of bronchiolitis in different care settings.

Taken from Hasegawa et al.(Hasegawa et al., 2014) highlighting the frequency of viral presentations in different clinical. It highlights that RSV is associated with more severe disease and so is found in higher numbers of inpatients and in emergency departments. hRV is linked to preschool wheeze and so may be more pronounced in outpatient settings as it is less acute and relates to more chronic disease.

The outer surface of the viral envelope is made up of two transmembrane glycoproteins that are key in bronchiolitis infectivity. The F protein plays a pivotal role in cell entry by mediating attachment and penetration into host cell membranes (Techaarpornkul et al., 2001, Canedo-Marroquín et al., 2017, Breese Hall, 2009). Furthermore, the large glycoprotein G can act as a decoy for the host's neutralising antibodies, enabling evasion from the immune response (Canedo-Marroquín et al., 2017).

It is currently believed that the main receptors implicated in RSV entry are Nucleolin and IGF1 (Griffiths et al., 2020, Mastrangelo et al., 2021, Tayyari et al., 2011). Furthermore, it was found that these act via the RSV-F surface molecule. Other molecules have been associated with RSV

entry as co-receptors or co-factors. These include intracellular adhesion molecule (ICAM)-1, heparin, annexin II and toll-like receptor (TLR)-4, CXC3R1 (Krusat and Streckert, 1997, Behera et al., 2001, Malhotra et al., 2003, Marr and Turvey, 2012, Tripp et al., 2001, Mastrangelo and Hegele, 2012).

1.4.2 Non-RSV Causes

Approximately 30% of bronchiolitis is caused by non-RSV viruses. With the development and clinical use of multiplex polymerase chain reaction assays, the detection of more non-RSV pathogens has increased. These include, but are not limited to hRV, human metapneumovirus, adenovirus, coronaviruses, influenza, and parainfluenza viruses as demonstrated in ***Figure 1.2*** (Hasegawa et al., 2014, Mansbach et al., 2012).

hRV infection is the most prevalent of the non-RSV bronchiolitis pathogens being detected in 20%-40% of bronchiolitis infections (Hasegawa et al., 2014). hRV is more prevalent in older children (greater than one year old) with bronchiolitis. Presentation can resemble asthma suggesting an overlap with pre-school wheeze or asthma (Mansbach et al., 2016).

Although the presentation of non-RSV bronchiolitis has been found to be mostly similar to RSV bronchiolitis, a few differences have been reported (Szczawińska-Popłonyk et al., 2019). In RSV bronchiolitis, crackles and decreased breath sounds are more frequently observed whereas fever is more often associated with hRV bronchiolitis (Szczawińska-Popłonyk et al., 2019, Petrarca et al., 2018).

Viral co-infection or co-detection is commonly found in children hospitalised with bronchiolitis, with RSV and hRV being the most common combination of viruses found (Petrarca et al., 2018). The rates of co-infection have been cited as around 30% of bronchiolitis cases (***Figure 1.2***) (Petrarca et al., 2018, Hasegawa et al., 2014). It is possible that RSV infection may predispose to infections with other viruses and particularly hRV. RSV's ability to impair the body's anti-viral

response, and an already disrupted epithelium may allow enhanced hRV replication (Petrarca et al., 2018, Hasegawa et al., 2014). Although co-infection is a possibility, co-detection is a more likely scenario. A recent systematic review and meta-analysis demonstrated that there was no strong evidence to support co-infection causing increased rates of hospitalisation, length of stay (LoS), or supplemental oxygen requirement (Li et al., 2020). Several of the studies included highlighted that RSV co-infection with adenovirus, coronavirus-NL63 or parainfluenza were associated with a higher risk of ICU admission (Li et al., 2020, Richard et al., 2008, Mazur et al., 2017). However, this was not seen on metanalysis (Li et al., 2020). Of note, detection with other viruses such as adenovirus, bocavirus, or coronaviruses is found in healthy children without respiratory symptoms (Shi et al., 2015). Little is known about virus-virus interactions in the human respiratory tract, particularly how co-infection might result in increased severity of disease (DaPalma et al., 2010).

1.5 Risk Factors

A variety of factors can influence the severity of bronchiolitis. Several disease states are associated with an increased risk of severe bronchiolitis. Infants with chronic pulmonary disease (particularly bronchopulmonary dysplasia) and congenital heart disease are at increased risk of severe disease (Che et al., 2012, Alvarez et al., 2013, Robledo-Aceves et al., 2018). Neurological conditions, such as cerebral palsy, can cause an inability to clear secretions leading to an increased severity (Sommer et al., 2011). Additionally, Down's syndrome and immunocompromising conditions are associated with a higher risk severe disease (Sommer et al., 2011).

Non-environmental factors, such as male gender and younger age are associated with an increased severity of disease (Alvarez et al., 2013, Hall et al., 2009). Younger age during an RSV season is a risk factor for more severe bronchiolitis with studies finding children younger than two months during the winter season having an increased hospital length of stay, risk of PICU admission and requirement for ventilatory support (Alvarez et al., 2013, Hall et al., 2009,

Robledo-Aceves et al., 2018, Sommer et al., 2011). Likewise, prematurity is associated with more severe bronchiolitis due to less developed lungs (Robledo-Aceves et al., 2018, Sommer et al., 2011). Other non-environmental factors found to be associated with more severe bronchiolitis include maternal asthma or atopy, a history of atopic dermatitis, previous ventilatory support, caesarean section delivery and low birth weight on admission (Alvarez et al., 2013, Hall et al., 2009, Robledo-Aceves et al., 2018, Sommer et al., 2011). There is no consensus on the relationship between ethnicity and severity, with some studies indicating that white males are affected most severely, but contrasting evidence is also available (Alvarez et al., 2013).

A wide range of social and environmental factors affect bronchiolitis severity. These include maternal breastfeeding (with breastfeeding being protective), cigarette, smoke, environmental pollution exposure, overcrowding within households, having siblings, attendance to day-care settings, and household animals or pests in households (Alvarez et al., 2013, Hall et al., 2009, Robledo-Aceves et al., 2018, Sommer et al., 2011).

RSV infection is a key factor associated with increased severity of disease and a risk of requiring hospitalisation, oxygen supplementation and an increased LoS (Fretzayas and Moustaki, 2017). An increased viral load is thought to contribute to more severe disease, although there is still some debate surrounding this (Fretzayas and Moustaki, 2017, Uusitupa et al., 2020).

1.6 Genetic Factors

Twin studies have estimated that genetics effect the severity of bronchiolitis from 16% to 20% (Thomsen et al., 2008). Studies suggest that genetic differences affecting epithelial cell surface molecules such as TLRs, pro-inflammatory mechanisms (Interleukin (IL)-8, IL-10, IL-13 and CX3CK1), and surfactant proteins may account for differences in severity or susceptibility (Tahamtan et al., 2019, Thomsen et al., 2009) .

There is currently varying evidence on the relationship between TLR-4, a putative pattern recognition receptor for RSV, and bronchiolitis severity. Some studies suggest that there is no link, whereas others suggest that certain polymorphisms lead to a dysfunctional immune response (Alvarez et al., 2013, Löfgren et al., 2010, Mandelberg et al., 2006). Similarly, the role of polymorphisms and genetic haplotypes of interleukins are still not fully understood (Alvarez et al., 2013, Mulet and de Torres, 2010). However, a recent study on surfactant protein (SP) variations found that the occurrence of polymorphisms (in SP-A1, SP-A2 and SP-D genes) was associated with altered bronchiolitis disease severity (Alvarez et al., 2013, Ampuero et al., 2011).

1.7 Management

NICE guidance states that all children with suspected bronchiolitis should have oxygen saturations measured (NICE, 2015). It states that antibiotics, hypertonic saline, nebulised adrenaline, salbutamol, montelukast, ipratropium bromide and corticosteroids should not be used in the treatment of bronchiolitis (NICE, 2015). Where children are persistently unable to maintain oxygen saturations greater than 92% on room air, supplemental oxygen should be given (NICE, 2015). However Cunningham et al. found that infants managed at a lower target oxygen saturation of 90% regained feeding and returned to normal quicker, as well as had fewer respiratory readmissions (Cunningham et al., 2015). Continuous positive airway pressure should be considered in those who have impending respiratory failure (NICE, 2015). Capillary blood gas testing is reserved for those with worsening respiratory distress, or impending respiratory failure (NICE, 2015). Nasogastric or orogastric fluids are given to those who are unable to maintain adequate oral intake (NICE, 2015). Intravenous fluids may be necessary if the child cannot tolerate nasogastric or orogastric fluids, or where impending respiratory failure is apparent (NICE, 2015).

With regards to viral testing, the NICE guidance does not currently comment on the use of virological testing, although it is recommended by the Scottish Intercollegiate Guidelines Network (SIGN) guidance (NICE, 2015, Baumer, 2007).

Although current guidance recommends against the use of hypertonic saline in the treatment of bronchiolitis a recent Cochrane review found that those receiving hypertonic saline had a reduced mean length of stay as well as lower post-inhalation clinical scores (Zhang et al., 2017). However, the American Academy of Pediatrics (AAP) recently updated its guidelines stating that there is currently conflicting evidence and that they recommend against hypertonic saline's routine use in the treatment of bronchiolitis (Silver and Nazif, 2019). NICE has also called for a randomised controlled trial of combined adrenaline and corticosteroid treatment following evidence from a Cochrane review suggesting potential short-term benefit (Hartling et al., 2011, NICE, 2019).

1.7.1 Therapeutic interventions during acute management

Current recommendations suggest that children with bronchiolitis should receive supportive therapies. Corrections of oxygen saturations persistently less than 92% (using nasal canula, non-invasive or invasive ventilation depending on severity), dehydration through nasogastric, or orogastric feeding, or intravenous fluid administration may be necessary (NICE, 2015, Ralston et al., 2014, Baumer, 2007). Guidelines currently suggest that treatment with antibiotics, adrenaline, beta-2 agonists, corticosteroids is unnecessary (Baumer, 2007, NICE, 2015, Ralston et al., 2014). Key safety information should be given on discharge (Baumer, 2007, NICE, 2015).

1.7.2 Palivizumab

Palivizumab is a monoclonal antibody against RSV that when given prophylactically reduces the severity of RSV disease in high risk children (Wang D, 2011, British National Formulary). It is currently recommended for use in children under nine months with chronic lung disease, and in preterm children under six months with haemodynamically significant, acyanotic congenital heart disease (British National Formulary). It should further be considered in those under two years old with severe combined immunodeficiency syndrome, those under one year who require long-term ventilation and those between the ages of one and two years who require long term ventilation and have an additional comorbidity (British National Formulary). Although it is

effective in prevention, it provides no benefit when given acutely to hospitalised children (Baumer, 2007). Palivizumab does not offer a cost-benefit if used unselectively, reflecting its exclusive use in the patient groups stated (Wang D, 2011).

1.8 Outcomes for Children with Bronchiolitis

Bronchiolitis infection is associated with future respiratory issues such as recurrence of wheeze, coughing and decreased future lung function (Zomer-Kooijker et al., 2014, Noble et al., 1997). The effects of requiring hospitalisation due to RSV bronchiolitis are cited have been detected at multiple time points ranging from three to 18 years of age (Sigurs et al., 2010, Noble et al., 1997, Fjærli et al., 2005, Jeng et al., 2015). A previous longitudinal study from Arizona assessing a cohort of 1246 individuals estimated that those with childhood bronchiolitis have a 40-50% increased risk of developing subsequent asthma (Stein et al., 1999). A further study evaluated the relationship between RSV and future wheeze by administering palivizumab to otherwise healthy infants (Blanken et al., 2013). Those who received the intervention had a 61% reduction in reported wheezing days, thus suggesting that RSV infection increases the risk of future wheeze (Blanken et al., 2013). However, it was also found that in the intervention group, wheeze was not eliminated suggesting that RSV is not exclusively the cause of future wheeze (Blanken et al., 2013). Increased rates of asthma and wheeze, as well as allergies are also observed in those with a history of childhood RSV hospitalisation (Sigurs et al., 2010). Sigurs et al. found that children with RSV bronchiolitis had reduced airway function, elevated fractional exhaled nitric oxide, eosinophil counts, and reduced spirometry results compared to the control group at age 18 (Sigurs et al., 2010). Respiratory repercussions of bronchiolitis can also be detected later in life with diminished airway function and increased airway hyper-responsiveness (Stern et al., 2007, Sigurs et al., 2010, Beigelman and Bacharier, 2013).

hRV has further been observed to have a significant role in the development of asthma (Beigelman and Bacharier, 2013). Rates of recurrent wheeze development were highest in infants with hRV bronchiolitis compared to other respiratory pathogens (Beigelman and Bacharier, 2013,

Midulla et al., 2012). Furthermore, asthma prevalence is higher in hRV infected infants when measured against RSV bronchiolitis and children not hospitalised with bronchiolitis (Koponen et al., 2012). More specifically, this correlation between future wheeze and asthma in hRV patients is highest in those with rhinovirus C infection (Beigelman and Bacharier, 2013, Hasegawa et al., 2014).

With regards to bronchiolitis and a causal relationship to asthma, it has previously been identified in several studies that viral infection may be associated with allergic predispositions (Al-Garawi et al., 2012, Holt et al., 2012, Cheung et al., 2010). Twin studies have failed to identify this causational relationship (Thomsen et al., 2009, Poorisrisak et al., 2010). Reports have also demonstrated the possibility of viral bronchiolitis being a marker, rather than a cause, of asthma. They suggest that allergic sensitization and airway dysfunction act to increase susceptibility to bronchiolitis, and so predispose these infants to later wheeze and asthma (Chawes et al., 2012, Jackson et al., 2012). Overall, it is difficult to determine the true relationship between bronchiolitis and asthma. It is further possible that the causative and predictive relationships may be somewhat intertwined.

1.9 Impact of COVID-19

The COVID-19 pandemic has had a major impact on RSV infections and therefore bronchiolitis worldwide. In Australia, a dramatic drop in detection levels of influenza (98%) and RSV (99%) was observed (Hills et al., 2020, Yeoh et al., 2020). Similar results have been observed in Hong Kong, France, Belgium, and Finland (Kuitunen et al., 2020, Cowling et al., 2020, Angoulvant et al., 2020, Van Brusselen et al., 2021). This highlights how non-pharmacological interventions such as social distancing, mask-wearing, and handwashing can significantly impact viral transmission. Furthermore, the relaxation of public health measures in Australia has led to a surge of RSV bronchiolitis cases outside of the normal winter epidemic time (Foley et al., 2021). The peak observed was greater than that of the previous year, and interestingly the median age of those affected was significantly higher as well (18.4 months old) (Foley et al., 2021). Overall, despite

bronchiolitis prevalence being significantly reduced due to infection control measures, this has subsequently led to an altered and greater sized cohort of children with bronchiolitis. It remains to be seen what will happen to RSV infections and bronchiolitis admissions once the UK comes out of lockdown as anticipated in late July 2021.

1.10 Objectives

The subject areas and chapters contained within this thesis are varied because of the constraints and uncertainties brough by the COVID-19 pandemic. The content of this thesis does not attempt to address a single hypothesis but rather several different objectives. However, all chapters relate directly to bronchiolitis.

The specific objectives of this thesis are:

- To perform a systematic review identifying and assessing current bronchiolitis severity scores published for use in clinical practice, including evaluation of validity and reliability information available.
- To utilise Alder Hey Children's Hospital (AHCH) bronchiolitis admission data to determine the demographic, clinical and temporal characteristics of patients attending for bronchiolitis. As well as evaluating any trends in bronchiolitis hospitalisations.
- To investigate the impact of deprivation and air pollution on AHCH bronchiolitis admissions in Liverpool City Region (LCR).

Chapter 2- Systematic Review

2.1 Introduction

Children with bronchiolitis present to healthcare professionals in different settings in a variety of ways, from mild disease with few lower respiratory tract signs and symptoms, to dyspnoea, apnoea and impending respiratory failure (NICE, 2015, Baraldi et al., 2014). Given such variation in presentation, an assessment tool capable of detecting changes in clinical condition has the potential to be useful in the clinical management and as an outcome measure in research trials.

Severity scores are often easy and quick to use tools that assess the clinical condition on presentation of an individual or to make serial evaluations to assess changes in condition. Severity scoring systems therefore have the potential to guide management such as need for hospitalisation, and for risk stratification. They can also be used to evaluate clinical effectiveness. Examples of current scores cited for use in bronchiolitis include the Wang score, Tal score, Liu score, Lowell score and Kerem score (Wang et al., 1992, Kerem et al., 1991, Liu et al., 2004, Lowell et al., 1987, Tal et al., 1983). However, data regarding their validity and ability to predict clinical outcomes are limited. There was no mention of severity scores in the most recent bronchiolitis NICE guidance (NICE, 2015).

The objectives of this chapter are to identify any novel or modified severity scores used in the assessment of bronchiolitis, as well as the parameters assessed within the score. Information regarding validity, reliability will also be extracted.

2.2 Methods

The systematic review was devised to gain more knowledge in the subject area and to assess what scores for the assessment of the severity of bronchiolitis were currently available. A protocol was registered with PROSPERO (ID: CRD42020218816), available in ***Appendix 1***. The search strategy and findings are detailed below. This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA checklist) available in ***Appendix 2*** *(Moher et al., 2009).*

2.2.1 Objectives

The primary outcome for this systematic review was to identify any novel or modified severity scores used in the assessment of bronchiolitis in children aged under two years old. A novel severity score was defined as the first publication of the assessment tool. A modified severity score was defined as any future publication of a severity score where the score was altered from the original publication.

Secondary outcomes included gaining an understanding of the different items assessed in each score, the possible values each item could generate, how the item was assessed and the weighting of each item in the overall score. Information regarding country of origin and clinical setting, as well as factors such as whether the score was used in the assessment of an intervention or included premature infants were collated. Information regarding the validity of the score was sought. This encompassed the overall validity of the score, its reproducibility, reliability, discriminatory power, and utility.

2.2.2 Review Question Development

The review question was developed according the PICO model (Tovey) (***Table 2.1***).

Population	Intervention	Comparator	Outcomes
Children ≤ 2 years old with bronchiolitis	Severity score.	Other severity scores and accessible validity data	Novel or modified bronchiolitis severity score. The different items. The setting of the score. Further information regarding validity.

Table 2. 1 Table showing the development of review question

2.2.3 Evidence Gathering and Study Selection

Using the search strategy ***(Table 2.2)*** devised from the proposed research question the databases Medline, CINAHL, PubMed and EMCARE were searched up to November 30th 2020, with any preceding date and without any language restrictions. Limits were then applied for the databases to refine the pool of studies highlighted **(*Table 2.3*)**. The references of all full-text studies eligible for inclusion were searched to extract any potentially relevant studies not returned by the database search. The identified literature was exported for storage and assessed using both EndNote and Microsoft Excel.

Search Strategy used
Concept 1: • Paeditric or pediatric • Paedia* or pedia* • Infant • Pre-school
Concept 2: • Bronchiolitis or viral bronchiolitis • RSV bronchiolitis • Respiratory syncytial virus, human or respiratory syncytial virus infections
Concept 3: • Severity score • Severity of illness index • Disease assessment

Table 2. 2 Table listing the Search Strategy used for the databases described

Database	**Limits applied**
Medline	Infant, new-born, child, or preschool limit
EMCARE	Human age groups infant to one year
CINAHL	Human age groups Infant~ Newborn: birth-1 month OR Infant: 1-23 months
PubMed	*Not available

Table 2. 3 Table illustrating the different limits applied for each database

2.2.4 Eligibility Criteria

The following criteria were applied at each stage of study screening.

Inclusion Criteria:

- Types of Study

  Studies that contain a novel or modified severity score were included. This encompassed randomised control trials (RCTs), both retrospective and cohort studies. All studies were eligible no matter what year of publication, country of origin or language written in.

- Population

  Children with a clinical diagnosis of bronchiolitis less than two years old (NICE, 2015). Studies including children born prematurely were included.

- Severity score

  Any novel or modified severity score for use in a clinical setting was included. The score had to have been used in the assessment of bronchiolitis and assigned numerical values to items in the score calculation.

Exclusion Criteria:

- Types of Study

  Systematic reviews were not included but were reverse referenced to obtain all relevant studies.

- Population:

  Studies involving non-human participants were not included. Studies that incorporated children outside of the age group were not included.

- Severity Score:

  Scores were not included where items were not extractable. Studies that described use of specialist equipment not readily available at the bedside (such as laboratory blood tests or chest radiograph) as part of the score were excluded. Furthermore, studies that used interventions as part of the score were removed

e.g. if patients were assessed based on intubation, presence in ICU or nasogastric tube feeding. Scores assessing retrospective factors such as length of stay, or length of time in oxygen were omitted.

2.2.3 Study Exclusion and Data Extraction

2.2. 3.1 Study Exclusion Method

Once duplicates were removed, studies were screened at three levels. Studies were screened by title and abstract, then by full text using the inclusion and exclusion criteria stated above. To minimise bias in study selection, this was additionally performed by a second reviewer, Emma Wilkinson. Any disagreements at each stage were discussed. Any discrepancies not settled were raised with a supervising clinician (Dr Dan Hawcutt) and resolved. Reasons for exclusion were documented at each stage. Any studies raising uncertainty concerning inclusion or exclusion were discussed with the second reviewer and educational supervisor.

2.2.3.2 Data Extraction

Once the exclusion process had been completed, data extraction from full text publications was performed by a single reviewer, eliciting an overall summary of study characteristics and all data relevant to the outcomes identified.

Study Characteristics extracted were:

- Author
- Title
- Source- database or reverse reference searching
- Year of publication
- Type of study
- Country of origin
- Population age range

Primary outcome assessment:

- Score name
- Whether the score was a novel or a modified score.

Secondary outcome assessment:

- Clinical location of score
- Assessor position
- The inclusion of preterm children
- Whether the score was designed based on intervention
- Items used, how they were assessed
- How the overall score was calculated
- Extraction of whether any validity or reliability measures were assessed

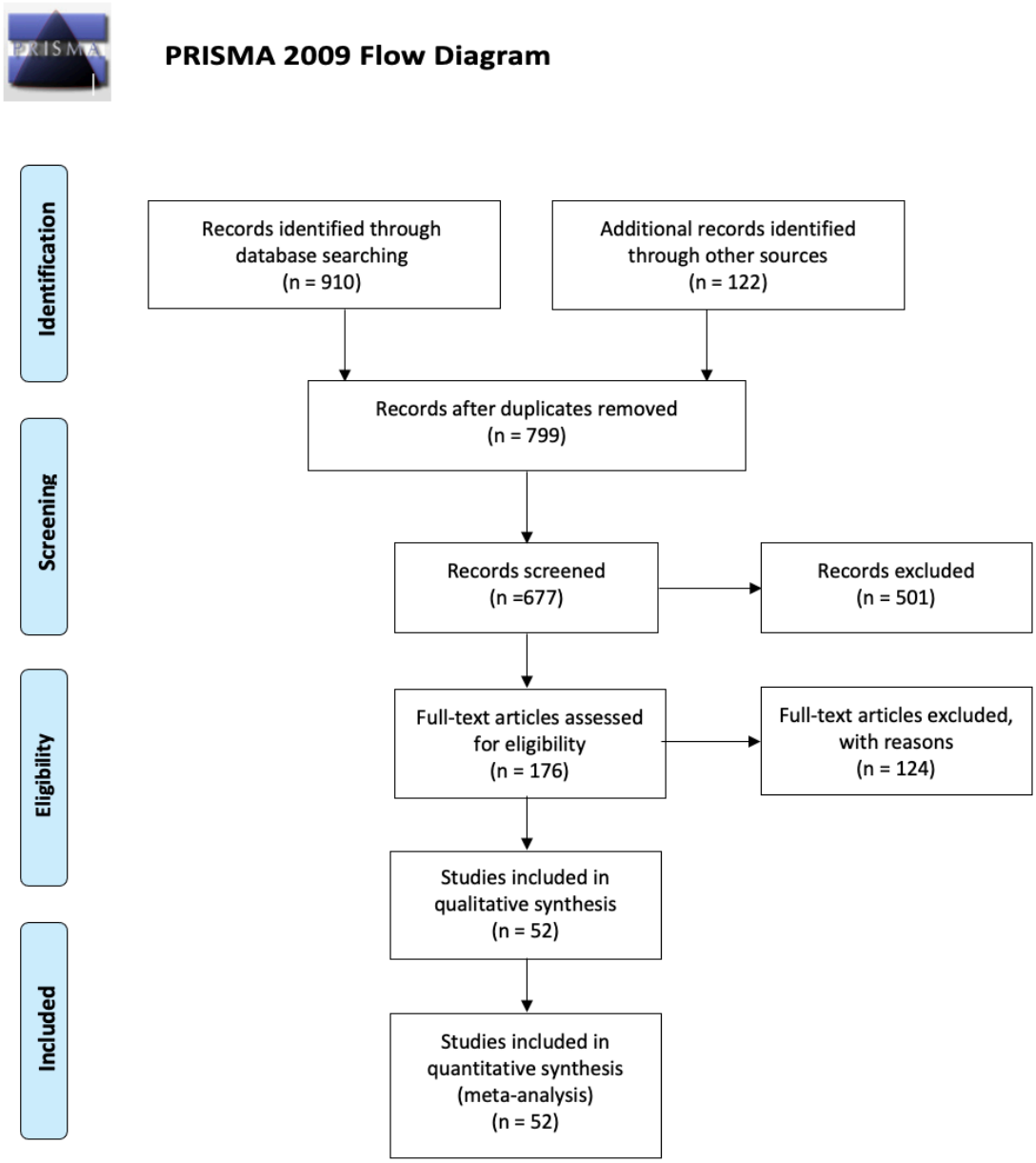
Once the data was extracted, further analysis was done based on the three most common items assessed. An item was defined as a clinical sign, symptom or measurement that was scored within the tool. These were then grouped into domains based on supervisory recommendation. This information was compiled into a tabular format using Microsoft Excel. This analysis can be viewed in ***Appendix 4***.

