אינדיקציות לפאליביזומאב, מהי מחלת ריאות כרונית?

פרופ' אביב גולדברט

רופא ריאות ילדים
מנהל מחלקת ילדים ב'
ביה"ח האוניברסיטאי סורוקה

גליליון 16 למרץ 2018

גילוי נאות

- ✓ הרצאות בשכר– MSD, טבע, אסטרה-זנקה, סנופי-אבנטיס, ABBVIE.
- ✓ מחקרים פעילים בתמיכה- MSD, איתמר, טבע,AIT
- ✓ Ark Biosciences, ABLINX.

נושאי השיחה

- הצגת מקרה.
- אוכלוסיות מיוחדות בדגש על מחלות ריאה כרוניות שיכולות (ולא נהנות)ממתן palivizumab
- לאיפה הולכים מכאן ? (הרופאים שמטפלים באוכלוסיות אלו, הרחבת/חידוד האינדיקציות)

Case Presentation

E.M. an 10 m.o. girl, under close f/u of a ped. Pulmonologist

Normal birth and delivery, non related parents.

First hospitalization at 4m with RSV bronchiolitis for 7 days. No further treatment or f/u

Second admission at 7 m with Adeno virus pneumonia

Since then on oxygen. Poor weight gain. Slow motor development

Currently diagnosed as having **Bronchiolitis Obliternas**

Case Presentation

Extensive w/u that included whole exome, consults with specialists in US and Europe and included immunoloogy battery , bronchoscopy plus BAL for several labs, ruled out any immunologic deficiency, Interstitial Lung Disease, CF, genetic disorders.

Case Presentation

.

The child improved after Systemic steroid pulse therapy

Currently receiving Azythromycin (3/week), Inh. Steroids (daily), oxygen at sleep (avg. oxygen sat. during sleep 86%)

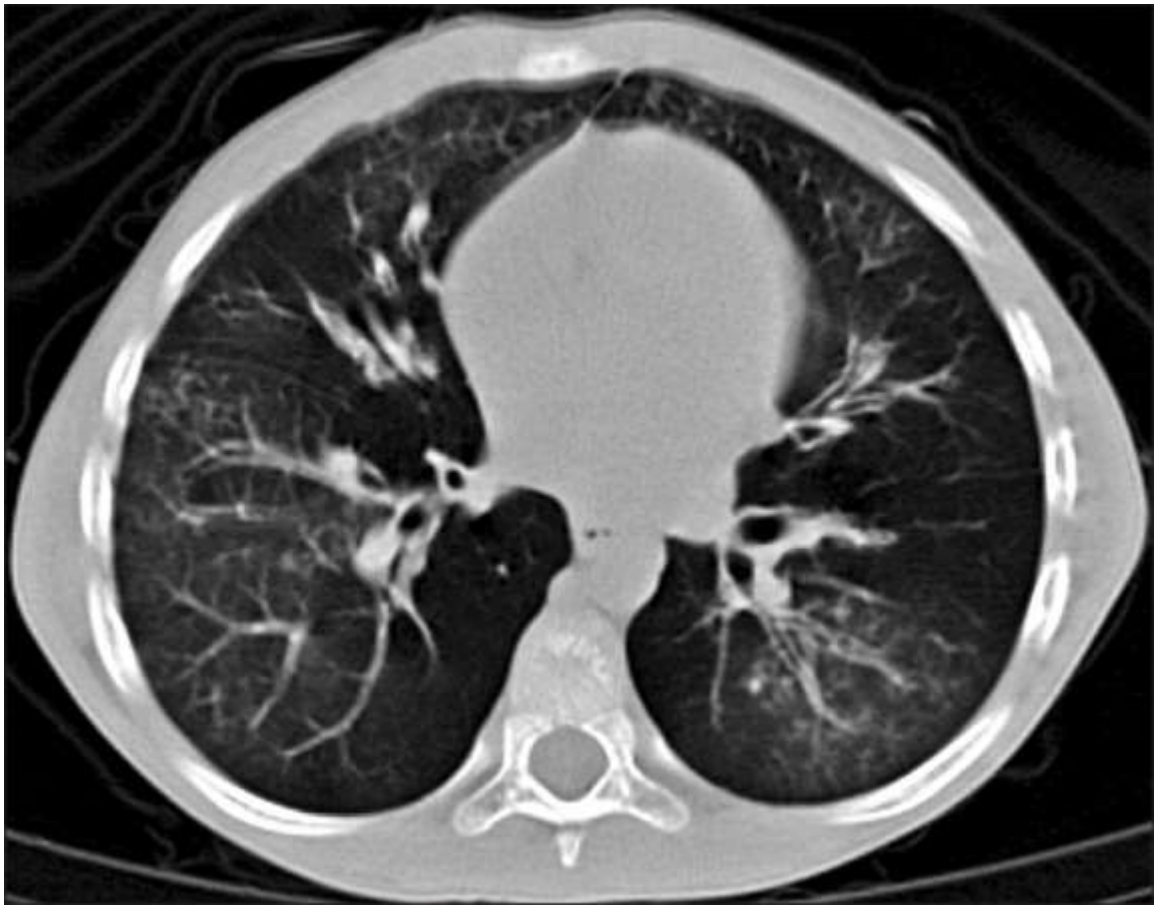
Was hospitalized twice during last 3 months due to viral LRTI for 4 and 5 days .

Mother stopped working and stays home for the last 6m.

A request for palvizumab was submitted to her HMO.

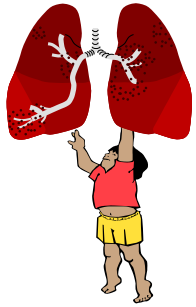
Case Presentation

- Chest CT reveals diffuse thickening of the bronchial walls associated with air trapping areas



Case Presentation

A request for palvizumab was submitted to her HMO……



איגוד רופאי ריאות ילדים (חיפ"פ)
איגוד רופאי הילדים בישראל
החברה הישראלית לפדיאטריה קלינית (חיפ"ק)

15.7.08

לכב'
מגר' טל מורגנשטיין
ועדת סל הבריאות
משרד הבריאות

שלום רב,

הנדון: חיסון למניעת RSV ברונכיוליטיס בתינוקות.

בסל הבריאות החדש נכללה אינדיקציה חדשה לחיסון למניעת RSV - סעיף ו.
ו. ילודים שלא מלאה להם שנה, הסובלים ממחלת ריאות כרונית קשה, ללא תלות בשבוע הלידה.

