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External validation of the discriminative validity of the ReSVinet score & development of simplified ReSVinet scores in secondary care

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Abstract

Background

There is no consensus on how to best quantify disease severity in infants with respiratory syncytial virus (RSV) and/or bronchiolitis; this lack of a sufficiently validated score complicates the provision of clinical care and, the evaluation of trials of therapeutics and vaccines. The ReSVinet score appears to be one of the most promising; however it is too time-consuming to be incorporated into routine clinical care. We aimed to develop and externally validate simplified versions of this score.

Methods

Data were used from a multinational (Netherlands, Spain & United Kingdom) multicentre case-control observational study of infants with RSV to develop simplified versions of the ReSVinet by conducting a grid search to determine the best combination of equally weighted parameters to maximise for the discriminative ability of the scores across a range of outcomes (hospitalisation, intensive care unit admission, ventilation requirement). Subsequently discriminative validity of the score for a range of secondary care outcomes was externally validated by conducting a secondary analysis of data collected in infants with respiratory infection from tertiary hospitals in Rwanda and Colombia.

Results

Three candidate simplified scores were identified using the development dataset; they were excellent (area under the receiver-operator characteristic curve [AUROC] >0.9) in the development dataset at discriminating for a range of outcomes, and their performance was not statistically significantly different to the original ReSVinet score despite having fewer parameters. In the external validation datasets, the simplified scores were moderate-excellent (AUROC 0.7-1) across a range of outcomes. In all outcomes, except for in a single dataset at predicting admission to the high dependency unit, they performed at least as well as the original ReSVinet score.

Conclusions

Three promising candidate simplified scores were developed; however further external validation work in larger datasets, ideally from resource-limited settings needs to be conducted before any recommendation regarding their use.

Keywords: RSV, severity score, validity

Introduction

There remains no consensus on how best to quantify the severity of bronchiolitis and/or respiratory syncytial virus (RSV) associated acute lower respiratory tract infections in infants; this is an important challenge as such a score can be useful indicator for clinicians when providing care and, serve as clinical endpoints in clinical trials for therapeutics and, increasingly importantly, vaccines. Of the various scores proposed, one of the most promising is the ReSVinet score [1-3].

The ReSVinet score was proposed almost a decade ago to quantify disease severity in infants (<24 months) with acute respiratory infections, including RSV [1]. It was designed based on an unreported literature review of previous related scores and subsequently evaluated by 90 paediatricians ensuring high face validity. The devised score consists of 7-parameters (feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnoea, general condition, fever) and has an overall total score of 20. The original developers of the score later proposed thresholds (based on the findings from two studies) to indicate grades of severity: 0-6 as signifying a mild infection, 7-13 for moderate distress, and ≥ 14 for a severe episode [4]. Notably, this score doesn't include either oxygen saturation or heart rate, objective indicators often included in other RSV/bronchiolitis severity scores, making it more widely usable, especially in settings with limited equipment (e.g. outpatient and inpatient settings in low-income countries) [2]. A parental version of this score has also been developed, although the focus of this paper will be on the version for health professionals.

The original study that proposed the score retrospectively validated it in a small sample of 170 infants (<24 months) hospitalised in 3 centres in Spain with an acute respiratory infection; in this study they demonstrated that the score had good internal consistency, strong inter-rater reliability (between investigators and, between investigators and parents) and moderate construct validity [1]. Subsequently, a number of prospective external validation studies have been conducted showing similar results; studies

assessing the validity of the clinician version of the ReSVinet score, that we are aware of, are summarised in *Supplementary Table 1* [1, 5-8]. As such it currently appears to be one of the most promising and best validated severity scores for acute respiratory infections in infants.

Anecdotally, the major reported weakness of the score is that it is too time-consuming to use, making it unfeasible for integrating it into routine clinical care (although still suitable for clinical trials). Therefore, we aimed to propose and externally validate a simplified version of the ReSVinet score. We additionally externally validated the original ReSVinet score in two new dataset.

Methods

The design and reporting of this study was guided, as far as possible within the pre-existing constraints of the datasets, by the Prediction model Risk Of Bias ASsessment Tool (PROBAST) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) checklist [9,10]; for the detailed populated checklists see *Online supplementary file, appendix 1&2*.

Data Sources

For this study, we made use of three existing datasets. One recently published dataset was used to develop candidate simplified scores [11,12], and these scores were subsequently externally validated in three additional datasets, all of which have already been used to validate the original ReSVinet score and their findings published [5, 13]. Further detail on each dataset can be found below; the inclusion and exclusion criteria of the datasets are listed in *Supplementary Table 2*.

Development dataset (RESCEU)

The dataset used to develop simplified ReSVinet scores was collected as part of a recently published multinational (Netherlands, Spain & United Kingdom) multicentre case-control observational study run by the REspiratory Syncytial virus Consortium in EUrope (RESCEU) to investigate biomarkers of RSV associated acute lower respiratory tract infection severity in infants (<12 months) (NCT03756766) [12]. The original study aimed to recruit 500 previously healthy infants with RSV, 50 infants with comorbidities and with RSV and 80 healthy controls without RSV. Patients were recruited between October 2017 to April 2021.

For the purpose of this study, we only included the cases (i.e. infants with RSV), including those with comorbidities. The eligibility criteria for this group can be found in *Supplementary Table 2*. An anonymised version of this dataset was provided by the RESCEU investigators. For each patient, basic demographic data (e.g. sex, gestational age), clinical data (e.g. heart rate, oxygen saturation) outcome data (e.g. hospitalisation, need for respiratory support) and the ReSVinet score parameters and total score at the time of recruitment were supplied. Score assessors were not blinded for outcomes if the outcomes had occurred by the time of score assessment. Outcome data were retrieved from patients' medical notes; outcomes used in our analysis were hospitalisation, admission to the intensive care unit (ICU) and requirement for synchronised intermittent mandatory ventilation (SIMV).

