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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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APPENDIX

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Supplemental methods

Polymerase Chain Reaction

For quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) an in-house developed kit was used.[20,21] RSV A and B were detected and quantified by duplex RT-qPCR using specific amplification primers and fluorescent probes designed to detect the RSV N gene. The process involves extraction of nucleic acids, conversion of RNA to complementary deoxyribonucleic (cDNA) by reverse transcription, and detection by real-time PCR reaction using a calibration curve (absolute quantitation). 200 µL of M4RT from nasal swab samples were used for the nucleic acid extraction (KingFisher, MagMax Core kit). Nucleic acids were eluted in a volume of 80 µL, 2.5 µl of the eluted solution was used for RT-PCR amplification. Limit of detections (LODs) were determined via probit approach, as recommended in the CLSI EP17-A2 guidance. Several dilutions of surrogate samples (M4RT transport medium spiked with different concentrations of RSV-A and RSV-B strains) were used for their determinations. The RSV A RT-PCR has a LOD of 304 copies/mL, while the LOD for the RSV B RT-PCR is 475 copies/mL. Clinical samples were considered positive when the load was higher than the respective LODs. RT-PCR of all samples was done at the same moment and location.

Table S1. Number and incidence rates after imputation for missing medical attendance status of all-cause ARI, MA-ARI, hospitalized ARI, by age group, according to season, recruitment site, cohort, season of birth, sex and birthweight. All cases, regardless of whether they have been tested were included.

	Incidence rate of all-cause ARI per 1,000 infant-months											
	hospitalized ARI				MA-ARI				ARI			
	< 3 months	3-<6 months	6-<12 months	<12 months	< 3 months	3-<6 months	6-<12 months	<12 months	< 3 months	3-<6 months	6-<12 months	<12 months
Number all-cause events	187	87	114	388	103	134	217	454	316	439	763	1518
All-cause incidence rate	6.82 (5.91-7.87)	3.18 (2.58-3.92)	2.08 (1.73-2.5)	3.54 (3.21-3.91)	37.19 (30.67-45.1)	49.46 (41.94-58.33)	39.13 (34.35-44.58)	41.23 (37.67-45.11)	106.48 (95.37-118.89)	149.77 (136.39-164.45)	130.9 (121.93-140.52)	129.44 (123.09-136.11)
Season (IR)												
2017-2018	5.96 (4.19-8.48)	3.35 (1.86-6.05)	1.49 (0.48-4.64)	4.29 (3.2-5.75)	54.89 (38.4-78.45)	73.7 (49.13-110.55)	18.77 (5.44-64.7)	55.98 (43.45-72.12)	169.99 (140.13-206.2)	152.26 (116.02-199.82)	33.92 (14.12-81.49)	146.14 (125.16-170.63)
2018-2019	7.41 (6.05-9.09)	3.22 (2.3-4.51)	2.87 (2.15-3.82)	4.41 (3.8-5.11)	30.26 (22.34-41)	37.31 (27.92-49.84)	45.8 (37.18-56.42)	38.69 (33.39-44.83)	91.86 (77.6-108.74)	119.42 (101.87-140)	155.2 (138.8-173.54)	125.87 (116.15-136.4)
2019-2020	6.51 (5.09-8.34)	3.26 (2.4-4.43)	2.12 (1.64-2.74)	3.26 (2.79-3.8)	36.54 (25.88-51.59)	54.9 (43.47-69.32)	40.32 (33.96-47.88)	43.18 (37.97-49.1)	87.44 (70.04-109.16)	178.45 (157.04-202.79)	135.02 (123.1-148.09)	137.68 (128.25-147.8)
Site												
Scotland	8.78 (6.76-11.41)	3.61 (2.4-5.43)	3.3 (2.44-4.46)	4.75 (3.97-5.67)	15.8 (8.24-30.29)	51.86 (36.47-73.75)	37.46 (27.61-50.82)	35.63 (28.74-44.17)	97.34 (75.42-125.63)	177.88 (147.18-214.99)	151.63 (131.13-175.34)	144.52 (130.11-160.53)
England	4.42 (3.01-6.5)	4.26 (2.88-6.3)	2.22 (1.51-3.26)	3.28 (2.63-4.1)	29.56 (18.19-48.02)	42.36 (27.76-64.65)	26.9 (18.65-38.81)	31.51 (24.84-39.95)	103.2 (80.29-132.63)	179.22 (147.74-217.4)	131.03 (111.47-154.02)	135.94 (121.64-151.92)
Spain	8.63 (5.96-12.51)	4.64 (2.8-7.7)	2.16 (1.28-3.65)	4.4 (3.4-5.71)	75.61 (56.59-101.03)	98.45 (75.78-127.9)	46.2 (35.43-60.24)	66.68 (57.02-77.98)	134.22 (108.1-166.65)	162.19 (132.92-197.9)	95.42 (79.42-114.64)	121.89 (108.7-136.68)
Finland	4.61 (3.2-6.64)	1.43 (0.75-2.76)	1.04 (0.6-1.78)	2.03 (1.54-2.67)	13.09 (6.17-27.8)	11.74 (5.6-24.62)	29.37 (21.07-40.95)	20.89 (15.77-27.67)	20.04 (11.38-35.29)	33.53 (21.63-51.98)	61.44 (48.84-77.28)	44.05 (36.38-53.34)
Netherlands	8.53 (6.43-11.32)	2.67 (1.61-4.43)	1.69 (1.08-2.65)	3.65 (2.94-4.53)	52.06 (35.96-75.37)	41.91 (27.84-63.1)	55.88 (43.6-71.62)	51.45 (42.83-61.8)	181.95 (149.86-220.92)	199.84 (166.05-240.49)	219.78 (194.01-248.97)	205.35 (187.44-224.98)
Sex												
Female	6.46 (5.23-7.99)	2.59 (1.85-3.62)	1.6 (1.18-2.16)	3.06 (2.63-3.58)	34.15 (25.59-45.55)	42.66 (33-55.16)	37.94 (31.25-46.07)	38.17 (33.24-43.82)	97.11 (82.23-114.67)	139.19 (121.05-160.05)	134.92 (122-149.21)	126.42 (117.48-136.03)
Male	7.21 (5.93-8.75)	3.75 (2.87-4.91)	2.55 (2.02-3.21)	4.01 (3.52-4.57)	40.09 (30.91-51.99)	55.91 (45.05-69.4)	40.23 (33.64-48.11)	44.11 (39.1-49.76)	115.45 (99.63-133.77)	159.3 (140.41-180.74)	127.15 (115.05-140.53)	132.21 (123.37-141.69)
Season of birth												
Spring	2.18 (1.29-3.69)	2.34 (1.41-3.88)	3.3 (2.44-4.47)	2.78 (2.2-3.51)	2.08 (0.37-11.65)	24.53 (15.55-38.69)	62.51 (50.99-76.63)	37.67 (31.33-45.29)	6.4 (2.66-15.38)	87.39 (68.9-110.83)	240.91 (217.51-266.83)	142.86 (130.13-156.84)
Summer	4.22 (2.95-6.04)	6.08 (4.51-8.2)	1.28 (0.81-2.03)	3.22 (2.62-3.96)	29.86 (20.09-44.39)	87.7 (69.76-110.26)	20.1 (14.14-28.56)	39.5 (33.25-46.93)	80.71 (63.96-101.84)	277.6 (244.48-315.2)	76.11 (64.04-90.44)	127.62 (116.21-140.15)

Fall	13.79 (11.34-16.78)	2.8 (1.81-4.34)	1.66 (1.11-2.47)	4.99 (4.24-5.87)	72.32 (55.22-94.71)	68.96 (51.78-91.84)	15.22 (10-23.16)	42.92 (35.93-51.26)	210.5 (179.93-246.27)	174.92 (146.9-208.29)	35.5 (27.05-46.59)	114.14 (102.53-127.06)
Winter	6.47 (4.79-8.72)	1.33 (0.69-2.57)	2.23 (1.56-3.19)	3.05 (2.46-3.79)	50.87 (34.85-74.27)	1.74 (0.24-12.34)	66.74 (53.25-83.66)	46.44 (38.31-56.28)	148.54 (119.94-183.95)	12.17 (5.8-25.52)	187.45 (163.94-214.32)	133.62 (119.44-149.49)
Birthweight (g)												
<2500	15.4 (7.7-30.8)	1.93 (0.27-13.68)	0.97 (0.14-6.87)	4.83 (2.6-8.97)	27.18 (6.8-108.67)	51.81 (17.1-156.99)	29.04 (10.9-77.33)	34.43 (18.08-65.56)	54.35 (20.4-144.82)	138.98 (74.78-258.31)	124.97 (78.74-198.35)	110.51 (78.15-156.26)
≥2500	6.67 (5.75-7.73)	3.21 (2.59-3.97)	2.11 (1.75-2.54)	3.53 (3.19-3.9)	37.72 (31.05-45.83)	49.74 (42.04-58.85)	39.46 (34.58-45.02)	41.59 (37.97-45.55)	108.25 (96.86-120.98)	149.74 (136.16-164.67)	130.82 (121.72-140.6)	129.84 (123.38-136.64)

Table S2: Clinical characteristics of hospitalized ARI in total cohort during the first year of life, according to RSV status. Only ARI hospitalizations with known RSV status were included.

	RSV-positive				RSV-negative			
	<3 months	**3-<6 months**	**6-<12 months**	**< 12 months**	**<3 months**	**3-<6 months**	**6-<12 months**	**< 12 months**
Total number of hospitalizations	N = 84	N = 32	N = 29	N = 145	N = 92	N = 35	N = 66	N = 193
Length of stay (median [Q1-Q3])	3 (2-6)	3 (1-5)	2 (1-3)	3 (2-5)	2 (1-4)	2 (1-3)	2 (1-3)	2 (1-4)
Final diagnosis (n (%))								
Bronchiolitis	74 (88%)	25 (78%)	23 (79%)	122 (84%)	34 (37%)	18 (51%)	27 (41%)	79 (41%)
URTI	2 (2%)	5 (16%)	2 (7%)	9 (6%)	2 (2%)	2 (6%)	8 (12%)	12 (6%)
Pneumonia	5 (6%)	1 (3%)	1 (3%)	7 (5%)	37 (40%)	8 (23%)	9 (14%)	54 (28%)
Croup	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (3%)	7 (11%)	9 (5%)
Viral-induced wheeze	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	3 (4%)	1 (3%)	3 (10%)	7 (5%)	18 (20%)	6 (17%)	14 (21%)	38 (20%)
Total ReSViNET score (median [Q1-Q3])	8 (6 - 10)	7 (6 - 9.5)	8 (5 - 10)	8 (6 - 10)	5 (4 - 7)	6 (5 - 7)	7 (5 - 8)	6 (4 - 8)
Respiratory support (n (%))	49 (58%)	15 (47%)	13 (45%)	77 (53%)	19 (21%)	5 (14%)	21 (32%)	45 (23%)
Invasive	3 (4%)	0 (0%)	0 (0%)	3 (2%)	3 (3%)	1 (3%)	0 (0%)	4 (2%)
CPAP / BiPAP	7 (9%)	1 (3%)	1 (3%)	9 (6%)	3 (3%)	0 (0%)	2 (3%)	5 (3%)
High-flow nasal canula	14 (17%)	4 (13%)	1 (3%)	19 (13%)	4 (4%)	3 (9%)	8 (12%)	15 (8%)
Low-flow nasal canula	26 (31%)	8 (25%)	4 (14%)	38 (26%)	12 (13%)	1 (3%)	8 (12%)	21 (11%)
O_2 (>21%)	29 (35%)	9 (28%)	10 (34%)	48 (33%)	6 (7%)	2 (6%)	8 (12%)	16 (8%)
Admission to the ICU (n (%))	6 (7%)	1 (3%)	1 (3%)	8 (6%)	6 (7%)	1 (3%)	2 (3%)	9 (5%)
Length of stay (median [Q1-Q3])	2.5 (2-3.75)	6 (6-6)	2 (2-2)	2.5 (2-4.5)	5 (2.5-7.5)	3 (3-3)	2 (2-2)	3 (2-6)
Any additional viral testing (n)*	48 (57%)	19 (59%)	18 (62%)	85 (59%)	80 (87%)	25 (71%)	49 (74%)	154 (80%)
Influenza virus (n)	1	0	2	3	14	4	3	21
Rhinovirus (n)	7	7	9	23	34	12	24	70
Metapneumovirus (n)	0	0	0	0	0	0	0	0
Parainfluenza (n)	0	0	1	1	8	2	8	18
Coronavirus (n)	2	0	2	4	5	3	2	10
Adenovirus	0	2	3	5	1	2	7	10
Other virus	1	0	2	3	3	1	1	5
Antibiotics given	16 (19%)	10 (31%)	7 (24%)	33 (23%)	21 (23%)	11 (31%)	23 (35%)	55 (28%)

* Number of cases tested for each virus unknown. Detected viruses are non-mutually exclusive.

