Virus Respiratorio Sinciziale nell'infanzia: la strada verso la prevenzione universale

Eugenio Baraldi

RSV presente e futuro

RSV: PRESENTE E FUTURO

Prof. Eugenio Baraldi
Dipartimento Salute Donna e Bambino
Azienda Ospedale-Università di Padova
Istituto di Ricerca Pediatrica 'Citta' Speranza'

ReSViNET
RESPIRATORY SYNCYTIAL VIRUS NETWORK

Fondazione
ISTITUTO DI RICERCA
PEDIATRICA

Dichiarazione sul Conflitto di Interessi

Il sottoscritto Eugenio Baraldi in qualità di relatore all'evento
'**VRS nell'infanzia, Padova 22 Giugno 2024**'
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 dell'Accordo Stato-Regione del 19 aprile 2012

Dichiara

che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

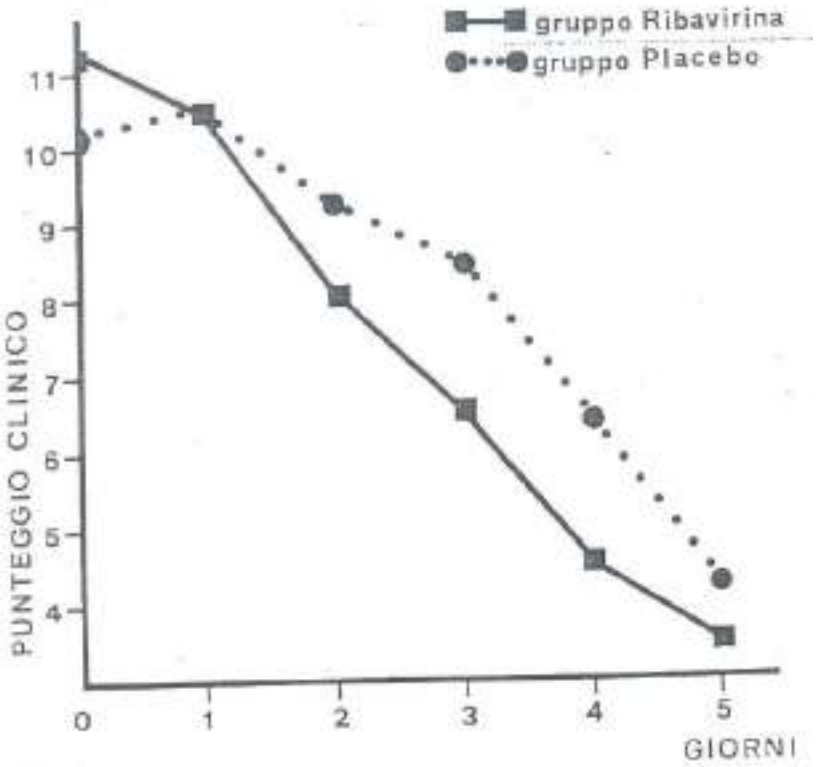
- **Astra-Zeneca, Chiesi, Sanofi**
- **Membro RESVINET,** network indipendente per lo studio della patologia respiratoria da VRS

Ribavirina per via aerosolica nel trattamento della bronchiolite da virus respiratorio sinciziale

1988

Aerosolized Ribavirin in the treatment of respiratory syncytial virus bronchiolitis

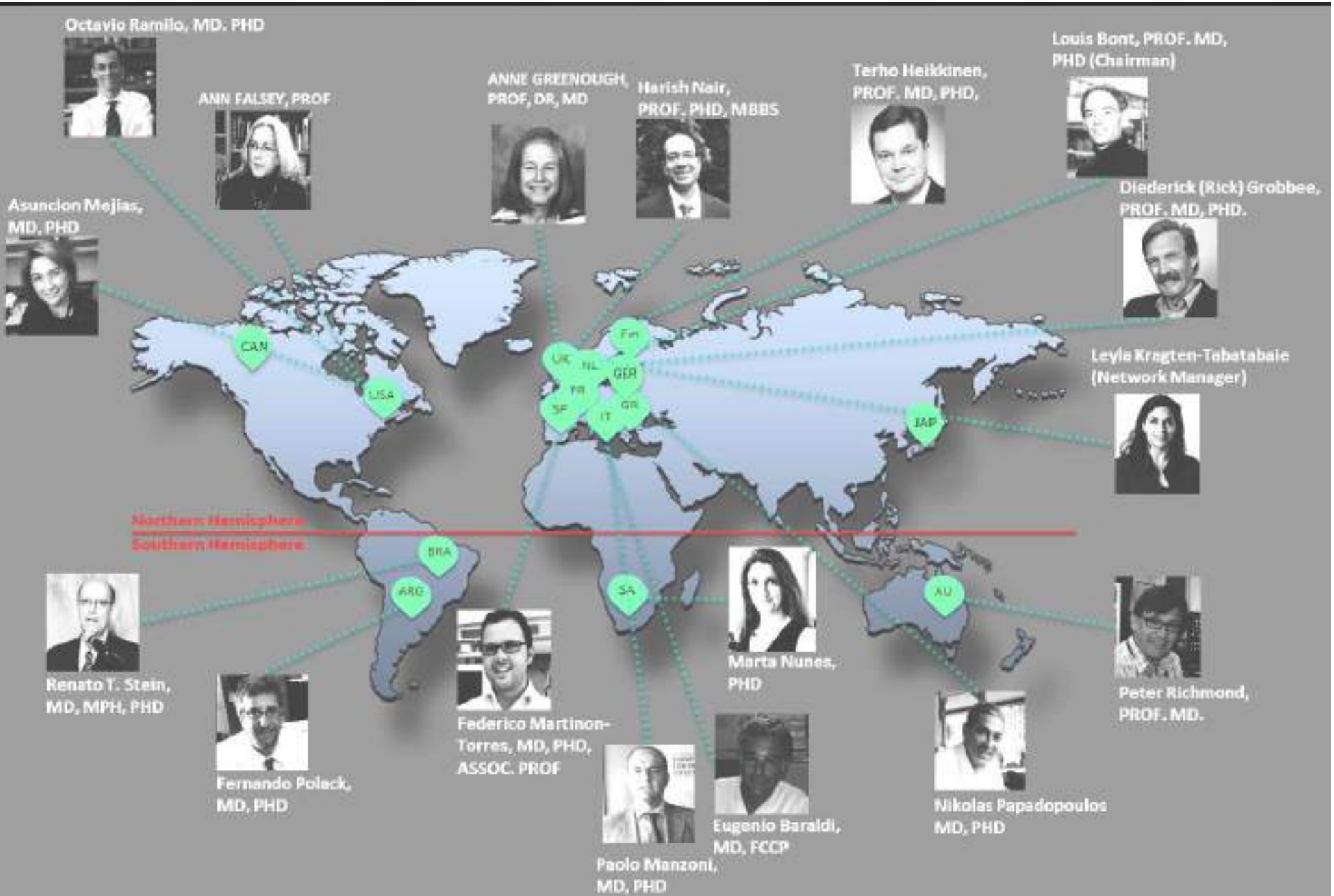
E. Baraldi, S. Zanconato, P. Biban, G. Rebeschini, L. Da Dalt, F. Donzelli, F. Zacchello
Dipartimento di Pediatria, Università di Padova



Riv. Ital. Ped. (I.J.P.), 14, 104-108, 1988

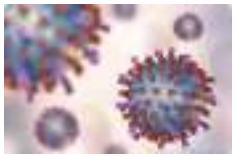
ReSViNET Foundation

An independent research network supporting research on RSV field



Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics

Natalie I Mazur, Federico Martinón-Torres, Eugenio Baraldi, Brigitte Fauroux, Anne Greenough, Terho Heikkinen, Paolo Manzoni, Asuncion Mejias, Harish Nair, Nikolaos G Papadopoulos, Fernando P Polack, Octavio Ramilo, Mike Sharland, Renato Stein, Shabir A Madhi, Louis Bont, in collaboration with Respiratory Syncytial Virus Network (ReSViNET)



ReSViNET

1 in 56 (1.8%) healthy infants are hospitalized with RSV in the first year (Wildenbeest Lancet RM 2023

Risk factors
- >13× mortality in very low birthweight (<1500 g) compared with >2500 g
- >30× mortality in HIV-positive children
- 4·3% mortality in immuno-compromised patients

Mortality burden
- >99% in low-income countries

Mortality
66 000–199 000 deaths in children <5 years
Highest in infants < 6 months

50% outside of hospitals

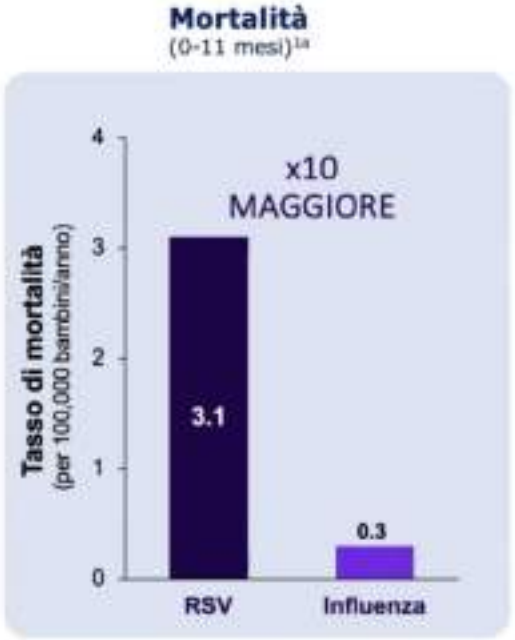
Hospitalisation
3·4 million LRTI episodes requiring hospitalisation
- 0·52% children <24 months of age
- Highest age-specific hospitalisation rate at 1 month
- 44% hospitalisations occur <2 months of age
- 79% of hospitalised children previously healthy

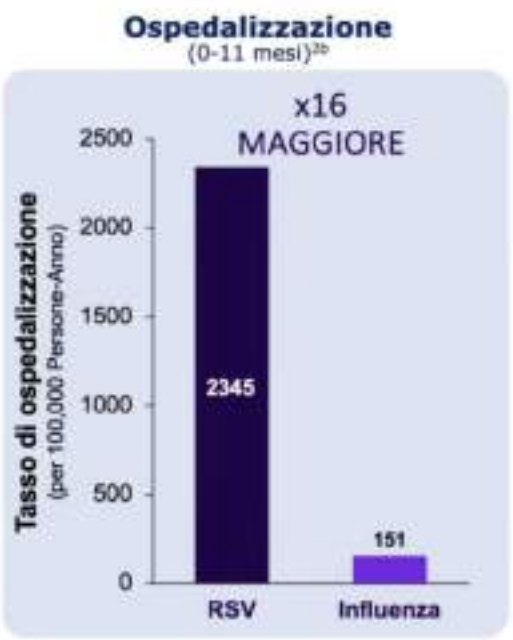
when the lungs are still developing

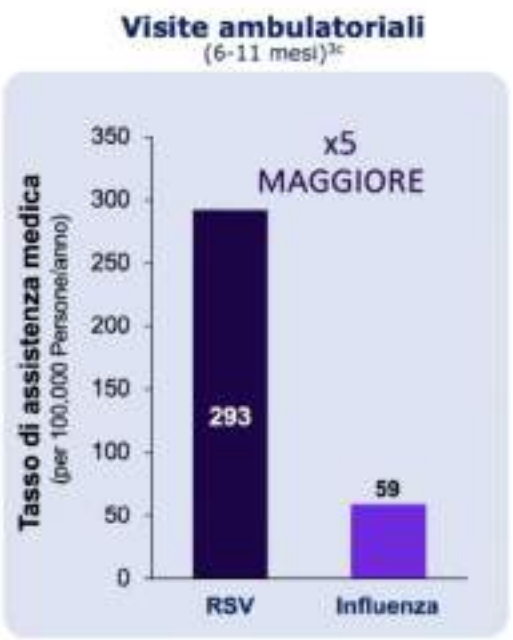
2015
Global incidence RSV LRTI
22% LRTI due to RSV
33·8 million RSV LRTI worldwide

Lancet RM 2015

Confronto RSV vs Influenza per mortalità, ospedalizzazioni e assistenza medica per infezioni respiratorie (bambini <1 anno)







1. Thompson WW, et al. *JAMA*. 2003; 289(2):179-186.
2. Zhou H, et al. *Clin Infect Dis*. 2012; 54(10):1427-1436.
3. Simpson MD, et al. *Open Forum Infect Dis*. 2016; 3(2):ofw081.
4. CDC. *MMWR Recomm Rep*. 2004 May 28;53(RR-6):1-40.

a. Estimated infant RSV-associated mortality for pneumonia and influenza deaths; CDC Data, 1990-1999.
b. Infant hospitalization rates for RSV and influenza; CDC Data, 1993-2008.
c. Estimated seasonal incidence of medically attended RSV and influenza; Marshfield, 2006-2010.
d. Data derives from different studies and over different years.

nature COMMUNICATIONS

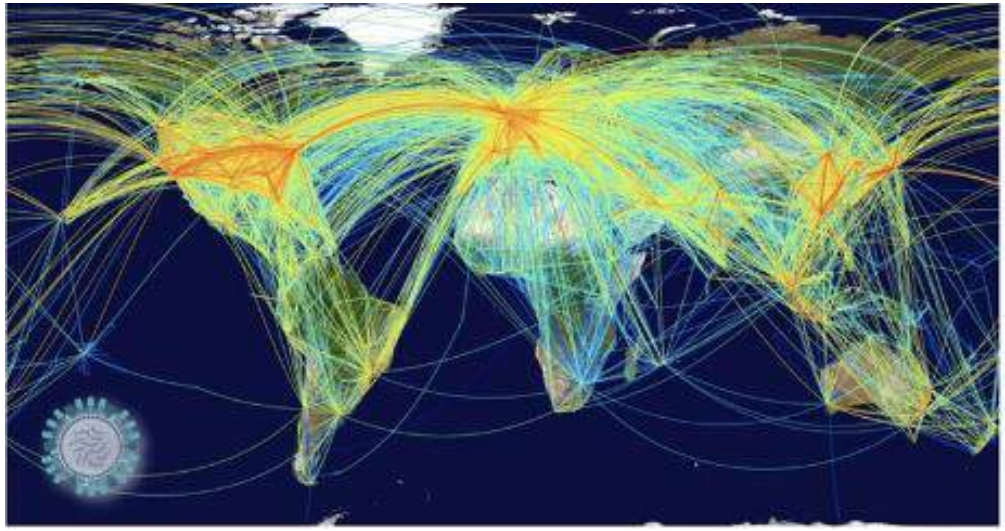
The Genomic Evolutionary Dynamics and Global Circulation Patterns of Respiratory Syncytial Virus

Annefleur C Langedijk[1], Bram Vrancken[2,3], Robert Jan Lebbink[4], Deidre Wilkins5, Elizabeth J Kelly[5], Eugenio Baraldi[6,7], Abiel Homero Mascareñas de Los Santos[8], Daria M Danilenko[9], Eun Hwa Choi[10], María Angélica Palomino[11], Hsin Chi[12], Christian Keller[13], Robert Cohen[14], Jesse Papenburg[15], Jeffrey Pernica[16], Anne Greenough[7,17], Peter Richmond[18], Federico Martinón-Torres[7,19], Terho Heikkinen[7,20], Renato T Stein[7,21], Mitsuaki Hosoya[22], Marta C Nunes[7,23,24], Charl Verwey[23,25], Anouk Evers[4], Leyla Kragten-Tabatabaie[7], Marc A Suchard[26,27,28], Sergei L Kosakovsky Pond[29], Chiara Poletto[30], Vittoria Colizza[30], Philippe Lemey[2], Louis J Bont[1,7*] and the INFORM-RSV Study Group.

Whole genome sequences (n=1282) from RSV samples (<5 yrs) collected in 17 countries worldwide over three RSV seasons (2017–2020).

