SUPPLEMENTARY INFORMATION

BIOMARKERS FOR DISEASE SEVERITY IN CHILDREN INFECTED WITH RESPIRATORY SYNCYTIAL VIRUS (RSV): A SYSTEMATIC LITERATURE REVIEW

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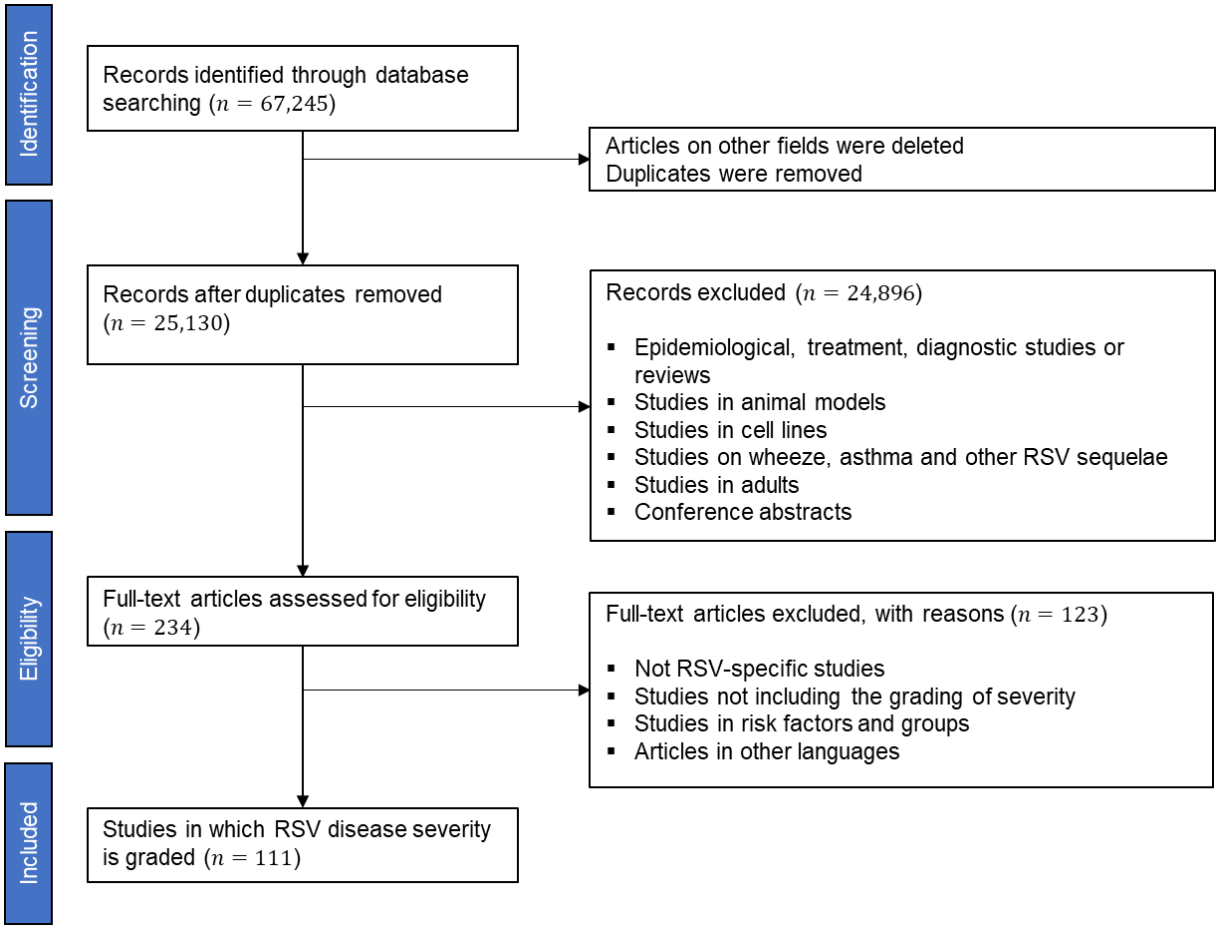
Supplementary methods

Quality of evidence and assessment of risk of bias

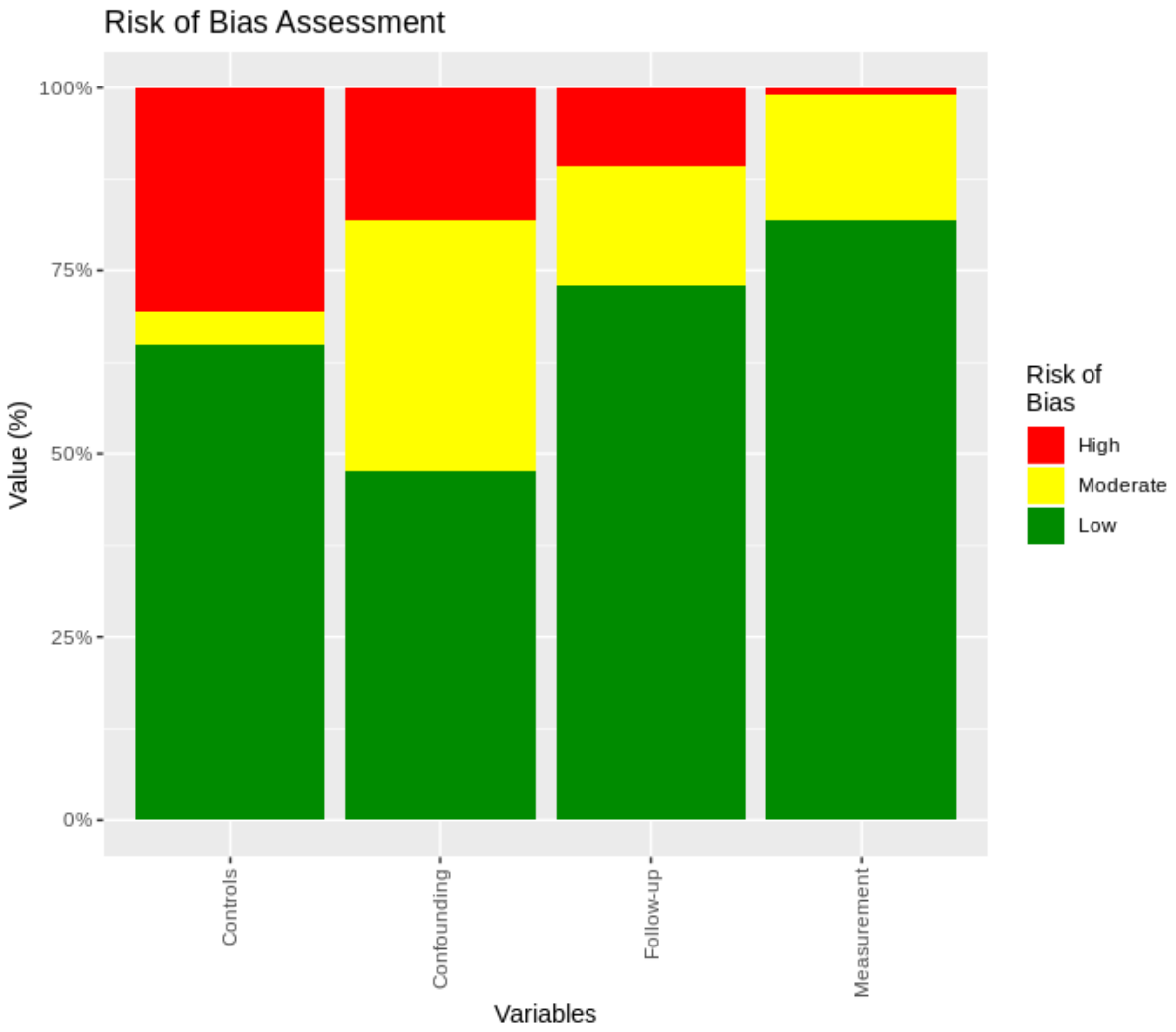
The grading is done by assigning low, moderate, and high risk of bias for each parameter, according to GRADE guidelines[3]. The interpretation of the risk of bias grading is done for each parameter: 1) inclusion of control population, 2) appropriate measurement of both exposure and outcome, 3) adequate control confounding, and 4) follow-up.