ועד האיגוד הישראלי לרפואת ריאות ילדים (חיפ"פ), יחד עם ועד איגוד רופאי הילדים בישראל והחברה הישראלית לפדיאטריה קלינית (חיפ"ק) ממליצים למשרד הבריאות לכלול את המקרים הבאים בהגדרה של "מחלת ריאות כרונית קשה ללא תלות בשבוע הלידה" , כולם מקרים בהם מהווה סיכון משמעותיRSVברונכיוליטיס מ

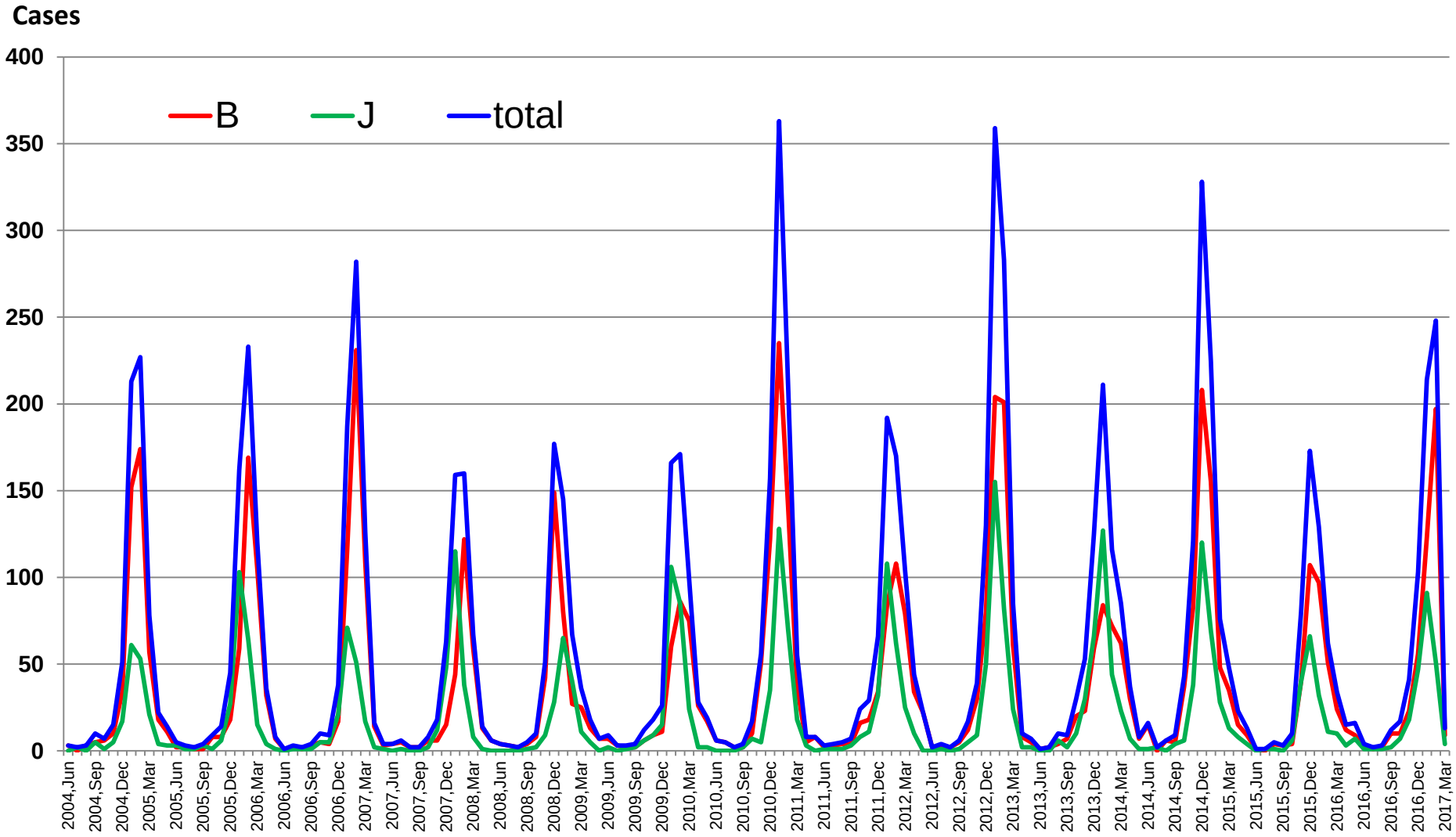
תינוקות עם CF , סימפטומטים במערכת הנשימה כבר בשנה הראשונה
תינוקות עם היפוטוניה קשה
תינוקות עם יתר לחץ דם ריאתי
תינוקות עם תסמונת דאון הסובלים מדלקות ריאה חוזרות כבר בשנה הראשונה
תינוקות עם מומים קשים במערכת הנשימה (לאחר תיקון בקע סרעפתי, סיבוכים של TEF – פיסטולה קנה-ושט)
תינוקות עם טרכיאוסטומיה
תינוקות עם הפרעה במערכת החיסון
תינוקות עם מחלה ממאירה
תינוקות עם סטרידור מולד בחומרה קשה (פייר רובין, לרינגומלציה קשה, שיתוק מיתר קול, היצרות תת-גלוטית, המנגיומה תת-גלוטית)
תינוקות עם ברונכיוליטיס אובליטרנס קשה (אחרי אדנו-וירוס)
תינוקות מושתלי ריאות – עד גיל שלוש שנים לפחות

פרופ' אשר טל פרופ' פרנסיס מימוני פרופ' דוד גרינברג
יו"ר חיפ"פ יו"ר איגוד רופאי ילדים בישראל יו"ר חיפ"ק

Bronchiolitis

- מחלת דרכי אויר תחתונות השכיחה ביותר בפעוטות.
- מתאפיינת בדלקת חריפה, בצקת ונמק של תאי אפיתל דרכי הנשימה הקטנות, יצור מוגבר של mucus וספזם של דרכי האויר.
- <u>סימנים:</u> נזלת, טכיפנאה,צפצופים ופקעים בהאזנה, שימוש בשרירי עזר / נשימת כנפי האף.
- <u>אתיולוגיה</u> : בעיקר RSV, אך גם *parainfluenza, influenza, adenovirus, rhino, hmpv*

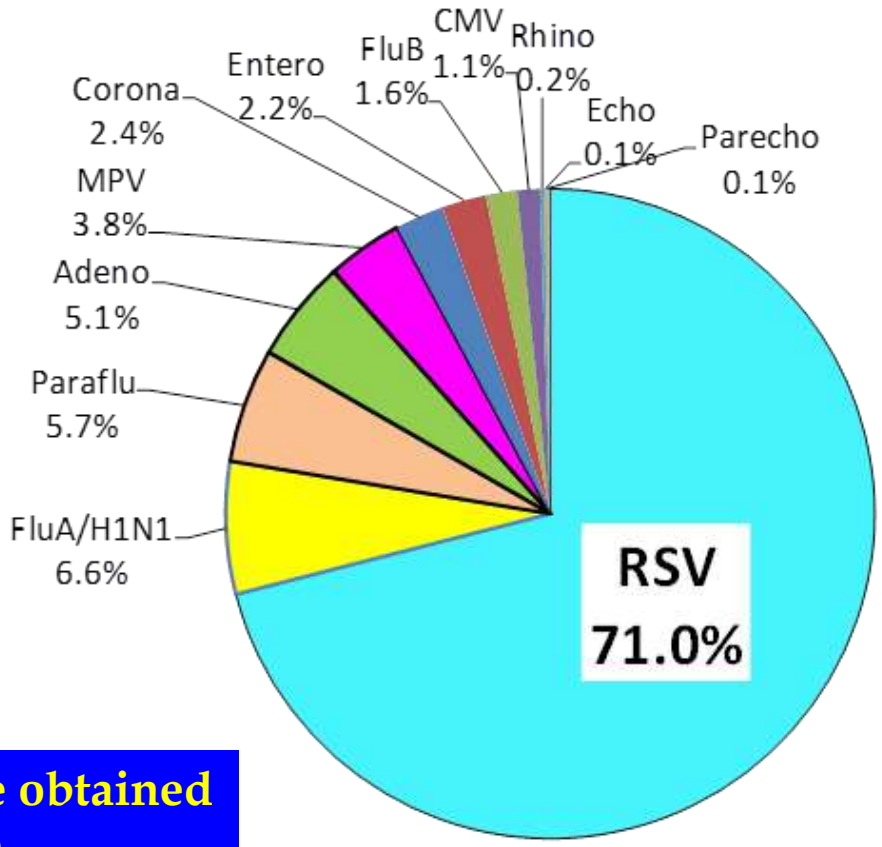
Hospitalization Bronchiolitis with RSV <12 months