External validation datasets (Camacho-Cruz & Hakizimana)

Subsequently we externally validated the simplified scores in two datasets, henceforth referred to as the Camacho-Cruz and Hakizimana datasets respectively. In this section, we provide a high-level summary of each dataset; however more detailed information on the methods can be found in the original study publications [5, 13].

The Camacho-Cruz dataset was collected in a prospective observational cohort study of children (<24 months) presenting to the emergency department at a single general hospital in Colombia with an acute respiratory infection with the aim of externally validating the reliability of the ReSVinet score [13]. The ReSVinet score was taken simultaneously by parents, paediatric doctor-professors (faculty) and residents in the emergency room. They were not blinded to the infant's outcome or to the other predictors. Information was gathered on enrolled infants via their electronic health records and phone consultation 10-days post-discharge. Outcomes analysed were hospitalisation and paediatric intensive care unit (PICU) admission.

The Hakizimana dataset was collected in a prospective cross-sectional study conducted in four tertiary hospitals (n=4) in Rwanda where infants (1-12 months) presenting with signs of respiratory distress were opportunistically enrolled to externally validate the ReSVinet score and the Liverpool Infant Bronchiolitis Severity Score (LIBSS) [5]. An anonymised version of this dataset was publicly available on the Harvard Dataverse [14]. The ReSVinet score of each infant was assessed independently by a nurse and resident within an hour of the infant presenting to hospital. Further information on enrolled infants was gathered through standardised questionaries filled in by health-care providers involved in the delivery of care to the infant; as such they were not blinded to the infant's outcomes or to the other predictors. The dataset contained no missing values. Outcomes analysed were hospitalisations, admission to the high dependency unit (HDU), admission to the PICU, intubation or ventilation and death.

Simplified score

To develop the simplified scores, we only made use of the development dataset (RESCEU). Specifically we performed a grid search to explore all the possible combinations of parameters and identified the equally-weighted combination of parameters giving the highest point estimate of area under the receiver operating

characteristic (AUROC), for requirement of admission to hospital, admission to ICU, and need for SIMV.

After developing the candidate simplified scores, we assessed the AUROC for a range of outcomes in the external validation datasets (Hakizimana & Camacho-Cruz datasets).

Validation of the original ReSVinet score

We additionally used the RESCEU and Camacho-Cruz datasets to externally validate the discriminative validity of the original ReSVinet score by assessing the AUROC for the outcomes mentioned above. This was not done for the Hakizimana dataset as this has already been done and reported in the original publication [5].

Statistical Analysis

For each of the above measures we calculated confidence intervals (CIs) of the AUROCs, and created p-value matrices. We considered a p-value <0.005 as constituting statistical significance, and used DeLong's method to calculate both CIs and paired p-values between AUROCs [15]. Paired p-values (as opposed to unpaired values) were calculated given that we were comparing AUROCs for the same outcomes in the same datasets. We used R version 4.1.2 and Python version 3.6.2 to conduct the analysis.

Missing data

In the development dataset, we excluded all infants with missing items for the ReSVinet score. The Hakizimana dataset had no missing data, as the participants with any missing data (n=7) had already been excluded in the dataset available publicly.

For outcome data, we excluded participants from specific analyses if the outcome was not available; in all cases we explicitly stated the number of participants included in each analysis.

Results

Included participants

The RESCEU study enrolled 325 RSV cases of which 14 had missing data for the ReSVinet score parameters and so were excluded; 11 had no data for any of the score parameters and the remaining 3 had no data for two parameters each. As such, overall 311 patients were included. The Camacho-Cruz study enrolled 191 patients of which three were excluded as two did not meet the inclusion criteria and one was lost to follow up; as such, overall data on 188 patients were included. The Hakizimana study recruited 107 patients, of which for 7 data collection was incomplete and so were excluded in the publicly available dataset; overall data on 100 infants were included.

Baseline characteristics

Baseline characteristic for included participants by dataset are summarised in *Supplementary Table 3*. Of note, the major difference across the datasets were the differences in age of enrolment across the 3 datasets the median age was 3, 7 and 10 months for the RESCEU, Hakizimana & Camacho-Cruz datasets respectively. Additionally across all 3 datasets there was a greater proportion of males to females.

Outcome data

The outcomes for included participants by dataset are summarised in *Supplementary Table 4.* In the RESCEU dataset (n=311) 75% of the included patients were hospitalised, 28% admitted to the PICU & 25% who were ventilated. In the Hakizimana dataset (n=100) 93% of the included patients were hospitalised, 22% admitted to HDU, 7% admitted to PICU, 5% ventilated and 6% who died. In the Camacho-Cruz dataset (n=188) 3% were admitted to the ICU and there were no deaths.

Development of simplified ReSVinet scores

Using all of the development dataset (i.e. the RESCEU dataset), the best combination of equally weighted parameters to maximise for the point-estimate of AUROC for discriminating by hospitalisation, ICU admission and SIMV requirement were determined; this produced three unique candidate simplified scores (ReSVinet-3, ReSVinet-4 and ReSVinet-6 – the suffix in this instance number of parameters included in the simplified score). ReSVinet-3 used the following parameters: respiratory difficulty, apnoea & general condition. ReSVinet-4 & ReSVinet-6 used the same parameters as ReSVinet-3 as well as medical intervention and, medical intervention, feeding intolerance & respiratory frequency respectively.

These scores, as assessed by their AUROC, were excellent in the RESCEU dataset at discriminating by the patients' hospitalisation status, ICU admission and requirement for SIMV (See [2,3] for cut-offs) (see *Table 1*). For ICU admission and requirement for SIMV, there were no statistically significant differences in the performance of the original and candidate scores (see *Supplementary Table 5* for p-value matrices). For hospitalisations although there were no statistically significant differences between each candidate scores and the original score, there were significant differences between the candidate scores; specifically, ReSVinet-6 was marginally better than both ReSVinet-3 & ReSVinet-4, and ReSVinet-4 marginally better than ReSVinet-3.

We additionally externally validated the discriminative validity of the original ReSVinet score in the RESCEU dataset (see *Table 1*); in this dataset it was excellent at discriminating on hospitalisation, and borderline-excellent for ICU and need for SIMV.

