Baseline predictors of hospital length of stay in children with respiratory syncytial virus infection: A retrospective analysis of three prospective observational studies

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Abstract

Background: Respiratory syncytial virus (RSV) is a common cause of hospitalisation in infants and children. This study aimed to identify common patient characteristics and baseline predictors of hospital length of stay (LOS) among infants diagnosed with RSV infection. Methods: This is a descriptive analysis of data from three separate prospective observational paediatric studies in Belgium, Japan, and New Zealand. Hospitalised children [?]5 years of age with a laboratory-confirmed diagnosis of RSV infection and an onset of symptoms [?]5 days prior to hospitalisation were considered for inclusion. We collected demographic and clinical information and the hospital LOS for each patient. LOS was assessed by age, presence of comorbidity, presence of prematurity, duration of symptoms and by country. Results: Overall, 181 patients were included in the analysis. The majority of patients (84%; 152/181) were otherwise healthy; only 16% (29/181) had comorbidity. Median hospital LOS was longer in Belgium and Japan than in New Zealand (5, 7, and 3 days, respectively). Presence of comorbidity prolonged hospital stay, with the effect on hospital LOS varying by country. Age, duration of symptoms prior to hospitalisation, and premature birth were not predictive of hospital LOS. Conclusion: In this cohort of children [?]5 years old hospitalised for RSV infection, medical practice varied greatly between countries. Although overall, comorbidity was associated with longer LOS, while other predictive factors were of little value in estimating LOS.

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Running title: RSV-associated hospitalisation in paediatrics

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Ethics approval statement

The study was performed in accordance with the protocol, current International Conference on Harmonisation guidelines on Good Clinical Practice, and applicable regulatory and country-specific requirements. This study was approved by the Ethics Committee UZ/KU Leuven, the Health and Disability Ethics Committee of New Zealand and the Keio University Ethics Committee, National Center for Child Health and Development, Japan.

Patient consent statement

Since data were collected retrospectively with no identifying patient characteristics, informed consent by patients was not required.

CONFLICTS OF INTEREST

Elli Makariadou, Roman Fleischhackl and Gabriela Ispas are employees of Johnson & Johnson and may be Johnson & Johnson stockholders. Isao Miyairi, Masayoshi Shinjoh and Noriyuki Tetsuka have received grants from Janssen Pharmaceutical KK. Els Keyaerts, Marijke Proesmans, Annabel Rector, Tristram Ingham, Bernadette Jones and Joanna Kirman have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Elli Makariadou, Gabriela Ispas and Roman Fleischhackl were responsible for data curation and formal analysis. Marijke Proesmans, Tristram Ingham, Isao Miyairi and Noriyuki Tetsuka were responsible for data acquisition and investigation. Gabriela Ispas and Roman Fleischhackl provided methodology, resources and project administration. Isao Miyairi, Masayoshi Shinjoh and Noriyuki Tetsuka acquired funding from Janssen pharamaceuticals for this project. Els Keyaerts, Annabel Rector, Joanna Kirman and Bernadette Jones provided supervision and validation. All authors were responsible for the development and review of drafts.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.#.

Abstract

Background: Respiratory syncytial virus (RSV) is a common cause of hospitalisation in infants and children. This study aimed to identify common patient characteristics and baseline predictors of hospital length of stay (LOS) among infants diagnosed with RSV infection.

Methods: This is a descriptive analysis of data from three separate prospective observational paediatric studies in Belgium, Japan, and New Zealand. Hospitalised children [?]5 years of age with a laboratory-confirmed diagnosis of RSV infection and an onset of symptoms [?]5 days prior to hospitalisation were considered for inclusion. We collected demographic and clinical information and the hospital LOS for each patient. LOS was assessed by age, presence of comorbidity, presence of prematurity, duration of symptoms and by country.