PIDU Soroka 2017 (unpublished data)

Distribution of viruses in CAP of all positive NP washes (n=1284) in children aged <5 years from 2004 to 2013

- **8061 cases of CAP during the study**
- **2249 NP washes were taken**
- **1284 (57.1%) were positive for virus**

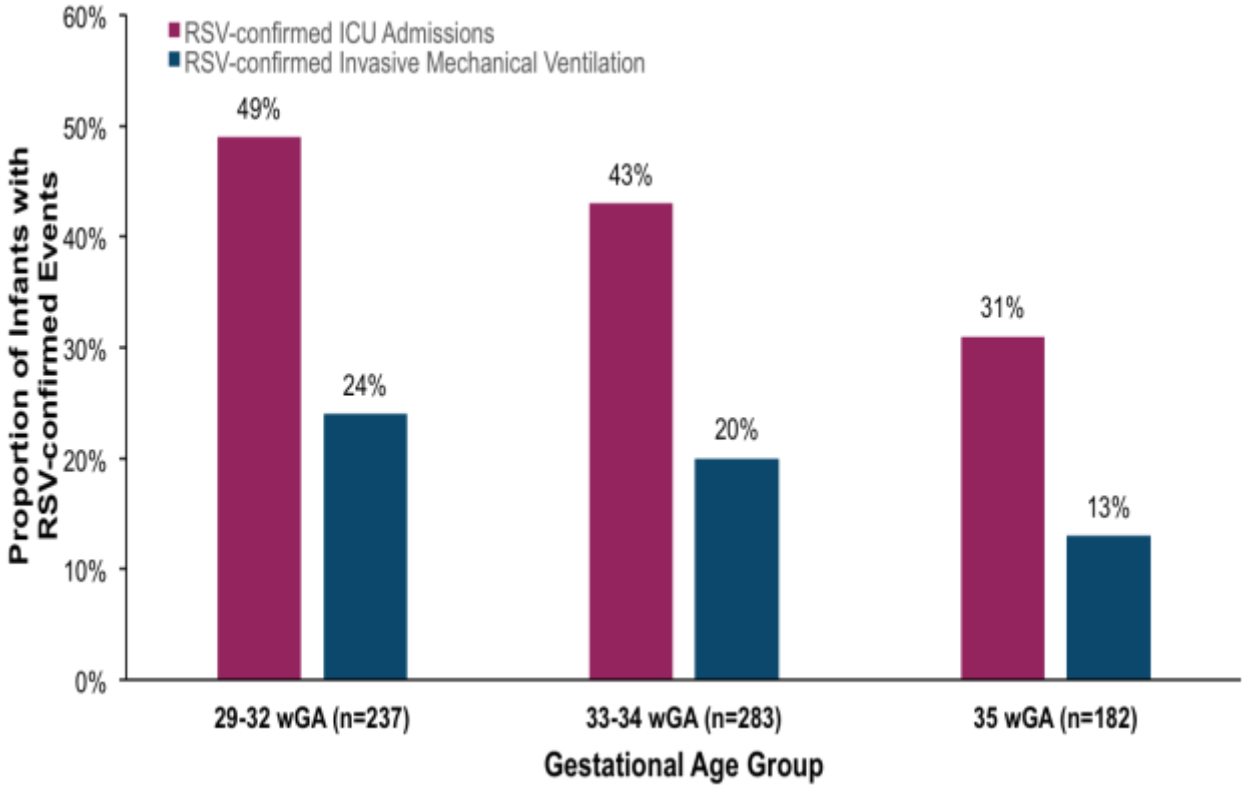


Of all CAPs for which NP washes were obtained 42.7% (960/2249) were RSV(+)

Greenberg D, et al. PIDU Soroka 2014; unpublished data

RSV-confirmed ICU Admissions and Need for IMV by Gestational Age Group for Infants With Community-acquired RSV (n=702)

Multivariate logistic regression analyses confirmed that both lower GA and younger chronological age **are associated with a higher frequency of ICU admissions and need for IMV**



[a]*P*=NS for 29 to 32 vs 33 to 34 weeks gestational age (wGA); *P*<0.001 for 29 to 32 vs 35 wGA; and *P*<0.01 for 33 to 34 vs 35 wGA (Pearson chi-square test).

[b]*P*=NS for 29 to 32 vs 33 to 34 wGA; *P*<0.01 for 29 to 32 vs 35 wGA; and *P*=NS for 33 to 34 vs 35 wGA (Pearson chi-square test).

Anderson E, et al. *Am J Perinatol.* 2016;11:e0150416.

Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series

Nienke M Scheltema, Angela Gentile, Florencia Lucion, D James Nokes, Patrick K Munywoki, Shabir A Madhi, Michelle J Groome, Cheryl Cohen, Jocelyn Moyes, Kentigern Thorburn, Somsak Thamthitiwat, Hitoshi Oshitani, Socorro P Lupisan, Aubree Gordon, José F Sánchez, Katherine L O'Brien, on behalf of the PERCH Study Group, Bradford D Gessner, Agustinus Sutanto, Asuncion Mejias, Octavio Ramilo, Najwa Khuri-Bulos, Natasha Halasa, Fernanda de-Paris, Márcia Rosane Pires, Michael C Spaeder, Bosco A Paes, Eric A F Simões, Ting F Leung, Maria Tereza da Costa Oliveira, Carla Cecília de Freitas Lázaro Emediato, Quique Bassat, Warwick Butt, Hsin Chi, Uzma Bashir Aamir, Asad Ali, Marilla G Lucero, Rodrigo A Fasce, Olga Lopez, Barbara A Rath, Fernando P Polack, Jesse Papenburg, Srđan Roglić, Hisato Ito, Edward A Goka, Diederick E Grobbee, Harish Nair, Louis J Bont**

