



# **Bronchiolitis season is here - what can we do to reduce its impact?**



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# DISCLOSURES

**The following relationships could be perceived as having a bearing on my presentation of this subject:**

- **The risk factor study was investigator-initiated by PICNIC supported by a grant-in-aid of research provided by Abbott Laboratories**
- **Co-investigator on the Northern RSV Arctic Region project –sponsored by Abbott International**

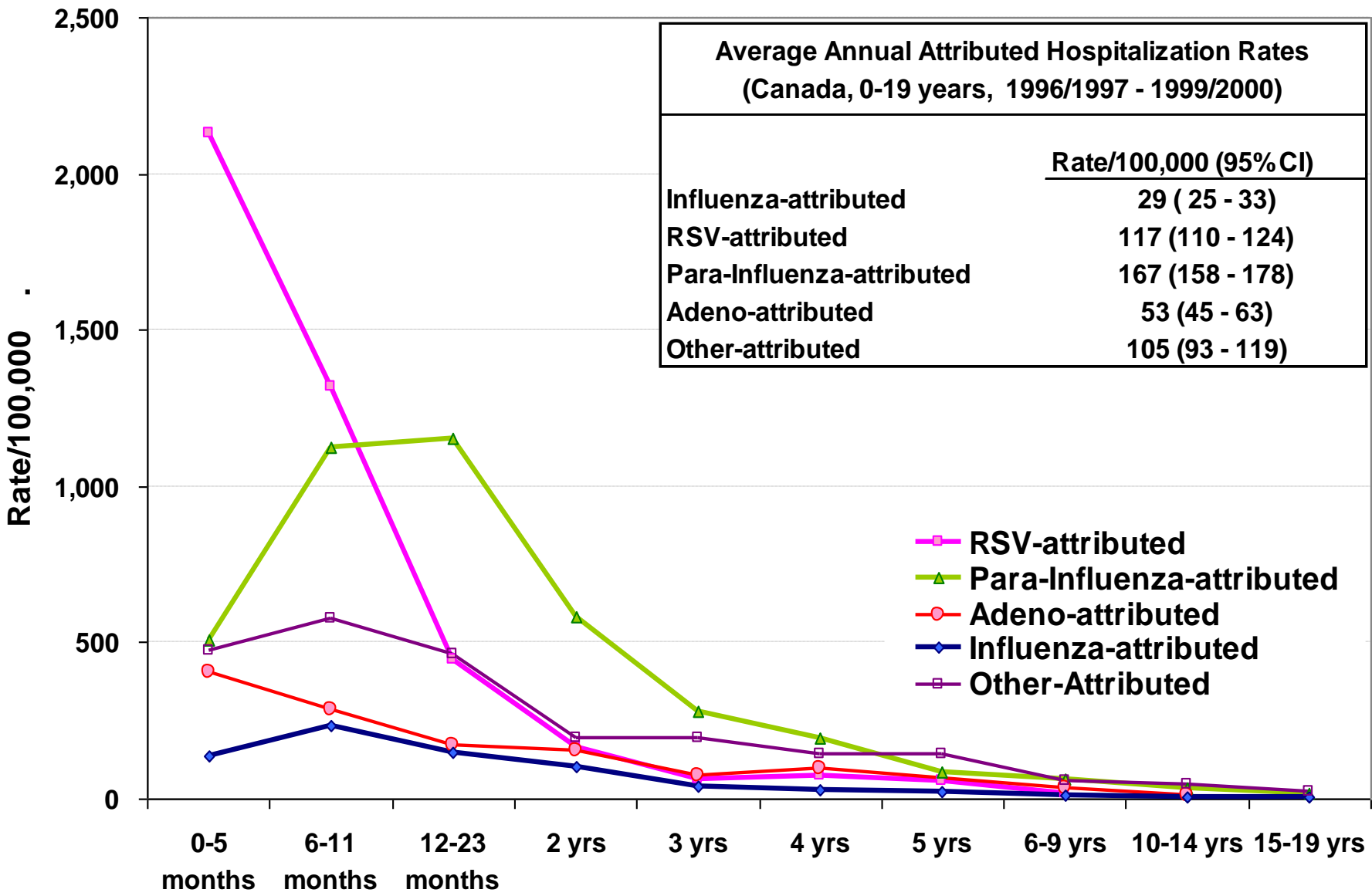
# OBJECTIVES



- Review the epidemiology and the impact of RSV disease and primary prevention
- Discuss early interventions: Ribavirin, RSV-IVIG
- Progress with monoclonal antibodies
- What's in the pipeline: Small molecules, siRNA (small interfering RNA)

# Attributable Pediatric Hospital Admissions, Canada, 1996/97-1999/2000

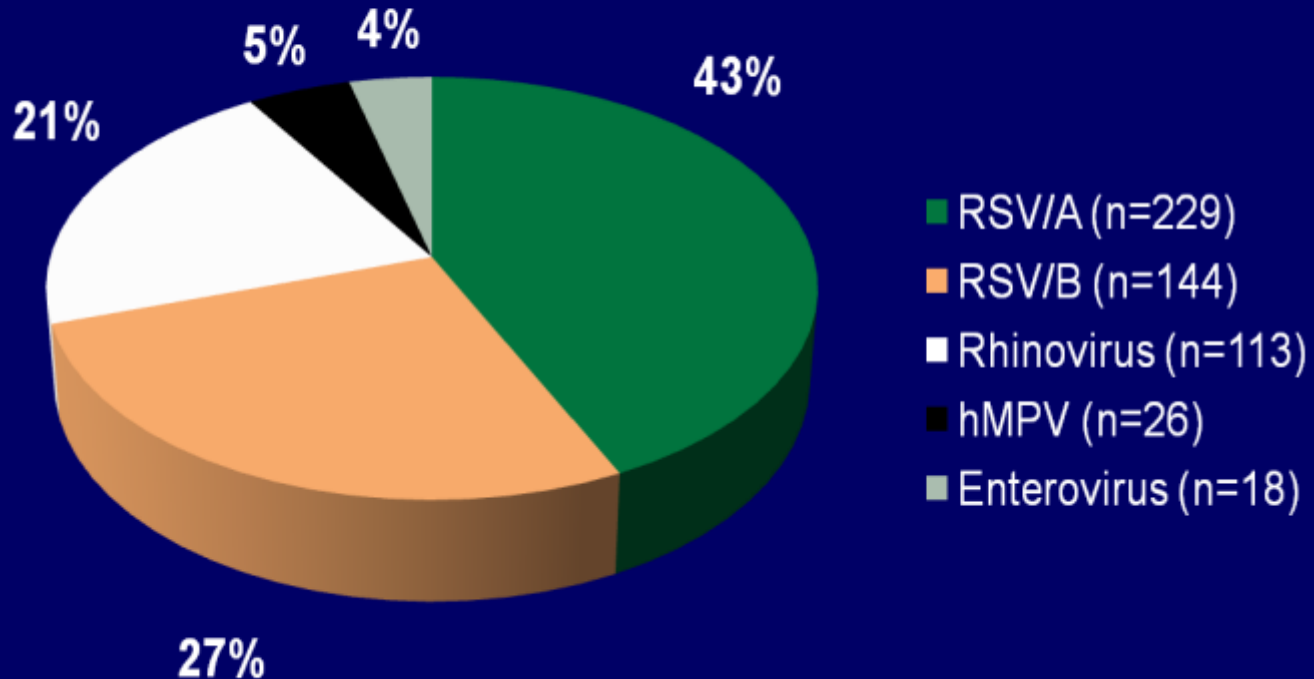
## Estimated Rate /100,000, By Age Group



# Prospective Multicenter Study of the Etiology of Bronchiolitis (2007-2008)

- 13 US Hospitals
- Viruses:
  - 1-367(71%)
  - 2-90(17%)
  - 3-5(1%)

Viruses Identified by RT-PCR (n=460/520 children had at least 1 of 12 viruses)



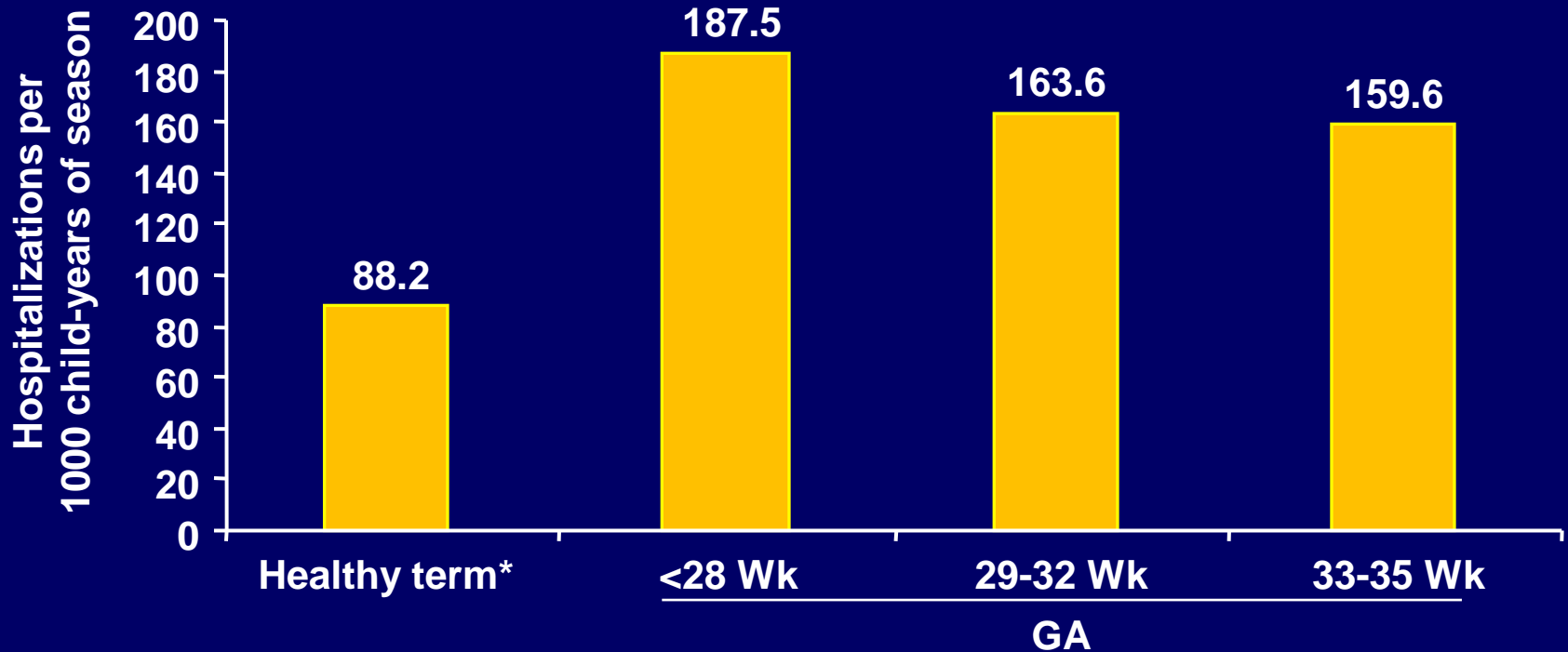
# Global burden of RSV disease

- In 2005, 33.8 million new episodes of RSV LRT infection in children < 5 yr
- RSVH in 3.4 million (2.8 - 4.3) cases
- Mortality in 66,000 – 199,000 children
- 99% of the deaths in developing countries