External validation

Subsequently we externally validated the three candidate simplified scores using the external validation datasets (Camacho-Cruz & Hakizimana) (see *Supplementary Table*

6). In these datasets, they generally performed similarly to the original score. There were only two instances in which there were statistically significant differences (see *Supplementary Table 7* for the p-value matrices). The first occurred in the Hakizimana dataset where both ReSVinet-3 & ReSVinet-4 performed extremely poorly at discriminating for HDU admission but both the original ReSVinet score, and ReSVinet-6 performed moderately well. The second occurred in the Camacho-Cruz dataset where all of the candidate scores outperformed the original score, and ReSVinet-4 outperformed both ReSVinet-6 & ReSVinet-3.

We additionally externally validated the discriminative validity of the original ReSVinet score in the Camacho-Cruz dataset (see *Supplementary Table 6*); in this dataset it was moderate at discriminating for both hospitalization and PICU admission.

Discussion

Overall, the candidate simplified scores were moderate-excellent at discriminating, in both the development and external validation datasets, for a range of outcomes spanning the entire range of secondary-care disease severity. They performed equally well or better than the original ReSVinet score at discriminating by all of the outcomes evaluated; the only exception to this was in one dataset (Hakizimana) where two (ReSVinet-3 & ReSVinet-4) out of three of the candidate scores performed extremely poorly at differentiating by admission to the HDU. Additionally, the ReSVinet score was externally validated in two new datasets (Camacho-Cruz & Hakizimana) in which it performed moderate to excellent.

Significantly, both of the external validation datasets (but not the development dataset) were collected in non-European countries, and they were collected in a low-income and middle-income country; this is relatively unusual as vast majority of previous validation efforts have occurred in high-income countries [2, 3].

In the three datasets used there were differences in when the ReSVinet score was taken. In the RESCEU dataset, the score was taken at the time of recruitment and so there is potentially a large degree of variability at the point in the disease course at which the scores were taken; whereas in the Hakizimana & Camacho-Cruz datasets the scores were taken within an hour of presentation and in the emergency room respectively. This greater variability reduces the usefulness of the validation in the RESCEU dataset. Additionally, it would be useful to have conducted additional analyses with a threshold on the time of the outcome since taking the score (e.g. discriminative validity of score at predicting need for admission to ICU within 24 hours) as the disease course is not always linear, and so we may be systematically making an error of the actual validity; this was not possible in our case as the required data for this was not collected.

There were also some differences in the inclusion criteria of the datasets, specifically the age ranges and, presence of RSV and comorbidities. The development dataset included 50 participants with comorbidities whereas the Camacho-Cruz dataset excluded all patients with significant comorbidities & the Hakizimana dataset excluded those with a history of chronic lung disease and those who presented with non-respiratory causes of respiratory distress. It is not clear, on the basis of our analysis, if these differences (age, RSV, comorbidities) affected the discriminative ability of the scores. However, recent analysis of the same published RESCEU dataset has indicated that fever is more commonly found in older infants (≥ 6 months), as well as more frequently in those with RSV-A and with higher viral loads [12]; however fever, viral load and RSV-subgroup were not found to be associated with severity.

To systematically assess bias, we used a modified version of the PROBAST tool to conduct an internal risk of bias assessment (see *Online supplementary file, appendix 2*). Based on this we deemed overall that there was a high risk that our estimates of the discriminative validity of these scores are biased.

The primary reason for this is due the small number of patients with positive outcomes owing to the small size of the datasets. Only in the RESCEU dataset for 1 outcome (hospitalisations) were the PROBAST thresholds (≥20 events per variable for validation [RESCEU]; ≥100 for validation [Hakizimana & Camacho-Cruz]) met. In 5 instances, the number of participants with the outcome of interests is a single-digit figure. This is similar to what is observed in published literature, presumably due to difficulties in collecting large datasets of these sorts. For illustration purposes, to be confident in reporting on the discriminative validity for death (assuming the same approximate ratio of deaths), the Hakizimana dataset would need to be approximately 17-times larger. Additionally, in an ideal world, we would have used multiple imputation for missing data instead of excluding patients with missing score-items and additionally assessed calibration; this was not done due to time constraints. Regardless, neither of these factors would have changed our overall classification of this study as having an associated high risk of bias.

To guide, as well as assess the transparency of reporting, the TRIPOD checklist was employed (see *Online supplementary file, appendix 1*). The overall score was 26/32 (81%). This is considerably better than the average score, 53%, found in our systematic review [3], although there still is room for improvement. The issues with reporting were that not all required information was reported in the title (due to length constraints), the number of positive outcomes were not reported in the abstract (due to word limit constraints), the number of centres enrolment took place at for the RESCEU study was not reported, that interaction terms were not tested for and, that calibration was not reported (as not assessed).

Implications on research, policy & practice

The findings indicate that fever as a criterion is redundant and may be excluded from the original ReSVinet score (i.e. ReSVinet-6 should be adopted). However, given the small number of other validation studies (see *Supplementary Table 1*) and more generally studies evaluating the ReSVinet score (e.g. reliability, responsiveness, utility), we cannot at this time recommend use of either the original ReSVinet score or ReSVinet-6 in routine clinical care or as a primary outcome for clinical trials.

Further research on much-larger datasets is required to validate the usefulness of the original ReSVinet score, as well as the simplified scores we have developed. Given the relatively small number of patients with positive outcomes in the development dataset, it would also be appropriate to repeat this exercise, using similar methods, in larger datasets to examine if different combinations of parameters (i.e. scores) are selected. Ideally the datasets employed for these exercise as well as being larger, may be gathered in resource-limited settings where the burden is disproportionately high [2,3].

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Author contributions

HN conceived the idea. HN, YL & ZS designed the approach. SBD, HR, JGW, JM, GLL, DÖ, JA, AJG, FMT, AJP, and LB collected and contributed data. ZS conducted the analysis and authored the manuscript. DÖ, JA, AJG, FMT, EP, YL, LB & HN commented critically on several drafts of the manuscript. PROMISE investigators reviewed the manuscript prior to submission.

