La prevenzione delle Infezioni Respiratorie Ricorrenti

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SAPIENZA
UNIVERSITÀ DI ROMA

self

Autoimmunità

Tumori

non self

Immunodeficienza

Ag microbici
Ag ambientali
Ag alimentari

Allergia

IRR: una sfida per il pediatra

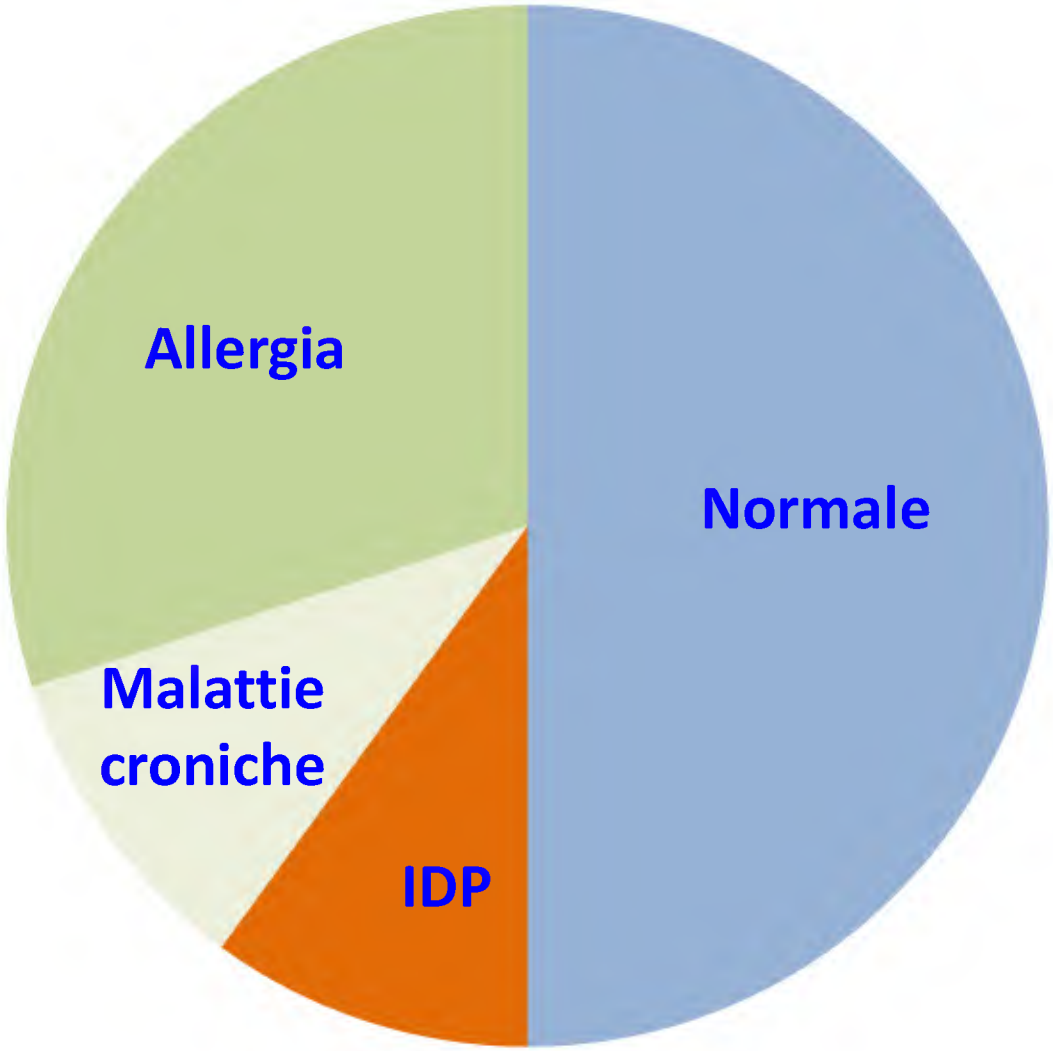
Più comune presentazione di esordio delle immunodeficienze primitive in età pediatrica (50% casi→ IDP umorali)

Significativa causa di morbilità/mortalità tra i pazienti con IDP

Età prescolare IRR di modesta gravità e a localizzazione prevalentemente alta**: «fisiologiche»**

Non medicalizzare il bambino sano, ma non ritardare una diagnosi di IDP

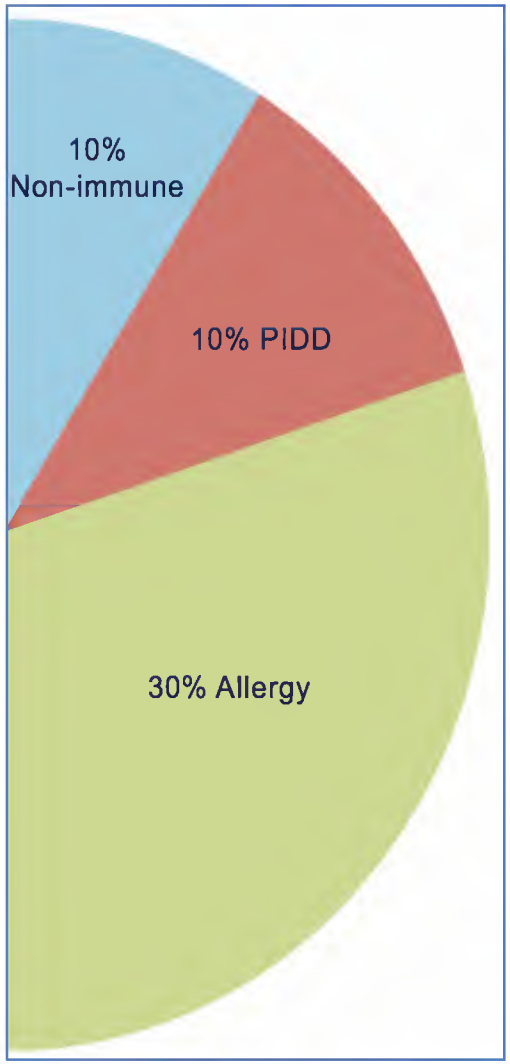
IRR: dati epidemiologici



Stiehm et al. 2015

IRR: il fenotipo “patologico”

SPUR
Severe
Persistent
Unusual
Recurrent



malattie croniche non immunomediate

Primary ciliary dyskinesia (PCD)
Cystic fibrosis (CF)
Nervous system and muscular abnormalities with ineffective cough
Bronchiectasis

Eustachian tube dysfunction
Sinus ostia obstruction
Tonsil and adenoid hypertrophy
Lymph node hyperplasia
Tumours
Foreign body aspiration
Vascular rings
Airway malacia

Cardiovascular abnormality

Developmental abnormalities of the airways and lungs

Mycobacterium tuberculosis
Persistent bacterial bronchitis (PBB)

Cigarette smoke
Gastro-oesophageal reflux disease (GORD)

IRR: il fenotipo “patologico”

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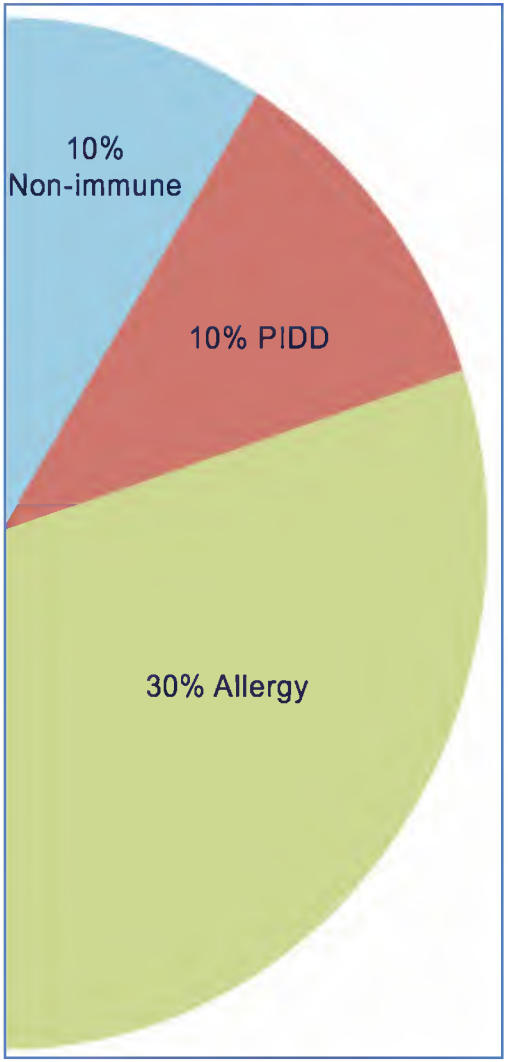


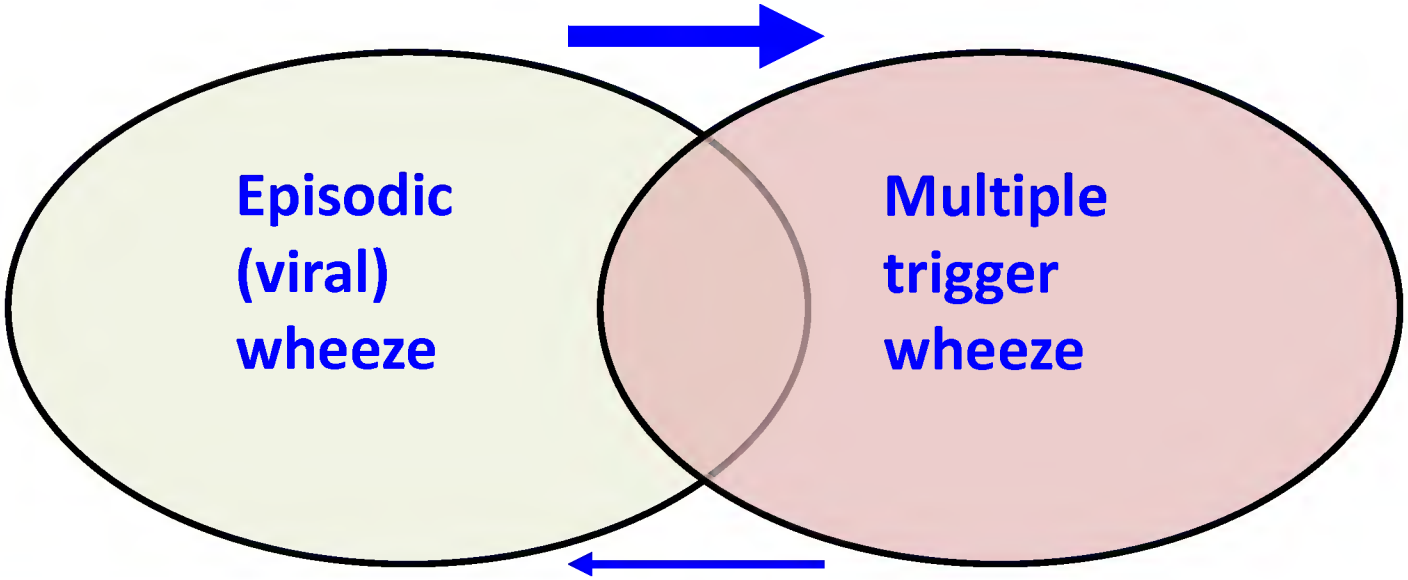
associato a malattie allergiche (scarso controllo)

< clearance mucociliare
> permeabilità mucosale
Alterata risposta immunitaria ai patogeni

31% pazienti con IDP: coesistenza allergia (CGD, Di George, WAS, Omenn, IPEX, HIES)

Wheezing phenotypes based on "temporal pattern"

Brand ERJ 2008



Children who wheeze intermittently and are well between episodes

Triggers: viruses

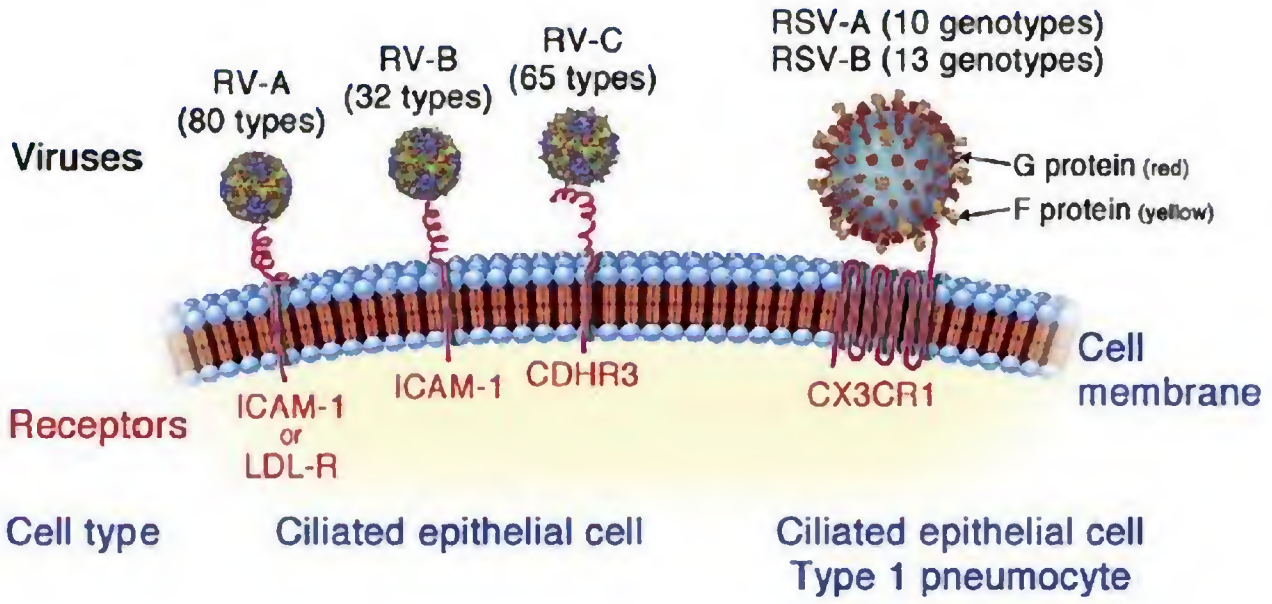
Wheeze both during and between exacerbations

Triggers: virus, smoke, allergenes, exercise

20%-30% bronchiolite nel 1° anno di vita

10%-20% 2° anno

Di questi: 50%-80% in famiglie atopiche



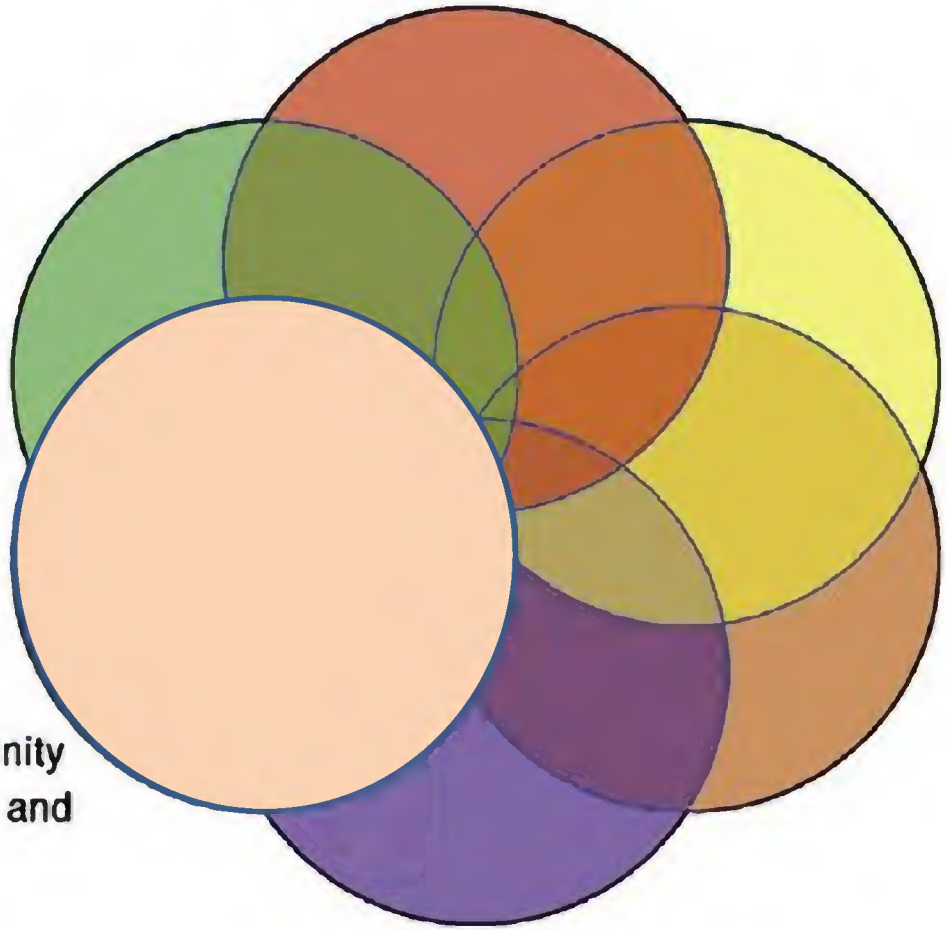
Indipendentemente da bronchiolite,

30%-50% almeni 1 wheezing acuto entro il 1° anno, di cui

30%-40% wheezing ricorrente

Jartti T & Gern JE, JACI 2017

Interacting factors that contribute to the severity of virus-induced wheezing illnesses and the risk for asthma