# Burden of RSV in Young Children

- Population based study in children < 5yrs
- ER (2000-2004); Pediatric offices (2002-2004)
- 5067 enrolled; 919(18%) RSV infections
- RSV associated with: 1 of 38 visits to the ER
- 1 of 13 visits to a primary care (FD) office
- Average RSVH: 17/1000 <6 months of age  
3/1000 < 5 years of age

# RSV Hospitalizations Similar in All Premature Infants Irrespective of GA



- Retrospective study of enrollees in Tennessee Medicaid, Jul 1989-Jun 1993,  $\leq 3$  years old
- Chart shows hospitalizations among infants  $\leq 6$  months old

\* Infants of  $\geq 36$  weeks GA without other medical conditions.  
GA = gestational age.

# Effect of Prematurity on 304 Infants

## Hospitalized with RSV (9 hospitals-Apr '95-Sept '96)

Horn SD et al J Pediatr 2003;143:S133

	<b>&lt; 32 wk</b> <b>N=28</b>	<b>33-35 wk</b> <b>N=31</b>	<b>36 wks</b> <b>N= 30</b>	<b>&gt;37 wk</b> <b>N=215</b>	<b>P value</b>
<b>ADMIT to ICU</b> <b>(%)</b>	<b>39.3</b> <b>N=11</b>	<b>48.4</b> <b>(N=15)</b>	<b>30</b> <b>(N=9)</b>	<b>27.9</b> <b>(N=60)</b>	<b>0.101</b>
<b>INTUBATION</b> <b>(%)</b>	<b>21.4</b> <b>(N=6)</b>	<b>38.7</b> <b>(N=12)</b>	<b>20</b> <b>(N=6)</b>	<b>12.1</b> <b>(N=26)</b>	<b>0.002</b>
<b>ICU LOS</b> <b>MEAN (SD)</b>	<b>5.8 (5.5)</b>	<b>7.7 (5.5)</b>	<b>4.2 (3.3)</b>	<b>3.8(4.1)</b>	<b>0.021</b>
<b>Hospital LOS</b> <b>MEAN (SD)</b>	<b>6.8(5.8)</b>	<b>8.4(6.9)</b>	<b>4.9 (3.6)</b>	<b>4.1(2.8)</b>	<b>&lt;0.0001</b>

# Follow-up Health Care of Infants with RSV LRTI (32-35 weeks GA)

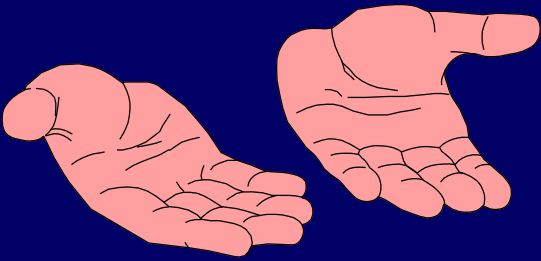
<b>MEAN (SD)</b>	<b>RSV COHORT (N=2415)</b>	<b>CONTROLS(N=20,254)</b>
	<small>(PROB= 2263; DEFINITE =152)</small>	
<b>Hospitalizations</b>	<b>2.96 (2.81)</b>	<b>1.28 (1.42)</b>
<b>Special care unit visits</b>	<b>0.67 (1.70)</b>	<b>0.40 (0.33)</b>
<b>Respiratory therapy use</b>	<b>0.31 (0.70)</b>	<b>0.13 (0.37)</b>
<b>MD consults</b>	<b>3.61 (4.54)</b>	<b>0.89 (1.12)</b>
<b>Procedures</b>	<b>1.05 (4.02)</b>	<b>0.81 (1.51)</b>
<b>Total hospital days</b>	<b>14.71 (18.69)</b>	<b>5.04 (7.09)</b>
<b>OPD visits</b>	<b>18.40 (10.58)</b>	<b>7.54 (4.31)</b>
<b>Total mortality</b>	<b>n=196 (8.11%)</b>	<b>n=320 (1.58%)</b>
<b>Sudden Death</b>	<b>n=148 (6.13%)</b>	<b>n=60 (0.30%)</b>

**P <0.001 for all values**

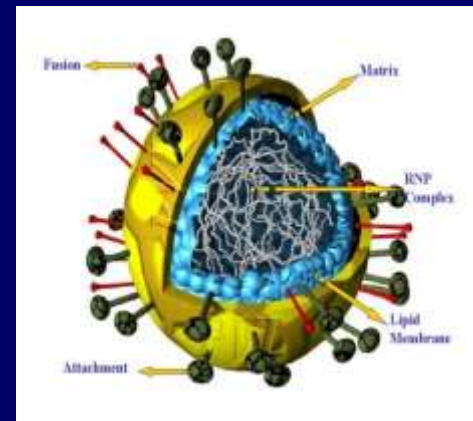
# Fatalities in RSV hospitalizations (1966-2009) – 36 studies

- **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%**

# Prevention + Treatment strategies for RSV infection

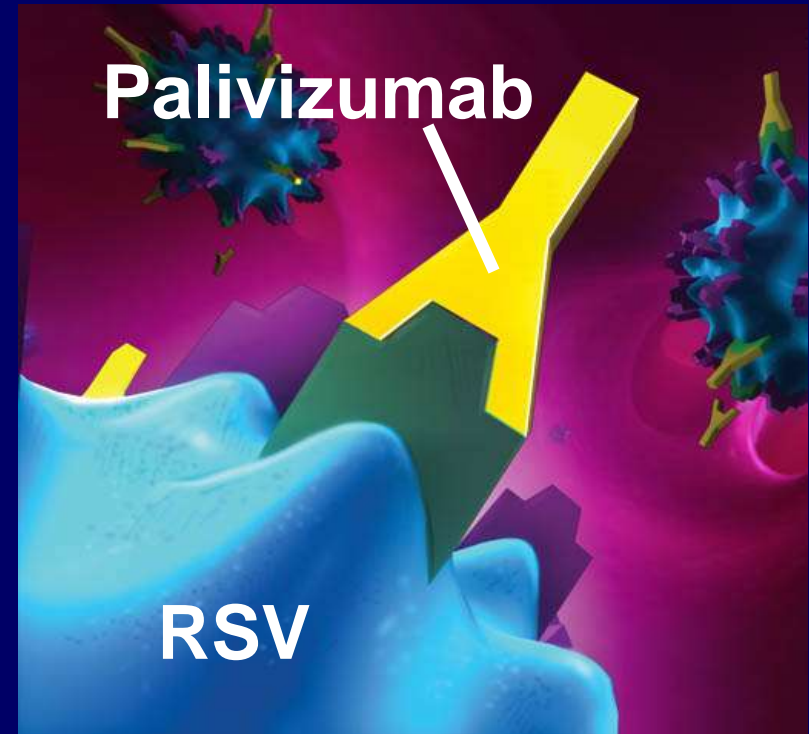


- Preventive: Handwashing
- Monoclonal Antibodies
- Vaccine- still on the horizon
- siRNA (Small interfering RNA) studies in the pipeline



# Synagis<sup>®</sup> (Palivizumab): Mechanism of Action

- **Binds the F protein of RSV**
- **Blocks the fusion of infected cells**
- **Reduces viral activity and cell-to-cell transmission of RSV**