Conflict of interest statement

None for ZS, EP, JM, GLL or HR.

YL has received funding from Wellcome Trust and GSK outside the submitted work. YL received personal fees from Pfizer.

SBD has received honoraria from MSD and Sanofi for taking part in RSV advisory boards and has provided consultancy and/or investigator roles in relation to product development for Janssen, AstraZeneca, Pfizer, Valneva, MSD, iLiAD and Sanofi with fees paid to St George’s, University of London.

JGW participated in the advisory board of Janssen with fees paid to UMCU.

DÖ and JA are employees of Janssen Pharmaceutical NV (Beerse, Belgium).

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Supplementary Table 1: Published studies validating the ReSVinet score.

(AUROC- Area under the receiver-operator characteristic curve; CI – confidence interval; HDU - high dependency unit; LIBSS - Liverpool Infant Bronchiolitis Severity Score; LOS – length of stay; n.d. – no date; NA - not applicable; OR – odds ratio; PICU – paediatric intensive care unit; RSV - respiratory syncytial virus; SD - standard deviation)

First author surname, year	**Study design(s)**	**Country**	**Sample size**	**Age range (months)**	**Clinical setting**	**RSV positivity rate (%)**	**RSV Test**	**Key Findings (95% CI)**
Development of the ReSVinet score								
Justicia-Grande, 2016 [1]	Multicentre (n=3) retrospective cohort study	Spain	170	<24	Secondary care	77.1% (only 166 tested)	Direct immunofluorescence of respiratory secretions	Discriminative Validity Patients admitted to PICU had statistically significantly (p<0.001) higher mean score; mean score (SD) was 15.7 (±2.6) vs 10.2 (±2.5), 15.4 (±2.7) vs 9.2 (±2.4), and 14 (±2.6) vs 9.4 (±2.4) among investigators, and 15.9 (±2.5) vs

								10.6 (±2.7) for parents. <u>Convergent validity</u> ReSVinet score correlated with Wood-Downes score (p<0.001). Spearman's correlation coefficients between hospital LOS & ReSVinet score was 0.48–0.60 for investigators (p<0.001) and 0.33–0.35 for parents (p=0.027).
External validation of the ReSVinet score								
Hakizimana, 2021 [5]	Multicentre (n=4) prospective cross-sectional study	Rwanda	100	1-12	Tertiary care	Not reported	NA	<u>Discriminative Validity</u> AUROC for hospital admission was 0.973 (0.94–1.0; p<0.001) and 0.956 (0.92–0.99; p<0.001) for nurse and resident respectively. AUROC for admission to PICU or

								HDU was 0.880 (0.80–0.96; p<0.001) & 0.872 (0.787–0.957; p<0.001) for nurse and resident respectively. AUROC for mortality was 0.974 (0.944–1.0; p<0.001) & 0.980 (0.954–1.0; p<0.001) for nurse and resident respectively. AUROC for patients having a longer hospital admission than the median LOS was 0.637 (0.531–0.747; p<0.001) & 0.639 (0.531–0.747; p<0.001) for nurse and resident respectively. <u>Convergent Validity</u> Pearson’s correlation coefficient

								between ReSVinet and LIBSS was 0.815 (0.70–0.93; p<0.001) & 0.836 (0.73–0.95; p<0.001) for resident and nurse respectively.
Justicia Grande, n.d. [6]	Unclear	Unclear	245	1-168 (1 month - 14 years)	Primary care	Not reported	NA	<u>Convergent validity</u> Pearson's correlation coefficient between ReSVinet Score and the Wood-Downes Score was 0.57 (p< 0.0001).
Tungsupreechameth, 2021 [7]	Retrospective case-control study	Thailand	269	1-60	Secondary care	100%	Immunoassay of nasopharyngeal swabs	<u>Discriminant validity</u> Those with a ReSVinet score ≥14 had a significantly longer hospital stay and were more likely to require ICU and mechanical ventilation. Adjusted OR of 19.56 (1.81-212.05; p=0.014) for hospital LOS>5 days for those with a ReSVinet score

								≥14 compared to those with a ReSVinet score < 14.
Vandendijck, 2022 [8]	Multicentre (n=10) prospective cohort study	Argentina, Chile, and the United States	124	≤36	Secondary care	100%	Rapid antigen assay or PCR	<u>Convergent validity</u> Pearson correlation coefficient between the PRESORSv6 Clinician-Reported Outcome questionnaire overall RSV severity score and ReSVinet score was 0.45; (0.30–0.58).

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Supplementary Table 2: Eligibility Criteria for included participants in the analysis. **Adapted** from [5, 11, 12, 13]. (PCR-Polymerase chain reaction; RSV - Respiratory syncytial virus; RESCEU-REspiratory Syncytial virus Consortium in Europe)

Name	**Development dataset**	**External validation dataset**	
	RESCEU [12,13]	*Camacho-Cruz [14]*	*Hakizimana [6]*
Inclusion criteria	Parent/carer of infant is willing and able to give informed consent for participation in the study.	Parents were invited to participate by filling out/completing the scale and those who completed it were included.	Parents could consent.
	Male or female, aged <12 months at enrolment.	Children aged < 2 years	Infants 1 to <12 months of age
	Positive RSV PCR test of nasopharyngeal swab.	Patients presenting with signs and symptoms of any type of acute respiratory infection (rhinopharyngitis, croup, bronchiolitis, wheezing episodes or pneumonia)	Presenting with respiratory distress due to any respiratory illness. Case definition of symptoms and signs indicative of respiratory distress were apnoea, subcostal

			or intercostal recession, tracheal tug, nasal flaring, head bobbing, grunting, cyanosis, oxygen desaturation, tachypnoea, wheezing, stridor, oxygen requirement, or reduced air-entry
	Hospitalised for <48 hours at enrolment.		
	Live near enough to a participating study centre for the 6-8 week home visit/hospital appointment to be feasible.		
	Parent has a telephone.		
		Parents spoke Spanish	
Exclusio	History of receipt of		

n criteria	medication to treat RSV infection (e.g. ribavirin). Prior exposure to an investigational RSV vaccine or medication		
		History of significant comorbidities, for example, heart disease, chronic lung disease, anatomical lung malformation, neurological diseases, severe malnutrition, any immune deficiency or cancer.	Infants with known chronic lung disease, or infants who presented with a non-respiratory cause of respiratory distress (e.g. cardiac disease).

