Disclosures

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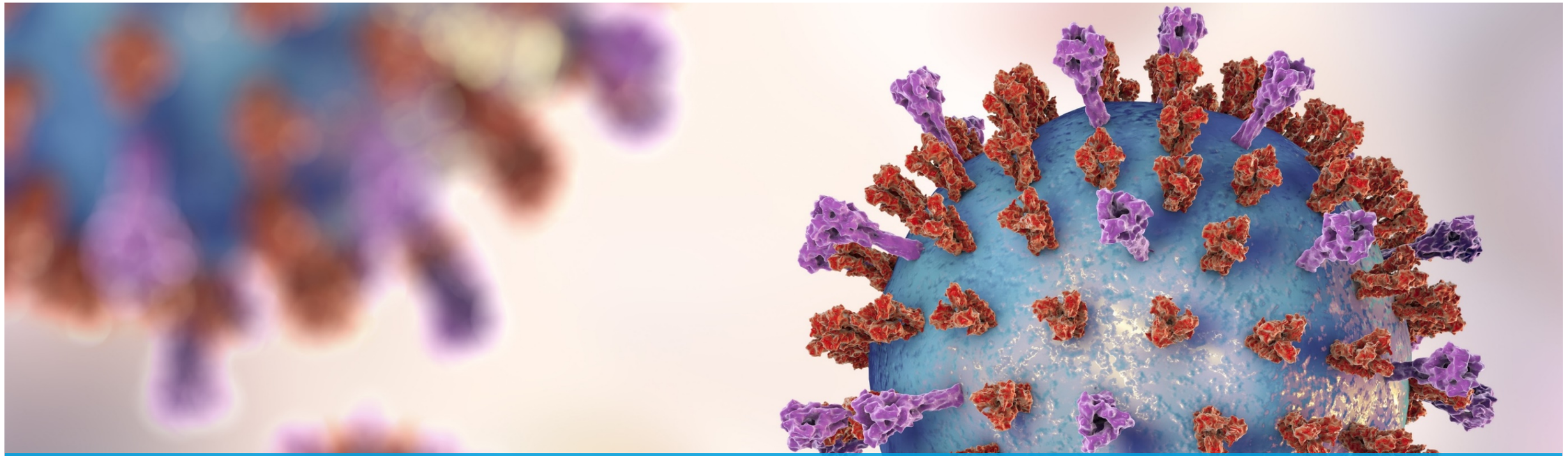

Psychometric Evaluation of the Pediatric RSV Electronic Severity and Outcomes Rating System (PRESORS) in Children Aged 1 to 36 Months Hospitalized with Respiratory Syncytial Virus (RSV) Infection

The structure of Respiratory Syncytial Virus (RSV)

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Introduction to Respiratory Syncytial Virus (RSV)

- RSV is a **common**, **contagious** virus that infects the **respiratory tract**[1–5]

- Every year, an estimated **33 million children under 5** are infected with RSV across the world and it is a **leading cause of hospitalization** in infants **under 1 year**[1–6]
  - RSV is the **most common cause** of **bronchiolitis** and **pneumonia** in children younger than one year[1,7,8]

- **Mortality is unacceptably high**, particularly in young infants in **developing countries**[9]

- The **standard of care** in children is **predominantly supportive** with **very limited therapeutic and prophylactic options** which are only for use in very narrow **high-risk populations**[10,11]
  - This creates a **very high clinical and socioeconomic burden** that is well-established despite **limited diagnostic testing** particularly in the **outpatient setting**[4,12]

There is an unmet need for pediatric RSV vaccines and treatments. In the absence of widely accepted and validated tools to identify RSV disease severity in infants, the development of these instruments (e.g. PRESORS) is a high priority

PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System

1. NIH. Respiratory Syncytial Virus (RSV). Available at: https://www.niaid.nih.gov/diseases-conditions/respiratory-syncytial-virus-rsv; 2. Black CP. Respir Care. 2003;48:209–31; 3. Mayo clinic. Respiratory syncytial virus (RSV). Available at: https://www.mayoclinic.org/diseases-conditions/respiratory-syncytial-virus/symptoms-causes/syc-20353098; 4. CDC. Respiratory Syncytial Virus Infection (RSV). Available at: https://www.cdc.gov/rsv/about/transmission.html; 5. Hall CB. Yale J Biol Med. 1982;55:219–23; 6. Shi T et al. Lancet. 2017;390:946–58 7. Coultas JA et al. Thorax. 2019;74:986–93; 8. Jain SJ et al. N Engl J Med. 2015;372:835–45; 9. Scheltema NM et al. Lancet Respir Med. 2018;6:257–64; 10. Chavez-Bueno S et al. Pediatr Infect Dis J. 2007;26:1089–93; 11. Empey KM, et al. Clin Infect Dis. 2010;50:1258–67; 12. Zhang S et al. J Infect Dis. 2020;222:S680–7

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Study design

- A set of questionnaires (**PRESORS**) were developed to assess the severity of the signs of RSV infection in children, based on observations by the **child's caregiver** (ObsRO) and **clinicians** (ClinRO)
- This is a Phase 0, prospective, observational study to investigate the **inter-rater reliability** of PRESORS **ClinRO** and the structure, scoring, reliability and validity of both ObsRO and ClinRO in infants hospitalized with RSV in centers in the US, Argentina and Chile

Inclusion criteria

- PCR-confirmed RSV infection
- Children aged ≤36 months
- Symptom onset within ≤5 days of study enrolment
- Hospitalized for >24 hours

N=124

Schedule of Assessment for PRESORS

PRESORS	Day 1	Days 2–6	Day 7
ClinRO Rater 1	**X***	X	X
ClinRO Rater 2	**X***		
Caregiver ObsRO	X	X	X

*Within <30 minutes of each other on Day 1.
Days 1–7 during hospitalization following enrolment in the study: caregivers assessed ObsRO three times daily for 7 days, clinicians assessed ClinRO twice daily for 7 days.

- **Primary endpoint:** to assess the inter-rater reliability of PRESORS ClinRO between scorers
- **Secondary endpoint:** to assess the measurement properties of ClinRO and ObsRO PRESORS scores (including internal consistency, known groups validity and convergent validity)

Initial analyses are presented first to determine the results for the primary endpoint.
PCR, polymerase chain reaction; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; PRESORS ClinRO, healthcare professional PRESORS; PRESORS ObsRO, caregiver PRESORS; PRO, patient-reported outcome.

PRESORS (ClinRO) questionnaire

Clinician-rated outcome with detailed concepts to capture severity of signs of RSV infection; constructed based on discussions with key opinion leaders and clinical experts

- 13 items (activity, sleep, feeding, dehydration, apnoea, retractions, tachypnea, breathing problems, cyanosis, cough, nasal secretions, wheezing)
- Also including some global impression of change questions
- Item levels relate to specific signs → psychometrics are used to map these 0 to 3 scores

Did the patient show any of these signs of increased work of breathing during the past 12 hours? (note all that apply)

☐ Nasal flaring

☐ Head bobbing

☐ Grunting

☐ Other signs of difficulty breathing, not already reported

☐ None of the above

The items presented in the PRESORS ClinRO questionnaire are identified as potentially clinically meaningful signs of RSV infection

PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; PRESORS ClinRO, healthcare professional PRESORS.

Baseline characteristics and MRU during hospitalization

n (%)	(N=124)
Median age, months (range)	5.0 (0.4–35.0)
Age group, months	
0 to <3 months	53 (42.7)
3 to <6 months	14 (11.3)
6 to <12 months	37 (29.8)
12 to <24 months	16 (12.9)
24 to ≤36 months	4 (3.2)
Sex	
Female	58 (46.8)
Male	66 (53.2)
Identified risk factors*	
Yes	26 (21.0)
No	98 (79.0)
Supplemental feeding/hydration required	
Yes	84 (67.7)
No	40 (32.3)
Oxygen supplementation required	
Yes	91 (73.4)
No	33 (26.6)
Median length of hospital stay, days (95% CI)	4.0 (4.0–5.0)

*Risk factors included congenital birth conditions, respiratory disorders and prematurity. The length of hospital stay was derived as the number of days from Day 1 (day of first available PRESORS ClinRO) to the date of discharge.
CI, confidence interval; MRU, medical resource utilization; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; PRESORS ClinRO, healthcare professional PRESORS.