**BUT.....IS Palivizumab  
TRULY EFFICACIOUS  
AND SAFE FOR INFANTS**

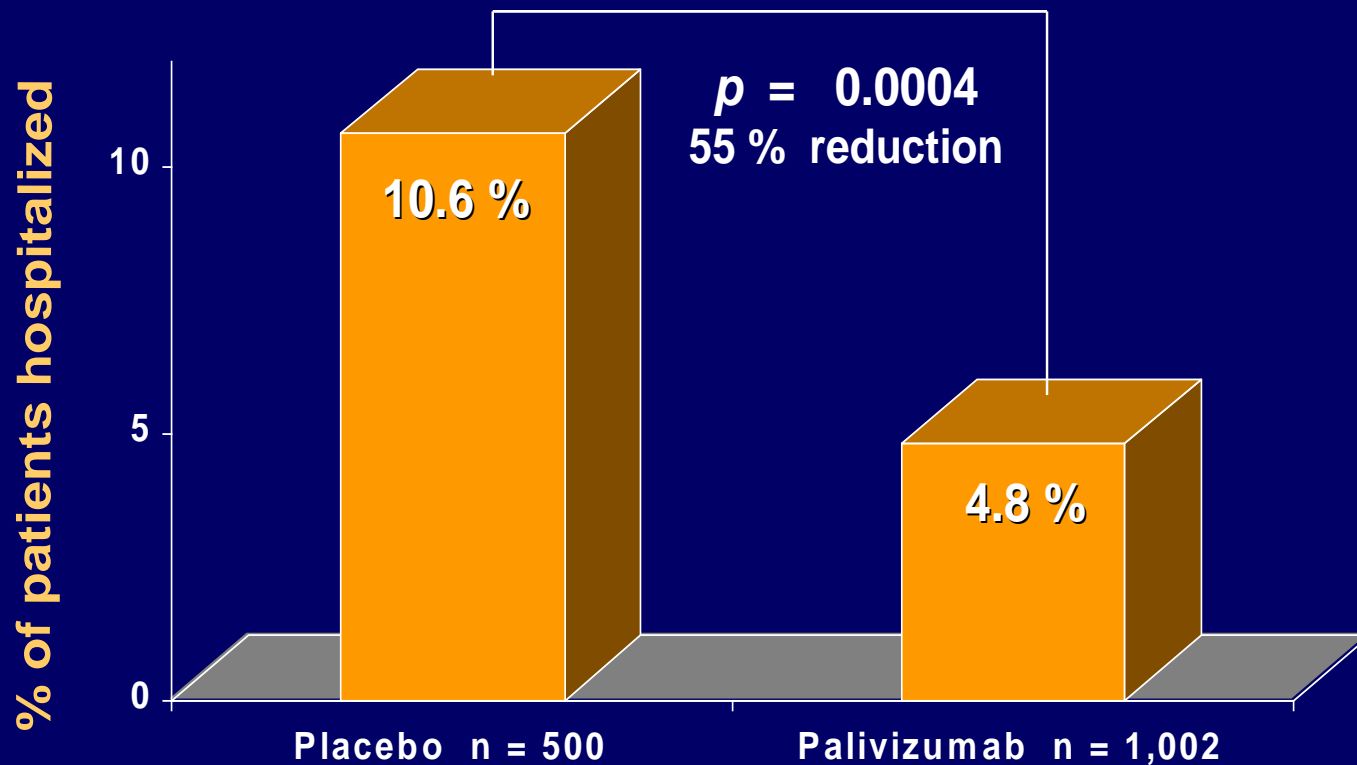


# IMpact Trial - Overview

- **Patients**
  - $\leq 2$  years w / BPD or
  - $\leq 6$  months and premature birth ( $\leq 35$  weeks GA)
- **Randomization (139 centres)**
  - 5 monthly placebo injections ( N = 500 )
  - 5 monthly injections of palivizumab 15 mg / kg ( N = 1,002 )
- **Design**
  - **Primary endpoint :**
    - hospitalization with confirmed RSV infection

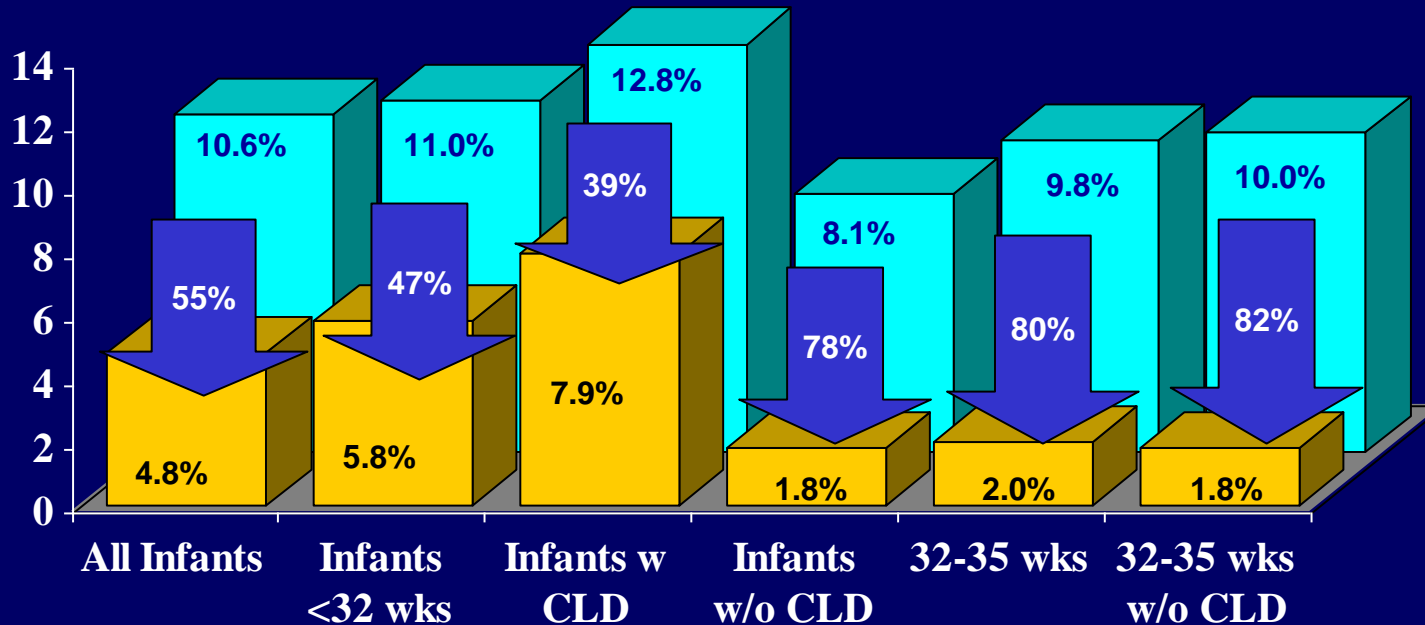
# IMpact Trial – Efficacy Results

## Primary Endpoint : RSV Hospitalizations



# Impact-RSV: Hospitalization Rates by Subgroup

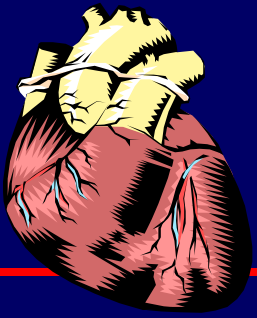
■ Palvizumab Group ■ Placebo Group



The Impact-RSV Study Group. Pediatrics. 1998;102(3):531-537.

# Impact Trial versus Combined Analysis (CA) of Studies

GA in Weeks	29 – 32	32 – 35	BPD < 2 yrs
N (# patients)	4854	2829	3675
# Studies	4	10	11
% reduction in RSV hospitalization Rates...Impact / CA	81/80	79/85	38/69
NNT (Impact / CA)	14/12	13/12	20/8



# Cardiac Study Design\*

- **Randomized, double-blind, placebo-controlled**
  - Stratification by hemodynamically significant cardiac lesion (cyanotic vs. other) and site. Infants <24 months
  - 1:1 randomization (Synagis vs placebo)
- **Multicenter (76 centres)**
  - US, Canada, France, Germany, Poland, Sweden, UK
- **Intent-to-treat**
  - Analysis of all patients as randomized

\*Design identical to IMpact-RSV study  
Except IMpact-RSV had 2:1 randomization

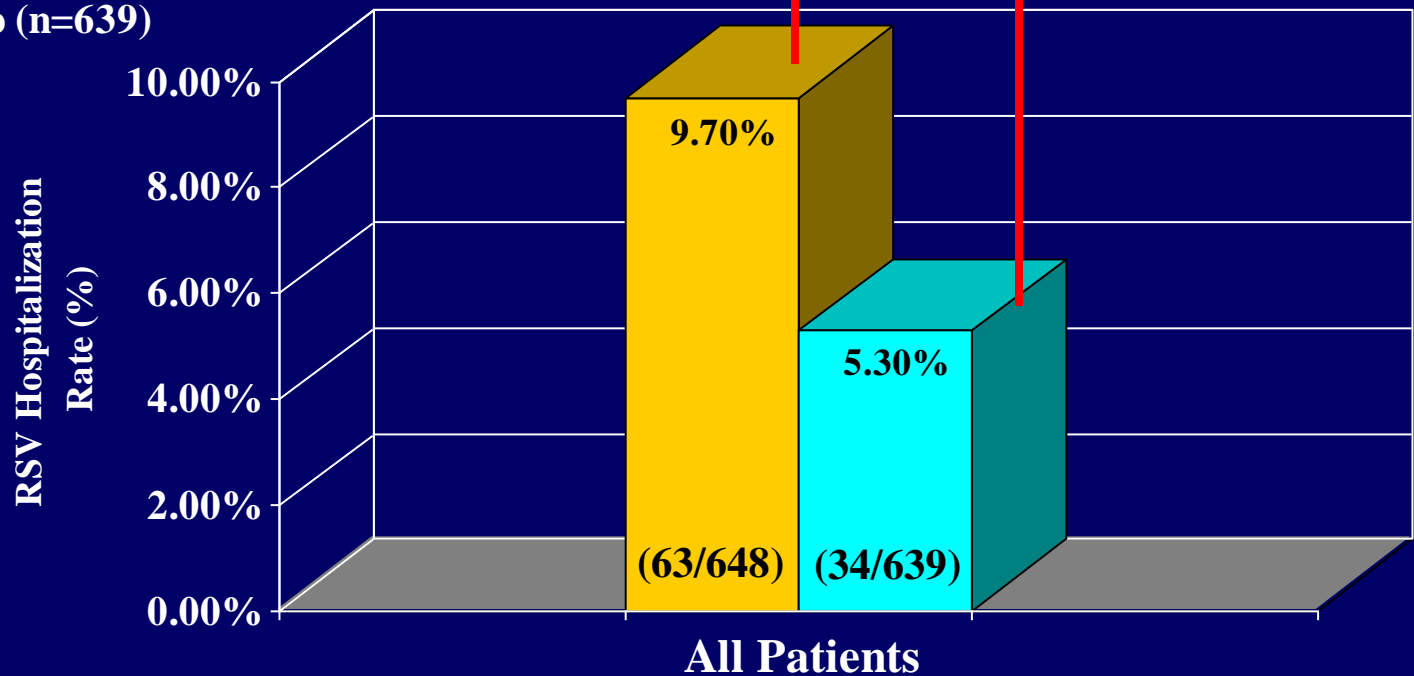
Feltes TF et al J.Pediatr 2003;143:532-40.