2.2.3.3 Assessment of Quality of Included Studies

Once the studies included were finalised, an assessment of study quality was performed. This was done to further minimise risk of bias as well as to ascertain the overall quality of the publications included in the study. For RCTs, the Cochrane risk of bias tool was used. The Newcastle-Ottawa Scale was used for cohort and case-control studies (Sterne et al., 2019, Wells GA). For any outlying studies, the applicable Joana Briggs Institute critical checklist was applied (Munn et al., 2020). This can be viewed in ***Appendix 2***.

2.3 Results

2.3.1 PRISMA results



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2. 1 PRISMA diagram showing the study selection process

Demonstrating the number of results at each stage of study screening

2.3.2 Study Characteristics

Out of the final 52 studies included, 52 scores were identified as 30 being novel scores and 22 scores modified from previously existing scores. The most common modifications were of the Wang score, Tal score or Kerem score (Kerem et al., 1991, Tal et al., 1983, Wang et al., 1992). It was found there were two duplicate variations of the same items among 5 scores. That is to say that Goebel et al., Teeratkulpisam et al. assessed the same items of respiratory rate, wheeze, oxygen saturation, muscle retractions and nasal flaring (Teeratakulpisarn et al., 2007, Goebel et al., 2000). Furthermore, Bajaj et al, Macias et al. and Ralston et al. assessed the same items of respiratory rate, wheeze, retractions, and air exchange (Bajaj et al., 2006, Macias et al., 2015, Ralston et al., 2010). However, in both cases this did not mean that the items chosen were measured in the same way, i.e., different respiratory rates were chosen.

Of the 52 studies included 16 originated from America, six from Israel, four from Italy, four from Spain, three from Canada, two from Australia, two from Greece, two from Norway, two from Singapore, and two from the UK. One study originated from each of the following countries: Belgium, Brazil, Egypt, France, India, Ireland, Pakistan, Taiwan, Thailand, and Turkey.

The year of publication for each of the studies ranged from 1973 to 2019, with most studies being published in 2004 (n=6). The types of study included were randomised controlled trials (RCT) (n=23), cohort (n=25) and cross-sectional studies (n=2). A published guideline was included as well as a non-randomised trial. ***Figure 2.2*** displays this information.

There were 27 scores that were used in EDs, seven on paediatric wards or departments, three in primary care facilities, two in outpatient areas and one in an intensive care setting. The setting of the score was not stated in 12 studies. Where recorded (n= 29), the role of the person that applied the score was most commonly doctors (n=18), nurses (n=7), or the term 'investigators' was used (n=9). Two studies stated that their score was used by respiratory therapists. This information was not included in 23 studies.

Age less than 24 months was most frequently cited as an inclusion criterion (n=17), with a further eight studies using age less than 12 months (***Figure 2.2***). With regards to the inclusion of premature infants, nine studies explicitly stated their inclusion, 13 stated their exclusion, and in 30 of the studies this was not stated. Twenty-nine of the studies did not use the score in relation to an intervention; 24 did and one of these (Conrad et al.) included aspects specific to the intervention within the score such as items relating to gastrointestinal upset (nausea, vomiting or diarrhoea) (Conrad et al., 1987). Further study characteristic information can be seen in ***Appendix 4*.**

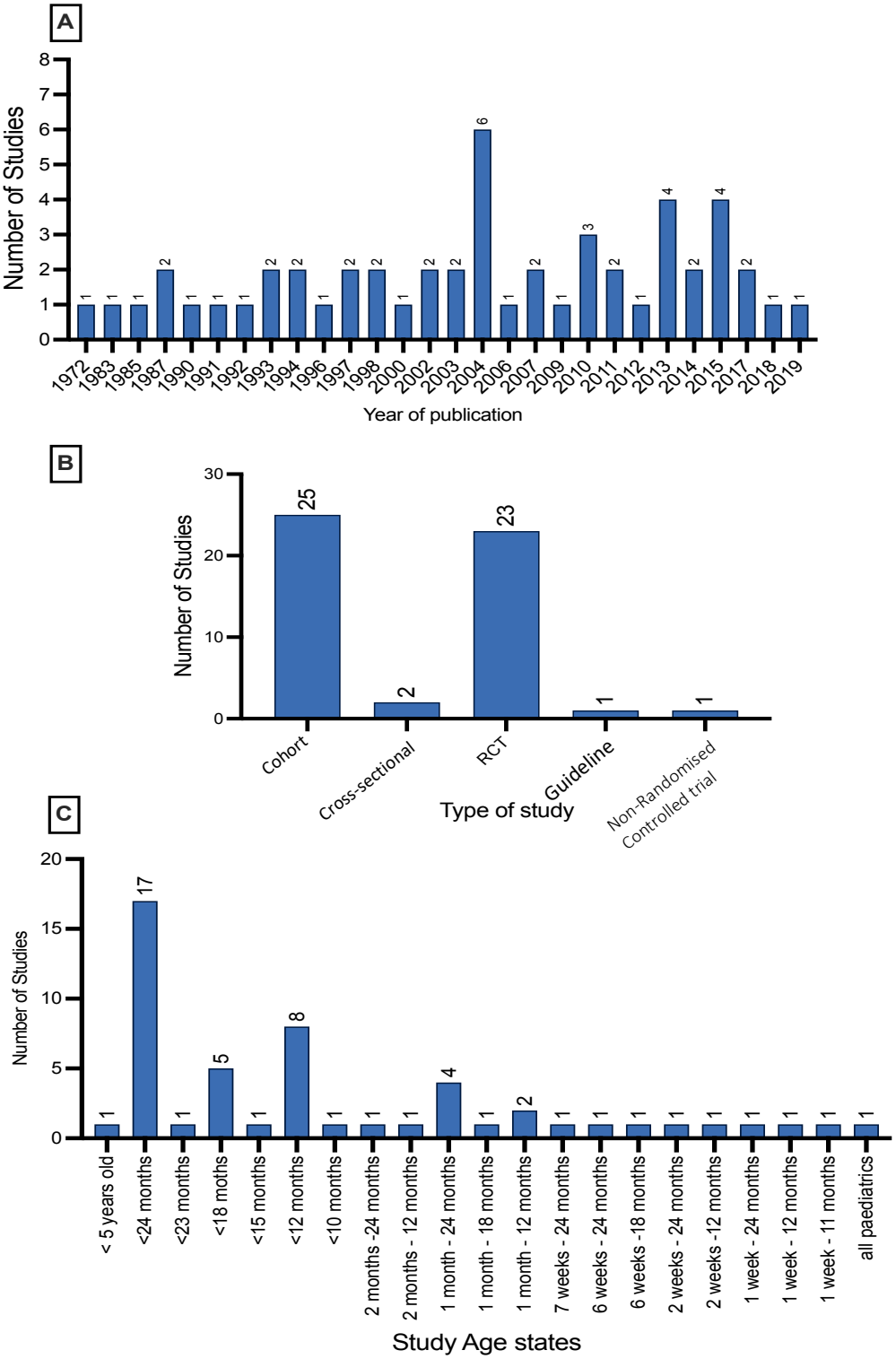


Figure 2. 2 Graphs demonstrating the characteristics information of the studies included

(A) *Bar-chart showing Frequency of year of publication from 1972-2019 demonstrating that the year in which most studies were published was 2004;* ***(B)*** *Bar-chart indicating the type of study included* ***(C)*** *Bar-chart showing the age of children included in the studies indicating wide variation, although most studies were for children less than 24 months of age.*

Primary author	Respiratory Rate	Heart Rate	Wheeze	retractions	Nasal Flaring	Oxygen Saturation
Bajaj et al.						
Bamberger et al.						
Basile et al.						
Beck et al.						
Berger et al.						
Bohé et al.						
Bressan et al.						
Can et al.						
Caserta et al.						
Chipps et al.						
Chong et al.						
Conrad et al.						
Constantopoulos et al.						
Conway et al.						
Dabbous et al.						
De Boeck et al.						
De Brasi et al.						
Ejaz et al.						
Gadomski et al.1994a						
Gadomski et al. 1994b						
Gajdos et al.						
Gal et al.						
Giugno et al.						
Goebel et al.						
Goh et al.						
Jacobs et al.						
Kerem et al. +						
Kristjansson et al.						
Lai et al.						
Lal et al.						
Liu et al. +						
Lowell et al. +						
Macias et al.						
Marlais et al.						
McCallum et al.						
Midulla et al.						
Ochoa Sangrador et al.						
Papadopalous et al.						
Ralston et al.						
Ramos Fernández et al.						
Raya et al.						
Rivera-Sepulveda et al.						
Rubin et al.						
Schuh et al.						
Skjerven et al.						
Tal et al.						
Teeratakulpisam et al.						
Wainwright et al. *						
Walsh et al. *						
Wang et al. +						
Webb et al.						
Wood et al. +						

Table 2. 4 Demonstrating 6 most common items found in the severity scores *White indicates where aspect was not assessed. Green indicates that a score assessed this aspect. Grey indicates that the score did not assess wheeze and where the information was not available. + indicates where score was commonly assessed. * indicates an algorithmic score*

2.3.4 Score Characteristics:

Overall, a total of 51 different items were identified and grouped into 9 domains. This information is available in ***Appendix 4***. The median number of items assessed per tool was four (range 2 to 9). Two of the studies generated their final score using an algorithm from individual items (Wainwright et al., 2003, Walsh et al., 2004). The tool used by Schuh et al. was an in-depth assessment of wheeze and muscle retractions (Schuh et al., 1990).

The most common items assessed were respiratory rate (RR) (46/52, 88%), wheeze (43/52, 83%), retractions or recessions (37/52, 71%) and nasal flaring (22/52, 42%). The six most commonly assessed items can be viewed in ***Table 2.4***. Full score characteristics and items assessed can be found in ***Appendix 4***.

The three most common items assessed (RR, wheeze, and retractions) were reviewed in more depth to extract similarities and differences in their evaluations as part of a score**.**

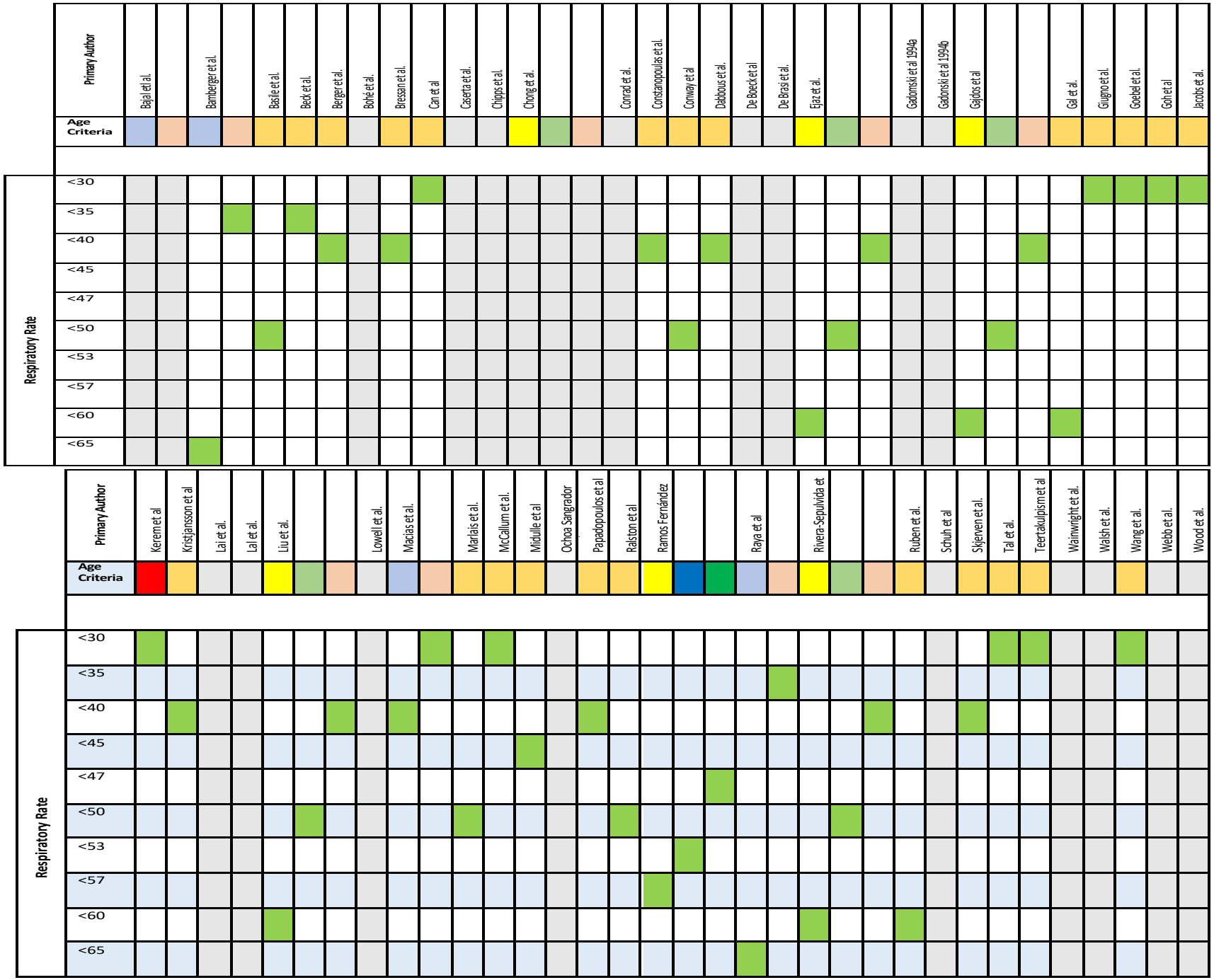
Within the identified scores, there was considerable variation in upper and lower limits selected in the assessment for RR within each tool (***Table 2.5*** & ***Table 2.6***). Thirteen scores had a RR of less than 30 breaths per minute as their lower limit. Lowest scoring RR limits ranged from less than 30 breaths to less than 65. An upper RR limit of greater than 60 breaths per minute was used as an upper boundary in 22 scores. Highest scoring RR limits varied from greater than 30 breaths, to greater than 80 breaths. Ten of the studies used different RR based on age categories. The age categories included were less than two or three months (n= 6), 0-12 months (n=4) ,2-6 months (n=1), 2-12 months (n=5), 6-12 months (n=1), and 12-24 months (n=9). Twenty-four scores did not measure RR in relation to age.

The most common aspects of wheeze assessed were the presence of end expiratory wheeze (23 scores), expiratory wheeze presence (22 scores), inspiratory and expiratory wheeze (20 scores), and wheeze being audible without a stethoscope (18 scores) (***Table 2.7)***.

Retractions were most commonly assessed as mild, moderate or severe in 20 scores. Intercostal muscle use was evaluated in 18 scores, subcostal retractions were specifically named in 13 of the scores and suprasternal retractions described in eight of them (***Table 2.8)*.**

2.3.5 Validity and reliability:

From the included studies, 15 included data regarding validity and reliability (***Table 2.10***). Construct validity was assessed in nine studies and content validity was evaluated in one. Reliability was assessed using inter-observer agreement (n=9) and internal reliability (n=2). The definitions of these terms can be found in ***Table 2.9***. The studies where construct validity was assessed analysed different outcomes such as requirement of supplemental oxygen or length of stay. Between studies, different methods of assessment of inter-observer agreement were noted.

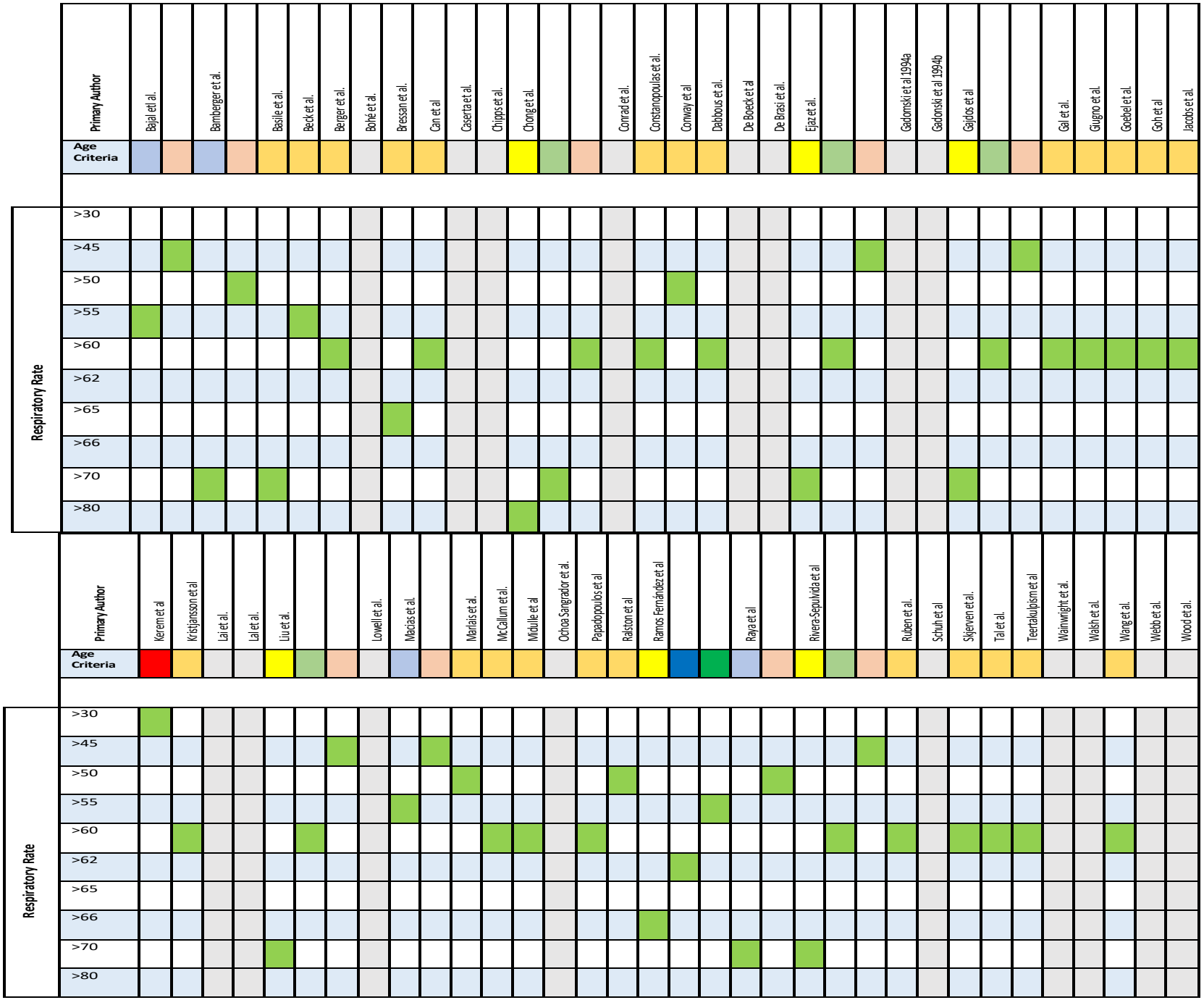


Key:

Age <2 (or <3 months)
Age 2-6 months
Age 6-12 months
Age 2- 12 months
Age 0-12 months
Age 12-24 months
Age 0-24 months
Age < 5 years

Table 2.5 Table demonstrating the assessment of Lower Respiratory Rate

See key for age categories. Green indicates where limit was used, grey indicates where information was not available.



Key:

Age <2 (or <3 months)
Age 2-6 months
Age 6-12 months
Age 2- 12 months
Age 0-12 months
Age 12-24 months
Age 0-24 months
Age < 5 years

Table 2.6 Table demonstrating the assessment of Upper Respiratory Rate

See key for age categories. Green indicates where limit was used, grey indicates where information was not available.

Primary author	Present	Mild/Moderate/Severe	End Expiratory	Expiratory	Part Inspiratory	Inspiratory	Inspiratory and Expiratory	Segmental-2/4 fields	Diffused- ¾ fields	All lung fields	Audible without stethoscope	Diminished Breath sounds	Silent Chest	Tracheosternal	Rales/Rhonchi
Bajaj et al.															
Bamberger et al.															
Basile et al.															
Beck et al.															
Berger et al.															
Bohé et al.															
Bressan et al.															
Can et al.															
Caserta et al.															
Chipps et al.															
Chong et al.															
Conrad et al.															
Constantopoulos et al.															
Conway et al.															
Dabbous et al.															
De Boeck et al.															
De Brasi et al.															
Ejaz et al.															
Gadomski et al. 1994a															
Gadomski et al. 1994b															
Gajdos et al.															
Gal et al.															
Giugno et al.															
Goebel et al.															
Goh et al.															
Jacobs et al.															
Kerem et al. +															
Kristjansson et al.															
Lai et al.															
Lal et al.															
Liu et al. +															
Lowell et al. +															
Macias et al.															
Marlais et al.															
McCallum et al.															
Midulla et al.															
Ochoa Sangrador et al.															
Papadopalous et al.															
Ralston et al.															
Ramos Fernández et al.															
Raya et al.															
Rivera-Sepulveda et al.															
Rubin et al.															
Schuh et al.															
Skjerven et al.															
Tal et al.															
Teeratakulpisam et al.															
Wainwright et al. *															
Walsh et al. *															
Wang et al. +															
Webb et al.															
Wood et al. +															

Table 2. 7 Table demonstrating the Assessment of Wheeze. *White indicates where aspect was not assessed. Green indicates that a score assessed this part. Grey indicated that the score did not assess wheeze and where the information was not available. + indicated where score was commonly assessed. * indicates an algorithmic score*

Primary author	Present	Mild/Moderate/Severe	General Accessory Muscle Use	Intercostal	Subcostal	Substernal	Suprasternal	Supraclavicular	Intracostal	Head bobbing	Tracheal Tug	Chest Indrawing	Tracheosternal	Neck or Abdominal
Bajaj et al.														
Bamberger et al.														
Basile et al.														
Beck et al.														
Berger et al.														
Bohé et al.														
Bressan et al.														
Can et al.														
Caserta et al.														
Chipps et al.														
Chong et al.														
Conrad et al.														
Constantopoulos et al.														
Conway et al.														
Dabbous et al.														
De Boeck et al.														
De Brasi et al.														
Ejaz et al.														
Gadomski et al. 1994a														
Gadomski et al. 1994b														
Gajdos et al.														
Gal et al.														
Giugno et al.														
Goebel et al.														
Goh et al.														
Jacobs et al.														
Kerem et al. +														
Kristjansson et al.														
Lai et al.														
Lal et al.														
Liu et al. +														
Lowell et al. +														
Macias et al.														
Marlais et al.														
McCallum et al.														
Midulla et al.														
Ochoa Sangrador et al.														
Papadopalous et al.														
Ralston et al.														
Ramos Fernández et al.														
Raya et al.														
Rivera-Sepulveda et al.														
Rubin et al.														
Schuh et al.														
Skjerven et al.														
Tal et al.														
Teeratakulpisam et al.														
Wainwright et al. *														
Walsh et al. *														
Wang et al. +														
Webb et al.														
Wood et al. +														

Table 2. 8 Table demonstrating the assessment of retractions. *White indicates where aspect was not assessed. Green indicates that a score assessed this part. Grey indicated that the score did not assess retractions and where the information was not available. + indicated where score was commonly assessed. * indicates an algorithmic score*

Term	Definition
Construct Validity	The degree to which the score relates to another measure that is consistent with theoretically derived hypotheses (Birken et al., 2004, Terwee et al., 2007)
Content Validity	The degree to which items of an assessment are representative of the domain the test seeks to measure (Salkind, 2010)
Inter-Observer Agreement	The degree to which multiple observers independently obtain similar scores (Birken et al., 2004, Terwee et al., 2007)
Internal Consistency	The extent to which all items measure the same characteristic (Terwee et al., 2007, Birken et al., 2004)

Table 2.9 Table showing Reliability and Validity Definitions

Primary Author	Concepts Assessed
Caserta et al.	Construct validity, content validity
Chong et al.	Construct validity
Gadomski et al. 1994a	Construct validity, inter-observer agreement
Gajdos et al.	Inter-observer agreement
Gal et al.	Construct validity
Jacobs et al.	Inter-observer agreement
Kerem et al.	Inter-observer agreement
Liu et al.	Inter-observer agreement
Marlais et al.	Construct validity
McCallum et al.	Construct validity, inter-observer agreement
Ramos Fernández et al.	Inter-observer agreement, internal consistency
Rivera-Sepulveda et al.	Inter-observer agreement, internal consistency
Walsh et al.	Construct validity
Wang et al.	Construct validity, inter-observer agreement
Wood et al.	Construct validity

Table 2.10 Table showing the assessment of Validity and Reliability.

2.4 Discussion

This review is a comprehensive and in-depth of assessment currently available severity tools used in bronchiolitis currently available. Severity scores have the potential to aid the prediction of patient outcomes, risk stratification and clinical decision making. This systematic review illustrates the current range of possible scores used for bronchiolitis assessment. It demonstrates that although there is a lot of variation between tools, there are also similarities, with most scores assessing respiratory rate, presence of wheezing and muscle retractions as per NICE guidance (NICE, 2015).

The upper age limit of bronchiolitis as defined within the NICE guidelines is two years of age (NICE, 2015). It is important that severity scores take into account the physiological differences between a neonate and a two-year-old child. It is not easy to find where the normal ranges for vital signs such as respiratory rate or heart rate in infants and children are derived from. Many guidelines and scores use the Advanced Paediatric Life Support (APLS) guidance to provide normal ranges for specific age groups (***Table 2.9***) (Group, 2016). However, Fleming et al. demonstrated discrepancies and lack of research supporting the choice of some of these 'normal' values (Fleming et al., 2011). They reviewed the findings of 20 studies on 3,881 children to produce centiles for respiratory rates. The results obtained demonstrated a natural decrease in RR with age as expected but that there is significant variation in the normal for each age category. Fleming et al. found that the median RR for children aged 6 months was 40 breathes per minute (Fleming et al., 2011). Applying this to the lower limits of the respiratory scores in this review, this RR would be considered abnormal in 10 of the tools when this is a normal resting RR. This underlines the importance of assessing disease with multiple items in a score and the benefits of having age-specific items.