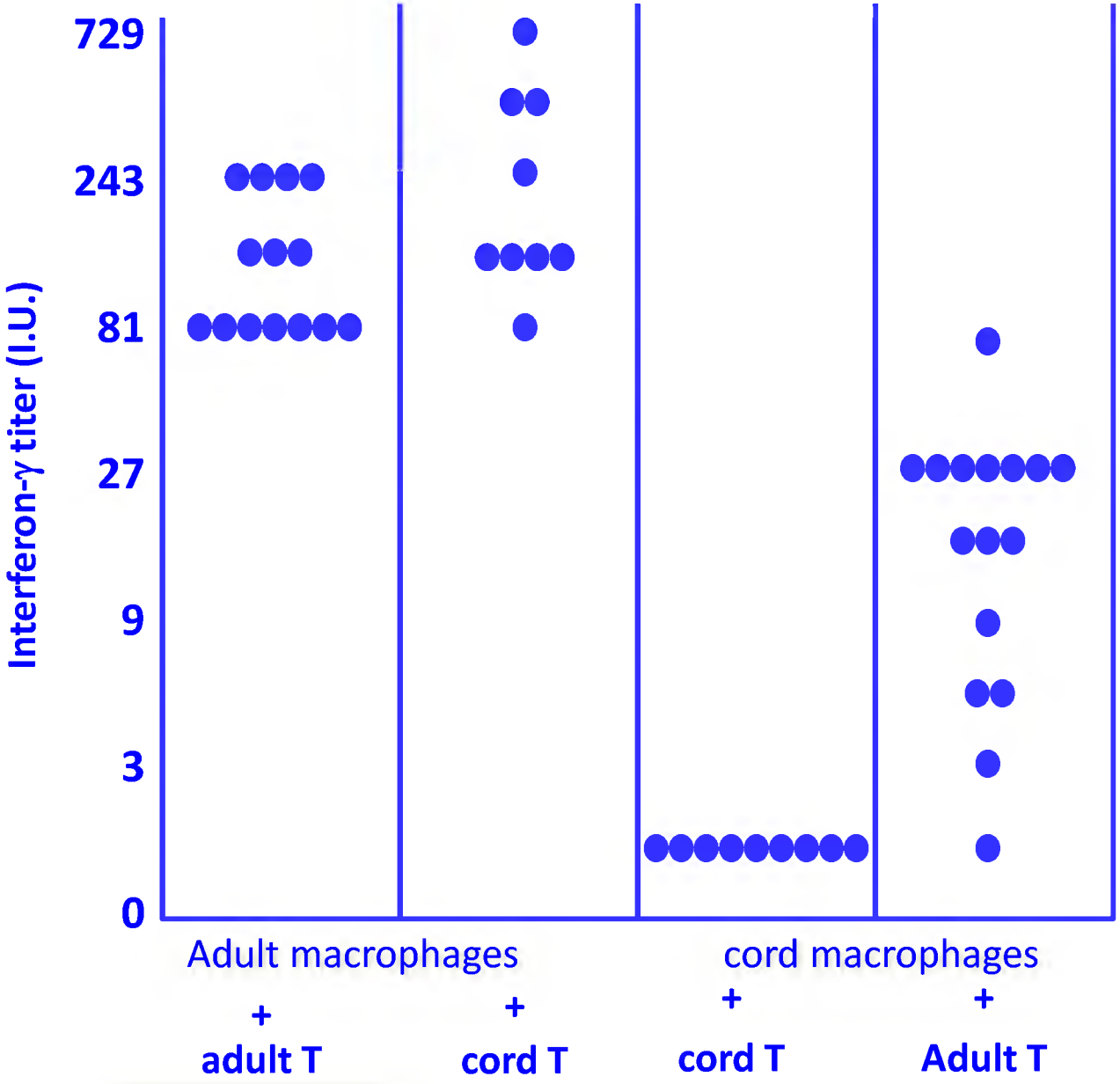


Genetics

- Family history of asthma or atopy
- Poor antiviral immunity
- Specific risk genes and single nucleotide polymorphisms

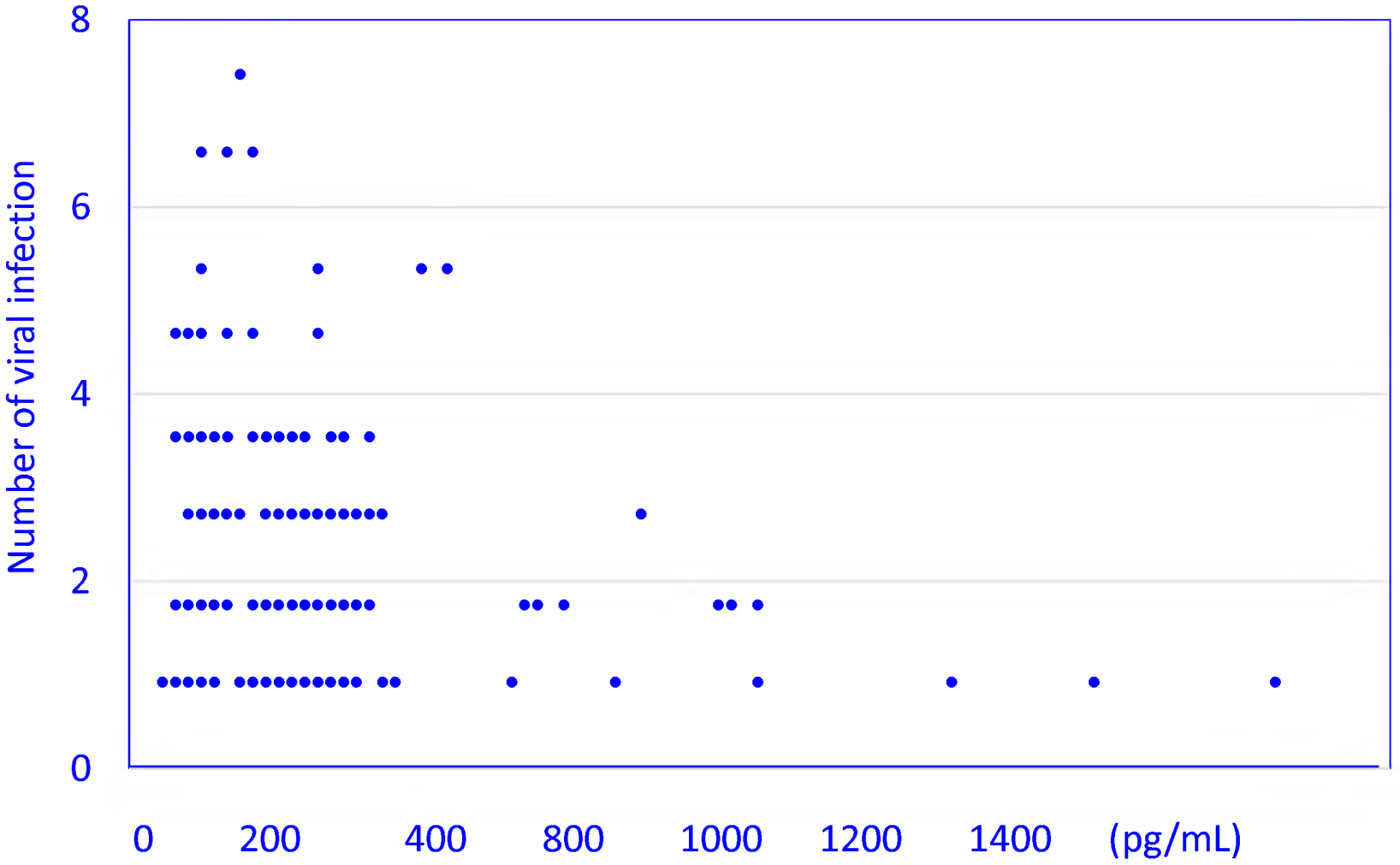
Jartti T & Gern JE, JACI 2017

IFN-γ production by neonatal macrophages



Imberti L. et al, 1992

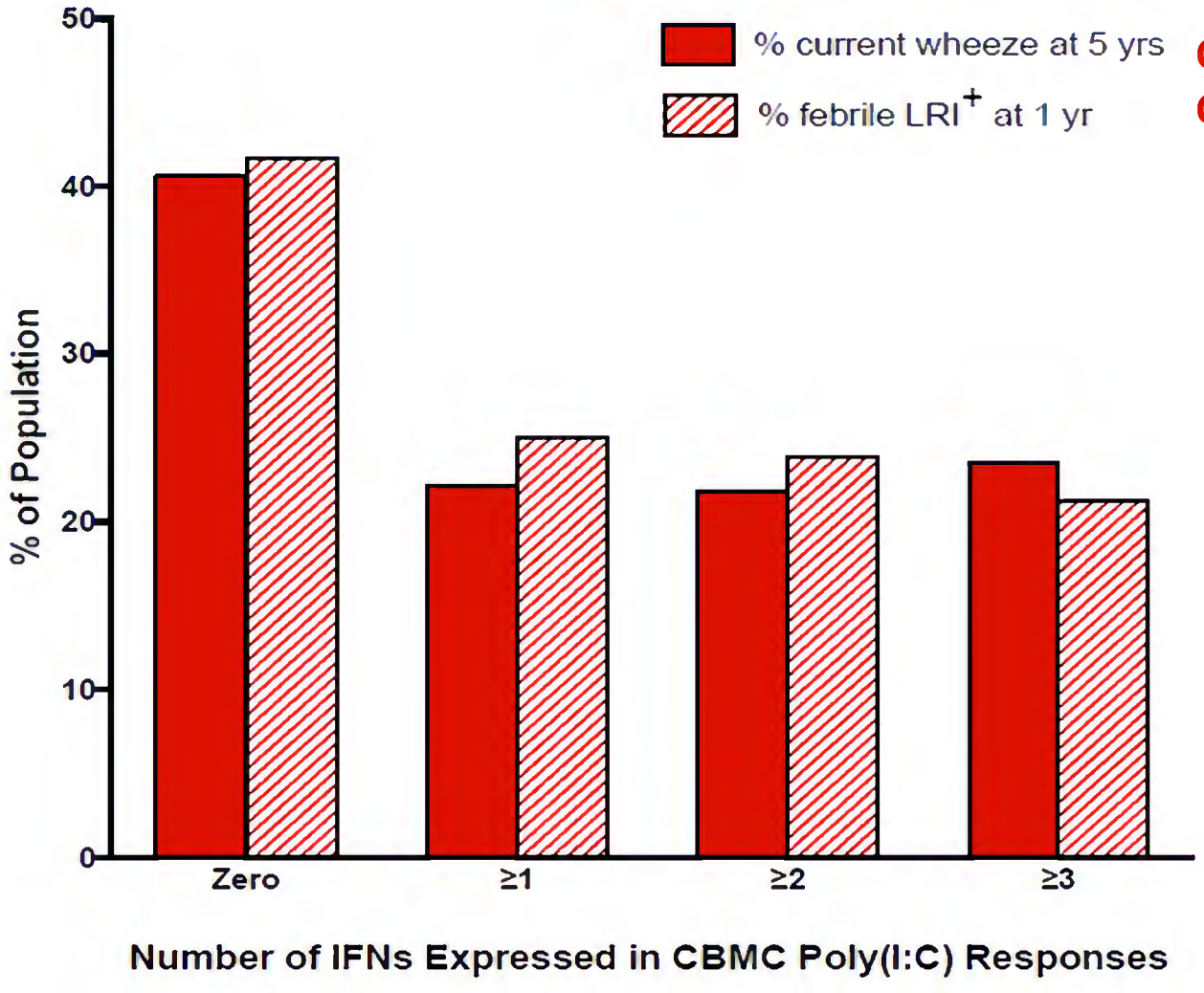
Cord blood PHA-induced IFN-γ



(Copenhaver CC et al, AJRCCM 2004)

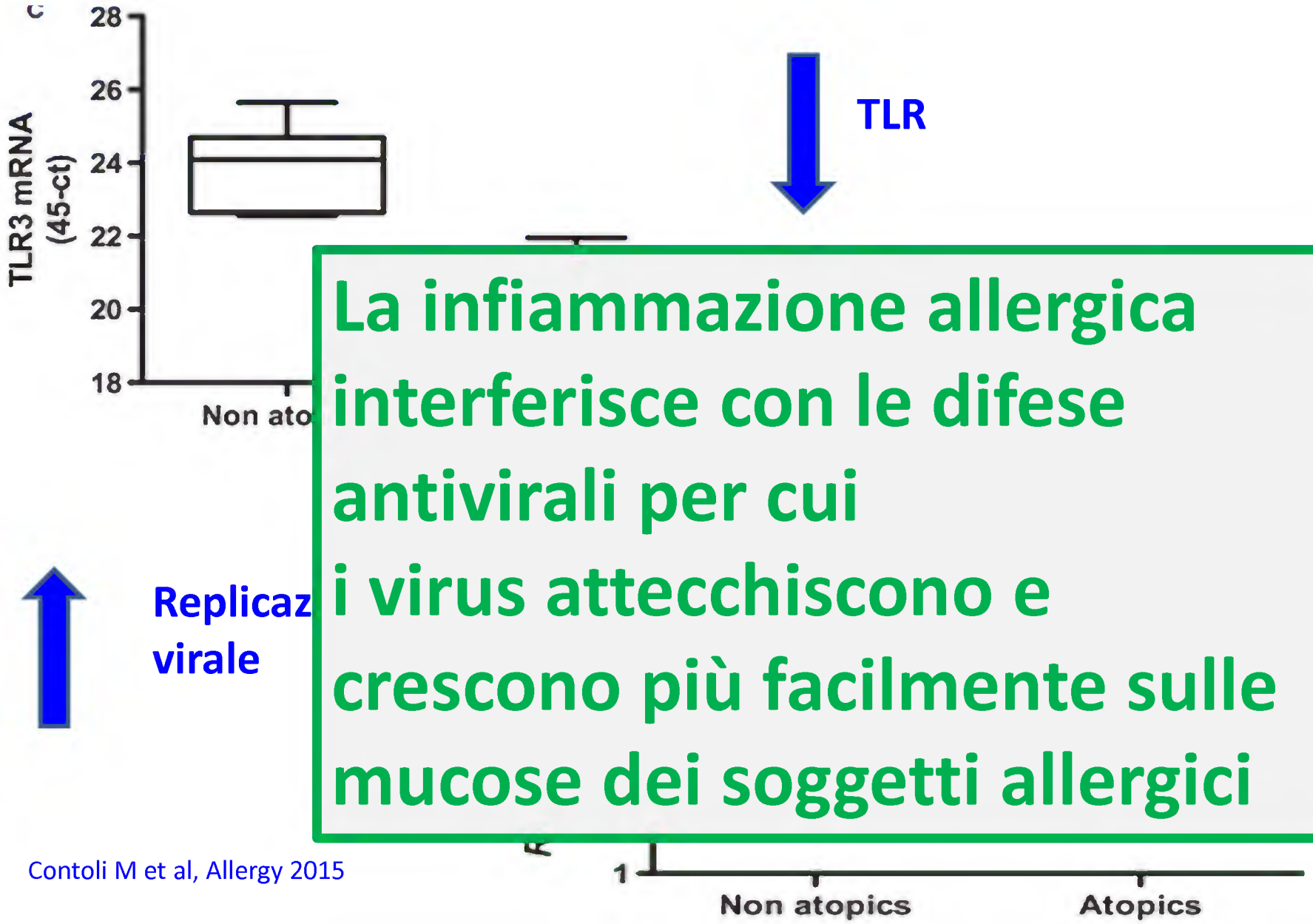
Childhood Asthma Study (CAS), birth cohort of infants at high risk of atopy (151 children; panel of 17 T1/3IFNs in response to the 71 viral mimic poly(I:C)

Susceptibility to early fLRI and wheeze at Yr5 in relation to IFN production capacity



Holt P, JACI 2018

RV-16 vRNA and TLR3 mRNA levels in the cultures of epithelial cells of the nasal mucosae, 0 and 8 h after infection by Rhinovirus