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Supplementary Table 3: Baseline Characteristics (Greyed out cell indicates data not available in dataset or not applicable. See the *Online supplementary file, appendix 3* for the number of missing values for each baseline characteristic by dataset) (%) (SD – Standard deviation)

Characteristics	**Development dataset**	**External validation datasets**	
	RESCEU	*Hakizimana*	*Camacho-Cruz*
Sex			
Male	179 (58%)	63 (63%)	110 (59%)
Female	132 (42%)	37 (37%)	78 (46%)
Country of site			
Netherlands	135 (43%)		
Spain	28 (9%)		
United Kingdom	148 (48%)		
Rwanda		100 (100%)	
Colombia			188 (100%)
Birth Body Weight (kg)			
Mean (SD)	3.32 (6.39)		
Range	1.04-5.03		
Current Body Weight (kg)			
Mean (SD)	6.12 (2.03)	6.56 (2.43)	
Range	2-12	2-13.3	
RSV Subgroup			
A (%)	149 (52%)		
A/B (%)	1 (0%)		
B (%)	137 (48%)		
Season			

2017-18 (%)	57 (20%)		
2018-19 (%)	113 (39%)		
2019-20 (%)	141 (49%)		
Gestational age (weeks)			
Very preterm (28-31) (%)	8 (3%)		
Moderate preterm (32-33) (%)	5 (2%)		
Late preterm (34-36) (%)	13 (4%)		
Early term (37-38) (%)	87 (28%)		
Late term (39-41) (%)	191 (62%)		
Post term (≥42) (%)	5 (2%)		
Premature		5 (5%)	
Age at enrolment (months)			
Median (SD)	3 (3.31)	7 (3.77)	10 (7.09)
Range	0.3-12	0.9-11.9	0.4-24
≤2	112 (37%)	16 (16%)	32 (17%)
>2-4	64 (21%)	17 (17%)	15 (8%)
>4-6	39 (13%)	12 (12%)	21 (11%)
>6-8	36 (12)	16 (16%)	14 (7%)
>8-10	32 (10%)	11 (11%)	19 (10%)
>10-12	23 (8%)	28 (28%)	14 (7%)

>12-14			16 (9%)
>14-16			13 (7%)
>16-18			8 (4%)
>18-20			15 (8%)
>20-22			9 (5%)
>22-24			12 (6%)
Diagnosis (%)			
None	24 (8%)		
Rhinopharyngitis			76 (40%)
Bronchiolitis	128 (41%)	36 (36%)	54 (29%)
Upper respiratory tract infection	141 (46%)	1 (1%)	
Croup	1 (0%)		32 (17%)
Wheezing	1 (0%)	6 (6%)	23 (12%)
Pneumonia	13 (4%)	51 (51%)	3 (2%)
Other	1 (0%)	6 (6%)	
Viral tests			
RSV	311 (100%)		17 (9%)
Adenovirus			3 (2%)
Parainfluenza 1			2 (1%)
Adenovirus and RSV			1 (1%)
Pre-existing condition			
No	270 (87%)		
Yes	41 (13%)		

Prematurity	26 (8%)	5 (5%)	
Malnutrition		12 (12%)	
Asthmatic		1 (1%)	
Human immunodeficiency virus		2 (2%)	
Other	15 (5%)		
Ubedehe Social Group			
High		47 (47%)	
Low		53 (53%)	
Residence			
Urban		32 (32%)	
Rural		68 (68%)	
Living sibling			
No		20 (20%)	
Yes		80 (80%)	
Vaccinations complete			
No		0 (0%)	
Yes		100 (100%)	
Maternal marital status			
Single		15 (15%)	
Married		84 (84%)	
Divorced		1 (1%)	
Widowed		0 (0%)	
Maternal age (years)			
15-19		11 (11%)	
20-24		21 (21%)	

25-29		26 (26%)	
30-34		19 (19%)	
35-39		17 (17%)	
40-44		5 (5%)	
45-49		1 (1%)	
Paternal age (years)			
15-19		3 (3%)	
20-24		11 (11%)	
25-29		24 (24%)	
30-34		24 (24%)	
35-39		19 (19%)	
40-44		12 (12%)	
45-49		6 (6%)	
50-55		1 (1%)	
Maternal occupation			
Unemployed		19 (19%)	
Manual labourer		64 (64%)	
Professional		17 (17%)	
Paternal occupation			
Unemployed		5 (5%)	
Manual labourer		67 (67%)	
Professional		28 (28%)	
Maternal educational level			
None		13 (13%)	
Primary		38 (38%)	
Secondary		28 (28%)	
Higher		21 (21%)	

Paternal educational level			
None		9 (9%)	
Primary		42 (42%)	
Secondary		30 (30%)	
Higher		18 (18%)	

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Supplementary Table 4: Outcomes. (First bracketed figure is the percentage, and the second figure, separated by a semicolon, is the number of patients for which data are missing. Greyed out cells indicate data not available in respective dataset.)
(HDU - high dependency unit; ICU - intensive care unit; PICU – Paediatric intensive care unit; RESCEU- REspiratory Syncytial virus Consortium in Europe; SIMV - synchronised intermittent mandatory ventilation)

Outcome	**Development dataset**	**External Validation datasets**	
	RESCEU (n=311)	*Hakizimana (n=100)*	*Camacho-Cruz (n=188)*
Hospitalised (%; missing)	232 (75%; 0)	93 (93%; 0)	
HDU Admission (%; missing)		22 (22%; 0)	
ICU/PICU Admission (%; missing)	86 (28%; 0)	7 (7%; 0)	5 (3%; 0)
SIMV (%; missing)	70 (25%; 31)		
Intubation or ventilation (%; missing)		5 (5%; 0)	
Death		6 (6%; 0)	0 (0%; 7)

