Epidemiological and clinical characterization of respiratory syncytial virus subtype-A and -B in infants with bronchiolitis

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Transparency Declaration

Nothing to declare

The main cause of bronchiolitis: respiratory syncytial virus

Bronchiolitis caused by RSV in 60-80% of cases

Risk factors for severe bronchiolitis: very young age, premature birth, underlying chronic diseases but…

....most hospitalized infants are previously healthy

Viral determinants of clinical severity: viral load??, coinfecting agents?, infecting RSV subtype (-A or -B)?

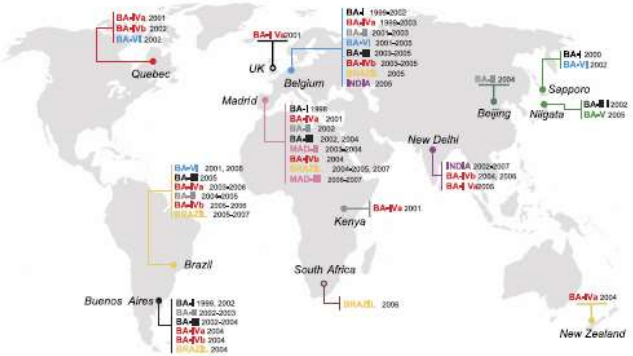
RSV-A has a more severe clinical course
(Walsh, 1997; Imaz, 2000; Gilca, 2006)
No differences in severity between -A and -B
(Fodha, 2007; Hirsh, 2014, Pengwei 2016)

RSV-A and -B different genotypes
may determine a different clinical course!!!

RSV genetic variability

RSV-A genotypes: GA1-GA7, SAA1, NA1–2, ON1–2
RSV-B genotypes: GB1–4, BA1–10, SAB1–4, URU1–2
Short-term genotype-specific immunity drive RSV interchanging
A new subtype may replace dominant strains for its antigenic diversity

RSV-B genotype BA since 1999



FROM: Ten Years of Global Evolution of the Human Respiratory Syncytial Virus BA Genotype with a 60-Nucleotide Duplication in the G Protein Gene
Trento A et al. J. Virol. 2010; 84, 15

RSV-A genotype ON1 since 2010

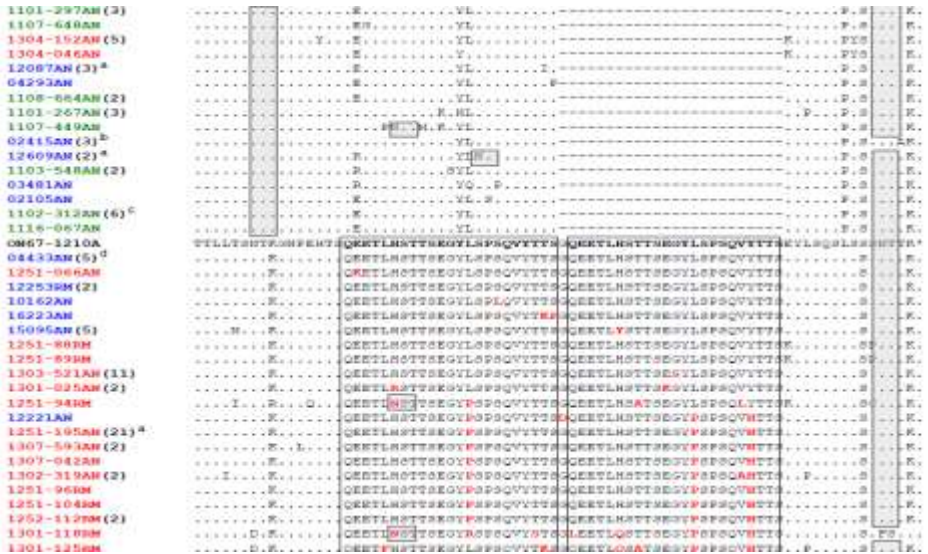
FROM: Genetic diversity and evolutionary insights of respiratory syncytial virus A ON1 genotype: global and local transmission dynamics
Duvvuri V Scientific Reports 2015; 5, 14268

Aims of the research and study group

- To compare clinical presentation and disease severity between RSV-A and -B in bronchiolitis
- To assess the impact of RSV genotype, in particular the novel RSV-A ON1

- From 2008/09 to 2015/16, full-term infants < 1 year, with no chronic disease, hospitalized for bronchiolitis consecutively enrolled
- Nasal washings tested for 14 respiratory viruses and RSV single infection selected
- Genotyping and phylogenetic analysis of the G gene
- Demographic and clinical data analyzed