Exploratory Factor Analysis

Correlation matrix observed between variables

	Sleep	Feeding	Activity	Retractions	Tachypnea	Breathing	Cyanosis	Cough	Nasal secretions	Wheezing
Sleep										
Feeding	0.566									
Activity	0.611	0.514								
Retractions	0.086	0.144	0.115							
Tachypnea	0.226	0.318	-0.069	0.539						
Breathing	0.337	0.430	0.261	0.675	0.645					
Cyanosis	-0.093	0.125	0.163	0.010	0.247	0.054				
Cough	0.594	0.287	0.189	0.445	0.691	0.660	-0.254			
Nasal secretions	0.376	0.120	0.245	0.579	0.345	0.610	-0.277	0.867		
Wheezing	0.346	0.269	0.110	0.457	0.466	0.541	-0.557	0.453	0.603	

Correlation between items

Minimum value, items are not correlated

Maximum value, items are correlated

EFA standardized solutions

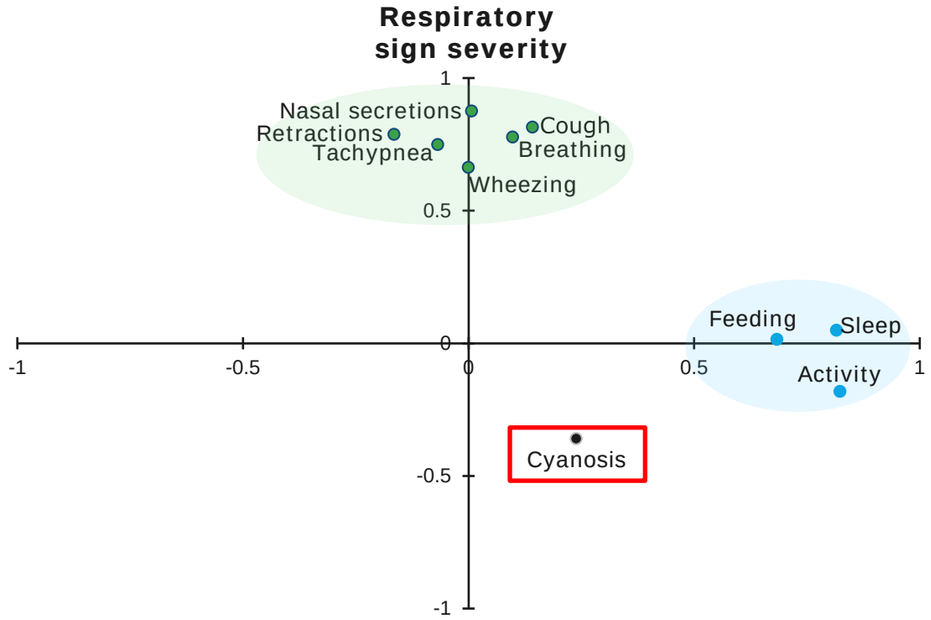
	Single-factor solution	2-factor solution	
	General illness behaviour	**General illness behaviour**	**Respiratory sign severity**
Sleep	0.663	0.815	0.049
Feeding	0.496	0.683	0.015
Activity	0.493	0.823	-0.182
Retractions	0.647	-0.166	0.788
Tachypnea	0.659	-0.069	0.749
Breathing	0.822	0.097	0.778
Cyanosis	-0.159	0.238	-0.360
Cough	0.879	0.141	0.815
Nasal secretions	0.830	0.006	0.876
Wheezing	0.619	-0.001	0.663