Results: Overall, 181 patients were included in the analysis. The majority of patients (84%; 152/181) were otherwise healthy; only 16% (29/181) had comorbidity. Median hospital LOS was longer in Belgium and Japan than in New Zealand (5, 7, and 3 days, respectively). Presence of comorbidity prolonged hospital stay, with the effect on hospital LOS varying by country. Age, duration of symptoms prior to hospitalisation, and premature birth were not predictive of hospital LOS.

Conclusion: In this cohort of children [?]5 years old hospitalised for RSV infection, medical practice varied greatly between countries. Although overall, comorbidity was associated with longer LOS, while other predictive factors were of little value in estimating LOS.

KEYWORDS

respiratory syncytial virus, paediatrics, hospitalisation, RSV, hospital length of stay

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1 INTRODUCTION

Globally, respiratory syncytial virus (RSV) is a major cause of respiratory tract infections (RTIs).[1-3] In older children and healthy adults, RSV infection typically results in mild upper RTIs, merely common cold-like symptoms.[4,5] However, in certain populations, including children <5 years old, adults with comorbidity, and adults [?]60 years old, RSV infection can progress to severe RTIs resulting in hospitalisation.[1-7]

RSV has been detected in >30% of children <5 years of age hospitalised with acute RTI caused by an identified viral pathogen.[8] Database analyses have demonstrated that RSV infection in the United States is responsible for 57 527- 132 000 hospitalisations, 1.5-1.7 million physician appointments and 402 000- 517 747 emergency department visits in children <5 years old annually.[5,9,10] RSV is the predominant cause of lower RTI (LRTI) in early childhood, resulting in 340 000 hospitalisations annually in children <5 years old in developed countries.[10] Globally, RSV is associated with 13-22% of acute LRTI mortality in young children.[11] Although the mortality rate is highest in children with comorbidity (eg, congenital heart disease or chronic lung disease), most cases of life-threatening RSV infection occur among children with no comorbidity, mainly in developing countries.[12] There is also increasing evidence that RSV LRTI in early childhood is associated with long-term complications, including recurrent wheezing, childhood asthma, and impaired pulmonary function.[13-16]

Despite reports from retrospective cohort studies describing hospitalisation rates among children with RSV infection, very few prospective observational studies have been conducted on the hospital length of stay (LOS), and factors affecting LOS in this population. The objective of our study was to perform a pooled analysis of three global observational studies; OBSERVERSV0001 (Belgium; NCT02133092), OBSERVERSV0002 (Japan; NCT02132923) and OBSERVERSV0004 (New Zealand; data on file). These studies were selected based on their prospective nature, laboratory confirmation of RSV infection, and robust methodology of high-quality data collection. The primary aim of this study was to determine common factors and baseline predictors of prolonged hospitalisation. The study analysed whether the following factors affected hospital LOS: age, duration of symptoms before hospital admission, presence of comorbidity, premature birth, gender, weight, birth weight, and country of residence.

2 METHODS

Data from the three prospective observational paediatric studies were pooled and analysed. These studies shared similar designs (analysed viral and clinical symptoms kinetics) and were conducted in hospital settings at three sites in Belgium, including two secondary medical centres and one tertiary medical centre; two tertiary medical centres in Japan; and two sites in New Zealand, including one secondary and one tertiary medical centre. The Belgian and Japanese studies started with the 2013-2014 RSV epidemics and extended through three seasons and two seasons, respectively. The New Zealand study began with the 2014 RSV season and lasted for three seasons. Patients eligible for the studies were observed daily for the duration of their hospitalisation, for a maximum of 7 days. Information captured by the database included demographic and study-specific baseline characteristics, medical-resource utilisation, and symptoms reported prior to and during hospitalisation. The study was performed in accordance with the protocol, current International Conference on Harmonisation guidelines on Good Clinical Practice, and applicable regulatory and country-specific requirements. This study was approved by the Ethics Committee UZ/KU Leuven, the Health and Disability Ethics Committee of New Zealand (14/CEN/76), and the Keio University Ethics Committee, National Center for Child Health and Development, Japan.