Table S3. Birth cohort studies reporting on RSV-associated hospitalisation incidence in healthy term-born children in the first year of life. Active surveillance. Pubmed was screened using the following search terms: RSV, birth cohort, infants, hospitalization. Only publications of birth cohorts which were followed up in the last 30 years were included.

Reference	Country	Year of publication	Study period	Total of children in birth cohort (N)	Number of RSV-related hospital admissions	Incidence (%)	Follow up (including method of active surveillance)	RSV testing	Prematurity and/or comorbidity
Current study	Netherlands, United Kingdom, Finland, Spain		2017-2021	9154	145	1.8 (after imputation)	Yearly questionnaire Weekly contact RSV season (subset), sampling of all reported ARI episodes	POCT and RT-PCR	Only healthy term infants
Thomas	Finland	2021	2017-2018	408	9	2.2	Daily symptom diaries. Nasal swab in clinic if ARI	RT-PCR	Including 27 premature infants
Takashima	Australia	2021	2010-2013	158	1	0.6	Weekly swabs and symptom diary if ARI	RT-PCR	Only healthy term infants
Kubale	Nicaragua	2020	2011-2016	833	19	2.58	Daily symptom diary and weekly home visits. Respiratory sample if ARI	RT-PCR	Not reported
Toivonen	Finland	2020	2008-2012	923	7	0.75	Daily symptom diaries. Nasal swab in clinic or by parents if ARI	RT-PCR	Including 38 premature infants
Zar	South-Africa	2020	2012-2017	1143	54 in first 2 years	5	Active surveillance by nurses. Nasopharyngeal swab if LRTI or wheezing episode	RT-qPCR	Including 17% premature infants
Kumar	India	2017	2012-2014	310	6	1.94	By phone 2-4 weekly. Clinic visit with nasopharyngeal swab if ARI	Multiplex RT-PCR	Only healthy term infants
Houben	Netherlands	2011	2006-2008	298	3	1	Daily recording of symptoms. Nose/throat swab by parents if ARI symptoms	RT-PCR	Only healthy term infants
Regamey	Switzerland	2008	1999-2004	197	2	1.02	By phone weekly. If first ARI: home visit with collection of nasal swab	Multiplex RT-PCR	Only healthy term infants
Nokes	Kenya	2008	2002-2005	635	6/562 child years of observation	1.3 (adjusted incidence) 1.07	Weekly home visits in RSV season, outside 1x/month, nasal wash if ARI	Antigen or immunofluorescence	Not reported
Kusel	Australia	2006	1996-1999	236	5	2.12	Daily symptom diary collected on monthly base; two control NPA samples when child was free of symptoms for at least 4 weeks	Multiplex RT-PCR	Only healthy term infants High-risk of atopy (at least 1 parent with a doctors diagnosis of asthma, hay fever of eczema)

Table S4: Incidence and incidence rates before imputation for missing RSV test results of RSV-associated hospitalized ARI, MA-ARI and ARI by age group, according to season, recruitment site, cohort, and season of birth.

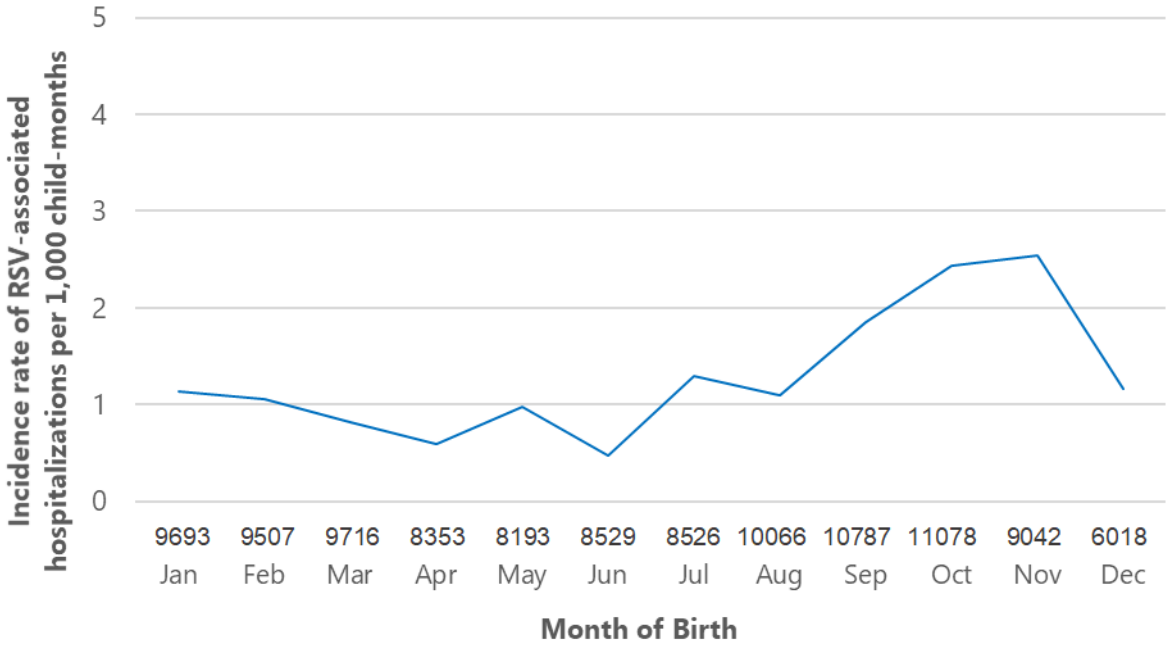
	RSV-associated hospitalized ARI				RSV-associated MA-ARI				RSV-associated ARI			
	< 3 months	**3-<6 months**	**6-<12 months**	<12 months	< 3 months	**3-<6 months**	**6-<12 months**	<12 months	< 3 months	**3-<6 months**	**6-<12 months**	<12 months
RSV incidence proportion (no (%))												
Overall	82/9154 (0.9%)	33/9129 (0.36%)	29/9118 (0.32%)	143/9154 (1.56%)	33/993 (3.32%)	39/981 (3.98%)	57/973 (5.86%)	129/993 (12.99%)	48/993 (4.83%)	86/981 (8.77%)	117/973 (12.02%)	249/993 (25.08%)
Site												
Scotland	24/2130 (1.13%)	9/2128 (0.42%)	15/2123 (0.71%)	48/2130 (2.25%)	3/203 (1.48%)	9/201 (4.48%)	12/200 (6%)	24/203 (11.82%)	7/203 (3.45%)	24/201 (11.94%)	25/200 (12.5%)	56/203 (27.59%)
England[#]	16/1972 (0.81%)	6/1957 (0.31%)	5/1953 (0.26%)	26/1972 (1.32%)	5/198 (2.53%)	8/194 (4.12%)	5/188 (2.66%)	18/198 (9.09%)	7/198 (3.54%)	17/194 (8.76%)	12/188 (6.38%)	36/198 (18.18%)
Spain	13/1080 (1.2%)	9/1079 (0.83%)	3/1079 (0.28%)	25/1080 (2.31%)	12/205 (5.85%)	12/200 (6%)	10/200 (5%)	34/205 (16.59%)	15/205 (7.32%)	21/200 (10.5%)	23/200 (11.5%)	58/205 (28.29%)
Finland	13/2093 (0.62%)	5/2092 (0.24%)	3/2091 (0.14%)	21/2093 (1%)	2/200 (1%)	2/199 (1.01%)	9/198 (4.55%)	13/200 (6.5%)	2/200 (1%)	5/199 (2.51%)	14/198 (7.07%)	21/200 (10.5%)
Netherlands	16/1879 (0.85%)	4/1873 (0.21%)	3/1872 (0.16%)	23/1879 (1.22%)	11/187 (5.88%)	8/187 (4.28%)	21/187 (11.23%)	40/187 (21.39%)	17/187 (9.09%)	19/187 (10.16%)	43/187 (22.99%)	78/187 (41.71%)
RSV incidence rate (/1000 months (95%CI))												
Overall	2.99 (2.38-3.71)	1.24 (0.86-1.74)	0.53 (0.35-0.76)	1.32 (1.12-1.56)	11.46 (7.93-16.01)	13.31 (9.46-18.19)	9.95 (7.56-12.86)	11.17 (9.34-13.25)	16.85 (12.51-22.21)	29.68 (23.77-36.61)	21.44 (17.85-25.55)	22.34 (19.72-25.22)
Site												
Scotland	3.76 (2.41-5.6)	1.41 (0.65-2.68)	1.18 (0.66-1.94)	1.88 (1.39-2.5)	4.95 (1.02-14.46)	14.96 (6.84-28.4)	10 (5.17-17.46)	9.97 (6.39-14.83)	11.55 (4.64-23.79)	41.56 (26.9-61.35)	21.66 (14.15-31.74)	24.09 (18.29-31.14)
England	2.72 (1.56-4.42)	1.19 (0.48-2.46)	0.43 (0.14-1)	1.19 (0.79-1.73)	8.46 (2.75-19.74)	13.92 (6.01-27.43)	4.46 (1.45-10.4)	7.87 (4.66-12.44)	11.84 (4.76-24.4)	29.58 (17.23-47.36)	10.7 (5.53-18.68)	15.74 (11.02-21.79)
Spain	4.01 (2.13-6.86)	2.79 (1.27-5.29)	0.46 (0.1-1.35)	1.93 (1.25-2.85)	19.64 (10.15-34.31)	20.06 (10.37-35.05)	8.37 (4.01-15.39)	14.14 (9.8-19.77)	26.19 (14.97-42.53)	35.11 (21.74-53.67)	20.09 (12.87-29.89)	25.38 (19.41-32.6)
Finland	2.07 (1.1-3.53)	0.8 (0.26-1.86)	0.24 (0.05-0.7)	0.84 (0.52-1.28)	3.34 (0.4-12.06)	3.35 (0.41-12.11)	7.57 (3.46-14.38)	5.45 (2.9-9.33)	3.34 (0.4-12.06)	8.38 (2.72-19.56)	11.78 (6.44-19.77)	8.81 (5.45-13.47)
Netherlands	2.84 (1.63-4.62)	0.71 (0.19-1.82)	0.27 (0.06-0.78)	1.02 (0.65-1.53)	21.41 (11.06-37.39)	14.27 (6.16-28.13)	19.58 (12.27-29.64)	18.71 (13.48-25.29)	32.11 (19.03-50.75)	33.9 (20.41-52.94)	43.6 (32.26-57.64)	38.31 (30.64-47.31)
Season												
2017-2018	3.66 (2.2-5.71)	1.83 (0.67-3.98)	0 (0-1.84)	2.38 (1.54-3.52)	14.85 (6.79-28.2)	11.71 (3.19-29.99)	0 (0-25.02)	11.87 (6.32-20.3)	19.8 (10.23-34.59)	17.57 (6.45-38.24)	0 (0-25.02)	16.44 (9.74-25.98)
2018-2019	2.79 (1.94-3.88)	0.85 (0.39-1.62)	0.61 (0.29-1.12)	1.37 (1.03-1.78)	8.17 (4.22-14.26)	8.64 (4.31-15.46)	9.57 (5.76-14.95)	8.89 (6.4-12.01)	11.57 (6.74-18.52)	18.86 (12.08-28.06)	19.65 (13.97-26.86)	16.92 (13.42-21.06)
2019-2020	2.89 (1.92-4.18)	1.51 (0.91-2.36)	0.68 (0.41-1.07)	1.32 (1.02-1.68)	14.57 (7.76-24.92)	18.23 (11.68-27.12)	11.7 (8.32-16)	13.71 (10.81-17.17)	23.54 (14.57-35.99)	43.28 (32.78-56.08)	25.8 (20.64-31.87)	29.59 (25.24-34.49)
Cohort												