Factor loadings

Minimum value

Maximum value

2-factor solution, graphically



Cyanosis did not fit well in the domains and was rarely reported, cyanosis was subsequently removed from the scale

For correlation matrix between variables a greater number denotes that items are correlated and likely measure the same domain. For EFA solutions, greater values suggest items are grouped together and measure a common domain.
EFA, exploratory factor analysis. EFA was performed to identify which items correlate with each other and to identify a set of latent domains underlying the PRESORS items

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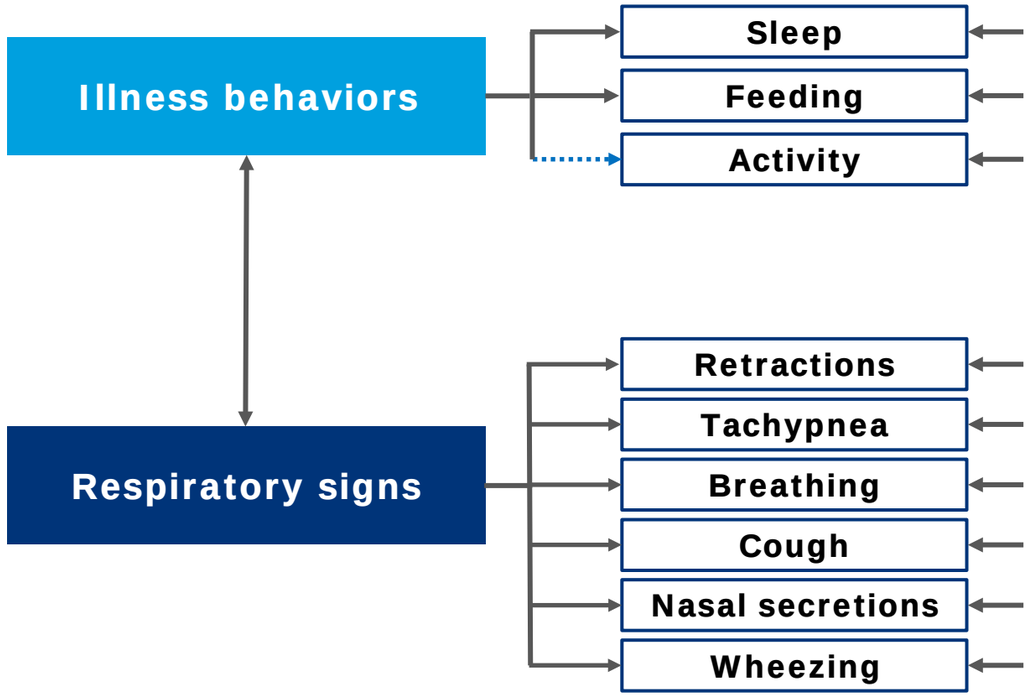
Confirmatory Factor Analysis: 2-factor model

CFA standardized factor loadings on Day 1

	General illness behavior	Respiratory sign severity
Sleep	0.916	0*
Feeding	0.707	0*
Activity	0.651	0*
Retractions	0*	0.686
Tachypnea	0*	0.717
Breathing	0*	0.844
Cough	0*	0.897
Nasal secretions	0*	0.872
Wheezing	0*	0.640

*The CFA model set the near-zero factor loadings to exactly 0

CFA model for Days 1–2 of hospitalization (measurement invariance)



CFA confirmed PRESORS measures two domains: respiratory signs and illness behaviours; the CFA model provided an acceptable fit to the data, establishing confidence in the two-dimensional PRESORS scale

Confirmatory Factor Analysis (CFA) was performed to confirm that the PRESORS measures two domains. The dotted line on the confirmatory factor analysis figure signifies some difference between factor loadings for Day 1 and Day 2; solid lines signify no difference between factor loadings on days 1 and 2.
*Factor loading was fixed to zero. RMSEA was 0.070; CFI, 0.973; TLI, 0.962.
CFA, confirmatory factor analyses; CFI, comparative fit index; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; RMSEA, root mean square error of approximation; TLI, Tucker–Lewis index.