2.1 Inclusion criteria

Children [?]5 years of age hospitalised with laboratory-confirmed RSV acute respiratory infection were included. Signed informed consent was obtained for all patients, after which diagnosis of RSV infection was

determined within 24 hours of hospital admission, with an onset of symptoms [?]5 days prior to hospital admission required for inclusion. The study did not interfere with standard of care. The duration of symptoms prior to hospital admission, up until the day of hospitalisation (denoted as 0), was calculated and based on whichever symptom occurred first.

Assessments

Investigator-defined data collected prospectively included demographic and baseline characteristics such as age (months), body weight, presence of comorbidity, sex, premature birth, and duration of RTI symptoms prior to hospital admission. The investigators captured each patient's medical history at screening, while the presence of comorbidity was indicated by the investigator via the screening questionnaire. Recorded comorbidities included previously diagnosed conditions such as asthma, immunodeficiency, congenital lung disease and congenital heart disease. Otherwise healthy children were defined as those without comorbidities and were non-premature at birth.

Data on study-related characteristics including hospital LOS, administration of oxygen supplementation, and administration of mechanical ventilation were collected during the study. Symptoms present during hospitalisation were captured by designated site personnel in Belgium and New Zealand to assess the dynamics of clinical symptoms. Symptom reporting was performed using a different scale in Japan than that of the other countries and was not included in this analysis. The type and frequency of concomitant medications each patient received at all sites during their hospitalisation was recorded and coded using the Anatomical Therapeutic Chemical class 2 index.[17]

2.2.1 Severity scoring: Similar disease severity scoring data were available in Belgium and New Zealand. The spectrum of severity from mild to severe and its evolution was captured based on the most commonly reported symptoms over time and was assessed daily using a Clinical Severity Score (CSS) (online supporting information Table S1), with severity captured for the most frequently reported symptoms. The CSS classified symptoms as none, mild, moderate, or severe (graded 0–3, respectively), with most data collected (and therefore analysed) for "cough", "nasal discharge," and "rales, rhonchi, or other symptoms".

2.2.2 Length of hospital stay: The main outcome of interest was LOS, based on the discharge date collected at the study site. This analysis aimed to identify whether selected baseline parameters (age [in months], premature birth [born alive <37 weeks of pregnancy completed], duration of symptoms before hospital admission, presence of comorbidity, sex, body weight, country, birth weight) were associated with hospital LOS. If the discharge date was missing, or the patient was not discharged within 7 days of hospitalisation, the discharge date was censored to the last available assessment date, however all data until that point was included in the analyses.

2.3 Statistical analyses

2.3.1 Demographic and study-related characteristics: Descriptive statistics were used to summarise patient-related characteristics eg, age (months), weight, presence of comorbidity, sex, premature birth, and duration of symptoms prior to hospital admission. Regarding the presence of comorbidity, a listing of all the underlying conditions identified in the database were generated.

Summary tables present information on study-related outcomes both overall and by country. More specifically, the administration of either oxygen supplementation or mechanical ventilation were assessed.

Qualitative variables are expressed with number of observations and percentages. The continuous variables are reported as medians with interquartile range values.

2.3.2 Length of hospital stay: The Kaplan-Meier estimates of the proportion of hospitalised patients were calculated and assessed graphically overall, by presence of comorbidity, and by country. The difference in the time to be discharged for each group was explored using the generalised Wilcoxon tests. An accelerated failure time (AFT) model was implemented to identify predictors of a prolonged hospitalisation in the

paediatric population. Under an AFT model, the estimated ratio of the expected time of hospital stay in function of the predictor variables is assessed and is defined as time ratio.[18] A time ratio <1 indicates that the LOS is shortened, while a time ratio >1 implies that the LOS is prolonged. Based on goodness-of-fit, a log-normal distribution was used throughout. The variables that were included in the model were age (months), body weight, presence of comorbidity, country, sex, premature birth and duration of RTI symptoms prior to hospital admission. Additionally, the interaction between presence of comorbidity and country was evaluated. The variables in the final model were selected with a backward variable selection method. The results from the model were summarised with time ratios and the corresponding 95% confidence interval (95% CI) adjusted for the covariates.