Normal ranges: respiratory rate (RR), heart rate (HR) and blood pressue (BP)							
	Guide weight (kg)		**RR At rest Breaths per minute 5th–95th centile**	**HR Beats per minute 5th–95th centile**	**BP Systolic**		
Age	**Boys**	**Girls**			**5th centile**	**50th centile**	**95th centile**
Birth	3.5	3.5	25–50	120–170	65–75	80–90	105
1 month	4.5	4.5					
3 months	6.5	6	25–45	115–160			
6 months	8	7	20–40	110–160			
12 months	9.5	9			70–75	85–95	
18 months	11	10	20–35	100–155			
2 years	12	12	20–30	100–150	70–80	85–100	110
3 years	14	14		90–140			
4 years	16	16		80–135			
5 years	18	18			80–90	90–110	111–120
6 years	21	20		80–130			
7 years	23	22					
8 years	25	25	15–25	70–120			
9 years	28	28					
10 years	31	32					
11 years	35	35					
12 years	43	43	12–24	65–115	90–105	100–120	125–140
14 years	50	50		60–110			
Adult	70	70					

Table 2. 11 the APLS reference ranges for respiratory rates based on age (Group, 2016).

An indicator of respiratory distress was included in most bronchiolitis severity scores. Head bobbing was included in 3 scores. This sign is present in younger infants who lack head support. When it appears, it is often a sign of worsening clinical condition (Nonoyama et al., 2019). Although it tends to not be present in older children, it is a key sign of respiratory distress in younger ones. This highlights the benefits of having age specific criteria in an assessment tool.

The assessment of accessory muscle use was often complex. Retractions were assessed in 37 scores with 14 different possible aspects assessed. These ranged from an assessment of severity

using mild, moderate and severe criteria, to requiring identification of the specific muscle groups used. Similarly with wheeze evaluation, some scores included end expiratory, part inspiratory, segmental, or diffuse wheeze and several stated terms such as rales and rhonchi within their assessment. The complexity involved in eliciting these signs limits the use of the scores to those with medical degrees or extensive experience. They also may not allow for swift evaluation in cases of severe disease. It is important that a severity score reflects its clinical setting and the competency of those using it.

Although it is important that these scores are quick and easy to apply if they are to be used clinically. With a simplified assessment involving terms such as mild, moderate, or severe, it is possible that subjectivity may become an issue. Where scores use this scale of mild, moderate, or severe, there exists a problem of personal threshold for severity. Marlais et al. alleviated this potential bias by using only objective measures of heart rate, respiratory rate, duration of symptoms, oxygen saturation as well as age and found an area under a receiver operating characteristic curve (AUROC) (a measure of overall performance of a clinical score) of 0.81 (Marlais et al., 2011, Melo, 2013). However, it is possible that by relying solely on objective measures, key aspects of bronchiolitis diagnosis such as the wheeze and retractions may be missed, resulting in misdiagnoses being made and inappropriate management. A balance is needed between subjectivity and observable factors.

Validity and reliability data were available for only 15 scores. This mostly consisted of construct validity (nine scores) and inter-observer agreement (nine scores). Internal consistency was available in two scores and content validity in one. A validated score should further look at aspects such as discriminatory power, face validity, criterion validity and responsiveness as has been performed previously in well validated asthma assessment tools (Parkin et al., 1996, Gorelick et al., 2004, Chalut et al., 2000). It is vital that more validity and reliability data is generated and should be a future focus of research. Factors that should be assessed as highlighted in the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist include reliability, internal consistency, content validity,

construct validity, criterion validity, hypotheses testing, responsiveness and interpretability (Mokkink et al., 2010).

Previous studies have assessed the validity of existing tools. Duarte-Dorado et al. found that a previously modified Wood-Clinical Asthma Score (M-WAS) and the existing Tal score positively correlated with each other; they were both performed with ease and had good inter-observer agreement (kappa =0.897). The M-WCAS for those requiring admission to PICU was significantly higher than those admitted to the paediatric ward (Tal et al., 1983, Duarte-Dorado et al., 2013, Wood et al., 1972). Chin and Seng et al. compared the reliability and validity of the Kristjansson and the Wang tools of bronchiolitis assessment (Chin and Seng, 2004, Kerem et al., 1991, Wang et al., 1992). They demonstrated a correlation between oxygen saturation and higher scores for both tools but overall found the Kristjansson score to have higher validity and reliability (Chin and Seng, 2004). A more recent study found that the Kristanjansson score had a higher inter-observer agreement (intra-class-correlation coefficient (ICC) = 0.78) than the Wang score (ICC = 0.69) (Pinto et al., 2020). Again, both tools correlated with oxygen saturation levels (Pinto et al., 2020). The Modified Tal Score (MTS) from McCallum et al. was found to be internally valid, reliable and able to predict supplemental oxygen requirement as well as increase LoS (Golan-Tripto et al., 2018, McCallum et al., 2013). As expected, the greatest variability between assessors with different levels of experience was in the subjective items such as auscultatory findings and accessory muscle use. Validity assessment of the McCallum MTS and a modified Wang score (not included in the study as it was not designed for bronchiolitis assessment) were found to be internally reliable and valid (Shinta Devi et al., 2019, McCallum et al., 2013). It was further determined that the McCallum MTS was more reliable and replicable. They confirmed its ability to predict LoS and oxygen requirements. It was found that the MTS had a high sensitivity and specificity. However, this study assessed these respiratory scores in relation to all respiratory infections in those aged less than two years old, and not exclusively bronchiolitis. This further highlights that many of the scores commonly used, or are cited for use in bronchiolitis were originally designed for the assessment of other respiratory conditions, namely asthma (such as the scores from Kerem and Wood), wheezing (Lowell) or a combination (Liu and Tal). The Wang

score was originally designed for use in pneumonia as well as bronchiolitis (Dabbous et al., 1966, Kerem et al., 1991, Liu et al., 2004, Lowell et al., 1987, Tal et al., 1983, Wang et al., 1992, Wood et al., 1972). Given that these scores were not designed specifically for bronchiolitis, there is a need for appropriate assessment of their validity and reliability. Overall, while inter-observer agreement for several scores has been illustrated, the McCallum MTS score is the most comprehensively validated for clinical use; further validation of other bronchiolitis severity scores is required.

Severity scores for the assessment of bronchiolitis can be used as outcome measures in clinical trials. The multitude of scores available emphasises the need for a uniform bronchiolitis score which would enable studies and trials to be more comparable if the same severity tool was used.

The incorporation of a chosen clinical severity tool into hospital technology would enable easy assessment of the scores' validity, sensitivity, and ability to predict outcomes. This could involve artificial intelligence in the future to predict clinical outcomes from initial, or serial recordings of the score as well as continual assessment of the usefulness of the assessment tool. Moreover, this could allow for comparative score studies to be done between trusts, or countries and their chosen scores.

2.5 Conclusion

In conclusion, there is a wide range of bronchiolitis severity scores currently used. They most commonly involve the assessment of respiratory rates, wheeze, and respiratory muscle use. However, between each of these scores there is little consistency in the evaluation of these items. Moreover, the construct validity and inter-observer agreement of the tools is most frequently assessed, yet there is little data regarding the other areas of validity and reliability of these scores.

2.6 Strengths & Limitations:

This review is a comprehensive review of scores used for bronchiolitis severity assessment. The primary search was well constructed and validated with the direction of a librarian with considerable experience in conducting searches for literature for systematic reviews. Moreover, the screening process was done by two independent reviewers enabling rigorous criteria implementation and preventing applicable studies from being lost.

A potential limitation of this review is the possibility that the search criteria to failed to detect all relevant studies. The criteria requiring that a novel, or modified score was assessed presents the ability for certain studies to be missed, especially those assessing the validity of existing scores. A search for the validity of existing scores could be addressed by future research as it is a review subject in of itself.

As with all systematic reviews, the data extracted is solely reliant on what is contained within the included studies. This poses a limitation, as several included confusing information or wording, and the tracing of a score's origin was not always possible in the screening stages due to confusing or inaccurate citations. An added limitation in data extraction occurred where scores were poorly described and so the information regarding who implemented the score, or the how the item was assessed was not obtainable.

Furthermore, a limitation exists within the definition of bronchiolitis. Strict age criteria and a clinical diagnosis of bronchiolitis were applied to mitigate risks, but it does not reflect how the definition of bronchiolitis varies between countries and has varied over time. The application of a protocol reduced the impact of this limitation.

Chapter 3- Bronchiolitis Admissions

3.1 Introduction

In the U.K. 46.1 per 1000 children are hospitalised with bronchiolitis each year (Green et al., 2016). Between 2004 and 2011, hospital admissions for bronchiolitis in England increased on average by 1.8% per year (Green et al., 2016). In Scotland, between 2001 and 2016, average admissions rose by 2.2 fold (Chung et al., 2020). This trend has also been demonstrated worldwide (Moore et al., 2019). There is a 5.3 fold difference in hospital admission rates across the 352 government areas in England which is likely due to local outbreaks, local resources and differences in socioeconomic factors such as housing conditions and family size (Green et al., 2016).

Alder Hey Children's Hospital is a large children's hospital Liverpool that delivers quaternary, tertiary, and secondary care to children from the Liverpool city region (LCR) and beyond. Liverpool has a population of 498,000 people with 17.5% being aged less than 15 years old (estimated on 3rd March 2021). The population is projected to reach 531,000 by 2030 (Liverpool City Council, 2021b). Liverpool was announced as a *UNICEF Child-Friendly City* in 2019*,* meaning prioritisation of children's health, well-being and development (Liverpool City council, 2019).

In 2019, Liverpool was ranked the third most deprived of the local authority areas in the UK and has in previous years been the most deprived area (2004, 2007 and 2010) (Liverpool City Council, 2020). 145 of the 298 Lower-Layer Super Output Areas (LSOAs) in Liverpool are in the most deprived 10% nationally (Liverpool City Council, 2020). The city has one LSOA in the top ten most deprived nationally, as well as 31 LSOAs in the most deprived 1% (Liverpool City Council, 2020).

Deprivation is a multifactorial concept encompassing all aspects of life. In England, the Indices of Multiple Deprivation (IMD) is used as a tool of measurement of deprivation. It includes local evaluations of income, employment, education, health, disability, crime, barriers to housing, and

quality of indoor and outdoor local environments as shown in ***Figure 3.1*** (Ministry of Housing, 2019). Many of these factors are known to have direct and indirect effects on children's respiratory health.

There are 7 domains of deprivation, which combine to create the Index of Multiple Deprivation (IMD2019):

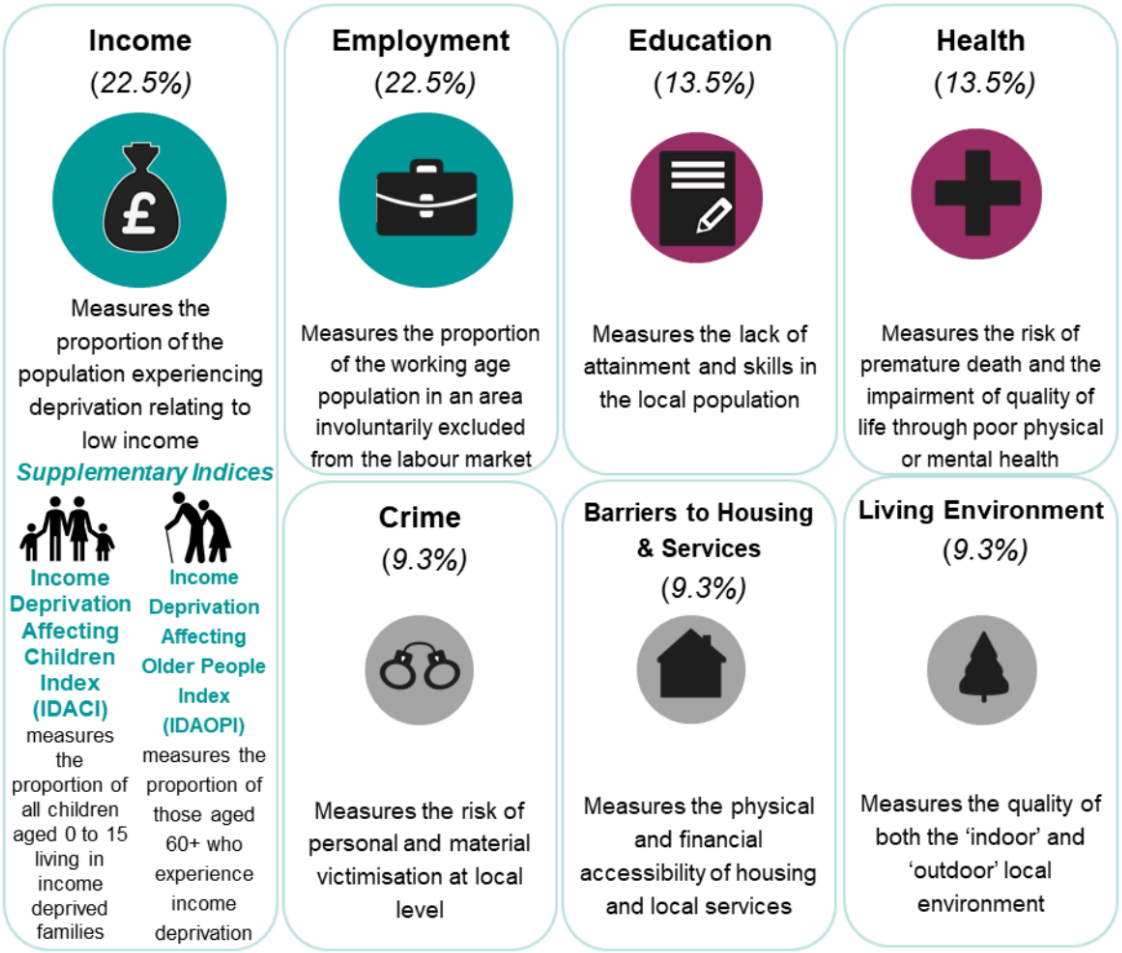


Figure 3. 1 Figure showing the 7 domains of deprivation (Ministry of Housing, 2019)

A strong relationship has previously been found between bronchiolitis and deprivation. Factors linking the two include overcrowding, poor housing and unemployment (Spencer et al., 1996). Lower socioeconomic status is associated with a 30-37% higher risk of hospitalisation and ICU admission (Chung et al., 2020). Aspects of this may be explained through decreased breastfeeding habits (across the UK 56% of mothers from the most deprived areas initiate breastfeeding, compared to 83% from the least deprived areas), day-care spread, parent's

perceptions of treatment, and decreased primary care interventions (Chung et al., 2020, Peregrino et al., 2018). Furthermore, these factors affect lung development, even foetal lungs, and have been demonstrated to impact future respiratory health (Foley et al., 2019, Jordan et al., 2006).

Ambient air pollution increases severity of respiratory infections (including bronchiolitis), generates more hospitalisations, and causes increased infant mortality due to respiratory conditions (Terrazas et al., 2019, Karr et al., 2009). Fine particulate matter ($PM_{2.5}$) is a chemical mix of solid and liquid particles from a variety of sources. In the UK, it is most often produced by the burning of fossil fuels because of traffic, heavy goods vehicles, and buses. UK data demonstrates that 80% of roadside nitrogen dioxide (NO_2) comes from vehicle emissions, mostly from diesel engines (Pino et al., 2004, DEFRA, 2017) (British Lung Foundation, 2020). A 10μm increase in levels was associated with a 5% increase in bronchiolitis incidence (Ségala et al., 2008).

Air pollutants act in a similar way to tobacco, diminishing muco-ciliary clearance, inducting oxidative stress and generating pro-inflammatory responses (Pino et al., 2004, Kelly, 2003). The oxidants in the pollutants initiate cytokine release, cause adhesion molecule and tight junction modifications thereby enabling inflammatory cell influx. This ultimately leads to increased lung permeability (Kelly, 2003). This background lung inflammation leaves the lung more susceptible to infection, enabling RSV and other viruses to infect the lower airway more easily. The synergistic effect of air pollution and RSV exposure is further seen by the fact that in RSV infected cells, IL-6 and IL-8 induction is reduced when cells are exposed to NO_2. (Yitshak-Sade et al., 2017).

The developing lung is thought to be most sensitive to high levels of pollution. In utero, foetal lungs are susceptible to lung toxicants at doses below no-effect levels for adults (Binkove B, 2004). Children are more susceptible to air pollution given their immature immune system, a greater air turnover and larger retainment of air pollution per unit of body weight compared to adults, as well as their higher respiratory rates (Barnett et al., 2005). Children also spend more time outdoors potentially being exposed to higher levels of pollutants than adults (Barnett et al.,

2005). Furthermore, air pollution increases hospital admissions, school absences, inhibits growth and other organ development (Barnett et al., 2005, Mathieu-Nolf, 2002). Air pollution exposure represents a major health inequality, especially to children, as the more deprived communities tend to be located in areas with higher levels of pollution despite these families often having the lowest rates of car ownership (Mitchell and Norman, 2012, Barnes et al., 2019).

Liverpool City Council (LCC) currently operates two air quality monitoring stations as well as 73 passive diffusion tubes both monitoring ambient NO_2 levels (Liverpool City Council, 2021a). The Air Quality Standards Regulations 2010 require that the annual mean concentration of NO_2 must not exceed 40 $\mu g/m^3$ (Department for Environment Food and Rural Affairs, 2021). Since 2010 the UK government has had levels of NO_2 that breach legal limits, and despite some action, around 90% of local authorities are still in breach of this level (Taskforce for Lung Health, 2020). Moreover, air quality in Liverpool City Region (LCR) alone has been linked to up to 1,040 deaths a year (British Lung Foundation, 2020).

3.2 Methods

3.2.1 Objectives:

The objectives were to characterise the demographic, clinical and temporal trends of bronchiolitis attendances to Alder Hey Children's Hospital between 1st September 2015 and 31st August 2020, as well as exploring the impacts of deprivation and air pollution on them.

3.2.2 Hypotheses

Hypothesis 1: Younger children are more likely to be admitted and to have worse clinical severity.
Hypothesis 2: Children living in areas of higher deprivation are more likely to be admitted and to have worse clinical severity.
Hypothesis 3: Children living in areas of high pollution are more likely to be admitted and to have worse clinical severity

3.2.3 Patient Selection:

Patients were identified via the Alder Hey information technology (IT) and coding systems. The data were obtained through the hospital Meditech database and included all those with a coded diagnosis of bronchiolitis as per the ICD-10-CM categorisation. Inclusion criteria were a diagnosis of bronchiolitis, residence in LCR and age less than two years old. Patients from areas without a Liverpool (L) postcode and attendances outside of the stated time frame (1st September 2015 to 31st August 2020) were excluded.

ICD-10-CM Code	Definition
J210	Acute bronchiolitis due to respiratory syncytial virus
J211	Acute bronchiolitis due to human metapneumovirus
J218	Acute bronchiolitis due to other specified organism
J219	Acute bronchiolitis, unspecified

Table 3.1 Table of the ICD-10-CM Code definitions for Acute bronchiolitis

3.2.4 Definitions

Bronchiolitis was defined according to the coding of patients on discharge from hospital. Patients were also stratified based on length of stay (LoS) in hospital and specifically a six-hour time point. Those with a LoS greater than six hours were classified as having been admitted to hospital. Those with a LoS less than six hours had generally (although not uniformly) been briefly observed on a medical observation ward adjacent to the emergency department. Patients were further classified based on the requirement for supplemental oxygen and admission to critical care. Information on need for supplemental oxygen came from Paediatric Early Warning Score (PEWS) data and was generated by the IT department from the electronic patient record. Critical care (CC) admission was defined based on any coded admission to high dependency unit (HDU) or paediatric intensive care unit (PICU).

3.2.5 Data Extraction

Demographic characteristics for children admitted with bronchiolitis such as age in days, sex, date of death and postcode were obtained. Information relating to the admission and discharge methods, dates and times, length of stay, and primary diagnosis were also source sourced. Other information obtained included supplemental oxygen use and critical care admission.

Postcode information enabled generation of the Indices of Multiple Deprivation using the 2019 government tool (Ministry of Housing, 2019). This allowed home addresses to be ranked into deciles reflecting levels of deprivation. The deciles ranged from 1 to 10, with 1 being the 10% most deprived, and 10 reflecting the 10% least deprived areas of the UK. The cohort was then contrasted with the data from the council regarding the deprivation decile characteristics for Liverpool (Liverpool City Council, 2020).

Data was generated from the local council regarding air pollution levels for all given postcodes. Information from the diffusion tubes and Automatic Urban and Rural Networks (AURN) were obtained in collaboration with LCC. The two AURNs covering Liverpool are located in Speke (South Liverpool) and on Queen's Drive (North Liverpool, which was closed in 2016, and so only the data until its closure was available) (Air Information Resource, 2021). There are 73 diffusion tubes across Liverpool arranged in five groups: Central, North, South, and along the number ten and 14 bus routes. There are a further 10 diffusion tubes at Liverpool John Lennon Airport.

The postcodes and admissions dates from the hospital records were then paired with the date and NO_2 levels recorded from the nearest site in order to assess the relationship between pollution levels, bronchiolitis admissions and their severity. Air pollution data was generated by LCC using the monthly NO_2 readings published in their Annual Status Reports for Air Quality over the time period 2015-2019 as available at the time of writing. Bronchiolitis patients from the study were included in the analysis if their postcode was located within 1km of a diffusion tube in order to assure the pollution data was representative of the area.

3.2.6 Analysis

A Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. All variables measured were not normally distributed and so non-parametric tests were used. Descriptive analysis was performed using median and interquartile range (IQR). Comparisons between two groups were made using a Chi-squared test for nominal data by inputting the values into SPSS. A p value of less than 0.05 was used to define statistical significance. Excel, SPSS and PRISM Graphpad were used to perform the analysis.

Analysis was performed looking at all patients to obtain an overall description of patients attending AHCH with bronchiolitis. The cohort was then analysed by grouping patients based on variables such as age, sex, IMD decile or supplemental oxygen required. Information regarding the temporal setting of the patients enabled investigation in to the hourly, daily, monthly and yearly trends.

Using patient's postcode and the location of diffusion tubes, Voronoi cells were generated with an area of influence of 1 kilometre. The postcodes within each of these cells were then tagged with the NO_2 reading at their closest station during the month their hospital attendance took place. Each attendance was then sorted into 1$\mu g/m^3$, giving the number of attendances occurring at each increment of NO_2. An average exacerbation count for each NO_2 bin was then calculated (Count of Exacerbations / Number of months during study period at that NO_2 reading). A simple linear regression aims to determine whether the relationship between two variables is linear. It was performed to relate the count of exacerbations to the monthly NO_2 readings. A residual plot was used to determine the appropriateness of the linear regression.

3.3 Results

3.3.1 Demographic Characteristics

Overall, 4417 patients were coded as attending AHCH with bronchiolitis between 1st September 2015 and 31st August 2020. The cohort was further refined using the inclusion criteria described

above and by excluding multiple admissions in 24 hours after the primary admission. The final cohort was 3559 patients. Most patients were admitted through Alder Hey Accident and Emergency (A&E) (n= 3523, 99%) with 50% being assessed by general paediatricians (n=1783), 47% via ED doctors (n=1685), and 3% through a specialist paediatrician (n=91). Of the patients highlighted, 20 died within the time frame, however only two of these occurred within the stated admission and an additional two within a month of discharge from their bronchiolitis admission.

The median age of all children was 120 days (IQR of 178 days) with a range from 0-725 days. Age-range frequency is shown in ***Figure 3.2*** with most admissions being infants aged 0-2 months (n=992).

There were 2153 (60%) males identified and 1406 (40%) females (***Figure 3.2***). The median age for males was 127 (IQR = 177) days and females 109 (IQR=179) days. The median length of stay for males was 16 (IQR = 62) hours and females 21 (IQR=77) hours. More males attending hospital with bronchiolitis were admitted than females (boys, 38%: girls 27%; Chi-square value=6.68, p-value= 0.0097, degrees of freedom =1).