Cohort A	2.72 (1.17-5.36)	2.05 (0.75-4.47)	0.69 (0.19-1.76)	1.54 (0.91-2.43)								
cohort P without cohort A	3.02 (2.37-3.8)	1.15 (0.76-1.66)	0.51 (0.33-0.75)	1.3 (1.08-1.54)								
Sex												
Female	2.97 (2.11-4.05)	1.14 (0.64-1.88)	0.46 (0.24-0.8)	1.26 (0.97-1.6)	10.48 (5.87-17.28)	9.18 (4.89-15.71)	10.32 (6.91-14.83)	10.08 (7.63-13.06)	16.77 (10.74-24.95)	26.14 (18.41-36.03)	22.07 (16.92-28.3)	21.75 (18.07-25.95)
Male	3.04 (2.2-4.09)	1.34 (0.81-2.1)	0.6 (0.35-0.96)	1.4 (1.11-1.74)	12.39 (7.46-19.35)	17.19 (11.23-25.18)	9.6 (6.43-13.79)	12.2 (9.58-15.31)	16.96 (11.08-24.85)	32.39 (23.96-42.82)	20.86 (16.03-26.69)	22.75 (19.11-26.88)
Season of birth												
Spring	0.47 (0.1-1.37)	0.47 (0.1-1.37)	0.79 (0.38-1.45)	0.63 (0.36-1.02)	0 (0-4.72)	5.14 (1.4-13.16)	17.02 (11.12-24.94)	9.72 (6.56-13.87)	0 (0-4.72)	16.71 (8.9-28.57)	40.59 (31.12-52.03)	24.3 (19.11-30.46)
Summer	1.41 (0.67-2.59)	3.4 (2.18-5.05)	0.21 (0.04-0.62)	1.31 (0.92-1.81)	7.96 (3.2-16.39)	31.49 (20.75-45.82)	1.77 (0.37-5.17)	10.78 (7.59-14.86)	13.64 (7.05-23.83)	72.31 (55.44-92.7)	4.13 (1.66-8.51)	23.6 (18.74-29.33)
Fall	7.72 (5.84-10.03)	0.84 (0.31-1.83)	0.14 (0.02-0.5)	2.22 (1.71-2.83)	31.04 (19.67-46.57)	11.11 (4.79-21.88)	1.37 (0.17-4.93)	11.28 (7.76-15.84)	45.88 (31.77-64.11)	16.66 (8.61-29.1)	4.1 (1.5-8.92)	17.77 (13.27-23.3)
Winter	1.95 (1.04-3.34)	0.15 (0-0.83)	1.04 (0.57-1.74)	1.04 (0.69-1.51)	7.07 (1.93-18.11)	0 (0-6.41)	23.65 (15.59-34.41)	13.58 (9.23-19.28)	7.07 (1.93-18.11)	0 (0-6.41)	43.8 (32.51-57.74)	23.66 (17.77-30.87)
Birthweight												
<2500 g	5.78 (1.19-16.88)	0 (0-7.11)	0 (0-3.57)	1.45 (0.3-4.23)	0 (0-50.13)	27.8 (3.37-100.41)	6.94 (0.18-38.68)	10.36 (2.14-30.28)	0 (0-50.13)	69.49 (22.56-162.17)	6.94 (0.18-38.68)	20.72 (7.6-45.1)
≥2500 g	2.9 (2.29-3.63)	1.28 (0.89-1.79)	0.55 (0.37-0.79)	1.32 (1.11-1.56)	11.83 (8.2-16.54)	13.04 (9.18-17.97)	10.09 (7.64-13.07)	11.27 (9.4-13.4)	17.4 (12.92-22.94)	28.54 (22.66-35.47)	21.77 (18.1-25.98)	22.36 (19.69-25.28)

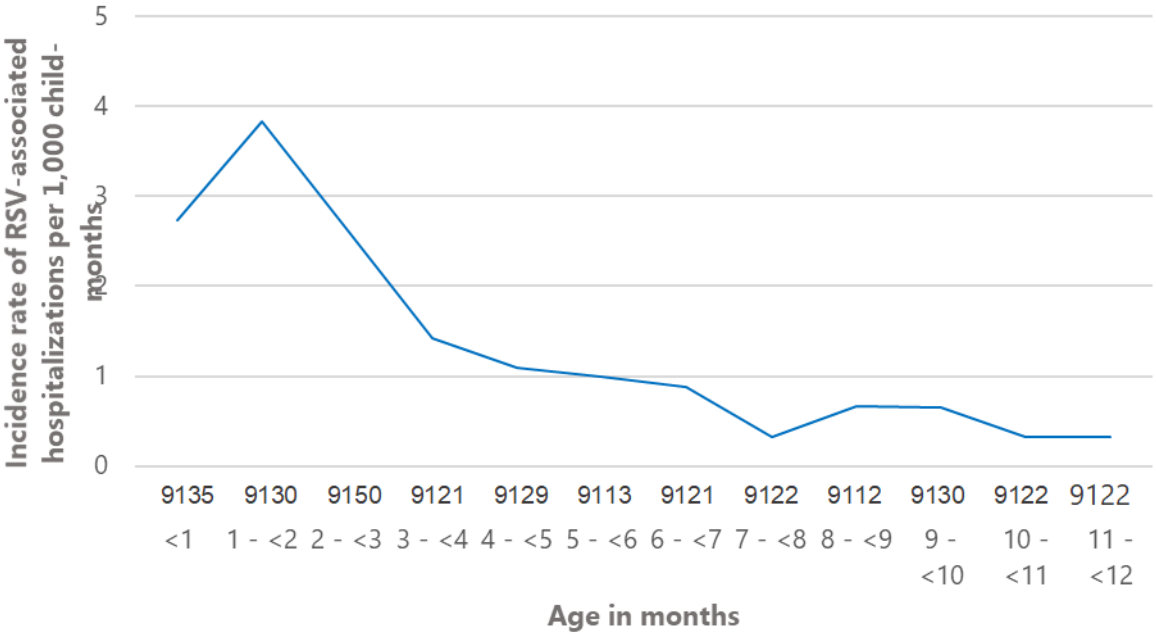
[#] For England 35% of ARI hospitalizations were not tested

Figure S1. Incidence rate of RSV-hospitalizations in the total cohort per 1,000 child-month by month of birth (A) and age in months (B). The numbers above the x-axis indicate the total number of child-month of observation per category.

A.



B.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	"a prospective birth cohort study" & "mulicenter, prospective observational birth cohort study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	"The incidence of RSV-associated hospitalizations in the first year of life was determined by parental questionnaires and hospital chart reviews. We performed active RSV surveillance in a nested cohort to determine the incidence of medically-attended RSV infection." & "The incidence of RSV hospitalization in the total cohort was 1·8% (95% CI 1·6-2·1). (…)Incidences of RSV infection confirmed by any diagnostic assay and medically-attended RSV infection in the active surveillance cohort were 26·2% (95% CI 24·0-28·6) and 14·1% (95% CI 12·3-16·0), respectively."
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7	"Although >97% of RSV-attributable deaths occur in low-income and middle-income countries, the healthcare burden of RSV infection in high-income countries is considerable" & "Accurate information about RSV healthcare burden in healthy infants is essential for decision-makers to evaluate the health and economic benefit of these new prevention strategies." & "Most large studies that aimed to determine RSV-associated hospitalization rates in young children included children with comorbidities, were country-specific, and partly based on estimates instead of actual numbers."
Objectives	3	State specific objectives, including any prespecified hypotheses	8	"The primary objective of this study was to determine the incidence of medically-attended and hospitalized RSV-associated respiratory infections in healthy term infants in Europe. Secondary objectives included to estimate the incidence of symptomatic RSV infections, the incidence of all-cause respiratory infections and the proportion of respiratory infections attributable to RSV."
Methods				
Study design	4	Present key elements of study design early in the paper	8	"In short, healthy term-born infants were enrolled at birth" & "All participating children were followed-up for at least one year." "At enrollment in all five sites, participants to the birth cohort were also invited to participate in a nested cohort"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9	"(…) enrolled at birth between July 2017 and July 2020 in in five sites each located in a different European country (…) (Spain, Finland, England, Scotland, and the Netherlands)." & "screen for hospitalization for acute respiratory infection (ARI) during the first year of life" & "Infants were actively followed until their first birthday during the RSV seasons of 2017-18, 2018-19 and 2019-20. Between 1 October and 1 May (or longer if RSV was still circulating), (…)"

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9	"Children born at ≥37 weeks of gestation with no evidence of significant (…) disorders were considered healthy term-born." & "parental questionnaires to screen for hospitalization" & "Hospital records, including RSV testing results, were retrospectively assessed in case of hospitalization for ARI" & "parents were contacted weekly to report ARI symptoms of their child. In case of an ARI, a study visit was planned within 72 hours of notification to obtain a nasal swab for RSV testing"
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10	"An RSV positive ARI episode was defined as a positive test result." & "An ARI episode was defined as the onset or worsening of any of the following symptoms for at least one day; runny or blocked nose, coughing, wheezing or dyspnea" & "Medically attended (MA)-ARI were defined as ARI episodes with at least one visit to a healthcare provider (…) or hospitalization. RSV-associated hospitalizations, RSV-ARI and RSV-MA-ARI were reported as incidence (i.e. the proportion infants experiencing the event at least once during their first year of life) and as incidence rate per 1000 infant-months (number of events per 1000 infant-months of follow-up)." & "Wheezing during the first year of life was defined as at least one wheezing episode"
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10	"parental questionnaires to screen for hospitalization" & "Hospital records, including RSV testing results, were retrospectively assessed" & "All participating hospitals tested for RSV during the RSV season as part of standard care" & "In case of an ARI, a study visit was planned within 72 hours of notification to obtain a nasal swab for RSV testing" & "completed a diary with respiratory symptoms and health care usage for 14 days after onset"
Bias	9	Describe any efforts to address potential sources of bias	11	"RSV status was assumed negative when hospitalization occurred outside of the RSV season. RSV status of hospitalizations during the RSV season and ARI in the active surveillance cohort with invalid or missing RSV test results were imputed using multiple imputation based on site, gender, age and meteorological season at time of hospitalization or ARI. Any missing observations for medical attendance of ARIs was subsequently imputed using the same set of predictors to which RSV status was added."
Study size	10	Explain how the study size was arrived at	11	"For sample size calculation of the total cohort, a yearly incidence of hospitalizations of 0·7% was assumed based on previous literature.2,22 A sample size of 8700 would produce a two-sided 95% Clopper-Pearson confidence interval with a half-width of 0·2% for this incidence. If accounting for 10% loss to follow-up 10,000 infants were to be included.19 Similarly, a sample size of 1,000 infants was estimated for the active surveillance cohort, which would produce a two-sided 95% Clopper-Pearson confidence interval with a half-width of 2%, for an assumed incidence of MA-ARI of 10%."