# Palivizumab CHD Study: RSV Hospitalization Rates

45% relative reduction  
(p=0.003)

■ Placebo (n=648)

■ Palivizumab (n=639)



# HSD

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- **Unrepaired or partially palliated (on cardiac medications) cyanotic heart disease**
- **Acyanotic lesion that requires anti-congestive medication (diuretic, afterload reduction) and /or presence of pulmonary hypertension (RV systolic pressure  $\geq$  40 mmHg)**
- **Any repaired CHD that has significant residual disease that requires anticongestive medication**

# RSV Hospitalization: US Outcomes Registry

	2003/04 Registry (N=6,050)	2002/03 Registry (N=6,291)	2001/02 Registry (N=5,084)	2000/01 Registry (N=2,049)	1996-97 IMpact Trial (N=1,002)	1996/97 IMpact Trial Placebo (N=500)
<b>All Patients (%)</b>	<b>0.7</b>	<b>1.1</b>	<b>1.5</b>	<b>2.9</b>	<b>4.8</b>	<b>10.6</b>
<b>Premature without CLD (%)</b>	<b>0.7</b>	<b>1.2</b>	<b>1.2</b>	<b>2.1</b>	<b>1.8</b>	<b>8.1</b>
<b>All &lt;32 Weeks Gestational Age (%)</b>	<b>1.1</b>	<b>1.6</b>	<b>1.7</b>	<b>4.5</b>	<b>5.8</b>	<b>11.0</b>
<b>All 32-35 Weeks Gestational Age (%)</b>	<b>0.2</b>	<b>0.7</b>	<b>1.3</b>	<b>1.6</b>	<b>2.0</b>	<b>9.8</b>
<b>Patients with CLD (%)</b>	<b>1.8</b>	<b>1.9</b>	<b>2.2</b>	<b>5.8</b>	<b>7.9</b>	<b>12.8</b>

# USA Palivizumab Outcomes Registry

## ICU Admits & Mechanical Ventilator Use

	2003-04 (n=6050)*	2002-03 (n=6291)*	2001-02 (n=5084)*	2000-01 (n=2049)*
<b>All Hospitalizations</b>	41/6050	72/6291	78/5084	64/2049
<b>All ICU Admissions</b>	11	10	13	20
<b>Percent w ICU Admit</b>	0.18%	0.16%	0.26%	0.98%
<b>Percent Requiring Vent</b>	0.05%	0.05%	0.10%	0.58%

\*Injection and hospitalization information available for (n) subjects listed

Courtesy. Cohen AH. MedImmune.Inc. 2005

# RISK Factors for RSV Hospitalization



# Study Team-16 centers/9 provinces



Abbott Laboratories: P. Manzi, A. Michaliszyn, D. Parison  
 JSS Medical Research: S. Boukas, F. Psaradellis J. Sampalis  
**23 Research Nurses Across Canada**

# Risk Factors for RSV Hospitalization

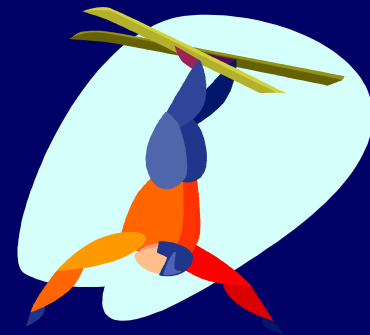
66 +RSV Hospitalized vs 1692 no LRTI Admission

Risk Factor	OR ( 95% CI )	P Value
Subject in day care	12.32 ( 2.56,59.34 )	0.002
Born in Nov-Jan	4.88 ( 2.57,9.29 )	<0.001
Any preschool age siblings	2.76 ( 1.51,5.03 )	0.001
B.Wt.<10%	2.19 ( 1.14,4.22 )	0.019
Male gender	1.91 ( 1.10,3.31 )	0.02
>2 smokers in household	1.71 ( 0.97,3.00 )	0.064
Total individuals in home>5	1.69 ( 0.93,3.10 )	0.088
Eczema in 1 <sup>st</sup> degree relatives	0.42 ( 0.18,0.99 )	0.049



**IRIS**

# **The FLIP Study**



**A Case-Control Study of the risk factors linked to RSV hospitalization in 33-35 week infants in Spain**

- **50 Spanish Hospitals**
- **186 cases hospitalized with RSV during October 2002-April 2003**
- **371 controls selected in June 2003**

# Risk Factors (FLIP) for RSV Hospitalization

## 186 +RSV Hospitalized vs 371 controls

Risk Factor Value	OR ( 95% CI )	P
Born in July-Dec	3.95 ( 2.65,5.90 )	<0.001
Breast Feeding $\leq$ 2 mos	3.26 ( 1.96,5.42 )	<0.001
School age siblings ( $\geq$ 1)	2.85 ( 1.88,4.33 )	<0.001
Individuals in home $\geq$ 4	1.91 ( 1.19,3.07 )	0.0074
History of wheezing in the family	1.90 ( 1.19,3.01 )	0.0068

Risk of hospitalization  $\uparrow$ 3.6x for infants with >2 risk factors

# Risk Factors for RSV hospitalization in 33-35 weeks GA Infants

Spanish Study (FLIP) <sup>1</sup>		Canadian Study (PICNIC) <sup>2</sup>	
Risk Factors	OR (P-value)	Risk Factors	OR (P-value)
*Chronological age at start of the RSV season ≤10 wk	3.95 (p<.001)	Born Nov, Dec or Jan	4.88 (p<.001)
*≥1 school-age siblings	2.85 (p<.001)	Pre-school age siblings	2.76 (p<.001)
≥4 residents or visitors	1.91 (p<.007)	>5 individuals in the home	1.69 (p=.088)
*Male gender	1.43(p=0.05)	Male gender	1.91 (p=0.02)
*Number/Family history of Wheezing/Atopy	1.90(p=0.068)	Eczema in 1 <sup>st</sup> degree relatives	0.42 (p=0.04)
Smoking not a risk factor. During the study smoking ↓ from 52% to 30%		>2 smokers in the household	1.71 (p=.064)
*Breast feeding <2 months	3.26 (p<.001)	Daycare attendance	12.32 (p=.002)
*Birth Weight	(p=0.042)	Small for GA (<10 <sup>th</sup> %)	2.19 (p=.019)

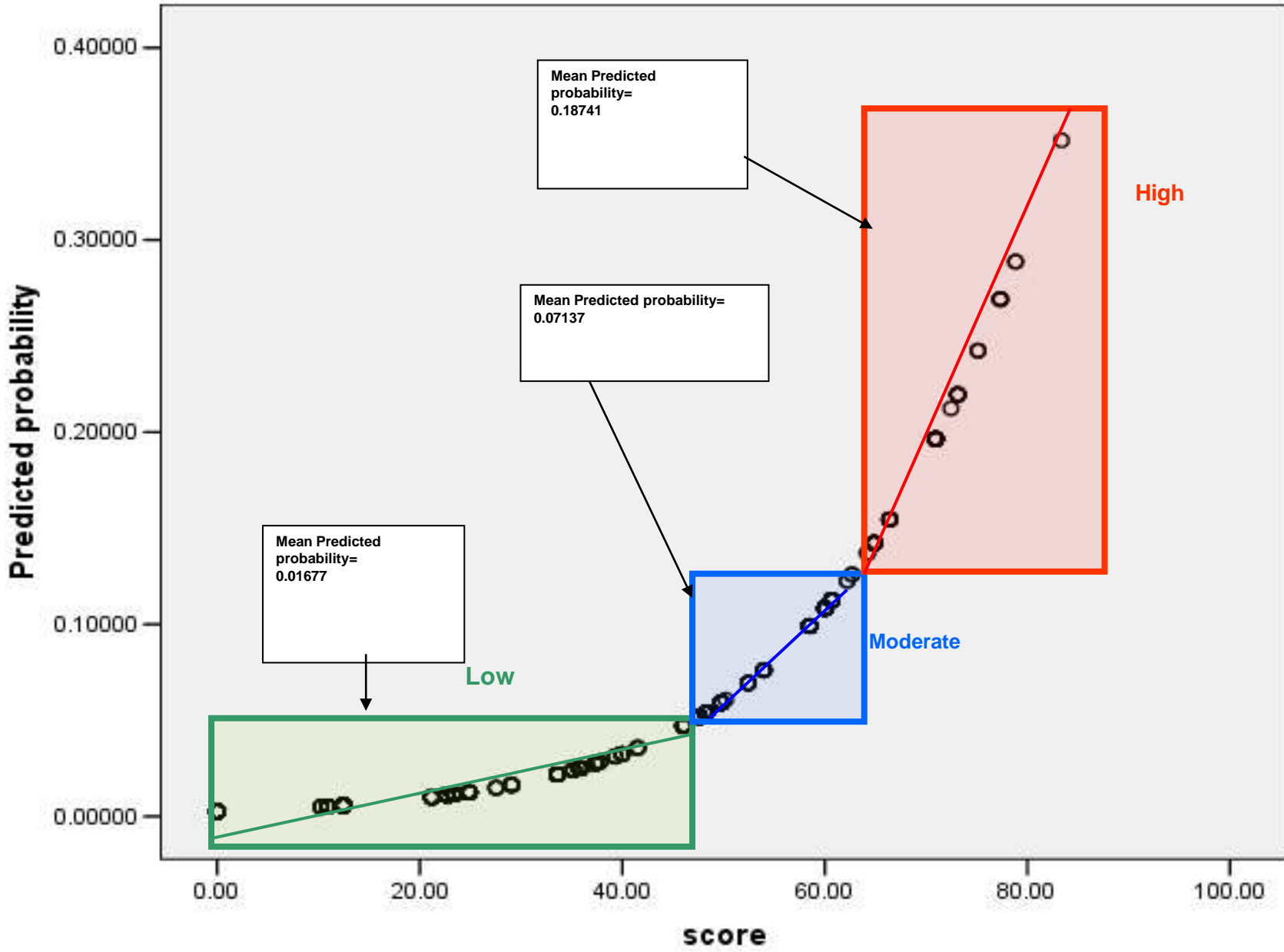
\*Significant in European Model only <sup>3</sup>