Lancet Glob Health 2017; 5: e984–91

See **Comment** page e951

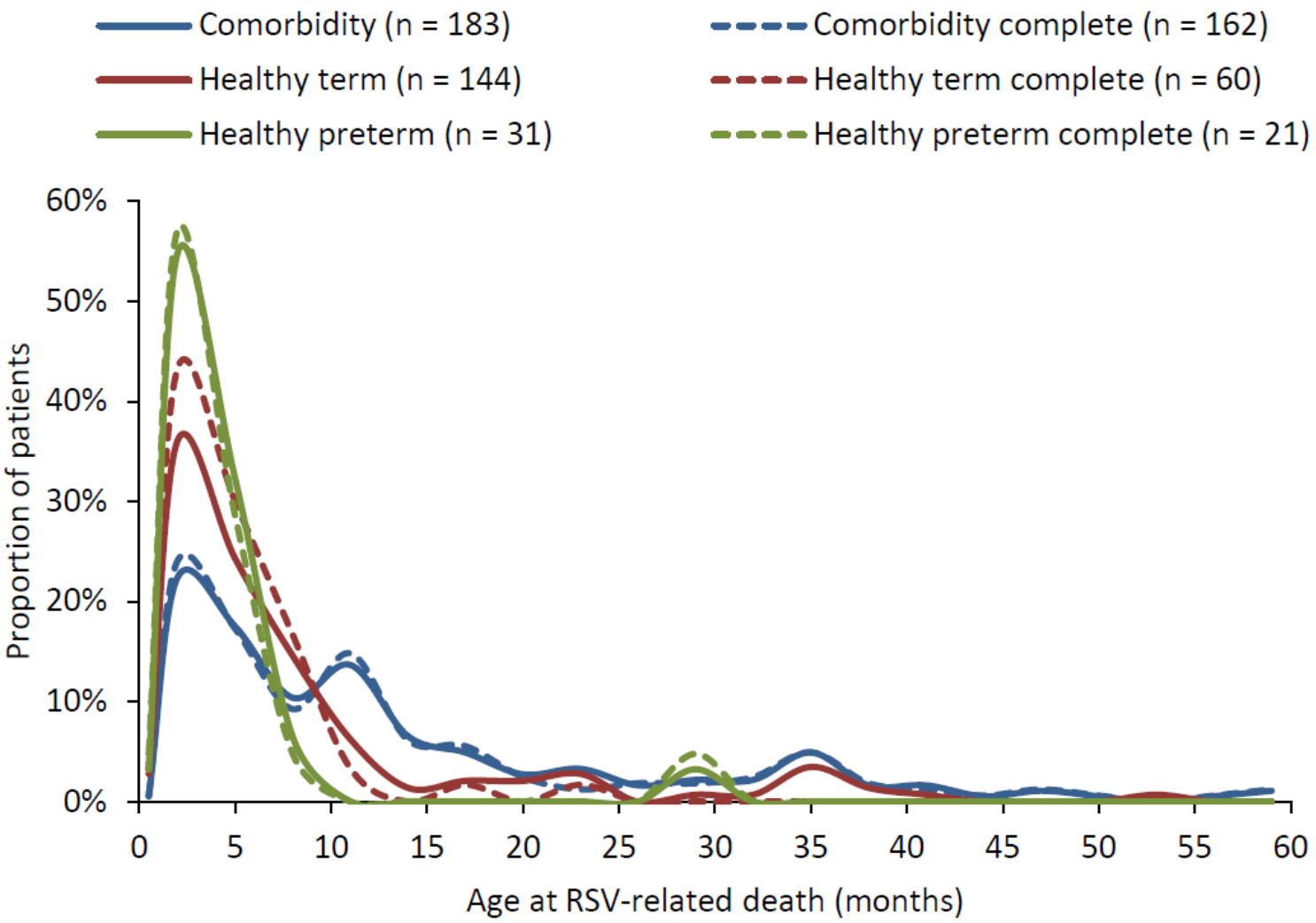
Summary

Background Respiratory syncytial virus (RSV) infection is an important cause of pneumonia mortality in young children. However, clinical data for fatal RSV infection are scarce. We aimed to identify clinical and socioeconomic characteristics of children aged younger than 5 years with RSV-related mortality using individual patient data.

Interpretation This study is the first large case series of children who died with community-acquired RSV infection. A substantial proportion of children with RSV-related death had comorbidities. Our results show that perinatal immunisation strategies for children aged younger than 6 months could have a substantial impact on RSV-related child mortality in low-income and middle-income countries.

Funding Bill & Melinda Gates Foundation.

Supplemental Figure 1. Sensitivity analysis for age distribution at RSV-related death excluding children with missing data for comorbidity or prematurity



Risk factors for RSV related death

	Low-income or lower middle-income countries (n=117)	p value*	Upper middle-income countries (n=77)	p value†	High-income countries (n=164)	p value‡
Male sex	58 (50%)	0·976	38 (49%)	0·247	94 (57%)	0·199
Age at death (months)	5·0 (2·3–11·0)	0·973	4·0 (2·0–10·0)	0·023	7·0 (3·6–16·8)	0·006
Younger than 6 months at death	68 (58%)	0·893	44 (57%)	0·014	66 (40%)	0·003
Prematurity§	9 (8%)	0·083	12 (16%)	0·043	45 (27%)	0·000
Gestational age (weeks)	38·0 (38·0–39·0); n=22	0·144	38·0 (34·5–38·0); n=38	0·250	38·1 (32·1–40·0); n=80	0·688
Comorbidity§	33 (28%)	0·008	36 (47%)	0·001	114 (70%)	0·000
Oxygen saturation on room air at hospital admission (%)	92·0% (85·8–97·3); n=94	0·022	87·0% (85·0–94·0); n=47	0·448	89·0% (76·5–91·0); n=37	0·001
Weight for age *Z* score of less than −2	64/111 (58%)	0·924	33/58 (57%)	0·370	49/99 (50%)	0·236
Contact with health-care provider before admission to hospital	28/65 (43%)	0·870	17/38 (45%)	0·123	41/68 (60%)	0·047
Time between onset of symptoms and admission (days)	5·0 (3·0–7·0); n=71	0·002	3·0 (2·0–4·0); n=45	0·387	3·0 (1·0–5·0); n=135	0·000
Length of stay in hospital (days)	3·0 (2·0–6·0)	0·000	7·0 (3·0–11·5)	0·000	15·0 (7·0–32·0); n=149	0·000
Availability of intensive care unit	28 (24%)	0·000	75 (97%)	0·038	164 (100%)	0·000
Intensive care unit admission	23/116 (20%)	0·000	27/56 (48%)	0·000	152 (93%)	0·000
Mechanical ventilation	23/114 (20%)	0·000	33/60 (55%)	0·000	138/155 (89%)	0·000
Urban living area	22/66 (33%)	0·000	39/40 (98%)	0·867	129/133 (97%)	0·000
At least one sibling present in household	30/39 (77%)	0·122	16/17 (94%)	0·003	62/109 (57%)	0·027
Time of death relative to RSV seasonality						
Death during RSV season	61/79 (77%)	0·004	35/64 (55%)	0·000	122/134 (91%)	0·005
Death within 1 month before or after RSV season	7/79 (9%)	0·050	13/64 (20%)	0·001	7/134 (5%)	0·303

Data are n (%), median (IQR), or n/N (%). Statistical comparisons with Mann-Whitney *U* test or χ^2 test with p values of less than 0·0167 taken to be significant according to Bonferroni correction for multiple testing. RSV=respiratory syncytial virus. *Low-income or lower middle-income country versus upper middle-income country. †Upper middle-income country versus high-income country. ‡Low-income or lower middle-income country versus high-income country. §Considered absent when missing.

Table: **Clinical characteristics and risk factors in RSV-related child deaths**

Supplemental Table 4. Additional characteristics and risk factors in RSV-related child deaths

	Low-income or lower middle-income countries (n = 117)	Upper middle-income countries (n = 77)	High-income countries (n = 164)
Comorbidity	33 (28%)	36 (47%)	114 (70%)
Genetic or chromosomal disease	4 (3%)	3 (4%)	31 (19%)
Down's syndrome	3 (3%)	2 (3%)	10 (6%)
Congenital heart disease	15 (13%)	9 (12%)	43 (26%)
Neurological disease	4 (3%)	5 (6%)	40 (24%)
Chronic lung disease	1 (1%)	0	45 (27%)
Airway abnormality	0	1 (1%)	7 (4%)
Primary immunodeficiency	0	1 (1%)	7 (4%)
Malignancy	0	0	2 (1%)
HIV infection	5 (4%)	18 (23%)	0
Tuberculosis infection	1 (1%)	2 (3%)	0
Other underlying disease	9 (8%)	4 (5%)	4 (2%)
Biliary atresia	0	1 (1%)	0
Liver disease	0	1 (1%)	0
Renal disease	0	1 (1%)	2 (1%)
Immunosuppression	5 (4%)	0	0
Congenital abnormality	3 (3%)	0	0
Adenoid cyst	1 (1%)	0	0
Metabolic disorder	0	1 (1%)	2 (1%)

Fatalities in RSV hospitalizations (1966-2009) – 36 studies

- Healthy Children: < 1%
- Chronic lung Disease : 3.5 – 23%
- Congenital Heart disease: 2 – 37%
- Prematurity: 0 – 6.1%
- Nosocomial RSV: 0 – 12.2%
- Require Intensive Care: 1 – 8.6%
- ECMO: 33%

Welliver RC Sr et al. CMRO 2010;26:2175-81

RSV Hospitalizations in Various Conditions

	N	Mean Age, y	Mean LOS, d	% ICU	% MV
Bronchopulmonary dysplasia	91	1.18	11	35	23
Pulmonary malformations	20	2.10	11	50	30
Recurrent aspiration pneumonitis	17	2.09	9	47	24
Tracheoesophageal fistula	9	1.94	13	22	22
Cystic fibrosis	8	0.64	11	12	0
Other respiratory disorders	8	1.42	9		0
Neurogenic disorders	6	3.12	5	50	33

LOS = hospital length of stay; ICU = intensive care unit; MV = mechanical ventilation.