RSV surveillance

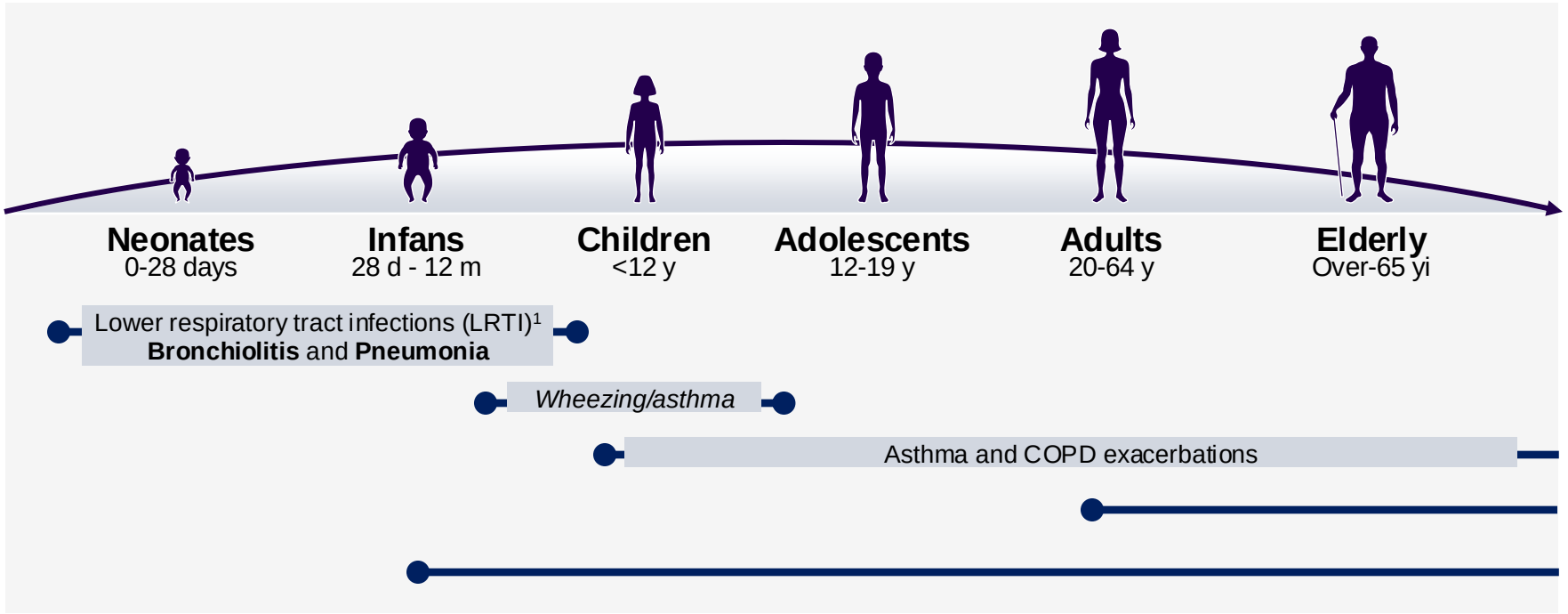
Air travel predicts global RSV spread



The Netherlands, Italy, Russia, Germany, Spain, South Korea, Finland,Canada, South Korea, Australia, Brazil, South Africa, Japan, UK, Taiwan, Chile, Mexico

Langedijk et al Nature Comm 2024

RSV infects at all ages



Openshaw PJM, et al. Annu Rev Immunol. 2017;35:501-532
Carvajal JJ, et al. Front Immunol. 2019;10:2152.

14 dicembre 2023

Picco di virus respiratori tra i bambini, in tutta Italia pronto soccorso e reparti pieni. Emergenza a Milano, i pazienti trasferiti a Brescia e Bergamo

▲ Fotogramma (fotogramma)

di Michele Bocci e Alessandra Corica

Al Buzzi di Milano arrivano ogni giorno 150 pazienti pediatrici. A Roma e Firenze incremento di casi di bronchiolite tra neonati e bimbi sotto i due anni

Seasonal outbreaks of RSV put major pressure on health-care system performance, ranging from primary care physician to specialised paediatric critical care settings.

The international journal of science / 15 December 2022

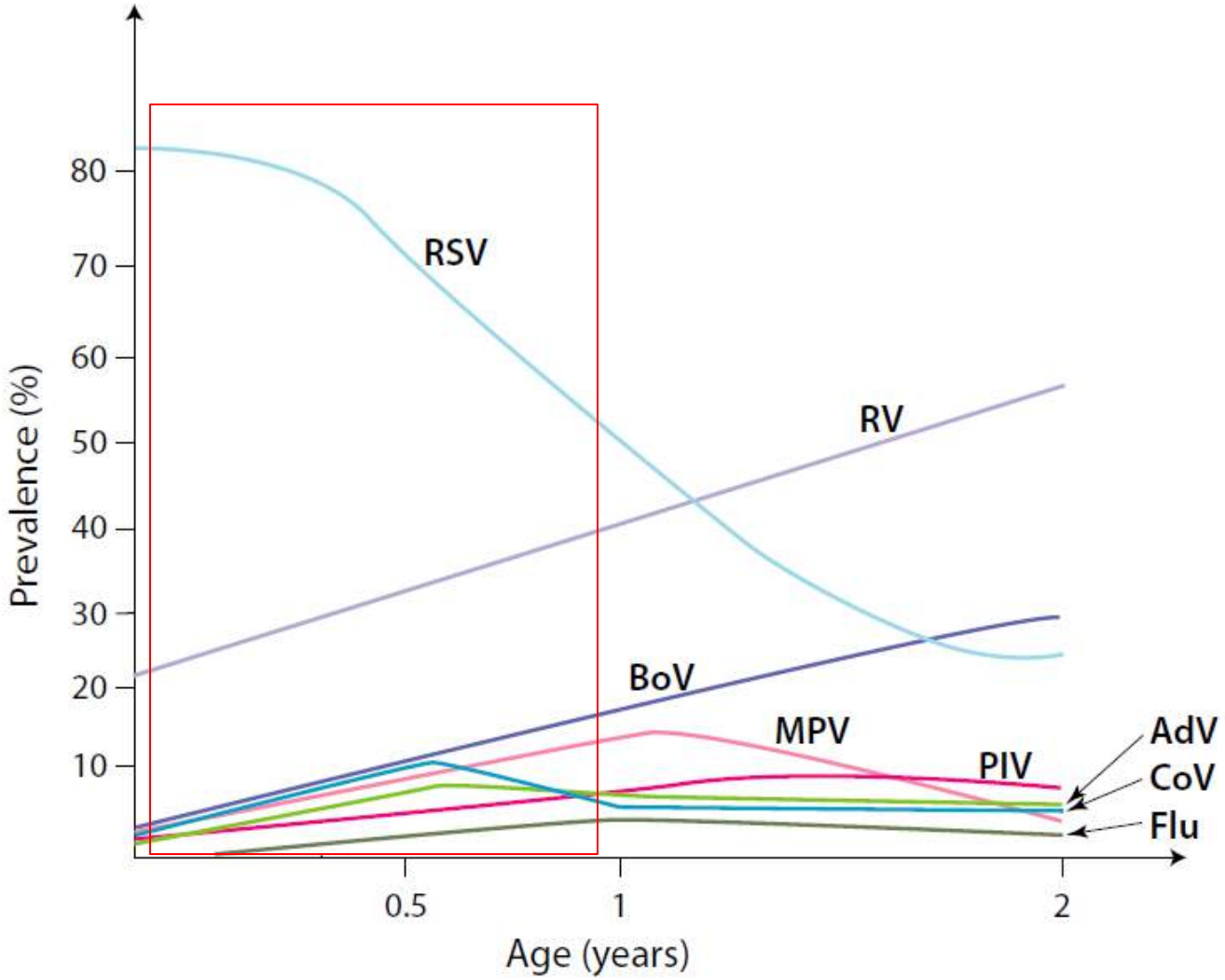
nature

NEWS EXPLAINER | 15 December 2022

RSV wave hammers hospitals — but vaccines and treatments are coming

Faibank - Nature 15 December 2022

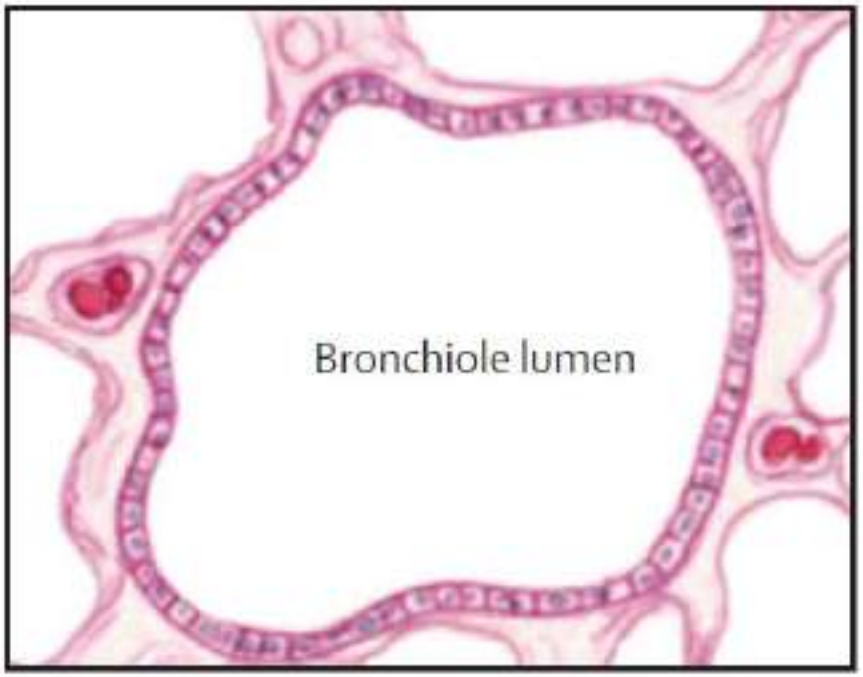
EPIDEMIOLOGY OF VIRUS RESPIRATORY INFECTIONS ACCORDING TO AGE

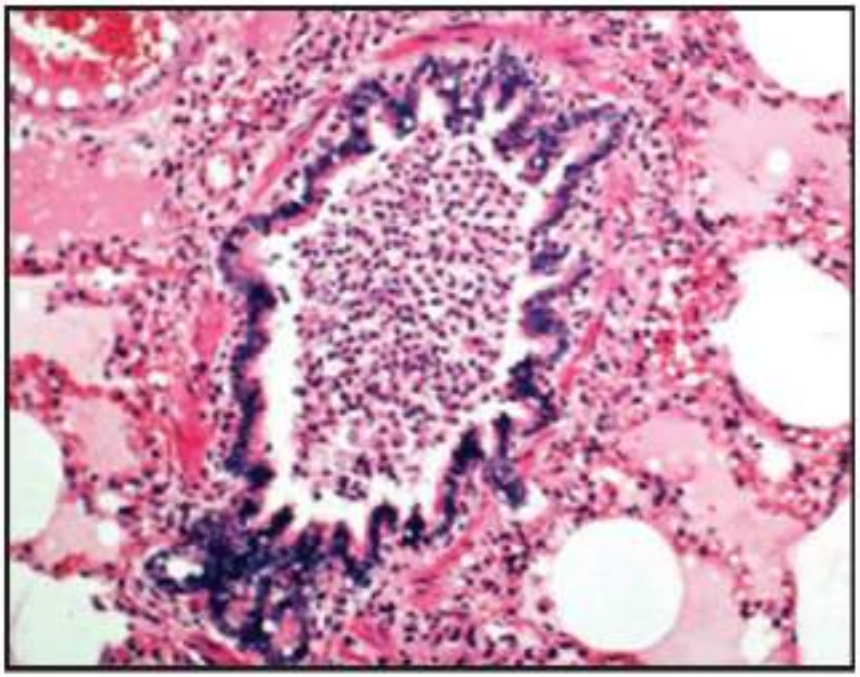


Jartti Allergy 2018

BoV-Bocavirus, MPV-Metapneumovirus, PIV-Parainfluenza

PATHOLOGY OF VIRAL BRONCHIOLITIS



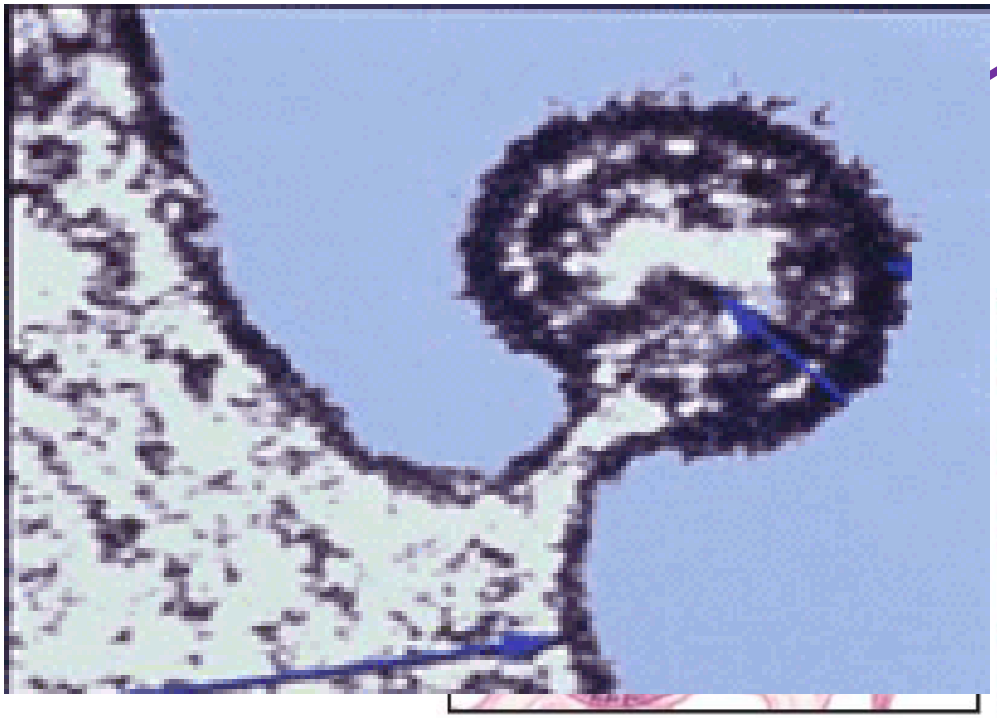


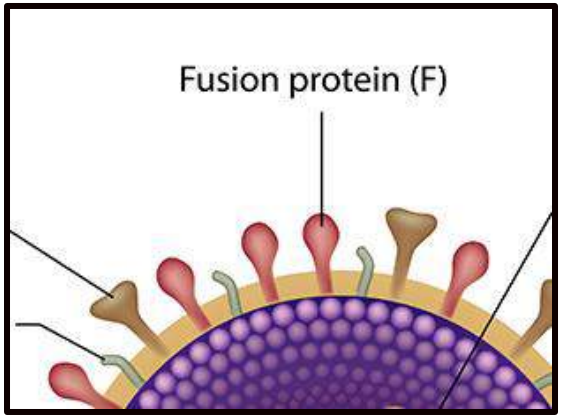
RSV disrupts airway epithelium
Bronchiolar obstruction with mucus and **cellular debris**