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11	"Baseline characteristics and clinical parameters were summarized by frequency and percentage for categorical variables and mean (+/-SD) and/or median (interquartile range) for continuous variables."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11	"Baseline characteristics were compared between groups using chi-square tests for categorical variables, Student's t-tests for normally distributed continuous variables and Mann-Whitney U tests for not normally distributed continuous variables." "(…) invalid or missing RSV test results were imputed using multiple imputation based on site, gender, age and meteorological season at time of hospitalization or ARI. Any missing observations for medical attendance of ARIs was subsequently imputed using the same set of predictors (…) After imputation, pooled 95% Wilson-score confidence intervals were calculated for the proportion of infants with at least one RSV hospitalization or ARI in the first year. Incidence rates were calculated together with 95% confidence intervals based on a Poisson distribution(…)."
		(*b*) Describe any methods used to examine subgroups and interactions	11	"Incidence rates were calculated together with 95% confidence intervals based on a Poisson distribution and compared between subgroups of infants using Poisson generalized linear models."
		(*c*) Explain how missing data were addressed	11	"RSV status was assumed negative when hospitalization occurred outside of the RSV season. RSV status of hospitalizations during the RSV season and ARI in the active surveillance cohort with invalid or missing RSV test results were imputed using multiple imputation based on site, gender, age and meteorological season at time of hospitalization or ARI. Any missing observations for medical attendance of ARIs was subsequently imputed using the same set of predictors to which RSV status was added."
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	10	"The use of incidence rates in addition to incidence was pre-defined in the statistical analysis plan to account for possible variation in follow-up time due to early drop-outs of participants"
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12	"9466 healthy term infants were recruited at birth, of whom 9154 (96·7%) were included in the primary analysis" & "1041 infants were enrolled in the active surveillance cohort and 993 (95·4%) who participated for at least four weeks were included in the analysis"
		(b) Give reasons for non-participation at each stage	12	"Due to the COVID-19 pandemic, 223 infants born after 1 April 2020 were excluded as RSV was not circulating during their first year of life." & Figure 1.
		(c) Consider use of a flow diagram	12	Figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12	"There was substantial and expected variation in baseline characteristics between countries (Table 1). (…)" & "Compared to the rest of the cohort, participants of the active surveillance cohort more frequently reported (…)"
		(b) Indicate number of participants with missing data for each variable of interest	13-16	"50 [ARI hospitalizations] (12·9%) occurred during the RSV season but were not tested for RSV (and status was imputed)." & "A nasal swab was collected during 1442 episodes (95%). Missed episodes was the main reason for not collecting a swab." & "Information about medical attendance was available for 1432 episodes (94·2%)." & "Information on wheezing in the first year of life was available for 7838 children (85·6% of participants) whose parents completed the 1-year questionnaire"
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA	Follow-up time per site reported in Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*	The total number of events is reported in Table 2. The distribution of events in time is reported in Figure 2.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA	The total number of events and the incidence and incidence rates before / after imputation are reported in Table 2.
		(*b*) Report category boundaries when continuous variables were categorized	NA	Age was categorized as <3 months, 3-<6 months, 6-<12 months, or reported for the <12 months (Table 3).
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA	NA
Discussion				

Key results	18	Summarise key results with reference to study objectives	16	"Our results showed an incidence of RSV-associated hospitalization of 1·8% in the first year of life. Almost half of all ARI hospitalizations in the first year of life were RSV-associated. The burden of RSV-associated hospitalization was highest in infants <3 months of age with an incidence rate of 3·3/1000 infant-months."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18	"This study also has limitations." & "When using a cohort study design with RSV testing results as primary outcome, missing test results will systematically lead to an underestimation of true incidence if assumed negative." & "the participants in the study may not be representative of the country population (…)This could have resulted in an underestimation of RSV incidence in the study population compared to the country population " & "it is possible that we missed ARI episodes despite weekly contacts with parents during the period of active surveillance (…)which could result in underestimating incidence rated and would be more pronounced in the older infants." & "The COVID-19 pandemic may have contributed to the lower incidence of RSV-associated hospitalization, MA-ARI and ARI in the study in Finland."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19	"Overall, study limitations have possibly resulted in a modest underestimation of actual RSV burden." & "The healthcare burden of RSV in healthy term-born infants in Europe is considerable with an incidence of RSV-associated hospitalization of 1·8% in the first year of life, which means that one in 56 healthy term-born infants is hospitalized with RSV annually."
Generalisability	21	Discuss the generalisability (external validity) of the study results	17	"the participants in the study may not be representative of the country population (…)This could have resulted in an underestimation of RSV incidence in the study population compared to the country population "
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4	"RESCEU has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116019. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and European Federation of Pharmaceutical Industries and Associations (EFPIA)."

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Statistical Analysis Plan (V13 – August 05, 2020)

Table of Contents

1. Abbreviations

ARTI = Acute respiratory tract infection
CRF = Case-report form
MA = Medically-attended
PCR = Polymerase Chain Reaction
POCT = Point of Care Testing
RSV = Respiratory syncytial virus
ED = emergency department

2. Introduction

2.1. SCOPE OF THE STATISTICAL ANALYSES PLAN

This statistical analysis plan (SAP) was developed based on the approved version of the protocol at Universitair Medisch Centrum Utrecht(version 3, from March 27th 2018). The version number and date of approval may differ between sites as ethics approval was obtained separately. Local protocol versions aligned on objectives and endpoints definitions but could differ for operational aspects.

The first version (SAP V01) was finalized on May 26th 2020 and submitted to RESCEU partners. The final version (SAP V13) was approved by the RESCEU team date 05 August 2020. It covers the main study objectives that can be addressed with data gathered during the first year of life and do not require other information than what was asked in case-report forms (CRF) and questionnaires, and polymerase chain reaction (PCR) test results for RSV on nasal swabs. Other objectives will be addressed in separate statistical analysis plans, including:

- The relationship between respiratory syncytial virus (RSV) infections and disease severity and recurrent wheezing.
- Healthcare costs and quality of life
- Biomarkers for severity of disease

2.2. STUDY DESCRIPTION

2.2.1. STUDY DESIGN

The “RESCEU Birth Cohort Study” is a multicenter prospective observational birth cohort study aiming at determining the incidence of respiratory syncytial virus (RSV) infections during the first year of life in the general population in Europe.

In total, 10,000 healthy term infants were to be recruited at birth and followed up until one year of age for hospital admissions related to acute respiratory tract infections (ARTI) (Fig. 1). They are referred to as cohort P in this document. A subset of about 1,000 infants was also actively followed during the RSV season(s) of their first year of life. This subset is referred to as cohort A in this document. The active follow-up was conducted during 3 seasons (2017-2018 to 2019-2020) and the passive follow-up was prolonged for an additional season (2017-2018 to 2020-2021).

For the active follow-up, participants in cohort A were contacted weekly during the RSV season to enquire about respiratory symptoms and tested for RSV every time they experienced an acute respiratory tract infection (Fig. 2).

All participants in cohort P hospitalized for an ARTI during their first year of life and all those included in cohort A will be subsequently followed up at two and three years of age to determine the sequelae associated with RSV infections (Fig. 1, Fig. 2).

Fig. 1: Follow-up cohort P. http://resc-eu.org/clinical-studies.

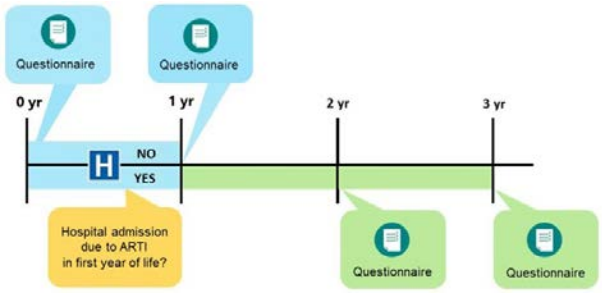
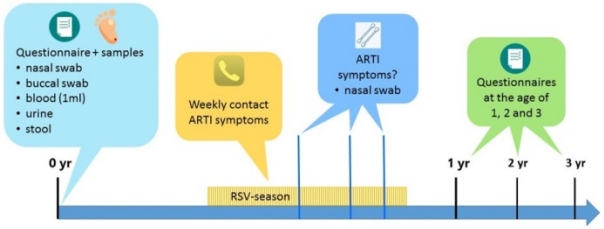


Fig. 2: Follow-up cohort A. http://resc-eu.org/clinical-studies.



2.2.2. SAMPLE SIZE

Sample size for cohort P and cohort A were calculated a priori and presented in the study protocol (Tab. 1).

For cohort P, sample size calculation was based on the expected incidence in RSV-associated hospitalized ARTI among healthy term infants. For cohort A, sample size was calculated based on the expected incidence of medically attended ARTI among healthy term infants.

For sample size estimation purposes, incidence was defined in the protocol as the number of observed outcomes divided by the number of participants included at baseline.

Tab. 1: Sample size calculation. REspiratory Syncytial virus Consortium in EUrope (RESCEU) study: Defining the burden of disease of Respiratory Syncytial Virus in Europe. Research Protocol. Version 3, March 27th 2018.[1]

Patient populations

	Sites	Outcome	Persons	RSV seasons	Expected Incidence (%)/y	CI Half-Width (%)
Healthy baby, at least AD 37^{+0} (full cohort)	NL, UK, SP, FI	RSV-hospitalization	10.000	1	0,7 [10,11]	0,5-1,3
Healthy baby, at least AD 37^{+0} (active cohort)	NL, UK, SP, FI	MA-RSV	1,000	1	10 [10-12]	8,0-12,0

[1] Tab.1 was extracted from the protocol. It displays sample size calculations for the full cohort and the active cohort which correspond to cohort P and cohort A respectively in the SAP.

2.3. SUMMARY OF THE STUDY OBJECTIVES AND ENDPOINTS

Specific endpoints for each primary and secondary objectives were developed based on the objectives listed in the protocol. Deviations from the objectives as stated in the protocols and endpoints that don't fully match the corresponding objective are indicated and explained in the paragraph below.