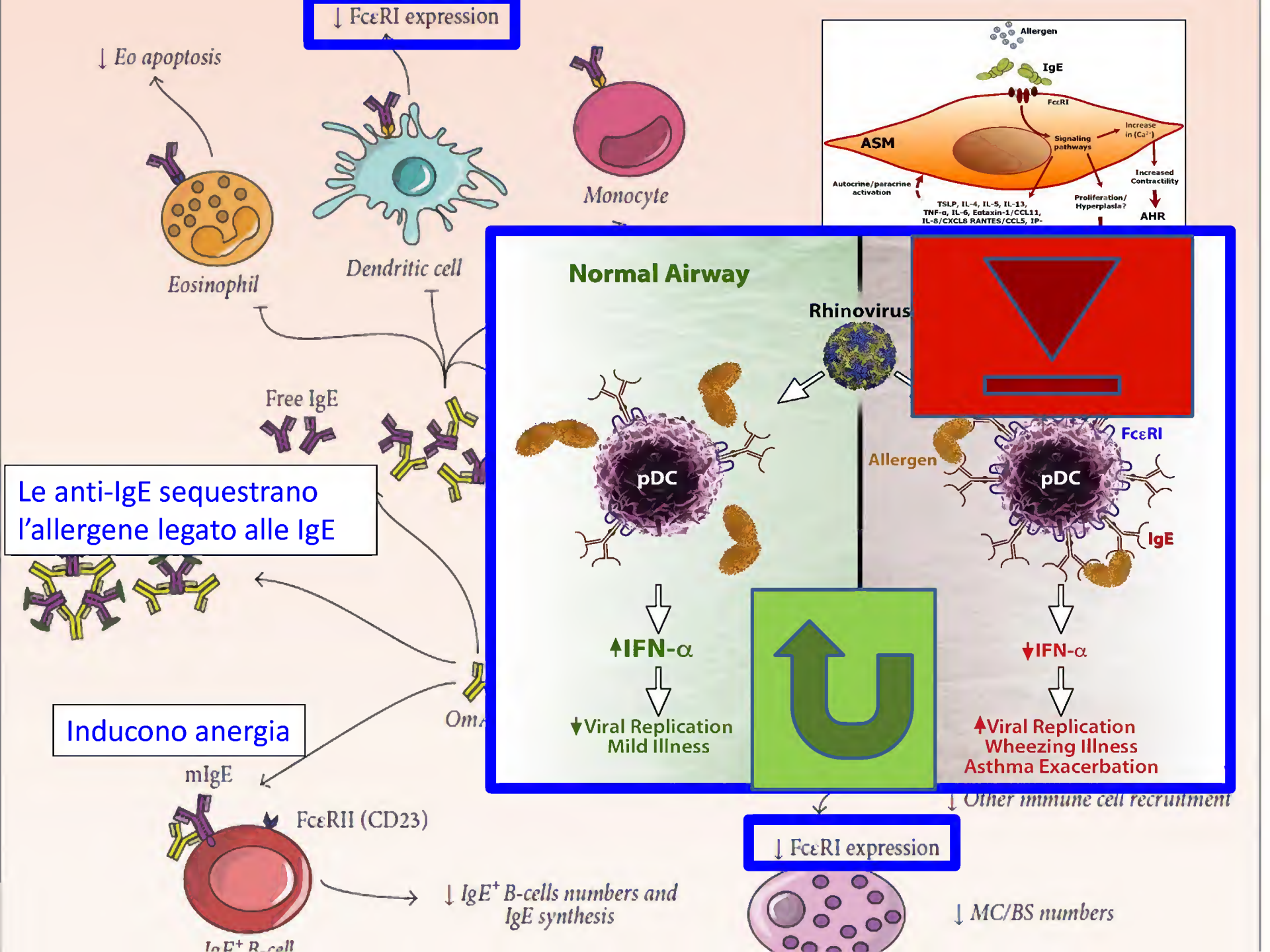
La infiammazione allergica interferisce con le difese antivirali per cui i virus attecchiscono e crescono più facilmente sulle mucose dei soggetti allergici

Contoli M et al, Allergy 2015

Predictor of current wheezer at 5 y of age in relation to time of atopic sensitization

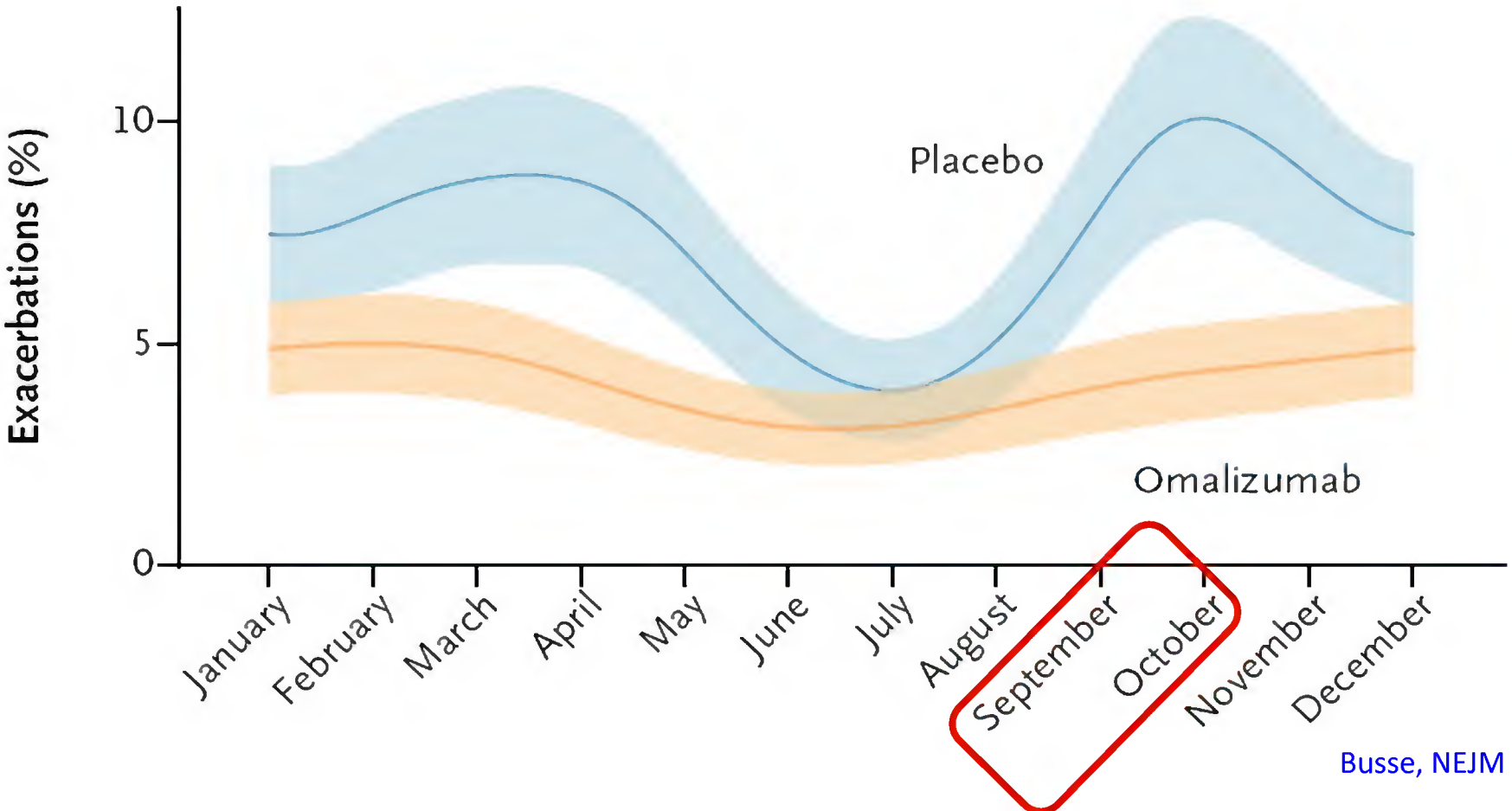
Type of ARI	Never atopic OR (95% CI) *P* value	Atopic by age of 2 years OR (95% CI) *P* value	Atopic after 2 years OR (95% CI) *P* value
Whole population regardless of ARI history	0.4 (0.2-0.8) 0.006*	3.1 (1.5-6.4) 0.05	2.9 (1.4-5.8) 0.05
Any wheezy LRI in first year	1.4 (0.4-5.1) 0.6	3.4 (1.2-9.7) 0.02	0.5 (0.1-3.5) 0.5
No. of wheezy LRI *(linear model)*	1.1 (0.5-2.8) 0.8	2.4 (1.2-4.7) 0.01	0.9 (0.2-4.1)0.9
0	Comparison group	Comparison group	Comparison group
1	1.6 (0.4-6.9) 0.5	1.9 (0.7-5.5) 0.2	(≥1) 0.5 (0.1-3.4) 0.5
>2	1.0 (0.1-9.1) 1.0	7.1 (1.3-38.4) 0.02	NA
Any febrile infections in first year	1.2 (0.4-3.8) 0.8	1.2 (0.8-1.8) 0.4	1.8 (0.3-9.6) 0.5
Any febrile URI	1.3 (0.4-4.1) 0.7	0.9 (0.5-1.5) 0.9	1.4 (0.3-7.1) 0.7
Any febrile LRI	1.0 (0.2-3.8) 1.0	4.2 (1.5-11.8) 0.006	1.3 (0.2-9.9) 0.8
Any wheezy or febrile LRI	1.0 (0.3-3.4) 1.0	3.9 (1.4-10.5) 0.007	0.7 (0.1-3.9) 0.7
Any wLRI associated with rhinovirus or RSV	0.8 (0.2-4.0) 0.8	4.1 (1.3-12.6) 0.02	0.9 (0.1-6.4) 0.9
Any wLRI associated with rhinovirus	1.6 (0.3-8.7) 0.6	3.2 (1.1-9.5) 0.03	2.1 (0.3-18.5) 0.5
Any wLRI associated with RSV	1.6 (0.3-8.7) 0.6	3.6 (1.0-13.3) 0.06	Insufficient number

Kusel MM et al, JACI 2007


↓ FcεRI expression
↓ Eo apoptosis
Eosinophil
Dendritic cell
Monocyte
Allergen
IgE
FcεRI
ASM
Signaling pathways
Increase in (Ca2+)
Increased Contractility
AHR
Autocrine/paracrine activation
TSLP, IL-4, IL-5, IL-13, TNF-α, IL-6, Eotaxin-1/CCL11, IL-8/CXCL8 RANTES/CCL5, IP-
Proliferation/ Hyperplasia?
Normal Airway
Rhinovirus
Free IgE
pDC
FcεRI
Allergen
pDC
IgE
Le anti-IgE sequestrano l'allergene legato alle IgE
↑IFN-α
↓Viral Replication
Mild Illness
↓IFN-α
↑Viral Replication
Wheezing Illness
Asthma Exacerbation
Inducono anergia
mIgE
FcεRII (CD23)
↓ IgE+ B-cells numbers and IgE synthesis
IgE+ B-cell
↓ Other immune cell recruitment
↓ FcεRI expression
↓ MC/BS numbers

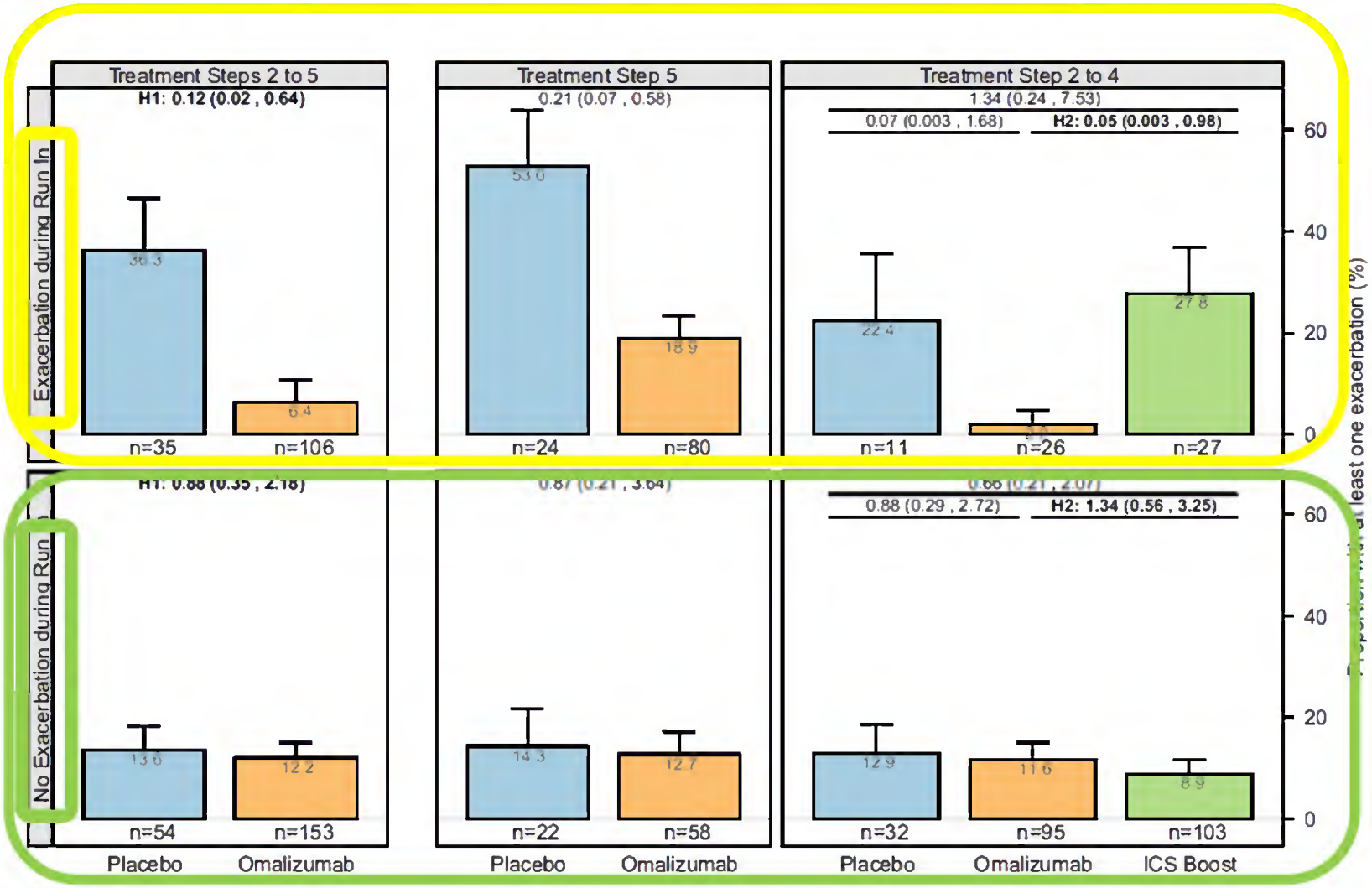
The NEW ENGLAND JOURNAL of MEDICINE

Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children



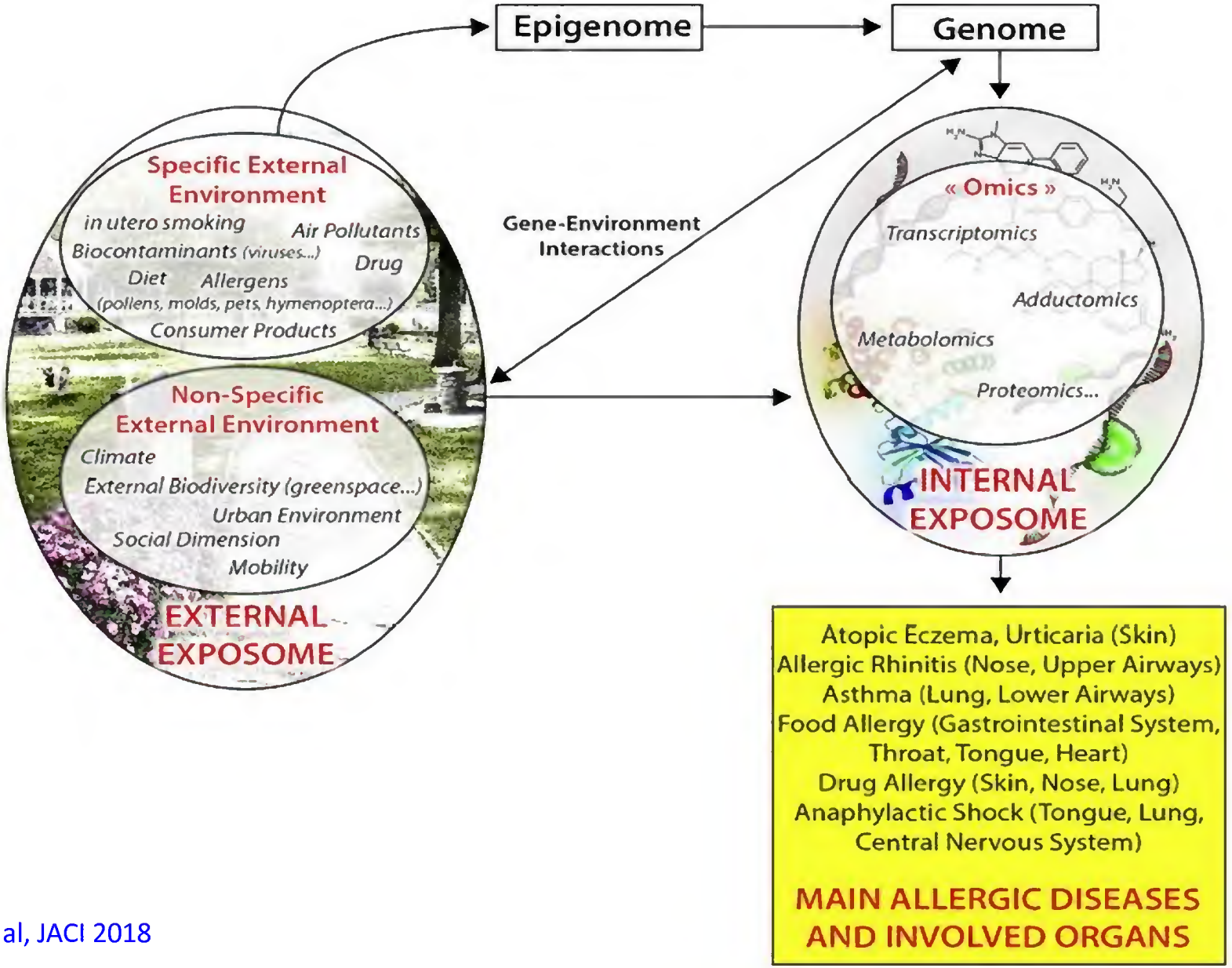
Busse, NEJM 2011

80% reduction in fall exacerbations



Teach et al. JACI 2015

Exposome involvement in allergy



Cecchi et al, JACI 2018

Witt et al. BMC Genomics (2018) 19:290
https://doi.org/10.1186/s12864-018-4652-7

BMC Genomics

RESEARCH ARTICLE Open Access

Impact on birth weight of maternal smoking throughout pregnancy mediated by DNA methylation