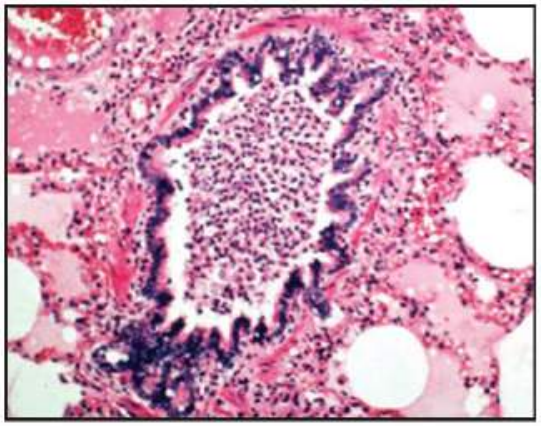
Florin et al Lancet 2017; 389: 211–24

RSV

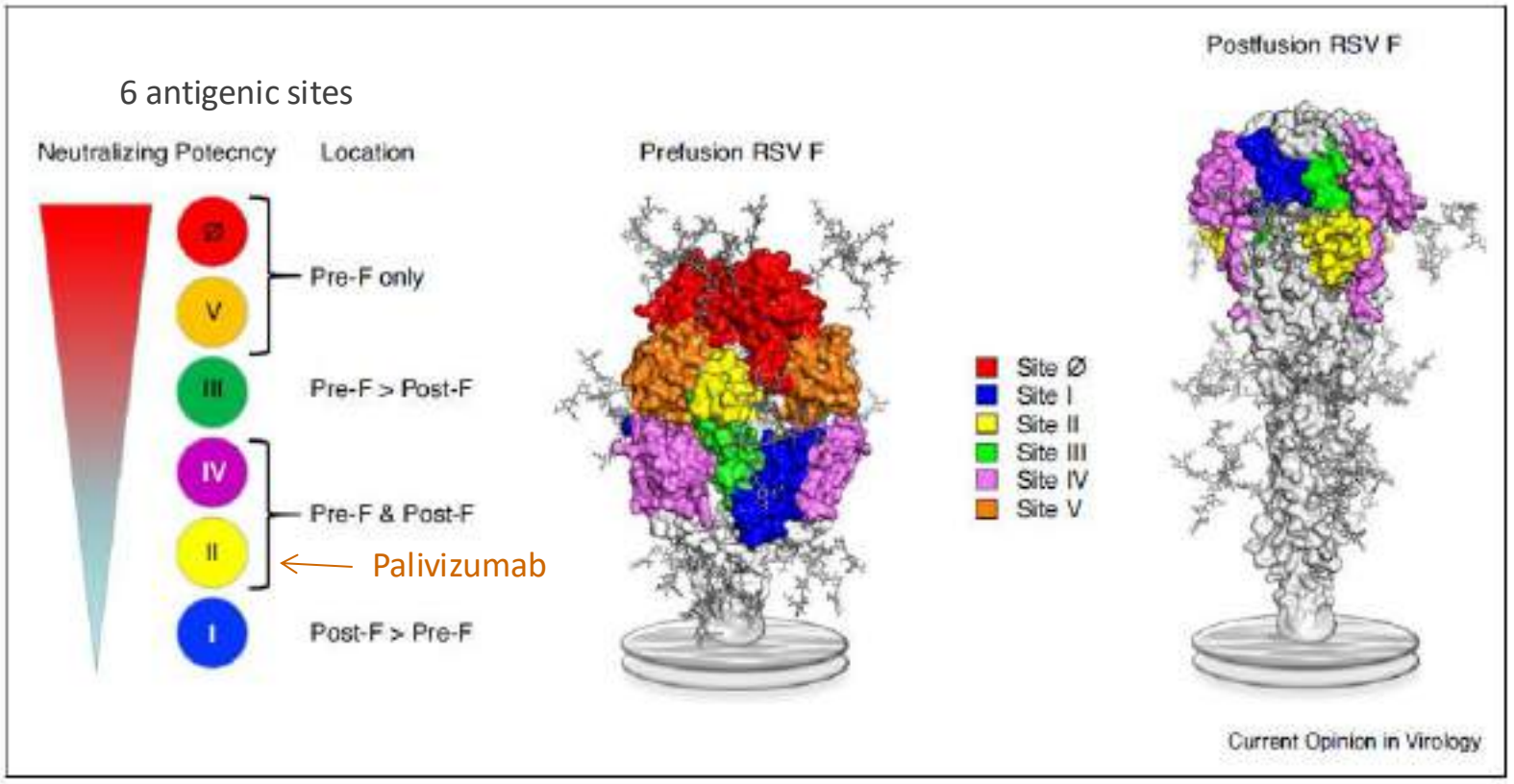
The F protein is required for viral entry







Antigenic sites on the RSV **F protein**



The F protein is required for viral entry and mediates membrane fusion between virus and cells.

Vaccines and new **monoclonal antibodies** in clinical trials utilize the pre-F protein as target.

The site **zero** induces the most potent neutralizing antibodies.

Graham - Curr Op Virol 2017, 23:107–112

MANAGEMENT OF BRONCHIOLITIS

"AN ANARCHIC SCENARIO"

Amoxicillin

Azithromycin

Furosemide

Ribavirin

Systemic steroids

Montelukast

Nitric oxide

Sedation

Salbutamol

Inhaled steroids

Adrenaline

Ribavirin

Ipratropium

Surfactant

Hypertonic saline

Antibiotics

Daily intranasal Palivizumab

EB 2009

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 25 1941

(UK)

ACUTE BRONCHIOLITIS IN CHILDREN

BY

DOUGLAS HUBBLE, M.D.

Physician to the Derbyshire Hospital for Sick Children

AND

G. R. OSBORN, M.B., B.S.Melb.

Pathologist to the Derbyshire Royal Infirmary and Derbyshire Hospital for Sick Children

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 25 1941

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JAN. 25, 1941 ACUTE BRONCHIOLITIS IN CHILDREN 169

In view of the great clinical importance of these plugs of mucus it would be interesting to know how they arise. Cartilage disappears from bronchi when they reach a diameter of about 1 mm.; the tubes smaller than this are known as bronchioles. Some state (e.g., Mansfield and Bloom, 1934) that the mucous glands disappear with the cartilage. Others (e.g., Lewis and Stobo, 1915) state that glands may extend beyond the cartilage and that goblet cells may be found until the ciliated columnar epithelium gives way to cuboidal and then respiratory epithelium. Miller (1940) states that cartilage disappears when the diameter reaches 0.6–0.7 mm. and that goblet cells become less as the diameter falls and disappear in bronchioles of about 0.4 mm. However this may be, it is notable that plugs of mucus are found in bronchioles much smaller than those which are said to have mucous glands. Was this mucus secreted by the epithelium before it was destroyed, or was it secreted by glands in larger bronchi?

Signs and Symptoms

The onset may be acute, with fever, very rapid and laboured breathing, cyanosis, severe cough, and prostration; but more often the child has for a day or two a slight temperature, pharyngeal cough, and some gastro-intestinal upset before the infection extends. The larynx may next be affected; the child develops a laryngeal cough together with soreness over the larynx, hoarseness of the voice, and sometimes aphonia. Dyspnoea and stridor, due to laryngeal spasm, may be present at this stage. From this phase the child may pass quite suddenly to bronchiolitis. The ultimate bronchioles become plugged with exudate and the clinical picture is dominated by *obstructive dyspnoea*. Respiratory distress is then very marked; the respiration rate is rapid—from 60 to 100 a minute. There is recession of the soft parts of the chest during inspiration. Cough is always incessant and disturbing. Cyanosis is often obvious quite early, but becomes extreme towards the end. Collapse is usually terminal, but sometimes the toxaemia appears to be profound from the start and the child is quickly apathetic and stuporous. The characteristic clinical picture is distressing and unforget-

Treatment

A student examining the measures advised by a score of authorities for the treatment of acute bronchitis and bronchopneumonia in children will find opinions so various that he may doubt if a multitude of counsellors achieves wisdom. He will discover that on such questions as fresh air, hydrotherapy, steam tents, oxygen, alcohol, digitalis, ureides, stimulants, mustard baths, plasters, poultices, venesection, blood transfusion, sedatives, and cough-mixtures there are as many opinions as authors. Abt (1939) represents mature opinion when he writes of the treatment of pneumonia in children: "We have long believed that one form of symptomatic treatment was as good as another provided neither harm did harm."

One of the general methods to be adopted in the treatment of acute bronchiolitis is that these children should be nursed in warm moist air, with an adequate oxygen supply. In garrigue jackets, in antiphlogistine, and in linseed and mustard poultices it is difficult to put both, but it is very difficult still to withstand the [illegible] of nurse and parents. Alcohol is the best sedative for children (and phenobarbitone the second-best). Brandy, whisky, or port may be used for children; dose may be individually determined, but 20 minims to 1 drachm two or three times in the twenty-four hours is an adequate dose for a child of 1 year. *No other sedative should be used for children with acute bronchiolitis, for if by sedatives their respiratory excursions are depressed and their coughs [illegible] they die; any derivative of opium may bring a sleep [illegible] to death.*

"All bronchial therapy is futile," wrote the great Osler, dying of an influenzal infection; and this death-bed pronouncement has a papal quality. Moreover, there is to-day no need to resort for help to the Virginian prune, the wild lettuce, or ipecacuanha. Least of all to ipecacuanha: children are either not ill enough to justify the use of it as emetic doses or are too ill for this to be a wise therapy. In the treatment of acute bronchiolitis there are four factors demanding separate consideration—the infection, the obstructive dyspnoea, the cyanosis, and the

Alcohol is the best sedative for children with bronchiolitis.
Brandy, whisky or **port** may be used for children.
1 drachm (3.5 ml) 2-3 times a day is an adequate dose.

2014

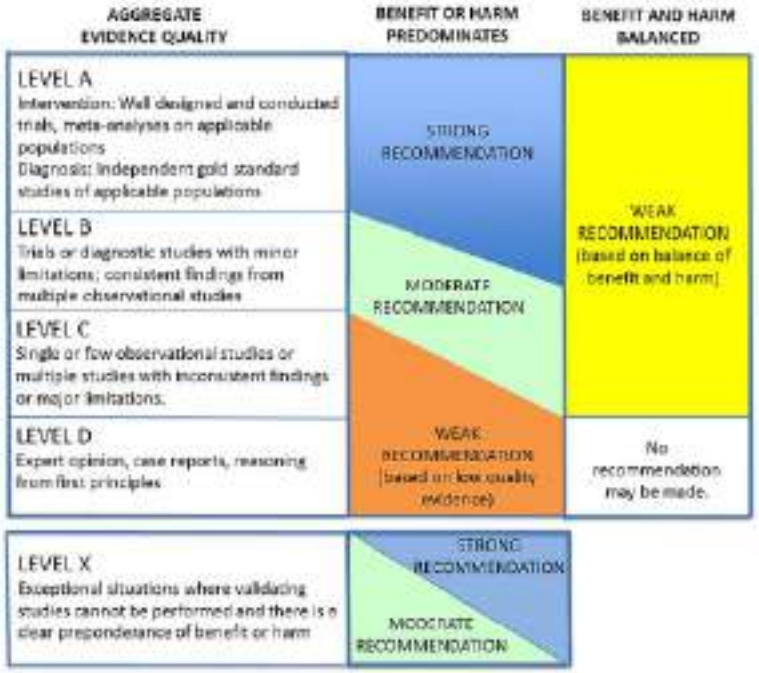
American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

CLINICAL PRACTICE GUIDELINE

Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis

24 m



14 recommendations:

10 focus on **tests or treatments to avoid!**

Extensors: 4 General Pediatricians, 4 Ped Pulmonologists
4 Ped Emergencies, 2 Infectious Dis….

Pediatrics 2014;134:e1474

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

2023

Sara Manti[1], Annamaria Staiano[2], Luigi Orfeo[3], Fabio Midulla[4], Gian Luigi Marseglia[5], Chiara Ghizzi[6], Stefania Zampogna[7], Virgilio Paolo Carnielli[8], Silvia Favilli[9], Martino Ruggieri[10], Domenico Perri[11], Giuseppe Di Mauro[12], Guido Castelli Gattinara[13], Antonio D'Avino[14], Paolo Becherucci[15], Arcangelo Prete[16], Giuseppe Zampino[17], Marcello Lanari[18], Paolo Biban[19], Paolo Manzoni[20,21], Susanna Esposito[22], Giovanni Corsello[23] and Eugenio Baraldi[24*]

ITALIAN JOURNAL OF PEDIATRICS

< 12 mesi

NEW!

Con l'egida di 16 società scientifiche pediatriche:

Ital J Pediatr 2023 Feb 10;49:19.

REVIEW Open Access

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

< 12 months

NEW!

- The document addresses care in both hospitals and primary care.
- **Collaboration** between Primary Care Pediatricians and Emergency Department is an important factor to reduce inappropriate therapies.
- Evidence suggests **no benefit** with use of salbutamol, steroids and antibiotics with potential risk of harm.
- **Prevention**: because of the lack of effective treatment, environmental and immuno-prophylaxis are essential.

Ital J Ped 2023

THE LANCET

Bronchiolitis

July 2022

Stuart R Dalziel, Libby Haskell, Sharon O'Brien, Meredith L Borland, Amy C Plint, Franz E Babl, Ed Oakley

	Australia and New Zealand, 2016[2]	NICE (UK), 2015[5]	AAP (USA), 2014[7]	CPS (Canada), 2014[8]	Italy, 2014[9]	France, 2013[10]	Spain, 2010[11]
Treatments							
β 2 agonists	Not recommended (including individuals with a personal or family history of atopy)	Not recommended	Not recommended	Not recommended	Not routinely recommended; carefully monitored trial might be appropriate	Not recommended in first episode of wheezing; consider trial in child with recurrent wheeze depending on atopic history, case history, and clinical features	Not routinely recommended; if used, must undergo carefully monitored trial
Corticosteroids	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Adrenaline or epinephrine	Not recommended except in peri-arrest or arrest situation	Not recommended	Not recommended	Not recommended; carefully monitored trial might be appropriate	Not recommended	Not routinely recommended	Not recommended
Hypertonic saline	Do not administer nebulised hypertonic saline	Not recommended	Not recommended in emergency department; weak recommendation for inpatients with average length of stay >72 h	Not recommended in emergency department or outpatient setting; might be beneficial in inpatients with long length of stay	Recommended	Recommended for inpatients who have moderate to severe bronchiolitis	Recommended for inpatients
Antibiotics	Not recommended (including azithromycin)	Not recommended	Not recommended unless concomitant bacterial infection, or strong suspicion of it	Not recommended unless clear and documented evidence of secondary bacterial infection	Not recommended unless clear and documented evidence of secondary bacterial infection	Not recommended; consider with signs of secondary bacterial infection or severe difficulty with ventilation	Not recommended unless clear bacterial infection

Lancet - July 1, 2022

THE LANCET

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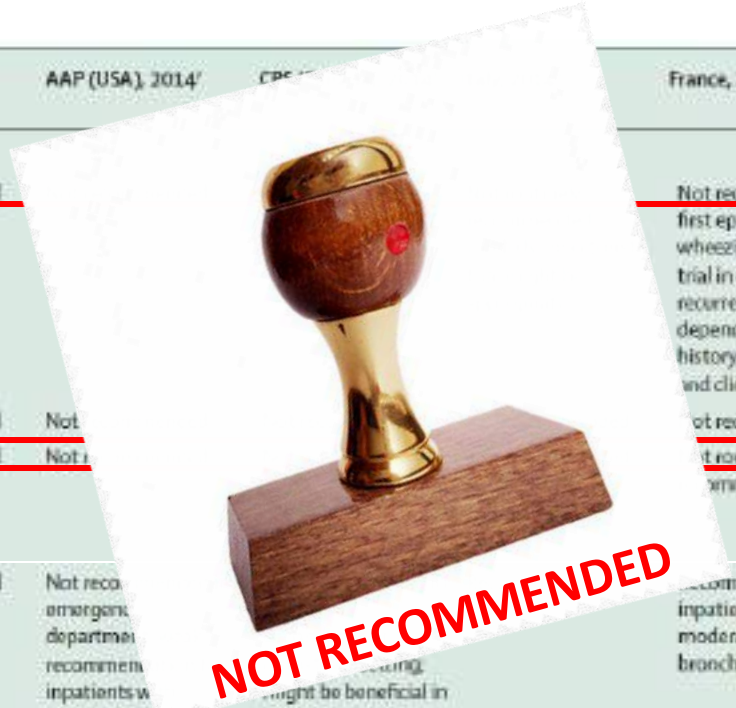
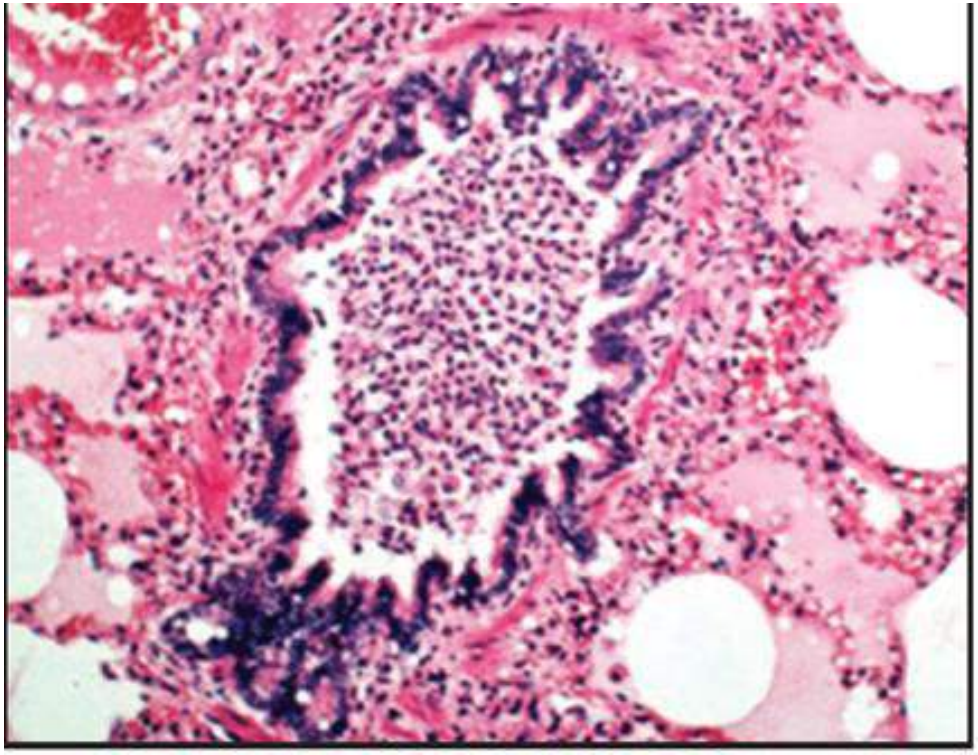


Lancet - July 1, 2022

Perchè i cortisonici NON funzionano nella bronchiolite?