Tab. 2: Objectives as stated in the protocol and associated endpoints

	Objectives as stated in the protocol.	Endpoints defined in the SAP
Primary	To determine the incidence of RSV-associated hospitalizations for ARTI during the first year of life.	Incidence of RSV-associated hospitalized ARTI during the first year of life in cohort P
	To determine the incidence of RSV-associated MA-ARTI during the RSV season in the first year of life.1	Incidence of RSV-associated MA-ARTI during the first year of life in cohort A.
Secondary	To determine the incidence of RSV-associated ARTI during the RSV season in the first year of life.1	Incidence of RSV-associated ARTI during the first year of life in cohort A.
	To determine the rate of all-cause medically attended (inpatient or outpatient) ARTI (active cohort).2	Incidence of all-cause hospitalized ARTI during the first year of life in cohort P. Incidence of all-cause MA-ARTI during the first year of life in cohort A. Incidence of all-cause ARTI during the first year of life in cohort A.
	To determine RSV-associated and all-cause mortality through all RSV seasons of follow-up.	All-cause mortality and RSV-associated mortality during the first year of life in cohort P.
	To determine the incidence rate of other respiratory pathogens associated with all medically attended (inpatient or outpatient) ARTI (active cohort)3	Number of other respiratory pathogens detected among hospitalized ARTI during the first year of life in cohort P.
	To determine the proportion of viral ARTI attributable to RSV (active cohort).4	Proportion of RSV-associated ARTI among all-cause ARTI during the first year of life in cohort A. Proportion of RSV-associated MA-ARTI among all-cause MA-ARTI during the first year of life in cohort A. Proportion of RSV-associated hospitalizations for ARTI among all-cause hospitalized during the first year of life in cohort P.
	To determine the incidence of RSV-related secondary bacterial respiratory tract infections within 21 days after onset of RSV infection and their association with antibiotic use in hospitalized RSV ARTI patients (all children) and non-hospitalized RSV ARTI patients (active cohort).5	Proportion of RSV-associated MA-ARTI treated with antibiotics in cohort A. Proportion of RSV-associated hospitalized ARTI treated with antibiotics in cohort P.
	To determine important risk factors for RSV infections by severity and healthcare utilization.	Odds ratios of potential risk factors for at least one RSV-associated hospitalized ARTI in cohort P. Hazards ratios of potential risk factors for RSV-associated MA-ARTI

2.4. DIFFERENCES WITH THE FINAL PROTOCOL VERSION 3, MARCH 27TH 2018

Related to primary endpoint

1. Original protocol: The incidence of RSV-associated ARTI was listed as one of the primary endpoints in the protocol
   Comment: This study utilized a very low severity threshold for the ARTI definition to ensure capturing all medically relevant events. Thus ARTIs include a broad spectrum of clinical disease that is less significant for estimating RSV burden than MA-ARTI or hospitalized ARTI.
   Change: The incidence of RSV-associated ARTI has been changed into a secondary endpoint in the statistical analyses plan.

Related to secondary endpoints

2. Original protocol: the rate of all-cause ARTI was to be estimated for MA-ARTI in cohort A.
   Comment: The proportion of ARTI attributable to RSV will be reported for hospitalized ARTI in cohort P and for MA-ARTI and ARTI in cohort A, which will require the incidence of all-cause ARTI to be estimated for each level of care.
   Change: Three endpoints have been defined to report the incidence of all-cause ARTI: for hospitalized ARTI in cohort P and for MA-ARTI and ARTI in cohort A.

3. Original protocol: The incidence rate of other respiratory pathogens was to be estimated among MA-ARTI in cohort A.
   Comment: As only qPCR specific for RSV will be performed on respiratory samples in cohort A, due to limited resources, no information regarding infections with other pathogens will be available for outpatients. For inpatients, study team was asked to indicated if any additional viral and bacterial testing was done and if applicable for which pathogens samples tested positive. As the number of inpatients tested for each respiratory pathogen is unknown, it will not be possible to estimate incidence.
   Change: The number of other respiratory pathogens detected among hospitalized ARTI in cohort P will be reported.

4. Original protocol: The proportion of ARTI attributable to RSV was to be reported among viral ARTI for cohort A, but the protocol did not specify the level of care and this measure require identification of all viral ARTI.
   Comment: Further specification on the severity level was needed for cohort A. As the proportion of hospitalizations associated with other respiratory pathogens will be estimated among hospitalized ARTI, the proportion of ARTI attributable to RSV will also be reported for hospitalized ARTI in cohort P for comparison purposes.
   As samples from cohort A will only be tested for RSV and not all hospitalized ARTI cases will be tested for other respiratory viruses, the attributable fraction will be estimated among all ARTI and not viral ARTI.
   Change: Three endpoints are distinguished, one for hospitalized ARTI in cohort P, one for all ARTI captured in cohort A and one for MA-ARTI (outpatients and inpatients) in cohort A.

5. Original protocol: the incidence of secondary bacterial infections and their association with antibiotics use was to be analyzed among hospitalized RSV-associated ARTI in cohort P and non-hospitalized ARTI in cohort A.
   Comment: As a nasal swab positive for bacteria may only indicate carriage and because the timing of RSV and bacterial infection is difficult to establish, we do not expect to be able to identify real secondary bacterial infections in our cohort. In addition, we would expect too few cases to be able to assess their association with antibiotics (1; 2).
   Change: to respect the limitations of the data, the proportion of RSV-associated ARTI episodes treated with antibiotics will be reported for hospitalized ARTI in cohort P and MA-ARTI in cohort A.

3. Variables definitions

3.1. DEFINITIONS FOR PRIMARY OUTCOMES

3.1.1. HOSPITALIZED ARTI

Reported by parents (1st year questionnaire or end of the diary questionnaire) OR found in local hospital records for participants with no 1st year questionnaire completed.

All reported hospitalizations were validated by a member of the study team who verified in medical records that

- the child was admitted to the hospital for an ARTI.
- the hospitalization occurred during the first year of life

Hospitalizations with the same admission and discharge date, will be excluded.

If caregivers did not complete the 1st year questionnaire the study team checked the local hospital records. If no admission was recorded, we assumed there was no hospitalization due to ARTI.

3.1.2. ARTI

Active participants were contacted weekly during the RSV season to ask about symptoms of ARTI by email, text messages and/or phone calls, the exact methods were tailored to the country and site. For each ARTI reported by participants caregivers, the study team was instructed to follow a validation algorithm to determine if the ARTI fitted the criteria to be considered a new episode. The decision by the study team to trigger the start of a new diary and a new home visit form will be considered as the occurrence of a validated new ARTI episode.

- According to the validation algorithm, respiratory symptoms had to meet the following definition to be considered a new ARTI episode: Respiratory symptoms reported by parents and validated by the study team as
  - new symptoms or
  - already existing symptoms that clearly worsened.
- Eligible respiratory symptoms are defined by the presence of at least one of the following for at least one day:
  - Blocked / runny nose
  - Shortness of breath
  - Wheezing at expiration
  - Cough AND fever

3.1.3. MA-ARTI

Any ARTI episode (as defined above) for which parents reported a medical consultation in the questionnaire completed at the end of diary OR hospitalizations for ARTI that occurred during the RSV season will be considered MA-ARTI.

Medical consultations will include visits to GP, out of hours clinics, emergency department (ED) and medical specialists. Caregivers who reported consultations for ARTI with “other health professionals”, were asked to specify which professional in an free text variable. These will be reclassified in the appropriate category if possible. The others will be considered on a case-by-case basis.

Similarly to the search of hospital records, missing information on medical attendance in cohort A, may be retrieved by contacting the corresponding participants and/or their GP, depending on the amount of missing information.

3.1.4. CONFIRMED RSV INFECTION

ARTI episodes with a PCR positive for RSV or a point of care test (POCT) positive for RSV, will be considered associated with RSV. RSV tests done on samples taken for this study or as part of routine clinical care will be included.

In cohort P, hospitalizations that occurred outside the RSV season (defined as the active surveillance period, see paragraph 3.2.1) will be assumed to be caused by another pathogen than RSV, even if no test for RSV was done.

In cohort A, only samples taken within 10 days of onset of symptoms will be used for the analysis. In a recent study (3) including 35 RSV positive non-hospitalized children younger than 18 months of age, median duration of shedding was 14 days among those <7months and 28 days among older children. In another study including 37 hospitalized children positive to RSV tested by PCR, 92% still tested positive to RSV 7 days after onset and 50% were still positive on day 14 (4). Shedding duration was longer among those younger than 12 months of age.

3.2. DEFINITIONS FOR SUBGROUPS AND COVARIATES

3.2.1. RSV SEASON DEFINITION

Unless specified otherwise, the RSV season is defined as the active surveillance period, from October 1st to May 1st, or longer if RSV was still circulating. Sites principal investigators monitored RSV detection in the hospital and/or local public health surveillance reports to assess if the surveillance period had to be extended. To ensure that the active surveillance period covered the entire season for each site and season, local public health reports will be checked and the reported detection period of RSV compared qualitatively with our season definition.

3.2.2. LENGTH OF STAY IN HOSPITAL

Length of stay in hospital will be calculated as the discharge date minus the admission date. Admission hours will not be available, and therefore not taken into account.

3.2.3. AGE AT ARTI

Age at ARTI in days will be defined as the date of onset minus date of birth for (MA-)ARTI. Where necessary, it will be divided by 7 to get age in weeks and by 365,25/12 to get age in months.

Age at hospitalization will be defined as the admission date minus the date of birth. Where necessary, it will be divided by 7 to get age in weeks and by 365,25/12 to get age in months.

3.2.4. BREASTFEEDING

Duration of any breastfeeding will be calculated by adding the number of weeks/months of exclusive and partial breastfeeding reported at one year of age.

Breastfeeding at the time of ARTI and time since breastfeeding will be defined using the duration of breastfeeding reported at one age and the age at ARTI occurrence.

3.2.5. DAYCARE/SCHOOL-AGED SIBLING

Having at least one sibling attending daycare, preschool or primary school will be defined with siblings ages and daycare or school attendance reported in the baseline questionnaire.

The number of siblings in age of attending daycare, preschool and primary school will be compared to the number of siblings attending daycare/(pre-)school, on the assumption that school attendance is more likely than preschool and daycare attendance. Age at admission to (pre-)school will be defined separately for each country based on local educational system and in consultation with the study team.

3.2.6. DAYCARE ATTENDANCE AT ARTI

Daycare attendance of participants during the first year of life will be defined as a (yes/no) binary variable based on parental report on the first year questionnaire. Daycare attendance at the time of ARTI will be defined as a binary (yes/no) variable, based on parental report on the first year questionnaire.

- A participant will be considered attending daycare at ARTI onset if age at onset is older than the age at which the child was admitted to daycare, in weeks or months.
- A participant will be considered as not attending daycare at ARTI onset if no daycare attendance was reported in the first year questionnaire, or if age at onset is equal or superior to age at admission to daycare, in weeks or months.

3.2.7. SMOKING IN THE HOUSE

The presence of someone regularly smoking in the participant house reported at baseline will be used to defined the exposure to avoid biased answers influenced by health outcomes of participants during the first year of life. Changes in exposure to smoking between birth and one year of age will be explored.

4. Analyses for primary outcomes

4.1. GENERAL DESCRIPTION

The incidence of RSV during the first year of life will be reported as the incidence rates of RSV-associated hospitalized ARTI and MA-ARTI per 1,000 person-months of follow-up during the RSV season. The attack rate of hospitalized ARTI- RSV during the first year of life will also be reported.

As cohort A participants were born throughout the entire year, they contributed to the active follow-up in different age group for varying length of time, depending on their age (0 to 11 months) at the beginning of the active surveillance period. Thus attack rates are not a valid measure for outcomes in the active cohort like MA-ARTI.

4.2. PRIMARY ENDPOINTS

4.2.1. INCIDENCE OF RSV-ASSOCIATED HOSPITALIZED ARTI IN COHORT P

RSV-associated hospitalized ARTI are defined as ARTI in cohort P meeting the definitions of hospitalized ARTI and confirmed RSV infection.

The **attack rate** of experiencing at least one RSV-associated hospitalized ARTI will be defined as the number of participants hospitalized at least once for RSV during their first year of life, divided by the number of participants included at baseline.

The **incidence rate** of RSV-associated hospitalized ARTI will be calculated by dividing the number of RSV-associated hospitalized ARTI by the number of child-month of follow-up.

4.2.2. INCIDENCE OF RSV-ASSOCIATED MA-ARTI IN COHORT A.

RSV-associated MA-ARTI are defined as ARTI in cohort A meeting the definitions of MA-ARTI and confirmed RSV infection.