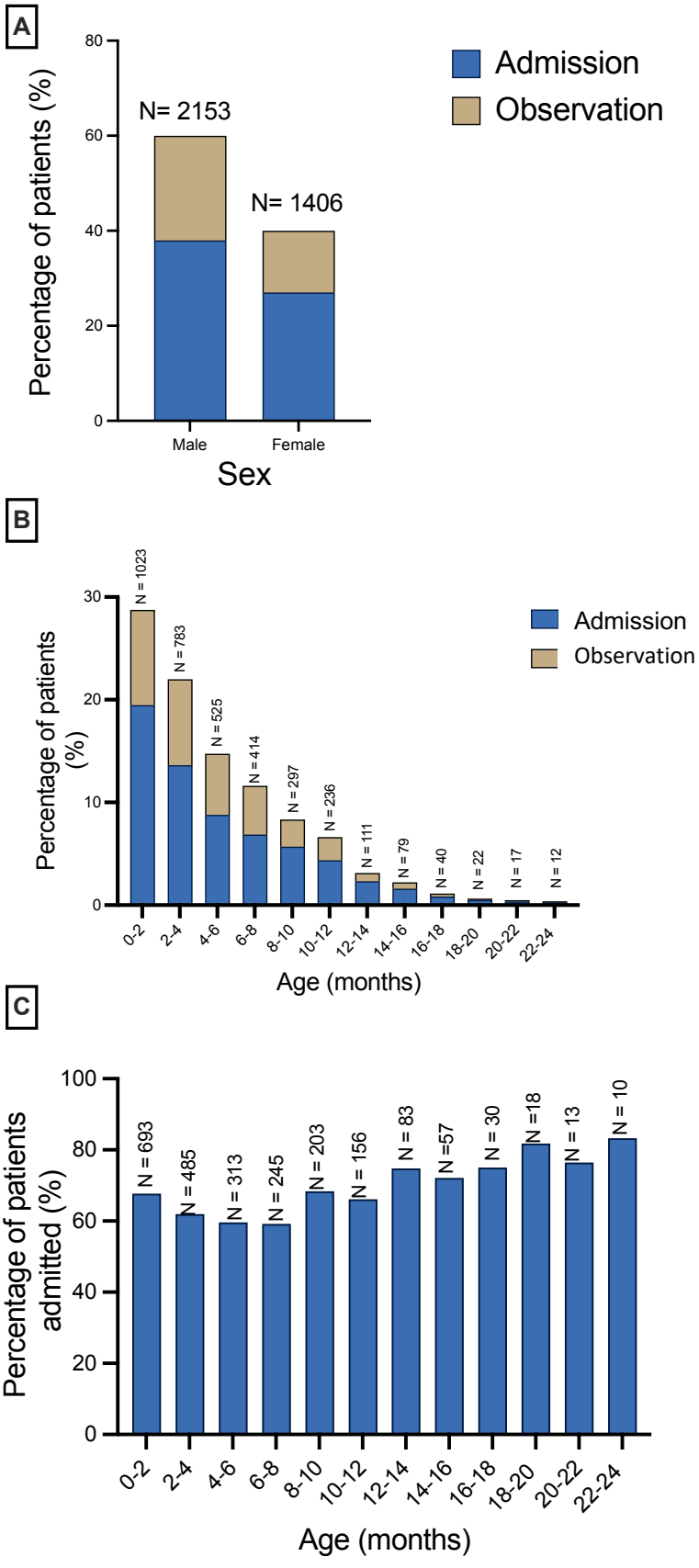


Figure 3. 2 Figures illustrating the demographic Results

*(**A**) Demonstrating the sex of the patients, with further refinement of the percentages of those admitted and those observed. It illustrates that more males had bronchiolitis (60%) as well as were more likely to be admitted with bronchiolitis (38%). (**B**) highlights the age distribution of the cohort as well as percentage of those admitted, showing that with increasing age the number of patients decreased. (**C**) Age and % of those admitted*

3.3.3 Clinical Characteristics

Most patients (52%, n= 1856) were coded as having unspecified bronchiolitis, 26% (n= 924) with RSV bronchiolitis, 11% (n=384) as bronchiolitis due to other specified organism, 9% (n=327) as other primary diagnosis and 2% (n= 68) bronchiolitis due to human metapneumovirus (HMPV) (***Figure 3.3***).

Length of stay for all attendances was found to have a median of 18 hours (IQR = 66), with a range of 0.12 hours to 11989 hours. Attendance greater than six hours was required in 65% (n=2306) patients, with 35% (n=1253) being observed (LoS less than six hours). The median length of stay and age for those admitted was 52 hours (IQR =82) and 118 (IQR = 190) days.

Overall, 28% of patients attending hospital required supplemental oxygen (n=996). It was found that 6% of patients were admitted to critical care (n=196). No differences were found between sex and admission to critical care, requirement of supplemental oxygen or IMD decile (***Figure 3.4***).

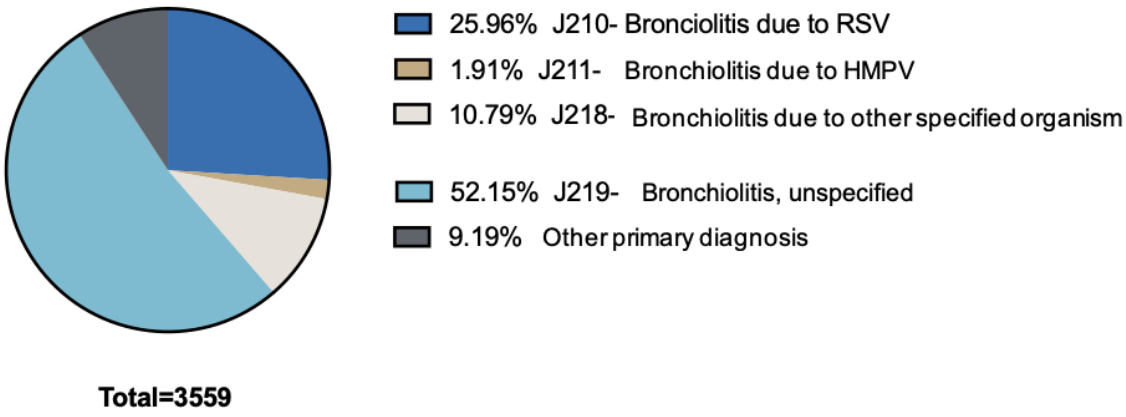


Figure 3. 3 Figure demonstrating the Bronchiolitis ICD-10 diagnoses within the cohort.

3.3.2 Temporal Trends

The median number of patients per year was 676 (IQR= 527.50) with rising numbers in more recent years, except for in 2020. As expected, most attendances occurred over the winter months with a peak in November (n=868, median = 169.50, IQR = 353.00). More hospital visits occurred on Mondays (n=595, 16.72%, median= 492.00, IQR= 77.00). It was determined that most hospital attendances occurred in the evening with the peak time being 21:00 (n=240, 6.74%, median = 168.00, IQR =179.00) and the lowest attendance time was seen at 07:00 and 08:00 each with 44 attendances (1.24%). This information can be visualised in ***Figure 3.5.***

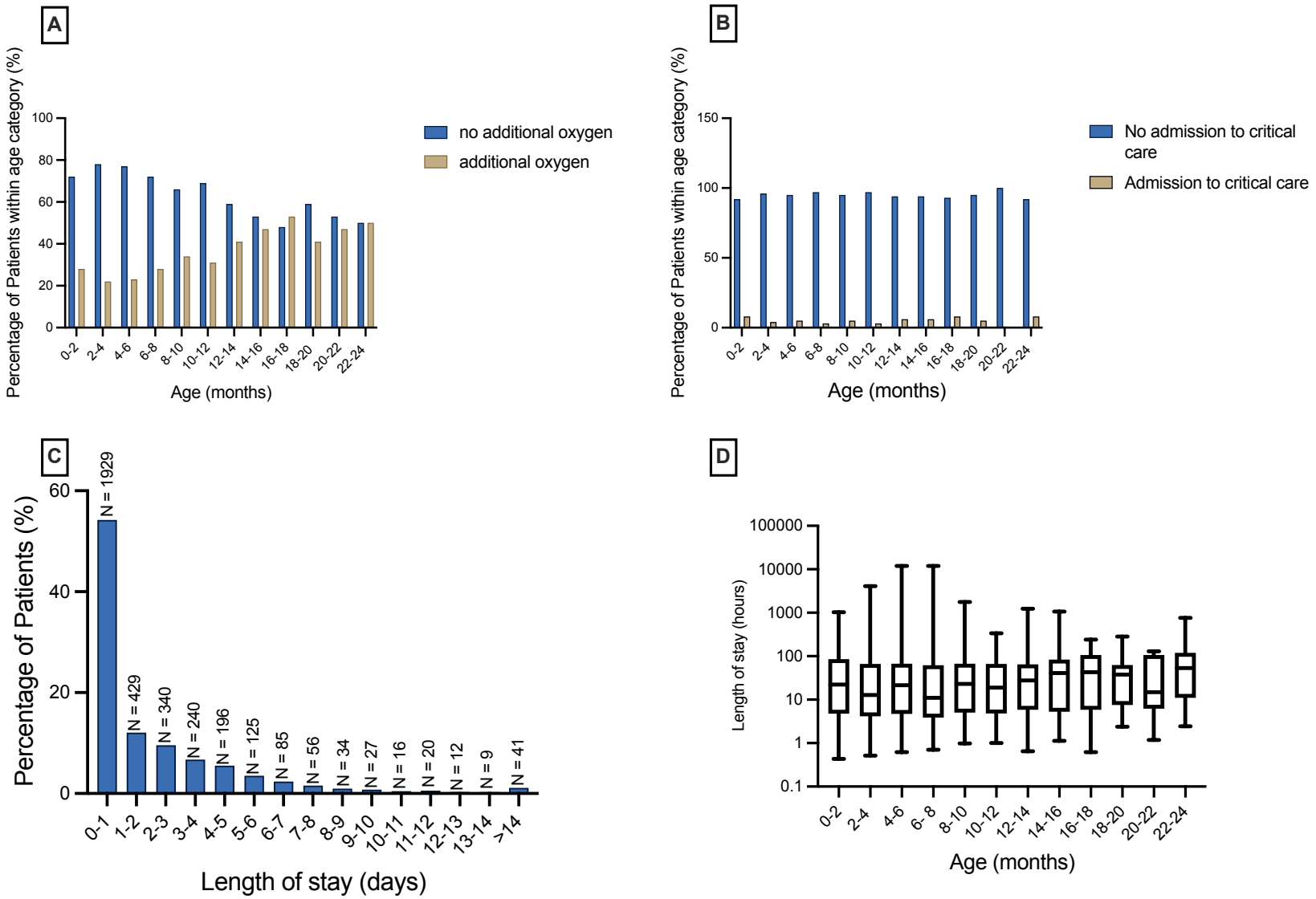


Figure 3. 4 Figures showing clinical findings for the entire patient group:

(A) *The relationship between age and percentage of patients receiving additional oxygen, highlighting that as age increased, the proportion of each two month age-range requiring oxygen increased* ***(B)*** *The relationship between age and admission to critical care, showing that a similar proportion of each two month age-range were admitted to critical care* ***(C)*** *The proportion of patients by length of stay in days showing that most patients were hospitalised for less than 1 day* ***(D)*** *Box and Whisker plot for length of stay for each age category, highlighting the median, IQR, minimum and maximum values, and using a log base 10 scale. It demonstrates that length of stay increased with age and there was significant variation for each category.*

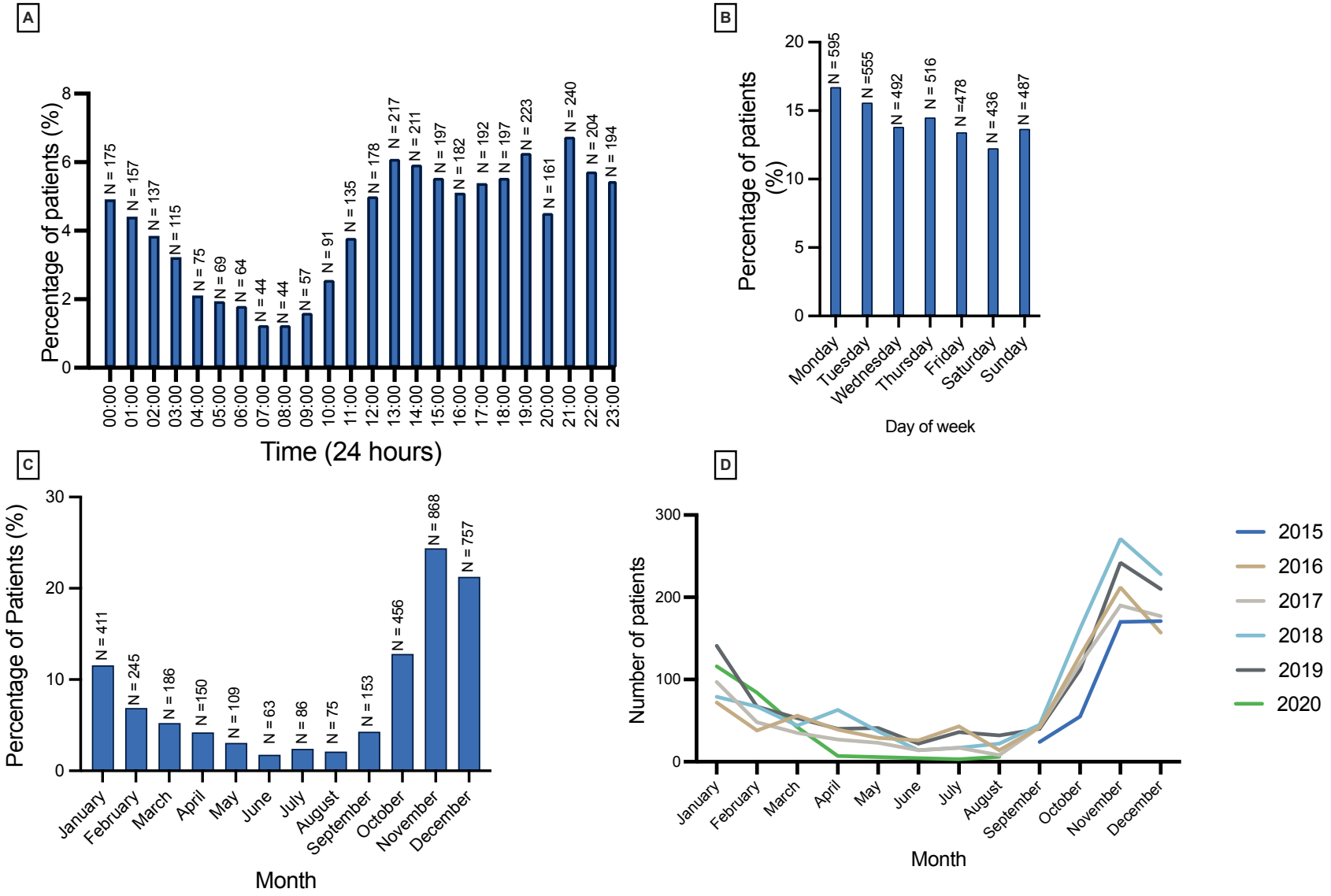


Figure 3. 5 Figures showing the temporal characteristics of bronchiolitis admissions to AHCH.

*(**A**) Hourly, showing that most attendances occur in the afternoon and evening **(B)** Daily, showing that most attendances occur on a Monday; **(C)** Monthly, highlighting that the epidemic occurs over winter months, generally peaking in November; **(D)** Yearly, showing hospital attendance at AHCH by year and that admissions have generally been high in recent years apart from 2020 because of the COVID-19 pandemic.*

3.3.4 Social Characteristics

The IMD decile data for the cohort was collected and compared against the available data from Liverpool in 2019 as (***Figure 3.6***). Most (59%, n=2088) were from decile one compared to 0.22% (n=8) from the tenth decile. No significant differences were found in the percentages admitted or observed between deciles**.** No further differences were seen in the length of stay, age, supplemental oxygen requirement or admission to critical care between the deciles.

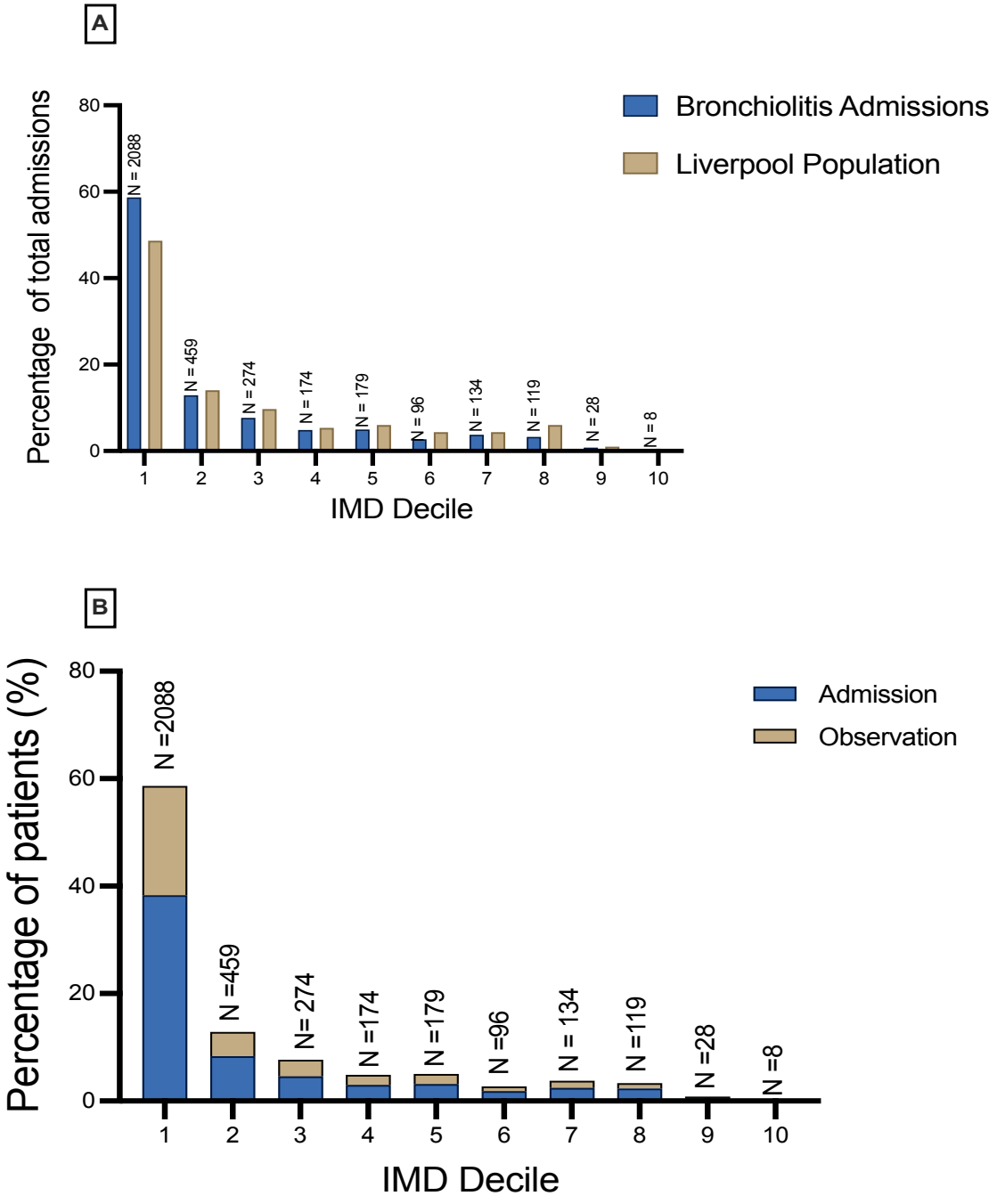


Figure 3. 6 Figures showing the deprivation analysis of bronchiolitis attendances to AHCH

(A) *Demonstrates the deprivation deciles from AHCH bronchiolitis cohort compared to the expected values from LCR. It shows a higher proportion of patients are from decile 1 from AHCH than expected, however there were no significant differences* ***(B)*** *the percentage of patients from each IMD decile cohort with the proportions admitted or observed. It shows similar relative proportions for each IMD Decile*

3.3.5 Air Pollution

There were 2050 patients included once the 1km radius Voronoi cell was applied. It was found that 66% of attendances (n=1346) occurred when NO_2 levels were greater than the 40 μg/m^3 DEFRA target. NO_2 levels for 64% of admissions were between 40 and 50 μg/m^3. Monthly average NO_2 level was 43 μg/m^3. When there were at least five bronchiolitis attendances per month the average NO_2 levels were 45 μg/m^3, and 51 μg/m^3 when there were at least ten bronchiolitis attendances. The number of exacerbations per increment of NO_2 can be viewed in ***Figure 3.7***.

The average number of attendances for each NO_2 level was generated and linear regression performed. A weak correlation was found (R^2 = 0.43, p-value= 0.62) (***Figure 3.8***). This relationship was not significant at a 95% confidence interval. The residual plot demonstrates that there is a some linear relationship at lower levels of NO_2 (less than 50 μg/m^3) but that it is not found at higher levels (***Figure 3.9***). However, this simple linear regression may not be able to adequately describe the complex relationship between these 2 variables.

Further information regarding the data included in the results section can be found in **Appendix 5**.

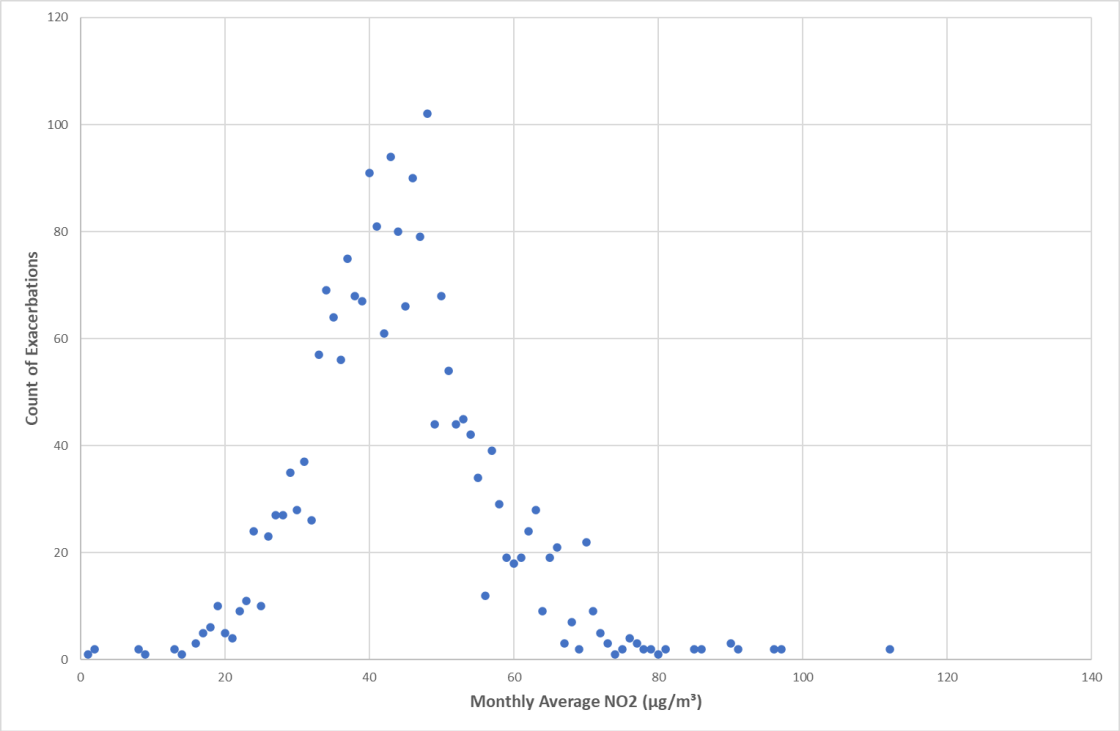


Figure 3. 7 Figure showing the count of exacerbations for monthly NO_2 level

Showing the number of exacerbations that occur for each increment of NO_2 levels, highlighting that the highest number of exacerbations occur when NO_2 levels are approximately 40 $\mu g/m^3$.

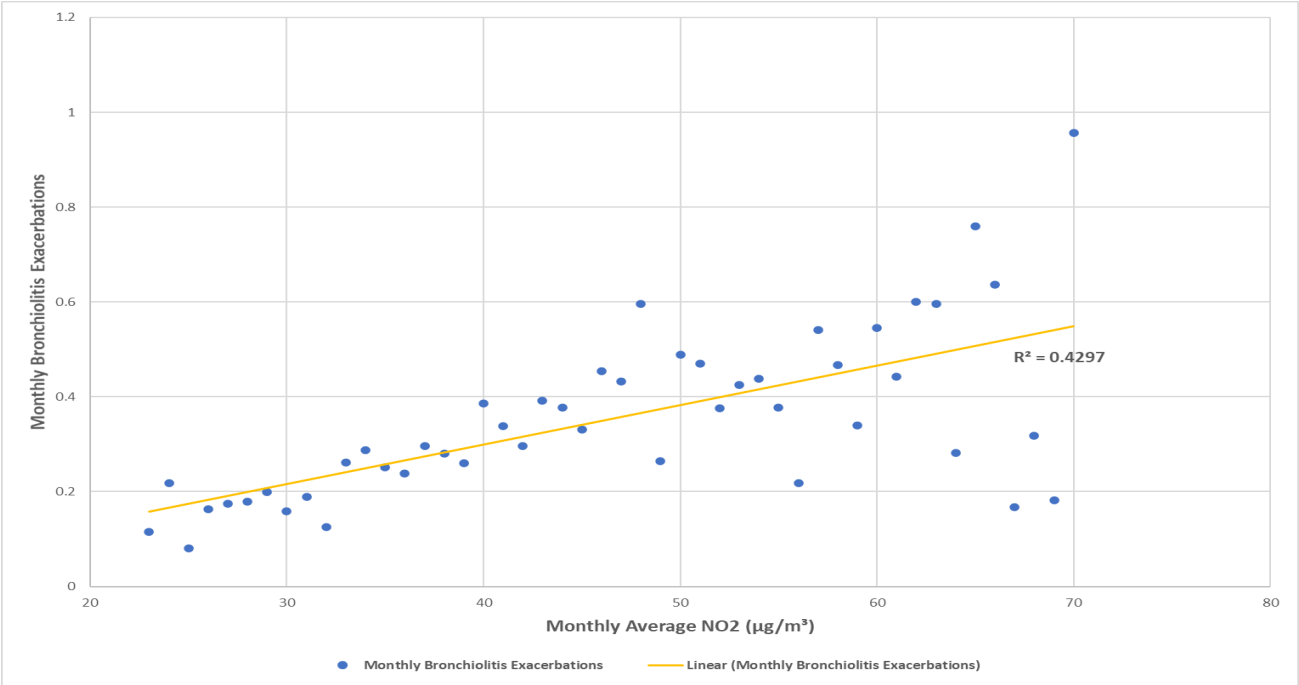


Figure 3. 8 Figure showing the linear regression analysis of bronchiolitis exacerbations and monthly NO_2 levels.