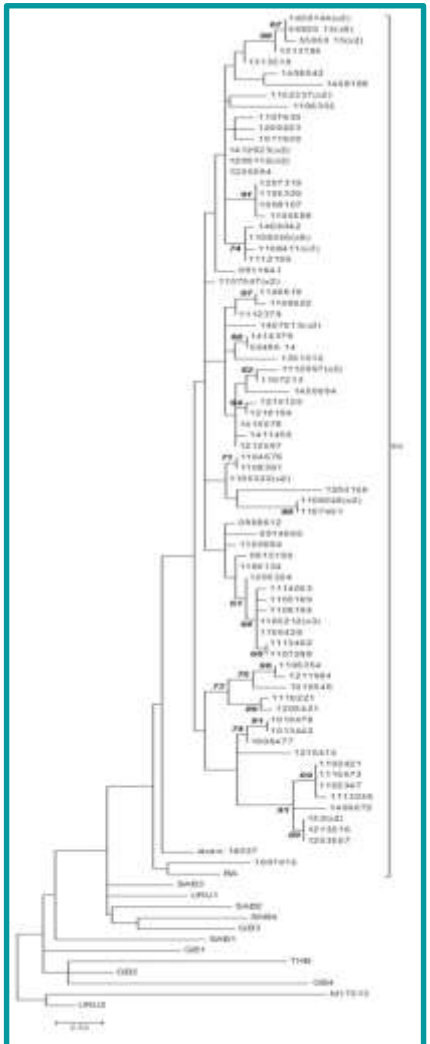
RSV-A phylogenetic analysis

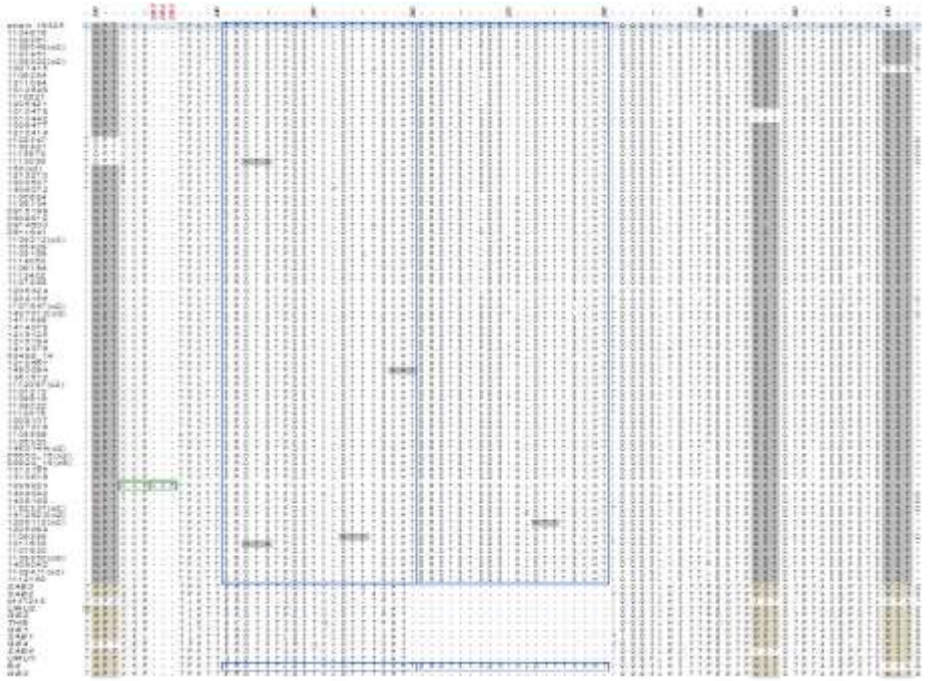


24-amino acid insertion in the G glycoprotein

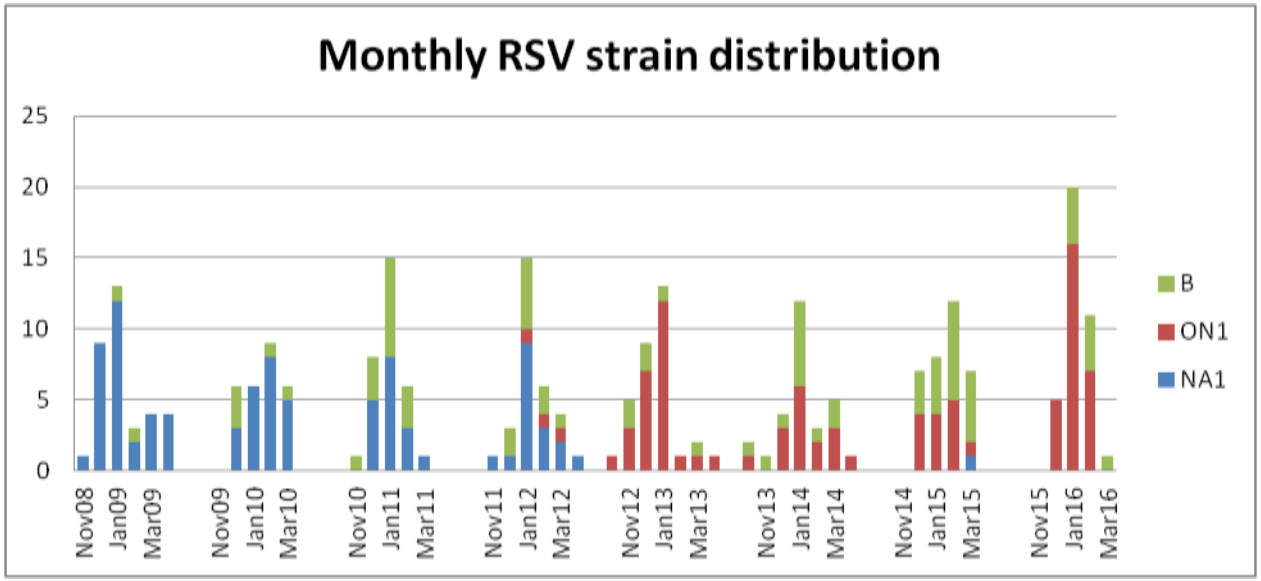
From: Rapid spread of the novel respiratory syncytial A ON1 genotype, central Italy, 2011-2013 Pierangeli et al Eurosurveillance 2014

RSV-B phylogenetic analysis





20-amino acid insertion in the G glycoprotein



RSV-A dominated in six seasons and RSV-B in two (2010/11 and 2014/15)

NA1 was the only RSV-A genotype in the first 3 seasons

ON1 appeared in early 2012 (20% of RSV-A cases) and then replaced NA1

Patient data comparison between RSV-A and -B

Patients (N=202)	RSV A (N=155)	RSV B (N=47)	p-value
Female	73/155 (47.0)	18/47 (41.1)	0.619
Age at hospital admission in months (Median)	1.90	2.47	**0.001**
Weight at hospital admission in kg	4.80	5.70	**<0.001**
Days in hospital	5.8	5.64	0.731
Fever (Temp > 37.5 ^{0}C)	56/155 (37.8)	26/47 (58.9)	**0.027**
	55 (15.5)	12/47 (25.5)	0.152
	55 (52.9)	26/47 (55.3)	
	55 (31.6)	2/47 (4.2)	
> 95%	90/155 (58.1)	27/47 (57.4)	0.320
95-90%	48/155 (30.9)	18/47 (38.3)	
< 90%	17/155 (10.9)	2/47 (4.3)	
Severity Score *			
Score 0-4 (%)	101/155 (65.2)	37/47 (78.7)	0.107
Score 5-8 (%)	54/155 (34.8)	15/47 (21.3)	

*Severity score based on:
respiratory rate (<45/min = 0, 45–60/min = 1, >60/min = 2), arterial oxygen saturation (>95% = 0, 95–90% = 1, <90% = 2), retractions (none = 0, present = 1, present+nasal flare = 2), and ability to feed (normal = 0, reduced = 1, intravenous = 2) then stratified in score values 0 to 4 and 5 to 8.