Specifics of the grading is as follows. For the inclusion of control population: “low” if a healthy control group is included in the study, “medium” if unclear, and “high” if no control group is included in the study. For the appropriate measurement of exposure and outcome: “low” if the study used a clinical severity score or assessed with a validated method; “medium” if the study mentioned the severity details and the laboratory outcomes however with insufficient details; “high” if severe RSV infection is defined by the laboratory outcomes. For the adequately control confounding: “low” if more than one confounding factor is mentioned clearly; “medium” if only one confounding factor is mentioned, or it unclear about the confounders; “high” if confounding factors are not mentioned. For the follow-up: “low” if the study includes no obvious to loss of follow up or no follow up; “medium” if there is no mention of the follow-up; “high” if there is a loss to follow-up.

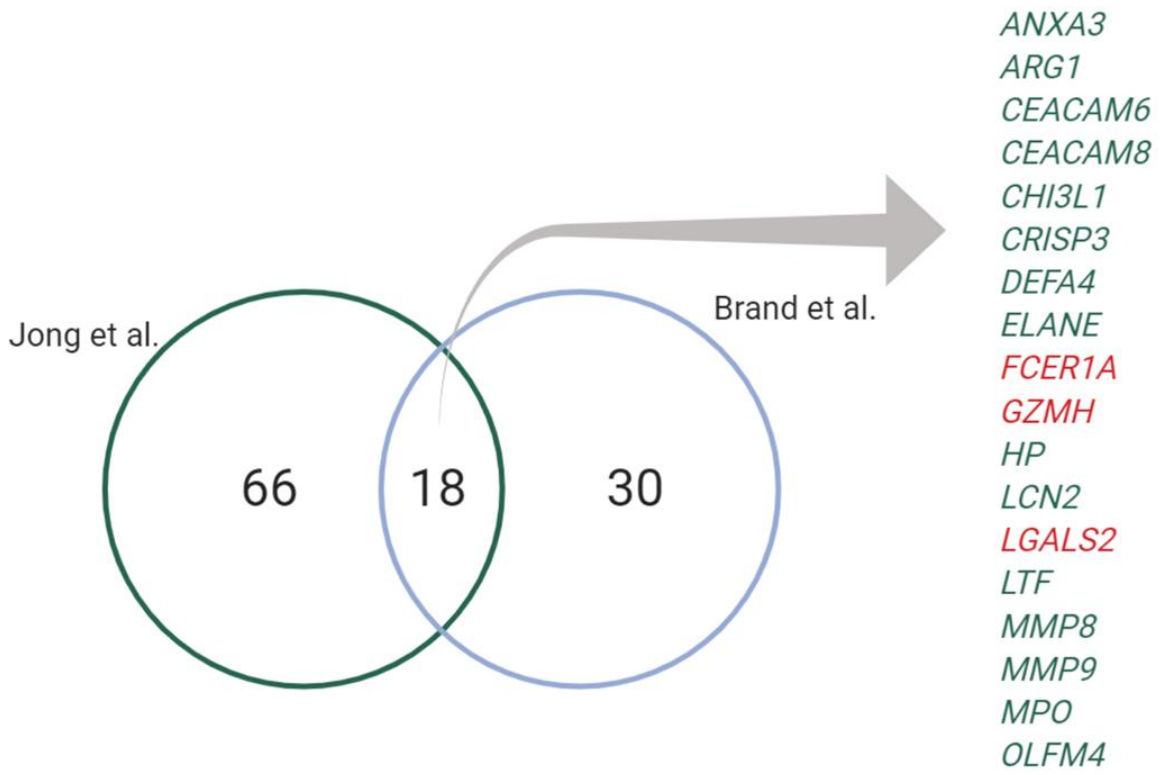
Supplementary figures and tables



Supplementary figure 1: PRISMA diagram[1]. Overview of data selection is represented.



Supplementary figure 2: Risk of bias assessment. The risk of bias assessment was performed according to the PRISMA guidelines. Inclusion of control population (controls), adequately control confounding (confounding), loss-of follow-up of patients (follow-up) and, appropriate measurement of both exposure and outcome measured were graded as high (coloured in red), moderate (coloured in yellow) and low (coloured in green) risk of bias.



Supplementary figure 3: Overview of comparison of transcriptomics studies assessing the association between severe RSV disease versus mild RSV disease in infants. Two whole genome transcriptomics studies comparing gene expression profiles in whole blood or PBMCs of severe and mild RSV disease in infants were identified[2,3]. Eighteen genes overlapped between the listed datasets compromising the genes that are differentially expressed in blood samples of infants with severe RSV disease versus mild RSV disease. The genes listed in green are reported to be upregulated genes, and the genes listed in red are reported to be downregulated genes.

Supplementary table 1: Summary of studies assessing the association of various genetic polymorphisms and RSV disease severity. Only the genes that are linked with severe RSV or with conflicted data (association or no association) were shown. Genes are represented according to the HUGO Gene Nomenclature Committee. N/A is noted when polymorphism is not associated with amino acid and codon change.