This demonstrates that as NO_2 levels increase the number of exacerbations increase as well.

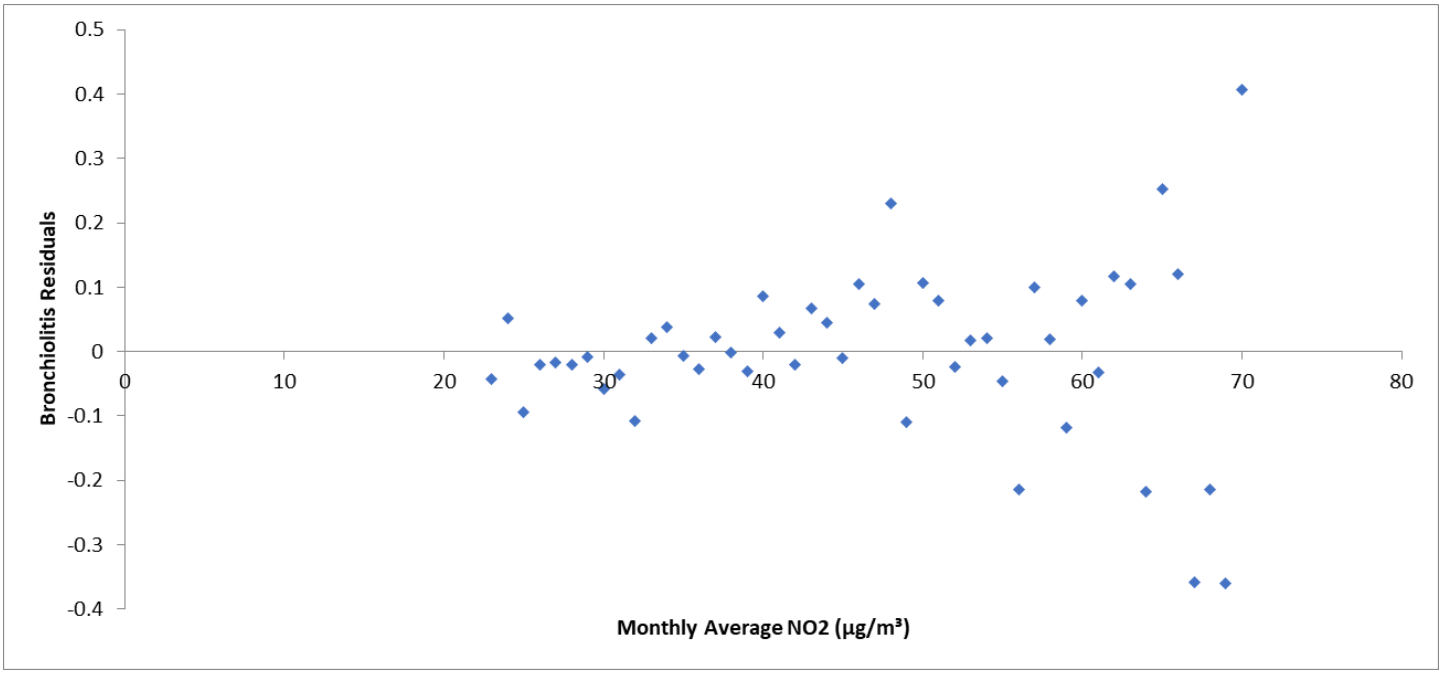


Figure 3. 9 Figure showing the residual Plot of bronchiolitis admissions and monthly NO_2 levels.

Demonstrating that there is a weak correlation at lower levels of NO_2 (less than 50 µg/m^3). However, this is not seen at higher levels of NO_2.

3.4 Discussion

This study has provided a snapshot of the attendances to AHCH for bronchiolitis from September 2015 to August 2020.

The median LoS was 18 hours in total and 52 hours for those admitted longer than six hours, with 54% of attendances lasting less than 24 hours. Previous studies have demonstrated varied median lengths of stay. Rodríguez-Martínez et al. found a mean length of stay of 4 days (or 96 hours), with a range from one to 25 days (Rodríguez-Martínez et al., 2018). Taking 25% of admissions over two years, Unger and Cunningham et al. found a median length of stay of 72 hours (Unger and Cunningham, 2008). A mean length of hospitalisation of 7.6 days was found by Milíc et al. who only included those with a stay longer than 24 hours (Milić et al., 2017). The variation in the length of stay above demonstrates the wide range of clinical severity in bronchiolitis. It may relate to varying hospital guidance, treatment thresholds and social settings

of the studies. Furthermore, it may be attributed to varying definitions of hospitalisations and admissions, and so highlighting the importance of adequate reporting.

Younger children were more frequently affect by bronchiolitis. Most (n=1023, 28%) were in the first two months of life, and only 29 (0.81%) were older than 20 months. This confirms previous research (Martínez-Baylach et al., 2004, Hall et al., 2013). However, older children were more frequently hospitalised (0-2 months = 68% admitted; 22-24 months=83% admitted). Moreover, older children more often required supplemental oxygen and had an increased length of stay. This differs to previous studies which have identified those aged less than one month as experiencing more severe disease (Hall et al., 2013, Vicente et al., 2003, Bozzola et al., 2021, Papenburg et al., 2012). This may be attributed to fewer patients from the older age categories, and so less reliable data. This also does not include other severity markers such as nasogastric or orogastric feeding, and intravenous fluids.

There were more males (60%) than females (40%) attending AHCH with bronchiolitis. Similar gender statistics have been found in studies across the world (male=59-63%, female= 41-37%) (Gil-Prieto et al., 2015, Corneli et al., 2012, Milić et al., 2017). Male children more frequently required hospital admission and supplemental oxygen. A possible explanation for these differences may relate increased testosterone secretion in utero in boys, which delays the surge in surfactant lipid production combined with oestrogen production in girls having a positive effect on surfactant lipid production and alveologenesis (Seaborn et al., 2010, LoMauro and Aliverti, 2018).

This research has demonstrated the most frequent days, hours, and months of bronchiolitis attendances. Almost all (99%) attendances occurred through A&E. The 'RSV season' generally started in October and peaked occurred in November each year. Monday was the most common day of attendance, this was also found NHS Summary Report of A&E activity for all A&E attendances (Secondary Care Analytical Team, 2020). Most attendances occurred in the afternoon and evening (highest number at 21:00). This sort of information is useful to know when

planning clinical trials of interventions in bronchiolitis. However, the COVID-19 pandemic has affected bronchiolitis and RSV epidemiology worldwide. It remains to be seen when and if the normal cycle of RSV disease returns (Kuitunen et al., 2020, Cowling et al., 2020, Angoulvant et al., 2020, Van Brusselen et al., 2021, Hills et al., 2020).

Most of the attendances came from the lowest IMD decile (IMD 1 n=2088). Increased deprivation levels were not associated with increased severity of disease (LoS, supplemental oxygen or CC). Previous studies have highlighted a relationship between increased deprivation levels and increased hospital admissions (Green et al., 2016, Spencer et al., 1996, Chalut et al., 2000). However, Cheung et al. previously found no association between IMD decile and increased length of stay but did identify a modest correlation between deprivation and admission rates (R=0.332, p=<0.0001). They suggested that the association may relate more to specific aspects of deprivation, such as lack of maternal breastfeeding, household smoking and overcrowding, rather than deprivation as a wider concept (Cheung et al., 2013). The results of this study in Liverpool may be explained by the fewer patients within the less deprived deciles (IMD 10^{th} decile included only 10 patients) and so providing less reliable data.

It has been demonstrated that many admissions occur when NO_2 levels are over 40, breaching DEFRA recommended levels (Department for Environment Food and Rural Affairs, 2021). This is a key finding demonstrating the need to address concerning air pollution levels. Furthermore, the landmark ruling confirming the cause of death in a 9-year-old as 'excessive air pollution' in London following an asthma attack further highlights the importance of addressing the air pollution levels in the U.K. as a whole (Vaughan, 2021). A weak positive correlation was observed between NO_2 levels and bronchiolitis admissions. Previous studies have demonstrated strong relationships between pollution and respiratory admissions (Pino et al., 2004, Ségala et al., 2008, Terrazas et al., 2019).

In this chapter, a snapshot of bronchiolitis admissions to Alder Hey Children's Hospital in Liverpool over the past five years has been provided. Future research should develop the

understanding of the relationship between bronchiolitis and deprivation by assessing other factors such as race, maternal health, smoking, or housing status. Moreover, by accessing additional years' data the cohort could be increased to enable better analysis of the subgroups with few patients. The positive correlation demonstrated between pollution and bronchiolitis admission provides some valuable preliminary data in support of reducing air pollution. Future research may focus on finding specific areas and times where air pollution levels are highest as well as assessing whether initiatives such as encouraging cycling, increasing green spaces or electric vehicles are truly beneficial in pollution reduction or if more drastic measures are necessary.

3.5 Conclusions

Most of the bronchiolitis hospital attendances to AHCH are in the first two months of life, with males being more frequently and more severely affected by bronchiolitis. Most admissions come from areas with the highest levels of deprivation. This work has highlighted that air pollution levels are excessive in Liverpool and that pollution levels correlate weakly with the number of admissions to hospital with bronchiolitis. There are likely to be many other confounding factors. Almost all attendances occurred through A&E, with higher levels of attendance seen in the afternoon and evening. Monday was the most frequent day for hospital attendance. Each year attendances peaked in November.

This information displays trends in hospital admissions for bronchiolitis in the LCR and describes the cohort of children affected. Furthermore, it provides clinical and demographic data potentially useful to designing interventional trials in bronchiolitis. This work highlights the need to address pollution levels in Liverpool.

3.6 Strengths and Limitations

This study has the strength of a large cohort size and extensive data available over a relatively long period of time. It includes various demographic factors as well as clinical outcomes. It

provides a strong basis for the performance of more refined analysis. The outcome measures and codes used to identify patients were carefully considered and refined multiple times to ensure they were suitable. However, it does rely on adequate clinic coding and reporting of patients. It is possible that those older that 12 months with bronchiolitis were coded as having viral induced wheeze. Moreover, aspects of the data may be less reliable due to smaller size groups. This includes most patients being aged less than one year old, and more patients being from IMD deciles 1-3.

Much of the paediatric population of Liverpool is served by AHCH, and so this data provides contextualisation of bronchiolitis within the local area. Yet, as this data is from a single site in a particular part of the UK, the information generated is not able to be applied to other regions.

The collaboration with Liverpool City Council allowed access to expertise in air pollution data and so generated promising preliminary data regarding NO_2 levels and its impact on bronchiolitis admissions. However, the areas where analysis was performed were limited by the locations of the diffusion tubes. Moreover, the diffusion tubes only provide month NO_2 figures not daily. As this study solely looked at NO_2 pollution, it does not reflect the impact of other air pollutants such as $PM_{2.5,}$ PM_{10} or SO_2.

Chapter 4- Overview

4.1 Discussion

The systematic review of severity tools for the assessment of bronchiolitis has highlighted both positive and negative aspects of current bronchiolitis severity scores. It has shown the lack of validity data involved in their development, and illustrated the range of items assessed, and variations in definition for respiratory rates, wheeze, and retractions. The analysis of bronchiolitis admissions to AHCH has revealed clinical and demographic characteristics of children hospitalised as well as temporal trends of attendance. These findings have been contextualised in relation to deprivation and air pollution.

A bronchiolitis severity tool has been developed in Liverpool according to guidance on validity and reliability (Liverpool Infant Bronchiolitis Severity Score) (van Miert et al., 2014). This is just about to enter its final stage of validation, a longitudinal assessment over time prior to publication.

As of late July 2021, a much-delayed RSV season has begun in the UK with admission at AHCH currently to the general paediatric wards, HDU and PICU. It will be interesting to watch how this season develops given the numbers of RSV naïve infants and young children in the community. Also, currently expectant mothers who have not been infected with RSV for two years because of the COVID-19 pandemic will be delivering infants with no immunity to RSV or other viruses that commonly cause bronchiolitis. Consequently, it is possible that we are at the start of a very prolonged RSV season. Equally, mask wearing has undoubtedly reduced non-SARS-CoV2 viral spread over the past few years and it is possible that this could continue through the coming autumn leading to less viral infection and therefore less bronchiolitis than would otherwise be seen. Repercussions of the COVID pandemic may be seen for several year with people being more conscious of seasonal illnesses as well as using non-pharmacological interventions, such as hand hygiene and mask wearing more regularly. Future research regarding bronchiolitis may assess

the impact of the pandemic on seasonal virus transmission, as well as the epidemiology of those affected including aspects such as viral aetiology or age.

Future research into other areas highlighted within this thesis may analyse in more depth the relationship between bronchiolitis and deprivation, specifically examining concepts such as race, housing, maternal breastfeeding, or income. It may aim to increase the cohort by contacting other local trusts, general practices and co-ordinating this information in order to determine further relationships. Future work may also aim to limit the impacts of confounding on the data as this is a limitation of the current work. There exist some inherent limitations in relying on information generated through coding. Coding is done at the point of clerking and so where there is uncertainty in diagnosis, it is not reflected in the coding. It is further difficult to determine the role of human error in coding which may arise when staff are under pressure. Further errors may arise during extraction of coding data. This may relate to the communication of complex data extraction requirements to the department. Some factors, such as supplemental oxygen requirement, were easiest extracted in a binary format and in future, it may be best to elicit the different types of oxygen therapy received. An additional limitation of supplemental oxygen coding relates to the under-prescription of oxygen (Al-Otaibi, 2019).

Future research on air pollution might include analysis of how admissions to hospital correlate with other pollutants such as particulate matter or sulphur dioxide. It might be possible to focus on those children who come into hospital most with respiratory disease (not just bronchiolitis) to find out when they are being exposed to potentially damaging pollutants with a view to undergo future interventional studies. Further research may also aim to highlight the benefits that pollution reduction may have and whether the effects identified are reversible. Future work may also aim to address the limitation that the data was reliant on postcodes, which although is beneficial, does not reflect the complexity of geography. It does not address the variations of the amount of greenery in locations. The use of postcodes in determination of IMD category may not also accurately capture this complexity in relation to levels of deprivation in small areas. Confounding is an important factor that should be considered. Variables contributing to air

pollution and deprivation levels are difficult to isolate and to measure, however future work may attempt to quantify or contextualise these. Some factors relating to air pollution are the amount of greenery in an area, wind, or humidity. Other factors relating to deprivation are maternal smoking, maternal education, or maternal breastfeeding.

Future research regarding the systematic review may aim to increase the number of papers screened. It may be beneficial to increase the age criteria of patient's included in review due to the varying definitions of bronchiolitis by geography. Further limitations of the review are in the data extraction, where only the headings of the score categories were described or only vague descriptions of the overall score were provided. Future research may should aim to provide full validation and reliability assessments of one score as per the as per the COSMIN checklist, or comparisons of different scores (Mokkink et al., 2010). This will hopefully identify the best score for bronchiolitis assessment.

4.1 Conclusion

This thesis has shown that there are a multitude of severity assessment tools relating to bronchiolitis available. The scores frequently included assessments of respiratory rate, presence of wheeze and assessment of retractions. However, validity and reliability of the identified scores was limited.

The description of attendances to AHCH for bronchiolitis demonstrated that most patients were male, of younger age and from the most deprived deciles of Liverpool. Male children were more likely to have severe disease. The information obtained describes trends in time, day of the week and month of admission which is important in resource allocation and beneficial for the implementation of future research. A weak positive correlation was found between air pollution and the number of bronchiolitis attendances. Air pollution levels were in breach of the current recommended level, highlighting the ever-growing need to reduce air contamination.

Bibliography

AIR INFORMATION RESOURCE. 2021. *Monitoring Networks* [Online]. Available: https://uk-air.defra.gov.uk/networks/ [Accessed].

AL-GARAWI, A., HUSAIN, M., ILIEVA, D., HUMBLES, A. A., KOLBECK, R., STAMPFLI, M. R., O'BYRNE, P. M., COYLE, A. J. & JORDANA, M. 2012. Shifting of immune responsiveness to house dust mite by influenza A infection: genomic insights. *J Immunol,* 188**,** 832-43.

AL-OTAIBI, H. M. 2019. Current practice of prescription and administration of oxygen therapy: an observational study at a single teaching hospital. *Journal of Taibah University Medical Sciences,* 14**,** 357-362.

ALVAREZ, A. E., MARSON, F. A., BERTUZZO, C. S., ARNS, C. W. & RIBEIRO, J. D. 2013. Epidemiological and genetic characteristics associated with the severity of acute viral bronchiolitis by respiratory syncytial virus. *Jornal de Pediatria (Versão em Português),* 89**,** 531-543.

AMPUERO, S., LUCHSINGER, V., TAPIA, L., PALOMINO, M. A. & LARRAÑAGA, C. E. 2011. SP-A1, SP-A2 and SP-D gene polymorphisms in severe acute respiratory syncytial infection in Chilean infants. *Infection, Genetics and Evolution,* 11**,** 1368-1377.

ANGOULVANT, F., OULDALI, N., YANG, D. D., FILSER, M., GAJDOS, V., RYBAK, A., GUEDJ, R., SOUSSAN-BANINI, V., BASMACI, R., LEFEVRE-UTILE, A., BRUN-NEY, D., BEAUJOUAN, L. & SKURNIK, D. 2020. COVID-19 pandemic: Impact caused by school closure and national lockdown on pediatric visits and admissions for viral and non-viral infections, a time series analysis. *Clin Infect Dis*.

BAJAJ, L., BOTHNER, J. & TURNER, C. G. 2006. A randomized trial of home oxygen therapy from the emergency department for acute bronchiolitis. *Pediatrics,* 117**,** 633-640.

BAMBERGER, E., SRUGO, I., ABU RAYA, B., SEGAL, E., CHAIM, B., KASSIS, I., KUGELMAN, A. & MIRON, D. 2012. What is the clinical relevance of respiratory syncytial virus bronchiolitis?: findings from a multi-center, prospective study. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology,* 31**,** 3323-3330.

BARALDI, E., LANARI, M., MANZONI, P., ROSSI, G. A., VANDINI, S., RIMINI, A., ROMAGNOLI, C., COLONNA, P., BIONDI, A., BIBAN, P., CHIAMENTI, G., BERNARDINI, R., PICCA, M., CAPPA, M., MAGAZZÙ, G., CATASSI, C., URBINO, A. F., MEMO, L., DONZELLI, G., MINETTI, C., PARAVATI, F., DI MAURO, G., FESTINI, F., ESPOSITO, S. & CORSELLO, G. 2014. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. *Italian Journal of Pediatrics,* 40**,** 65.

BARNES, J. H., CHATTERTON, T. J. & LONGHURST, J. W. 2019. Emissions vs exposure: Increasing injustice from road traffic-related air pollution in the United Kingdom. *Transportation research part D: transport and environment,* 73**,** 56-66.

BARNETT, A. G., WILLIAMS, G. M., SCHWARTZ, J., NELLER, A. H., BEST, T. L., PETROESCHEVSKY, A. L. & SIMPSON, R. W. 2005. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *American journal of respiratory and critical care medicine,* 171**,** 1272-1278.

BASILE, V., DI MAURO, A., SCALINI, E., COMES, P., LOFÙ, I., MOSTERT, M., TAFURI, S. & MANZIONNA, M. M. 2015. Lung ultrasound: a useful tool in diagnosis and management of bronchiolitis. *BMC pediatrics,* 15**,** 63.

BAUMER, J. H. 2007. SIGN guideline on bronchiolitis in infants. *Archives of disease in childhood - Education & practice edition,* 92**,** ep149.

BECK, R., ELIAS, N., SHOVAL, S., TOV, N., TALMON, G., GODFREY, S. & BENTUR, L. 2007. Computerized acoustic assessment of treatment efficacy of nebulized epinephrine and albuterol in RSV bronchiolitis. *BMC pediatrics,* 7**,** 1-6.

BEHERA, A. K., MATSUSE, H., KUMAR, M., KONG, X., LOCKEY, R. F. & MOHAPATRA, S. S. 2001. Blocking intercellular adhesion molecule-1 on human epithelial cells decreases respiratory syncytial virus infection. *Biochemical and biophysical research communications,* 280**,** 188-195.

BEIGELMAN, A. & BACHARIER, L. B. 2013. The role of early life viral bronchiolitis in the inception of asthma. *Current opinion in allergy and clinical immunology,* 13**,** 211-216.

BERGER, I., ARGAMAN, Z., SCHWARTZ, S. B., SEGAL, E., KIDERMAN, A., BRANSKI, D. & KEREM, E. 1998. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. *Pediatric pulmonology,* 26**,** 162-166.

BINKOVE B, B. M., CHATERRJEE A, CHAUHAN ! 2004. The effects of air pollution on children's health and development: a review of the evidence.

BIRKEN, C. S., PARKIN, P. C. & MACARTHUR, C. 2004. Asthma severity scores for preschoolers displayed weaknesses in reliability, validity, and responsiveness. *Journal of clinical epidemiology,* 57**,** 1177-1181.

BLACKMON, L. R., BATTON, D. G., BELL, E. F. & ENGLE, W. A. 2003. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics,* 111**,** 914-914.

BLANKEN, M. O., ROVERS, M. M., MOLENAAR, J. M., WINKLER-SEINSTRA, P. L., MEIJER, A., KIMPEN, J. L. L. & BONT, L. 2013. Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants. *New England Journal of Medicine,* 368**,** 1791-1799.

BOHÉ, L., FERRERO, M. E., CUESTAS, E., POLLIOTTO, L. & GENOFF, M. 2004. Indications of conventional chest physiotherapy in acute bronchiolitis. *Medicina,* 64**,** 198-200.

BORCHERS, A. T., CHANG, C., GERSHWIN, M. E. & GERSHWIN, L. J. 2013. Respiratory syncytial virus--a comprehensive review. *Clinical reviews in allergy & immunology,* 45**,** 331-379.

BOZZOLA, E., CIARLITTO, C., GUOLO, S., BRUSCO, C., CERONE, G., ANTILICI, L. & SCHETTINI, L. 2021. Respiratory Syncytial Virus Bronchiolitis in Infancy: The Acute Hospitalization Cost. *Frontiers in Pediatrics***,** NA.

BREESE HALL, C. 2009. Respiratory Syncytial Virus. *Principles and Practice of Clinical Virology.*

BRESSAN, S., BALZANI, M., KRAUSS, B., PETTENAZZO, A., ZANCONATO, S. & BARALDI, E. 2013. High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: a pilot study. *European journal of pediatrics,* 172**,** 1649-1656.

BRITISH LUNG FOUNDATION 2020. The health and economic impacts of toxic air in Liverpool City Region. British Lung foudnation website.

BRITISH NATIONAL FORMULARY. *Respiratory syncytial virus* [Online]. NICE. Available: https://bnf.nice.org.uk/treatment-summary/respiratory-syncytial-virus.html [Accessed 2021].

CAN, D., İNAN, G., YENDUR, G., ORAL, R. & GÜNAY, İ. 1998. Salbutamol or mist in acute bronchiolitis. *Pediatrics International,* 40**,** 252-255.

CANEDO-MARROQUÍN, G., ACEVEDO-ACEVEDO, O., REY-JURADO, E., SAAVEDRA, J. M., LAY, M. K., BUENO, S. M., RIEDEL, C. A. & KALERGIS, A. M. 2017. Modulation of Host Immunity by Human Respiratory Syncytial Virus Virulence Factors: A Synergic Inhibition of Both Innate and Adaptive Immunity. *Frontiers in cellular and infection microbiology,* 7**,** 367-367.

CARROLL, K. N., GEBRETSADIK, T., GRIFFIN, M. R., WU, P., DUPONT, W. D., MITCHEL, E. F., ENRIQUEZ, R. & HARTERT, T. V. 2008. Increasing Burden and Risk Factors for Bronchiolitis-Related Medical Visits in Infants Enrolled in a State Health Care Insurance Plan. *Pediatrics,* 122**,** 58.

CASERTA, XING, Q., TESINI, B., LU, W., MURPHY, A., CORBETT, A., TOPHAM, D. J., FALSEY, A. R., HOLDEN-WILTSE, J., WALSH, E. E., QIU, X. & WANG, L. 2017. Development of a Global Respiratory Severity Score for Respiratory Syncytial Virus Infection in Infants. *Journal of Infectious Diseases,* 215**,** 750-756.

CHALUT, D. S., DUCHARME, F. M. & DAVIS, G. M. 2000. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. *The Journal of pediatrics,* 137**,** 762-768.

CHAWES, B. L., POORISRISAK, P., JOHNSTON, S. L. & BISGAARD, H. 2012. Neonatal bronchial hyperresponsiveness precedes acute severe viral bronchiolitis in infants. *J Allergy Clin Immunol,* 130**,** 354-61.e3.

CHE, D., NICOLAU, J., BERGOUNIOUX, J., PEREZ, T. & BITAR, D. 2012. Bronchiolite aiguë du nourrisson en France : bilan des cas hospitalisés en 2009 et facteurs de létalité. *Archives de Pédiatrie,* 19**,** 700-706.

CHEUNG, C. R., SMITH, H., THURLAND, K., DUNCAN, H. & SEMPLE, M. G. 2013. Population variation in admission rates and duration of inpatient stay for bronchiolitis in England. *Archives of disease in childhood,* 98**,** 57-59.

CHEUNG, D. S., EHLENBACH, S. J., KITCHENS, R. T., RILEY, D. A., THOMAS, L. L., HOLTZMAN, M. J. & GRAYSON, M. H. 2010. Cutting edge: CD49d+ neutrophils induce FcepsilonRI expression on lung dendritic cells in a mouse model of postviral asthma. *J Immunol,* 185**,** 4983-7.

CHIN, H. J. & SENG, Q. B. 2004. Reliability and validity of the respiratory score in the assessment of acute bronchiolitis. *The Malaysian journal of medical sciences: MJMS,* 11**,** 34.