Stephanie H. Witt[1*†], Josef Frank[1†], Maria Gilles[2], Maren Lang[1], Jens Treutlein[1], Fabian Streit[1], Isabell A. C. Wolf[2], Verena Peus[2], Barbara Scharnholz[2], Tabea S. Send[2], Stefanie Heilmann-Heimbach[3,4], Sugirthan Sivalingam[3,4], Helene Dukal[1], Jana Strohmaier[1], Marc Sütterlin[5], Janine Arloth[6], Manfred Laucht[7,8], Markus M. Nöthen[3,4], Michael Deuschle[2] and Marcella Rietschel[1]

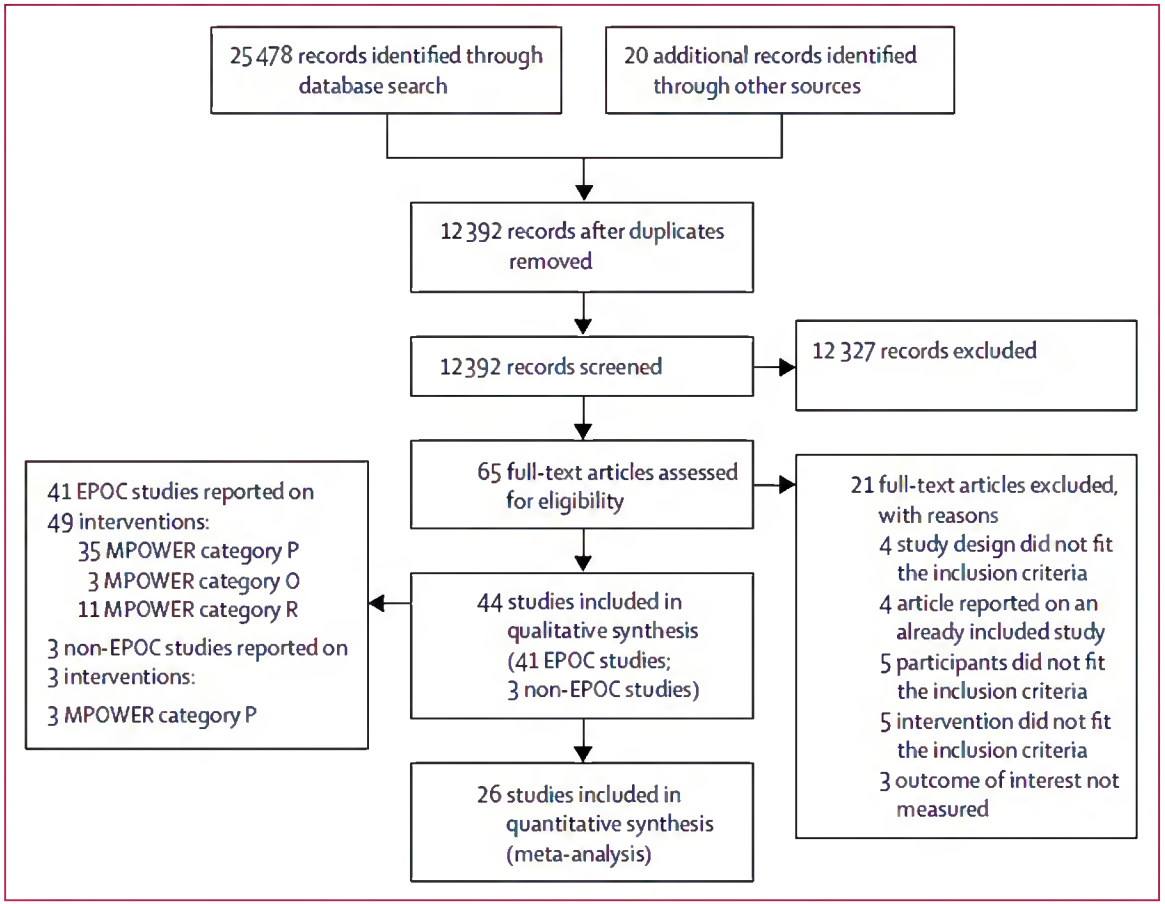
Effect of tobacco control policies on perinatal and child health: a systematic review and meta-analysis

Timor Faber, Arun Kumar, Johan P Mackenbach, Christopher Millett, Sanjay Basu, Aziz Sheikh, Jasper V Been

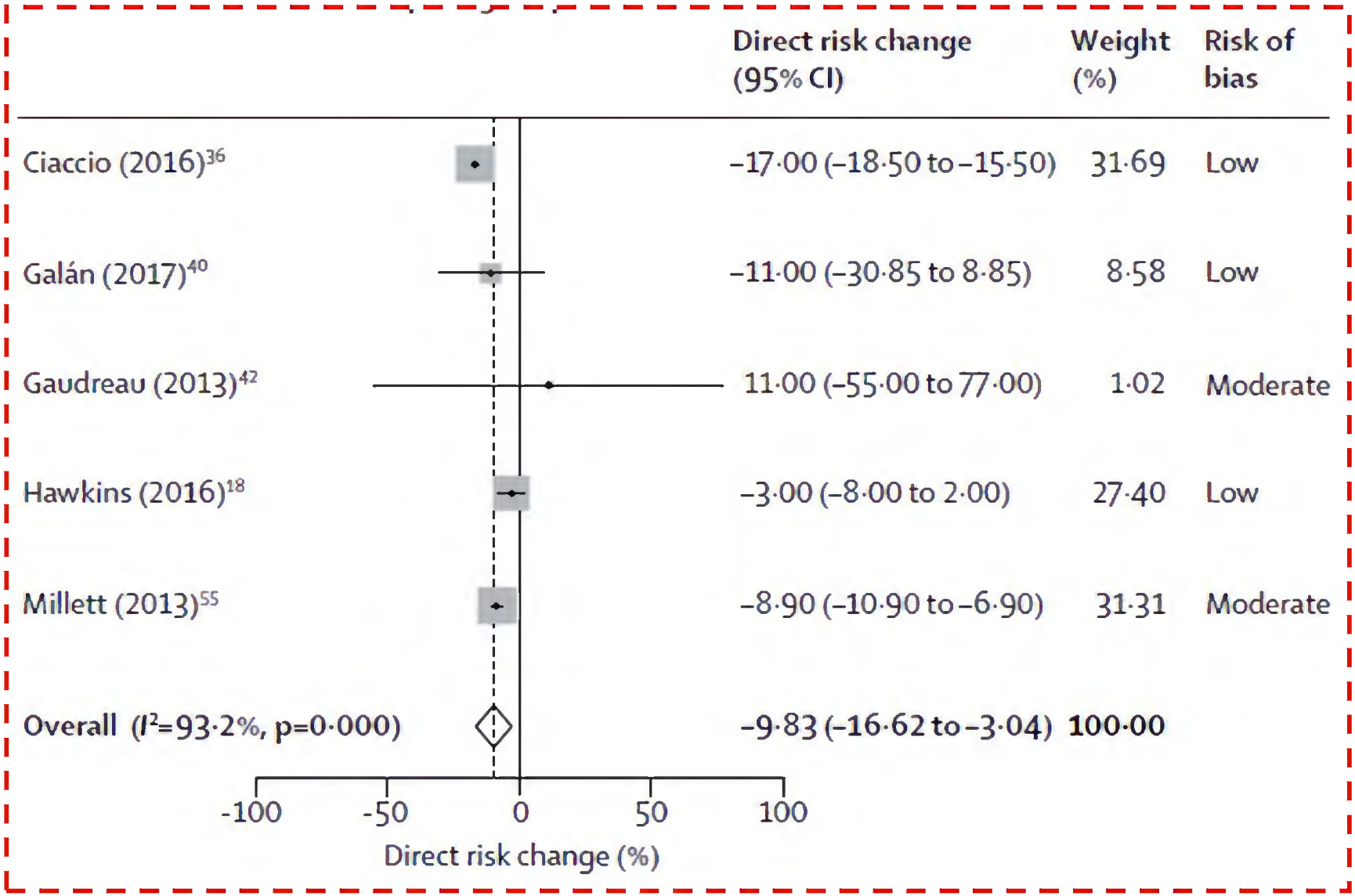
Summary

Background Tobacco smoking and smoke exposure during pregnancy and childhood cause considerable childhood

Lancet Public Health 2017;

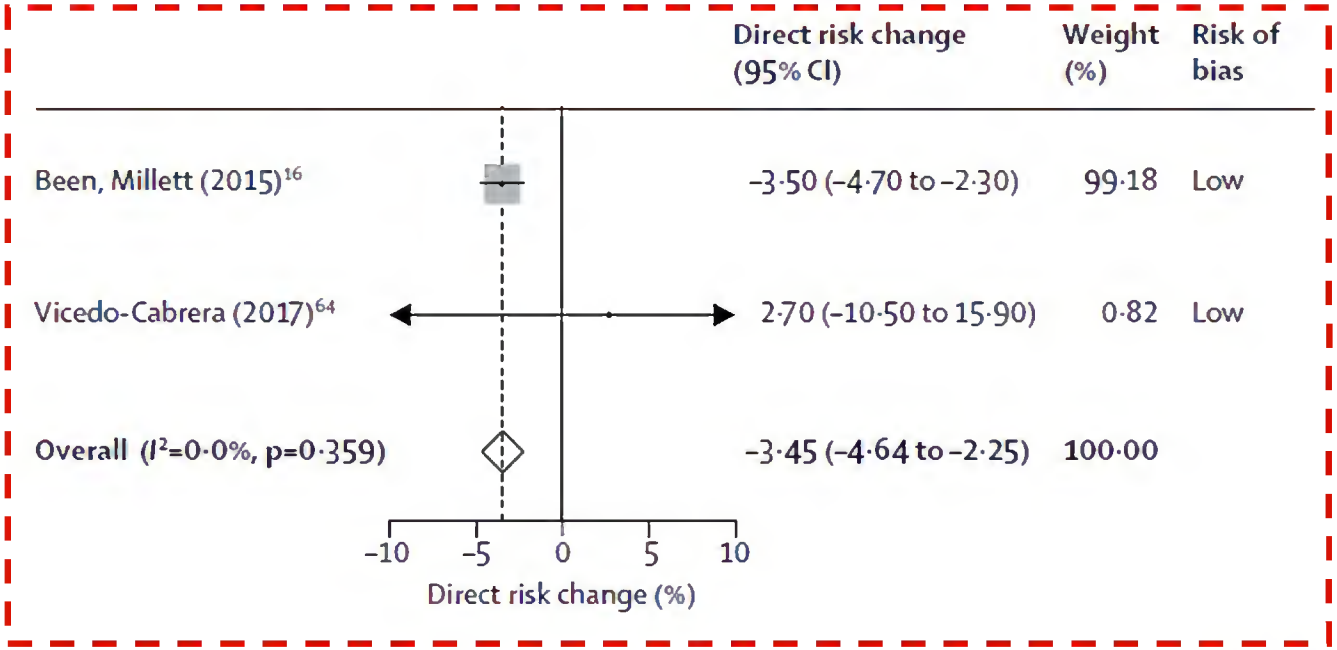


Accessi in ospedale per asma acuto 685.000 riduzione del 9.8%



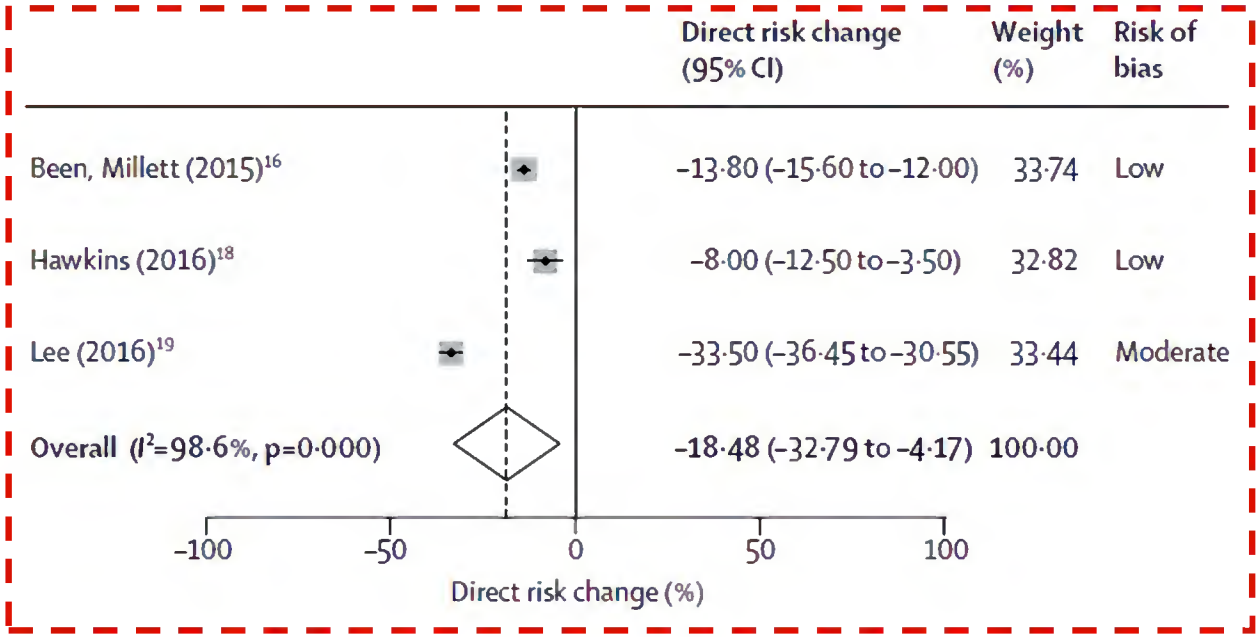
Faber T et al, Lancet Public Health 2017

IR ricoveri in ospedale 2.3 milioni



- 18.5%

IR basse vie



Faber T et al, Lancet Public Health 2017

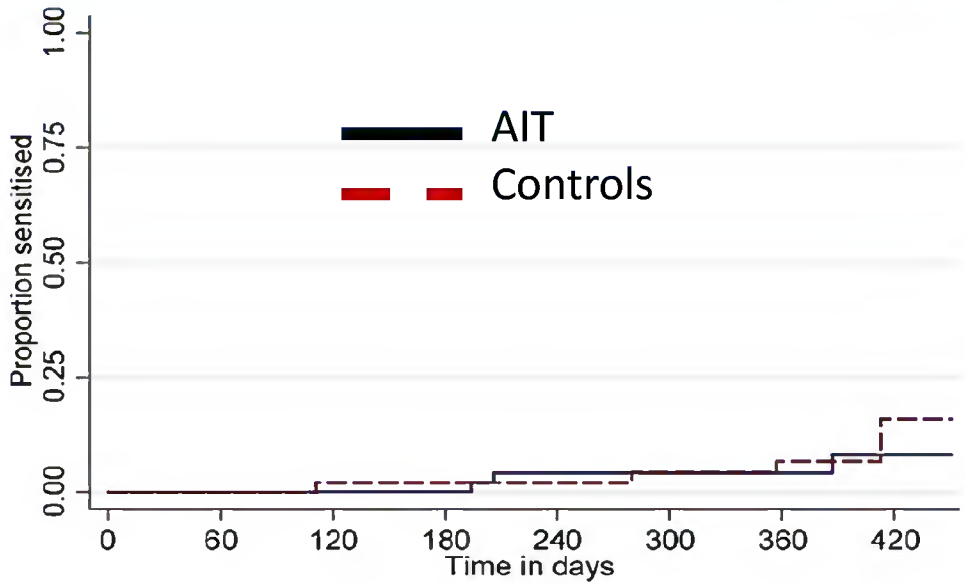
% nonsmokers with serum cotinine levels 0.05–10 ng/mL, by age group and race/ethnicity — National Health and Nutrition Examination Survey, United States, 1999–2012

Characteristic	1999–2000 %	1999–2000 (95% CI)	2003–2004 %	2003–2004 (95% CI)	2007–2008 %	2007–2008 (95% CI)	2011–2012 %	2011–2012 (95% CI)	Relative % decline† (1999–2000 to 2011–2012)
Aged 3–11 yrs									
White, non-Hispanic	63.3	(48.7–78.0)	68.9	(56.8–81.0)	58.8	(47.9–69.6)	37.2	(30.0–44.4)	41.2
Black, non-Hispanic	84.7	(79.2–90.3)	80.7	(70.2–91.2)	64.9	(53.0–76.7)	67.9	(57.1–78.6)	19.8
Mexican American	49.0	(39.1–58.9)	38.7	(28.9–48.6)	29.7	(20.2–39.1)	29.9	(20.4–39.4)	39.0
Aged 12–19 yrs									
White, non-Hispanic	61.8	(52.6–71.1)	56.9	(48.0–65.8)	47.9	(33.9–61.8)	35.8	(28.6–43.0)	42.1
Black, non-Hispanic	80.4	(76.0–84.7)	74.0	(67.7–80.4)	60.2	(51.6–68.8)	54.6	(43.0–66.2)	32.1
Mexican American	48.3	(40.8–55.8)	35.1	(26.6–43.6)	29.1	(18.3–39.9)	16.9	(7.0–26.9)	65.0
Aged ≥20 yrs									
White, non-Hispanic	45.7	(39.3–52.0)	40.7	(31.6–49.8)	36.3	(29.3–43.3)	17.9	(13.8–21.9)	60.8
Black, non-Hispanic	68.2	(62.5–73.8)	61.7	(52.9–70.5)	52.2	(46.6–57.9)	39.6	(32.6–46.6)	41.9
Mexican American	41.2	(34.0–48.4)	31.9	(22.6–41.1)	28.0	(23.2–32.7)	23.8	(16.2–31.4)	42.2