Adapted from Arnold SR et al. The Canadian PICNIC study. *Pediatr Infect Dis J.* 1999;18:866-869.

Pre-existing disease is associated with higher risk of death in severe RSV infection

RISK FACTORS FOR DEATH:

- All had pre-existing disease (RR 2.36);54% had >2 diseases
- Cardiac anomaly (RR 2.98)
- Nosocomial RSV infection (RR 2.89)

PRE-EXISTING DISEASE:

- Chromosomal abnormalities (29%)
- Cardiac lesions (27%)
- Neuromuscular (15%)
- CLD (12%)
- Large Airway Anomaly (9%)
- Immunodeficiency (9%)

Thorburn K . ADC 2009;94:99-103

Incidence Rate Ratios for Congenital Chronic Conditions risk of RSVH

Condition	RSV/Total (%)	IRR (95%CI)	P Value
Respiratory Tract Malformations			
Cleft lip/Palate	50/855 (6.4)	1.52(1.14-2.01)	0.004
Larynx/Trac/Bronc	41/440 (9.3)	1.54 (1.12-2.14)	0.009
Other Respiratory Tract Disorders			
Lungs	7/51 (13.7)	2.20 (1.00-4.81)	0.049
BPD	89/504 (17.7)	2.58 (2.06-3.24)	<0.001
CF	13/72 (18.1)	4.32 (2.42-7.71)	<0.001
Esop. atresia	26/115 (22.6)	2.84 (1.64-4.93)	<0.001
Neuromuscular			
Encephalocele	58/542 (10.7)	1.54 (1.14-2.08)	0.005
Spina Bifida	17/172 (9.90	2.16 (1.31-3.55)	0.002
Musc. Dystrophy	13/82 (15.9)	2.49 (1.36-4.56)	0.003
CP	93/905 (10.3)	1.59 (1.27-1.99)	<0.01
Other Congenital Anomalies			
CHD	292/2720 (10.7)	1.70 (1.45-1.99)	<0.001
Down Syndrome	78/399 (19.5)	3.43 (2.66-4.42)	<0.001
Chromosome An.	4/17 (23.5)	5.08 (1.67-15.48)	0.004
GI Anomalies	94/1078 (8.7)	1.60 (1.25-2.04)	<0.001
Urinary Tract	82/1232 (6.7)	1.53 (1.22-1.92)	<0.001
Cong. Immunodef	26/122 (21.3)	3.80 (2.49-5.80)	<0.001
Inborn Errors	29/276 (10.5)	2.38 (1.62-3.48)	<0.001

Kristensen K et al. Clin Infect Dis . Jan 2012

Incidence rate ratios (IRRs) for RSV hospitalization (RSVH) Acquired Chronic Disease

RSVH rates were 6-fold higher in interstitial lung disease; 4-fold higher in liver disease + 2-fold higher in epilepsy, acquired heart disease and cancer

CONDITION	RSV %	IRR (95%CI)	P value
Interstitial lung disease	27.3%	6.45 (1.74-23.91)	.005
Epilepsy	10.5%	2.64 (2.05-3.42)	<.001
Acquired heart disease	12.4%	2.00 (1.47-2.71)	<.001
GERD	6.6%	1.48 (1.07-2.05)	.019
Cancer	8.4%	2.58 (1.19-5.59)	.017
Liver disease	18.7%	4.02 (1.97-8.20)	<.001

Kristensen K et al. Clin Infect Dis . Jan 2012

Distinct Disease Syndromes Associated with RSV Infection

- Bronchiolitis in infants
- Sudden infant death syndrome (SIDS)/apnea
- Post-infection wheezing/childhood asthma
- Severe disease in the institutionalized elderly leading to excess mortality and exacerbation of underlying conditions
- Giant cell pneumonia in persons with deficient T-cell immunity
- Extrapulmonary manifestations of severe respiratory syncytial virus infection

Hull J, et al. *Thorax.* 2000;55:1023-7; Kneyber MC, et al. *Eur J Pediatr*. 1998;157:331-5; Lindgren C. *Acta Paediatr.* 1993;82(Suppl)389:67-9; Martinez FD. *Pediatr Infect Dis J.* 2003;22(2 Suppl):S76-82; Openshaw PJ, et al. *Vaccine* 2001;20(Suppl1):S27-31

High Risk Populations

- Cardiovascular
- Trisomy 21
- Neuromuscular
- Immunocompromised
- Chronic lung disease

Cardiovascular

- A higher admission rate for those with congenital heart disease in comparison to those without , due to RSV between 313
- Key factors: cardiomyopathy, profound hemodynamically cong. Heart disease.
- Critical age<one year of age.

Archives Disesae of Childhood 2008

Cardiovascular

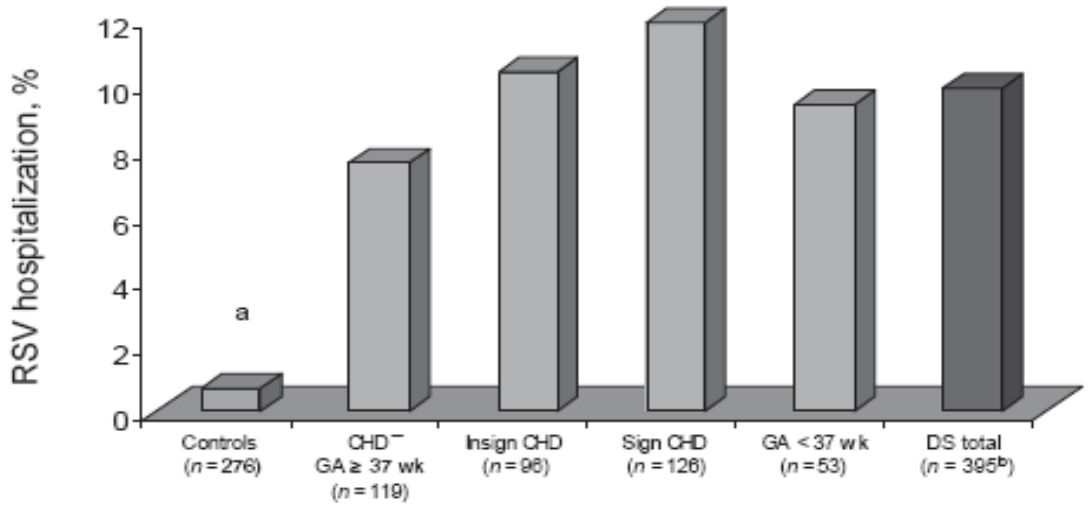
Table 1: Risk factors for RSV hospitalisation in children with heart disease