The **incidence rate** of RSV-associated MA-ARTI will be calculated by dividing the number of RSV-associated MA-ARTI by the number of child-month of follow-up.

4.3. SUBGROUPS

To assess if incidence varies with **age**, the incidence of RSV-associated hospitalized ARTI and MA-ARTI will be compared between months of age if the number of events is sufficient and age groups otherwise (<3 months, 3-5 months, 6-11 month), using the definition for age at ARTI occurrence in section 3.2.3. .

To assess in incidence varies with **sex**, the incidence of RSV-associated hospitalized ARTI and MA-ARTI will be compared between male and female participants.

To assess if incidence varies between **countries**, the incidence of RSV-associated hospitalized ARTI and MA-ARTI will be compared between recruitment sites.

To assess if incidence varies with **month of birth**, the incidence of RSV-associated hospitalized ARTI and MA-ARTI will be compared between months of birth. Grouping will be considered if the number of observed events is too small.

To assess if the incidence in **active cohort** was similar to that in the passive cohort, the incidence of RSV-associated hospitalized ARTI will be compared between cohort P and cohort A.

To assess the variation of incidence by **RSV season**, the incidence of RSV-associated hospitalized ARTI and RSV-associated MA-ARTI will be estimated for each RSV season separately.

To assess if incidence varies with **birthweight**, the incidence of RSV-associated hospitalized ARTI and MA-ARTI will be compared between infants that weighted <2500g, 2500g - <5000g and >5000g at birth.

4.4. SENSITIVITY ANALYSIS

In the main analyses, the incidence of RSV-associated ARTI hospitalizations is based on RSV-confirmed admissions for ARTI that could be validated with medical records. Thus, it will likely be underestimated due to missed ARTI admissions or RSV testing. Similarly, as the incidence of RSV-associated MA-ARTI will rely on validated ARTI episodes for which information regarding medical attendance and RSV status is known, it will likely be underestimated due to missed ARTI episodes or unknown RSV status and medical attendance.

The sensitivity analysis will attempt to estimate RSV incidence underestimation and to assess the impact on of analytical choices such as excluding RSV tests results when samples were taken more than 10 days after onset of symptoms.

4.4.1. SENSITIVITY ANALYSIS FOR RSV-ASSOCIATED HOSPITALIZED ARTI

The admissions validated in medical records will be used as basis to estimate the number of relevant admissions at other hospitals than study sites, and the number of missed RSV cases among validated hospitalized ARTI during the RSV season. It will also estimate the impact of excluding hospitalizations with the same admission and discharge date from the incidence calculations.

As we expect hospitals to test for RSV only during the season, it will not be possible to estimate the number of sporadic RSV-associated hospitalizations occurring outside the RSV season.

The step-by-step description of the sensitivity analysis is available in Annex A: sensitivity analysis for the incidence of RSV-associated hospitalized ARTI.

4.4.2. SENSITIVITY ANALYSIS FOR RSV-ASSOCIATED MA-ARTI

The three main reasons why MA-ARTI episodes may have been missed are failure to get respiratory symptoms reported, and for reported ARTI episodes, unknown medical attendance and unknown RSV status.

The detection of ARTI episodes relies on weekly contact with caregivers or their spontaneous reporting of respiratory symptoms. Hospitalized ARTI found in medical records that occurred during the RSV season but were not captured by the active surveillance will be used to estimate the number of unreported ARTI. The number of weeks with successful / failed contacts with parents will also be explored for sites with this information available.

Medical attendance was collected in the questionnaire sent 15 days after symptoms onset and RSV test results availability is conditional on sampling during home visits. ARTI information with known medical attendance and RSV test results will be used to estimate the number of missing cases.

The sensitivity analysis will also estimate the effect of choosing to include RSV tests for which sampling was done within 10 days after onset by changing it to 7 or 14days. If some RSV cases were diagnosed by POCT only, this information will be used to assess the number of potentially missed cases in the sites not using POCT.

The step-by-step description of the sensitivity analysis is available in Annex B: Sensitivity analysis for the incidence of RSV-associated MA-ARTI.

5. Analyses for secondary outcomes

5.1. GENERAL DESCRIPTION

The incidence of confirmed RSV-associated ARTI in cohort A will be estimated in the same way as the incidence of MA-ARTI but episodes with unknown or no medical attendance reported will be included.

The incidence of all-cause ARTI will be calculated in the same manner as the incidence of RSV-confirmed ARTI for each level of care, but RSV-negative episodes and those without RSV test results will be included.

The proportion of ARTI attributable to RSV for each level of care will be derived from all-cause and RSV-associated ARTI incidence.

Other secondary outcomes include number of other pathogens detected among hospitalized ARTI, RSV-associated and all-cause mortality and the proportion of RSV-associated ARTI treated with antibiotics.

Multivariate analysis will be conducted to identify risk factors for RSV-associated hospitalizations and RSV-associated MA-ARTI among pre-identified variables.

5.2. SECONDARY ENDPOINTS

5.2.1. INCIDENCE OF CONFIRMED RSV-ASSOCIATED ARTI IN COHORT A

The **incidence rate** of RSV-associated ARTI will be calculated by dividing the number of RSV-associated ARTI by the number of child-month of follow-up.

5.2.2. INCIDENCE OF ALL-CAUSE ARTI

The **incidence of all-cause hospitalized ARTI** will be estimated among all participants in cohort P.

- The **attack rate** of experiencing at least one all-cause hospitalized ARTI will be calculated as the number of first hospitalized ARTI all year round divided by the number of participants included at baseline.
- The **incidence rate** of all-cause hospitalized ARTI will be calculated by dividing the number of hospitalized ARTI by the number of child-month of follow-up.

The **incidence rate of all-cause MA-ARTI** will be estimated among participants in cohort A by dividing the number of MA-ARTI by the number of child-month of follow-up.

The **incidence rate of all-cause ARTI** will be estimated among participants in cohort A by dividing the number of ARTI by the number of child-month of follow-up.

5.2.3. PROPORTION OF ARTI ATTRIBUTABLE TO RSV

The proportion of RSV-associated ARTI for each level of care will be estimated among ARTI that were tested for RSV.

The **proportion of RSV-associated hospitalized ARTI** among all-cause hospitalized ARTI will be estimated in cohort P. It will be calculated as the number of RSV-associated hospitalized ARTI divided by the number of all-cause hospitalized ARTI.

The **proportion of RSV-associated MA-ARTI** among all-cause MA-ARTI will be estimated in cohort A. It will be calculated as the number of RSV-associated MA-ARTI divided by the number of all-cause MA-ARTI.

The **proportion of RSV-associated ARTI** among all-cause ARTI will be estimated in cohort A. It will be calculated as the number of RSV-associated ARTI divided by the number of all-cause ARTI.

5.2.4. NUMBER OF OTHER PATHOGENS DETECTED AMONG HOSPITALIZED ARTI

This outcome depends on the availability of results for other testing done during hospitalization. The decision to test for other respiratory pathogens was at the discretion of the treating clinician, thus the total number of inpatients tested for a given pathogen is unknown. The number of hospitalized ARTI that tested positive for other respiratory pathogen than RSV will be reported in cohort P.

5.2.5. RSV-ASSOCIATED AND ALL-CAUSE MORTALITY

Mortality during the first year of life will be reported in cohort P. All-cause mortality will include all deaths that occurred in the cohort. RSV-associated mortality will include deaths that occurred during hospitalization for a RSV-associated ARTI or within 30 days after discharge of a hospitalization for a RSV-associated ARTI.

As the number of deaths expected in a cohort of full-term healthy infant is small, the number of deaths observed in the cohort and their eventual connection to a (RSV-associated) ARTI episode will be described. Mortality rates will not be presented.

5.2.6. PROPORTION OF RSV-ASSOCIATED ARTI TREATED WITH ANTIBIOTICS

The proportion of RSV-associated hospitalized ARTI treated with antibiotics in cohort P will be calculated as the number of RSV-associated hospitalized ARTI treated with antibiotics according to the hospitalization CRF, divided by number of hospitalized ARTI for which this information is available.

Similarly, the proportion of RSV-associated MA-ARTI treated with antibiotics will be estimated in cohort A. It will be calculated as the number of RSV-associated MA-ARTI for which parents reported treatment with antibiotics in the end of the diary questionnaire divided by number of MA-ARTI for which this information is available.

5.2.7. RISK-FACTORS FOR RSV

Risk factors for RSV will be identified among a list a pre-identified candidate variables based on literature and expert opinion using **multivariate analysis**.

The main analysis will focus on risk factors for at least one RSV-associated hospitalizations (yes/no) using logistic regression. This model was chosen for simplicity and because it was most often used in previous studies, increasing comparability.

As logistic regression does not account for varying follow-up times between participants, it can not be used to identify risk factors for RSV-associated ARTI in cohort A. Risk factors for RSV-associated MA-ARTI during the weeks of RSV season in the first year of life will be analysed using a Cox regression model (1; 2).

Risk factors for being hospitalized at least once for RSV infection during the first year of life.

To identify important risk factors for being hospitalized at least once for RSV infection during the first year of life in cohort P, a **multivariate logistic regression** will be performed. The outcome binary variable will be defined as hospitalized at least once / never hospitalized for RSV.

The final model will be selected with a backward selection method. If there are too many risk factors compared to the number of events, further selection of risk factors will be done before modelling, including the strongest risk factors based on literature. All risk factors candidates will be added to the initial model and removed one by one starting with the

least significant. Before validating the final model, all dropped risk factor candidates will be added to the model again to see if it improves the model.

The following variables will be considered as **candidate risk factors** for RSV: age, month of birth, site, sex, multiple birth, birth weight (continuous), low birthweight, delivery type, hospitalization at birth, respiratory support at birth, antibiotics at birth, vaccination during pregnancy, smoking during pregnancy, smoker in household, smoking in the house, number of caregiver, more than five persons living in the house at birth, breastfeeding, daycare attendance, sibling attending daycare, sibling attending primary school, family history of atopy, maternal history of atopy, pets in household, age of the mother at birth, mother highest education level, father highest education level, mother ethnicity, father ethnicity.

Risk factors for RSV associated MA-ARTI during the RSV season in the first year of life.

Risk factors for RSV-associated MA-ARTI during the weeks of active follow-up in the first year of life will be analyzed with a time-to-event analysis using a **Cox regression model**. The outcome of interest will be the occurrence of a RSV-positive MA-ARTI and the weeks of active follow-up during the RSV season in their first year of life will be used as the underlying time variable. Risk factors will be selected with a backward selection method, in a similar manner than for the multivariate logistic regression. Seasonality will be accounted for by integrating a term for the intensity of RSV circulation in the model.

Candidate risk factors will be those considered for the logistic regression except for the ones that can be introduced as time dependent variables including age, and if data quality allows it, daycare attendance and breastfeeding. Other candidate risk factors will be fixed. The model will control for seasonality by taking into account the variation of intensity of RSV circulation throughout the surveillance period.

6. Statistical analysis

Drafts of illustrations are available in Annex C: Outputs outline

6.1. HANDLING OF MISSING DATA

Multiple imputation of missing data will be considered if reliable assumptions can be made on the pattern of missing data regarding RSV testing, medical attendance and risk factors used in the analysis.

However, variables are expected to be missing in groups depending on which questionnaire was not completed, rendering making assumptions difficult. In addition, as we expect the odds of testing positive to RSV to vary with multiple variables and between sites, the assumptions would likely rely on too few participants. This is also expected for medical attendance.

If multiple imputation is not possible, the main analysis will include all available non-missing cases for each outcome. The potential impact of missing values on the primary outcome estimates will be assessed in the sensitivity analysis.