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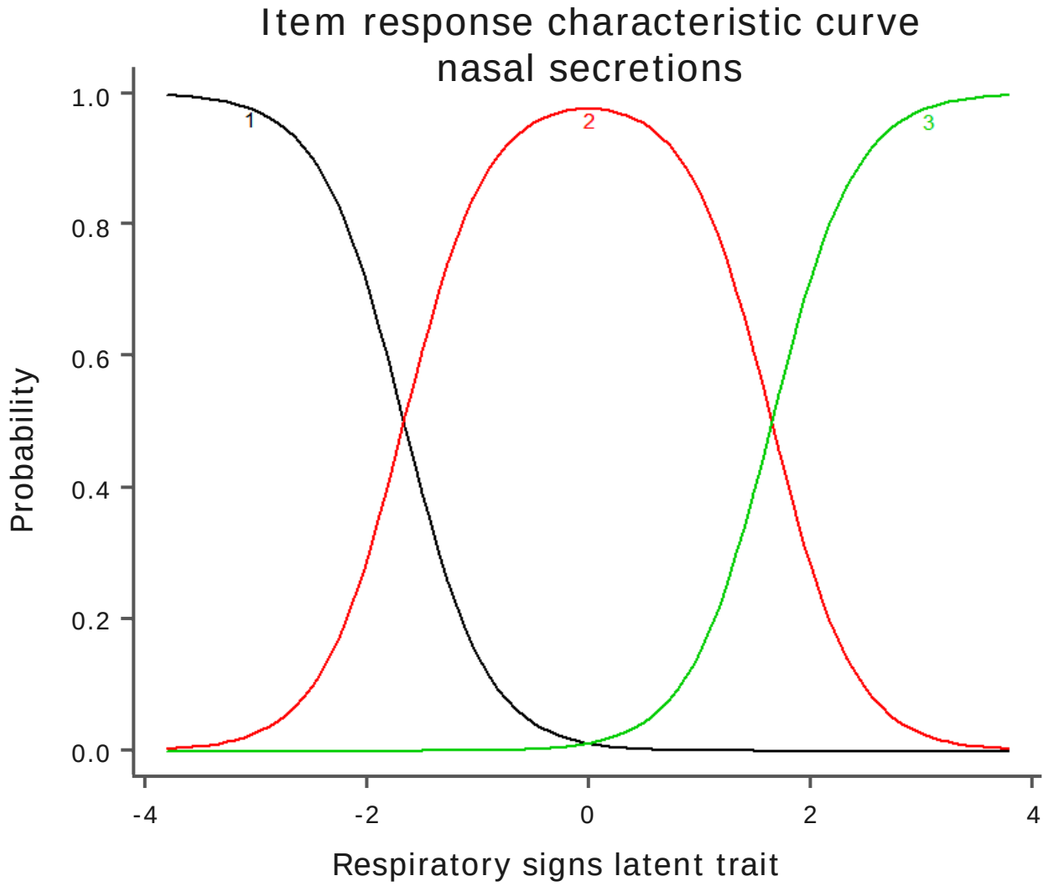
Item response theory application to dimensions of PRESORS



- IRT analyses were used to refine response scales and create summary scores for: respiratory signs, illness behaviors and overall RSV disease severity
- **For example**, nasal secretions and the respiratory signs scale, displayed graphically

Nasal secretions during prior 12 hours:

- None or minimal, easily cleaned with suctioning
- Moderate, but could be cleaned with suctioning
- Extensive, requires frequent suctioning

IRT creates a single dimension for RSV disease severity and item-level responses

IRT, item response theory; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System.