		Cases (n) 313	Controls (n) 313	OR (95 % CI)	Adjusted OR* (95 % CI)
Sex	Ref[6].: girls	165	158	1.10 (0.80 - 1.50)	1.14 (0.81 – 1.59)
underlying condition	None	223	263	Ref.	Ref.
	Down	50	18	3.23 (1.82 – 5.74)	3.24 (1.80 – 5.80)
	Other	40[1]	32[1]	1.54 (0.93 – 2.57)	1.49 (0.88 – 2.52)
Preterm	Ref.: term	49[2]	49[2]	1.00 (0.65 – 1.54)	1.03 (0.65 – 1.64)
Heart disease (type)	Structural	290[3]	291[3]	Ref.	Ref.
	Cardiomyopathy	13[4]	3[4]	5.45 (1.21 – 24.57)	5.84 (1.26 – 27.16)
	Arrhythmia alone	10[5]	19[5]	0.60 (0.27 – 1.30)	0.74 (0.33 – 1.65)
Surgery (in structural heart disease)	Ref.: no surgery	136	111	1.55 (1.08 – 2.21)	1.37 (0.94 – 1.98)
completed surgery	Ref.: surgery not completed	78	69	0.82 (0.48 – 1.43)	1.08 (0.56 – 2.11)
Spontaneous cure	Ref.: no spontaneous cure	25	31	0.92 (0.51 – 1.64)	1.08 (0.58 – 2.02)
Haemodynamically significant	Ref: not haemodynamically significant	118	89	1.64 (1.14 – 2.38)	1.53 (1.04 – 2.26)
Cyanosis[6]	Ref.: no cyanosis	36	29	0.84 (0.45 – 1.54)	0.98 (0.52 – 1.87)
decompensation[6,7]	Ref.: no decompensation	60	35	1.58 (0.92 – 2.73)	1.19 (0.67 – 2.12)
Left – right shunt[6]	Ref.: no left – right shunt	49	38	1.12 (0.80 – 1.56)	1.11 (0.78 – 1.56)
Other	Ref: cyanosis, decompensation and/or left-right shunt	13	11	0.79 (0.34 – 1.88)	0.99 (0.39 – 2.48)

Archives Disesae of Childhood 2008

Down syndrome and RSV

- 10% of babies born with Down will be admitted for RSV LRTI.(0.5-2 in general)
- Prolonged hospitalization (10 days)
- 13% need mechanical ventilation!



Pediatrics 2007;120:1076-81

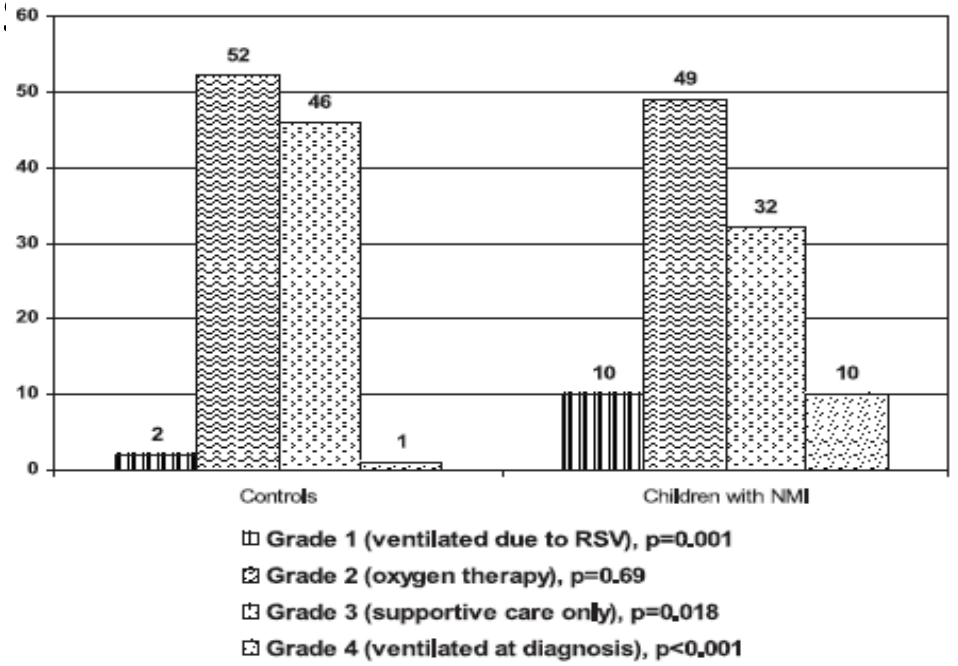
Palivizumab for Down pt.

- Multicenter, post-marketing surveillance study (December 2013 to December 2015), children aged ≤24 months.
- Of 304 patients receiving palivizumab, 167 (54.9%) had immunocompromised conditions, and 138 (45.4%) had Down syndrome;
- The annual number of doses was 5.3 (±2.4) per season.
- Overall, 220 AEs occurred in 99 patients (32.6%), In four patients, five SADRs, none were considered drug-related.
- During the observation period, five RSV infections occurred and two patients required hospitalization.

Kashiwagi T. Pediatric Drugs sep. 2017

Neuromuscular patients

- NM disease is associated with increased risk for PICU admission, and mech. Ventilation!!!
- The attributable risk to die was 10 folds higher!
- 73 NM Vs 1495 control



(*Pediatr Infect Dis J* 2007;26: 485–491)

Palivizumab Prophylaxis for RSV in Canada and Italy: An International, Prospective Cohort Study.

- Premature infants who received palivizumab (≤35 completed weeks' gestational age; group1) were compared with infants given palivizumab for underlying disorders regardless of gestational age (group 2).
- A total of 14,468 palivizumab-exposed infants were enrolled
- (group 1, n = 9093; group 2, n = 4856).

Manzoni P. Pediatric Inf Dis J. 2017

Palivizumab Prophylaxis for RSV in Canada and Italy: An International, Prospective Cohort Study.

- After multivariable logistic regression, **neuromuscular disease** [OR] 4.29, airway anomalies (OR 3.23, **Down syndrome** (OR 2.25, hemodynamically significant **congenital heart disease** (OR 2.24, **prematurity ≤28** completed weeks' gestational age (OR)and bronchopulmonary dysplasia (OR 1.81) significantly predicted RSVH.
- No significant association was detected with the number of doses administered or the time elapsed after the previous dose.

Manzoni P. Pediatric Inf Dis J. 2017

Palivizumab Prophylaxis for RSV in Canada and Italy: An International, Prospective Cohort Study.

TABLE 3. Multivariable Logistic Regression Controlling for Factors Associated With Respiratory Syncytial Virus Hospitalization (Different Underlying Conditions Versus Preterm Neonates)

RSVH	OR (95% CI)	*P*
Chronologic age at first PVZ dose	1.00 (1.00–1.00)	0.603
Sex	0.97 (0.79–1.18)	0.748
HSCHD	**1.84 (1.37–2.47)**	**<0.001**
BPD	**2.10 (1.55–2.83)**	**<0.001**
Miscellaneous	1.51 (0.95–2.41)	0.084
Neuromuscular	**3.68 (2.05–6.60)**	**<0.001**
Airway anomaly	**2.69 (1.69–4.27)**	**<0.001**
Cardiac	2.33 (0.72–7.51)	0.157
Cystic fibrosis	0.56 (0.18–1.77)	0.324
Down syndrome	**1.83 (1.13–2.95)**	**0.014**
Pulmonary disorders	1.62 (0.91–2.86)	0.099
>35 weeks' gestational age	**0.40 (0.17–0.99)**	**0.047**

Bold text indicates $P < 0.05$.