***Gene* symbol (protein)**	**Name of the polymorphism (rsnumber)**	**Amino acid change Codon change**	**Publication**	**Number of patients**	**Association**	**Severity parameters**
CNR2 (CB2)	rs35761398	Gln63Arg Q [CAA] > R [CGG]	Tahamtan *et al*, 2017[4]	45 inpatients; 38 outpatients	Increased risk of hospitalisation was associated with carrying Q allele (OR = 2.148; 95% CI = 1.092–4.224; p = 0.026)	Hospitalisation
CX3CR1 (CX3CR1)	rs3732378	Thr280Met T [ACG] > M [ATG]	Amanatidou *et al*, 2006[5]	82 infants hospitalised for RSV-induced bronchiolitis; 120 healthy controls	Carrying M allele was associated with lower oxygen saturation (OR = 3.8; 95% CI = 1.5–9.8; p = 0.006) and with the need for supplemental oxygen (OR= 2.2; 95% CI = 1.1–4.4; p = 0.019)	Oxygen saturation; need for supplemental oxygen

IFNG (IFNγ)	rs3138557 (CA microsatellite)	N/A	Huang *et al*, 2014[6]	218 infants hospitalised with RSV bronchiolitis and 303 healthy controls	CA12+/CA12+ and CA12+/CA12- genotypes were associated with RSV severity [2.84 ± 0.40 (mean ± SD) and 2.95 ± 0.44 (mean ± SD), respectively]	RSV severity score: Respiratory rates; oxygen saturation; wheezing; rales; retractions
IFNG (IFNγ)	rs2430561	N/A	Gentile *et al*, 2003[7]	77 infants hospitalised due to RSV-infection; 107 healthy controls	*IFNG* genotypes were associated with severity score ($\beta = 0.22$; $r^2 = 0.05$; $p = 0.061$), duration of ICU stay ($\beta = 0.24$; $r^2 = 0.06$; $p = 0.021$), and frequency of the otitis media ($\beta = -0.85$; $r^2 = 0.06$; $\chi^2=4.3$; $p = 0.04$)	Severity score (respiratory rate, oxygen saturation, wheeze, retraction); duration of ICU stay; frequency of otitis media

IL10 (IL-10)	rs1800896, rs1800871, rs1800872	N/A N/A N/A	Gentile *et al*, 2003[7]	77 infants hospitalised due to RSV-infection; 107 healthy controls	*IL-10* genotypes were associated with frequency of diagnosed pneumonia (β = -1.78; $r^2 = 0.07$; $\chi^2 = 5.6$; p = 0.02) and physical exam score (β = 0.27; $r^2 = 0.07$; $\chi^2 = 2.69$; p = 0.009)	Frequency of pneumonia; physical exam score
IL10 (IL-10)	rs1800896; rs1800890	N/A N/A	Wilson *et al*, 2005[8]	580 infants with RSV bronchiolitis; 580 healthy controls	For rs1800896 (IL-10 -1117), allele G (OR = 1.68; p = 0.004 and genotype GG (OR = 2.06; p = 0.006), and for rs1800890 (IL10 -3585), allele A (OR = 1.58; p = 0.01) and genotype AA (OR = 1.91; p = 0.01) were associated with the need of mechanical ventilation	Need of mechanical ventilation

IL1RL1 (IL1RL1)	rs1921622	N/A	Faber *et al*, 2012[9]	465 infants with RSV bronchiolitis; 930 control subjects	Overrepresentation of G allele (p=0.011) and genotype (GG and/or GA) level (p=0.04) were associated with need for mechanical ventilation	Need for mechanical ventilation
IL6 (IL-6)	rs1800795	N/A	Gentile *et al*, 2003[7]	77 infants hospitalised due to RSV-infection; 107 healthy controls	*IL-6* genotypes were associated with duration of oxygen supplementation (β = -0.22; r^2 = 0.05; p = 0.025) and hospital stay (β = -0.27; r^2 = 0.07; p = 0.009)	Duration of supplemental oxygen; hospital stay
CXCL8 (IL-8)	rs4073	N/A	Hull *et al*, 2000[10]	117 nuclear families with a child requiring hospitalisation due to RSV infection	Likelihood transmission of the IL-8-251A allele was associated with need for oxygen therapy (%95 CI: 54 – 76, p = 0.011) and duration of supplemental oxygen (%95 CI: 58 to 84, p = 0.05)	Need for oxygen therapy; duration of supplemental oxygen
SFTPA2 (SP-A2)	rs1059046	Thr9Asn T [ACC] > S [AGC]	El Saleeby *et al*, 2010[11]	291 RSV-induced infections	Homozygosity of $1A^0$ allele was found to be protective against hospitalisation (OR	Hospitalisation; ICU admission;

					= 0.15, p = 0.001). Homozygous or heterozygous Asn 9 was associated with ICU admission (OR = 2.15; p = 0.022), require intubation (OR = 3.04; p = 0.005), and longer duration of hospitalisation (OR = 1.89; p = 0.02)	need for intubation; duration of hospitalisation
SFTPD (SP-D)	rs2243639	Thr160Ala T [ACA] > A [GCA]	Ampuero *et al*, 2011[12]	59 severe; 34 moderate; 25 mild RSV-infected infants; 104 blood donors as control subjects	Thr160 allele was associated with RSV severity (OR = 2.33, p = 0.015), and Ala160 allele was associated with milder RSV disease (OR = 0.42, p = 0.015)	Clinical severity scoring: Length of hospitalisation; ICU stay; need for supplemental oxygen; need for mechanical ventilation; duration of

						supplemental oxygen
TGFB1 (TGF-β1)	rs1800470; rs1800471	P (Pro) > L (Leu or Arg) P [CCG] > L [CTG]; R (Arg) > P (Pro or Gln) R [CGG] > P [CCG]	Gentile *et al*, 2003[7]	77 infants hospitalised due to RSV-infection; 107 healthy controls	*TGFB1* genotypes were associated with oxygen saturation at presentation (β = -0.29; r^2 = 0.09; p = 0.008)	Oxygen saturation
TIMP1 (TIMP1)	rs4898	F (Phe) > F (Phe) F [TTT] > F [TTC]	Schuurhof *et al*, 2012[13]	465 infants hospitalised due to RSV infection (81 of whom required mechanical ventilation); 930 control subjects	T-allele had higher frequency in males with need for mechanical ventilation (OR = 2.168; 95 % CI = 1.161 -4.049)	Need for mechanical ventilation