Homa DL et al, Morbidity and Mortality Weekly Report 2015

Pharmacological	
Suplatast tosilate compared with ketotifen for at least 24 months in infants	Significant reduction in asthma outcomes at 2–3 years
Cetirizine for 18 months in infants 1–2 years	No reduction in asthma outcomes at 2–4 years
Inhaled fluticasone for 2 years in children 2–3 years	No reduction in asthma outcomes 12 months after intervention
Ketotifen in infants aged 2–34 months for 52 weeks	Reduction in asthma outcomes
Pharmacological or clinical	
Optimisation of asthma management during pregnancy	Reduced bronchiolitis episodes at 12 weeks
Immunotherapy	
Oral house dust mite allergen extract for 48 months in children aged 12–30 months	No reduction in wheeze
Sublingual immunotherapy (house dust mite, cat, timothy grass) daily for 12 months in infants between 12 and 30 months	No reduction in asthma outcomes 36 months after treatment completion
Subcutaneous immunotherapy for 3 years in children 6–14 years	Reduced asthma outcomes at 10 years
Allergen	
Stringent, multi-area house dust mite avoidance prenatally and postnatally	No reduction in wheeze or asthma at 3 years
House dust mite avoidance from birth	No reduction in asthma outcomes at 8 years
House dust mite avoidance from birth to 5 years	No reduction in asthma outcomes at 11·5 years

	Active	Placebo	Odds ratios (95% CI)*
Allergic sensitization‡ (yes)			
ITT§	88.0% (22/25)	76.0% (19/25)	2.32 (0.51-10.5)
PP‖	88.9% (16/18)	73.7% (14/19)	2.86 (0.48-17.1)
Current asthma (yes)¶			
ITT§	16.0% (4/25)	16.0% (4/25)	1.00 (0.16-6.1)
PP‖	5.6% (1/18)	5.3% (1/19)	1.06 (0.01-87.7)
Allergic sensitization# to house dust mite, *Der P* (yes)			
ITT§	76.0% (19/25)	60.0% (15/25)	2.11 (0.63-7.1)
PP‖	77.8% (14/18)	52.6% (10/19)	3.15 (0.75-13.2)
Allergic sensitization# to house dust mite, *Der F* (yes)			
ITT§	72.0% (18/25)	56.0% (14/25)	2.02 (0.62-6.6)
PP‖	77.8% (14/18)	47.4% (9/19)	[illegible]
Allergic sensitization# to timothy grass (yes)			
ITT§	80.0% (20/25)	60.0% (15/25)	2.67 (0.75-9.5)
PP‖	83.3% (15/18)	52.6% (10/19)	4.50 (0.97-20.8)
Allergic sensitization# to cat (yes)			
ITT§	60.0% (15/25)	60.0% (15/25)	[illegible]
PP‖	66.7% (12/18)	52.6% (10/19)	1.80 (0.48-6.8)
Allergic sensitization to aeroallergen not** in the treatment mix (yes)			
ITT§	68.0% (17/25)	68.0% (17/25)	1.00 (0.31-3.3)
PP‖	83.3% (15/18)	63.2% (12/19)	2.92 (0.62-13.8)

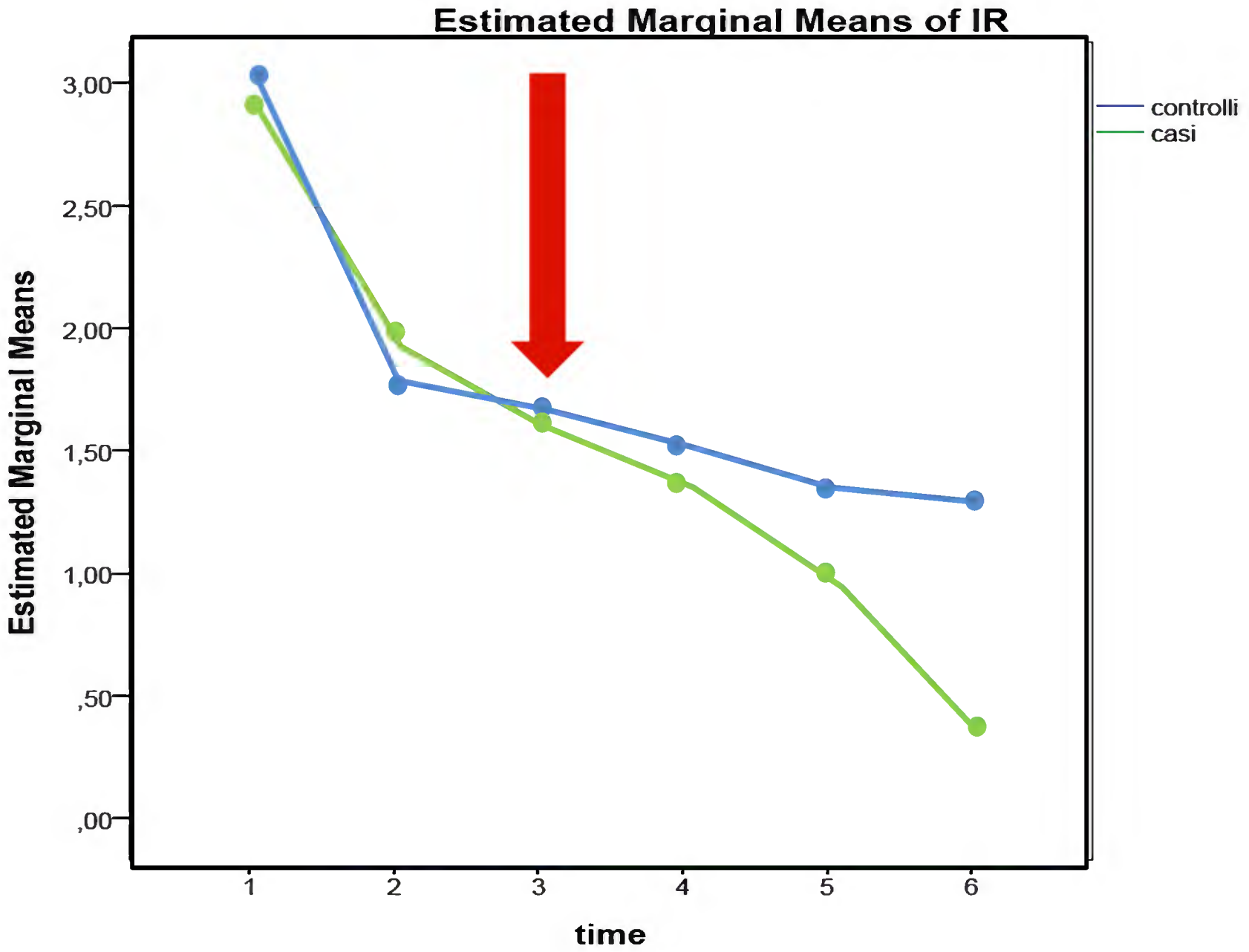


Holt P, JACI 2013

Zolkipli Z et al, JACI 2015

	CASI	CONTROLLI
N.	143	122
M/F	92/51	77/45
ETÀ (anni)	9.71 ± 3.2	9.56 ± 3.4
RINITE	45	38
ASMA	23	30
ASMA+RINITE	75	54

Rinosinusiti
Otiti
Faringotonsilliti
Laringotracheiti
Bronchiti
Polmoniti

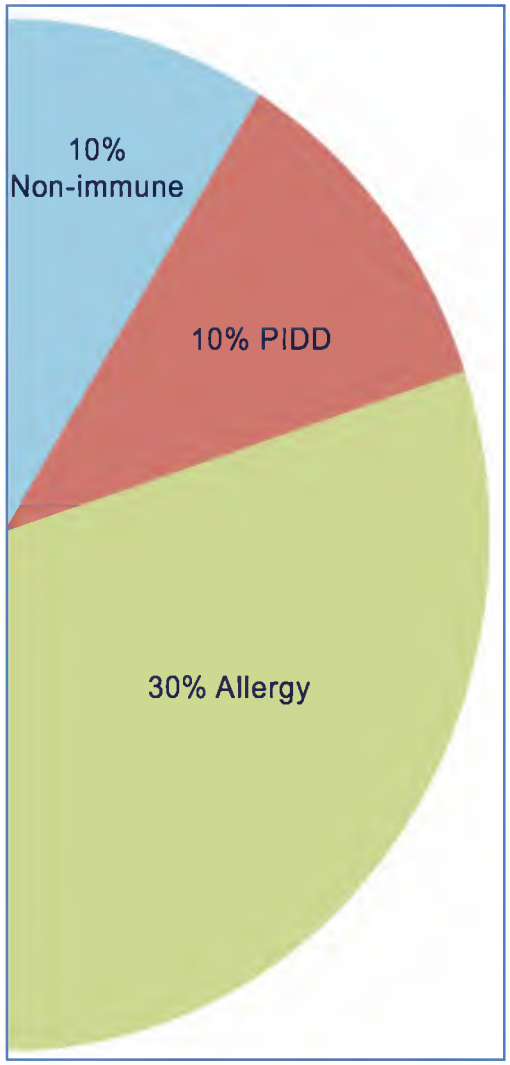

Estimated Marginal Means of IR
Estimated Marginal Means
3,00
2,50
2,00
1,50
1,00
,50
,00
1
2
3
4
5
6
time
controlli
casi

La SLIT sembra essere efficace nella prevenzione delle infezioni delle alte vie aeree a partire dal secondo anno di terapia

Riduzione % del numero di infezioni all'anno dei bambini in terapia con SLIT rispetto ai controlli

Primo anno	12,92%
Secondo anno	31,26%
Terzo anno	66.7%

IRR: il fenotipo “patologico”



SPUR
Severe
Persistent
Unusual
Recurrent

associato a PID

- >2 otiti/1aa
- >2 sinusiti batterica/1aa
- infezioni invasive da germi poco virulenti o opportunisti
- infezioni ricorrenti da stesso patogeno (anche banale)
- danno d’organo da infezioni
- trattamenti antibiotici protratti

Anamnesi Familiare

decessi per infezioni età pediatrica, poliabortività materna, consanguineità

APP

-infezioni poliorgano (candidiasi ricorrente, ascessi, sepsi, meningiti)

-diarrea cronica, -complicanze in seguito a vaccino vivo attenuato

-autoimmunità, -ritardo distacco cordone ombelicale (>30 giorni)

-iatrogene, protidodispersione, nutrizionali,ecc (secondarie)

Esami

Emocromo, Immunoglobuline

Celestino 3 a e 2/12

Ricovero per polmonite febbrile e enterite (S. typhi)

Benessere fino a 2 anni

In 14 mesi 17 episodi febbrili trattati con antibiotici, 4 ricoveri: per polmonite (2) e gastroenterite (2)

DD

1. **Asma**
2. **Sinusite cronica**
3. **Fibrosi cistica**
4. **Immunodeficienza**
5. **Discinesia ciliare**
5. **Tubercolosi**

	15
Globuli Rossi	4.83
HGB	11.9
HCT	35.2
MCV	67
MCH	20
MCHC	33.2
RDW	15.9
Globuli Bianchi	**2.77**
Neutrofili #	1.75
Linfociti #	**0.11**
Monociti #	0.66
Eosinofili #	0.20
Basofili #	0.05
LUC#	0.05
Piastrine	323
MPV	7.6

Gherardo 26 mesi, **ricovero per polmonite**

3 mesi	OMA
4 mesi	OMA
5 mesi	bronchiolite
7 mesi	OMA: inizia asilo nido
⬇	
26 mesi	wheezing ricorrente e almeno un episodio di febbre /mese. faringotonsilliti
26 mesi	polmonite lobo medio

*Nando 28 m*esi, polmonite basale destra

3 mesi	OMA
9 mesi	rinorrea purulenta e tosse; ricaduta una settimana dopo la sospensione dell'antibioticoterapia
10 mesi	wheezing persistente; da allora circa 1 episodio/settimana
13 mesi	OMA con otorrea, inizia la frequenza all'asilo
13 - 28 mesi	febbre ad ogni immissione all'asilo con rinorrea purulenta, tosse, wheezing. 4 OMA

	Gherardo	Nando	v.n.
IgG	330 mg/dL	230 mg/dL	(v. n. 460 – 1700)
IgA	10 mg/dL	< 5 mg/dL	(v. n. 27 – 170)
IgM	180 mg/dL	38 mg/dL	(v. n. 60 – 260)

Quali altri accertamenti clinici vi possono guidare?

Stazioni linfonodali

Parametri auxologici

Palpazione addome (fegato-milza)

Ispezione faringe/tonsille

otoscopia

	Gherardo	Nando	v.n.
IgG	330 mg/dL	230 mg/dL	(v. n. 460 – 1700)
IgA	10 mg/dL	< 5 mg/dL	(v. n. 27 – 170)
IgM	180 mg/dL	38 mg/dL	(v. n. 60 – 260)

Quali altri accertamenti fareste di prima istanza?

Prick test

Sottoclassi IgG

Sottopopolazioni linfocitarie

Titoli anticorpali

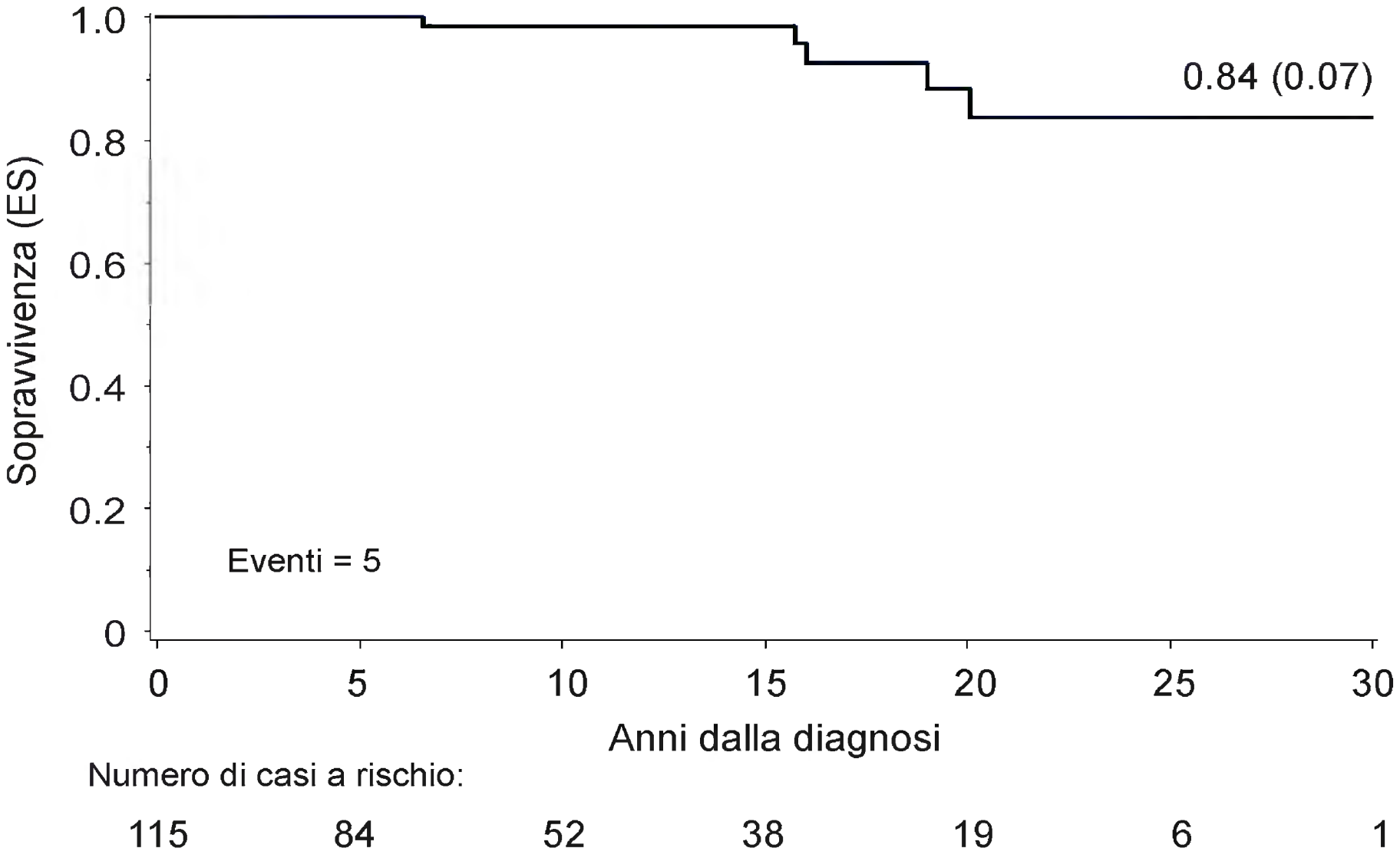
IgA secretorie

	Gherardo	Nando	v.n.
IgG	330 mg/dL	230 mg/dL	(v. n. 460 – 1700)
IgA	10 mg/dL	< 5 mg/dL	(v. n. 27 – 170)
IgM	180 mg/dL	38 mg/dL	(v. n. 60 – 260)
Ab αTT	titolo protettivo	assenti	
Ab αHib	titolo protettivo	assenti	