All statistical analyses were performed using SAS or R studio.

3 RESULTS

3.1 Baseline and study-related characteristics

In total, 181 children ([?]5 years of age) were analysed, with 41% (74/181) hospitalised in Belgium, 32% (58/181) in New Zealand, and 27% (49/181) in Japan.

Baseline demographics and study-related characteristics were similar across studies (Table 1). The overall median age of patients was 5 months, with patients in Japan having the highest median age (7 months). Gender distribution was balanced, with 51% (92/181) male patients. Overall, 17% (30/181) of patients were born pre-term; in Belgium and New Zealand, pre-term-born infants accounted for 19% of patients (14/74 and 11/58 respectively) whereas in Japan 10% were pre-term-born infants (5/49). Overall, 56% (102/181) of patients presented in the hospital within [?]3 days of symptom initiation, although 57% [28/49] of patients in Japan reported a duration of symptoms >3 days prior to hospital admission.

Oxygen supplementation during hospitalisation was given on at least 1 day for 57% (104/181) of patients, with the administration of oxygen supplementation among patients higher in Belgium and Japan (60% [44/74] and 67% [33/49], respectively) than New Zealand (47% [27/58]). While no patients required mechanical ventilation, no patients in the intensive care unit (ICU) were included as obtaining nasal swabs was not possible.

Overall, 17% of the total population (30/181) were born prematurely. Patients with comorbidity accounted for 16% (29/181) of the population. Among patients with comorbidity, asthma was the most common (41% [12/29]), while a heart condition was present in 34% (10/29). Of the 29 patients with comorbidities, 31% (9/29) were born prematurely. Overall, 5% (9/181) of patients had both a comorbidity and premature birth. A complete list of the present underlying comorbidities overall and by country can be found in Table 2.

3.2 Length of hospital stay

The LOS, shown by the percentage of patients hospitalised each day over the 7-day period is presented for the pooled study population, by presence of comorbidity and by country in Figures 1, 2 and 3 respectively. This includes the data of 42% (76/181) of patients with censored data (ie, did not have discharge data so the exact hospital LOS was not known), with 15% (28/181) censored at day 7. Overall, the median hospital LOS was 5 days (Figure 1), with a median LOS longer in Belgium and Japan than in New Zealand (5, 7, and 3 days respectively). In an analysis of LOS differences based on the Wilcoxon tests, there was significant difference between countries ($P < .0001$), patients from Japan had the longest hospital LOS (37% [18/49] of patients hospitalised for [?]7 days). There was a significant increase in time to hospital discharge in children with comorbidity compared with otherwise healthy children ($P = .015$).

In the AFT analysis performed on the time until hospital discharge, presence of comorbidity, country of hospitalisation, and their interaction were statistically significant predictors of outcome. The interaction between country and presence of comorbidity was statistically significant ($P = .0232$), indicating that the impact of comorbidity on hospital LOS was not the same in each country (Figure 4). Particularly in New

Zealand, comorbidity was associated with a significant increase in hospital LOS (2.4-fold increase, 95% CI: 1.46-3.95). However, in Belgium and Japan, this increase was small and not significant (8% [95% CI: -19-44%] and 24% [95% CI: -18-89%] in Belgium and Japan, respectively). There was a substantial proportion of patients in each country who had reported no comorbidity, although having a hospital LOS [?]7 days.

Premature birth, symptom duration prior to hospitalisation, sex, and birth weight were not associated with an increased hospital LOS. Most (94% [170/181]) hospitalised patients were <2 years old (30% 0 to <3 months old, 21% 3 to <6 months old, and 49% 6 to 60 months of age) (online supporting information Figure S1), although this was not associated with longer hospital LOS (online supporting information Figure S2).