TLR4 (TLR4)	rs4986790; rs4986791	Asp299Gly D [GAT] > V [GTT]; Thr399Ile T [ACC] > I [ATC]	Mandelberg *et al*, 2006[14]	21 ambulatory infants; 26 infants hospitalised on ward; 5 infants admitted to ICU	*TLR4* mutations were overrepresented in moderate and severe RSV compared to mild RSV disease ($p < 0.005$).	Ambulatory infants (mild); Hospitalisation on ward (moderate); admission to ICU (severe)
TLR4 (TLR4)	rs4986790; rs4986791	Asp299Gly D [GAT] > V [GTT]; Thr399Ile T [ACC] > I [ATC]	Tal *et al*, 2004[15]	82 infants with mild RSV bronchiolitis (ambulatory); 99 infants hospitalised with severe RSV bronchiolitis; 90 healthy controls	Asp299Gly (OR = 5.1; $p = 0.014$) and Thr399Ile (OR = 4.0; $p = 0.01$) are associated with hospitalisation.	Hospitalisation
GC (DBP)	rs7041	D (Asp) > E (Glu) D [GAT] > E [GAG])	Randolph *et al*, 2014[16]	98 infants with severe RSV infection; 333 parents. Validation	C allele was overrepresented in hospitalised infants (OR = 1.12; 95% CI = 1.02 – 1.4, $p = 0.003$) and infants with	Hospitalisation; need for

				cohort - 465 infants hospitalised due to RSV bronchiolitis; 930 healthy controls	need of mechanical ventilation (OR = 1.57; 95% CI = 1.12 – 2.22, p = 0.009)	mechanical ventilation

Supplementary table 2: Overview of studies assessing the association between various cytokine/chemokine levels in respiratory samples (*e.g.* nasal wash, nasopharyngeal aspirates, broncho-alveolar lavage [BAL]) and RSV disease severity. "(-)" indicates negative association, "(+)" indicates a positive association, and "(na)" indicates no association observed by the corresponding publication.

Cytokine/ chemokine	**Publication**	**Association**	**Age group**	**Number of patients**	**Severity parameters**
RANTES (CCL5)	Thwaites *et al*, 2018[17]	(-)	2 weeks to 24 months	12 infants with severe RSV, 18 infants with moderate RSV disease	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate)

	Vieira *et al*, 2010[18]	(na)	< 3 months	30 RSV LRTI	Clinical severity score (Respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment); duration of oxygen therapy; duration of mechanical ventilation; length of hospital stay
	Tabarani *et al*, 2013[19]	(na)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
RANTES (CCL5): IL-10 ratio	Hornsleth *et al*, 2001[20]	(+)	< 9 months	25 infants with severe RSV, 21 infants with mild RSV disease	Clinical severity score: Duration of hospital stay; need of respiratory support
EGF	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80	Need for mechanical ventilation (severe); hospitalisation without the need for

				infants with severe RSV; 126 healthy controls	mechanical ventilation (moderate); not requiring hospitalisation (mild)
FGF-β	Garcia *et al*, 2011[21]	(-)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Length of stay
HGF	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
IFN-α	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
IFN-γ	Bennett *et al*, 2007[22]	(-)	< 24 months	101 infants hospitalised due to bronchiolitis	Duration of supplemental oxygen therapy

	Bont *et al* 2001[23]	(-)	< 13 months	17 infants with RSV LRTI requiring mechanical ventilation; 43 infants with RSV LRTI with no mechanical ventilation	Need for mechanical ventilation
	Garcia *et al*, 2011[21]	(-)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Length of hospitalisation; duration of supplemental oxygen
	Legg *et al*, 2003[24]	(-)	[mean days (sd)] LRTI group: 147 (84); URTI group: 219 (125)	9 RSV LRTI; 19 RSV URTI	Acute URTI versus acute bronchiolitis
	Semple *et al*, 2007[25]	(-)	< 24 months	56 infants with severe RSV; 114 infants with moderate RSV; 27 infants with mild RSV	Hospitalised infants requiring mechanical ventilation (severe); Hospitalised infants need of supplemental oxygen; hospitalised infants not requiring oxygen (mild)

	Thwaites *et al*, 2018[17]	(-)	2 weeks to 24 months	12 infants with severe RSV, 18 infants with moderate RSV disease	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate)
	Assefa *et al*, 2011[26]	(na)	< 6 months	13 term infants hospitalised due to RSV bronchiolitis; 11 preterm infants hospitalised due to RSV bronchiolitis	Clinical severity score (respiratory rate; wheezing, retractions, general appearance); peripheral oxygen saturation; duration of oxygen supplement
	Bermejo-Martin *et al*, 2007[27]	(na)	< 24 months	22 severe RSV LRTI; 22 healthy controls	M-WCAS scoring system
IL-10	Vieira *et al*, 2010[18]	(+)	< 3 months	30 RSV LRTI	Clinical severity score: Respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment
	Bennett *et al*, 2007[22]	(-)	< 24 months	101 infants hospitalised due to bronchiolitis	The duration of supplemental oxygen therapy

	Bont *et al*, 2001[23]	(na)	< 13 months	17 infants with RSV LRTI requiring mechanical ventilation; 43 infants with RSV LRTI with no mechanical ventilation	Need for mechanical ventilation
	Garcia *et al*, 2011[21]	(na)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Clinical severity score (Oxygen saturation; respiratory rate; presence of retractions; wheezing; need for intravenous fluid and general condition); length of hospitalisation; duration of supplemental oxygen; admission to PICU; mechanical intubation
	Welliver *et al*, 2007[28]	(na)	< 12 months	45 RSV-infected infants (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu-infected infants (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI, LRTI, oxygen saturation

	Legg *et al*, 2003[24]	(na)	[mean days (sd)] LRTI group: 147 (84); URTI group: 219 (125)	9 RSV LRTI; 19 RSV URTI	Acute URTI versus acute bronchiolitis
IL-17A	Christiaansen *et al*, 2016[29]	(-)	< 12 months	23 RSV-infected infants; 17 healthy controls	Difficulty in breathing; retractions
IL-1R-α	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Bermejo-Martin *et al*, 2008[30]	(-)	< 24 months	14 infants with RSV/A infection; 8 infants with RSV/B infection; 11 infants with co-infection; 27 healthy controls	M-WCAS scoring system

IL–1β	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Diaz *et al*, 2013[31]	(+)	< 12 months	49 RSV bronchiolitis (25of whom have severe bronchiolitis)	Clinical severity score (days of hospitalisation; need for oxygen; maximum oxygen fraction; outpatients; ICU stay)
	Christiaansen *et al*, 2016[29]	(-)	< 12 months	23 RSV-infected infants; 17 healthy controls	Difficulty in breathing; retractions
	Bennett *et al*, 2007[22]	(na)	< 24 months	101 infants hospitalised due to bronchiolitis	Need of hospitalisation; duration of IVF therapy; the duration of supplemental oxygen therapy
	Bermejo-Martin *et al*, 2007[27]	(na)	< 24 months	22 severe RSV LRTI; 22 healthy controls	M-WCAS scoring system