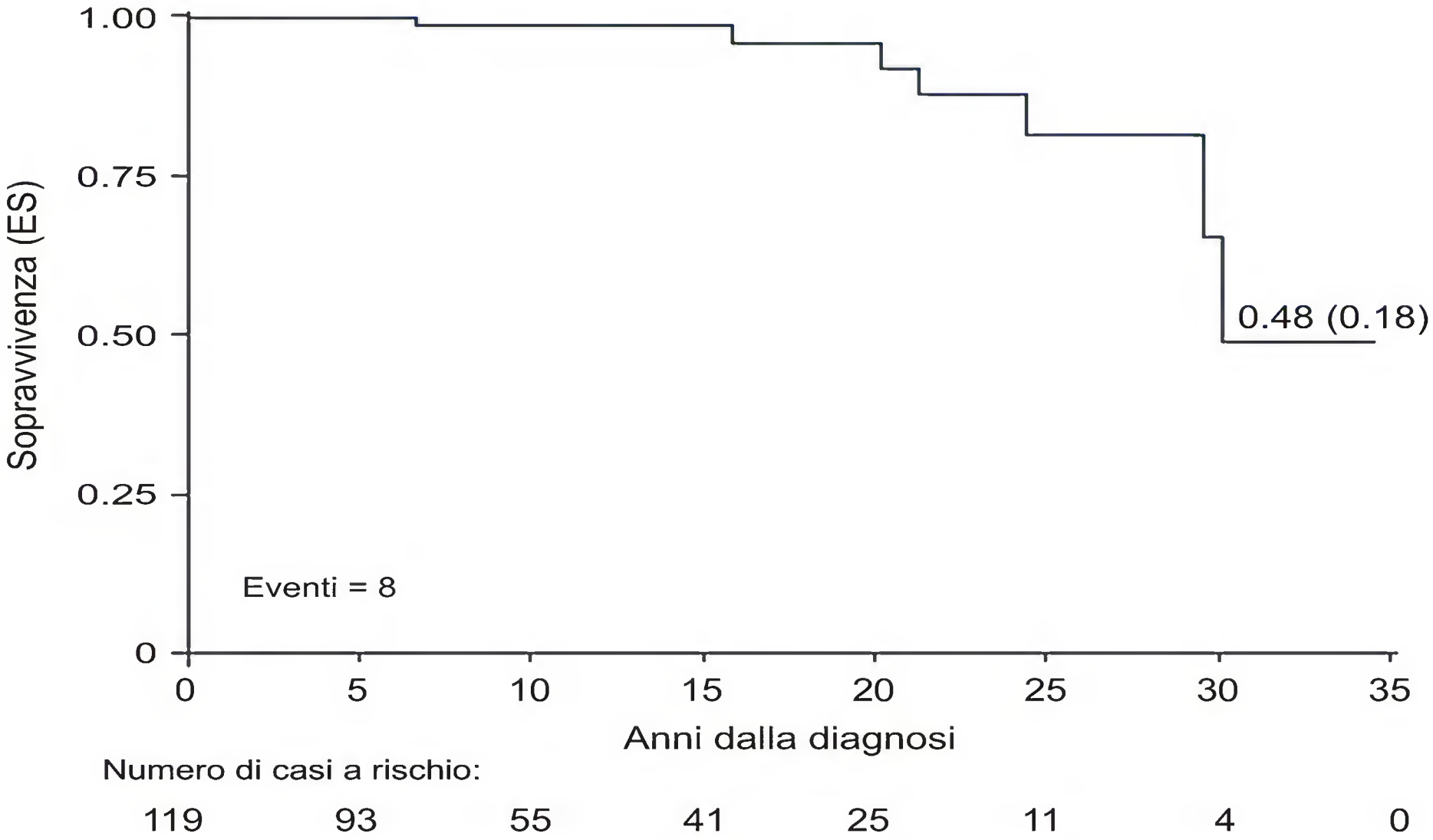
CD19	12%	3%
CD20	9%	1%

Prick test + alternaria

AIEOP XLA: sopravvivenza



AIEOP XLA: sopravvivenza



Francesco, 9 anni, viene per……

Terzo episodio di polmonite (Tosse, rX: ispessimento interstiziale e Infoadenopatie reattive) in 6 mesi.

Le precedenti avevano mostrarto scarsa risposta agli antibiotici (ev, ampio spettro).

Puntate capricciose e irregolari di febbre

Deperimento (-5 kg) in diarrea cronica (4aa)

Deficit di IgA (6aa)

Deficit di IgM (8 aa, ignorato)

Notevole linfoadenopatia apprezzabile in tutte le stazioni linfonodali superficiali

Epatomegalia (2 cm dall'arco)

Splenomegalia: margine in fossa iliaca di consistenza aumentata

Auscultazione polmonare: rantoli a piccole bolle alle basi e rumori umidi diffusi. Spirometria: diminuzione dei volumi polmonari di tipo restrittivo

TC torace-addome-pelvi: linfoadenopatia generalizzata a livello mediastinico, pelvico e addominale, spesso con pacchetti conglobati.

A livello polmonare si osservano multiple (almeno venti) sfumate aree di addensamento a morfologia pseudonodulare di diametro medio di 1 cm

Agoaspirato midollare negativo

Biopsia linfonodale

Linfonodo caratterizzato da area (diametro cm 0.5) dismorfica, con follicoli linfatici ingranditi, dotati di centri germinativi serpiginosi.

Lo studio fenotipico della popolazione linfoide non evidenzia alterazioni sospette per linfoma.

Il quadro descritto orienta per una linfoadenopatia reattiva, a tipo trasformazione progressiva dei centri germinativi dei follicoli, la cui etiologia sarà meglio determinata su base clinica

Data	IgG (7.07-19.19 g/L)	IgM (0.61-2.76 g/L)	IgA (0.6-2.7 g/L)	Linfociti n.a.
06/04/2016	17.67 g/L	0.1 g/L	0.01 g/L	2.650/mmc
03/05/2016	16.03 g/l	0.13 g/L	0.02 g/L	
30/05/2018	6.4 g/L	0.03 g/L	0.02 g/L	1.410/mmc
08/06/2018	5.8 g/L			
22/06/2018	5.4g/L	0.04 g/L	0.05 g/L	1.880/mmc

ANA positivi, ENA, antidsDNA negativi

Percentuali calcolate nel gate dei linfociti CD3pos:

- CD3pos alpha/beta pos = 86.4%
- CD3pos gamma/delta pos= 9.2%

- CD3pos alpha/beta pos doppi negativi (CD4neg/CD8neg)= 1.4%

SOTTOPOPOLAZIONI LINFOCITARIE				
CD3 PanT	88.5	>	%	58.0 - 75.0
CD4 T Helper	62.0	>	%	29.0 - 47.0
CD8 T Suppr/Cytotox	20.4		%	17.0 - 33.0
CD19 Pan B	4.8	<	%	14.0 - 30.0
CD16+CD56+	5.3		%	4.0 - 17.0

Validazione clinica: I
Validazione clinica: I

Test proliferazione cellule T : dopo stimolo con PHA e OKT, la proliferazione delle cellule T è ridotta: si osserva una proliferazione spontanea in assenza di stimolo.

Test proliferazione e differenziazione cellule B: dopo stimolo con CpG, la proliferazione e il differenziamento in plasmacellule delle cellule B sono ridotti. In accordo nel sovranatante si rilevano immunoglobuline di tutti gli isotipi, ma a livelli molto bassi

linfadenopatia generalizzata: sierologie negative.
Proliferazione spontanea dei T linfociti (ALPS?): % linfociti alfa/beta doppi negativi < 6% (1.4%), vitamina B12: <1500 pg/ml, ipogammaglobulinemia: no ALPS

Addensamenti polmonari e formazioni linfonodulari
Mantoux e quantiferon negativi. Biopsia?

Ipogammaglobulinemia (primitiva? Secondaria?)
Diarrea cronica dall'età di 4 anni: celiachia e calprotectina fecale negativi già a 7 anni, protidemia e albuminemia nella norma, non spiccata linfopenia
Episodi infettivi (?): 3 polmoniti da Agosto 2017, livelli borderline di B linfociti, deficit di IgA evoluto in ipogammaglobulinemia: CVID?.

Nel 10-30% dei casi di Immunodeficienza Comune Variabile (CVID) è presente una condizione polmonare peculiare definita Granulomatous Lymphocytic Interstitial Lung Disease (**GLIDL**) caratterizzata da infiltrato linfocitario, con granulomi, organizzato a formare strutture nodulari delle dimensioni minori di 3 cm in un contesto di linfoadenomegalia generalizzata

Biopsia polmonare

Aumento dell'infiltrato polmonare con ulteriore diminuzione della ventilazione, febbre capricciosa a puntate imprevedibili

Il parenchima polmonare mostra aree di addensamento della trama alveolare, caratterizzate da infiltrati leucocitari, prevalentemente linfocitari CD3+, CD20+, catene kappa > lambda, formanti aggregati con centri germinativi reattivi, con presenza di plasmacellule ed eosinofili. L'infiltrato leucocitario è osservabile anche nei setti alveolari ed, in minor misura nel connettivo peribronchiolare pleurico. Si associano spazi alveolari similcistici, limitate aree di reazione gigantocellulare diretta contro materiale colesterinico (focolai di polmonite ab-ingestis) e stravasi ematici. Negativa la ricerca di EBV LMP.

Polmonite interstiziale linfocitaria di Carrington e Liebow

Sequenziamento NGS per deficit umorali

Rituximab (ab anti-CD20), con protocollo linfoma
1 infusione/settimana x 4 settimane

Netta riduduzione della massa linfomatosa
Completa risoluzione della diarrea
Completa risoluzione della febbre
Netto miglioramento condizioni generali

Dopo un mese dalla sospensione:
Febbre capricciosa, senso di costrizione toracica, diarrea

Mutazione del gene LRBA: NM_006726: ex30, ex55: c4967 del A; C8149T: p.N1566Mfs*22,Q2717* che comporta un difetto di espressione del carrier intracitoplasmatico della proteina di superficie CTLA-4.

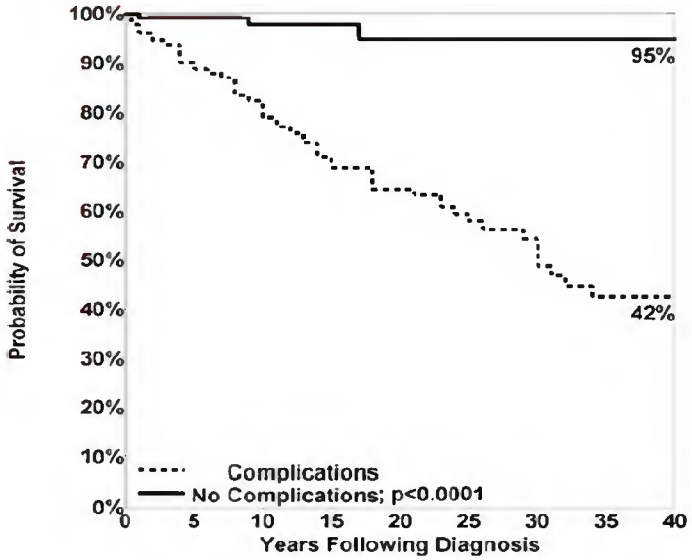
Inizia terapia sostitutiva con Ig CTLA-4 (Abatacept)

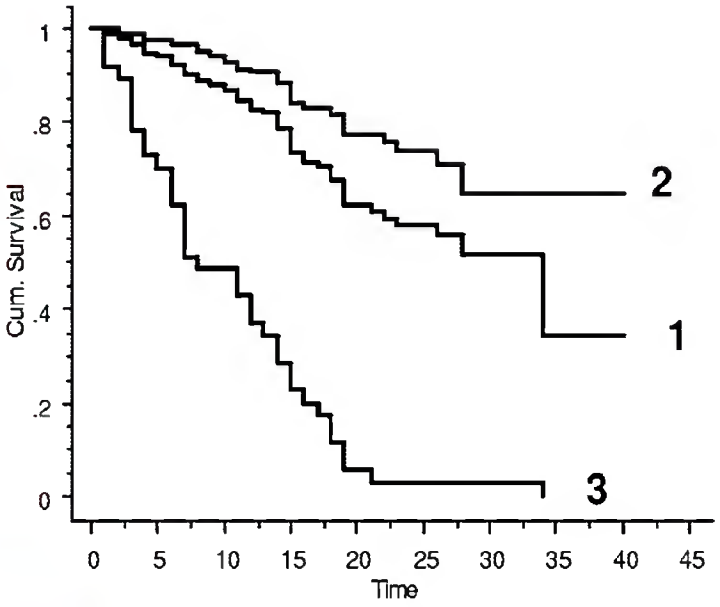
TABLE 1 | Autoimmune manifestations in humoral immun

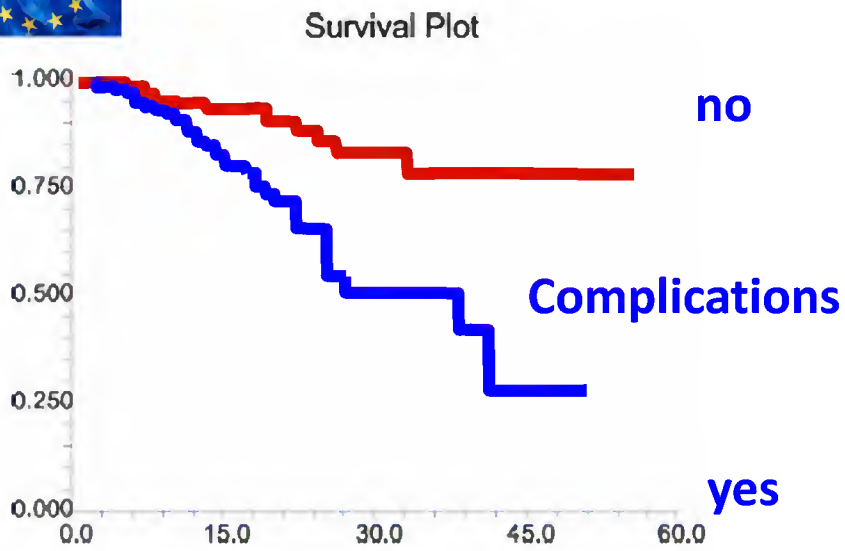
1. SIgAD
   - Juvenile idiopathic arthritis
   - Rheumatoid arthritis
   - ITP, AHA
   - IBD
   - Sjogren's disease
   - Polyarteritis nodosa
   - SLE
   - Celiac disease
   - T1D
2. CVID
   - ITP, AHA
   - SLE
   - IBD
3. PRKCD deficiency
   - Glomerulonephritis
   - Polychondritis
   - Antiphospholipid syndrome
   - LES
4. LRBA deficiency
   - IBD
   - AHA, ITP
   - Granulomatous-lymphocytic interstitial lung disease
   - T1D
   - Neutropenia
   - Chronic autoimmune hepatitis
   - Eczema
   - Uveitis
   - Alopecia
5. Hyper-IgM syndrome
   - IBD
   - Seronegative arthritis
   - Hypothyroidism
   - SLE
   - Autoimmune hepatitis
   - ITP, AHA
   - T1D
   - Uveitis

4. LRBA deficiency
   - IBD
   - AHA, ITP
   - Granulomatous-lymphocytic interstitial lung disease
   - T1D
   - Neutropenia
   - Chronic autoimmune hepatitis
   - Eczema
   - Uveitis
   - Alopecia

Pignata C et al, Frontiers Immunol 2017



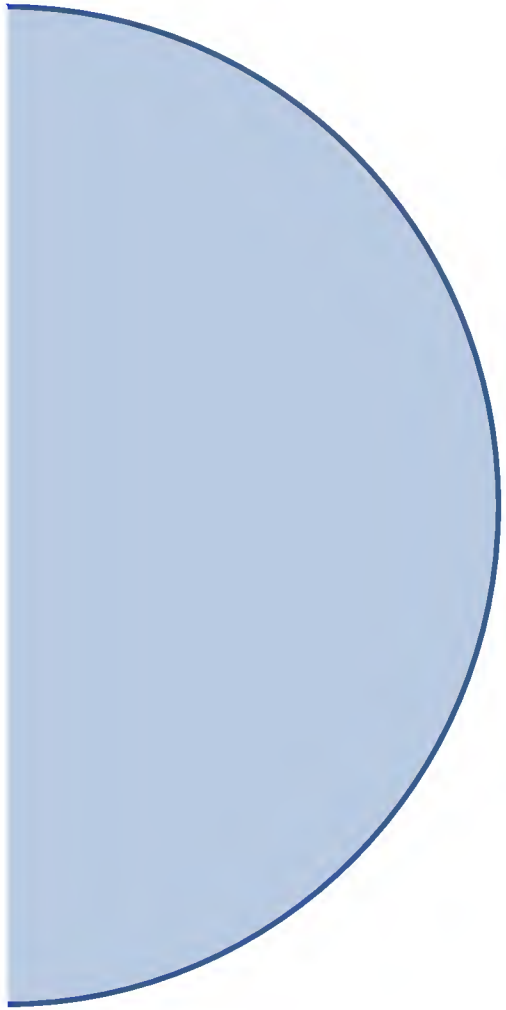




Resnick ES et al, Blood 2011
Quinti I et al, Blood 2012

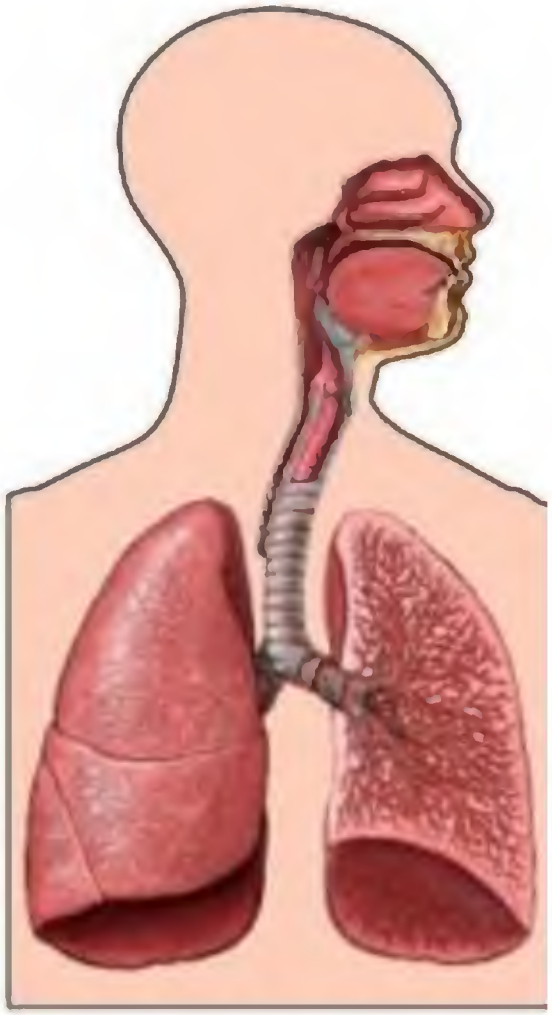
IRR: il fenotipo ”fisiologico”

- 4-8 IRR/anno (2-4 vv > se scolarizzato)
- Durata media 8-14 g (10% persiste tosse a 25gg da infez)
- Più spesso infezioni virali delle alte vie
- Rapida risposta a terapia appropriata, benessere intercritico
- EO e lab nella norma



Prevalenza delle IRR da 2 a 8 anni.