1. Figueras-Aloy J et al. PIDJ 2004;23:815-20
2. Law BJ et al. PIDJ 2004;23:806-14
3. Simoes EA. Ped Res 2008;9:78

# Variables in the final Logistic Regression Model (Risk Scoring Tool- PICNIC Study)

Variable	Score
SGA (GA <10%) [ Yes/No ]	12
Gender (Male/Female)	11
Birth Month (Nov,Dec,Jan)	25
Subject or Siblings in Day Care [ Yes/No ]	17
Family History without eczema [ Yes/No ]	12
>5 individuals in the home counting the subject [ Yes/No ]	13
Two or more smokers in the house [Yes/No ]	10
<b>Total</b>	<b>100</b>

# Total Score vs Predicted Probability of an RSV Hospitalization by Risk Category





# OBJECTIVE

- To study the impact of the Risk-Scoring Tool as a strategy for targeting palivizumab prophylaxis effectively in 33-35 week GA infants by evaluating the incidence of RSV infections resulting in emergency room visits (ER) and hospitalization

QUESTION	ANSWER	
	YES	NO
Birth month is Nov, Dec or Jan	25	0
Infant to attend daycare or siblings in daycare	17	0
More than 5 individuals in the home including the Infant	13	0
SGA ( Birth Weight <10% for gestational age)	12	0
Immediate family (mother, father, sibling) history without eczema ( Without eczema =YES )	12	0
Male gender	11	0
2 or more smokers in the household	10	0
<b>TOTAL SCORE:</b>		
<b>Eligible to receive Palivizumab if score is between 49-100</b>		

# METHODS

- **Design**: Prospective, descriptive study
- 430 infants were recruited between 2005-2008
- Infants at moderate (score 49-64) and high risk (65-100) received prophylaxis
- Parents were contacted by telephone at the end of each RSV season and medical records checked for RSV hospitalization
- **Analysis**: Chi-square + ANOVA ( $p=0.05$ )

# OUTCOMES

78/430 (18.1%) received prophylaxis  
100% follow-up rate

Eligible 33-35 GA  
Infants

8 Infants not eligible  
Motavizumab Study

Risk Assessment Score Performed  
(N=430)

Low Risk Score  
(0-48)

N=346

5 RSV + Hospitalizations  
1 ER Visit. Discharged

Moderate Risk Score  
(49-64)

N=57

No RSV + Hospitalizations  
No ER Visits

6 refused  
prophylaxis

High Risk Score  
(65-100)

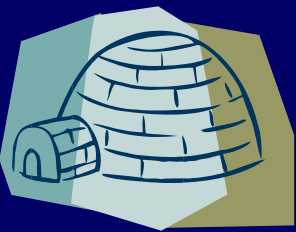
N=27

No RSV + Hospitalizations  
1 ER Visit. Discharged

# SUMMARY

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- **The RST is a valuable, user-friendly instrument to guide judicious use of RSV prophylaxis in 33-35 week GA infants**
- **81.9% of the total cohort did not receive prophylaxis (cost-effective)**
- **Sets the stage for comprehensive guidelines based on evolving scientific evidence**



# Canadian Paediatric Society Guidelines - 2009

(Paediatr Child Health 2009;14:521-26)

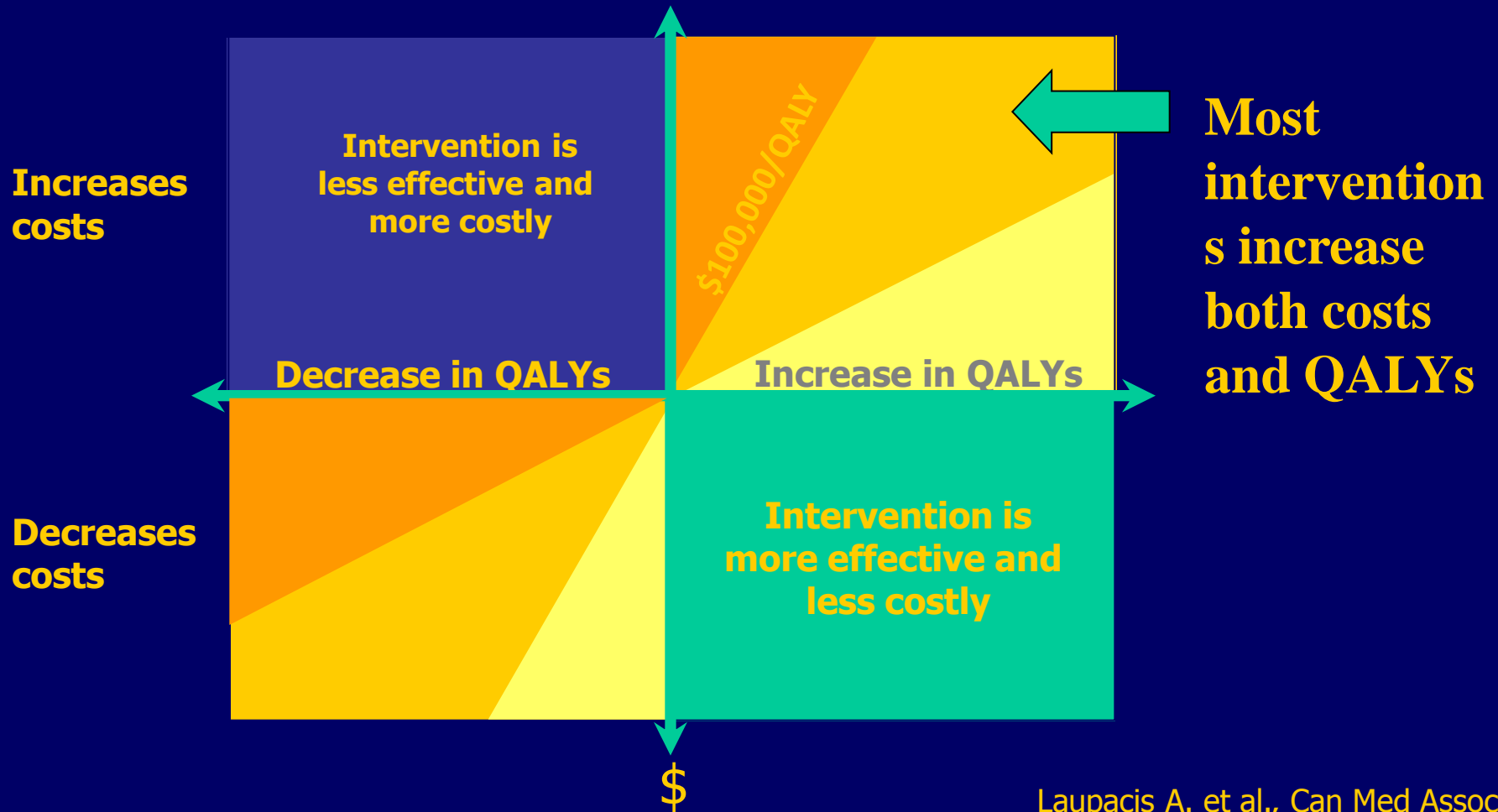


- Preterm Infants < 32 weeks gestation and < 6 months at the start of the RSV season
- Infants <2 years of age with CLD / BPD requiring medical therapy (oxygen/steroids or daily bronchodilators/) 6months preceding the RSV season or pulmonary disorders requiring oxygen therapy
- Children <2 years with hemodynamically significant cardiac disease
- Moderate-high risk infants, 33-35 weeks GA < 6 months of age at the start of the RSV season – provincial decision based on RST
- Infants <36 weeks gestation and all full term Inuit infants < 6 months of age at the start of the winter season who live in remote northern communities and require air transportation to medical care

**How do we compare  
palivizumab to other  
medications?**



# What is the usual impact of a technology on costs and health?



# How do other vaccines compare?

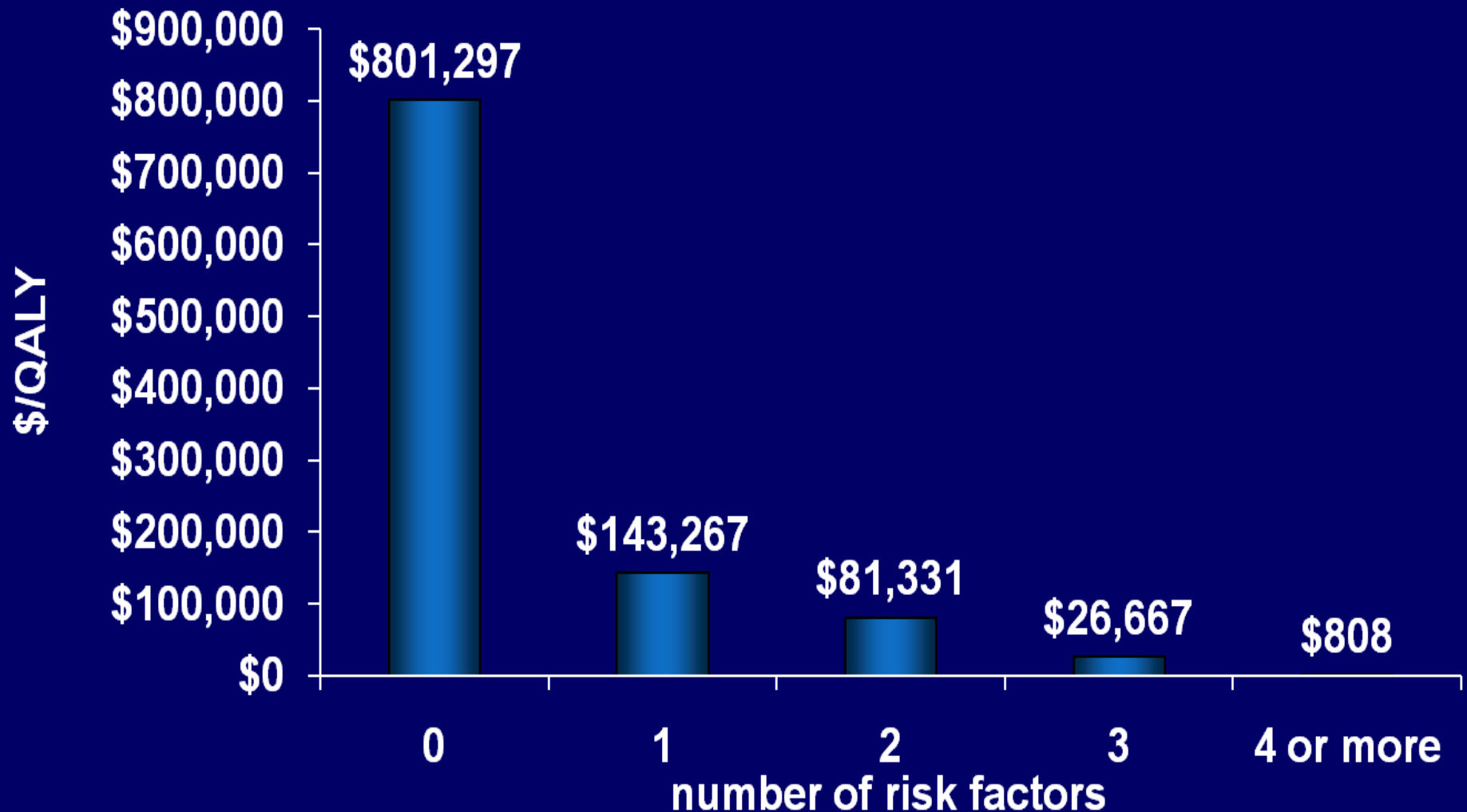


- Pneumococcal conjugate vaccine
  - USD\$175,300 / LYG
- RSV-IG
  - USD\$138,600 / LYG
- Palivizumab
  - USD\$66,200 / LYG
- Strutton DR, Stang PE. J Pediatr. 2003 Nov;143(5 Suppl):S157-62.