	Garcia *et al*, 2011[21]	(na)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Clinical severity score (oxygen saturation; respiratory rate; presence of retractions; wheezing; need for intravenous fluid and general condition); length of hospitalisation; duration of supplemental oxygen; admission to PICU; mechanical intubation
	Welliver *et al*, 2007[28]	(na)	< 12 months	45 RSV (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI versus LRTI, oxygen saturation
IL-2	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)

	Bennett *et al*, 2007[22]	(na)	< 24 months	101 infants hospitalised due to bronchiolitis	Need of hospitalisation; duration of IVF therapy; the duration of supplemental oxygen therapy
	Bermejo-Martin *et al*, 2008[30]	(na)	< 24 months	14 infants with RSV/A infection; 8 infants with RSV/B infection; 11 infants with co-infection; 27 healthy controls	M-WCAS scoring system; oxygen saturation
	Welliver *et al*, 2007[28]	(na)	< 12 months	45 RSV (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI versus LRTI, oxygen saturation
	Giugno *et al*, 2004[32]	(na)	< 24 months	62 infants hospitalised due to RSV infection (26 mild, 24 moderate, 5 severe, 7 normal)	Oxygen saturation; modified clinical score system (duration of oxygen supplement, length of hospital stay, and need for mechanical ventilation)

IL-2R	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
IL-23	Christiaansen *et al*, 2016[29]	(-)	< 12 months	23 RSV-infected infants; 17 control subjects	Difficulty in breathing; retractions
IL-4	Legg *et al*, 2003[24]	(+)	[mean days (sd)] LRTI group: 147 (84); URTI group: 219 (125)	9 RSV LRTI; 19 RSV URTI	Acute URTI versus acute bronchiolitis
	Assefa *et al*, 2011[26]	(na)	< 6 months	13 term infants hospitalised due to RSV bronchiolitis; 11 preterm infants hospitalised due to RSV bronchiolitis	Clinical severity score (respiratory rate; wheezing, retractions, general appearance); peripheral oxygen saturation; duration of oxygen supplement

	Bennett *et al*, 2007[22]	(na)	< 24 months	101 infants hospitalised due to bronchiolitis	Need of hospitalisation; duration of IVF therapy; the duration of supplemental oxygen therapy
	Welliver *et al*, 2007[28]	(na)	< 12 months	45 RSV (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI, LRTI, oxygen saturation
IL-4:IFN-γ ratio	Legg *et al*, 2003[24]	(+)	[mean days (sd)] LRTI group: 147 (84); URTI group: 219 (125)	9 RSV LRTI; 19 RSV URTI	Acute URTI versus acute bronchiolitis
IL-6	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)

	Brand *et al* 2013[33]	(+)	< 24 months	52 infants with RSV infection (11 mild, 22 moderate, 19 severe)	Need for mechanical ventilation (severe); need for supplemental oxygen and/or nasopharyngeal feeding (moderate); no need for supportive treatment (mild)
	Diaz *et al*, 2013[31]	(+)	< 12 months	49 RSV bronchiolitis (25 severe bronchiolitis)	Clinical severity score (days of hospitalisation, need for oxygen, maximum oxygen fraction delivered during hospitalisation, outpatients, and ICU stay)
	Moreno-Solis *et al*, 2015[34]	(+)	1-12 months	45 RSV-AB; 27 control subjects	Need for oxygen supplement
	Bennett *et al*, 2007[22]	(-)	< 24 months	101 infants hospitalised due to bronchiolitis	Duration of supplemental oxygen therapy
	Garcia *et al*, 2011[21]	(na)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Clinical severity score (oxygen saturation; respiratory rate; presence of retractions; wheezing; need for intravenous fluid and

					general condition); length of hospitalisation; duration of supplemental oxygen; admission to PICU; mechanical intubation
	Welliver *et al*, 2007	(na)	< 12 months	45 RSV (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI versus LRTI, oxygen saturation
	Vieira *et al*, 2010[18]	(na)	< 3 months	30 RSV LRTI	Clinical severity score (Respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment); duration of oxygen therapy; duration of mechanical ventilation; length of hospital stay
IL-6:TNF-α ratio	Hornsleth *et al*, 1998[35]	(-)	< 9 months	46 infants with RSV infection (25 severe, 21 mild)	Clinical severity score: Duration of hospital stay; the need of respiratory support

IL-7	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Welliver *et al*, 2007[28]	(na)	< 12 months	45 RSV (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI, LRTI, oxygen saturation
IL-8	Assefa *et al*, 2011[26]	(+)	< 6 months	13 term infants hospitalised due to RSV bronchiolitis; 11 preterm infants hospitalised due to RSV bronchiolitis	Clinical severity score (respiratory rate; wheezing, retractions, general appearance)
	Diaz *et al*, 2013[31]	(+)	< 12 months	49 RSV bronchiolitis (25of whom have severe bronchiolitis)	Clinical severity score (days of hospitalisation; need for oxygen; maximum oxygen fraction; outpatients; ICU stay)

	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Bennett *et al*, 2007[22]	(-)	< 24 months	101 infants hospitalised due to bronchiolitis	Duration of supplemental oxygen therapy
	Welliver *et al*, 2007[28]	(na)	< 12 months	45 RSV (6 URTI, 30 bronchiolitis, 9 fatal bronchiolitis); 47 Flu (24 URTI, 12 bronchiolitis, 11 fatal bronchiolitis)	URTI versus LRTI, oxygen saturation
	Bermejo-Martin *et al*, 2007[27]	(na)	< 24 months	22 severe RSV LRTI; 22 healthy controls	M-WCAS scoring system
IL-8:RANTES ratio	Hornsleth *et al*, 2001[20]	(+)	< 9 months	46 infants with RSV infection (25 severe, 21 mild)	Clinical severity score: Respiratory rate; alveolar or peribranchial infiltration;

					duration of hospital stay; the need of respiratory support
MCP-1	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Bennett *et al*, 2007[22]	(na)	< 24 months	101 infants hospitalised due to bronchiolitis	Need of hospitalisation; duration of IVF therapy; the duration of supplemental oxygen therapy
	Garcia *et al*, 2011[21]	(na)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Clinical severity score (Oxygen saturation; respiratory rate; presence of retractions; wheezing; need for intravenous fluid and general condition); length of hospitalisation; duration of supplemental

					oxygen; admission to ICU; mechanical intubation
MIP-1α	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
MIP-1β	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Moreno-Solis *et al*, 2015[34]	(+)	1-12 months	45 RSV-AB; 27 healthy controls	Need for oxygen supplement
	Bennett *et al*, 2007[22]	(-)	< 24 months	101 infants hospitalised due to bronchiolitis	Duration of supplemental oxygen therapy