Supplementary Table 5: P-value matrices score in development (RESCEU) dataset. (Cells where p<0.005 [i.e. cut-off adopted for statistically significant difference] are highlighted in green)

(ICU - intensive care unit; SIMV - synchronised intermittent mandatory ventilation)

Hospitalisation (n=311)				
	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	1			
ReSVinet-3	0.012	0.0007127		
ReSVinet-4	0.4268	0.00092 68427	0.002591	

ICU Admission (n=311)				
	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.02776			
ReSVinet-3	0.09679	0.3828		
ReSVinet-4	0.03306	0.2698	0.913	

SIMV requirement (n=280)				
	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.02169			
ReSVinet-3	0.05608	0.2942		
ReSVinet-4	0.005922	0.05091	0.1783	

Supplementary Table 6: AUROC for original ReSVinet & candidate simplified scores in external validation datasets (AUROC- Area under the receiver-operator characteristic curve; CI - confidence interval; HDU - high dependency unit; ICU - intensive care unit; PICU – Paediatric intensive care unit)

Score	**AUROC (95% CI)**													
	Hakizimana (n=100)										**Camacho-Cruz (n=188)**			
	Nurse					*Resident*					*Faculty*		*Resident*	
	Hospitalisation	*HDU Admission*	*PICU Admission*	*Intubation or ventilation*	*Death*	*Hospitalisation*	*HDU admission*	*PICU Admission*	*Intubation or ventilation*	*Death*	*Hospitalisation*	*PICU Admission*	*Hospitalisation*	*PICU Admission*
ReSVinet	0.9731 (0.9442-1)	0.7955 (0.6909-0.9)	0.9178 (0.8284-1)	0.9053 (0.7779-1)	0.9743 (0.9454-1)	0.9562 (0.9167-0.9957)	0.7838 (0.6767-0.8909)	0.8994 (0.7659-1)	0.8726 (0.6835-1)	0.9796 (0.9543-1)	0.8031 (0.7408-0.8654)	0.8219 (0.6541-0.9896)	0.8084 (0.7455-0.8714)	0.8213 (0.6563-0.9864)
ReSVi	0.9747	0.777	0.920	0.902	0.970	0.9547	0.775	0.927	0.903	0.979	0.8843	0.875	0.8861	0.871

net-6	(0.9471-1)	7 (0.6742-0.8811)	9 (0.8274-1)	1 (0.7688-1)	7 (0.9386-1)	(0.9157-0.9937)	1 (0.669-0.8812)	8 (0.8353-1)	2 (0.7718-1)	6 (0.9514-1)	(0.8376-0.9311)	4 (0.7417-1)	(0.8387-0.9335)	6 (0.7361-1)
ReSVinet-3	0.937 (0.8808-0.9932)	0.2745 (0.1782-0.3708)	0.9224 (0.811-1)	0.8989 (0.7392-1)	0.9867 (0.9666-1)	0.9416 (0.8931-0.9901)	0.2678 (0.1712-0.3644)	0.9194 (0.8052-1)	0.8958 (0.7322-1)	0.9858 (0.9648-1)	0.8787 (0.8322-0.9253)	0.9213 (0.8553-0.9873)	0.8779 (0.8301-0.9256)	0.9082 (0.832-0.9843)
ReSVinet-4	0.9616 (0.912-1)	0.2666 (0.1714-0.3618)	0.9194 (0.81-1)	0.9 (0.7425-1)	0.9814 (0.9579-1)	0.9539 (0.9155-0.9924)	0.2637 (0.1675-0.3599)	0.9194 (0.8053-1)	0.8979 (0.734-1)	0.9832 (0.9609-1)	0.9255 (0.8879-0.9631)	0.9377 (0.8848-0.9906)	0.9318 (0.892-0.9716)	0.9311 (0.8731-0.9892)

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Supplementary Table 7: P-values matrices for external validation datasets. (Cells where p<0.005 [i.e. cut-off adopted for statistically significant difference] are highlighted in green)

(HDU - high dependency unit; PICU – Paediatric intensive care unit)

Hakizimana: Nurse, Hospitalisations (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.8192			
ReSVinet-3	0.1326	0.06958		
ReSVinet-4	0.5983	0.4818	0.1288	

Hakizimana: Nurse, HDU (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.2716			
ReSVinet-3	4.69e-08	3.715e-07		
ReSVinet-4	2.661e-08	6.224e-08	0.06422	

Hakizimana: Nurse, PICU (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.6844			
ReSVinet-3	0.7932	0.918		
ReSVinet-4	0.9225	0.9049	0.4164	

Hakizimana: Nurse, Intubation or ventilation (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.7002			
ReSVinet-3	0.7686	0.8785		
ReSVinet-4	0.7979	0.9145	0.6954	

Hakizimana: Nurse, Death (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.5909			
ReSVinet-3	0.1782	0.1977		
ReSVinet-4	0.3408	0.2805	0.2707	

Hakizimana: Resident, Hospitalisations (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				

Hakizimana: Resident, HDU (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSV	0.65			

Hakizimana: Resident, PICU (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReS	0.20			

Hakizimana: Resident, Intubation or ventilation (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				

Hakizimana: Resident, Death (n=100)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReS	0.73			

ReSVinet-6	0.8497			
ReSVinet-3	0.3827	0.3702		
ReSVinet-4	0.8721	0.9441	0.3671	

inet-6	32			
ReSVinet-3	7.356e-08	2.118e-07		
ReSVinet-4	7.714e-08	1.506e-07	0.124	

Vinet-6	21			
ReSVinet-3	0.1109	0.5729		
ReSVinet-4	0.1058	0.5538	1	

ReSVinet-6	0.3337			
ReSVinet-3	0.1774	0.751		
ReSVinet-4	0.1264	0.8185	0.6115	

Vinet-6	95			
ReSVinet-3	0.3826	0.3948		
ReSVinet-4	0.5892	0.5171	0.5862	

Camacho-Cruz: Faculty, Hospitalisations (n=188)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	5.13e-07			
ReSVinet-3	0.0012044	0.7172		
ReSVinet-4	3.789e-07	0.001689	4.335e-05	