6.2. STATISTICAL TESTS AND CI CALCULATIONS

Proportions will be compared using the Chi-Square test, or Fisher's exact test if any cell of the contingency table show fewer than ten observations. Continuous variables will be checked for normality. If normally distributed, an independent T-test will be performed for comparison. If data is not normally distributed, if possible a transformation, or a non-parametric Mann-Whitney U test will be used. Incidence rates with 95% confidence intervals will be estimated using binomial Clopper-Pearson exact method.

6.3. SOFTWARE

All analyses will be performed in R version 3.5.1.

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1. *High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis.* **Thorbum, K, et al., et al.** 7, s.l. : Thorax, 2006, Vol. 61. doi:10.1136/thx.2005.048397.

2. *Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection.* **Hall, C.B, et al., et al.** 2, s.l. : J Pediatr., 1988, Vol. 113.

3. *Antibody response to respiratory syncytial virus infection in children <18 months old.* **Esposito, S, et al., et al.** 2016, Human Vaccines and Immunotherapeutics, pp. 12(7), 1700–1706.

4. *Respiratory syncytial virus shedding by children hospitalized with lower respiratory tract infection.* **Takeyama, A, et al., et al.** 2016, Journal of Medical Virology, pp. 88(6), 938–946.

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6. *Risk Factors for Hospitalization for Respiratory Syncytial Virus Infection: A Population-based Cohort Study of Danish Children.* **Haerskjold , A, et al., et al.** 2016, Pediatr Infect Dis J., pp. 35(1):61-5.

Annex A: sensitivity analysis for RSV-associated hospitalized ARTI

The sensitivity analysis will account for missed cases by estimating the number of relevant admissions that occurred at other hospitals than study sites, and the number of missed RSV cases among hospitalized ARTI during the RSV season. It also estimates the impact of excluding hospitalizations with the same admission and discharge date from the incidence estimate.

Cells with a grey background are known quantities which will be used to estimate the unknown quantities in the white background cells. If the number of observations is sufficient, these steps will be done for each site and age groups separately.

1) Estimate the number of admissions at other hospitals than study site among participants with no 1st year questionnaire, assuming a similar proportion than for participants who completed the questionnaire.

	1st year questionnaire	**No 1st year questionnaire**
Admissions	N	X + Y1
At study sites	A (a%)	X
At other hospitals	B (b%)	– Y1 = X x B /A

2) Estimate the number of admissions for ARTI among admissions at other hospitals than study sites (i.e. not validated by medical records), by multiplying with the proportions of admissions to study sites reported by parents in the 1st year questionnaire that were actually due to an ARTI.

	1st year questionnaire		**No 1st year questionnaire**
	Admissions to study sites	Admissions to other hospitals	Admissions to other hospitals
Admissions	N1 *(reported by parents)*	N2 *(reported by parents)*	N3 *(Y in step 1)*
For ARTI	A (a%)	Y2=N2 x a%	Y3= N3 x a%
For other reasons	B (b%)		

3) Estimate the number of admissions for ARTI to other hospitals than study sites that occurred during the RSV season, applying the proportion of admissions that occurred during the RSV season among known hospitalizations to study sites.

	At study sites			**At other hospitals**	
	1stYQ*	**No 1stYQ***	**Total**	**1stYQ***	**No 1stYQ***
Admissions for ARTI	N1 *(parents + med records)*	N2 *(med records)*	N1 + N2	Y2 *(see step 2)*	Y3 *(see step 2)*
During RSV season	A	C	A + C (ac%)	Y4 = Y2 x ac%	Y5 = N4 x ac%
Outside RSV season	B	D	B + D (bd%)		
1stYQ = 1st Year questionnaire					

4) Estimate the number of RSV-positive cases among admissions for ARTI that occurred during the season with unknown RSV status, applying the positivity rates for RSV among validated admissions with tests results available.

Admissions for ARTI that occurred during the season with unknown RSV status include: admissions to other hospitals than study sites and validated hospitalizations with no RSV test results available (sum(Y6:Y9) in table below).

	to study sites					**to other hospitals**	
	Tested for RSV			**RSV status unknown**		**RSV status unknown**	
	1stYQ*	No 1stYQ*	Total	1stYQ*	No 1stYQ*	1stYQ*	No 1stYQ*
Admissions for ARTI during the RSV season	N1 *(parents + med records)*	N2 *(med records)*	N1 + N2	N3 *(parents + med records)*	N4 *(med records)*	Y4 *(see 3)*	Y5 *(see step 3)*
RSV-positive	A	C	A + C (ac%)	Y6 = N3 x ac%	Y 7 = N4 x ac%	Y8 = N5 x ac%	Y9 = N6 x ac%
RSV-negative	B	D	B + D (bd%)				
1stYQ = 1st Year questionnaire							

5) Do not exclude hospitalizations with the same admission and discharge date.

Annex B: Sensitivity analysis for RSV-associated MA-ARTI

The sensitivity analysis account for potentially missed cases by quantifying underreporting of ARTI episodes, and by estimating the number of missed RSV cases missed medical attendance among known ARTI. It also estimates the impact of including only cases sampled within 10 days after onset and potentially missed cases by not using POCT at all sites.

Cells with a grey background are known quantities which will be used to estimate the unknown quantities in the white background cells. If the number of observations is sufficient, these steps will be done for each site and age groups separately.

1) Estimate the number of missed ARTI episodes from the proportion of hospitalized ARTI found in medical records that are not linked to a ARTI episode reported to the active surveillance.

	Cohort A	
	Hospitalized ARTI	**All ARTI**
N episodes during active surveillance period	N0	X/a%
Reported by parents at weekly contact	A (a%) *(active surveillance)*	X *(active surveillance)*
Not reported	B (b%)*(med records)*	N0 - X

2) Estimate the number of MA-ARTI and RSV positive among ARTI episodes with either information missing, by using complete cases.

Home visits could have been missed more often at special time of the year (e.g. Christmas or school vacations) that do not necessarily overlap with RSV circulation. Thus, this part of the sensitivity analysis will be stratified between weeks of intense RSV circulation and other weeks of the active surveillance period, if the number of observations allow it. Intense circulation will be defined for each site based on the weekly number of RSV-confirmed cases.

	ARTI episodes in cohort A				
	Known RSV status			**Unknown RSV status**	
	All	**RSV positive**	**RSV negative**	**All unknown**	**Missed RSV positive**
Known medical attendance	N	M1	M2	Y	
MA-ARTI	MA	MA1	MA2	YA	YA x (MA1 / MA)
Non MA-ARTI	MB	MB1	MB2	YB	YA x (MB1 / MB)
Unknown medical attendance	X	X1	X2	Z	Z x (M1 / N)
Missed MA-ARTI		X1 x (MA1 / M1)	X2 x (MA2 / M2)	Z x (MA / N)	

3) To estimate the impact of varying the delay between onset and sampling deemed acceptable for the validity of RSV testing, repeat step 3 for two other scenarios. The first one will consider RSV test results as unknown if sampling was not done within 7 days after onset, and the second one will include samples done within 14 days after onset.

4) Estimate the number of RSV cases missed by not using POCT testing at all sites, using the number of cases diagnosed by POCT testing only.

	Sites using POCT	**Sites not using POCT**
N samples positive to RSV	**N**	**X + Y**
POCT positive only	A (a %)	X = Y x (a% / b%)
PCR positive (PCR only or PCR and POCT)	B (b%)	Y

Annex C: Outputs outline

Figure 1. Flow chart of participants in RESCEU birth cohort study, included in the passive cohort (Cohort P) and the nested active cohort (Cohort A).

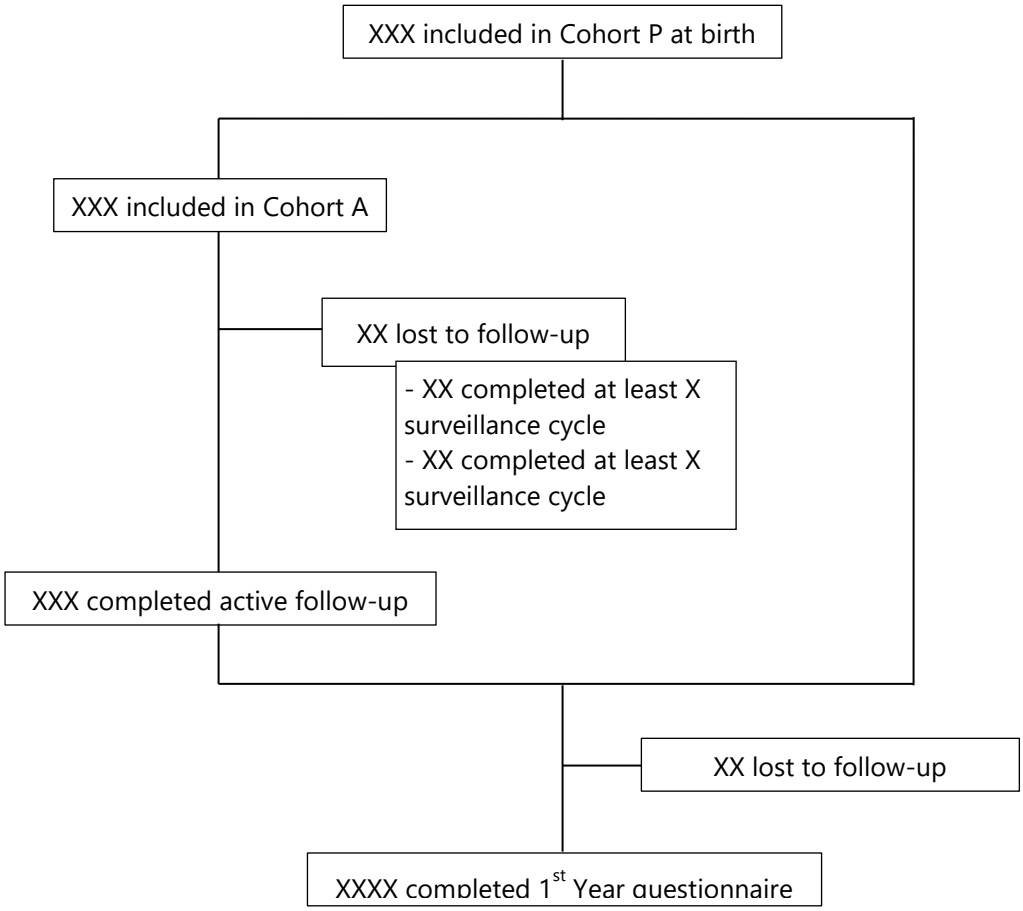

Figure 2. Number of all-cause and RSV-associated ARTI by months (A) all ARTI in cohort A (B) MA-ARTI in cohort A (C) hospitalized ARTI in cohort P..