CHIPPS, B. E., SULLIVAN, W. F. & PORTNOY, J. 1993. Alpha-2A-interferon for treatment of bronchiolitis caused by respiratory syncytial virus. *The Pediatric infectious disease journal,* 12**,** 653-658.

CHONG, S. L., TEOH, O. H., NADKARNI, N., YEO, J. G., LWIN, Z., ONG, Y. G. & LEE, J. H. 2017. The modified respiratory index score (RIS) guides resource allocation in acute bronchiolitis. *Pediatric pulmonology,* 52**,** 954-961.

CHUNG, A., REEVES, R. M., NAIR, H. & CAMPBELL, H. 2020. Hospital Admission Trends for Bronchiolitis in Scotland, 2001-2016: A National Retrospective Observational Study. *J Infect Dis,* 222**,** S592-s598.

COARASA, A., GIUGNO, H., CUTRI, A., LOTO, Y., TORRES, F., GIUBERGIA, V., OSSORIO, M. F., DURÁN, P., GONZÁLEZ PENA, H. & FERRERO, F. 2010. [Validation of a clinical prediction

tool to evaluate severity in children with wheezing]. *Archivos argentinos de pediatria,* 108**,** 116-123.
CONRAD, D. A., CHRISTENSON, J. C., WANER, J. L. & MARKS, M. I. 1987. Aerosolized ribavirin treatment of respiratory syncytial virus infection in infants hospitalized during an epidemic. *The Pediatric infectious disease journal,* 6**,** 152-158.
CONSTANTOPOULOS, A. G., KAFETZIS, D. A., SYROGIANNOPOULOS, G. A., ROILIDES, E. J., MALAKA-ZAFIRIU, E. E., SBYRAKIS, S. S. & MARCOPOULOS, M. L. 2002. Burden of respiratory syncytial viral infections on paediatric hospitals: a two-year prospective epidemiological study. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology,* 21**,** 102-107.
CONWAY, E., SCHOETTKER, P. J., RICH, K., MOORE, A., BRITTO, M. T. & KOTAGAL, U. R. 2004. Empowering respiratory therapists to take a more active role in delivering quality care for infants with bronchiolitis. *Respiratory care,* 49**,** 589-599.
CORNELI, H. M., ZORC, J. J., HOLUBKOV, R., BREGSTEIN, J. S., BROWN, K. M., MAHAJAN, P., KUPPERMANN, N. & NETWORK, B. S. G. F. T. P. E. C. A. R. 2012. Bronchiolitis: clinical characteristics associated with hospitalization and length of stay. *Pediatric emergency care,* 28**,** 99-103.
COWLING, B. J., ALI, S. T., NG, T. W., TSANG, T. K., LI, J. C., FONG, M. W., LIAO, Q., KWAN, M. Y., LEE, S. L. & CHIU, S. S. 2020. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. *The Lancet Public Health,* 5**,** e279-e288.
CUNNINGHAM, S., RODRIGUEZ, A., ADAMS, T., BOYD, K. A., BUTCHER, I., ENDERBY, B., MACLEAN, M., MCCORMICK, J., PATON, J. Y. & WEE, F. 2015. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *The Lancet,* 386**,** 1041-1048.
DABBOUS, I. A., TKACHYK, J. S. & STAMM, S. J. 1966. A double blind study on the effects of corticosteroids in the treatment of bronchiolitis. *Pediatrics,* 37**,** 477-484.
DAPALMA, T., DOONAN, B. P., TRAGER, N. M. & KASMAN, L. M. 2010. A systematic approach to virus-virus interactions. *Virus research,* 149**,** 1-9.
DE BOECK, K., VAN DER AA, N., VAN LIERDE, S., CORBEEL, L. & EECKELS, R. 1997. Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study. *The Journal of pediatrics,* 131**,** 919-921.
DE BRASI, D., PANNUTI, F., ANTONELLI, F., DE SETA, F., SIANI, P. & DE SETA, L. 2010. Therapeutic approach to bronchiolitis: why pediatricians continue to overprescribe drugs? *Italian journal of pediatrics,* 36**,** 67.
DEFRA 2017. UK plan for tackling roadside nitrogen dioxide concentrations.
DEPARTMENT FOR ENVIRONMENT FOOD AND RURAL AFFAIRS. 2021. *National Statistics Concentrations of nitrogen dioxide* [Online]. gov.uk. Available: https://www.gov.uk/government/statistics/air-quality-statistics/ntrogen-dioxide [Accessed 2021].
DUARTE-DORADO, D. M., MADERO-OROSTEGUI, D. S., RODRIGUEZ-MARTINEZ, C. E. & NINO, G. 2013. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. *The Journal of asthma : official journal of the Association for the Care of Asthma,* 50**,** 1056-1061.

EJAZ, I., SIDDIQUE, A., RATHORE, A. & KHAN, H. 2015. Hypertonic Saline (3%) vs Normal Saline (0.9%) Nebuliztion for Acute Viral Bronchiolitis: A Randomized Control Trial. *Pak Paed J,* 39**,** 248-51.

ERICKSON, E. N., BHAKTA, R. T. & MENDEZ, M. D. 2020. Pediatric Bronchiolitis. *StatPearls [Internet]*.

FERNANDES, R. M., ANDRADE, M. G., CONSTANT, C., MALVEIRO, D., MAGALHÃES, M., ABREU, D., AZEVEDO, I., SOUSA, E., SALGADO, R. & BANDEIRA, T. 2016. Acute viral bronchiolitis: physician perspectives on definition and clinically important outcomes. *Pediatric pulmonology,* 51**,** 724-732.

FJÆRLI, H.-O., FARSTAD, T., RØD, G., UFERT, G. K., GULBRANDSEN, P. & NAKSTAD, B. 2005. Acute bronchiolitis in infancy as risk factor for wheezing and reduced pulmonary function by seven years in Akershus County, Norway. *BMC pediatrics,* 5**,** 1-8.

FLEMING, S., THOMPSON, M., STEVENS, R., HENEGHAN, C., PLÜDDEMANN, A., MACONOCHIE, I., TARASSENKO, L. & MANT, D. 2011. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet (London, England),* 377**,** 1011-1018.

FOLEY, D., BEST, E., REID, N. & BERRY, M. J. 2019. Respiratory health inequality starts early: The impact of social determinants on the aetiology and severity of bronchiolitis in infancy. *Journal of paediatrics and child health,* 55**,** 528-532.

FOLEY, D. A., YEOH, D. K., MINNEY-SMITH, C. A., MARTIN, A. C., MACE, A. O., SIKAZWE, C. T., LE, H., LEVY, A., MOORE, H. C. & BLYTH, C. C. 2021. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of Coronavirus Disease 2019–Related Public Health Measures. *Clinical Infectious Diseases*.

FRETZAYAS, A. & MOUSTAKI, M. 2017. Etiology and clinical features of viral bronchiolitis in infancy. *World Journal of Pediatrics,* 13**,** 293-299.

GADOMSKI, A. M., AREF, G. H., EL DIN, O. B., EL SAWY, I. H., KHALLAF, N. & BLACK, R. E. 1994a. Oral versus nebulized albuterol in the management of bronchiolitis in Egypt. *The Journal of pediatrics,* 124**,** 131-138.

GADOMSKI, A. M., LICHENSTEIN, R., HORTON, L., KING, J., KEANE, V. & PERMUTT, T. 1994b. Efficacy of albuterol in the management of bronchiolitis. *Pediatrics,* 93**,** 907-912.

GAJDOS, V., BEYDON, N., BOMMENEL, L., PELLEGRINO, B., DE PONTUAL, L., BAILLEUX, S., LABRUNE, P. & BOUYER, J. 2009. Inter-observer agreement between physicians, nurses, and respiratory therapists for respiratory clinical evaluation in bronchiolitis. *Pediatric pulmonology,* 44**,** 754-762.

GAL, S., RISKIN, A., CHISTYAKOV, I., SHIFMAN, N., SRUGO, I. & KUGELMAN, A. 2015. Transcutaneous PCO2 monitoring in infants hospitalized with viral bronchiolitis. *European journal of pediatrics,* 174**,** 319-324.

GIL-PRIETO, R., GONZALEZ-ESCALADA, A., MARÍN-GARCÍA, P., GALLARDO-PINO, C. & GIL-DE-MIGUEL, A. 2015. Respiratory syncytial virus bronchiolitis in children up to 5 years of age in Spain: epidemiology and comorbidities: an observational study. *Medicine,* 94.

GIUGNO, K. M., MACHADO, D. C., AMANTÉA, S. L. & BARRETO, S. S. M. 2004. Concentrations of interleukin-2 in the nasopharyngeal secretion of children with acute respiratory syncytial virus bronchiolitis. *Jornal de pediatria,* 80**,** 315-320.

GLEZEN, W. P., TABER, L. H., FRANK, A. L. & KASEL, J. A. 1986. Risk of primary infection and reinfection with respiratory syncytial virus. *American journal of diseases of children,* 140**,** 543-546.

GOEBEL, J., ESTRADA, B., QUINONEZ, J., NAGJI, N., SANFORD, D. & BOERTH, R. C. 2000. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clinical pediatrics,* 39**,** 213-220.

GOH, A., CHAY, O. M., FOO, A. L. & ONG, E. K. 1997. Efficacy of bronchodilators in the treatment of bronchiolitis. *Singapore medical journal,* 38**,** 326-328.

GOLAN-TRIPTO, I., GOLDBART, A., AKEL, K., DIZITZER, Y., NOVACK, V. & TAL, A. 2018. Modified Tal Score: Validated score for prediction of bronchiolitis severity. *Pediatric Pulmonology,* 53**,** 796-801.

GORELICK, M. H., STEVENS, M. W., SCHULTZ, T. R. & SCRIBANO, P. V. 2004. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Academic emergency medicine,* 11**,** 10-18.

GREEN, C. A., YEATES, D., GOLDACRE, A., SANDE, C., PARSLOW, R. C., MCSHANE, P., POLLARD, A. J. & GOLDACRE, M. J. 2016. Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. *Archives of disease in childhood,* 101**,** 140-146.

GRIFFITHS, C. D., BILAWCHUK, L. M., MCDONOUGH, J. E., JAMIESON, K. C., ELAWAR, F., CEN, Y., DUAN, W., LIN, C., SONG, H., CASANOVA, J.-L., OGG, S., JENSEN, L. D., THIENPONT, B., KUMAR, A., HOBMAN, T. C., PROUD, D., MORAES, T. J. & MARCHANT, D. J. 2020. IGF1R is an entry receptor for respiratory syncytial virus. *Nature,* 583**,** 615-619.

GROUP, A. L. S. 2016. *dvanced paediatric life support: the practical approach.,* Advanced Paediatric Life Support Group, Wiley Blackwell.

HALL, C. B., WEINBERG, G. A., BLUMKIN, A. K., EDWARDS, K. M., STAAT, M. A., SCHULTZ, A. F., POEHLING, K. A., SZILAGYI, P. G., GRIFFIN, M. R., WILLIAMS, J. V., ZHU, Y., GRIJALVA, C. G., PRILL, M. M. & IWANE, M. K. 2013. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics,* 132**,** e341-8.

HALL, C. B., WEINBERG, G. A., IWANE, M. K., BLUMKIN, A. K., EDWARDS, K. M., STAAT, M. A., AUINGER, P., GRIFFIN, M. R., POEHLING, K. A. & ERDMAN, D. 2009. The burden of respiratory syncytial virus infection in young children. *New England Journal of Medicine,* 360**,** 588-598.

HANCOCK, D. G., CHARLES-BRITTON, B., DIXON, D. L. & FORSYTH, K. D. 2017. The heterogeneity of viral bronchiolitis: a lack of universal consensus definitions. *Pediatric pulmonology,* 52**,** 1234-1240.

HARTLING, L., BIALY, L. M., VANDERMEER, B., TJOSVOLD, L., JOHNSON, D. W., PLINT, A. C., KLASSEN, T. P., PATEL, H. & FERNANDES, R. M. 2011. Epinephrine for bronchiolitis. *Cochrane Database of Systematic Reviews*.

HASEGAWA, K., MANSBACH, J. M. & CAMARGO, C. A., JR. 2014. Infectious pathogens and bronchiolitis outcomes. *Expert Review of Anti-Infective Therapy,* 12**,** 817-28.

HASEGAWA, K., TSUGAWA, Y., BROWN, D. F. M., MANSBACH, J. M. & CAMARGO, C. A., JR. 2013. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. *Pediatrics,* 132**,** 28-36.

HILLS, T., KEARNS, N., KEARNS, C. & BEASLEY, R. 2020. Influenza control during the COVID-19 pandemic. *Lancet,* 396**,** 1633-1634.

HOLT, P. G., STRICKLAND, D. H. & SLY, P. D. 2012. Virus infection and allergy in the development of asthma: what is the connection? *Curr Opin Allergy Clin Immunol,* 12**,** 151-7.

JACKSON, D. J., EVANS, M. D., GANGNON, R. E., TISLER, C. J., PAPPAS, T. E., LEE, W. M., GERN, J. E. & LEMANSKE, R. F., JR. 2012. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. *Am J Respir Crit Care Med,* 185**,** 281-5.

JACOBS, J. D., FOSTER, M., WAN, J. & PERSHAD, J. 2014. 7% Hypertonic saline in acute bronchiolitis: a randomized controlled trial. *Pediatrics,* 133**,** e8.

JENG, M.-J., LEE, Y.-S., TSAO, P.-C., YANG, C.-F. & SOONG, W.-J. 2015. A longitudinal study on early hospitalized airway infections and subsequent childhood asthma. *PLoS One,* 10**,** e0121906.

JORDAN, R., VERLANDER, N., OLOWOKURE, B. & HAWKER, J. I. 2006. Age, sex, material deprivation and respiratory mortality. *Respiratory Medicine,* 100**,** 1282-1285.

KARR, C. J., RUDRA, C. B., MILLER, K. A., GOULD, T. R., LARSON, T., SATHYANARAYANA, S. & KOENIG, J. Q. 2009. Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. *Environmental research,* 109**,** 321-327.

KELLY, F. J. 2003. Oxidative stress: its role in air pollution and adverse health effects. *Occupational and environmental medicine,* 60**,** 612-616.

KEREM, E., CANNY, G., REISMAN, J., BENTUR, L., LEVISON, H., TIBSHIRANI, R. & SCHUH, S. 1991. Clinical-physiologic correlations in acute asthma of childhood. *Pediatrics,* 87**,** 481-486.

KOPONEN, P., HELMINEN, M., PAASSILTA, M., LUUKKAALA, T. & KORPPI, M. 2012. Preschool asthma after bronchiolitis in infancy. *Eur Respir J,* 39**,** 76-80.

KRISTJANSSON, S., CARLSEN, K. L., WENNERGREN, G., STRANNEGÅRD, I. & CARLSEN, K. 1993. Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers. *Archives of disease in childhood,* 69**,** 650-654.

KRUSAT, T. & STRECKERT, H.-J. 1997. Heparin-dependent attachment ofrespiratory syncytial virus (RSV) to host cells. *Archives of virology,* 142**,** 1247-1254.

KUITUNEN, I., ARTAMA, M., MÄKELÄ, L., BACKMAN, K., HEISKANEN-KOSMA, T. & RENKO, M. 2020. Effect of Social Distancing Due to the COVID-19 Pandemic on the Incidence of Viral Respiratory Tract Infections in Children in Finland During Early 2020. *The Pediatric Infectious Disease Journal,* 39.

LAI, C. C., TAI, H. Y., SHEN, H. D., CHUNG, W. T., CHUNG, R. L. & TANG, R. B. 2004. Elevated levels of soluble adhesion molecules in sera of patients with acute bronchiolitis. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi,* 37**,** 153-156.

LAL, S. N., KAUR, J., ANTHWAL, P., GOYAL, K., BAHL, P. & PULIYEL, J. M. 2018. Nasal Continuous Positive Airway Pressure in Bronchiolitis: A Randomized Controlled Trial. *Indian pediatrics,* 55**,** 27-30.

LEADER, S. & KOHLHASE, K. 2003. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *The Journal of pediatrics,* 143**,** 127-132.

LI, Y., PILLAI, P., MIYAKE, F. & NAIR, H. 2020. The role of viral co-infections in the severity of acute respiratory infections among children infected with respiratory syncytial virus (RSV): A systematic review and meta-analysis. *Journal of global health,* 10.

LIU, L. L., GALLAHER, M. M., DAVIS, R. L., RUTTER, C. M., LEWIS, T. C. & MARCUSE, E. K. 2004. Use of a respiratory clinical score among different providers. *Pediatric pulmonology,* 37**,** 243-248.

LIVERPOOL CITY COUNCIL. 2019. *Unicef Child Friendly City Programme* [Online]. Available: https://liverpool.gov.uk/children-and-families/unicef-child-friendly-city-programme/ [Accessed 2021].

LIVERPOOL CITY COUNCIL 2020. The Index of Multiple Deprivation 2019
A Liverpool analysis. Liverpool City Council.

LIVERPOOL CITY COUNCIL. 2021a. *Air Quality Monitoring Data for Liverpool* [Online]. Available: https://www.liverpoolair.org.uk/ [Accessed 2021].

LIVERPOOL CITY COUNCIL. 2021b. *Demographics headline indicators* [Online]. Liverpool city coucil: Liverpool city council. Available: https://liverpool.gov.uk/council/key-statistics-and-data/headline-indicators/demographics/ [Accessed 2021].

LÖFGREN, J., MARTTILA, R., RENKO, M., RÄMET, M. & HALLMAN, M. 2010. Toll-like receptor 4 Asp299Gly polymorphism in respiratory syncytial virus epidemics. *Pediatric Pulmonology,* 45**,** 687-692.

LOMAURO, A. & ALIVERTI, A. 2018. Sex differences in respiratory function. *Breathe (Sheffield, England),* 14**,** 131-140.

LOWELL, D. I., LISTER, G., VON KOSS, H. & MCCARTHY, P. 1987. Wheezing in infants: the response to epinephrine. *Pediatrics,* 79**,** 939-945.

MACIAS, C. G., MANSBACH, J. M., FISHER, E. S., RIEDERER, M., PIEDRA, P. A., SULLIVAN, A. F., ESPINOLA, J. A. & CAMARGO JR, C. A. 2015. Variability in inpatient management of children hospitalized with bronchiolitis. *Academic pediatrics,* 15**,** 69-76.

MALHOTRA, R., WARD, M., BRIGHT, H., PRIEST, R., FOSTER, M. R., HURLE, M., BLAIR, E. & BIRD, M. 2003. Isolation and characterisation of potential respiratory syncytial virus receptor (s) on epithelial cells. *Microbes and infection,* 5**,** 123-133.

MANDELBERG, A., TAL, G., NAUGOLNY, L., CESAR, K., ORON, A., HOURI, S., GILAD, E. & SOMEKH, E. 2006. Lipopolysaccharide hyporesponsiveness as a risk factor for intensive care unit hospitalization in infants with respiratory syncitial virus bronchiolitis. *Clinical & Experimental Immunology,* 144**,** 48-52.

MANSBACH, J. M., CLARK, S., TEACH, S. J., GERN, J. E., PIEDRA, P. A., SULLIVAN, A. F., ESPINOLA, J. A. & CAMARGO JR, C. A. 2016. Children hospitalized with rhinovirus bronchiolitis have asthma-like characteristics. *The Journal of pediatrics,* 172**,** 202-204. e1.

MANSBACH, J. M., PIEDRA, P. A., TEACH, S. J., SULLIVAN, A. F., FORGEY, T., CLARK, S., ESPINOLA, J. A., CAMARGO, C. A., JR. & INVESTIGATORS, M.-. 2012. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Archives of pediatrics & adolescent medicine,* 166**,** 700-706.

MARLAIS, M., EVANS, J. & ABRAHAMSON, E. 2011. Clinical predictors of admission in infants with acute bronchiolitis. *Archives of disease in childhood,* 96**,** 648-652.

MARR, N. & TURVEY, S. E. 2012. Role of human TLR4 in respiratory syncytial virus-induced NF-κB activation, viral entry and replication. *Innate immunity,* 18**,** 856-865.

MARTÍNEZ-BAYLACH, J., CASTAN, A. R. & RIERÓ, J. C. 2004. Estudio clínico y epidemiológico de la bronquiolitis aguda en pacientes menores de un año de edad. *Acta Pediatrica Espanola,* 62**,** 275.

MASTRANGELO, P., CHIN, A. A., TAN, S., JEON, A. H., ACKERLEY, C. A., SIU, K. K., LEE, J. E. & HEGELE, R. G. 2021. Identification of RSV Fusion Protein Interaction Domains on the Virus Receptor, Nucleolin. *Viruses,* 13**,** 261.

MASTRANGELO, P. & HEGELE, R. G. 2012. The RSV fusion receptor: not what everyone expected it to be. *Microbes and Infection,* 14**,** 1205-1210.

MATHIEU-NOLF, M. 2002. Poisons in the air: a cause of chronic disease in children. *Journal of Toxicology: Clinical Toxicology,* 40**,** 483-491.

MAZUR, N. I., BONT, L., COHEN, A. L., COHEN, C., VON GOTTBERG, A., GROOME, M. J., HELLFERSCEE, O., KLIPSTEIN-GROBUSCH, K., MEKGOE, O., NABY, F., MOYES, J., TEMPIA, S., TREURNICHT, F. K., VENTER, M., WALAZA, S., WOLTER, N. & MADHI, S. A. 2017. Severity of Respiratory Syncytial Virus Lower Respiratory Tract Infection With Viral Coinfection in HIV-Uninfected Children. *Clin Infect Dis,* 64**,** 443-450.

MCCALLUM, G. B., MORRIS, P. S., WILSON, C. C., VERSTEEGH, L. A., WARD, L. M., CHATFIELD, M. D. & CHANG, A. B. 2013. Severity scoring systems: are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis? *Pediatric pulmonology,* 48**,** 797-803.

MELO, F. 2013. Area under the ROC Curve. *In:* DUBITZKY, W., WOLKENHAUER, O., CHO, K.-H. & YOKOTA, H. (eds.) *Encyclopedia of Systems Biology.* New York, NY: Springer New York.

MIDULLA, F., BONCI, E., DE ANGELIS, D., BERARDI, R., MORETTI, C., SCAGNOLARI, C., PIERANGELI, A. & ANTONELLI, G. 2010. Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. *Archives of Disease in Childhood,* 95**,** 35-41.

MIDULLA, F., PIERANGELI, A., CANGIANO, G., BONCI, E., SALVADEI, S., SCAGNOLARI, C., MORETTI, C., ANTONELLI, G., FERRO, V. & PAPOFF, P. 2012. Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J,* 39**,** 396-402.

MILIĆ, P., SIKIRCA, M., KRŽELJ, V. & MARKIĆ, J. 2017. Characteristics of infants hospitalized with bronchiolitis at University Hospital of Split between 2011 and 2015. *Paediatria Croatica,* 61**,** 53-57.

MILLER, E. K., GEBRETSADIK, T., CARROLL, K. N., DUPONT, W. D., MOHAMED, Y. A., MORIN, L.-L., HEIL, L., MINTON, P. A., WOODWARD, K. & LIU, Z. 2013. Viral etiologies of infant bronchiolitis, croup, and upper respiratory illness during four consecutive years. *The Pediatric infectious disease journal,* 32.

MINISTRY OF HOUSING, C. L. G. 2019. *English indices of deprivation 2019* [Online]. Available: https://imd-by-postcode.opendatacommunities.org/imd/2019 [Accessed 2021].

MITCHELL, G. & NORMAN, P. 2012. Longitudinal environmental justice analysis: Co-evolution of environmental quality and deprivation in England, 1960–2007. *Geoforum,* 43**,** 44-57.

MOHER, D., LIBERATI, A., TETZLAFF, J., ALTMAN, D. G. & GROUP, P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine,* 6**,** e1000097.

MOKKINK, L. B., TERWEE, C. B., PATRICK, D. L., ALONSO, J., STRATFORD, P. W., KNOL, D. L., BOUTER, L. M. & DE VET, H. C. 2010. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Quality of life research,* 19**,** 539-549.

MOORE, H. C., DE KLERK, N., BLYTH, C. C., GILBERT, R., FATHIMA, P., ZYLBERSZTEJN, A., VERFÜRDEN, M. & HARDELID, P. 2019. Temporal trends and socioeconomic differences in acute respiratory infection hospitalisations in children: an intercountry comparison of birth cohort studies in Western Australia, England and Scotland. *BMJ open,* 9**,** e028710.

MORRIS, J., BLOUNT JR, R. & SAVAGE, R. 1956. Recovery of cytopathogenic agent from chimpanzees with goryza. *Proceedings of the Society for Experimental Biology and Medicine,* 92**,** 544-549.

MULET, J. F. & DE TORRES, B. O. R. Viral induced bronchiolitis and genetics. Anales de pediatria (Barcelona, Spain: 2003), 2010. 159-161.

MUNN, Z., BARKER, T. H., MOOLA, S., TUFANARU, C., STERN, C., MCARTHUR, A., STEPHENSON, M. & AROMATARIS, E. 2020. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth,* 18**,** 2127-2133.

NICE. 2015. *Bronchiolitis in Children: diagnosis & management* [Online]. NICE. Available: https://www.nice.org.uk/guidance/ng9/chapter/Update-information [Accessed 10/09/2020 2020].

NICE 2019. 2019 surveillance of bronchiolitis in children: diagnosis and management (NICE guideline NG9). NICE.

NOBLE, V., MURRAY, M., WEBB, M. S. C., ALEXANDER, J., SWARBRICK, A. S. & MILNER, A. D. 1997. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Archives of Disease in Childhood,* 76**,** 315.

NONOYAMA, M. L., KUKRETI, V., PAPACONSTANTINOU, E. & D'CRUZ, R. R. 2019. Assessing physical and respiratory distress in children with bronchiolitis admitted to a community hospital emergency department: A retrospective chart review. *Canadian journal of respiratory therapy: CJRT= Revue canadienne de la therapie respiratoire: RCTR,* 55**,** 16.