Camacho-Cruz: Faculty, PICU (n=188)

	ReSVinet	ReSVinet-6	ReSVinet-3	ReSVinet-4
ReSVinet				
ReSVinet-6	0.1072			
ReSVinet-3	0.09639	0.3396		
ReSVinet-4	0.0732	0.2223	0.05062	

Camacho-Cruz: Resident, Hospitalisations (n=188)

	ReSVinet	ReSVinet-	ReSVinet-	ReSVinet-

Camacho-Cruz: Resident, PICU (n=188)

	ReSVinet	ReSVinet-	ReSVinet-	ReSVinet-

	t	6	3	4
ReSVinet				
ReSVinet-6	1.275e-06			
ReSVinet-3	0.0024755	0.5334		
ReSVinet-4	6.03e-07	0.00 0636	8.355e-06	

	t	6	3	4
ReSVinet				
ReSVinet-6	0.122			
ReSVinet-3	0.1068	0.4266		
ReSVinet-4	0.07007	0.2336	0.03829	

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Online supplementary file

Appendix 1: Detailed Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) score

TRIPOD Explanation & advice: Moons et al. [11]

Table: TRIPOD for data project.

(D – Development; V – Validation).

A green cell indicates adherence, a red cell lack of adherence and a grey cell lack of applicability.

Section /Topic		**Validation / Development**	**Checklist Item**	
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	

Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
	5b	D;V	Describe eligibility criteria for participants.	
	5c	D;V	Give details of treatments received, if relevant.	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analys	10a	D	Describe how predictors were handled in the analyses.	
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for	

			internal validation.	
	10c	V	For validation, describe how the predictions were calculated.	
is methods	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	
Model	14a	D	Specify the number of participants and outcome events	

develo			in each analysis.	
pment	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specifi cation	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
	15b	D	Explain how to the use the prediction model.	
Model perfor mance	16	D;V	Report performance measures (with CIs) for the prediction model.	
Model - updati ng	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion				
Limita tions	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interp retatio n	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	
Implic ations	20	D;V	Discuss the potential clinical use of the model and implications for future research.	
Other information				
Supple mentar	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web	

y information			calculator, and data sets.	
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Appendix 2: Detailed Prediction model Risk Of Bias ASsessment Tool (PROBAST) checklist

To systematically assess the risk of bias, a modified version of the PROBAST checklist was employed. Given that this was not as a part of a scoping review, the questions regarded applicability were ignored. For the ease of the readers, the filled in PROBAST checklist is presented separately for each dataset.

PROBAST Explanation & advice: Moons et al., 2019 [10]

Table: Modified PROBAST for data project.

(N – No; NA – Not applicable; PN – Probably No; PY – Probably Yes; Y – Yes)

Grey shaded box indicates inapplicability according to PROBAST recommendations.

	RESCEU	**Hakizimana**	**Camacho-Cruz**
Type of prediction study	Development	Validation	
Models of interest	ReSVinet ReSVinet-6 ReSVinet-3 ReSVinet-4		
Outcome of interest	Hospitalisation ICU Admission SIMV requirement	Hospitalisation HDU Admission PICU Admission Intubation or	Hospitalisation PICU Admission

		ventilation Death	
DOMAIN 1: Participants			
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Y	Y	Y
1.2 Were all inclusions and exclusions of participants appropriate?	Y	Y	Y
Risk of bias introduced by selection of participants (low/ high/ unclear)	Low	Low	Low
Rationale:			
DOMAIN 2: Predictors			
2.1 Were predictors defined and assessed in a similar way for all participants?	Y	Y	Y
2.2 Were predictor assessments made without knowledge of outcome data?	PN	PN	PN
2.3 Are all predictors	Y	Y	Y

available at the time the model is intended to be used?			
Risk of bias introduced by predictors or their assessment (low/ high/ unclear)	Low	Low	Low
Rationale:			
DOMAIN 3: Outcome			
3.1 Was the outcome determined appropriately?	Y	Y	Y
3.2 Was a pre-specified or standard outcome definition used?	Y	Y	Y
3.3 Were predictors excluded from the outcome definition?	Y	Y	Y
3.4 Was the outcome defined and determined in a similar way for all participants?	Y	Y	Y
3.5 Was the outcome determined without knowledge of	PN	PN	PN

predictor information?			
3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Y	Y	Y
Risk of bias introduced by the outcome or its determination (low/ high/ unclear)	Low	Low	Low
Rationale:			
DOMAIN 4: Analysis			
4.1 Were there a reasonable number of participants with the outcome?	Y for hospitalisations. N for ICU Admission or SIMV requirement.	N for all.	N for all.
4.2 Were continuous and categorical predictors handled appropriately?	Y	Y	Y
4.3 Were all enrolled participants included	N	N	Y

in the analysis?			
4.4 Were participants with missing data handled appropriately?	N	N	Y
4.5 Was selection of predictors based on univariable analysis avoided?	NA		
4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?	Y	Y	Y
4.7 Were relevant model performance measures evaluated appropriately?	N	N	N
4.8 Were model overfitting and optimism in model performance accounted for?	Y		
4.9 Do predictors and their assigned weights in the final model correspond to	NA		

the results from multivariable analysis?			
Risk of bias introduced by the analysis (low/ high/ unclear)	High	High	High
Rationale	Patients were excluded with missing predictors (4.3), and excluded from analyses with missing outcome data (4.4). Calibration was not assessed (4.7)	Patients with incomplete data were excluded (4.3, 4.4). Calibration was not assessed (4.7)	Not all enrolled patients were included, but the reason for exclusion was reasonable (4.3). Calibration was not assessed (4.7)
Overall judgement of risk of bias			
Overall judgement of risk of bias (low/ high/ unclear)	**High**	**High**	**High**

Summary of sources of potential bias:	Small number of participants with positive outcome data for ICU admission and SIMV requirement. Exclusion of participants with missing data. Calibration not assessed.	Small number of participants with positive outcomes. Exclusion of participants with missing data. Calibration not assessed.	Small number of participants with positive outcomes. Calibration not assessed.