PATHOLOGY OF VIRAL BRONCHIOLITIS



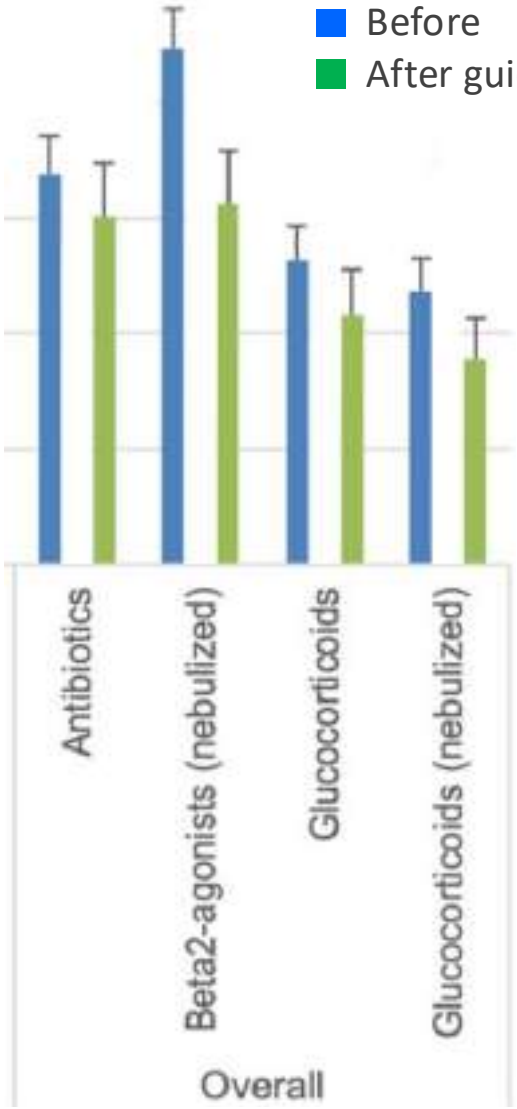
RSV disrupts airway epithelium
with **neutrophilic** infiltration

Florin - Lancet 2017; 389: 211–24
McNamara - Arch Dis Child 2003

Provate a pensare alle ultime
5 bronchioliti che avete visto

Impact of bronchiolitis guidelines publication on primary care prescriptions in the Italian pediatric population

Elisa Barbieri[1 ✉], Anna Cantarutti[2], Sara Cavagnis[1], Luigi Cantarutti[3], Eugenio Baraldi[4], Carlo Giaquinto[1] and Daniele Donà[1]



REAL LIFE

1581 episodes of bronchiolitis.
134 Family Pediatricians
(Pedianet Database)

The rate of treated bronchiolitis with AB, $Beta_2$, steroids decreased from **66% to 57%.**

1/3 of the children received **antibiotics** and the prescription rate did not changed.

Primary Care Respiratory Medicine 2021

Agreements and controversies of national guidelines for bronchiolitis: Results from an Italian survey

Hospital pediatricians (30% - 71/234)
Residents in pediatrics (39%)
Family pediatricians (18%)
University pediatricians (11%)

- **Systemic Steroids = 64%**
- Inhaled Salbutamol = 39%
- Inhaled Epinephrine = 21%
- ICS = 17%

Manti et al. SIAP - Immun Inflam Dis 2021

REVIEW Open Access

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

< 12 months

NEW!

- **Collaboration between Primary Care Pediatricians and Emergency Department is an important factor to reduce inappropriate therapies.**

Universal DE-IMPLEMENTATION of unnecessary therapies

Ital J Ped 2023

Evitiamo di tornare alla medicina del Medioevo!

…quando si diceva ‘nella mia personale esperienza il cortisone funziona…..’

Oggi abbiamo la medicina basata sulle evidenze!

Dobbiamo avere il coraggio di cambiare!

Cochrane Database of Systematic Reviews 2023

Nebulised hypertonic saline solution for acute bronchiolitis in infants (Review)

Zhang L, Mendoza-Sassi RA, Wainwright CE, Aregbesola A, Klassen TP

34 trials involving 5205 infants with acute bronchiolitis treated with hypertonic saline (HS).

Nebulised HS may <u>modestly</u> reduce length of stay amongst infants hospitalised with acute bronchiolitis and may slightly improve clinical severity score. Treatment with nebulised HS may also reduce the risk of hospitalisation amongst outpatients and ED patients.

REVIEW Open Access

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

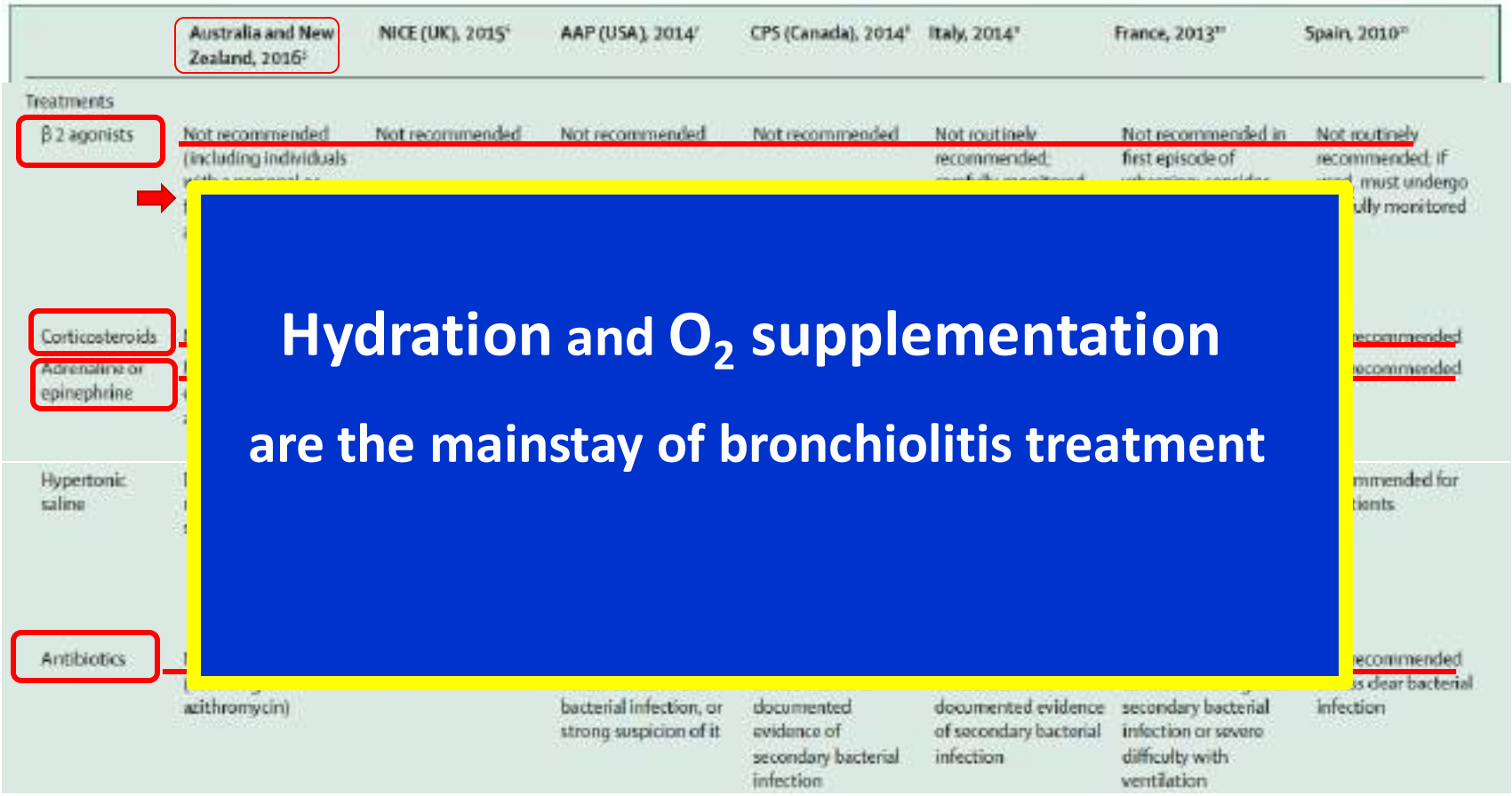
There is not enough evidence to routinely recommend nebulized HS 3%

THE LANCET

Bronchiolitis

July 2022

Stuart R Dalziel, Libby Haskell, Sharon O'Brien, Meredith L Borland, Amy C Plint, Franz E Babl, Ed Oakley



	Australia and New Zealand, 2016[2]	NICE (UK), 2015[5]	AAP (USA), 2014[7]	CPS (Canada), 2014[8]	Italy, 2014[9]	France, 2013[10]	Spain, 2010[11]
Treatments							
β 2 agonists	Not recommended (including individuals	Not recommended	Not recommended	Not recommended	Not routinely recommended;	Not recommended in first episode of	Not routinely recommended; if must undergo fully monitored
Corticosteroids							recommended
Adrenaline or epinephrine							recommended
Hypertonic saline							mmended for tients
Antibiotics	azithromycin)		bacterial infection, or strong suspicion of it	documented evidence of secondary bacterial infection	documented evidence of secondary bacterial infection	secondary bacterial infection or severe difficulty with ventilation	recommended s clear bacterial infection

Hydration and O_2 supplementation

are the mainstay of bronchiolitis treatment

Lancet - July 1, 2022

REVIEW Open Access

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

NEW!

Supplemental O_2 should be administered if **O_2 saturation** levels are persitently **below 92%.**

HFNC should not be used as a primary treatment but only if standard subnasal O_2 therapy fails in hypoxic infants.

Ital J Ped 2022

Viral bronchiolitis

Todd A Florin, Amy C Plint, Joseph J Zorc

NICE (UK), 2015[13]	AAP (USA), 2014[39]	CPS (Canada), 2014[40]	SIGN (Scotland), 2006[41]	Italy, 2014[42]	Spain, 2010[43]	Australia, 2008[44]	France, 2013[45]

…and if standard Oxygen and

Hydration are not enough?

HFNC Oxygen delivery

DEFINITION

A flow higher than the patient's inspiratory flow of the patient

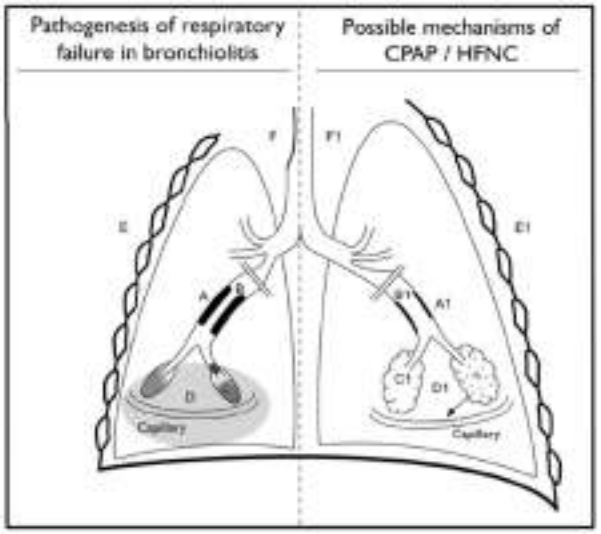
1.5-2 L/kg/min (max 10 L/min)

H_3 **H**igh: 1.5-2L/kg/min

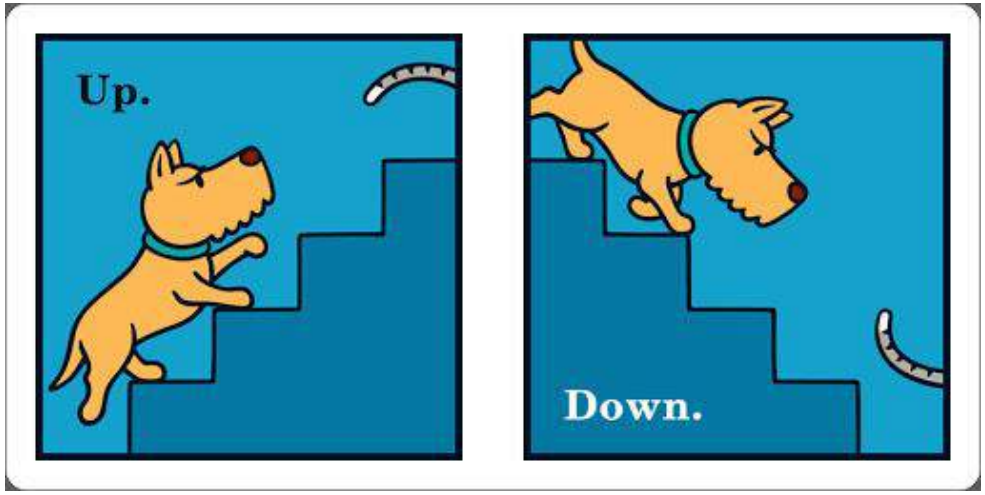
Heated: 35°-37°

Humidified: nearly 100%

Flow **N**asal **C**annula



HFNC Oxygen Therapy



Criticisms of HFNC as an effective therapy for bronchiolitis is mounting

Coon - Lancet CAH 2019
Ralston - JAMA Ped 2020
Treasure - Hosp Pediatr 2021
Kooiman - Arch Dis Child 2023
Durand - ERJ 2022

INFECTIOUS DISEASE

Preventing respiratory syncytial virus (RSV) disease in children

After many decades, promising strategies for RSV immunization are on the horizon

Because of the lack of effective treatment

RSV prevention is

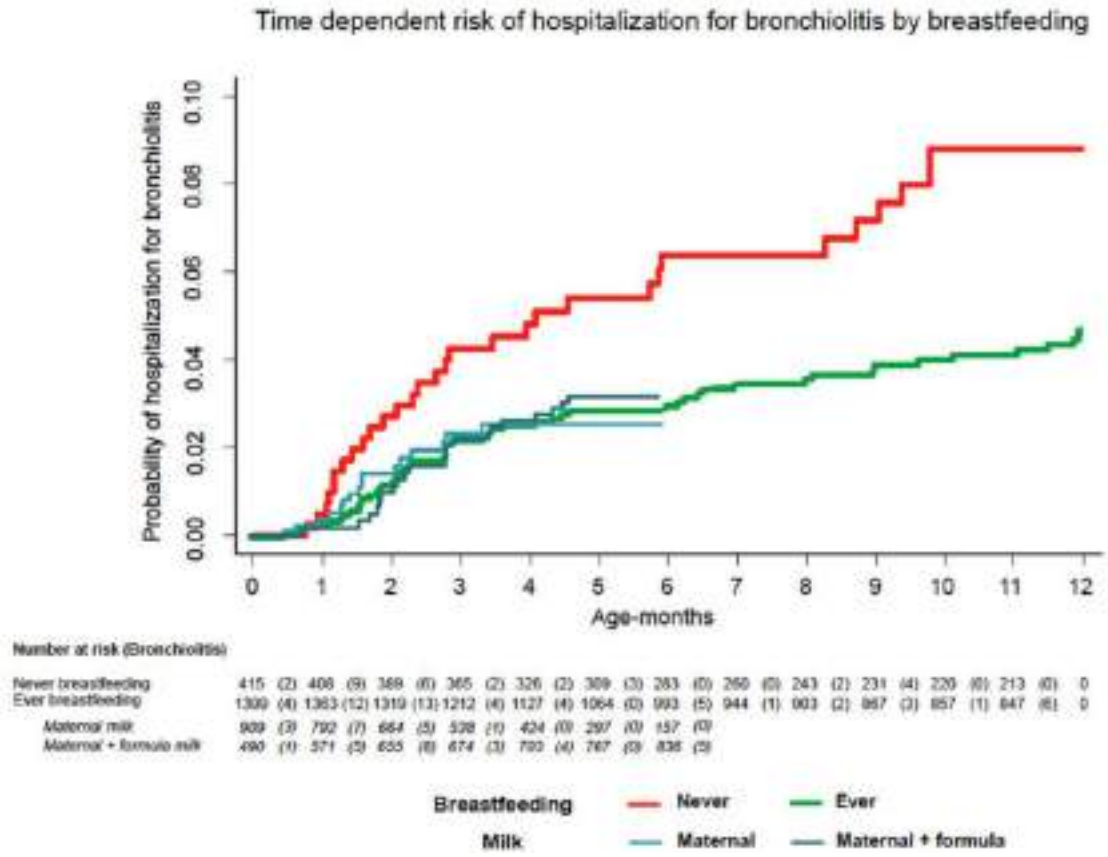
the present and the future

Karron - Science 2021; 372:686

BRONCHIOLITIS PREVENTION

Maternal milk protects infants against bronchiolitis during the first year of life. Results from an Italian cohort of newborns

Breastfeeding



- Prospective database
- 1,814 preterms >33 WGA
- Follow-up interview, 12m

Lanari EHD 2013

Importance of non-pharmaceutical preventive hygiene measures

Extracorporeal viral survival up to 7 hours !!