OCHOA SANGRADOR, C., GONZÁLEZ DE DIOS, J. & RESEARCH GROUP OF THE A, B. P. 2012. Management of acute bronchiolitis in emergency wards in Spain: variability and appropriateness analysis (aBREVIADo Project). *European journal of pediatrics,* 171**,** 1109-1119.

PAPADOPOULOS, N. G., GOURGIOTIS, D., JAVADYAN, A., BOSSIOS, A., KALLERGI, K., PSARRAS, S., TSOLIA, M. N. & KAFETZIS, D. 2004. Does respiratory syncytial virus subtype influences the severity of acute bronchiolitis in hospitalized infants? *Respir Med,* 98**,** 879-82.

PAPADOPOULOS, N. G., MOUSTAKI, M., TSOLIA, M., BOSSIOS, A., ASTRA, E., PREZERAKOU, A., GOURGIOTIS, D. & KAFETZIS, D. 2002. Association of rhinovirus infection with increased disease severity in acute bronchiolitis. *American journal of respiratory and critical care medicine,* 165**,** 1285-1289.

PARKIN, P. C., MACARTHUR, C., SAUNDERS, N. R., DIAMOND, S. A. & WINDERS, P. M. 1996. Development of a clinical asthma score for use in hospitalized children between 1 and 5 years of age. *Journal of clinical epidemiology,* 49**,** 821-825.

PEREGRINO, A. B., WATT, R. G., HEILMANN, A. & JIVRAJ, S. 2018. Breastfeeding practices in the United Kingdom: Is the neighbourhood context important? *Matern Child Nutr,* 14**,** e12626.

PERET, T. C., HALL, C. B., SCHNABEL, K. C., GOLUB, J. A. & ANDERSON, L. J. 1998. Circulation patterns of genetically distinct group A and B strains of human respiratory syncytial virus in a community. *J Gen Virol,* 79 (Pt 9)**,** 2221-9.

PETRARCA, L., NENNA, R., FRASSANITO, A., PIERANGELI, A., LEONARDI, S., SCAGNOLARI, C., ANTONELLI, G., PAPOFF, P., MORETTI, C. & MIDULLA, F. 2018. Acute bronchiolitis: Influence of viral co-infection in infants hospitalized over 12 consecutive epidemic seasons. *Journal of Medical Virology,* 90**,** 631-638.

PINO, P., WALTER, T., OYARZUN, M., VILLEGAS, R. & ROMIEU, I. 2004. Fine particulate matter and wheezing illnesses in the first year of life. *Epidemiology***,** 702-708.

PINTO, F. R., CORREIA-COSTA, L. & AZEVEDO, I. 2020. Comparison of Kristjansson Respiratory Score and Wang Respiratory Score in infants with bronchiolitis in a hospital emergency department. *Hong Kong Physiotherapy Journal,* 40**,** 145-153.

POORISRISAK, P., HALKJAER, L. B., THOMSEN, S. F., STENSBALLE, L. G., KYVIK, K. O., SKYTTHE, A., SCHIOETZ, P. O. & BISGAARD, H. 2010. Causal direction between respiratory syncytial virus bronchiolitis and asthma studied in monozygotic twins. *Chest,* 138**,** 338-44.

RALSTON, S., HILL, V. & MARTINEZ, M. 2010. Nebulized hypertonic saline without adjunctive bronchodilators for children with bronchiolitis. *Pediatrics,* 126**,** e520-e525.

RALSTON, S. L., LIEBERTHAL, A. S., MEISSNER, H. C., ALVERSON, B. K., BALEY, J. E., GADOMSKI, A. M., JOHNSON, D. W., LIGHT, M. J., MARAQA, N. F. & MENDONCA, E. A. 2014. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics,* 134**,** e1474-e1502.

RAMOS FERNÁNDEZ, J. M., CORDÓN MARTÍNEZ, A., GALINDO ZAVALA, R. & URDA CARDONA, A. 2014. [Validation of an acute bronchiolitis severity scale]. *Anales de pediatria (Barcelona, Spain : 2003),* 81**,** 3-8.

RAYA, B. A., BAMBERGER, E., KASSIS, I., KUGELMAN, A., SRUGO, I. & MIRON, D. 2013. Bordetella pertussis infection attenuates clinical course of acute bronchiolitis. *The Pediatric infectious disease journal,* 32**,** 619-621.

RICART, S., ROVIRA, N., GARCIA-GARCIA, J. J., PUMAROLA, T., PONS, M., MUÑOZ-ALMAGRO, C. & MARCOS, M. A. 2014. Frequency of Apnea and Respiratory Viruses in Infants with Bronchiolitis. *The Pediatric Infectious Disease Journal,* 33.

RICHARD, N., KOMURIAN-PRADEL, F., JAVOUHEY, E., PERRET, M., RAJOHARISON, A., BAGNAUD, A., BILLAUD, G., VERNET, G., LINA, B., FLORET, D. & PARANHOS-BACCALÀ, G. 2008. The impact of dual viral infection in infants admitted to a pediatric intensive care unit associated with severe bronchiolitis. *Pediatr Infect Dis J,* 27**,** 213-7.

RIMA, B., COLLINS, P., EASTON, A., FOUCHIER, R., KURATH, G., LAMB, R. A., LEE, B., MAISNER, A., ROTA, P., WANG, L. & CONSORTIUM, I. R. 2017. ICTV Virus Taxonomy Profile: Pneumoviridae. *Journal of General Virology,* 98**,** 2912-2913.

RIVERA-SEPULVEDA, A. & ISONA, M. 2021. Assessing Resident Diagnostic Skills Using a Modified Bronchiolitis Score. *Pediatric oncall,* 18**,** 11.

ROBLEDO-ACEVES, M., MORENO-PEREGRINA, M. D. J., VELARDE-RIVERA, F., ASCENCIO-ESPARZA, E., PRECIADO-FIGUEROA, F. M., CANIZA, M. A. & ESCOBEDO-MELENDEZ, G. 2018. Risk factors for severe bronchiolitis caused by respiratory virus infections among Mexican children in an emergency department. *Medicine,* 97**,** e0057-e0057.

RODRÍGUEZ-MARTÍNEZ, C. E., SOSSA-BRICEÑO, M. P. & NINO, G. 2018. Predictors of prolonged length of hospital stay for infants with bronchiolitis. *Journal of Investigative Medicine,* 66**,** 986.

RUBIN, F. M. & FISCHER, G. B. 2003. [Clinical and transcutaneous oxygen saturation characteristics in hospitalized infants with acute viral bronchiolitis]. *Jornal de pediatria,* 79**,** 435-442.

SALIMI, V., VIEGAS, M., TRENTO, A., AGOTI, C. N., ANDERSON, L. J., AVADHANULA, V., BAHL, J., BONT, L., BRISTER, J. R., CANE, P. A., GALIANO, M., GRAHAM, B. S., HATCHER, E. L., HELLFERSCEE, O., HENKE, D. M., HIRVE, S., JACKSON, S., KEYAERTS, E., KRAGTEN-TABATABAIE, L., LINDSTROM, S., NAUWELAERS, I., NOKES, D. J., OPENSHAW, P. J., PERET, T. C., PIEDRA, P. A., RAMAEKERS, K., RECTOR, A., TROVÃO, N. S., VON GOTTBERG, A., ZAMBON, M., ZHANG, W., WILLIAMS, T. C., BARR, I. G. & BUCHHOLZ, U. J. 2021. Proposal for Human Respiratory Syncytial Virus Nomenclature below the Species Level. *Emerging infectious diseases,* 27**,** 1-9.

SALKIND, N. 2010. *Encyclopedia of Research Design,* Thousand Oaks, California.

SCHUH, S., CANNY, G., REISMAN, J. J., KEREM, E., BENTUR, L., PETRIC, M. & LEVISON, H. 1990. Nebulized albuterol in acute bronchiolitis. *The Journal of pediatrics,* 117**,** 633-637.

SEABORN, T., SIMARD, M., PROVOST, P. R., PIEDBOEUF, B. & TREMBLAY, Y. 2010. Sex hormone metabolism in lung development and maturation. *Trends Endocrinol Metab,* 21**,** 729-38.

SECONDARY CARE ANALYTICAL TEAM, N. D. 2020. Hospital Accident & Emergency Activity 2019-20. *In:* BARNES, M. (ed.). NHS Digital.

SÉGALA, C., POIZEAU, D., MESBAH, M., WILLEMS, S. & MAIDENBERG, M. 2008. Winter air pollution and infant bronchiolitis in Paris. *Environmental Research,* 106**,** 96-100.

SHI, T., MCLEAN, K., CAMPBELL, H. & NAIR, H. 2015. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: a systematic review and meta–analysis. *Journal of global health,* 5.

SHINTA DEVI, N. L. P., WANDA, D. & NURHAENI, N. 2019. The Validity of the Modified Tal Score and Wang Respiratory Score Instruments in Assessing the Severity of Respiratory System Disorders in Children. *Compr Child Adolesc Nurs,* 42**,** 9-20.

SIGURS, N., ALJASSIM, F., KJELLMAN, B., ROBINSON, P. D., SIGURBERGSSON, F., BJARNASON, R. & GUSTAFSSON, P. M. 2010. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax,* 65**,** 1045-52.

SILVER, A. H. & NAZIF, J. M. 2019. Bronchiolitis. *Pediatrics in Review,* 40**,** 568.

SKJERVEN, H. O., HUNDERI, J. O. G., BRÜGMANN-PIEPER, S. K., BRUN, A. C., ENGEN, H., ESKEDAL, L., HAAVALDSEN, M., KVENSHAGEN, B., LUNDE, J. & ROLFSJORD, L. B. 2013. Racemic adrenaline and inhalation strategies in acute bronchiolitis. *New England Journal of Medicine,* 368**,** 2286-2293.

SMYTH, R. L. & BREAREY, S. P. 2006. BRONCHIOLITIS. *Encyclopedia of Respiratory Medicine***,** 268-275.

SOMMER, C., RESCH, B. & SIMÕES, E. A. 2011. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. *Open Microbiol J,* 5**,** 144-54.

SPENCER, N., LOGAN, S., SCHOLEY, S. & GENTLE, S. 1996. Deprivation and bronchiolitis. *Archives of Disease in Childhood,* 74**,** 50.

STEIN, R. T., SHERRILL, D., MORGAN, W. J., HOLBERG, C. J., HALONEN, M., TAUSSIG, L. M., WRIGHT, A. L. & MARTINEZ, F. D. 1999. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *The Lancet,* 354**,** 541-545.

STERN, D. A., MORGAN, W. J., WRIGHT, A. L., GUERRA, S. & MARTINEZ, F. D. 2007. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet (London, England),* 370**,** 758-764.

STERNE, J. A. C., SAVOVIĆ, J., PAGE, M. J., ELBERS, R. G., BLENCOWE, N. S., BOUTRON, I., CATES, C. J., CHENG, H. Y., CORBETT, M. S., ELDRIDGE, S. M., EMBERSON, J. R., HERNÁN, M. A., HOPEWELL, S., HRÓBJARTSSON, A., JUNQUEIRA, D. R., JÜNI, P., KIRKHAM, J. J., LASSERSON, T., LI, T., MCALEENAN, A., REEVES, B. C., SHEPPERD, S., SHRIER, I., STEWART, L. A., TILLING, K., WHITE, I. R., WHITING, P. F. & HIGGINS, J. P. T. 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj,* 366**,** l4898.

STEWART, C. 2015. Variations in the diagnosis and management of bronchiolitis in older infants: a UK survey. *Archives of disease in childhood***,** archdischild-2015-308966.

SZCZAWIŃSKA-POPŁONYK, A., KOMASIŃSKA, P., TĄPOLSKA-JÓŹWIAK, K., WIĘCKOWSKA, B. & BRĘBOROWICZ, A. 2019. RSV versus non-RSV bronchiolitis in infants and young children–the bedside characteristics of one epidemic season. *Pediatria Polska-Polish Journal of Paediatrics,* 94**,** 18-24.

TAHAMTAN, A., ASKARI, F. S., BONT, L. & SALIMI, V. 2019. Disease severity in respiratory syncytial virus infection: Role of host genetic variation. *Reviews in Medical Virology,* 29**,** e2026.

TAL, A., BAVILSKI, C., YOHAI, D., BEARMAN, J. E., GORODISCHER, R. & MOSES, S. W. 1983. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics,* 71**,** 13-18.

TASKFORCE FOR LUNG HEALTH. 2020. *Air Quality- NO2 air pollution* [Online]. Task Force for Lung Health. Available: https://www.blf.org.uk/taskforce/data-tracker/air-quality/no2 [Accessed 2021].

TAYYARI, F., MARCHANT, D., MORAES, T. J., DUAN, W., MASTRANGELO, P. & HEGELE, R. G. 2011. Identification of nucleolin as a cellular receptor for human respiratory syncytial virus. *Nature Medicine,* 17**,** 1132-1135.

TECHAARPORNKUL, S., BARRETTO, N. & PEEPLES, M. E. 2001. Functional analysis of recombinant respiratory syncytial virus deletion mutants lacking the small hydrophobic and/or attachment glycoprotein gene. *Journal of virology,* 75**,** 6825-6834.

TEERATAKULPISARN, J., LIMWATTANANON, C., TANUPATTARACHAI, S., LIMWATTANANON, S., TEERATAKULPISARN, S. & KOSALARAKSA, P. 2007. Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: A randomized, double-blind, placebo-controlled trial. *Pediatric pulmonology,* 42**,** 433-439.

TERRAZAS, C., CASTRO-RODRIGUEZ, J. A., CAMARGO JR, C. A. & BORZUTZKY, A. 2019. Solar radiation, air pollution, and bronchiolitis hospitalizations in Chile: An ecological study. *Pediatric Pulmonology,* 54**,** 1466-1473.

TERWEE, C. B., BOT, S. D., DE BOER, M. R., VAN DER WINDT, D. A., KNOL, D. L., DEKKER, J., BOUTER, L. M. & DE VET, H. C. 2007. Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of clinical epidemiology,* 60**,** 34-42.

THOMSEN, S. F., STENSBALLE, L. G., SKYTTHE, A., KYVIK, K. O., BACKER, V. & BISGAARD, H. 2008. Increased concordance of severe respiratory syncytial virus infection in identical twins. *Pediatrics,* 121**,** 493-496.

THOMSEN, S. F., VAN DER SLUIS, S., STENSBALLE, L. G., POSTHUMA, D., SKYTTHE, A., KYVIK, K. O., DUFFY, D. L., BACKER, V. & BISGAARD, H. 2009. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med,* 179**,** 1091-7.

TOVEY, D. *How to clarify a clinical question* [Online]. BMJ. Available: https://bestpractice.bmj.com/info/toolkit/learn-ebm/how-to-clarify-a-clinical-question/ [Accessed 2020].

TRIPP, R. A., JONES, L. P., HAYNES, L. M., ZHENG, H., MURPHY, P. M. & ANDERSON, L. J. 2001. CX3C chemokine mimicry by respiratory syncytial virus G glycoprotein. *Nat Immunol,* 2**,** 732-8.

UNGER, S. & CUNNINGHAM, S. 2008. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. *Pediatrics,* 121**,** 470-475.

UUSITUPA, E., WARIS, M. & HEIKKINEN, T. 2020. Association of Viral Load With Disease Severity in Outpatient Children With Respiratory Syncytial Virus Infection. *The Journal of Infectious Diseases,* 222**,** 298-304.

VAN BRUSSELEN, D., DE TROEYER, K., TER HAAR, E., VANDER AUWERA, A., POSCHET, K., VAN NUIJS, S., BAEL, A., STOBBELAAR, K., VERHULST, S., VAN HERENDAEL, B., WILLEMS, P., VERMEULEN, M., DE MAN, J., BOSSUYT, N. & VANDEN DRIESSCHE, K. 2021. Bronchiolitis in COVID-19 times: a nearly absent disease? *European journal of pediatrics,* 180**,** 1969-1973.

VAN MIERT, C., ABBOTT, J., VERHEOFF, F., LANE, S., CARTER, B. & MCNAMARA, P. 2014. Development and validation of the Liverpool infant bronchiolitis severity score: a research protocol. *J Adv Nurs,* 70**,** 2353-62.

VAUGHAN, A. 2021. Rosamund Kissi-Debrah: Clean air 'Ella's law' would honour her memory . *NewScientist*.

WAINWRIGHT, C., ALTAMIRANO, L., CHENEY, M., CHENEY, J., BARBER, S., PRICE, D., MOLONEY, S., KIMBERLEY, A., WOOLFIELD, N., CADZOW, S., FIUMARA, F., WILSON, P., MEGO, S., VANDEVELDE, D., SANDERS, S., O'ROURKE, P. & FRANCIS, P. 2003. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *The New England journal of medicine,* 349**,** 27-35.

WALSH, P., ROTHENBERG, S. J., O'DOHERTY, S., HOEY, H. & HEALY, R. 2004. A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis. *European journal of emergency medicine : official journal of the European Society for Emergency Medicine,* 11**,** 265-272.

WANG D, B. S. M. C. 2011. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: systematic review and additional economic modelling of subgroup analyses.

WANG, E. E., MILNER, R. A., NAVAS, L. & MAJ, H. 1992. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *The American review of respiratory disease,* 145**,** 106-109.

WEBB, M., MARTIN, J., CARTLIDGE, P., NG, Y. & WRIGHT, N. 1985. Chest physiotherapy in acute bronchiolitis. *Archives of disease in childhood,* 60**,** 1078-1079.

WELLS GA, S. B., O'CONNELL D, PETERSON J, WELCH V, LOSOS M, ET AL. *The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized*

studies in meta-analyses [Online]. The Ottawa Hospital Research Institure. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 2020].

WOOD, D. W., DOWNES, J. J. & LEEKS, H. I. 1972. A clinical scoring system for the diagnosis of respiratory failure: preliminary report on childhood status asthmaticus. *American journal of diseases of children,* 123**,** 227-228.

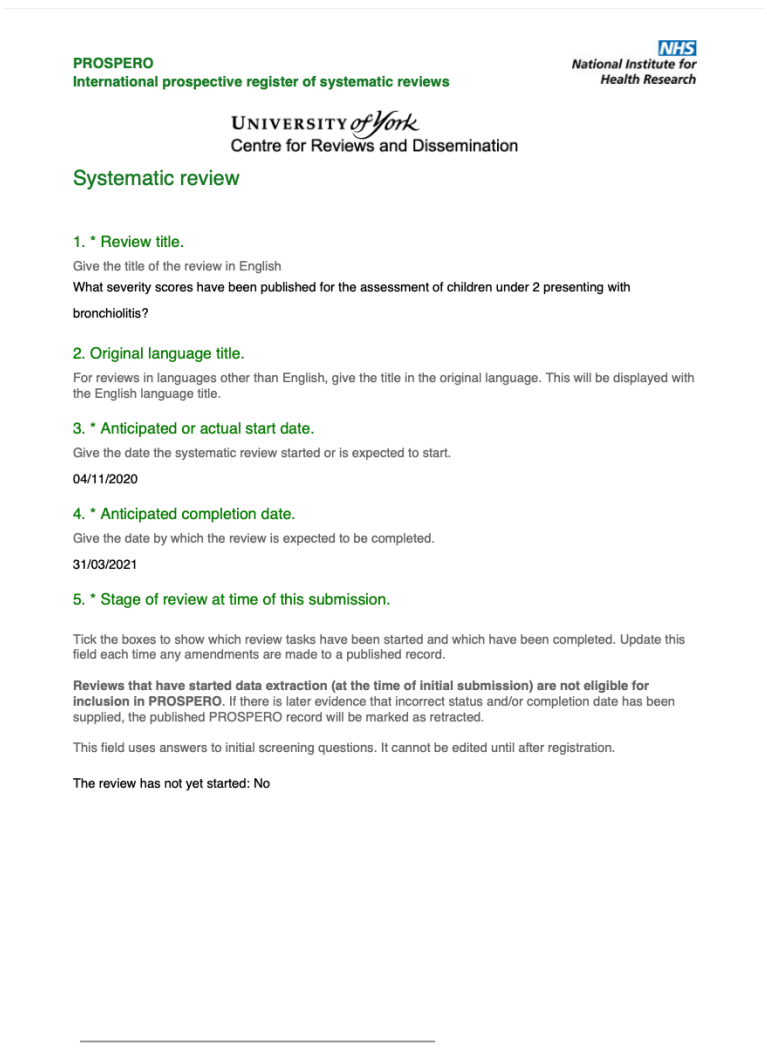
YEOH, D. K., FOLEY, D. A., MINNEY-SMITH, C. A., MARTIN, A. C., MACE, A. O., SIKAZWE, C. T., LE, H., LEVY, A., BLYTH, C. C. & MOORE, H. C. 2020. The impact of COVID-19 public health measures on detections of influenza and respiratory syncytial virus in children during the 2020 Australian winter. *Clin Infect Dis*.

YITSHAK-SADE, M., YUDOVITCH, D., NOVACK, V., TAL, A., KLOOG, I. & GOLDBART, A. 2017. Air Pollution and Hospitalization for Bronchiolitis among Young Children. *Annals of the American Thoracic Society,* 14**,** 1796-1802.

ZHANG, L., MENDOZA-SASSI, R. A., WAINWRIGHT, C. & KLASSEN, T. P. 2017. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database of Systematic Reviews*.

ZOMER-KOOIJKER, K., VAN DER ENT, C. K., ERMERS, M. J., UITERWAAL, C. S., ROVERS, M. M. & BONT, L. J. 2014. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One,* 9**,** e87162.

Appendix 1-Prospero Registration Form



PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

What severity scores have been published for the assessment of children under 2 presenting with bronchiolitis?

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

04/11/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/03/2021

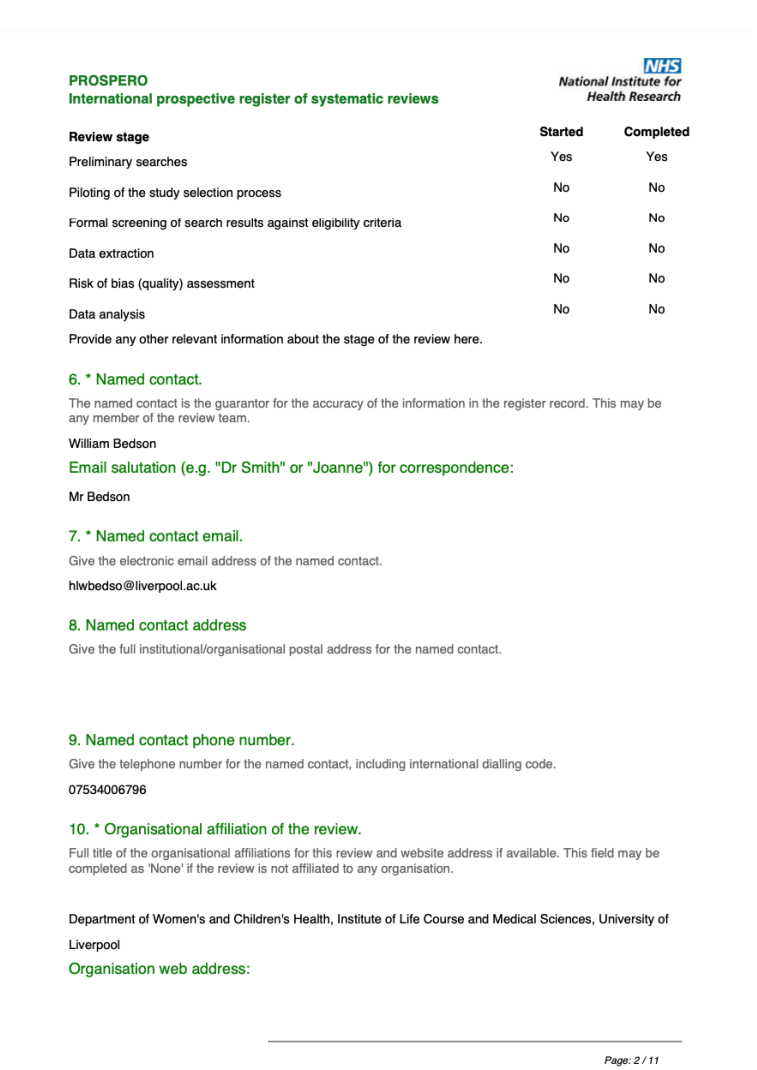
5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No



PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

William Bedson

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Bedson

7. * Named contact email.

Give the electronic email address of the named contact.

hlwbedso@liverpool.ac.uk

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

07534006796

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool

Organisation web address:

Page: 2 / 11

Appendix Figure 1. 1 PROSPERO registration form

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr William Bedson. University of Liverpool
Miss Emma Wilkinson. Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool
Dr Dan Hawcutt. Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What severity scores have been published for the assessment of children under 2 presenting with bronchiolitis and how well have these been validated for use?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

MEDLINE, CINAHL, PubMed and EMBASE databases will be searched without any date or language restrictions. Exclusion criteria will include those involving non-human participants and those not assessing bronchiolitis. Papers found in the search will be screened by title, abstract and full-text. Bibliographic searching will be done by using known papers to find further severity scores through those referenced in relevant papers. EndNote will be used to log and combine the searches from the individual databases.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Bronchiolitis- the most common lower respiratory tract infection affecting children under 2 years old.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

The population will consist of children age 0-2 who have presented to a healthcare setting with bronchiolitis.

Studies must included must contain children who present with a diagnosis of bronchiolitis.

Exclusion criteria includes, those studies found that involve non-human participants, as well as studies exclusively involving children that do not meet the age criteria.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

The intervention is any clinical score that is used to assess the severity of the presentation of bronchiolitis.

The score must assign a numerical value to at least two parameters to generate an overall severity score.