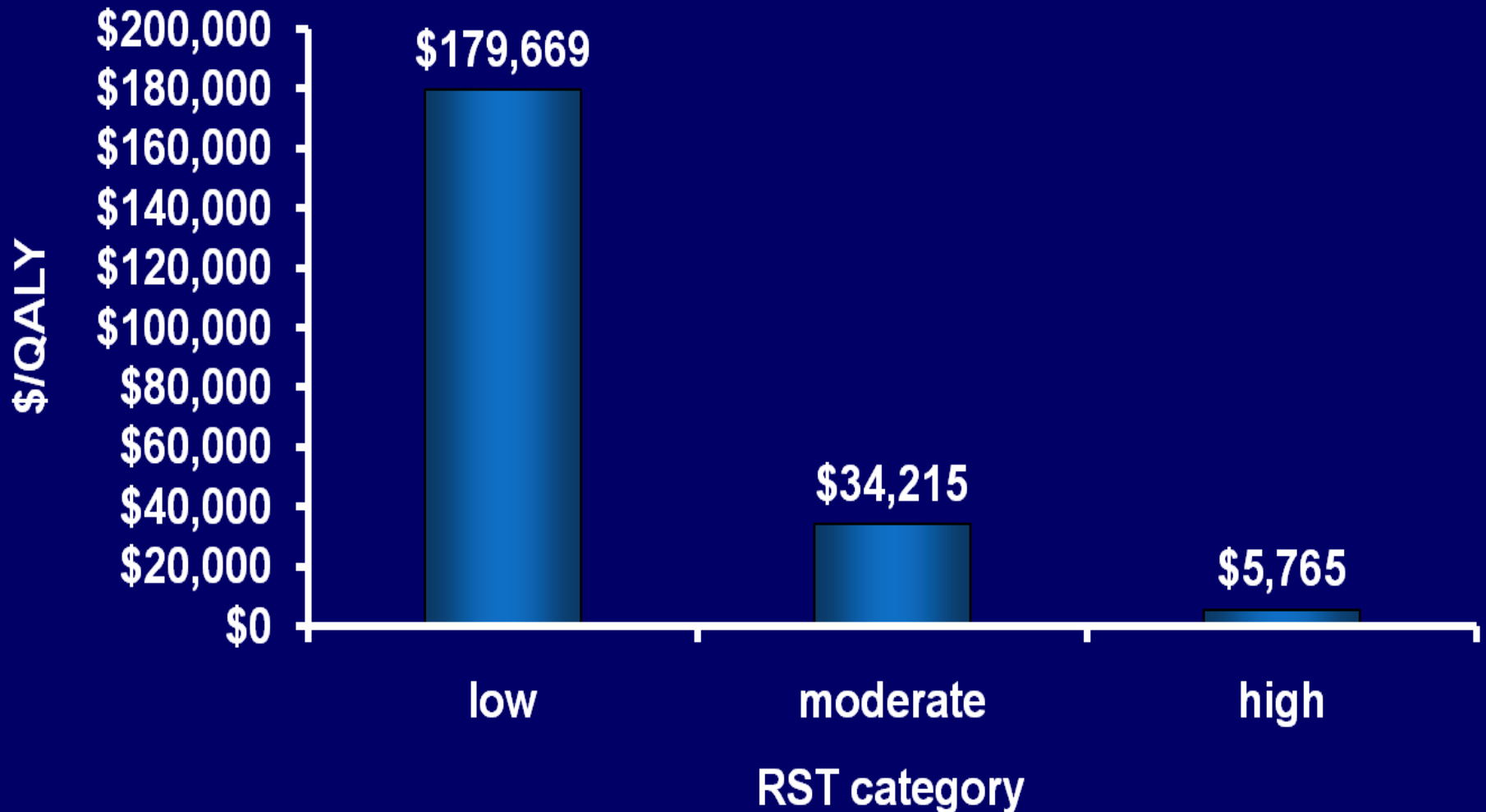


- Pneumococcal conjugate vaccine
  - 2000 CAD\$79,000 / LYG (Lebel et al 2003)
- Palivizumab—our results
  - Premature 32-35 wk GA → \$30,320 / LYG

# Impact of varying number of risk factors on cost-effectiveness



# Impact of varying type of risk factors on cost-effectiveness



\*RST= Risk scoring tool



**Where do we go  
from here?**

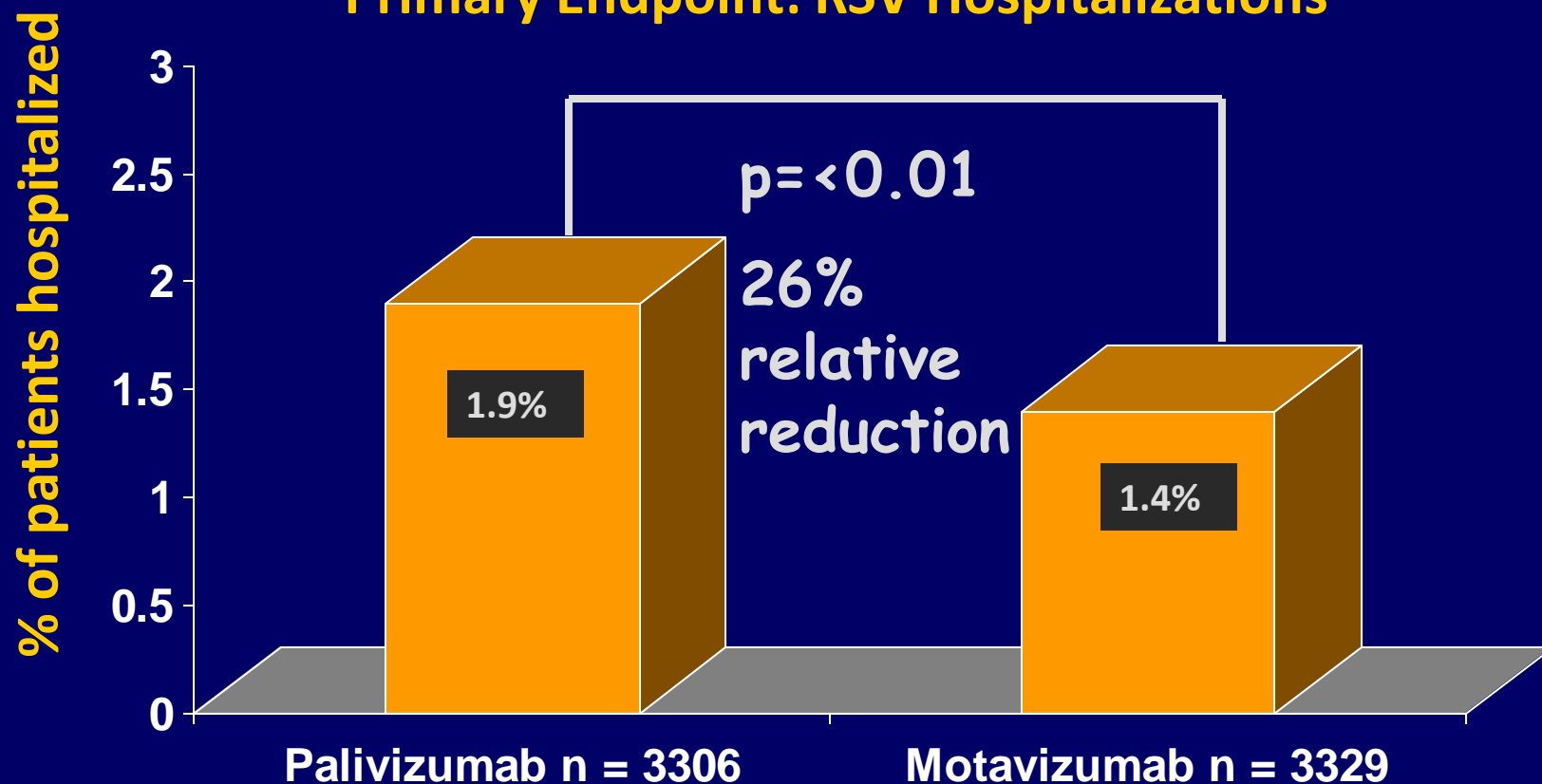
- **Palivizumab is safe, cost-effective and efficacious – important for a pediatrician**
- **Can we improve the effectiveness of palivizumab?**