Manzoni P. Pediatric Inf Dis J. 2017

Immune deficient patients

- Thirty-five out of 1584 patients hospitalized due to RSV infection were diagnosed having compromised immune function.
- In comparison with other groups these infants showed the longest durations of hospital stay with a median of 39 days (J Peds 1992
- Similar findings in canda (J Peds 1995)
- צריך לדון מול האימונולוגים מי להערכתם שמזוהה עם פגם חיסוני זקוק להגנה של פאליביזומב.

Cystic Fibrosis

- CF infants may benefit from palivizumab (Speer M ,PIDJ 2008:27,6))
- Palivizumab prophylaxis is not considered the standard of care in most CF centers in US and Canada.(Ped Pul 2008)
- A RSV-IG double blind did not show significant changes (cohen 2005) , in one study (186 infants up to two years old) comparing five monthly doses of palivizumab (N=92) to placebo (N=94) over one RSV season.(Cochrane 2010)

Cohen AH, Boron ML, Dingivan C. A phase IV study of the
safety of Synagis® (Palivizumab) for prophylaxis of respiratory syncytial virus disease in children with cystic fibrosis. American Thoracic Society Conference San Diego, USA. 2005.:A178.

A survey for CF centers directors

TABLE 1—Results of Palivizumab Prophylaxis Survey Related to 2007 RSV Season

	US	Canadian
Infants diagnosed with CF	412	23
Symptomatic infants (chronic cough, wheeze, chest congestion requiring antibiotics)	160	10
Infants infected with RSV (documented by rapid viral antigen or culture)	69	5
RSV infected infants who were treated with Palivizumab	11	3
RSV infected infants who responded to outpatient management	28	3
RSV infected infants who required hospitalization	38	2
RSV infected infants requiring ICU care/intubation	3	0
Persistent chest X-ray changes following RSV	11	1
Persistent wheezing (>2 weeks after RSV)	35	1

TABLE 2—Responses to Questions Concerning Prescription Patterns and Standard of Care

	Yes (US)	Yes (Can)	No (US)	No (Can)
Do you prescribe Palivizumab?	55 (75%)	6 (60%)	18 (25%)	4 (40%)
Do you prescribe for 2nd RSV season?	29 (40%)	4 (40%)	73 (60%)	6 (60%)
Do you have difficulty with insurance coverage for Palivizumab?	28 (41%)	2 (25%)	41 (59%)	6 (75%)
Is Palivizumab prophylaxis the standard of care for infants with CF?	31 (43%)	3 (30%)	41 (57%)	7 (70)
Does your state/province have CF NBS?	32 (44%)	41 (56%)	0	10

Giusty R . Ped Pulm. 2008

Is palivizumab effective as a prophylaxis of respiratory syncytial virus infections in cystic fibrosis patients? A meta-analysis

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[b] *Pediatric Pulmonology and Cystic Fibrosis Units, ''Vall d'Hebron'' Children's University Hospital, Autonomous University of Barcelona, Barcelona, Spain*
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Abstract

Background: Infections by respiratory syncytial virus (RSV) are more severe in patients with cystic fibrosis (CF), and many CF units use palivizumab as prophylaxis; however, information about palivizumab efficacy in CF patients is almost lacking.

Methods: A literature search up to December 2012 on the morbidity of RSV bronchiolitis in CF patients and on the safety and efficacy of palivizumab in those patients was performed. A random-effects meta-analysis was conducted for those studies meeting pre-specified search criteria. Historical controls were allowed.

Results: The number of patients who received palivizumab was 354 and the hospital admission rate was 0.018 (95% CI 0.0077–0.048). The corresponding number in the non-treated groups was 463 patients with an admission rate of 0.126 (95% CI 0.086–0.182) ($Q = 13.9$; $p < 0.001$).

Conclusion: Palivizumab may have a role in the prevention of severe lower airway infection by RSV in CF patients.

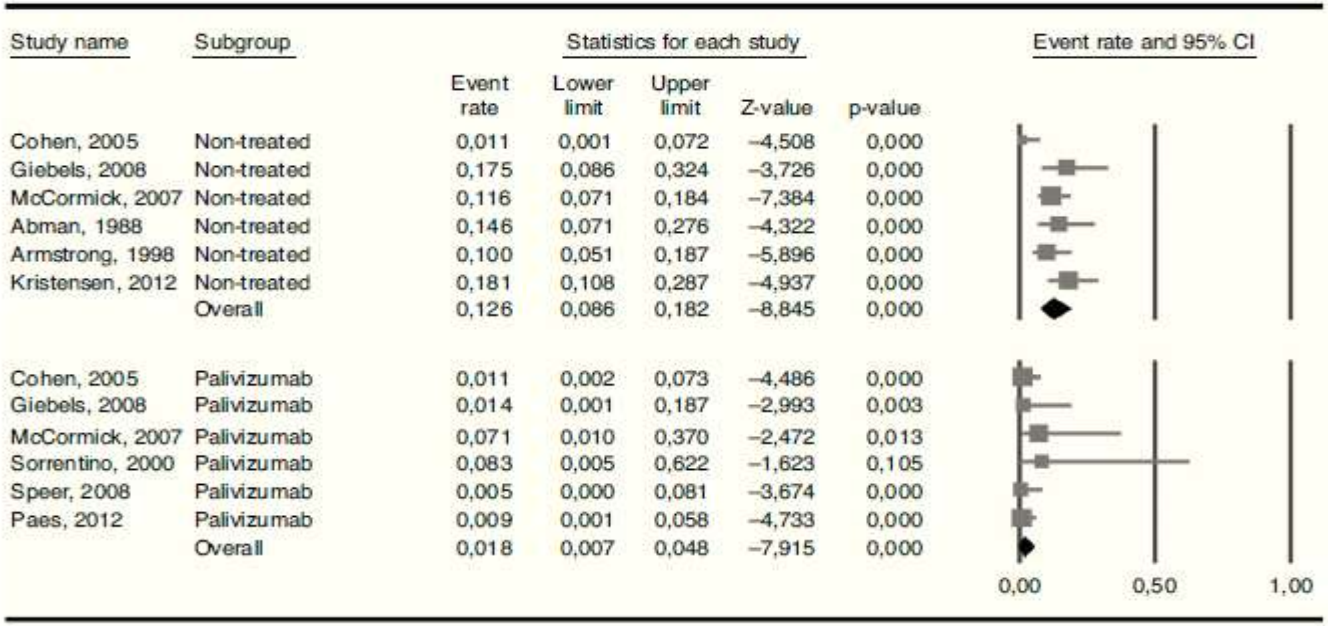


Figure 2 Admission rates in the group of patients treated with palivizumab and in the non-treated group. The difference between the overall admission rates in each group (0.126 vs. 0.018) was statistically significant (Q-test for heterogeneity: 13.9; $p < 0.001$). Heterogeneity (I^2) was 0% in the treated and 50.6% in the non-treated patients.

Table 2 Patients included in the meta-analysis.

Author	Subgroup	Admitted for RSV LRTI	Sample size
Cohen et al.[11]	Placebo control	1	94
	Palivizumab	1	92
Giebels et al.[18]	Non-treated	7	40
	Palivizumab	0	35
McCormick et al.[15]	Non-treated	15	129
	Palivizumab	1	14
Sorrentino et al.[19]	Palivizumab	0	5
Speer et al.[20]	Palivizumab	0	91
Paes et al.[21]	Palivizumab	1	117
Abman et al.[1]	External control	7	48
Armstrong et al.[6]	External control	8	80
Kristensen et al.[22]	External control	13	72

Lung Transplanted Children

- J Heart Lung Transplant. 2016 Feb;35(2):213-21.
- ALN-RSV01 (a small interfering RNA targeting RSV replication) for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients.
- Am J Respir Crit Care Med. 2011 Feb 15;183(4):531-8
- RNA interference therapy in lung transplant patients infected with respiratory syncytial virus.
- **Why not palivizumab???**

Asthma prevention

- The RSV-Asthma link is under investigation for more than 30 years.
- Recently , a first study demonstrated in a population based across a decade, increased tendency to present asthma up to 7 years of age.