The scores must be a new or modified version of a previous severity score. The score must be applied in a clinical setting.

Reasons for exclusion include scores that use specialist equipment not widely available (such as biochemical marker blood tests), and they must not involve the possible interventions or settings that the child may present with- e.g. marked on length of hospitalisation, need of oxygen, or whether the child is treated in ICU. Scores that do not provide a numerical value parameters will be excluded, and scores that do not detail the parameters used, or the calculation of the score will be excluded

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

The relevant scores found during the literature search will be compared against each other, as well as their

Appendix Figure 1. 2 *PROSPERO registration form*

associated validity data

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

All study designs will be included except systematic reviews. Guidelines, protocols and commentaries will be excluded.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

New or modified severity scores published for use in children under 2 years old presenting with bronchiolitis.

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The sensitivity and specificity of each score for predicting its selected outcome- e.g. children requiring admission. These will be compared for each score.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

The different parameters used in each severity score, the possible values that each parameter could generate in each score, and the weighting that each parameter holds in the overall calculation will be extracted. The clinical setting that these scores are applied, and details of how to apply each scoring system will be assessed. Other outcomes will relate to the quality of the study; such as the validity, reproducibility, discriminatory power, utility and reliability.

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The sensitivity and specificity of each score for predicting its selected outcome- e.g. children requiring admission. These will be compared for each score.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

This review will use a PRISMA framework; results will be deduplicated & refined using inclusion and exclusion criteria. This will be performed by two reviewers separately and then compared. Any discrepancies in inclusion/exclusion will be discussed between the two reviewers to reach a consensus, and then assessed by a third reviewer if required. References will be stored on an Excel spreadsheet and include each stage of title, abstract and full-text screening, as well as any reasons for exclusion during the process. This will enable a clear data trail throughout.

All papers that reach the full-text screening stage will be accessed and then reviewed further using the same criteria, noting any reasons for exclusion in the table generated previously.

Once a consensus is reached regarding all full text, data extraction will begin. This will be facilitated using an excel spreadsheet to derive all the necessary information. This will be the name of the score used; the parameters assessed, the possible values assigned for parameters and the weighting of each parameter. Further information will be the aspects such as the number of participants, the validity and the realiability.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Risks of bias will be be assessed independently by the two researchers, and will involve a third party assessment where consensuses cannot be reached. The necessary risk of bias tool will be used for each study where appropriate, and a statistician will input should it be required.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

A formal narrative synthesis will be undergone. This will compare factors assessed in each score, ways of measuring these, the ability to capture these on health records and their interchangeability. An example can be the scoring of head bobbing and accessory respiratory muscle used; these may be differentiated and given independent scores, or may be assessed under the same parameter (work of breathing). The review will assess how the parameter is measured and its weighting in the contribution to the overall score.

The primary outcome for the data is any new or modified severity score used in the assessment of bronchiolitis and the name of it. Secondary outcomes include any parameter assessed, the possible values allocated to each parameter and the final weighting of each parameter as part of the score. Further information that will be extracted if available as part of the secondary outcome will be aspects including, but

Appendix Figure 1. 3 *PROSPERO registration form*

not limited to, the number of participants, the country of origin, any validity, reproducibility or reliability (such as inter-rater reliability or consistency) assessments, who the score is assessed by (e.g. parental, nurse led or clinician), the utility of these scores and discriminatory power. This will allow methodological assessment of the study in which each score was developed.

These aspects will be extracted and culminated in tabular format using Excel. At least two scores are required for data synthesis. There is no meta-analysis planned or no necessary statistical software required.

The interpretation of results will lead to an overall view of what scores are available bronchiolitis as well as providing an assessment of what parameters are common in these scores, the weighting they represent as well as the the validity and reliability of these scores in the assessment of bronchiolitis.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

not planned

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
Yes

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
Yes

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education

Appendix Figure 1. 4 *PROSPERO registration form*

No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
Yes

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Appendix Figure 1. 5 *PROSPERO registration form*

No

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

bronchiolitis, viral bronchiolitis, RSV-bronchiolitis, severity score, clinical score, children, paediatric, acute, human

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

This is a record that was previously rejected, and a similar review being undertaken regarding viral-induced wheeze received feedback to aide in the re-submission. The methodology proposed for this review is similar to that to a previously PROSPERO registered systematic review undertaken by Hawcutt et al. titled Paediatric acute asthma scoring systems: a systematic review, accepted by PROSPERO in 2018 and published in JACEP Open in June 2020.

This form was amended as required, as further elaboration was asked for in section #28

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Appendix Figure 1. 6 *PROSPERO registration form*

Appendix 2- PRISMA Checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	

Appendix Figure 2. 1 PRISMA checklist (Moher et al., 2009)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix Figure 2. 1 *PRISMA Checklist (Moher et al., 2009)*

Appendix 3- Quality Assessment

Author	Type of Study	Level of Concerns of Quality
Bajaj	RCT	high
Bamberger	Prospective obse	some concerns
Basile	cohort study	high
Beck	RCT	some concerns
Berger	RCT	low
Bohe	RCT	some concerns
Bressan	Prospective obse	some concerns
Can	RCT	some concerns
Caserta	cohort	some concerns
Chipps	RCT	some concerns
Chong	prospective obse	low
Conrad	cohort	some concerns
Constantopoulos	prospective epide	some concerns
Conway	guideline	low
Dabbous	RCT	low
De Boeck	RCT	some concerns
De Brasi	cohort?	some concerns
Ejaz	RCT	some concerns
Gadomski 1994a	RCT	some concerns
Gadomski 1994 b	RCT	some concerns
Gajdos	controlled trial ?	some concerns
Gal	cohort	some concerns
Giugno	RCT	high
Goebel	RCT	some concerns
Goh	cohort	some concerns
JacobsJD	RCT	some concerns
Kerem	cohort	high
Kristjansson	RCT	high
Lai	cohort	some concerns
Lal	RCT	high
Liu	cohort	some concerns
Lowell	RCT	some concerns
Macias, C	cohort	some concerns
Marlais	cohort	some concerns
McCallum	cohort	low
Midulla	cohort	low
Ochoa Sangrador	cross-sectional	some concerns
Papadopolous	cohort	some concerns
Ralston	cohort	some concerns
Ramos-Fernández	cohort	some concerns
Raya	cohort	some concerns
Rivera-Sepulveda	cross-sectional	high
Rubin	cohort	some concerns
Schuh	RCT	some concerns
Skjerven	RCT	low
Tal, A	RCT	some concerns
Teeratakulpisam	RCT	some concerns
Wainwright	RCT	low
Walsh	Cohort	some concerns
Wang	cohort	some concerns
Webb	RCT	high
Wood	cohort	high

Appendix Table 3. 1 Quality Assessment of Studies included in Systematic Review

Appendix 4- Systematic Review Results

Primary Author	Year	Paper Title	Type of Study	Country
Bajaj	2006	A randomized trial of home oxygen therapy from the emergency department for acute bronchiolitis.	RCT	America
Bamberger	2012	What is the clinical relevance of respiratory syncytial virus bronchiolitis?: findings from a multi center prospective study	Prospective observational study	Israel
Basile	2015	Lung ultrasound: a useful tool in diagnosis and management of bronchiolitis	cohort study	Italy
Beck	2007	Computerised acoustic assessment of treatment of efficacy of nebulised epinephrine and albuterol in RSV bronchiolitis	RCT	Israel
Berger	1998	Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up	RCT	Israel
Bohe	2004	Indications of conventional chest physiotherapy in acute bronchiolitis	RCT	Spain
Bressan	2013	High-flow nasal cannula oxygen for bronchiolitis in a paediatric ward: a pilot study	Prospective observational study	Italy
Can	1998	Salbutamol or mist in acute bronchiolitis	RCT	Turkey
Caserta	2017	Development of a Global Respiratory Severity Score for Respiratory Syncytial Virus Infection in Infants	cohort	America
Chipps	1993	Alpha-2A interferon for treatment of bronchiolitis caused by respiratory syncytial virus	RCT	America
Chong	2017	The modified respiratory index score (RIS) guides resource allocation in acute bronchiolitis	prospective observational study'	Singapore
Conrad	1987	Aerosolized ribavirin treatment of respiratory syncytial virus infection in infants hospitalized during an epidemic	cohort	America
Constantopoulos	2002	Burden of Respiratory Syncytial Viral infection on paediatric hospitals: a two-year prospective epidemioligcal study	prospective epidemiological study	Greece
Conway	2004	Empowering Respiratory Therapists to Take a more active role in delivering quality care for infants with bronchiolitis	guideline	America
Dabbous	1996	A double blind study on the effects of corticosteroids in the treatment of bronchiolitis	RCT	America
De Boeck	1997	Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study	RCT	Belgium
De Brasi	2010	Therapeutic approach to bronchiolitis: why paediatricians continue to overprescribe drugs	cohort?	Italy
Ejaz	2015	Hypertonic Saline (3%) vs Normal Saline (0.9%)Nebuliztion for Acute Viral Bronchiolitis: A RandomizedControl Tria	RCT	Pakistan
Gadomski	1994	Efficacy of Albuterol in the Management of Bronchiolitis	RCT	America
Gadomski	1994	Oral versus nebulised albuterol in management of bronchiolitis in Egypt	RCT	Egypt
Gajdos	2009	Inter-observer agreement between physicians, nurses, and respiratory therapists for respiratory clinical evaluation in bronchiolitis	controlled trial ? Not randomised	France
Gal	2015	Transcutaneous PCO2 monitoring in infants hospitalized with viral bronchiolitis	cohort	Israeal
Giugno	2004	Concentrations of interleukin-2 in the nasopharyngeal secretion of children with acute respiratory syncytial virus bronchiolitis	RCT	America
Goebel	2000	Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis.	RCT	Singapore
Goh	1997	Efficacy of bronchodilators in the treatment of bronchiolitis	cohort	Brazil
JacobsJD	2014	7% hypertonic saline in acute bronchiolitis	RCT	America
Kerem	1991	Clinical-physiologic correlations in acute asthma of childhood.	cohort	Canada
Kristjansson	1993	Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers	RCT	Norway
Lai	2004	Elevated levels of soluble adhesion molecules in sera of patients with acute bronchiolitis	cohort	Taiwan
Lal	2018	Nasal Continuous Positive Airway Pressure in Bronchiolitis: A Randomized Controlled Trial	RCT	India
Liu	2004	Use of respiratory clinical score among different providers.	cohort	America
Lowell	1987	Wheezing in infants: the response to epinephrine.	RCT	America
Macias, C	2015	Variability in inpatient management of children hospitalized with bronchiolitis	cohort	America
Marlais	2011	Clinical predictors of admission in infants with acute bronchiolitis	cohort	UK
McCallum	2013	Clinical predictors of admission in infants with acute bronchiolitis	cohort	Australia
Midulla	2010	Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants	cohort	Italy
Ochoa Sangrador	2011	Management of acute bronchiolitis in emergency wards in Spain: variability and appropriateness anayysis	cross-sectional	Spain
Papadopolous	2002	Association of rhinovirus infection with increased disease severity in acute bronchiolitis	cohort	Greece
Ralston	2010	Nebulized hypertonic saline without adjunctive bronchodilators for children with bronchiolitis	cohort	America
Ramos-Fernández	2014	[Validation of an acute bronchiolitis severity scale]	cohort	Spain
Raya	2013	Bordetella pertussis Infection Attenuates Clinical Course of Acute Bronchiolitis	cohort	Israel
Rivera-Sepulveda	2019	Assessing Resident Diagnostic Skills Using a Modified Bronchiolitis Score	cross-sectional	America
Rubin	2003	Clinical and transcutaneous oxygen saturation characteristics in hospitalized infants with acute viral bronchiolitis	cohort	Spain
Schuh	1990	Nebulized albuterol in acute bronchiolitis	RCT	Canada
Skjerven	2013	Racemic Adrenaline and Inhalation Strategies in Acute Bronchiolitis	RCT	Norway
Tal, A	1983	Dexamethasone and salbutamol in the treatment of acute wheezing in infants	RCT	Israel
Teeratakulpisam	2007	Efficacy of Dexamethasone Injection for Acute Bronchiolitis in Hospitalized Children: A Randomized, Double-Blind, Placebo-Controlled Trial	RCT	thailand
Wainwright	2003	Multicenter, Randomized, Double-Blind, Controlled Trial of Nebulized Epinephrine in Infants with Acute Bronchiolitis	RCT	Australia
Walsh	2004	A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis	Cohort	Ireland
Wang	1992	Observer agreement for respira-tory signs and oximetry in infants hospitalized with lower respiratoryinfections	cohort	Canada
Webb	1985	Chest physiotherapy in acute bronchiolitis	RCT	UK
Wood	1972	A Clinical Scoring System for the Diagnosis of Respiratory Failure: Preliminary Report on Childhood Status Asthmaticus	cohort	America

Appendix Table 4. 1 Table demonstrating characteristics of studies included in systematic review.

Primary Author	Year	Population Age (months)	Average (mean) age (months)	Number of participants	does it include preterm	Setting	Assesor	Did paper invole intervention
Bajaj	2006	2-24	7.8	92	N	ED	-	N
Bamberger	2012	< 24	4.0	366	-	Paediatric department	-	N
Basile	2015	< 12 (does not state specific criteria)	2.86 months	118	Y	Paediatric unit	attending doctor	N
Beck	2007	2-12	4.4	87	N	ED	investigator	Y
Berger	1998	1-18	5	42	-	ED	investigator	Y
Bohe	2004	0-24 months	2.7	32	N	ICU	-	Y
Bressan	2013	7 (days)- 12 months	1.3	80	Y	ED	-	N
Can	1998	7 weeks- 24 months	7.1	156	-	ED	-	Y
Caserta	2017	<10	3.5	193	N	GP, paediatric department and ED	study physician or nurse	N
Chipps	1993	< 24 mothhs	-	22	-	-	investigator	Y
Chong	2017	< 24 months	10.8 (median)	1818	N	ED	doctor who noted	N
Conrad	1987	-	5.75	134	Y	-	physician	Y
Constantopoulos	2002	2 weeks- 24 months	5.98	1710	Y	Paediatric ward	-	N
Conway	2004	< 12 months	9.2	195	Y	ED	-	N
Dabbous	1996	< 24	6.45	53	-	Paediatric department	study physician	Y
De Boeck	1997	<24	6.4	32	N	Paediatric ward	investigator	Y
De Brasi	2010	1-12 months	3.5	90	Y	Paediatric ward	-	N
Ejaz	2015	1- 24 months	-	80	-	ED & Paediatric inpatient	-	Y
Gadomski	1994	0-15	5.4	93	-	ED	-	Y
Gadomski	1994	< 18 months	6.1	169	-	outpatient and ED	investigator	Y
Gajdos	2009	< 18 months	2.1	180	-	ED	2 care providers independently- physicians, nurses, raspiratory therapists	N
Gal	2015	< 18 months	3.6	60	-	ED	-	N
Giugno	2004	<23 months	4.25	51	N- < 36 weeks	ED	-	Y
Goebel	2000	<24 months	6.05	99	-	Paediatric department	-	Y
Goh	1997	0-24 months	2.2	96	-	ED & ICU	-	N
JacobsJD	2014	6 weeks- 18 months	5.8	114	N (< 34 weeks)	ED	study physician	Y
Kerem	1991	>5 year	10	71	-	ER	-	N
Kristjansson	1993	<18 months	-	34	-	Paediatric department	-	Y
Lai	2004	1-24 months	18	47	-	Paediatric ward	-	N
Lal	2018	1-24 months	5.35	72	-	Paediatric ward	doctor, staff nuse	Y
Liu	2004	all paediatrics, but valid select for <2	24.5	55	-	Paediatric ward	nurses, respiratory therapist, physicians	N
Lowell	1987	< 24 months	9.4	30	-	ED & GP	investigator	Y
Macias, C	2015	< 24 months	4.4	3910	-	ED, clinic or primary care	-	N
Marlais	2011	<12 months	23 weeks	464	-	ED	-	N
McCallum	2013	< 24 months	5.4	138	-	-	study nurses	N
Midulla	2010	7 days- 11 months	2.45	182	-	ED	-	N
Ochoa Sangrador	2011	<24 months	6.4	2430	-	ED	-	N
Papadopolous	2002	<18 months	3.9	119	Y -8 premature	-	study physician	N
Ralston	2010	< 12 months	6.1	158	-	-	-	Y- post suction score
Ramos-Fernández	2014	<12 months	-	75	<35 weeks excluded	-	doctor	N
Raya	2013	<24 months	3.4	309	-	Paediatric department	house-staff' and later research staff	N
Rivera-Sepulveda	2019	<24 months	6	20	N	ED	general paediatrician (or trainee)	N
Rubin	2003	<12 months	-	111	-	-	-	N
Schuh	1990	6 weeks - 24 months	5.7	40	N	ED	investigator	Y
Skjerven	2013	<12 mohts	4.2	404	-	Paediatric department	study physician	Y
Tal, A	1983	1-12 months	3.3 & 8.8	32	-	-	investigator/ physician	Y
Teeratakulpisam	2007	4 weeks-24 moths	10.7	261	N	outpatient clinic/ ED	doctor (paediatrician)	Y
Wainwright	2003	<12 months	4.44	194	Y	-	nurse	Y
Walsh	2004	<24 months	5.95	132	Y	ED	-	N
Wang	1992	< 24 months	-	56 (43 bronchiolitis)	N	-	paediatric infectious diseases consultant	N
Webb	1985	-	4.6	90	-	-	investigator	N
Wood	1972	-	-	18	-	-	physician	N

Appendix Table 4. 1 *Table demonstrating characteristics of studies included in systematic review.*

Domain	Item
Objective Measures	Respiratory Rate
	Heart Rate
	inspiration to expiration ratio
	dyspnoea
Auscultation	Wheeze
	crepitations
	Aeration/ Air entry/ air exchange
	Silent chest
	stridor
	rales
	tubular breath sounds
	rhonchi
	Resonance
Oxygen Measurements	Oxygen saturation
	Cyanosis
	capillary refill time
Breathing behaviour	Retractions/ recessions
	Nasal Flaring
	Accessory muscle use
	head bobbing
	grunting
	Tracheal Tug
General Behvaiour	Feeding
	agitation
	lethargy- including loss of consciousness
	General appearance
	dehydration
	Nasal Discharge
	Nasal Obstruction
	Cough
	Airway secretion
Additional Support	supplemental oxygen
	nebulisation
	Intravenous infusion
Gastrointestinal	anorexia
	Vomiting
	Nausea
	Diarrhoea
	Abdominal Pain
	Liver/ spleen palpation
Ogranic Factors	Duration of symptoms
	Age at presentation
	temperature
Other	dysphagia
	dysphonia
	exudate
	headache
	myalgia
	arthralgia
	rash
	pulsus paradoxus

Appendix Table 4. 2 Illustrating the different domains and items identified across all tools in the systematic review

Domain	Item	Bajaj	Bamberger	Basile	Beck	Berger	Bohe	Bressan	Can	Caserta	Chipps	Chong	Conrad	Constantopoulos	Conway	Dabbous	De Boeck	De Brasi	Ejaz	Gadomski 1994a	Gadomski 1994b	Gajdos	Gal	Giugno	Goebel
Objective Measures	Respiratory Rate																								
	Heart Rate																								
	inspiration to expiration ratio																								
	dyspnoea																								
Auscultation	Wheeze						+												+						
	crepitations																								
	Aeration/ Air entry/ air exchange																								
	Silent chest						+												+						
	stridor												+												
	rales												+												
	tubular breath sounds												+												
	rhonchi												+												
	Resonance																								
Oxygen Measurements	Oxygen saturation																								
	Cyanosis																								
	capillary refill time																								
Breathing behaviour	Retractions/ recessions											+	+						+			+	+		+
	Nasal Flaring						&					+							+			+	+		+
	Accessory muscle use						&												+						
	head bobbing											+							+						
	grunting																								
	Tracheal Tug																								
General Behvaiour	Feeding																								
	agitation											&													
	lethargy- including loss of consciousness											&													
	General appearance																								
	dehydration																								
	Nasal Discharge												&												
	Nasal Obstruction												&												
	Cough												+												
	Airway secretion																								
Additional Support	supplemental oxygen																								
	nebulisation																								
	Intravenous infusion																								
Gastrointestinal	anorexia												*												
	Vomiting												*												
	Nausea												*												
	Diarrhoea												*												
	Abdominal Pain												*												
	Liver/ spleen palpation																								
Ogranic Factors	Duration of symptoms																								
	Age at presentation																								
	temperature																								
Other	dysphagia												-												
	dysphonia												-												
	exudate												-												
	headache												>												
	myalgia												>												
	arthralgia												>												
	rash												>												
	pulsus paradoxus																								

Appendix Table 4. 3 Full Assessment of Score

highlighting the items assessed under each item. Green indicates where a score assessed the aspect. Lilac shows scores that incorporated assessment of an intervention. Blue indicates commonly cited scores. Yellow highlights algorithmic scores. Dark green shows the score that assessed two aspects in depth. &, +, - and > were used to demonstrate where items were assessed under the same scoring point

Domain	Item	Goh	Jacobs	Kerem	Kristjannson	Lai	Lal	Liu	Lowell	Marcias	Marlais	McCallum	Midulla	Ochoa Sangrador	Papadopolous	Ralston	Ramos-Fernández	Raya	Rivera-Sepulv	Rubin	Schuh	Skjerven	Tal	Veeratakulpisar	Wainwright	Walsh	Wang	Webb	Wood
Objective Measures	Respiratory Rate																												
	Heart Rate																												
	inspiration to expiration ratio																												
	dyspnoea																												
Auscultation	Wheeze		+																			+							
	crepitations		+																										
	Aeration/ Air entry/ air exchange																												
	Silent chest																												
	stridor																												
	rales																					+							
	tubular breath sounds																												
	rhonchi																					+							
	Resonance																												
Oxygen Measurements	Oxygen saturation																												
	Cyanosis														+														
	capillary refill time																												
Breathing behaviour	Retractions/ recessions											+					+												
	Nasal Flaring						+														+								
	Accessory muscle use																				+								
	head bobbing											+																	
	grunting						+																						
	Tracheal Tug											+																	
General Behvaiour	Feeding														+												&		
	agitation		&																								&		&
	lethargy- including loss of consciousness		&																								&		&
	General appearance																												
	dehydration																												
	Nasal Discharge																												
	Nasal Obstruction																												
	Cough																												
	Airway secretion																												
Additional Support	supplemental oxygen																												
	nebulisation																												
	Intravenous infusion																												
Gastrointestinal	anorexia																												
	Vomiting																												
	Nausea																												
	Diarrhoea																												
	Abdominal Pain																												
	Liver/ spleen palpation																												
Ogranic Factors	Duration of symptoms																												
	Age at presentation																												
	temperature																												
Other	dysphagia																												
	dysphonia																												
	exudate																												
	headache																												
	myalgia																												
	arthralgia																												
	rash																												
	pulsus paradoxus																												

Appendix Table 4. 3 *Full Assessment of Score: highlighting the items assessed under each item. Green indicates where a score assessed the aspect. Lilac shows scores that incorporated assessment of an intervention. Blue indicates commonly cited scores. Yellow highlights algorithmic scores. Dark green shows the score that assessed two aspects in depth.*

&, +, - and > were used to demonstrate where items were assessed under the same scoring point

Appendix 5- Bronchiolitis Admissions

		Number	Percentage	Oxygen	Proportion Receiving oxygen	Critical Care	Proportion Receiving Critical Care	Median Age	Median Length of Stay
IMD	1	2088	58.67%	606	29.02%	196	5.27%	119.5788194	18.63333333
	2	459	12.90%	125	27.23%	110	6.75%	125.1208333	21.11666667
	3	274	7.70%	61	22.26%	31	4.38%	107.9548611	11.29166667
	4	174	4.89%	44	25.29%	12	5.75%	118.1923611	13.63333333
	5	179	5.03%	54	30.17%	10	6.15%	97.577778	16.2
	6	96	2.70%	29	30.21%	11	8.33%	100.255556	25.95
	7	134	3.77%	37	27.61%	8	4.48%	162.744792	18.5416667
	8	119	3.34%	30	25.21%	6	2.52%	141.004861	15.366667
	9	28	0.79%	7	25.00%	3	7.14%	111.315971	39.91667
	10	8	0.22%	3	37.50%	2	37.50%	294.492056	109.35
	total	3559	100.00%	996	0.279853892	3	5.51%	119.651389	18.1833333

Appendix Table 5.1 IMD analysis.

Demonstrating the data obtained based on IMD decile

Age	Number	Hospitalised	Observed	Proportion Hospitalised
0-2 months	1023	693	330	67.74%
2-4 months	783	485	298	61.94%
4-6 months	525	313	212	59.62%
6-8 months	414	245	169	59.18%
8-10 months	297	203	94	68.35%
10-12 months	236	156	80	66.10%
12-14 months	111	83	28	74.77%
14-16 months	79	57	22	72.15%
16-18months	40	30	10	75.00%
18-20months	22	18	4	81.82%
20-22-months	17	13	4	76.47%
22-24 months	12	10	2	83.33%

Appendix Table 5.2 Age Analysis.

Demonstrating the data obtained based on age categories

Hour	Number	Month	Number	Day of the week	Number	Year	Number
00-02	332	January	411	Monday	595	2015	331
02-04	252	February	245	Tuesday	555	2016	688
04-06	144	March	186	Wednesday	492	2017	663
06-08	108	April	150	Thursday	516	2018	832
08-10	101	May	109	Friday	478	2019	829
10-12	226	June	63	Saturday	436	2020	216
12-14	395	July	86	Sunday	487		
14-16	408	August	75				
16-18	374	September	153				
18-20	420	October	456				
20-22	401	November	868				
22-24	398	December	757				

Appendix Table 5.3 Temporal Setting.

Demonstrating the data obtained for the different hours, day of the week, month, and year.