# Motavizumab Trial Overview

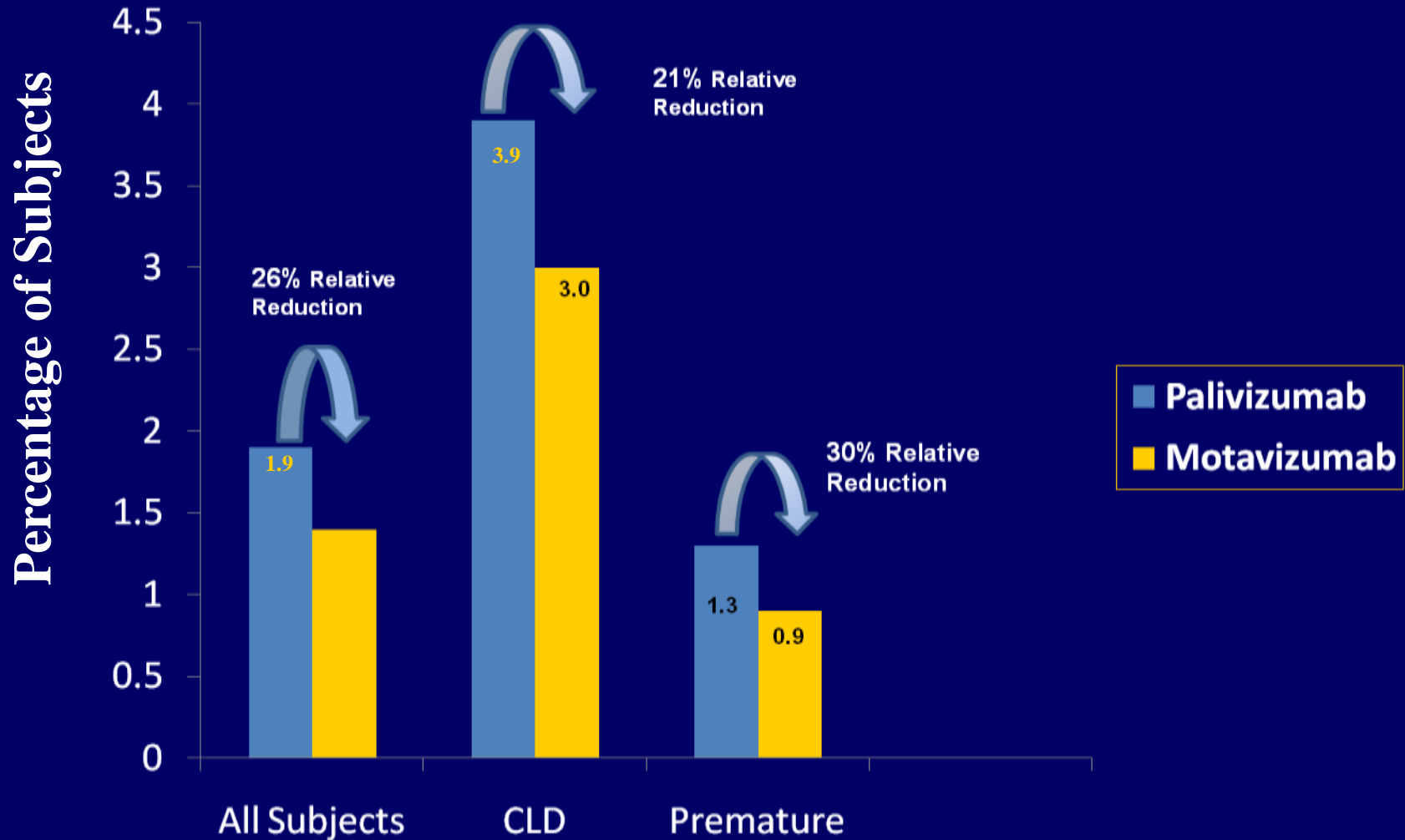
- Patients ( N= 6635) recruited over 2 RSV seasons (Nov 1 2004 - Dec 2005)
  - $\leq$  2 years w / BPD or
  - $\leq$  6 months and premature birth (  $\leq$  35 weeks GA)
- Randomization (347 centres in 24 countries)
  - 5 monthly injections of motavizumab 15mg/kg (N=3329)
  - 5 monthly injections of palivizumab 15 mg/kg (N=3306)
- Design- randomized, double-blind, controlled study
  - **Primary endpoints :**
    - Hospitalization with confirmed RSV infection
    - Safety

# Motavizumab vs Palivizumab: Efficacy Results

## Primary Endpoint: RSV Hospitalizations

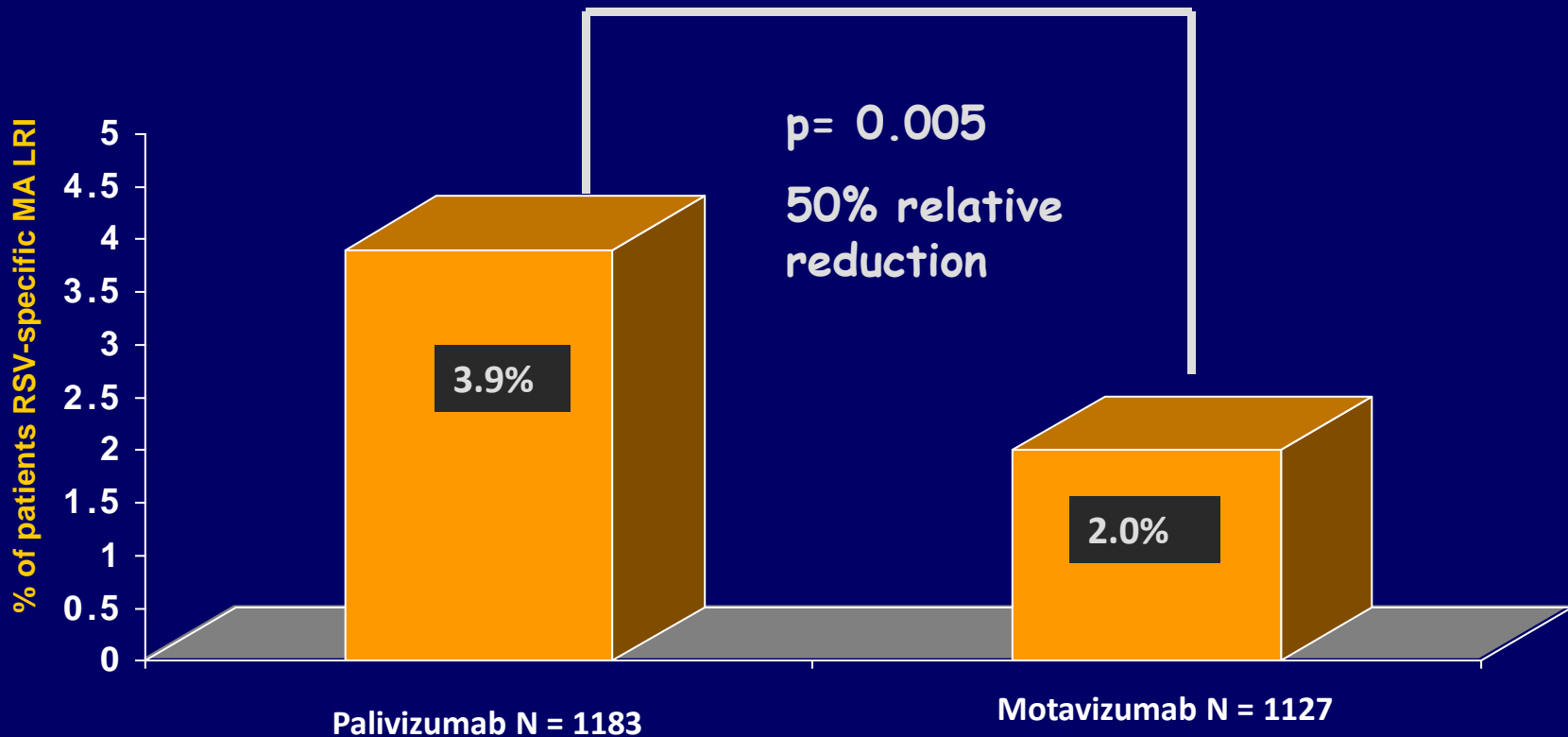


# Motavizumab is Non-inferior to Palivizumab in Reducing the rate of RSV Hospitalization



# Motavizumab vs Palivizumab: Efficacy Results

Secondary Endpoint : RSV- specific outpatient medically attended LRI (133/347 sites)



MA LRI = outpatient medically attended lower respiratory tract infection

# Antivirals for RSV: Small Molecules

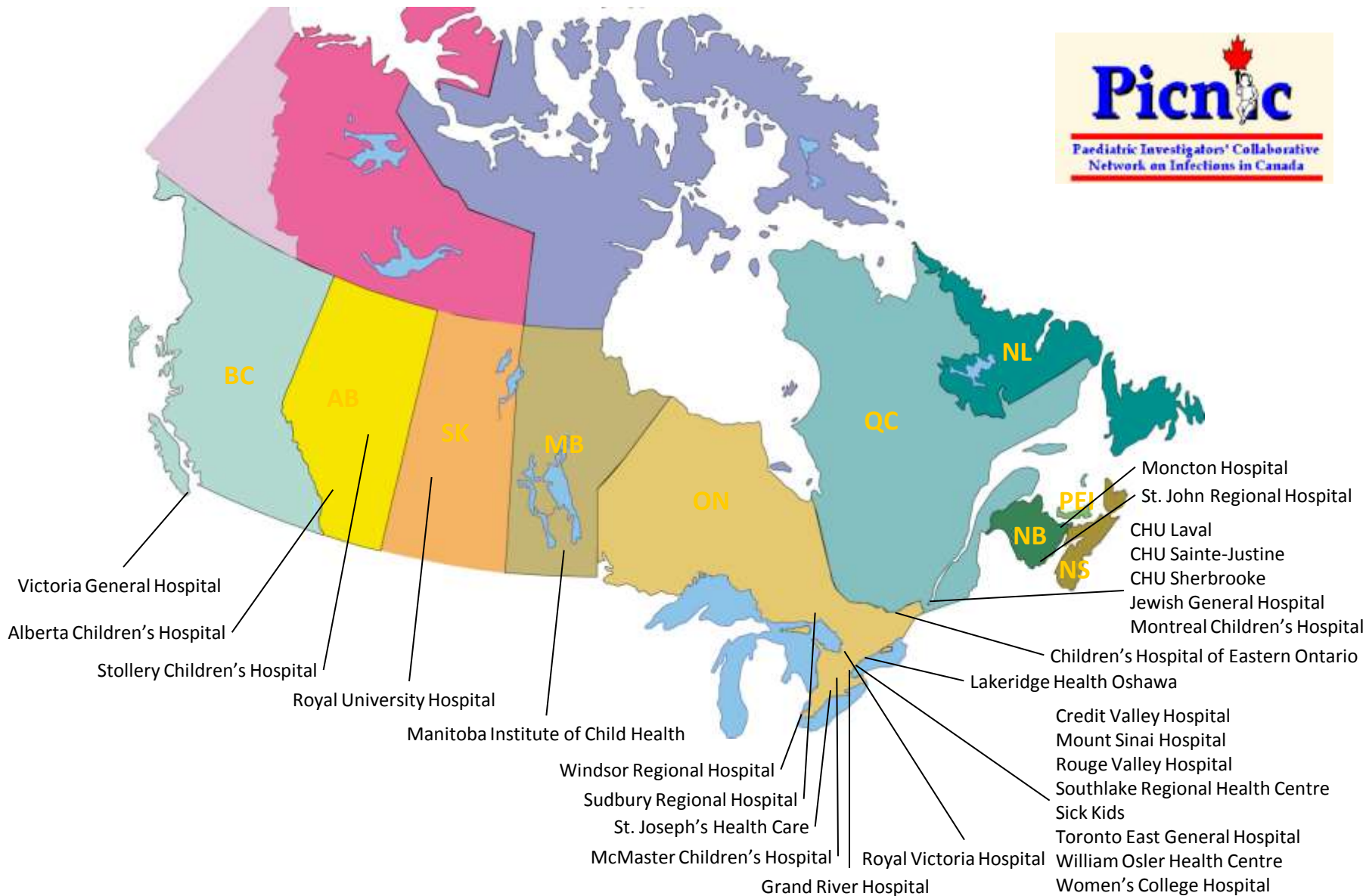
- Fusion protein inhibitors:
- Inhibitors of viral replication
- siRNA (small interfering RNA's): Work through RNA interference to ↓ protein production by inhibiting target mRNA in a sequence-specific manner. Intranasal administration in the mouse model can inhibit RSV replication