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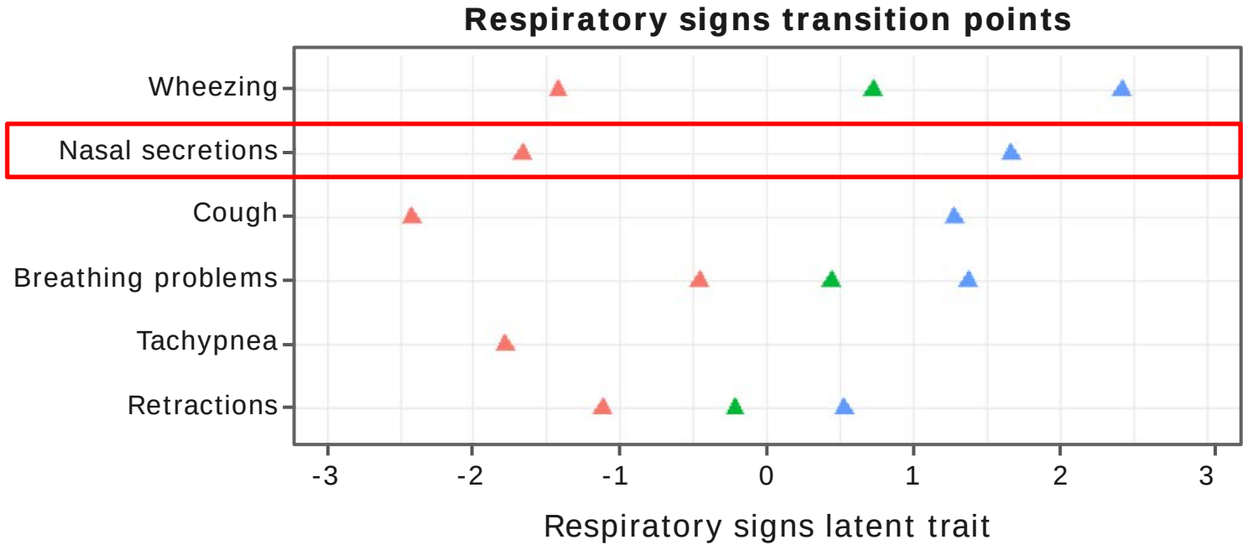
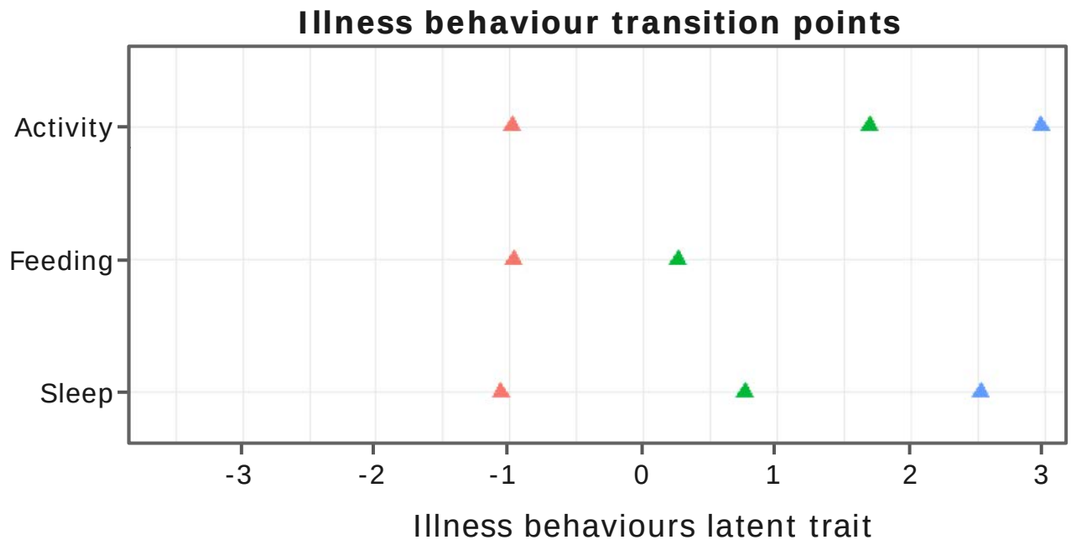
Item response theory analyses to group response scales of PRESORS





For example, with **nasal secretions** during prior 12 hours:

None or minimal, easily cleaned with suctioning (0 points)

Moderate, but could be cleaned with suctioning (1 point)

Extensive, requires frequent suctioning (3 points)

Symptom Scoring transition

- None, 0 to 1 point
- Moderate, 1 to 2 points
- Severe, 2 to 3 points

IRT assisted in the creation of a scoring system by setting scores such that transition points were grouped distinguishing between RSV disease severity

IRT, item response theory; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System.