Età	IRR n. episodi	Controlli	p
2 anni	6,2	1,4	< 0,001
7 anni	3,1	1,2	< 0,01
8 anni	2,4	0,8	< 0,05



URTI

LRTI

Quali accertamenti?
Qualie terapia?

Immunostimolanti?

Steroidi topici?

Vaccini polibatterici?

Vaccinazioni?

Integratori/polivitaminici?

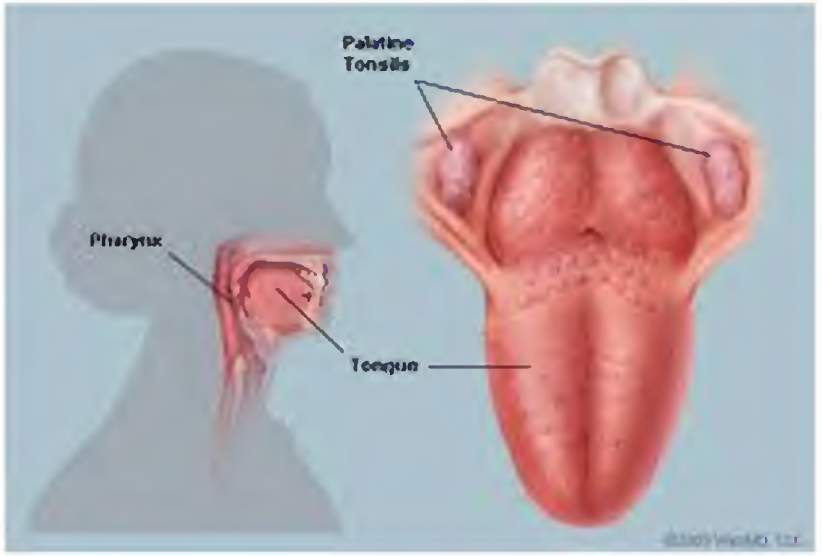
Profilassi antibiotica?

Rimedi naturali?

ITS?

Adenoiditi e OMA

Tonsilliti



OMA in 156 children 1-4y old

(Mattila et al,Arch Dis. Child. 2009)

	Adenoidectomy with tympanostomy (n=89) *	Tympanostomy only (n=77) *	Mean difference or odds ratio (95% CI)	p-value
No. of girls	42 (47%)	34 (44%)	1.13 (0.61 to 2.09) **	0.76
Mean age (SD)	4.9 (0.7)	4.9 (0.7)	0.01 (-0.21 to 0.23)	0.95
Age distribution				
4.0-4.9 y	59 (66%)	49 (64%)	1.12 (0.59 to 2.13) **	0.75
5.0-5.9 y	20 (22%)	21 (27%)	0.77 (0.38 to 1.57) **	0.59
6.0-6.9 y	10 (11%)	7 (9%)	1.27 (0.46 to 3.50) **	0.80
Persistent middle ear effusion at the start of the trial	27 (30%)	21 (27%)	1.16 (0.59 to 2.28) **	0.73
Mother smokes tobacco at the end of the follow-up	32 (36%)	17 (22%)	1.98 (0.98 to 3.95) **	0.06
Mean number of otitis media episodes during				
the first year of follow-up (SD)	1.8 (1.8)	1.4 (1.5)	0.42 (-0.08 to 0.93)	0.10
the second year of follow-up (SD)	1.5 (1.5)	1.1 (1.7)	0.39 (-0.11 to 0.88)	0.14
the third year of follow-up (SD)	0.7 (1.1)	0.8 (1.5)	-0.05 (-0.45 to 0.35)	0.84

Otitis Media and Tonsils – Role of Adenoidectomy in the Treatment of Chronic Otitis Media with Effusion

Keehyun Park

Department of Otolaryngology, Ajou University School of Medicine, Suwon, South Korea

We can summarize that children suffering from recurrent or chronic OME may benefit from adenoidectomy due to the removal of an infectious source in the nasopharynx rather than the removal of a large adenoidal mass.

Advance in Oto-rhino-laryngol 2011

AT
Giorni di faringite

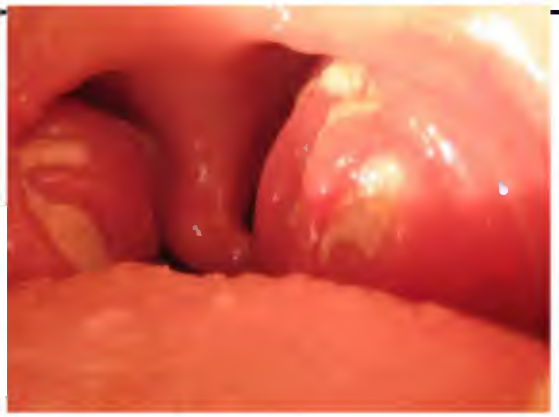
THE COCHRANE COLLABORATION®

Outcome: 3 Sore-throat days (including those immediately post-surgery)

Study or subgroup	Surgery N	Surgery Mean(SD)	No Surgery N	No Surgery Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Paradise 1984	31	16.3 (14.3)	33	18.9 (14.6)		18.3 %	-2.60 [-9.68, 4.48]
Paradise 2002a	95	19.5 (14.5)	54	25 (21)		23.0 %	-5.50 [-11.81, 0.81]
Paradise 2002b	60	23 (20)	68	24 (17)		21.8 %	-1.00 [-7.48, 5.48]
van Staaij 2004	111	12.68 (9.5)	107	18.92 (24.59)		36.9 %	-6.24 [-11.22, -1.26]
Total (95% CI)	**297**		**262**			**100.0 %**	**-4.26 [-7.29, -1.23]**

Heterogeneity: $Chi^2 = 1.94$, $df = 3$ ($P = 0.59$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.76$ ($P = 0.0058$)



-10 -5 0 5 10

Favours surgery Favours no surgery

Burton MJ, Glasziou PP, 2009

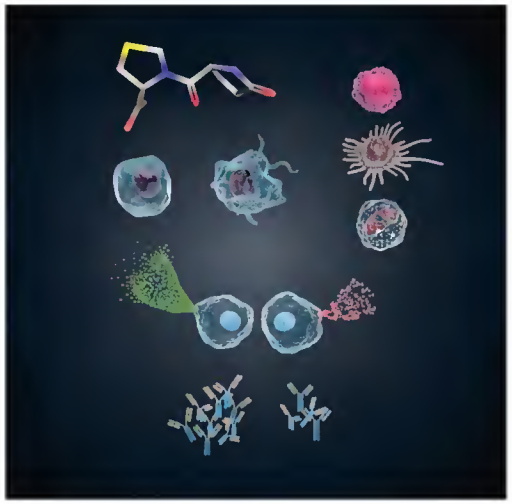
Ferrario *et al. Clinical and Molecular Allergy* (2015) 13:8
DOI 10.1186/s12948-015-0012-1

CLINICAL AND
MOLECULAR ALLERGY

REVIEW Open Access

Pidotimod: the state of art

Beatrice E Ferrario*†, Silvia Garuti*†, Fulvio Braido* and Giorgio W Canonica*

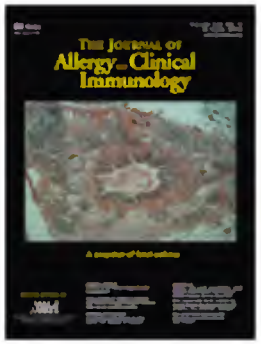


Main clinical outcomes are the reduction of the number of infectious episodes, lesser severity of signs and symptoms and, consequently, a reduction in use of antibiotics and symptomatic drugs, less working and school days lost, less mortality and morbidity.

The studies considered give positive results, confirming Pidotimod's efficacy, even when compared to other immunostimulants or combined with antibiotic therapy.

The immunostimulant OM-85 BV prevents wheezing attacks in preschool children

Cem Hasan Razi, MD,[a] Koray Harmancı, MD,[a] Ayhan Abacı, MD,[b] Osman Özdemir, MD,[b] Şamil Hızlı, MD,[b] Rahime Renda, MD,[c] and Fersin Keskin, MD[d] *Ankara, Turkey*



OM-85 BV contains 3.5 mg of standardized lyophilized fractions per capsule from the following bacteria: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Neisseria catarrhalis*.

Cumulative number of acute nasopharingitis

Period (mo)	OM-85 BV	Placebo	Mean difference (95% CI)	Cumulative % difference	*P* value*
0-3	1.45 ± 0.95 1 (1-2)	1.97 ± 0.97 2 (1-3)	−0.52 (−0.96 to −0.07)	26.4	.032
0-6	2.37 ± 1.13 3 (1-3)	3.55 ± 1.29 3 (3-4)	−1.17 (−1.74 to −0.61)	32.9	<.001
0-9	3.14 ± 1.37 3 (2-4)	4.87 ± 1.63 4.5 (4-6)	−1.73 (−2.43 to −1.03)	35.5	<.001
0-12*	3.51 ± 1.56 3 (3-5)	5.62 ± 1.99 5 (4-7)	−2.11 (−2.94 to −1.27)	37.5	<.001

Values are shown as means ± SDs and medians (25th-75th percentiles).

*The *P* value is for comparison of OM-85 BV with placebo. A *P* value of less than .0125 was considered statistically significant according to the Bonferroni correction.

REVIEW

Esposito s et al, Curr Opin Allergy Clin Immunol 2018

OPEN

CURRENT OPINION

Nonspecific immunomodulators for recurrent respiratory tract infections, wheezing and asthma in children: a systematic review of mechanistic and clinical evidence

Susanna Esposito[a], *Manuel E. Soto-Martinez*[b], *Wojciech Feleszko*[c], *Marcus H. Jones*[d], *Kun-Ling Shen*[e], *and Urs B. Schaad*[f]

KEY POINTS

- Because of immunological immaturity and the increasing reliance of high-risk mixed social environments, recurrent RTIs cause a major burden of care in children.
- Despite their overwhelmingly viral cause, childhood RTIs are a significant source of antibiotic misuse and are associated with both direct costs and an increased risk of wheezing and asthma in later life.
- Prevention is key in order to reduce this burden of care and the associated increased risk of asthma and can be split into three fundamental aspects: parental education, active immunization (where available) and nonspecific immunomodulation.

Table 1. Characteristics of included immunomodulators and proposed mechanisms of action for infection prevention

Therapy	Constituents	Antigen-presenting cells	Innate immunity	Adaptive
OM-85	Alkaline lysis of 21 strains of eight species of respiratory tract pathogens: *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans* and *Moraxella catarrhalis*	Maturation of mesenteric DCs [13,14,15▪] Modulated activation suggesting prealert anti-infective state [14,16▪▪] Innate and adaptive cytokine release [17] PRR yet to be determined [14,16▪▪,18,19]	Release of antimicrobial peptides [human beta-defensin-1 (hβD-1)] and C1q-R) [20,21▪] ICAM downregulated in lung epithelium [21▪] Rapid neutrophil recruitment in murine model of influenza infection [15▪] Cytokines promoting NK-cells, monocytes, phagocytosis, neutrophils (CCL2, CCL3, CXCL1, CXCL5, CXCL6 and CXCL8) [14,17] Macrophage activation (IL-1b, IL-6 and TNFα mRNA) [16▪▪,18,19] Antiviral cytokine release (INFβ) [16▪▪]	DC-induced T-cell activation [22,23] Airway $CD8^+$ T cells in murine influenza model [15▪] Pro-B-cell cytokines (IL-6, BAFF and IL-10) [14,23] Serum IgA/IgG (murine/human) [15▪,18,20] B-cell maturation from mouse splenocytes [15▪] Airway/salivary murine IgA/IgG [15▪,18,24] Immune maturation (pro-INFγ and IgG2/anti-IL-4) [25] Release of antiviral cytokines INFα/INFγ [14,21▪,25,26]
Pidotimod	Synthetic thymic dipeptide (3-l-pyroglutamyl-l-thiaziolidine-4 carboxylic acid)	Mucosal DC maturation and increased antigen presentation [27,28,29▪,30] Increased TLR2 and TLR4 [29▪,30] Innate and adaptive cytokine release [28,29▪]	Increased TLR2 expression in lung epithelial cells *in vitro* [31] Release of antimicrobial peptides (CAMP, LCN2, LTF and MPO) [29▪] Improved mucociliary transport [32] Cytokines promoting macrophages, monocytes, NK cells and neutrophils (CCL3, CXCL1, CXCL2, IL-18 and IL-8) [29▪,33]	Activation of cytotoxic and helper T cells ($CD3^+$, $CD4^+$ and $CD4^+/CD8^+$) [34] Immune maturation (pro-IL-12, IFNγ, IL-10 and IL-18/anti-IL-4) [33–36,37▪,38] Increased mucosal sIgA [39] Release of antiviral cytokines INFγ [39]
Ribomunyl	Bacterial proteoglycans and ribosomes of common respiratory tract pathogens: *K. pneumoniae* (proteoglycans and ribosomes) and *K. pneumoniae, S. pneumoniae, S. pyogenes* and *H. influenza* (ribosomes)	DC maturation [13,40,41] Innate and adaptive cytokine release [41]	Increased neutrophil adhesion molecules (+CD11c and +CD103) and phagocytosis [42,43]	DCs-induced T cells activation causing release of antiviral INFγ ($CD4^+$) [13,41] Possible release of pro-TH1 cytokines (IL-12, IL-10) [13,40] Increase in $CD4^+$ and $CD8^+$ T cells [44] B cell production (humoural, tonsils, mesenteric/cervical lymph nodes) [44] Salivary sIgA [45,46] Serum IgA and IgG [44,47,48]
PMBL	Bacterial lysates of eight bacterial species: *S. aureus, S. viridans, S. pyogenes, K. pneumoniae, K. ozaenae, H. influenzae serotype B, M. catarrhalis and S. pneumoniae*	–	Putative macrophage activation (pro-IL-12) [49]	T cell activation ($CD4^+$ and $CD8^+$) [49] B cell activation [49] IgM memory B cell expansion [50] Immune maturation (+IL-2, +IL-10, IL-12 and +IFNγ) [49] Release of antiviral cytokines INFγ [49] Release of salivary sIgA [51]
LW50020	Bacterial lysates of seven bacterial species: *S. aureus, Streptococcus mitis, S. pyogenes, S. pneumoniae, K. pneumoniae, M. catarrhalis* and *H. influenza*	DC maturation [13]		DC-induced T cells activation [13]

TNFα, tumour necrosis factor-alpha.