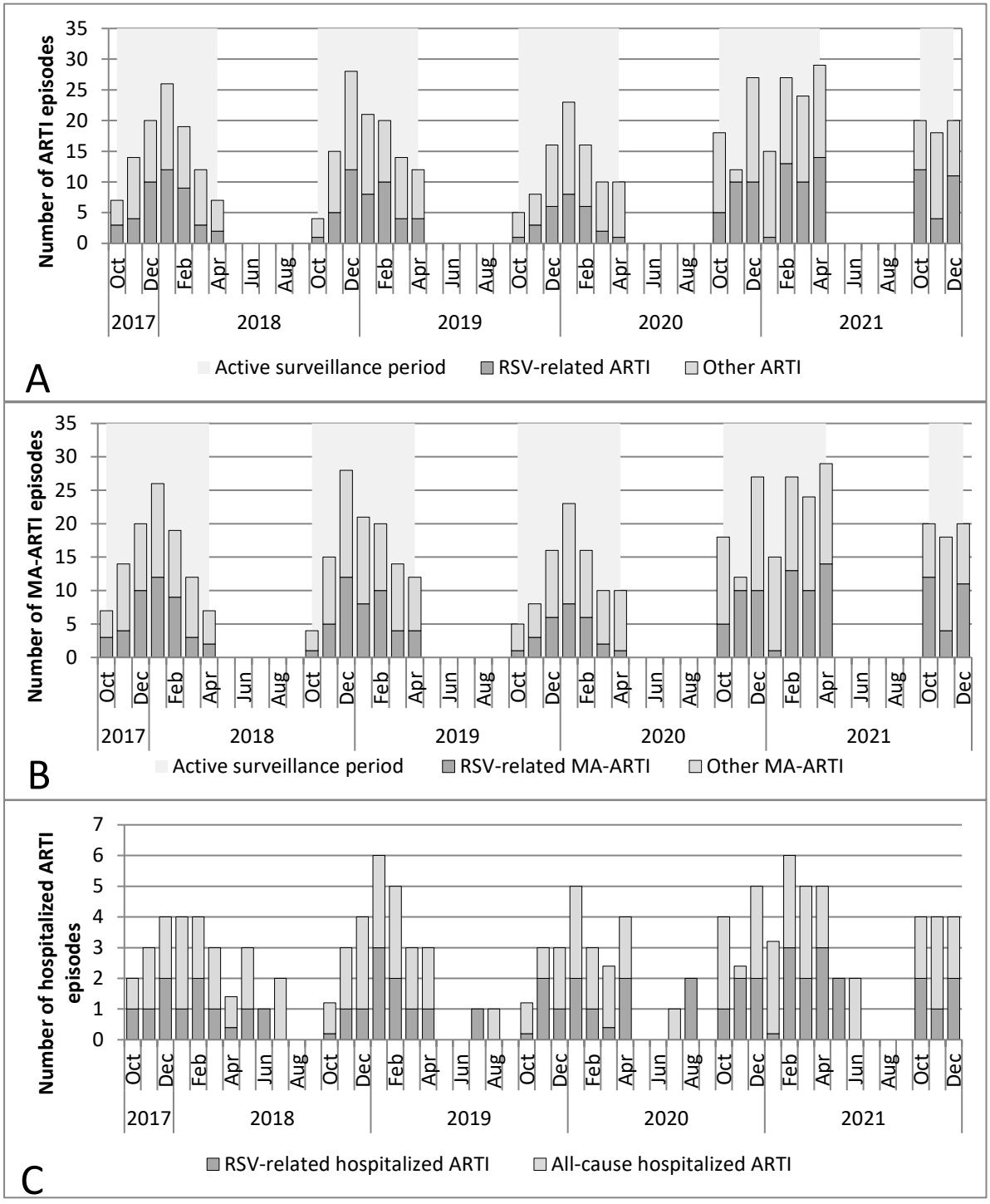

Table 1. Baseline characteristics of participants by recruitment sites.

	Cohort P						Nested cohort A					
	ED	**OX**	**SE**	**TU**	**UU**	**All sites**	**ED**	**OX**	**SE**	**TU**	**A**	**All sites**
Total number of participants	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**	**N=**
Pregnancy												
Vaccination (n (%))												
Influenza												
Pertussis												
Smoking (n (%))												
Birth												
Month of birth (n (%))												
Oct - Dec												
Jan - Mar												
Apr - Jun												
Jul - Sept												
Male sex (n (%))												
Multiple birth (n (%))												
Gestational age (mean (sd))												
Birth weight <2500g (n (%))												
Respiratory support required (n (%))												
Antibiotics <72h post-partum												
Family												
Number of siblings (mean (sd))												
<6 years of age												
6-12 years of age												
13 years of age or older												
At least one sibling attending…												
daycare												
primary school												
Smokers in the family												
Mother												
Father												
Other family member												
Smoking in the house												
Pets												
Family history of allergy												
Asthma												
Other												
Sibling(s) uses or used respiratory medicine												
Ethnic origin of the mother												
Northwest Europe												
Southern Europe												
Other												
Ethnic origin of the father												
Northwest Europe												
Southern Europe												
Other												
Highest level of education of the mother												
Secondary school / vocational school												
University of applied sciences / sciences												
Other												
Highest level of education of the father												
Secondary school / vocational school												
University of applied sciences / sciences												
Other												
Employement of the mother before birth												
Full-time												
Part-time												
Other												
Employement of the father before birth												
Full-time												
Part-time												
Other												

Figure 3. Incidence of RSV-hospitalizations in cohort P and RSV-associated MA-ARTI in cohort A, per 1,000 child-month by in months.

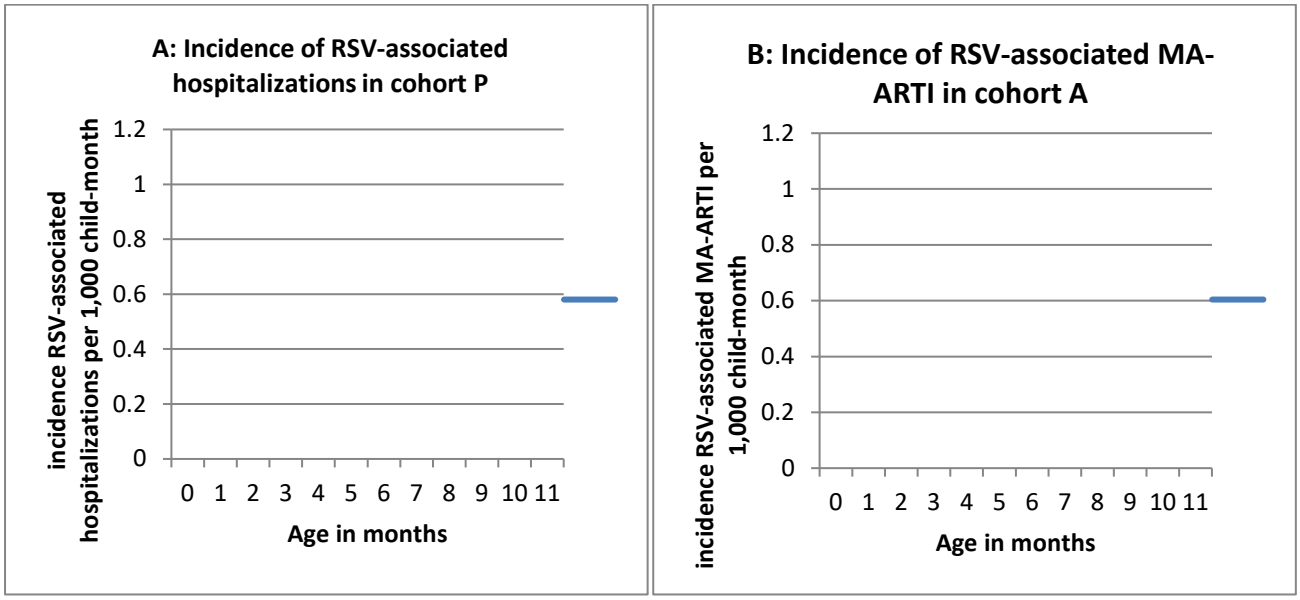

Table 2: Incidence rates of RSV-associated ARTI, MA-ARTI, hospitalized ARTI, by age group, according to the season, recruitment site, cohort, and months of birth

	Incidence rate of RSV-associated ARTI per 1,000 infant-months											
	RSV-associated hospitalized ARTI				RSV-associated MA-ARTI				RSV-associated ARTI			
	< 3 months	3-5 months	6-11 months	<12 months	< 3 months	3-5 months	6-11 months	<12 months	< 3 months	3-5 months	6-11 months	<12 months
Overall RSV incidence												
Season												
2017-2018												
2018-2019												
2019-2020												
2020-2021												
Site												
Scotland												
England												
Spain												
Finland												
Netherlands												
Cohort												
cohort P												
cohort A												
Sex												
Male												
Female												
Month of birth (by month or groups)												
January												
February												
March												
April												
May												
June												
July												
August												
September												
October												
November												
December												
Birthweight (g)												
<2500												
2500- <5000g												
≥5000g												

Table 3: Number and incidence rates of all-cause ARTI, MA-ARTI, hospitalized ARTI, by age group and number and proportion of RSV-confirmed cases among all-cause ARTI, MA-ARTI, hospitalized ARTI by season, site and months of birth.

	Incidence rate of all-cause ARTI per 1,000 infant-months											
	hospitalized ARTI				MA-ARTI				ARTI			
	< 3 months	3-5 months	6-11 months	<12 months	< 3 months	3-5 months	6-11 months	<12 months	< 3 months	3-5 months	6-11 months	<12 months
All-cause incidence												
N all-cause												
N RSV-associated (% among all-cause)												
Season												
2017-2018												
2018-2019												
2019-2020												
2020-2021												
Site												
Scotland												
England												
Spain												
Finland												
Netherlands												
Sex												
Male												
Female												
Months of birth (by month or groups)												
January												
February												
March												
April												
May												
June												
July												
August												
September												
October												
November												
December												
Birthweight (g)												
<2500												
2500- <5000g												

≥5000g

Table 4: Clinical characteristics of hospitalized ARTI in cohort P during the first year of life, according to RSV status.

	RSV-positive				**RSV-negative**			
	<3 months	**3-5 months**	**6-11 months**	**< 12 months**	**<3 months**	**3-5 months**	**6-11 months**	**< 12 months**
Total number of hospitalizations	N=	N=	N=	N=	N=	N=	N=	N=
Length of stay (median [Q1-Q3])								
Final diagnosis (n (%))								
Bronchiolitis								
URTI								
Pneumonia								
Croup								
Wheeze								
Other								
Total ReSVinet score (mean (stdev))								
Respiratory support (n (%))								
Invasive								
CPAP / BiPAP								
High flow nasal canula								
Low flow nasal canula								
O2 (>21%)								
Admission to the ICU (n (%))								
Length of stay (median [Q1-Q3])								
Any additional viral testing (n)*								
Influenza A (n)								
Influenza B (n)								
Metapneumovirus (n)								
Parainfluenza (n)								
…								
Any Bacterial testing(n)*								
…								

* Number of cases tested for each virus unknown. Detected viruses are non-mutually exclusive.

* Number of cases tested for each bacteria unknown. Detected viruses are non-mutually exclusive.

Table 5. Risk factors for RSV-associated hospitalizations during the first year of life in cohort P.

	Hospitalized ARTI			
	Hospitalized at least once for RSV	**Never hospitalized for RSV**	**Univariate**	**Multivariate**
	n (%)	**n (%)**	**OR (95% CI)**	**OR (95% CI)**
Month of birth				
Season (1/2/3/4)				
Site (1/2/3/4/5)				
Male sex				
Multiple birth				
Low birth weight <2500 g				
Gestational age (weeks)				
Delivery type vaginal delivery/CS?				
Hospitalization at birth yes/no				
Respiratory support at birth yes/no				
Antibiotics at birth				
Vaccination during pregnancy				
Pertussis				
Influenza				
Smoking during pregnancy				
Smokers in household				
Smoking in house				
Number of caregivers				
>5 persons in household				
Breastfeeding yes/no				
Daycare attendance				
Sibling attending daycare				
Sibling attending school				
Family history of allergy (any)				
Asthma				
Eczema				
Hay fever / dust mite				
Other				
Pets in household yes/no				
Mother highest education high/lower				
Father highest education				
Mother ethnicity				
Father ethnicity				
Personal history of any MA-ARTI yes/no				