PDGF-ββ	Garcia *et al*, 2011[21]	(-)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Clinical severity score (Oxygen saturation; respiratory rate; presence of retractions; wheezing; need for intravenous fluid and general condition); length of stay; days of supplemental oxygen
sICAM-1	Vieira *et al*, 2010[18]	(+)	< 3 months	30 RSV LRTI	Clinical severity score: Respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment
SP	Semple *et al*, 2007[25]	(-)	< 24 months	56 infants with severe RSV; 114 infants with moderate RSV; 27 infants with mild RSV	Hospitalised infants requiring mechanical ventilation (severe); Hospitalised infants need of supplemental oxygen; hospitalised infants not requiring oxygen (mild)
TNF-R1:RANTES ratio	Hornsleth *et al*, 2001[20]	(+)	< 9 months	46 infants with RSV infection (25 severe, 21 mild)	Clinical severity score: Respiratory rate; alveolar or peribronchial infiltration;

					duration of hospital stay; the need of respiratory support
TNF-α	Tabarani *et al*, 2013[19]	(+)	< 5 years	268 infants with mild RSV; 503 infants with moderate RSV; 80 infants with severe RSV; 126 healthy controls	Need for mechanical ventilation (severe); hospitalisation without the need for mechanical ventilation (moderate); not requiring hospitalisation (mild)
	Bennett *et al*, 2007[22]	(na)	< 24 months	101 infants hospitalised due to bronchiolitis	Need of hospitalisation; duration of IVF therapy; the duration of supplemental oxygen therapy
	Bermejo-Martin *et al*, 2007[27]	(na)	< 24 months	22 severe RSV LRTI; 22 control infants	M-WCAS scoring system
	Garcia *et al*, 2011[21]	(na)	< 24 months	19 infants with RSV infection; 18 infants with HRV-induced LRTI	Clinical severity score (oxygen saturation; respiratory rate; presence of retractions; wheezing; need for intravenous fluid and general condition); length of

					hospitalisation; duration of supplemental oxygen; admission to PICU; mechanical intubation
	Vieira *et al*, 2010[18]	(na)	< 3 months	30 RSV LRTI	Clinical severity score (Respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment); duration of oxygen therapy; duration of mechanical ventilation; length of hospital stay
	Christiaansen *et al*, 2016[29]	(na)	< 12 months	23 RSV-infected infants; 17 control subjects	Difficulty in breathing; retractions

Supplementary table 3: Overview of studies assessing the association between respiratory microbiome and RSV disease severity. "(-)" indicates negative association, "(+)" indicates a positive association observed by the corresponding publication.

Bacteria		**Publication**	**Association**	**Age group**	**Number of patients**	**Severity parameters**
Gram negative	*Moraxella catarrhalis*	Teo *et al*., 2015[36]	(+)	< 12 months	234 infants	LRTI versus URTI; fever in LRTI
		Teo *et al*., 2018[37]	(+)	*< 5 years*	244 infants	LRTI versus URTI
		Suárez-Arrabal et al., 2015[38]	(+)	< 2 years	136 RSV bronchiolitis; 23 healthy controls	Duration of oxygen supplementation
	Haemophilus influenzae	Teo *et al*., 2015[36]	(+)	< 12 months	234 infants	LRTI versus URTI
		Teo et al., 2018[37]	(+)	*< 5 years*	244 infants	LRTI versus URTI

		Jiang et al., 2015[39]	(+)	< 2 years	608 bronchiolitis cases (252 RSV; 188 positives for potentially pathogenic bacteria or PPB)	Length of hospitalization
		Suárez-Arrabal et al., 2015[38]	(+)	< 2 years	136 RSV bronchiolitis; 23 healthy controls	Duration of oxygen supplementation
		de Steenhuijsen Piters et al., 2016[40]	(+)	< 24 months	84 RSV inpatients and 22 RSV outpatients, 26 control subjects	Hospitalisation
		Ederveen et al., 2018[41]	(+)	< 6 months	54 infants infected with RSV (9 mild, 27 moderate, 18 severe); 21 healthy controls	Need for mechanical ventilation (severe); need for supplemental oxygen (moderate); no hypoxemia (mild)

Gram positive	*Staphylacoccus aureus*	*de Steenhuijsen Piters et al., 2016*[40]	(-)	< 24 months	84 RSV inpatients and 22 RSV outpatients, 26 healthy controls	Hospitalisation
	Streptococcus pneumoniae	Teo *et al*., 2015[36]	(+)	< 12 months	234 infants	LRTI versus URTI
		Teo et al., 2018[37]	(+)	*< 5 years*	244 infants	LRTI versus URTI
		de Steenhuijsen Piters et al., 2016[40]	(+)	< 24 months	84 RSV inpatients and 22 RSV outpatients, 26 control subjects	Hospitalisation
		Brealey et al., 2018[42]	(+)	< 24 months	58 infants hospitalised due to respiratory infection	M-WCAS scoring system

Supplementary table 4: Overview of studies assessing the association between various cytokine/chemokine levels in blood and RSV disease severity. "(-)" indicates negative association, "(+)" indicates a positive association, and "(na)" indicates no association observed by the corresponding publication.

Cytokine / chemokine	**Publication**	**Association**	**Age group**	**Number of patients**	**Severity parameters**
RANTES	*Brand et al, 2013*[33]	(-)	< 24 months	52 infants with RSV infection (19 severe, 22 moderate, 11 mild)	Need for mechanical ventilation (severe); need for supplemental oxygen (moderate); no need for supportive treatment (mild)
	Vieira et al, 2010[47]	(na)	< 3 months	30 RSV LRTI	Clinical severity score (Respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment); duration of oxygen therapy; duration of mechanical ventilation; length of hospital stay