Hands decontamination (alcohol based rubs)
is the most important step in preventing nosocomial spread of RSV

Hands should be decontaminated:

- **before and after direct contact with patients**
- **after removing gloves**

Gloves should be used
Face masks should be used
Stethoscope decontamination!

REVIEW Open Access

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

NEW!

Educating parents (educational materials, video) is essential to prevent RSV infection and avoid inappropriate prescriptions.

Ital J Ped 2022

ORIGINAL ARTICLE

Immunity, Inflammation and Disease — WILEY

Maternal awareness, acceptability and willingness towards respiratory syncytial virus (RSV) vaccination during pregnancy in Ireland

Siobhan McCormack[1] | Claire Thompson[1] | Miriam Nolan[2] | Mendinaro Imcha[3] | Anne Dee[4] | Jean Saunders[5] | Roy K Philip[1,6]

[1]Division of Neonatology, Department of Paediatrics, University Maternity Hospital Limerick, Limerick, Ireland

[2]Department of Midwifery, University Maternity Hospital Limerick, Limerick, Ireland

[3]Department of Obstetrics and Gynaecology, University Maternity Hospital Limerick, Limerick, Ireland

[4]Department of Public Health Medicine, Health Service Executive, Limerick, Ireland

[5]Claddagh Statistical Consulting Services (CSCS), Shannon & Limerick, Limerick, Ireland

[6]University of Limerick School of Medicine, Limerick, Ireland

Correspondence
Roy K Philip, Consultant Neonatologist, University Maternity Hospital Limerick and University of Limerick School of Medicine, Ennis Rd, Limerick V94 C566, Ireland.
Email: roy.philip@hse.ie

Abstract

Background: Respiratory syncytial virus (RSV) is the world's leading cause of viral acute lower respiratory infections (ALRI) in infants. WHO has identified maternal RSV vaccination a priority and candidate vaccines are in development; however, vaccine hesitancy remains an impediment to successful implementation of maternal immunization. This study, the largest antenatal survey conducted to-date, aimed to examine maternal RSV awareness, likely acceptance of RSV vaccination in pregnancy, and attitudes to maternal vaccination.

Methods: Pregnant women of all gestations attending antenatal clinic of a university maternity hospital in Ireland were invited to participate. An information leaflet provided, consent obtained, and survey administered examining RSV awareness, willingness to avail of antenatal RSV vaccination, factors influencing acceptability and preferred sources of assistance. Research Ethics Committee (REC) approval obtained, and general data protection regulation (GDPR) guidelines followed.

Results: 528 women completed the survey. A large proportion (75.6%) had never heard of RSV, yet 48.5% would still avail of a vaccine, 45.8% were undecided and only 5.3% would not. The main factor making vaccination acceptable to women (76.4%) was that it protects their infant from illness ($p < .001$, CV 0.336 for association with acceptance) and general practitioner (GP) was the preferred guidance source in decision-making (57.7%).

Conclusions: Despite low levels of maternal awareness of RSV, pregnant women in Ireland are open to availing of antenatal vaccination. Maternal immunization strategies need to focus on infant's protection from RSV-associated ALRI along with vaccine safety, and build on an interdisciplinary collaboration of maternal, neonatal, primary care and public health services.

528 pregnant women
75.6% had never heard of RSV

Immun Inflamm Dis. 2024

VRS E BRONCHIOLITE

TUTTO QUELLO CHE I GENITORI DEVONO SAPERE

Come posso proteggere il mio bambino dal VRS?

- Il latte materno contiene anticorpi contro numerosi agenti infettivi e riduce il rischio di infezioni gravi da VRS e di ospedalizzazione per bronchiolite.
- Lava le mani con acqua e sapone o con un gel alcolico prima di toccare il bambino e chiedi di fare altrettanto ad altre persone che vadano in contatto con il piccolo.
- Usa la mascherina in caso di raffreddore quando ti avvicini al bambino. Se hai il raffreddore astieniti dal baciare il bambino ed evita di toccarti la faccia.
- Tieni lontano il tuo bambino da altri bambini o adulti con il raffreddore
- Non fumare in casa; il fumo aumenta il rischio di infezione
- Se il tuo bambino è prematuro o affetto da malattie cardiache o polmonari chiedi al tuo pediatra se vi sono le indicazioni all'utilizzo degli anticorpi monoclonali per la prevenzione delle infezioni da VRS
- Tutte queste misure aiutano a prevenire anche le infezioni respiratorie causate da altri virus e batteri

Baraldi E (ReSViNET), Midulla F (SIMRI), Esposito S (SIP)

I lattanti hanno bisogno di anticorpi neutralizzanti per difendersi dal VRS

Italian Journal of Pediatrics 2015

Tabella riassuntiva delle Raccomandazioni

PALIVIZUMAB (1998)	Livello di prova	Forza della raccomandazione
Prevenzione igienico ambientale	II	A
Efficacia e sicurezza della prevenzione con palivizumab	II	A
Dose di 15 mg/Kg una volta al mese e per 5 mesi	II	A
Profilassi nei soggetti con EG <29 settimane ed età ≤ 12 mesi all'inizio della stagione epidemica	II	A
Profilassi nei soggetti con EG 29-35 settimane ed età ≤ 6 mesi all'inizio della stagione epidemica	IV	B
Profilassi con palivizumab nei lattanti con Displasia broncopolmonare ed età ≤ 12 mesi all'inizio della stagione epidemica e durante il secondo anno di vita nei bambini che necessitano di terapia medica	II	A
Profilassi in lattanti con cardiopatia congenita grave ed età ≤ 12 mesi all'inizio della stagione epidemica	II	A
Profilassi in lattanti con fibrosi cistica, sindrome di Down, ernia diaframmatica congenita, patologie neuromuscolari, immunodeficienze, patologie da accumulo, atresia esofagea, trapianto polmonare	V	B

Expert consensus on palivizumab use for respiratory syncytial virus in developed countries

Manuel Sánchez Luna [a], Paolo Manzoni [b,c], Bosco Paes [d], Eugenio Baraldi [e,c], Veerle Cossey [f], Amir Kugelman [g], Rupesh Chawla [h], Andrea Dotta [i], Rosa Rodríguez Fernández [j], Bernhard Resch [k], Xavier Carbonell-Estrany [l,*]

Summary of recommendations.

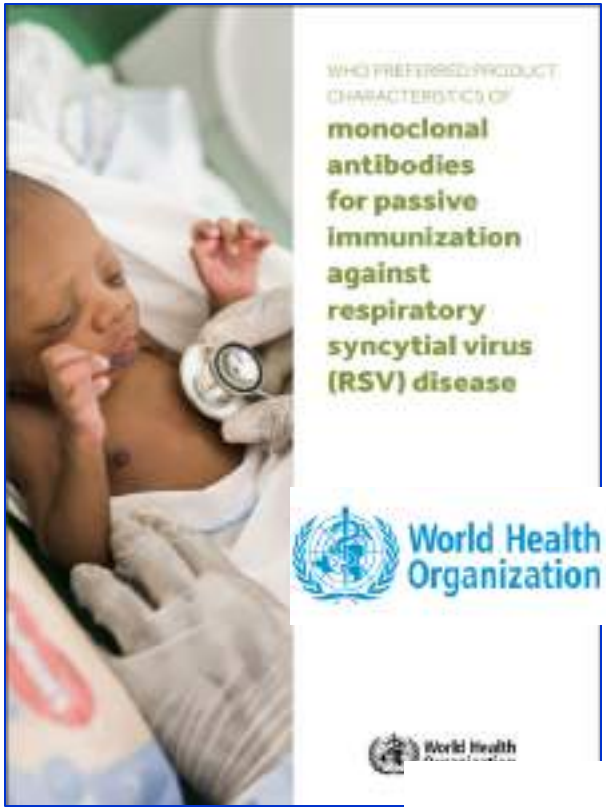
Recommendation	Level of evidence	Strength of recommendation/GRADE
Preterm infants without other comorbidities Palivizumab is recommended for infants: • <29 (<28[6]) wGA and <9 months at the start of the RSV season • 29–31 (29[0] to 31[6]) wGA and <6 months at the start of the RSV season • 32–35 (32[0] to 35[6]) wGA and high-risk (score: 50–56) using a country-specific or generalisable risk factor scoring tool [52] (Fig. 2)	1a	A
Children with CLD/BPD Palivizumab is recommended: • For infants <12 months at the start of the RSV season • During the second year of life in children who remain at high-risk*BPD/CLD and those at high-risk in the second year of life to be defined according to local experience and practice*	1a	A
Children with CHD Palivizumab is recommended for: • Infants <12 months with haemodynamically significant cyanotic or acyanotic disease • Children 12–24 months, cyanotic or acyanotic, who remain haemodynamically unstable	1a	A
Down syndrome (without other comorbidities) Palivizumab is recommended for: • Children with Down syndrome <24 months	2c	B
Cystic Fibrosis (without other comorbidities) Palivizumab is recommended for: • Infants <12 months • Children in the second year of life with manifestations of severe lung disease or weigh < 10th percentile	2c	C
Anatomic pulmonary abnormalities or neuromuscular disorder Palivizumab is recommended for: • Children <24 months with significant neuromuscular disease or congenital anomalies that compromises the respiratory tract (e.g. hypotonia, cerebral palsy, chronic interstitial pulmonary disease, airway and pulmonary malformations, tracheostomy)	4	C
Immunocompromised Palivizumab is recommended for: • Children <24 months who are profoundly immunocompromised (e.g. primary immunodeficiency syndromes, immune suppression following haematopoietic stem cell transplantation, solid organ transplantation or cytotoxic chemotherapy)	4	C

Ped Resp Rev 2020


A New Philosophy

High mortality in low-income countries (100.000/year)

80% of hospitalized infants were previously healthy



UNIVERSAL IMMUNOPROPHYLAXIS

Primary focus:
development of new RSV mAbs
with an extended half-life intended
for use in all infants globally

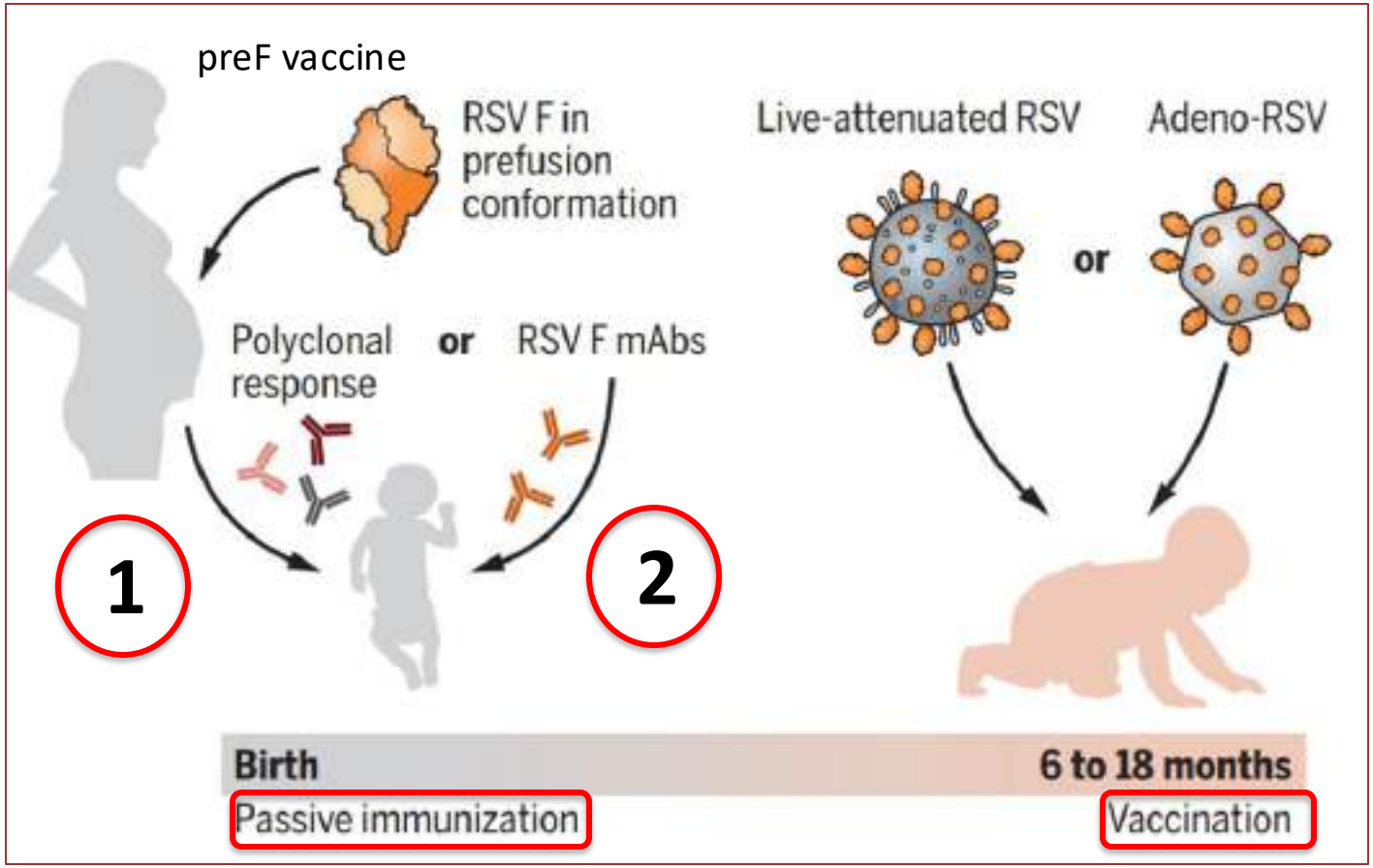
Neonates need neutralizing antibodies!