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Primary endpoint: Inter-rater reliability of PRESORS

ClinRO	Inter-rater reliability (ICC) (95% CI)
Respiratory signs	0.60 (0.47–0.70)
Illness Behaviors	0.62 (0.50–0.72)
PRESORS RSV Severity	0.66 (0.55–0.75)

ICC values of <0.5 denote poor, 0.5–0.75 moderate, 0.75–0.90 good and >0.95 excellent reliability[1]
the primary objective was to achieve an ICC of >0.65

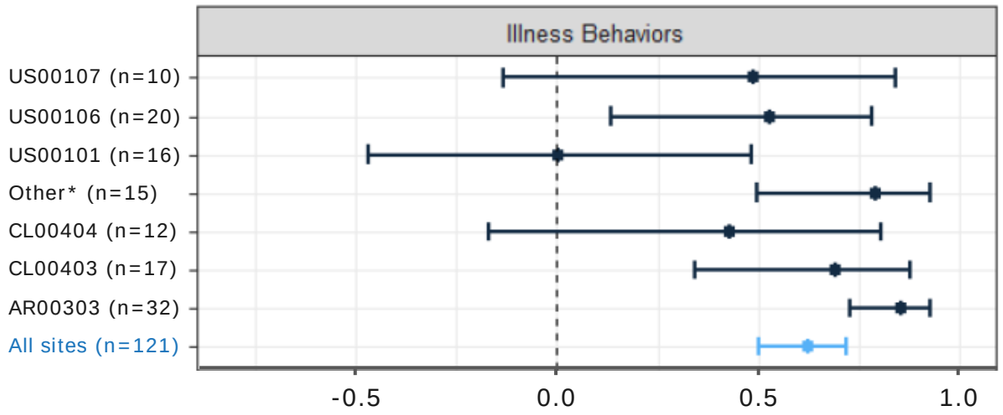
Dimensions and scoring of PRESORS were compared to assess the **similarity between scorers** when assessing the **same infant**; the overall reliability of PRESORS ClinRO to measure RSV disease severity was an ICC of **0.66** (0.55–0.75)

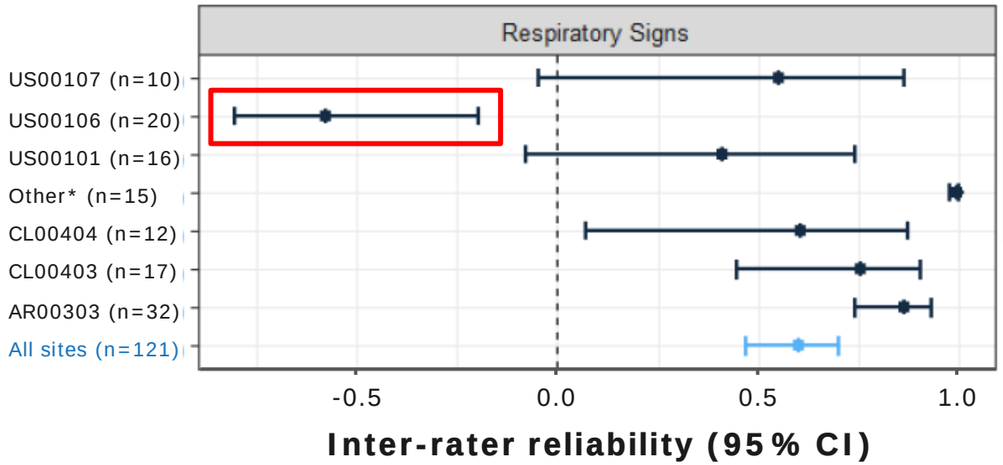
The overall reliability of 0.66 met the primary objective of the study. The value was adequate and reflects the slight differences in assessment of the same infant by different clinical scorers

CI, confidence interval; ICC, intraclass correlation coefficient; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; PRESORS ClinRO, Healthcare Professional PRESORS.