G-CSF	*Brand et al, 2013*[33]	(+)	< 24 months	52 infants with RSV infection (19 severe, 22 moderate, 11 mild)	Need for mechanical ventilation (severe); need for supplemental oxygen (moderate); no need for supportive treatment (mild)
IFN-γ	*Bendelja et al, 2000*[43]	(+)	3 weeks - 24 months	30 infants with RSV (6 pneumonia, 17 bronchiolitis, 7 URTI); 10 healthy controls	Pneumonia; bronchiolitis; URTI
	Aberle et al, 1999[44]	(-)	3-44 weeks	20 infants hospitalised due to RSV LRTI; 6 healthy controls	Need for supplemental oxygen
	Bont et al, 1999[45]	(-)	< 13 months	14 infants with severe RSV bronchiolitis; 36 infants with mild-moderate RSV bronchiolitis; 27 healthy controls	Need for mechanical ventilation (severe); other hospitalised infants (mild-moderate)
	Chen et al, 2002[50]	(-)*	2-24 months	Cohort 1: 44 infants hospitalised due to RSV infection. Cohort 2: 41 non-RSV LRTI; 30 healthy controls	Severe group: Oxygen saturation lower than 90%, arterial oxygen partial pressure lower than 60mmHg, need for oxygen supplementation,

					mechanical ventilation; others are considered as mild group. *Decrease in IFN-γ in CD3+CD8+ cells were observed. No changes were observed in CD3+CD8- cells and in whole blood.
	Pinto et al, 2006[46]	(-)	< 12 months	21 inpatients (severe RSV); 21 outpatients (mild RSV); 21 healthy controls	Hospitalised infants (severe group) were scored with Tal clinical severity score and compared with the ambulatory infants (mild group).
	Fernández et al, 2005[47]	(na)	< 12 months	196 infants with RSV infection	Hypoxia (disease severity based on length of supplementary oxygen therapy); non-hypoxia
	Brandenburg et al, 2000[48]	(na)	< 6 months	111 hospitalised infants (50 confirmed severe RSV infection, 45 mild infection)	Severe infection: pCO_2 > 6,6kPa, oxygen saturation < 90%, or need for mechanical ventilation; mild infection; other hospitalised infants

	Larrañaga et al, 2009[49]	(na)	< 6 months	75 infants with RSV infection (37 severe, 38 moderate); 24 healthy controls	Clinical severity score: Hospitalisation; need for supplemental oxygen; no maximal FIO2 (%)
	Moreno-Solis et al, 2015[55]	(na)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; need for supplemental oxygen
IL-10	*Fernández et al, 2005*[47]	(+)	< 12 months	196 infants with RSV infection	Hypoxia (disease severity based on length of supplementary oxygen therapy); non-hypoxia
	Bont et al, 2000[51]	(na)	< 13 months	30 infants with RSV bronchiolitis requiring mechanical ventilation	Duration of mechanical ventilation
	Brand et al, 2013[33]	(na)	< 24 months	52 infants with RSV infection (19 severe; 22 moderate; 11 mild)	Need for mechanical ventilation (severe); need for supplemental oxygen (moderate); no need for supportive treatment (mild)
	Brandenburg et al, 2000[48]	(na)	< 6 months	111 hospitalised infants (50 confirmed severe RSV infection, 45 mild infection)	Severe infection: pCO_2 > 6,6kPa, oxygen saturation < 90%, or need for mechanical

					ventilation; mild infection: other hospitalised infants
	Pinto et al, 2006[46]	(na)	< 12 months	21 inpatients (severe RSV); 21 outpatients (mild RSV); 21 healthy controls	Hospitalised infants (severe group) were scored with Tal clinical severity score and compared with the ambulatory infants (mild group).
	Larrañaga et al, 2009[49]	(na)	< 6 months	75 infants with RSV infection (37 severe, 38 moderate); 24 healthy controls	Clinical severity score: Hospitalisation; need for supplemental oxygen; no maximal FIO2 (%)
	Mella et al, 2013[52]	(na)	< 24 months	66 RSV LRTI (20 PICU patients, 46 floor patients); 14 healthy controls	Admission to PICU (severe); floor patients (mild-moderate). Severity is defined by a scoring system (length of hospitalization, need for supplemental oxygen, duration of supplemental oxygen)
	Vieira et al, 2010[47]	(na)	< 3 months	30 RSV LRTI	Clinical severity score (respiratory rate; wheezing; oxygen saturation; accessory muscle

					recruitment); duration of oxygen therapy; duration of mechanical ventilation; length of hospital stay
	Moreno-Solis et al, 2015[55]	(na)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; Need for oxygen supplement
IL-12	*Bont et al, 2000*[51]	(-)	< 13 months	30 infants with RSV bronchiolitis requiring mechanical ventilation	Duration of mechanical ventilation
	Pinto et al, 2006[46]	(-)	< 12 months	21 inpatients (severe RSV); 21 outpatients (mild RSV); 21 healthy controls	Hospitalised infants (severe group) were scored with Tal clinical severity score and compared with the ambulatory infants (mild group).
	Chen et al, 2002[50]	(na)	2-24 months	Cohort 1: 44 infants hospitalised due to RSV infection (26 LRTI, 18 pneumonia). Cohort 2: 41 non-RSV LRTI; 30 healthy controls	Severe group: Oxygen saturation lower than 90%; arterial oxygen partial pressure lower than 60mmHg; need for oxygen supplementation; mechanical ventilation; others are considered as mild group

IL-17	*Larrañaga et al, 2009*[49]	(-)	< 6 months	75 infants with RSV infection (37 severe, 38 moderate); 24 healthy controls	Clinical severity score: Hospitalisation; need for supplemental oxygen; no maximal FIO2 (%)
IL-4	*Bendelja et al, 2000*[43]	(-)	3 weeks - 24 months	30 infants with RSV (6 pneumonia, 17 bronchiolitis, 7 URTI); 10 healthy controls	Pneumonia; bronchiolitis; URTI
	Bont et al, 1999[45]	(-)	< 13 months	14 infants with severe RSV bronchiolitis; 36 infants with mild-moderate RSV bronchiolitis; 27 healthy controls	Need for mechanical ventilation (severe); other hospitalised infants (mild-moderate)
	Chen et al, 2002[50]	(na)	2-24 months	Cohort 1: 44 infants hospitalised due to RSV infection (26 LRTI, 18 pneumonia). Cohort 2: 41 non-RSV LRTI; 30 healthy controls	Severe group: Oxygen saturation lower than 90%; arterial oxygen partial pressure lower than 60mmHg; need for oxygen supplementation; mechanical ventilation; others are considered as mild group

IL-4: IFN-γ ratio	*Legg et al, 2003*[24]	(+)	[mean days (sd)] LRTI group: 147 (84); URTI group: 219 (125)	9 RSV LRTI; 19 RSV URTI	Acute URTI; acute bronchiolitis
	Chen et al, 2002[50]	(na)	2-24 months	Cohort 1: 44 infants hospitalised due to RSV infection (26 LRTI, 18 pneumonia). Cohort 2: 41 non-RSV LRTI; 30 healthy controls	Severe group: Oxygen saturation lower than 90%; arterial oxygen partial pressure lower than 60mmHg; need for oxygen supplementation; mechanical ventilation; others are considered as mild group
IL-6	*Brand et al, 2013*[33]	(+)	< 24 months	52 infants with RSV infection (19 severe, 22 moderate, 11 mild)	Need for mechanical ventilation (severe); need for supplemental oxygen (moderate); no need for supportive treatment (mild)