BMJ Open

Association between respiratory syncytial viral disease and the subsequent risk of the first episode of severe asthma in different subgroups of high-risk Australian children: a whole-of-population-based cohort study

Table 2 HR for first asthma hospitalisation beyond the age of 2 years in different subgroups of children who had severe RSV disease in the first 2 years of life compared with those who did not: NSW 2000–2010

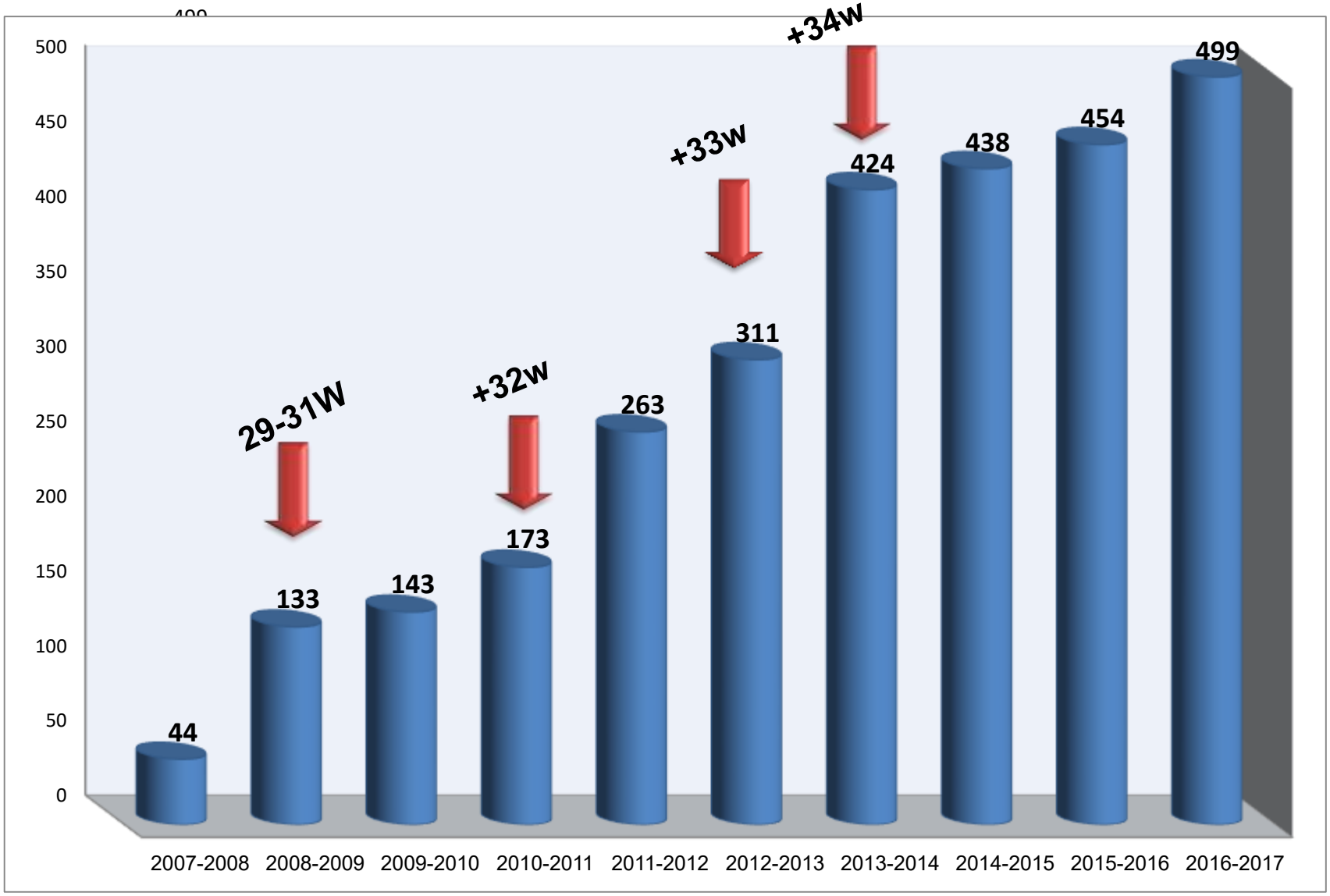
	Non-Indigenous standard risk children		High-risk children		Indigenous children	
Age at first asthma hospitalisation (years)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	UnAdjusted HR (95% CI)
2–3	4.1 (3.9 to 4.4)	3.9 (3.7 to 4.1)	4.7 (4.2 to 5.3)	4.5 (4.0 to 5.1)	4.1 (3.4 to 4.9)	4.0 (3.3 to 4.8)
3–5	3.0 (2.9 to 3.2)	2.8 (2.7 to 3.0)	3.1 (2.7 to 3.5)	3.0 (2.7 to 3.4)	2.2 (1.8 to 2.7)	2.2 (1.8 to 2.6)
5–7	2.4 (2.2 to 2.7)	2.3 (2.1 to 2.5)	2.6 (2.1 to 3.2)	2.6 (2.1 to 3.2)	2.6 (1.9 to 3.4)	2.5 (1.9 to 3.3)
>7	2.8 (2.4 to 3.2)	2.6 (2.3 to 3.0)	3.5 (2.7 to 4.5)	3.4 (2.6 to 4.3)	2.0 (1.4 to 3.1)	1.9 (1.2 to 2.9)

*HR after adjusting for mother's age at birth of the cohort child, parity, maternal smoking during pregnancy, index of socioeconomic disadvantage of the mother's residential postcode at birth, season of birth and sex of the child.
NSW, New South Wales; RSV, respiratory syncytial virus.

מי מטפל באוכלוסיות בסיכון ל RSV

- רופא ריאות ילדים (פגים, "צפצפנים" מחלת ריאות כרונית על חמצן ,נוירומוסקולריים)
- קרדיולוג ילדים (DOWNואחרים)
- נאונטולוג (פגים)
- נוירולוג/ רופא התפתחות הילד (DOWNואחרים)
- אימונולוג (חסר חיסוני)

שינויים בסל הזכאות לפאליביזומב בעשור האחרון



Pediatrics. 2014 Aug;134(2).

Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection.

American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee.

The risk of RSV hospitalization is not well defined in children with neuromuscular disorders that impair the ability to clear secretions from the upper airway because of ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy

הצעה להגדרת מחלת ריאות כרונית לטובת הסל לפאליביזומב

- "מחלת ראות כרונית קשה לצורך מתן חיסון בשנת החיים הראשונה הינה מחלה ריאתית או בדרכי הנשימה הפוגעת ביכולת פינוי ההפרשות מדרכי הנשימה או שהחולה בה ללא רזרבה נשימתית לעמוד בזיהום ב RSV על פי המלצת מומחה ראות ילדים עם תיעוד אוביקטיבי לחומרת המחלה ותכלול: מחלה ברונכיאקטטית (ציסטיק פיברוזיס, הפרעה ראשונית בתנועתיות הציליה), מחלת ראות אינטרסטיציאלית, מחלה חסימתית קשה (ברונכיוליטיס אובליטרנס), טרכאוסטמיה, או היפוטוניה קשה ."

Thank you!