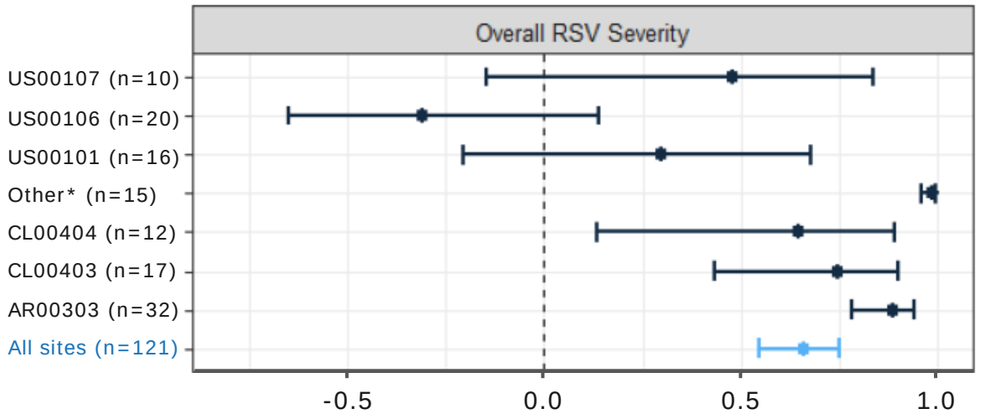
1. Koo et al. J Chiropr Med. 2016 Jun; 15(2):155–163.

Inter-rater reliability of ClinRO by study site





One study site in the US deviated from the other sites, with an ICC of –0.58 for respiratory signs



	ICC (95% CI)	
	With study site	**Without** study site
Respiratory signs	0.60 (0.47–0.70)	**0.81** (0.74–0.87)
Illness behaviors	0.62 (0.50–0.72)	**0.63** (0.50–0.74)
RSV severity	0.66 (0.55–0.75)	**0.79** (0.71–0.86)

Large study site variability was observed; appropriate training on the concepts and evaluating any language barriers of the scorers is required for valid use of PRESORS

*Other sites included CL00402 (n=3), US00102 (n=1), US00104 (n=10), and US00108 (n=2). The study site excluded from the subsequent analysis was US00106.
AR, study sites in Argentina; CI, confidence interval; CL, study sites in Chile; ICC, intraclass correlation coefficient; US, study sites in the United States; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; PRESORS ClinRO, Healthcare Professional PRESORS.

Summary

- Development of the **PRESORS tool** may assist in **accurate severity scoring** of **infants with RSV infection**
- **PRESORS** consists of **two dimensions**, **respiratory signs and illness behaviors**
  - These dimensions were **consistent** and showed measurement invariance over time

- The **inter-rater reliability of PRESORS was 0.66, suggesting adequate inter-rater reliability** when **assessing** the **same infant**
- **Sensitivity analysis** (removing one outlying site) provided an **inter-rater reliability** of >**0.75,** suggesting **training of scorers** is required for **valid use** of **PRESORS**

- Following a similar methodology for PRESORS ObsRO, both **PRESORS ClinRO** and **ObsRO** produced summary scores with **acceptable internal consistency, known-groups validity, and convergent validity**

- **PRESORS** provides **invaluable insight** to the signs and behaviours of **RSV infection**
- **Further development** and use of PRESORS to monitor RSV severity in **clinical trials** is **ongoing**

IRT, item response theory; MI, measurement invariance; PRESORS, Pediatric RSV Electronic Severity and Outcomes Rating System; PRESORS ClinRO, healthcare professional PRESORS; PRESORS ObsRO, caregiver PRESORS; PRO, patient-reported outcome.

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