3.3 Symptom severity in Belgium and New Zealand

At day 1 of hospitalisation, the most commonly reported severe symptom was cough (41%; 53/130), while severe symptoms of "rales, rhonchi, or other" were reported in 34% (44/128) of patients. On day 1, cough was reported as moderate or mild in 45% (59/130) and 14% (18/130) of patients, respectively. On day 7 of hospital stay, 76% of patients (16/21) still had symptoms of nasal discharge (at least mild) and 62% (13/21) reported moderate to severe cough.

4 DISCUSSION

In this study, the presence of comorbidity tended to prolong hospital LOS, although this effect was only statistically significant in New Zealand and not Belgium nor Japan. In the overall study population, 16% of patients had comorbidities, 17% had premature births and only 5% had both comorbidity and premature birth, confirming the substantial burden of RSV infection in otherwise healthy children. This is consistent with previous studies that have suggested that most RSV-related hospitalisations occur in infants and young children born at term without comorbidity.[12] Symptom severity remained substantial throughout the hospital stay, with at least mild symptoms persistent at day 7 in many cases.

This also demonstrates that country of residence is a significant factor in prolonged hospitalisation, with patients in Japan and Belgium more likely to have a longer hospital LOS than those in New Zealand. However, this is unlikely due to differences in the characteristics of a typical patient, but rather multiple confounding factors including differences in clinical practice, which are difficult to assess based on these data. For example, there is a general lack of consensus on discharge criteria. While most guidelines internationally state a need for adequate feeding before discharge, oxygen saturation discharge criteria range from >90% to >94% or state "improved saturations" as a criterion without specifying a specific value.[6] The Australasian bronchiolitis guidelines oxygen saturation discharge criteria are [?]92%, there are no specific Belgian guidelines, and Japanese guidelines do not state discharge criteria.[6]

In addition, Japan, has longer hospital LOS for acute care than other Organisation for Economic Co-operation and Development (OECD) countries for acute care, with an average of 16.1 days for all hospital beds in 2018 compared with 6.6 for Belgium (no data for New Zealand).[19] These factors highlight the lack of a universal consensus on what constitutes acceptable recovery from RSV, and can contribute to wide variability in hospital LOS, as observed in other bronchiolitis studies.[20,21] Additionally, hospital LOS is a consequence of multiple elements including clinical, social, financial and logistical factors. For example, a study in New Zealand revealed 19% of acute RTI admissions for children under 2 years old could be prevented if all housing were free from damp and mold.[22] Moreover, it has been documented that bronchiolitis guidelines are often not well adhered to in clinical practice.[23-26] Therefore, hospital LOS cannot be assessed easily or taken as a complete measurement of disease severity. While these studies are not RSV-specific, bronchiolitis is caused by RSV in the vast majority of cases. It should be noted that our study, while likely to be dominated by bronchiolitis, particularly in the younger children, will also include RSV-positive patients admitted to hospital without this diagnosis (eg, pneumonia, bronchitis or asthma exacerbations, particularly in older children).

Across all countries, no clear association was observed between hospital LOS and premature birth (which was analysed separately to comorbidities), sex, birth weight, patient age, or duration of symptoms prior to hospitalisation. Younger age was associated with being admitted to hospital (online supporting information Figure S1), which is likely in part due to younger children being more susceptible to severe disease than older children.[27,28] However, in this study younger age did not impact hospital LOS, which is in line with the observations of other studies.[29,30]

The current findings differ from a previous study, in which positive predictors for prolonged hospital LOS were age and premature birth.[31] However, this differs from the current study as it was a single-center study including infants hospitalised with bronchiolitis, not strictly an RSV-confirmed RTI. In a retrospective global questionnaire study analysing infants with RSV-related mortality, 51% of patients had comorbidity.[12] This would suggest children with pre-existing conditions have increased risk of severe RSV infection. In our study, while the presence of comorbidity predicted longer hospital LOS, there was a substantial proportion of patients without comorbidity with a LOS [?]7 days, which suggests multiple or even unknown drivers for hospital LOS. In addition, the presence of comorbidity could influence decisions to admit patients to hospital, as even in mild and moderate cases, physicians may be more likely to admit a patient with comorbidity than a patient without one.