WHO/DRAFT-V0.1/MAR2020

INFECTIOUS DISEASE

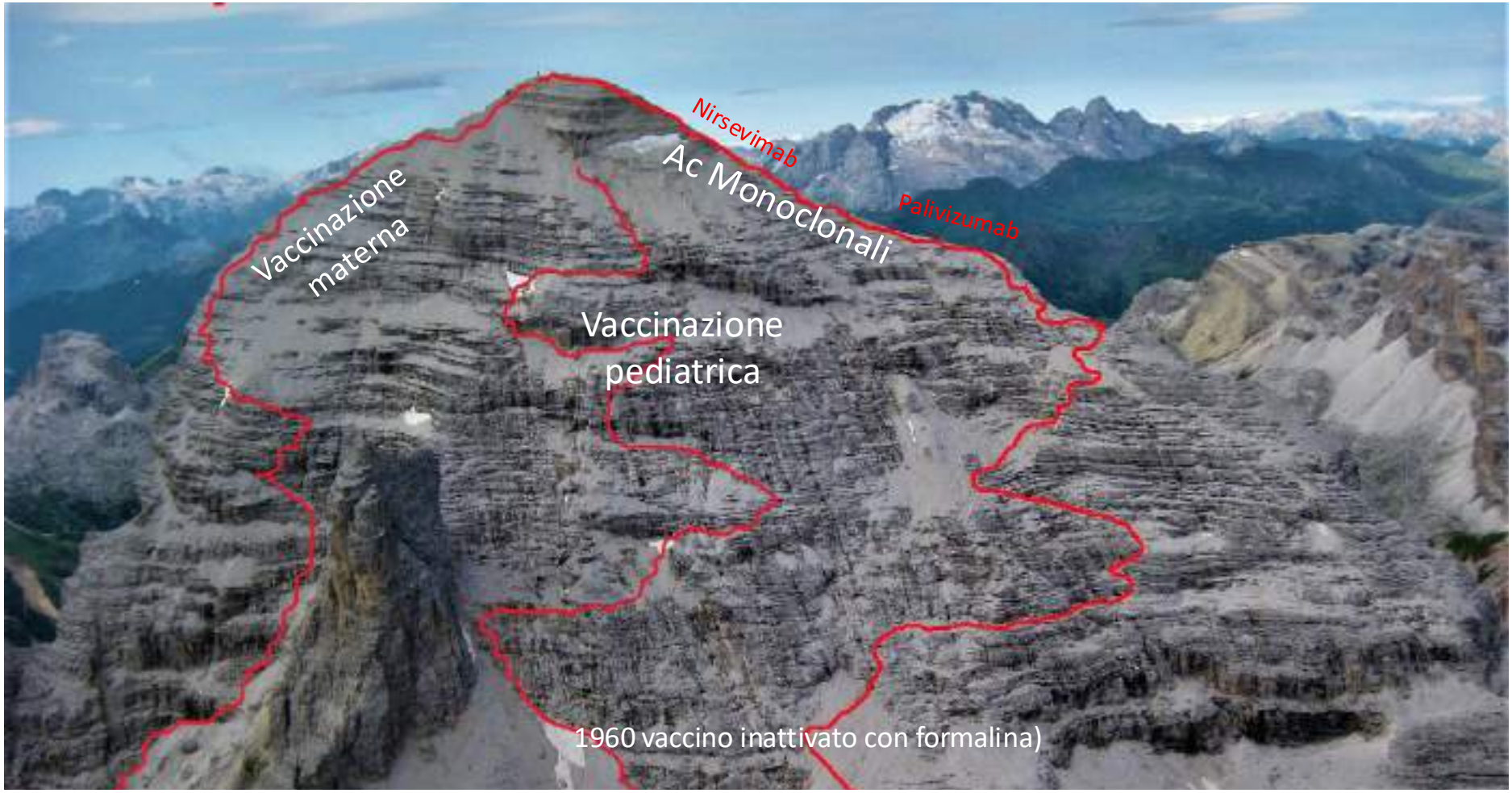
Preventing respiratory syncytial virus (RSV) disease in children

After many decades, promising strategies for RSV immunization are on the horizon



Karron Science 2021; 372:686

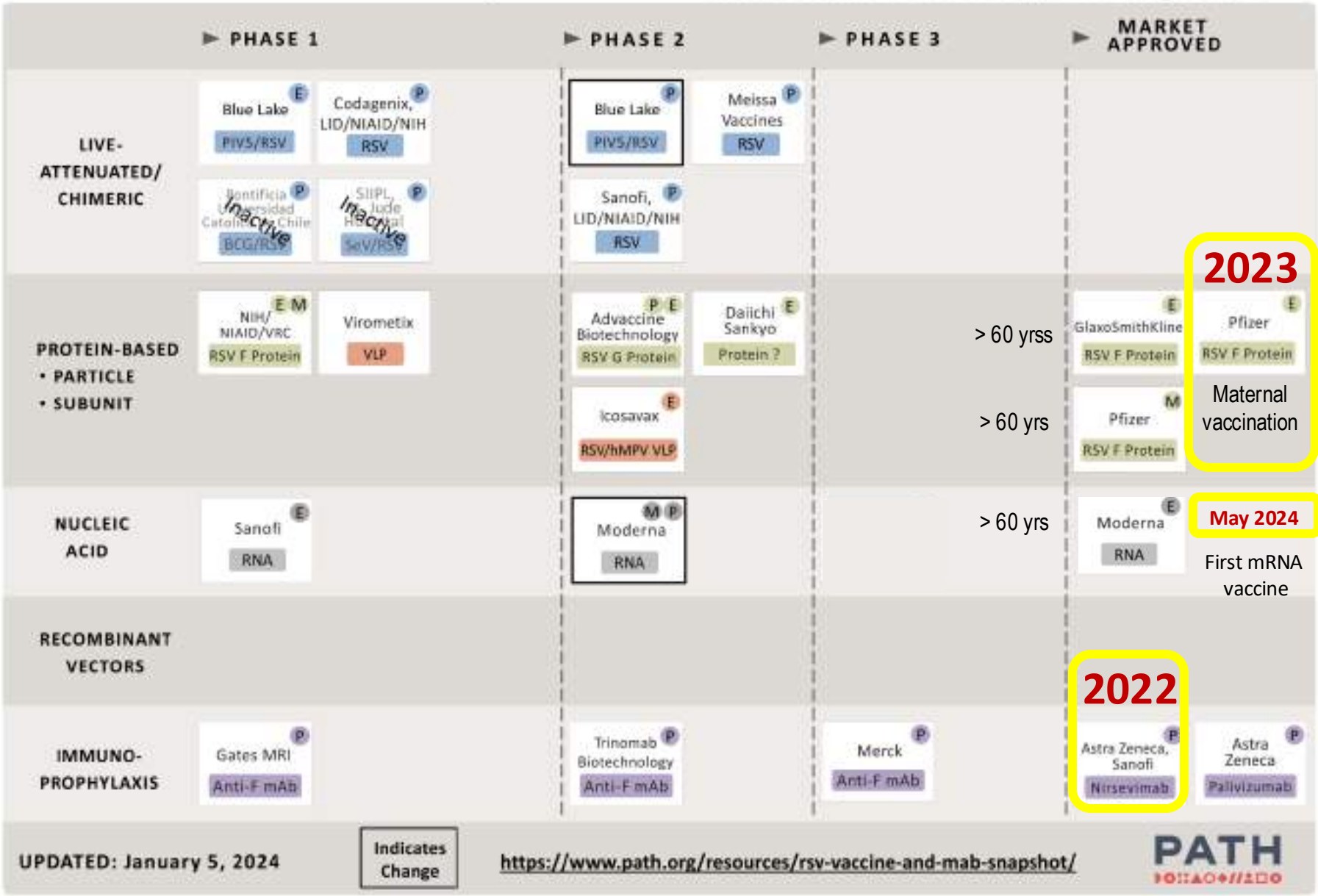
UNA NUOVA ERA PER LA PREVENZIONE DELLE INFEZIONI DA VRS



Tofana di Rozes mt 3225 La regina delle Dolomiti

RSV Vaccine and mAb Snapshot

TARGET INDICATION: P =PEDIATRIC M =MATERNAL E =ELDERLY



UPDATED: January 5, 2024

Indicates Change

https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

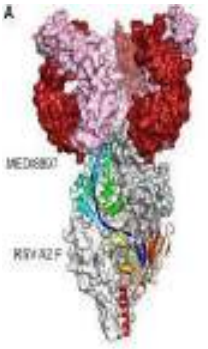
PATH

LONG-ACTING mAbs

	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	MARKET APPROVED
IMMUNO-PROPHYLAXIS	Gates MRI (P) Anti-F mAb	Trinomab Biotechnology (P) Anti-F mAb	Merck (P) Anti-F mAb	Astra Zeneca, Sanofi (P) Nirsevimab	Astra Zeneca (P) Palivizumab

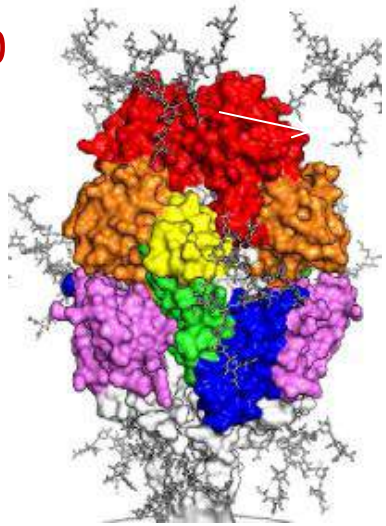
Nirsevimab

binds the site 0



Prefusion RSV F

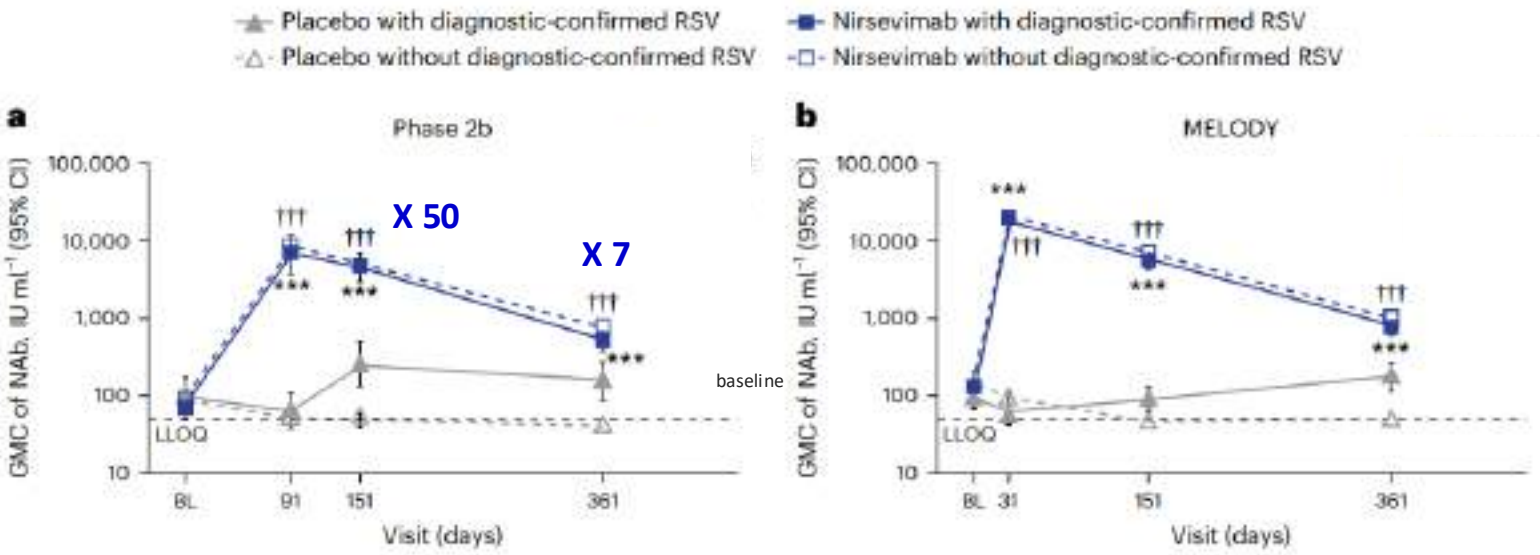
Site 0



- **Single shot** for the whole RSV season (> **150 days**).
- **Immediate protection**
- **All infants** entering or born during RSV season
- **Doses**: 50 mg < 5 kg; 100 mg > 5 kg

nature medicine

Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants



Following a single dose most Nirsevimab recipients still had higher RSV MAb levels than placebo recipients **after 1 yr**.

Wilkins et al - Nature Med 2023

The NEW ENGLAND JOURNAL of MEDICINE

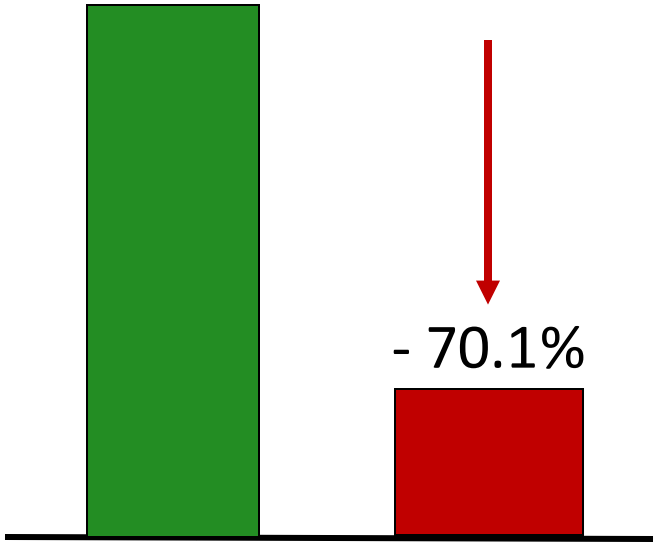
Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

29-35 w GA

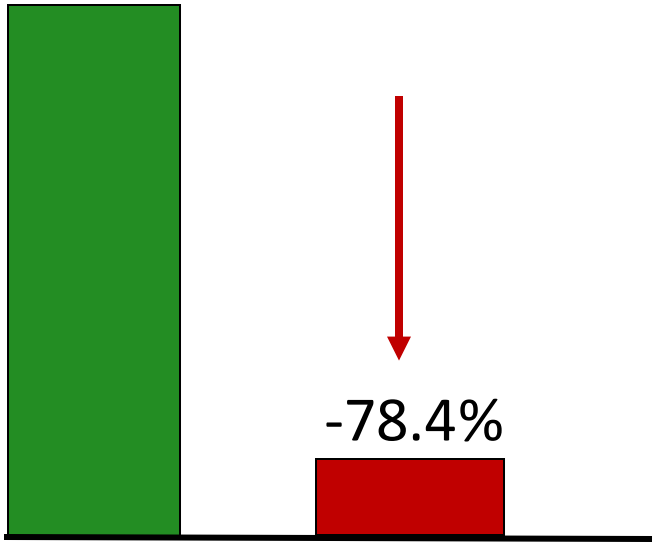
- **Single shot** for the whole RSV season (**150 days**)
- **50-fold** greater neutralizing activity than palivizumab

Placebo (n=484)
Nirsevimab (n=969)

Trial conducted in 23 countries.
Italy: PD, VR, TO, GE



RSV-confirmed medically attended LRTI

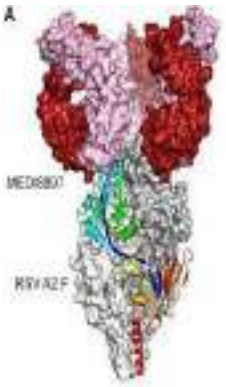


RSV-confirmed hospitalizations

Griffin et al NEJM 2020

Nirsevimab, mAb per tutti i neonati e bambini alla prima stagione di RSV

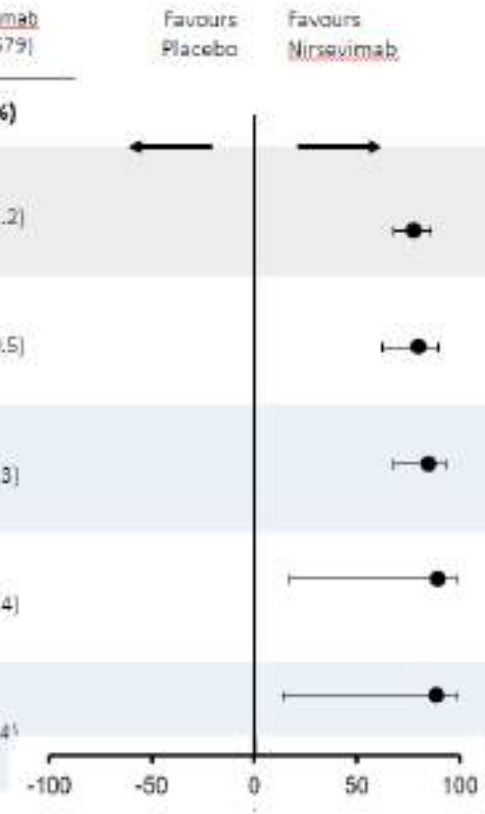
Nirsevimab



Efficacia nirsevimab 80%-90% nei diversi outcome clinici di prevenzione delle LRTI da RSV nei neonati e bambini alla loro prima stagione di RSV

Fase 2b + fase 3 MELODY
N= 3.872

	Placebo (N=1293) n (%)	Nirsevimab (N=2579) n (%)	Efficacia (%)
LRTI-RSV che richiedono assistenza medica	80 (6.5)	31 (1.2)	79.0%
LRTI-RSV con ospedalizzazione	33 (2.6)	12 (0.5)	80.6%
LRTI-RSV molto grave	28 (2.2)	7 (0.3)	86.2%
LRTI-RSV in terapia intensiva	6 (0.5)	1 (0.4)	90.1%
LRTI-RSV che richiedono un supporto respiratorio	6 (0.5)	1 (0.4)	89.8%



Simões E et al. Lancet CAH 2023. Madhi S et al. ESPID 2023.