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589 Appendix 3: Missing data for baseline characteristics

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591 **Table:** Missing data for baseline characteristics by dataset (Greyed out cell indicates

592 data not available in dataset or inapplicability)

Characteristics	**Development dataset**	**External Validation datasets**	
	RESCEU	*Hakizimana*	*Camacho-Cruz*
Sex	0	0	0
Country of site	0	0	0
Birth Body Weight	8		
Current Body Weight	7	0	
RSV Subgroup	24		
Season	0		
Gestational age	2		
Premature			
Age at enrolment	5	0	0
Diagnosis	2	0	0
Viral tests	0		?
Pre-existing condition	0		
Prematurity	0	0	
Malnutrition		0	
Asthmatic		0	
Human immunodeficienc		0	

y virus			
Ubedehe Social Group		0	
Residence			
Living sibling		0	
Vaccinations complete		0	
Maternal marital status		0	
Maternal age		0	
Paternal age		0	
Maternal occupation		0	
Paternal occupation		0	
Maternal educational level		0	
Paternal educational level		1	

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595 Appendix 4: Summary data on predictors

Predictor	**Development dataset**	**External Validation datasets**			
	RESCEU	*Hakizimana*		*Camacho-Cruz*	
		Resident	*Nurse*	*Resident*	*Faculty*
Median total score (SD)	9 (4.74)	10 (3.53)	10 (3.41)	6 (2.46)	6 (2.60)
Feeding intolerance (frequency)					
0	32	7	6	44	43
1	126	33	30	112	122
2	48	36	43	27	18
3	105	24	21	5	5
Medical intervention (frequency)					
0	51	1	0	0	3
1	91	12	11	119	116
2	77	78	79	68	68
3	92	9	10	1	1
Respiratory difficulty (frequency)					
0	44	0	0	75	73
1	73	23	24	49	60
2	122	62	63	62	53
3	72	15	13	2	2
Respiratory frequency (frequency)					
0	69	1	0	172	173
1	109	32	32	13	12
2	89	53	55	1	1
3	44	14	13	2	2
Apnoea (frequency)					
0	277	93	92	188	188
1			1*		
2		1*	1*		
3	34	6	6	0	0
General condition (frequency)					
0	21	4	2	10	22
1	113	16	17	79	63
2	110	66	67	97	100
3	67	14	14	2	3
Fever (frequency)					
0	211	31	31	82	82
1	55	49	49	34	33
2	45	20	20	72	73

596 *Invalid score.

Appendix 5: Original ReSVinet Score

Source: Justicia-Grande et al., 2016 [1]

Table 1. ReSVinet scale. This table presents the original scale, and was the one used by the three investigators.

	Item	0 points	1 points	2 points	3 points
1	**Feeding intolerance**	**No**	**Mild** Decreased appetite and/or isolated vomits with cough.	**Partial** Frequent vomits with cough, rejected feed but able to tolerate fluids sufficiently to ensure hydration.	**Total** Oral intolerance or absolute rejection of oral feed, not able to guarantee adequate hydration orally. Required nasogastric and/or intravenous fluids
2	**Medical intervention**	**No**	**Basic** Nasal secretions aspiration, physical examination, trial of nebulized bronchodilators, antipyretics.	**Intermediate** Oxygen therapy required. Complementary exams were needed (chest X-rays, blood gases, hematimetry. . .). Maintained nebulized therapy with bronchodilators.	**High** Required respiratory support with positive pressure (either non-invasive in CPAP, BiPAP or high-flow O2; or invasive through endotracheal tube).
3	**Respiratory difficulty**	**No**	**Mild** Not in basal situation but does not appear severe. Wheezing only audible with stethoscope, good air entrance. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates mild severity.	**Moderate** Makes some extra respiratory effort (intercostal and/or tracheosternal retraction). Presented expiratory wheezing audible even without stethoscope, and air entrance may be decreased in localized areas. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates moderate severity.	**Severe** Respiratory effort is obvious. Inspiratory and expiratory wheezing and/or clearly decreased air entry. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates high severity.
4	**Respiratory frequency**	**Normal** < 2 m: 40–50 bpm 2–6 m: 35–45 bpm 6-12m: 30–40 bpm 12-24m:25–35 bpm 24-36m: 20–30 bpm	**Mild or occasional tachypnea** Presented episodes of tachypnea, well tolerated, limited in time by self-resolution or response to secretion aspiration or nebulization.	**Prolonged or recurrent tachypnea** Tachypnea persisted or recurred despite secretion aspiration and/or nebulization with bronchodilators.	**Severe alteration** Severe and sustained tachypnea. Very superficial and quick breath rate. Normal/low breath rate with obvious increased respiratory effort and/or mental status affected. Orientative rates of severe tachypnea: < 2 m: > 70 bpm 2–6 m: > 60 bpm 6-12m: >55 bpm 12-24m: >50 bpm 24-36m: >40 bpm
5	**Apnea**	**No**			**Yes** At least one episode of respiratory pause medically documented or strongly suggested through anamnesis.
6	**General Condition**	**Normal**	**Mild** Not in basal situation, child was mildly uncomfortable but does not appear to be in a severe condition, not impress of severity. Parents are not alarmed. Could wait in the waiting room or even stay at home.	**Moderate** Patient looks ill, and will need medical exam and eventually further complementary exams and/or therapy. Parents are concerned. Cannot wait in the waiting room.	**Severe** Agitated, apathetic, lethargic. No need of medical training to realize severity. Parents are very concerned. Immediate medical evaluation and/or intervention were required.
7	**Fever**	**No**	**Yes, mild** Central T < 38.5°C	**Yes, moderate** Central T > 38.5°C	

(m = months)

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