In a UK study of infants with bronchiolitis (84% of which were RSV-positive), most of the variation in hospital LOS in this population was explained by variables not measured and may include random factors, which supports the unpredictability observed in our study.[32] Our study did not collect data on non-clinical factors that may have contributed to LOS. Additionally, while a prospective multicentre study in the United States found that younger children (<1 month of age) and those with gestational age <32 weeks were more likely to have a hospital LOS [?]3 days, the difference was relatively small.[33] These studies support our findings in that, while there is variability between patients and sites, there are no strong baseline predictors which contribute to hospital LOS in RSV-infected children, with the possible exception of country and/or site.

As a retrospective analysis of prospective studies, this analysis has some limitations. Patients were followed in the hospital for a maximum of 7 days or until hospital discharge. For many patients, the exact discharge date was unknown; thus, the hospital LOS was censored. The reason for these censors are largely unknown, as the data simply were not recorded due to this not being a requirement of the original studies included in the pooling. In addition, some patients were censored as they had a LOS >7 days, meaning our dataset only includes partial data for patients with particularly long hospital stays. While it would be ideal to identify the duration that patients remained in hospital after 7 days, it is likely that this is a small proportion of patients. Patients with an onset of symptoms for >5 days prior to hospitalisation were excluded from analysis, and it is not clear how these patients may have affected the data. They may have had short hospital stays, as there would have been sufficient time for natural viral clearance, or they may have had longer stays if they had mild RSV that later developed into severe disease. Moreover, onset of symptoms is difficult to determine retrospectively, particularly as symptoms can be initially mild. In addition, we are limited by the data recorded for this study, so certain factors of interest (eg, oxygen saturation) were only reported during hospitalisation, and not at baseline. While sample sizes were large enough for statistical comparisons (eg, between countries), they still only represent a small percentage of RSV admissions during the time of studies, which means selection bias is possible. For example, parents of patients needed to consent to daily nasal swabs being taken as well as symptom scoring, which may be less likely in more severely ill patients, and was not possible in patients admitted to the ICU, meaning some of the most severely ill patients were not included in this study. We are also limited in the comparisons we can make between sites as there was a mix of secondary and tertiary hospitals. The Japan site also used a different scoring system for clinical symptoms, preventing any comparisons being made with the Belgian and New Zealand sites. The symptom scores, like any symptom score, do not capture the full burden of RSV disease. For example, this score did not include decrease in food intake, which can often be difficult to determine in children. However, they did capture the main symptoms of RSV.

The current study benefits from patients having a laboratory-confirmed RSV diagnosis, rather than just a clinical diagnosis of any-cause bronchiolitis. This is not often the case in retrospective studies, which tend to rely on the use of International Classification of Diseases (ICD) codes for diagnosis. In such circumstances, admission to hospital is dependent upon the organisation of medical systems and standard of care, so therefore may not be an ideal indicator for disease severity and burden. Furthermore, there is a potential for data bias in retrospective cohort studies due to the inconsistencies in the use of diagnostic testing and subsequent reporting. More detailed and accurate data such as hospital LOS, complication rates and the impact of the presence of comorbidities are necessary to characterise burden and to predict the risk of severe illness. Our prospectively collected data set is advantageous in that it describes patient history, details infection severity and gives an overview of the patient journey through hospital.

In conclusion, this study explores the several factors underlying RSV infection and hospital LOS, which carry a substantial burden in children [?]5 and particularly children [?]2 years of age. While the presence of comorbidity tended to prolong hospital LOS, the degree of extended stay was not the same across all countries. Significant differences in hospital LOS were observed between countries, suggesting differences in local standards of care, or other non-clinical factors affecting discharge planning (eg, home environment, social support). According to this assessment, there are no clear predictors of longer hospital LOS for patients diagnosed with RSV, and while the presence of comorbidity tends to increase hospital LOS, most hospitalisations are in otherwise healthy patients. Younger age was associated with admission to hospital, but not with a longer hospital LOS. This shows that RSV disease has an unpredictable disease course, with or without comorbidity.