July 17, 2023: FDA approved Beyfortus (Nirsevimab) to protect infants against RSV disease

Nirsevimab a new long-acting mAb for all infants, single shot for the whole RSV season (>150 days)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15.11.2022

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Nirsevimab

Beyfortus Share RSS

nirsevimab

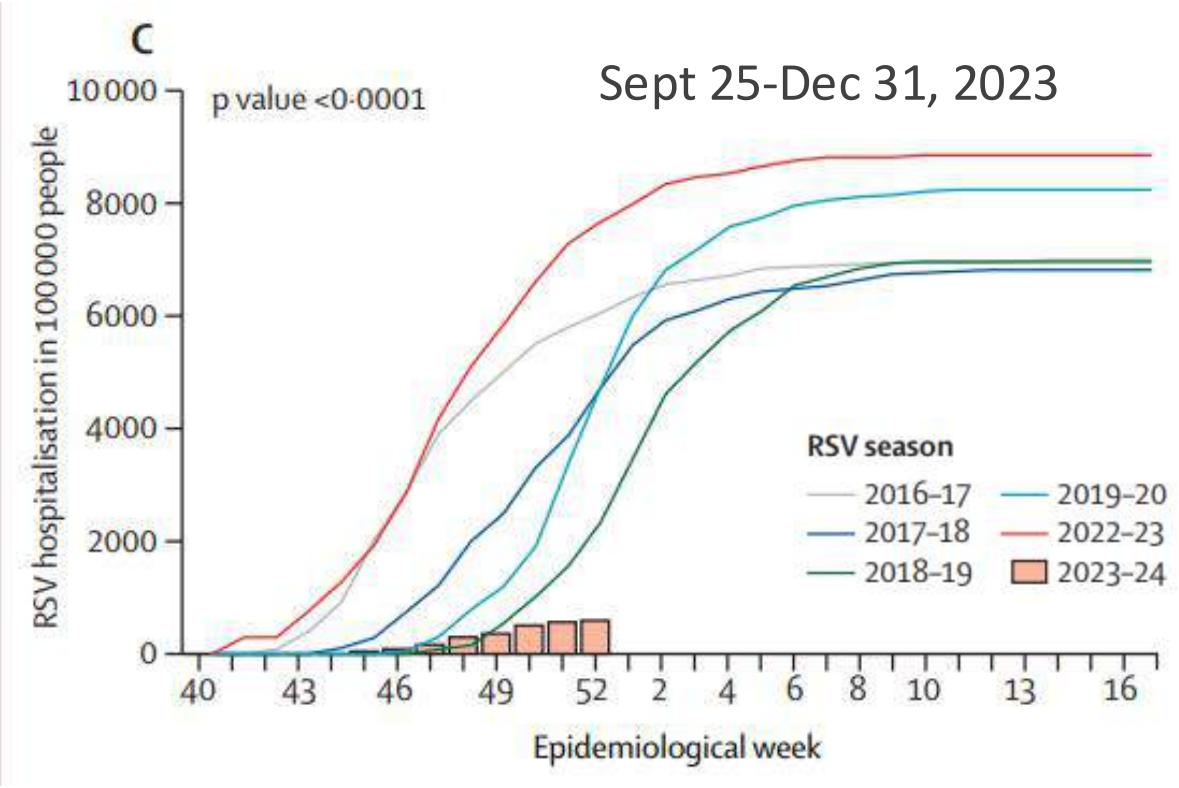
AUTHORISED
This medicine is authorised for use in the European Union.

La stagione 2023/24 sarà la prima in cui tutti i neonati e bambini alla loro prima stagione di RSV potranno essere protetti con nirsevimab

Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study

Real-word study

(n=9408 infants)



Effectiveness of :

82% for hospitalizations

86·9% against severe RSV disease requiring O2

Ares-Gomes, Martinon et al Lancet ID - April 30, 2024

Galizia 2023-2024

Copertura di nirsevimab

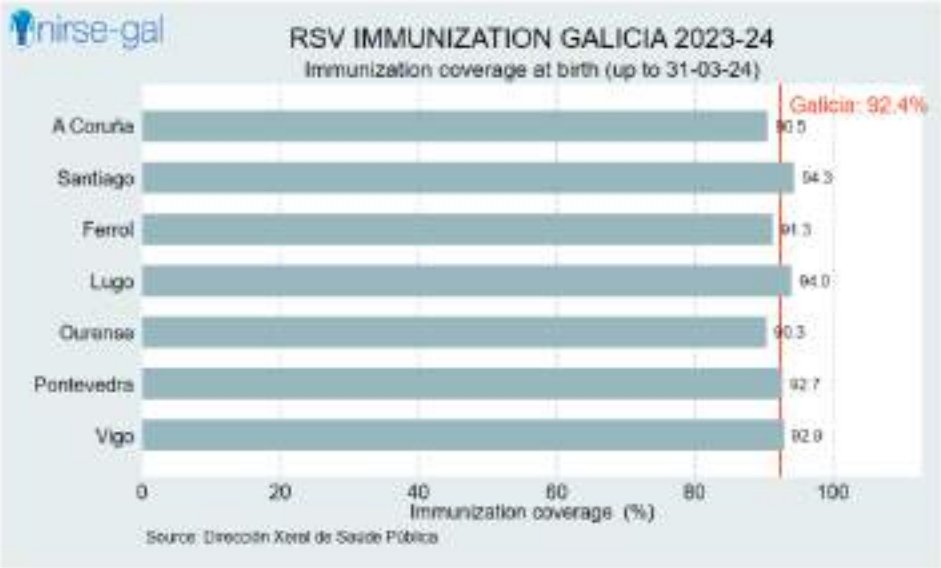
tra i bambini nati in stagione è 92.4%

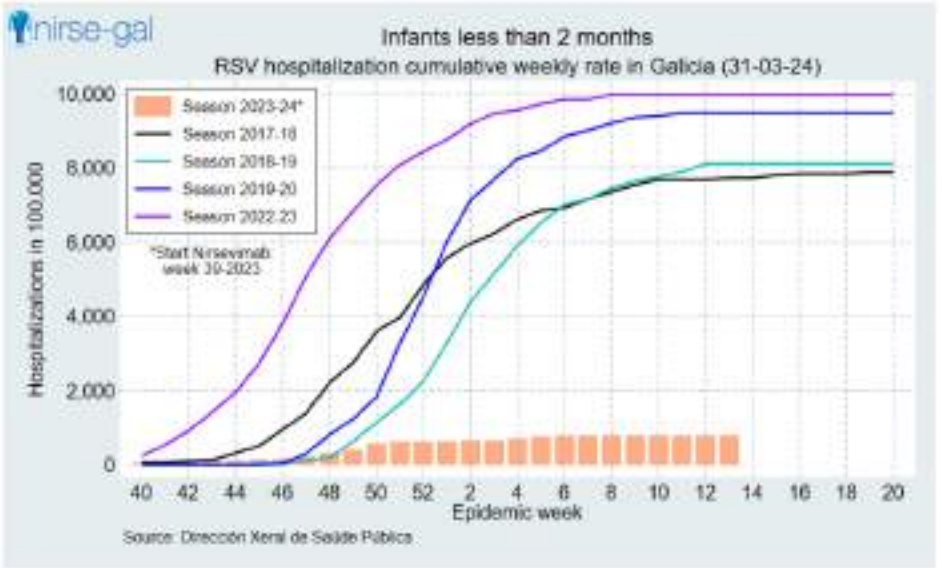
(immunizzati alla nascita in ospedale)

- 90% riduzione ospedalizzazioni da RSV

tra i bambini di età <2 mesi (nati in stagione RSV)

(immunizzati alla nascita in ospedale)





Settimana 13-2024

Dati fino al **31 marzo 2024**

Servizo Galego de Saude. VRS. Link:
https://www.sergas.es/Saude-publica/Virus-Sincitial-Respiratorio

CDC

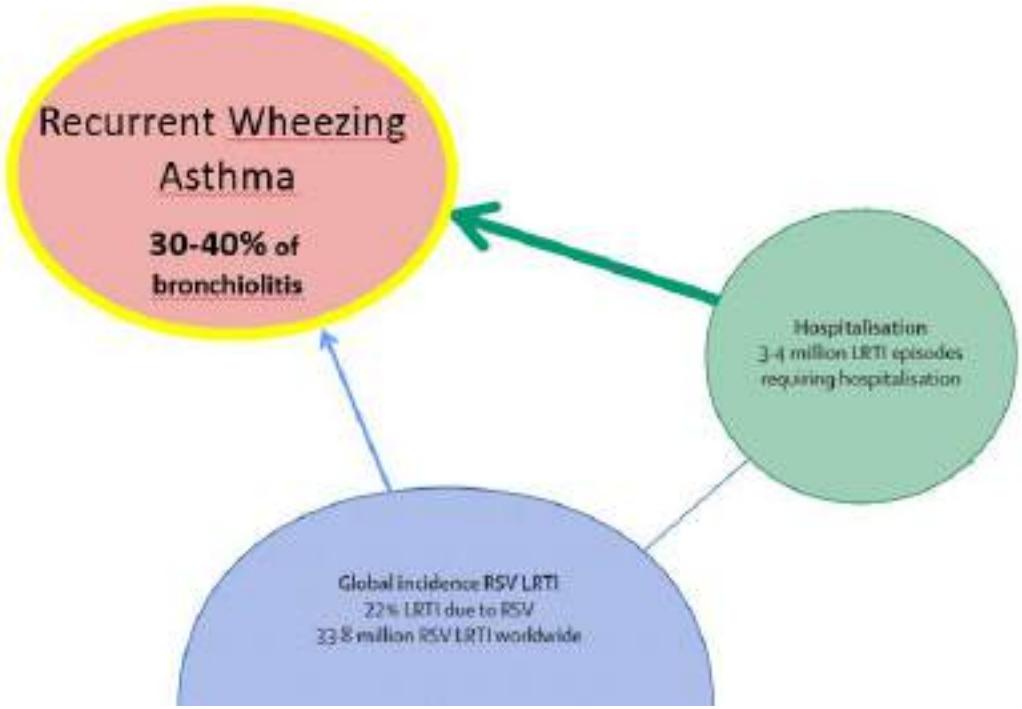
In a US study (n=699) nirsevimab effectiveness was 90% against RSV-associated hospitalizations

[Early Estimate of Nirsevimab Effectiveness for Prevention of RSV–Associated Hospitalization Among Infants Entering Their First RSV Season — New Vaccine Surveillance Network, October 2023–February 2024 | MMWR (cdc.gov)]

REVIEW Open Access

UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants

LONG-TERM CONSEQUENCES OF BRONCHIOLITIS

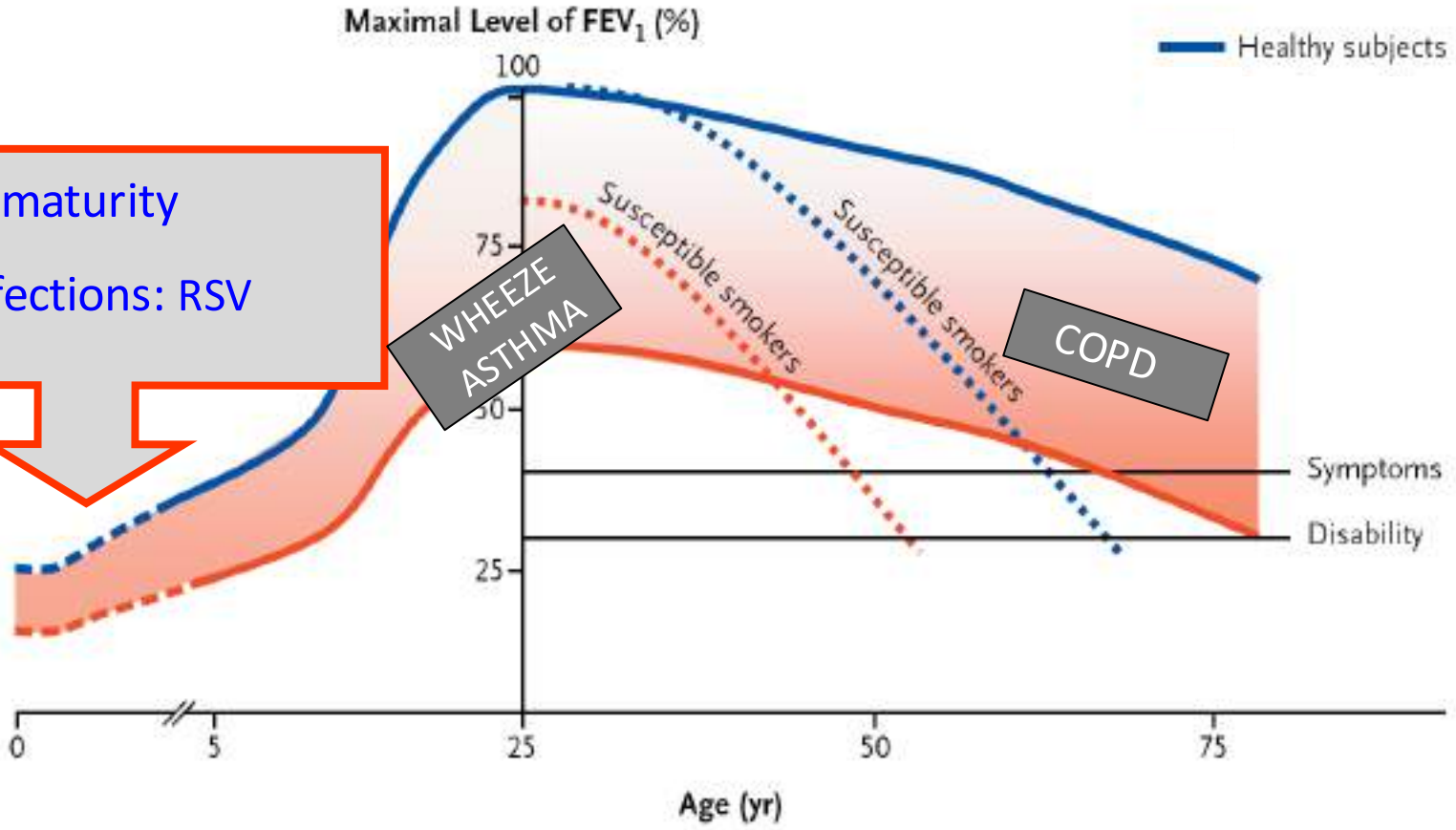


Ital J Ped 2023

EARLY INSULTS MAY CAUSE FAILURE TO ACHIEVE MAXIMAL LUNG FUNCTION.