	Brandenburg et al, 2000[48]	(+)	< 6 months	111 hospitalised infants (50 confirmed severe, 45 mild RSV infection)	Severe infection: pCO_2 > 6,6kPa, oxygen saturation < 90%, or need for mechanical ventilation; mild infection: other hospitalised infants
	Diaz et al, 2013[31]	(+)	< 12 months	49 RSV bronchiolitis (25 severe bronchiolitis, 24 moderate)	Clinical severity score: days of hospitalisation, need for oxygen, maximum oxygen fraction delivered during hospitalisation, outpatients, and ICU stay
	Vieira et al, 2010[47]	(+)	< 3 months	30 RSV LRTI	Clinical severity score (respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment); duration of oxygen therapy; length of hospital stay
	Mella et al, 2013[52]	(+)*	< 24 months	66 RSV LRTI (20 PICU patients, 46 floor patients); 14 healthy controls	Admission to PICU (severe); floor patients (mild-moderate). Severity is defined by a scoring system (length of hospitalization; the need for

					supplemental oxygen; duration of supplemental oxygen) *IL-6 concentrations were positively correlated with the length of hospitalisation and length of PICU stay in PICU patients.
	Larrañaga et al, 2009[49]	(na)	< 6 months	75 infants with RSV infection (37 severe, 38 moderate); 24 healthy controls	Clinical severity score: Hospitalisation; need for supplemental oxygen; no maximal FIO2 (%)
	Hornsleth et al, 1998[35]	(na)	< 4 years	105 RSV LRTI	Clinical severity score: Respiratory rate; alveolar or peri bronchial infiltration; respiratory support; duration of hospitalisation
IL-6	*Moreno-Solis et al, 2015*[55]	(na)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; need for oxygen supplement
IL-8	*Bermejo-Martin et al, 2007*[27]	(+)	< 24 months	22 RSV LRTI; 22 healthy controls	Oxygen saturation (positive correlation with RSV severity)

	Bont et al, 1999[53]	(+)	< 13 months	14 infants with severe RSV bronchiolitis; 36 infants with mild-moderate RSV bronchiolitis; 27 healthy controls	Need for mechanical ventilation (severe); other hospitalised infants (mild-moderate)
	Brand et al, 2013[33]	(+)	< 24 months	52 infants with RSV infection (19 severe, 22 moderate, 11 mild)	Need for mechanical ventilation (severe); need for supplemental oxygen (moderate); no need for supportive treatment (mild)
	Brandenburg et al, 2000[48]	(+)	< 6 months	111 hospitalised infants (50 confirmed severe, 45 mild RSV infection)	Severe infection: pCO_2 > 6,6kPa, oxygen saturation < 90% or need for mechanical ventilation; mild infection: other hospitalised infants
	Larrañaga et al, 2009[49]	(+)	< 6 months	75 infants with RSV infection (37 severe, 38 moderate); 24 healthy controls	Clinical severity score: Hospitalisation; need for supplemental oxygen; no maximal FIO2 (%)

	Mella et al, 2013[52]	(+)*	< 24 months	66 RSV LRTI (20 PICU patients, 46 floor patients); 14 healthy controls	Admission to PICU (severe); floor patients (mild-moderate). Severity is defined by a scoring system (length of hospitalization; the need for supplemental oxygen; duration of supplemental oxygen) *IL-8 concentrations were positively correlated with length of hospitalisation and higher severity score only in PICU patients. IL-8 production capacity is negatively associated with length of stay and RSV severity score
	Moreno-Solis et al, 2015[55]	(na)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; need for oxygen supplement
LL-37	*Mansbach et al, 2017*[54]	(-)	< 12 months	1005 enrolled infants	Intensive care stay; duration of hospital stay

MIP-1β	*Moreno-Solis et al, 2015*[55]	(-)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; need for oxygen supplement
MIP-1α	*Bermejo-Martin et al, 2007*[27]	(-)	< 24 months	22 RSV LRTI; 22 healthy controls	Wood's Clinical Asthma Score (M-WCAS) scoring system
	Moreno-Solis et al, 2015[55]	(na)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; Need for oxygen supplement
PDGF-ββ	*Bermejo-Martin et al, 2007*[27]	(+)	< 24 months	22 RSV LRTI; 22 healthy controls	Length of hospital stay, Oxygen saturation (positive correlation with RSV severity)
sCD25	*Fernández et al, 2005*[47]	(+)	< 12 months	196 infants with RSV infection	Hypoxia (oxygen saturation < 95%) versus non-hypoxia
TNF-α	*Geevarghese et al, 2014*[56]	(+)	1 month - 5 years	29 infants with RSV infection	Length of hospitalization
	Mella et al, 2013[52]	(na)*	< 24 months	66 RSV LRTI; 14 healthy controls	Admission to PICU (severe); floor patients (mild-moderate). Severity is defined by a scoring system (length of hospitalization; the need for

					supplemental oxygen; duration of supplemental oxygen) *(-) TNF-α production capacity is associated with length of stay and RSV severity score
	Brandenburg et al, 2000[48]	(na)	< 6 months	111 hospitalised infants (50 confirmed severe, 45 mild RSV infection)	Severe infection: pCO_2 > 6,6kPa, oxygen saturation < 90% or need for mechanical ventilation; mild infection: other hospitalised infants
	Larrañaga et al, 2009[49]	(na)	< 6 months	75 infants with RSV infection (37 severe, 38 moderate); 24 healthy controls	Clinical severity score: Hospitalisation; need for supplemental oxygen; no maximal FIO2 (%)
	Hornsleth et al, 1998[35]	(na)	< 4 years	105 RSV LRTI	Clinical severity score: Respiratory rate; alveolar or peri bronchial infiltration; respiratory support; duration of hospitalisation

	Vieira et al, 2010[47]	(na)	< 3 months	30 RSV LRTI	Clinical severity score (respiratory rate; wheezing; oxygen saturation; accessory muscle recruitment); duration of oxygen therapy; duration of mechanical ventilation; duration of hospitalisation
	Moreno-Solis et al, 2015[55]	(na)	1-12 months	45 RSV-AB; 27 healthy controls	Clinical severity score; need for supplemental oxygen
VEGF	*Bermejo-Martin et al, 2007*[27]	(+)	< 24 months	22 RSV LRTI; 22 control infants	Oxygen saturation (positive correlation with RSV severity)

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