REFERENCES

T**ABLE1**Baselinedemographicsandstudy-relatedcharacteristics

				Dataset	**Dataset**	**Dataset**
		Overall (n = 181)	**Belgium (OB-SERVERSV0005) (n = 74)**	**Belgium (OB-SERVERSV0005) (n = 74)**	**Japan (OB-SERVERSV0002) (n = 49)**	**New Zealand (OB-SERVERSV000 (n = 58)**
Male, n (%)	92 (51)	92 (51)	40 (54)	40 (54)	21 (43)	31 (53)
Age (months) Median (IQR)	5.0 (2.0-13.0)	5.0 (2.0-13.0)	4.0 (1.0-11.0)	4.0 (1.0-11.0)	7.0 (3.0-16.0)	6.0 (2.0-10.0)
Presence of comorbidity No, n (%) Yes, n (%)	152 (84) 29 (16)	152 (84) 29 (16)	63 (85) 11 (15)	63 (85) 11 (15)	38 (78) 11 (22)	51 (88) 7 (12)
Weight at baseline (kg) Median (IQR)	7.5 (5.5-9.7)	7.5 (5.5-9.7)	6.9 (5.1-9.2)	6.9 (5.1-9.2)	8.1 (5.8-10.0)	7.5 (6.1-9.8)[a]
Weight at birth (kg) Median (IQR)	3.2 (2.8-3.6)	3.2 (2.8-3.6)	3.4 (2.9-3.7)	3.4 (2.9-3.7)	2.9 (2.6-3.2)	3.4 (2.8-3.8)

				Dataset	Dataset	Dataset
Premature birth No, n (%) Yes, n (%)	151 (83) 30 (17)	151 (83) 30 (17)	60 (81) 14 (19)	60 (81) 14 (19)	44 (90) 5 (10)	47 (81) 11 (19)
Symptom duration prior to hospitalisation [?]3 days, n (%) >3 days, n (%)	102 (56) 79 (44)	102 (56) 79 (44)	42 (57) 32 (43)	42 (57) 32 (43)	21 (43) 28 (57)	39 (67) 19 (33)
Administration of oxygen supplementation No, n (%) Yes, n (%)	77 (43) 104 (57)	77 (43) 104 (57)	30 (40) 44 (60)	30 (40) 44 (60)	16 (33) 33 (67)	31 (53) 27 (47)

Abbreviation: IQR, interquartile range.

No patients in the studies received mechanical ventilation.

[a]Three patients from New Zealand did not have their weight at baseline recorded.

TABLE 2 Underlying comorbidities overall and by country

Condition, n	**Overall (n = 29)**	**Belgium (n = 11)**	**Japan (n = 11)**	**New Zealand (n = 7)**
Asthma	12	5	5	2
Heart condition	10	4	4	2
Congenital lung disease	3	NCR	NCR	3
Atopy	2	2	NCR	NCR
Bronchopulmonary dysplasia	2	NCR	1	1
Liver condition	2	NCR	2	NCR
Patent ductus arteriosus	2	NCR	1	1
Immunodeficiency	1	1	NCR	NCR
Neurologic condition	1	NCR	1	NCR
Pulmonary hypertension	1	NCR	1	NCR

Abbreviation: NCR, No cases reported.

Patients may have had more than one underlying comorbidity present.

FIGURE 1 Kaplan-Meier estimates of the proportion of patients hospitalised – overall population

FIGURE 2 Kaplan-Meier estimates of the proportion of patients hospitalised by presence of comorbidity

FIGURE 3 Kaplan-Meier estimates of the proportion of patients hospitalised by country

FIGURE 4 Time ratios with 95% CIs