PEOPLE WHO ENTER ADULT LIFE WITH LOWER LUNG FUNCTION ARE AT INCREASED RISK OF CHRONIC RESPIRATORY DISEASES LATER IN LIFE

- Lung immaturity
- Early infections: RSV



modified by Baraldi NEJM 2007

BMJ Open Association between early bronchiolitis and the development of childhood asthma: a meta-analysis

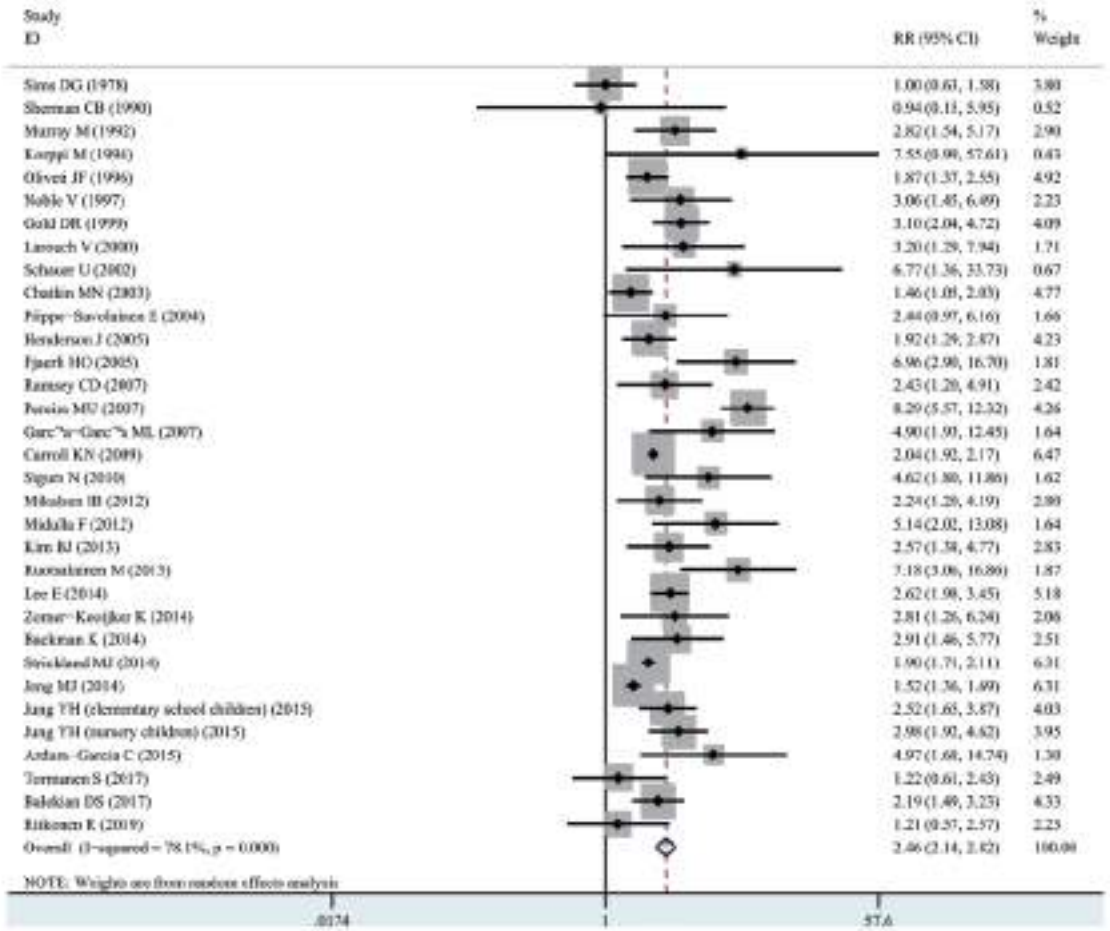


Figure 2 Forest plot of the overall association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma.

32 studies with 292 844 participants.

Bronchiolitis was associated with an increased risk of subsequent wheezing/asthma.

Relative risk=2.46, 95% CI 2.14 to 2.82, p<0.001.

Wang et al. BMJ Open 2021

A UNIQUE BIOLOGICAL MODEL!

RSV bronchiolitis plays a central role in the inception of Recurrent Wheeze and Asthma

RSV infection is not merely ‘in-and-out’
but may cause chronic lung disease

BMJ Open

Association between early bronchiolitis and the development of childhood a

Can prophylaxis with monoclonal antibodies play a role for the primary prevention of recurrent wheeze/asthma after RSV bronchiolitis?

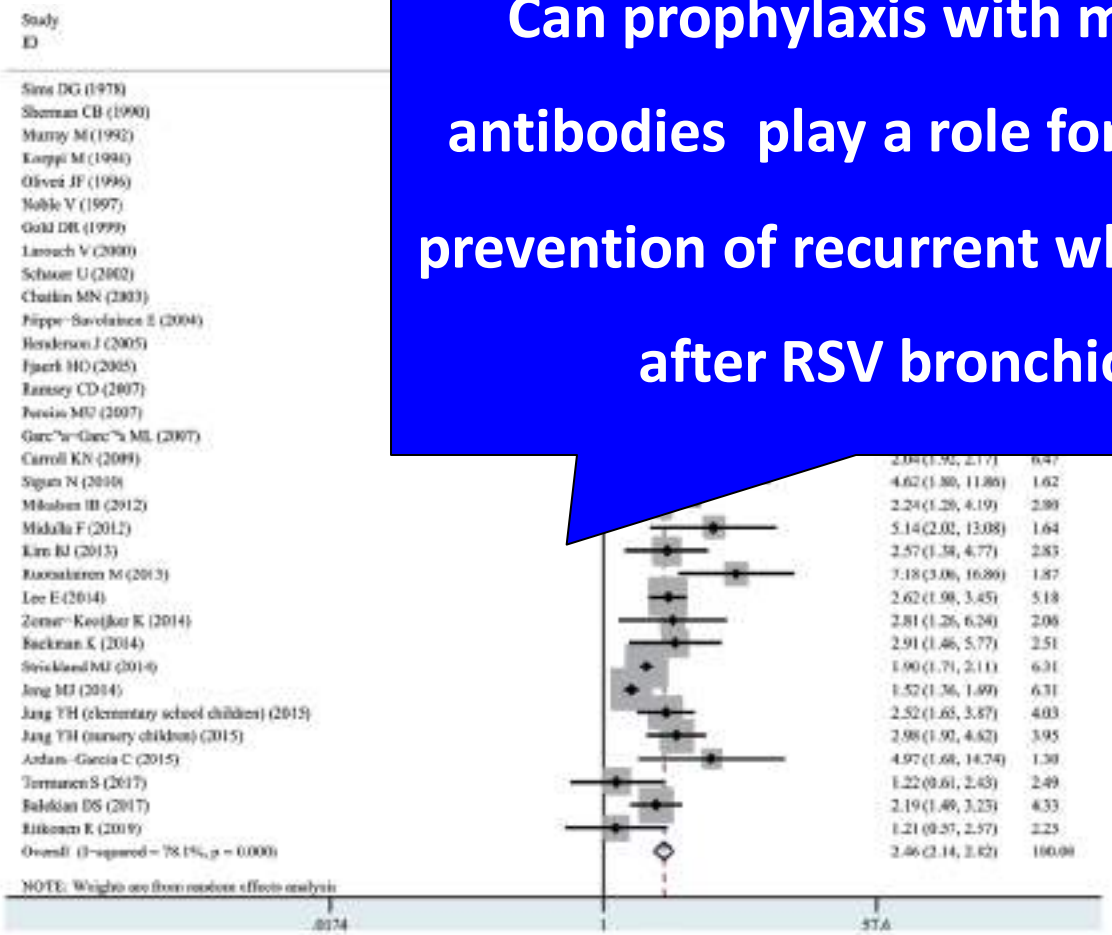


Figure 2 Forest plot of the overall association between bronchiolitis before 2 years of age and the subsequent development of wheezing/asthma.

44 participants.

ssociated with
f subsequent
wheezing/asthma.

Relative risk=2.46, 95% CI 2.14 to 2.82, p<0.001.

Wang et al. BMJ Open 2021

Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants

Healthy preterm (33-35 ga) infants “late preterm”

214 Palivizumab vs 215 placebo

Proof-of-concept study

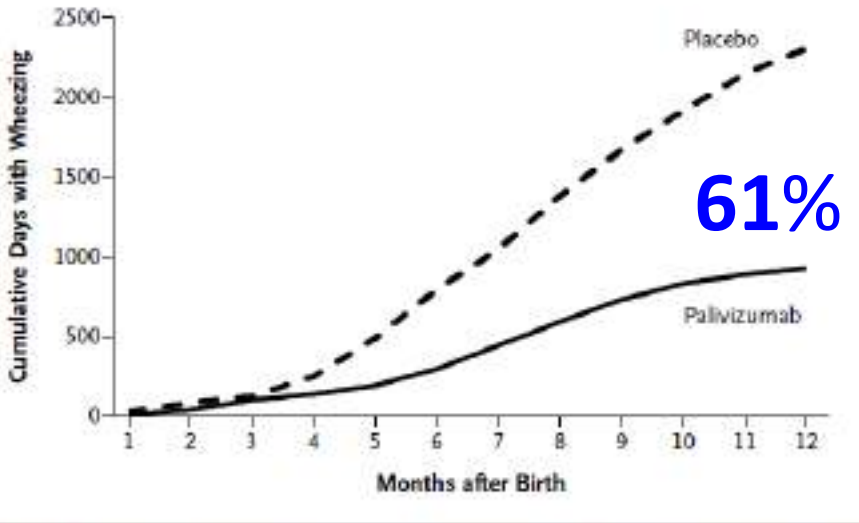


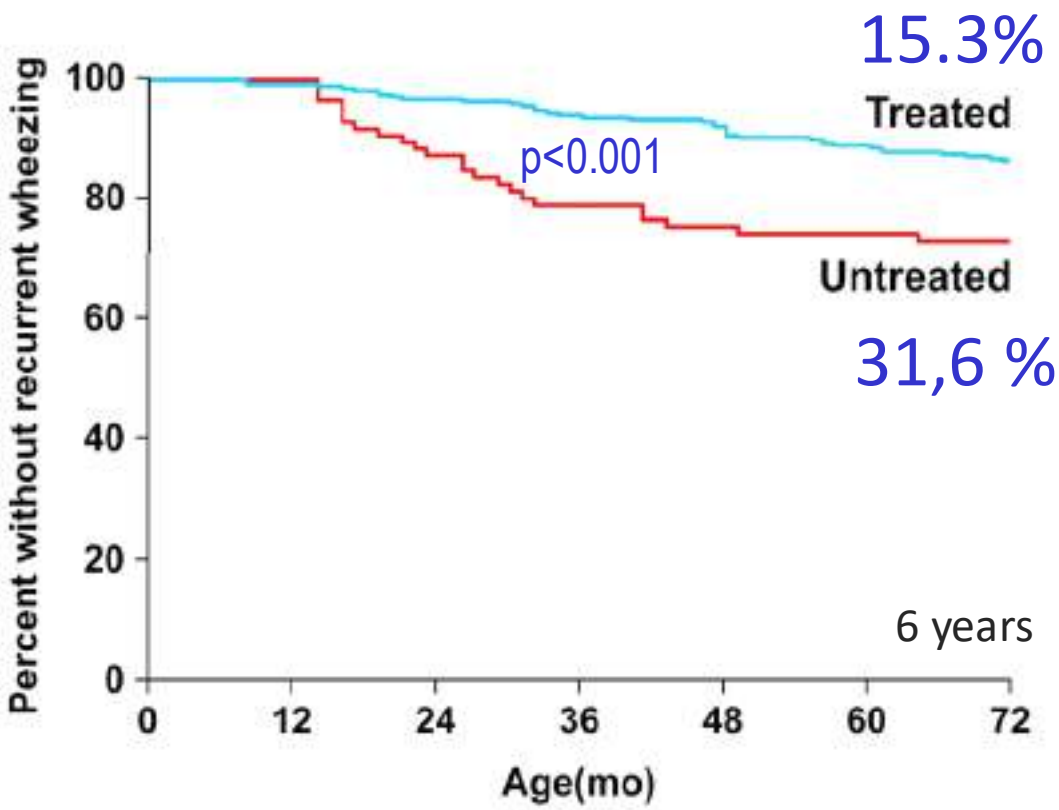
Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.

61% reduction in the n° of wheezing days in the first year of life

(hospitalization 12% vs 22%)

Blanken NEJM 2013

Palivizumab prophylaxis in preterm infants and subsequent Recurrent wheezing: 6 Year Follow up Study



444 children, palivizumab prophylaxis to preterm infants of 33-35 weeks g.a. (standard of care in Japan)

Significant reduction (50%) in recurrent wheezing (p<0.001)

but **no reduction in atopic (IgE) asthma** (p=0.57)
(underpowered for asthma)

Mochizuki et al AJRCCM 2017

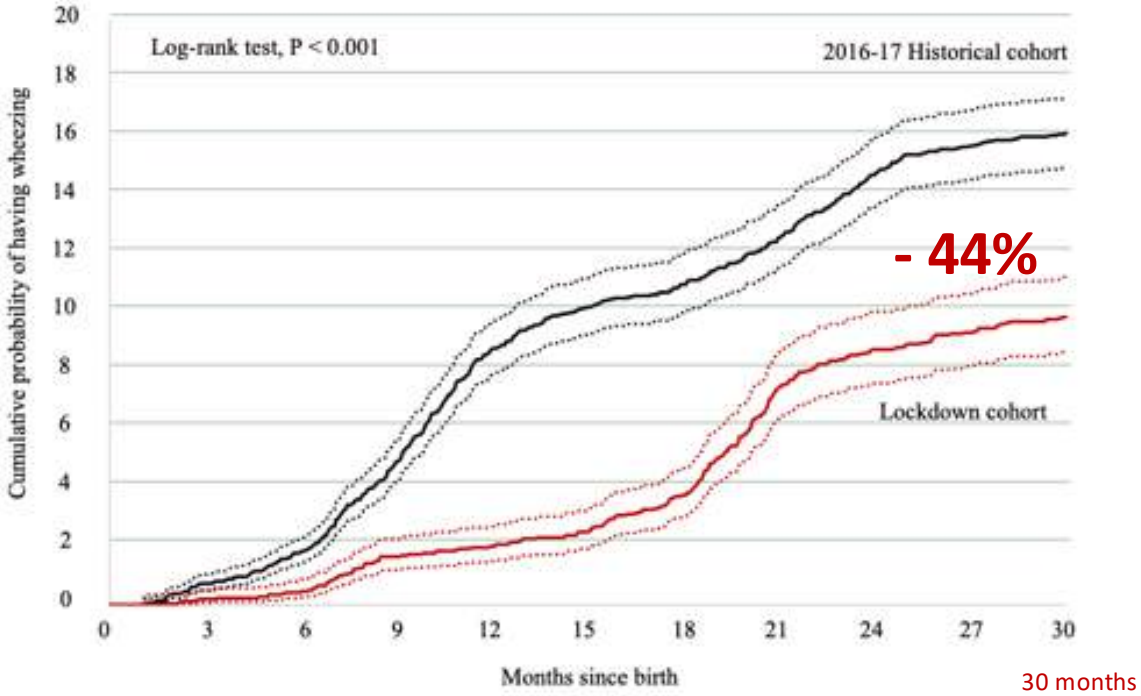
Could universal prophylaxis with nirsevimab reduce later wheezing and asthma in the pre-school age?

INFANTS NOT EXPOSED TO BRONCHIOLITIS DURING THE 2020 LOCKDOWN PRESENT A REDUCTION OF SUBSEQUENT WHEEZING ILLNESSES: A POPULATION DATABASE ANALYSIS

Historical cohort (n=3889) born Feb-Apr 2016 and 2017

Lockdown cohort (n=2192) born Feb-Apr 2020

} Follow-up 30 months



30 months

Reducing RSV infection in the first months of life decreases the risk of recurrent wheezing in the first years of life supporting the role of RSV in the inception of recurrent wheeze (and the rationale for an universal immunoprophylaxis).

ESPID 2023 LISBON & ONLINE 8 - 12 MAY

Barbieri et al JAMA Open 2024

The NEW ENGLAND JOURNAL of MEDICINE

April 2023

RSV Illness in the Young and the Old — The Beginning of the End?

Ruth A. Karron, M.D.

Science Immunology

Game over for RSV?

Strine MS, Wilen CB.