Patients (N=202)	NA1 (N=106)	ON1 (N=49)	RSV B (N=47)	p-value
Female	51/106 (47.0)	22/49 (44.9)	18/47 (41.1)	0.527
Age at admission in months median (range)	1.91 (0.23-7.40)	1.80 (0.53-7.50)	2.47 (1.06-8.72)	**0.005**
Weight at admission in kg median (range)	4.80 (2.90-8.66)	4.79 (3.50-8.58)	5.70 (3.48-10.00)	**0.002**
Weight at birth in kg	3.21 (2.10-4.50)	3.31 (2.45-4.20)	3.30 (2.40-4.10)	0.300
Days in hospital median (range)	5 (1-27)	5 (3-16)	6 5 (2-12)	0.653
Fever (Temp > 37.5 ^{0}C)	41/106 (38.7)	15/49 (30.6)	26/47 (58.9)	**0.040**
Antibiotic treatment	87/106 (82.1)	35/49 (71.1)	33/47 (70.2)	0.167
Maternal smoking	11/106 (10.6)	9/49 (18.4)	12/47 (25.5)	**0.049**
Respiratory rate, breaths per minute				
< 45/m	15/106 (14.1)	9/49 (18.4)	12/47 (25.5)	**0.037**
45-60/m	51/106 (48.1)	31/49 (63.3)	26/47 (55.3)	
>60/m	40/106 (37.7)	9/49 (18.4)	9/47 (19.12)	
Oxygen saturation in room air				
> 95%	62/106 (58.5)	28/49 (57.1)	27/47 (57.4)	**0.031**
95-90%	28/106 (26.4)	20/49 (40.8)	18/47 (38.3)	
< 90%	16/106 (15.1)	1/49 (2.1)	2/47 (4.3)	
Retractions				
no	13/106 (12.2)	4/49 (8.1)	13/47 (27.7)	**<0.0001**
yes	66/106 (62.3)	43/49 (87.8)	34/47 (72.3)	
yes+nasal flare	27/106 (25.5)	2/49 (40.1)	0/47 (0)	
Severity Score				
Score 0-4 (%)	59/106 (55.7)	42/49 (85.7)	37/47 (78.7)	**<0.0001**
Score 5-8 (%)	47/106 (44.3)	7/49 (14.3)	15/47 (21.3)	
White blood cells (n/mm^3): median (range)	10549 (4180-25700)	11480 (6020-29300)	10860 (4110-29250)	0.216
Lymphocytes (n/mm^3): median (range)	4310 (1800–11100)	4537 (1780–12010)	4520 (1570–11740)	0.407
Neutrophils (n/mm3): median (range)	3514 (510–15108)	3910 (1270–13030)	4765 (990–18810)	0.251
Eosinophils (n/mm^3): median (range)	70 (4–638)	120 (10–620)	90 (5–1030)	0.366

Multinomial logistic regression analysis

	ON1 vs NA1		RSV-B vs NA1	
	Unadjusted RR	Adjusted RR	Unadjusted RR	Adjusted RR
Respiratory rate (FR) breaths per minute < 45/m=0 45-60=1 >60=2	FR=1 vs FR=0 1.020 (0.455-2.289) FR=2 vs FR=0 0.321 (0.125- 0.667)	FR=1 vs FR=0 0.886 (0.385-2.036) FR=2 vs FR=0 **0.282** (0.105-0.757)	FR=1 vs FR=0 0.628 (0.277- 1.428) FR=2 vs FR=0 0.254 (0.10- 0.665)	FR=1 vs FR=0 0.638 (0.265-1.534) FR=2 vs FR=0 **0.304** (0.109- 0.858)
SAO_2 > 95%=0 95-90%=1 <90%=2	SAO_2=1 vs SAO_2=0 1.515 (0.826-2.280) SAO_2=2 vs SAO_2=0 0.079 (0.010-0.631)	SAO_2=1 vs SAO_2=0 1.44 (0.776-2.674) SAO_2=2 vs SAO_2=0 **0.087** (0.010-0.712)	SAO_2=1 vs SAO_2=0 1.386(0.713- 2.694) SAO_2=2 vs SAO_2=0 0.202 (0.043-0.938)	SAO_2=1 vs SAO_2=0 1.434(0.05- 2.871) SAO_2=2 vs SAO_2=0 **0.264** (0.064-1.312)
Retractions no=0 yes=1 yes+nasal flare=2	Retr=1 vs Retr=0 1.449 (0.578-3.631) Retr=2 vs Retr=0 0.068 (0.013- 0.362)	Retr=1 vs Retr=0 1.219 (0.473-3.138) Retr=2 vs Retr=0 **0.061** (0.011- 0.339)	Retr=1 vs Retr=0 0,524 (0.226-1.214) Retr=2 vs Retr=0 0.061 (0.015- 0.248)	Retr=1 vs Retr=0 0.512 (0.208-1.260) Retr=2 vs Retr=0 **0.073** (0.017- 0.315)
Fever (Temp > 37.5 ^{0}C)	Yes vs No 1.059 (0.596- 1.885)	Yes vs No 1.086 (0.582- 1.950)	Yes vs No 2.053 (1.088- 3.873)	Yes vs No **1.823** (0.641- 3.603)

Conclusions

- RSV clinical severity depends on the infecting strain
- At hospital admission a distinctive characteristic of RSV-B infected infants may be presentation with fever
- Despite its enhanced biological fitness, ON1 showed a milder clinical course in bronchiolitis
- RSV surveillance should be set in Europe to define viral determinants of severity, in view of the upcoming vaccine formulation