Devincenzo JP et al. Am J Respir Crit Care Med. 2010 Jul 9.

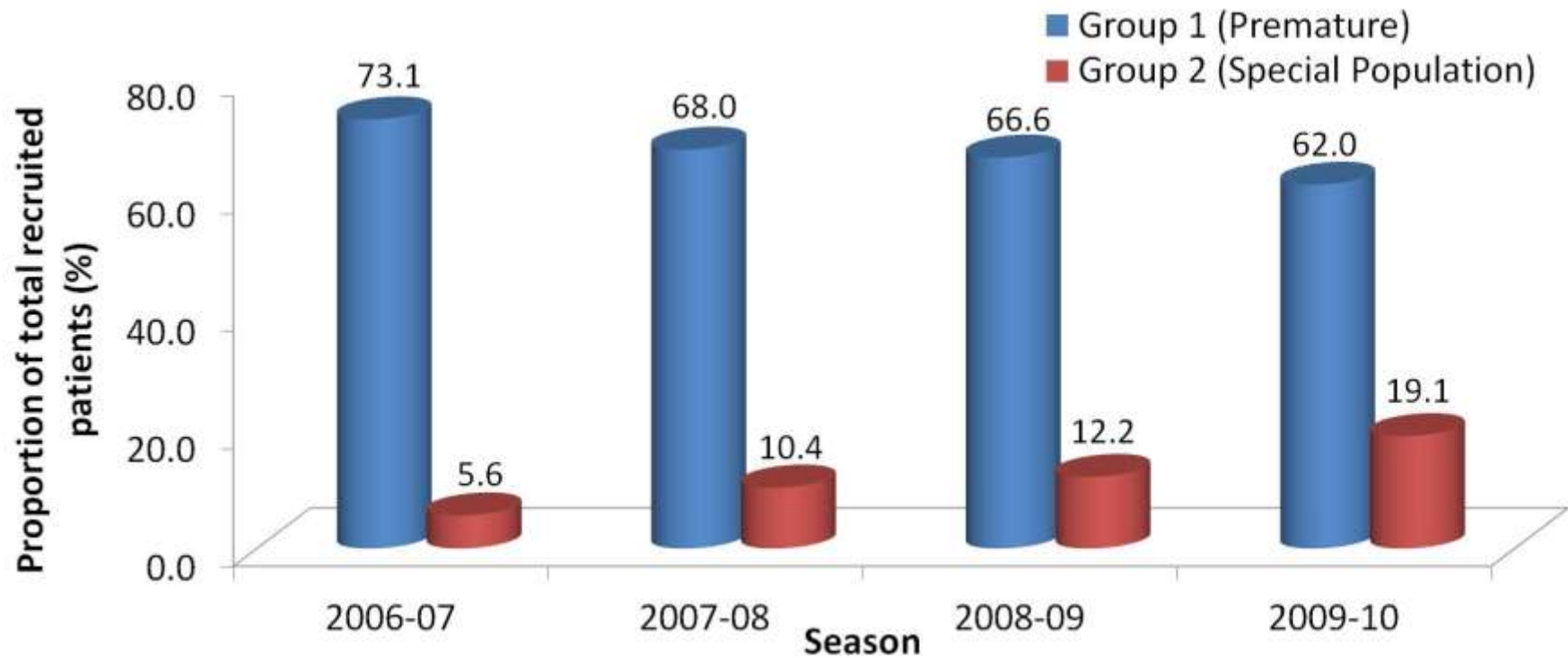
Devincenzo JP et al. Proc Natl Acad Sci U S A. 2010 May 11;107(19):8800-5

Ramilo O. Paediatr Resp Rev 2009;10:23-25

# 29 CARESS Sites (2005-2010; n= 7699)

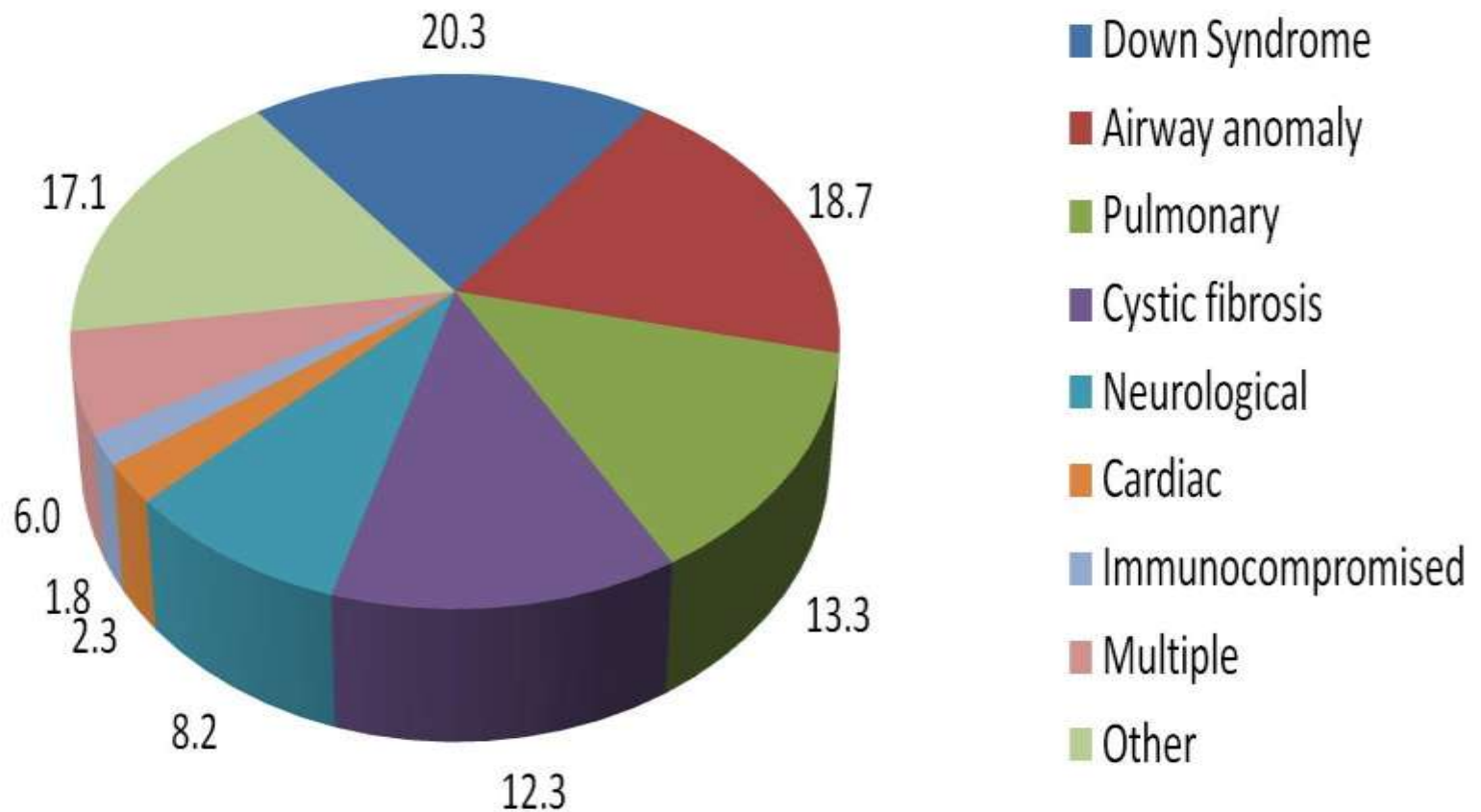


# Enrolment across 2006-2010 RSV Seasons (CARESS Registry)



3.4- fold increase from 5.6% to 19.1%

# Sub-Categories of Group 2 infants



## SUMMARY

- Palivizumab is safe, efficacious and cost-effective in country specific high-risk populations
- The CPS supports use in moderate-high risk 33-35 weeks GA infants based on current evidence
- Motavizumab is awaiting US FDA approval
- New drugs for the treatment of RSV are in the pipeline
- Preliminary trials of a RSV vaccine have been completed in adults but it will be several



BAYLOR COLLEGE OF MEDICINE ARCHIVES



*Thanks ...*



*Questions?*