Efficacia della vaccinazione antiinfluenzale nelle IRR

Recurrent Respiratory Tract Infections

Household Contacts	Vaccinated	Controls	*P*
Loss of maternal work due to care for the ill child	0.64 ± 1.86	4.05 ± 5.34	<0.0001
Loss of paternal work due to care for the ill child	0.11 ± 0.46	0.97 ± 2.24	0.001
Need for help due to care for the ill child	53.5%	74.7%	0.012
No. with respiratory illness	1.88 ± 1.68	2.90 ± 1.68	0.0005
No. of medical visits	1.22 ± 1.37	2.06 ± 1.77	0.002
No. of hospitalizations	0.01 ± 0.12	0	0.354

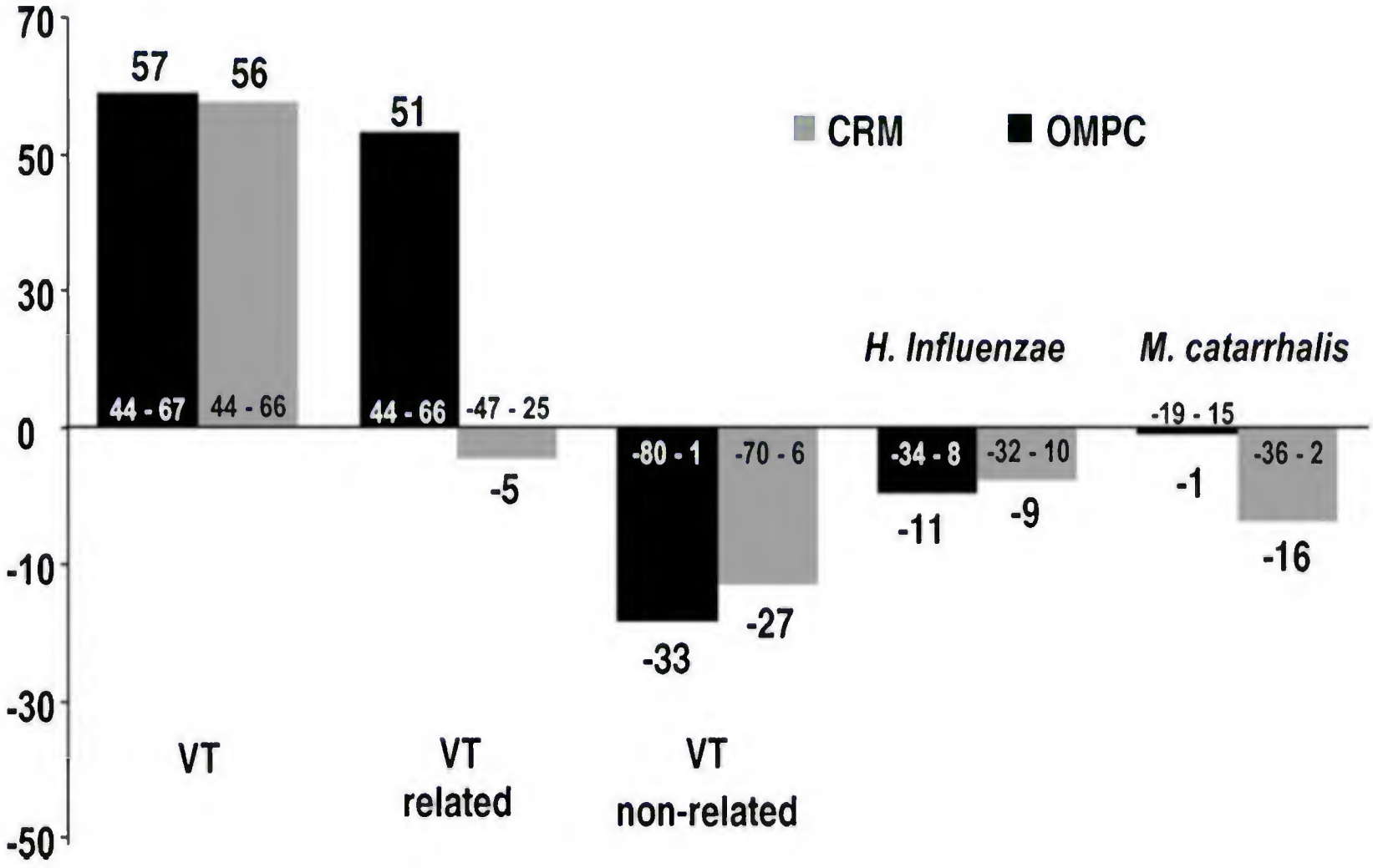
Esposito S, Ped Inf Dis J 2008

Vaccinazione antipneumococcica in soggetti con asma e COPD

	COPD		Controls		*P* value	Asthma		Controls		*P* value
N	16,074		14,028			2,746		1,345		
Year of vaccination, *N* (%)					<0.001					0.274
1998	5,367	(33.4)	4,020	(28.7)		742	(27.0)	337	(25.1)	
1999	3,120	(19.4)	2,684	(19.1)		503	(18.3)	274	(20.4)	
2000	2,694	(16.8)	2,461	(17.5)		479	(17.4)	254	(18.9)	
2001	2,820	(17.5)	2,774	(19.8)		572	(20.8)	263	(19.6)	
2002	2,073	(12.9)	2,089	(14.9)		450	(16.4)	217	(16.1)	
Overall health care utilization, avg. (SD)										
Hosp	0.45	(1.0)	0.20	(0.6)	<0.001	0.18	(0.6)	0.23	(0.9)	0.060
ED visits	0.92	(2.0)	0.42	(1.2)	<0.001	0.84	(1.8)	0.46	(1.2)	<0.001
Outpt	20.62	(22.7)	14.54	(18.3)	<0.001	18.33	(21.8)	15.56	(22.8)	<0.001

Lee T A,et al, J Asthma 2007

Efficacy of eptavalent pneumococcal vaccine on OMA

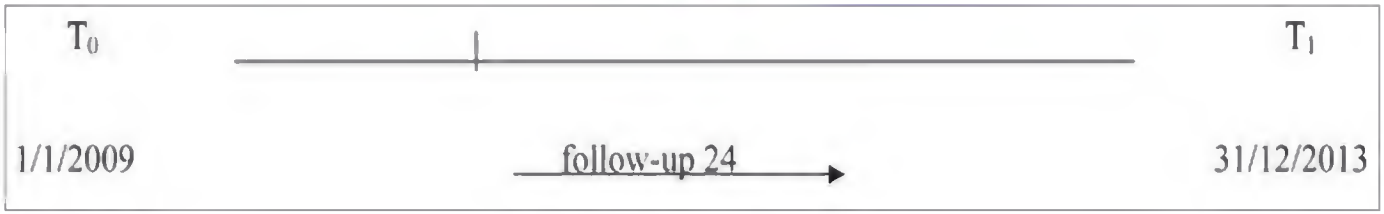


Dagan, Vaccine 2008

Database ASL RomaA
Vaccinati MRP

11.004
bambini

Database dimissioni
ospedaliere
ASL RomaA
ICD-9



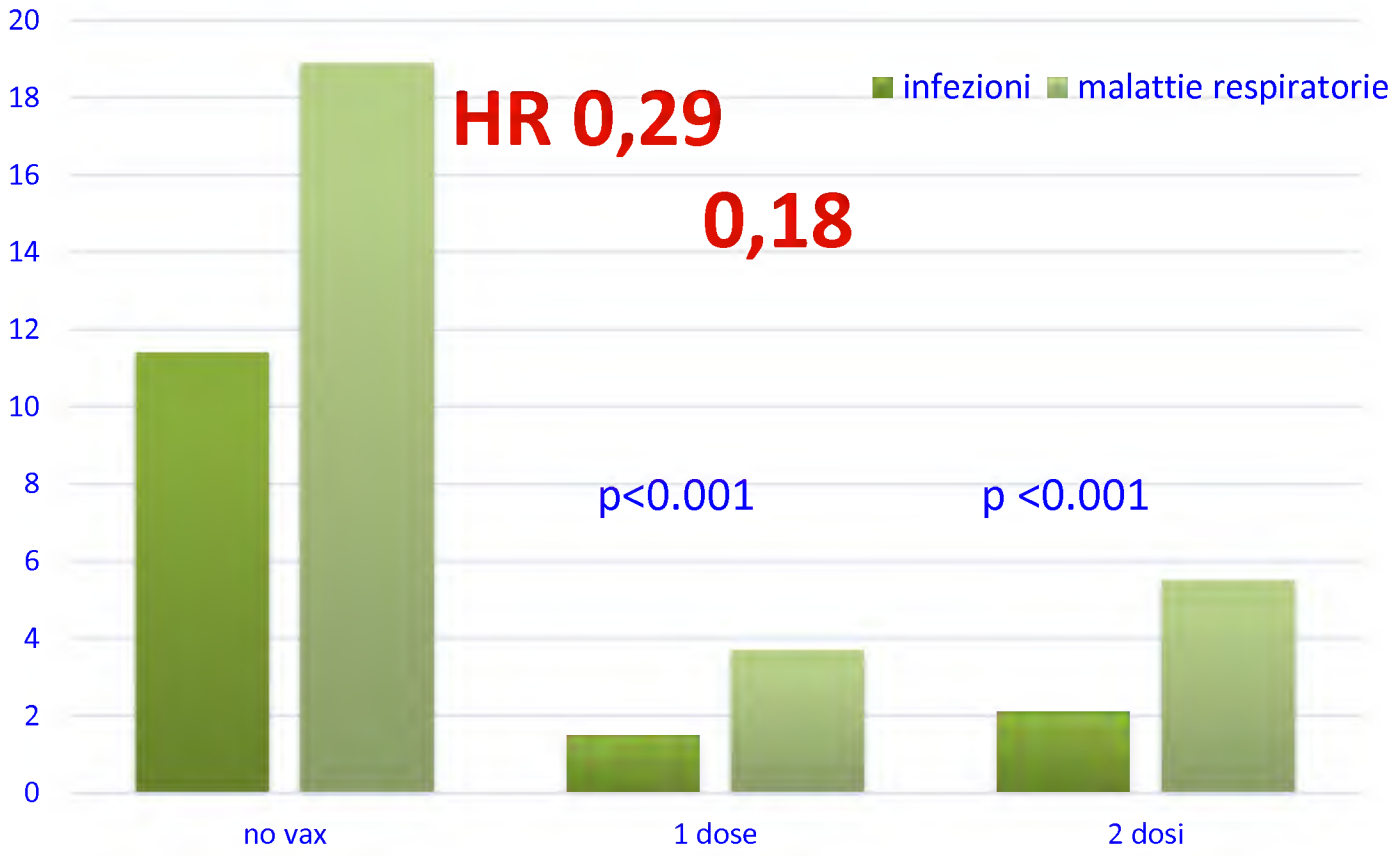
2302 (21%) non vaccinati

La Torre G et al, Human Vacc Ther 2017

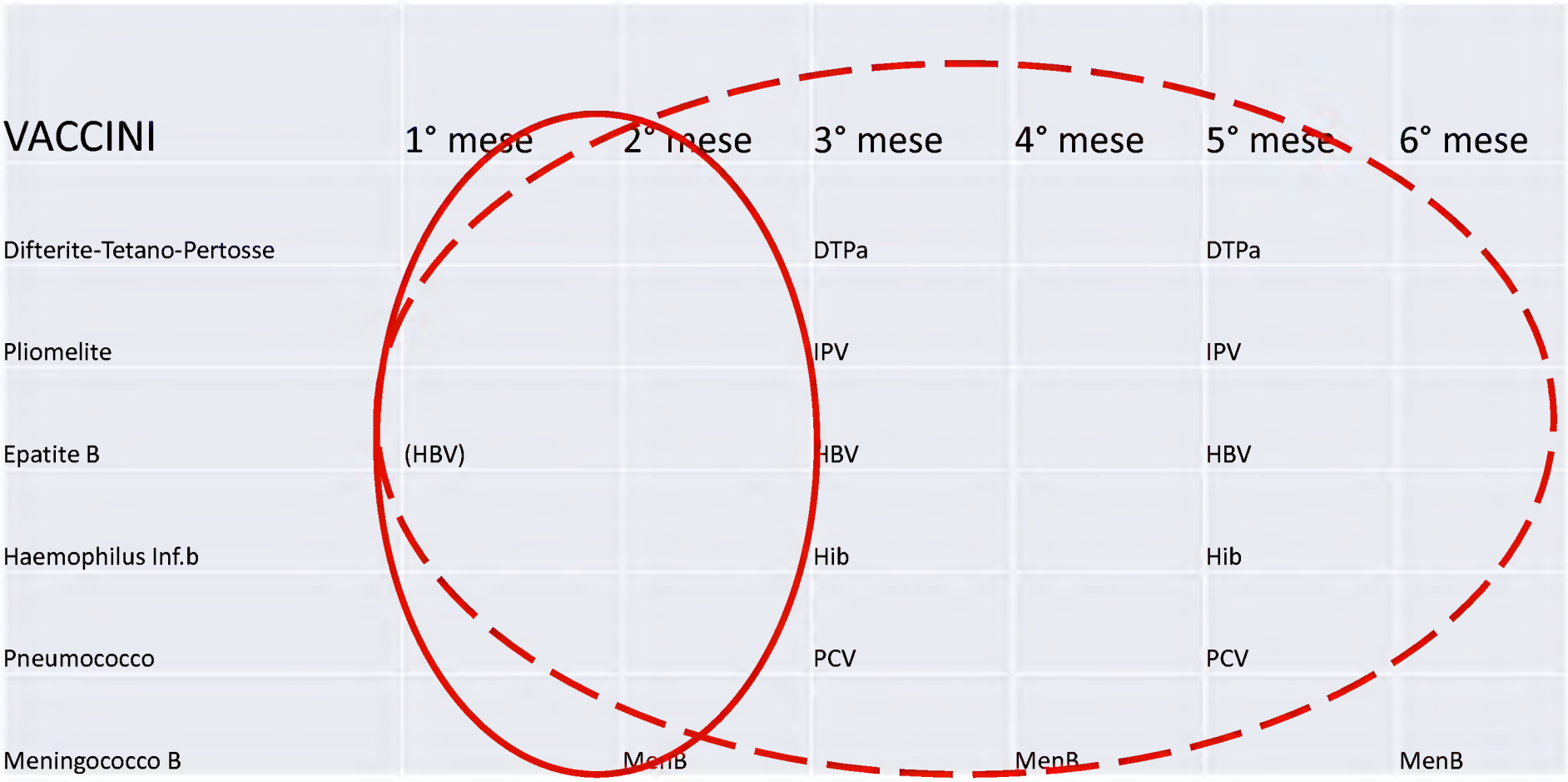
Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

The effectiveness of measles-mumps-rubella (MMR) vaccination in the prevention of pediatric hospitalizations for targeted and untargeted infections: A retrospective cohort study



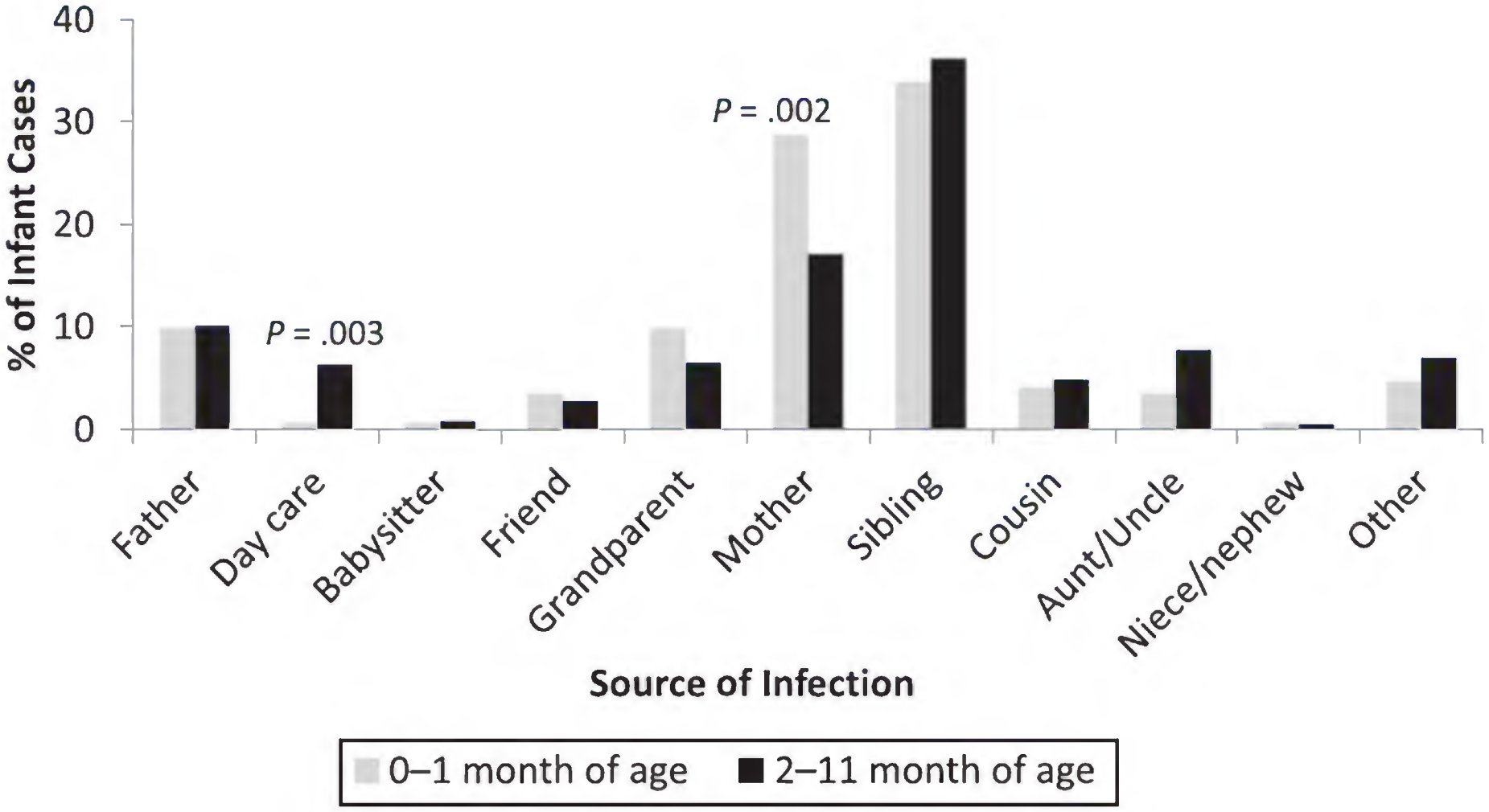
The period of vulnerability for infant infectious disease



VACCINI	1° mese	2° mese	3° mese	4° mese	5° mese	6° mese
Difterite-Tetano-Pertosse			DTPa		DTPa	
Pliomelite			IPV		IPV	
Epatite B	(HBV)		HBV		HBV	
Haemophilus Inf.b			Hib		Hib	
Pneumococco			PCV		PCV	
Meningococco B		MenB		MenB		MenB

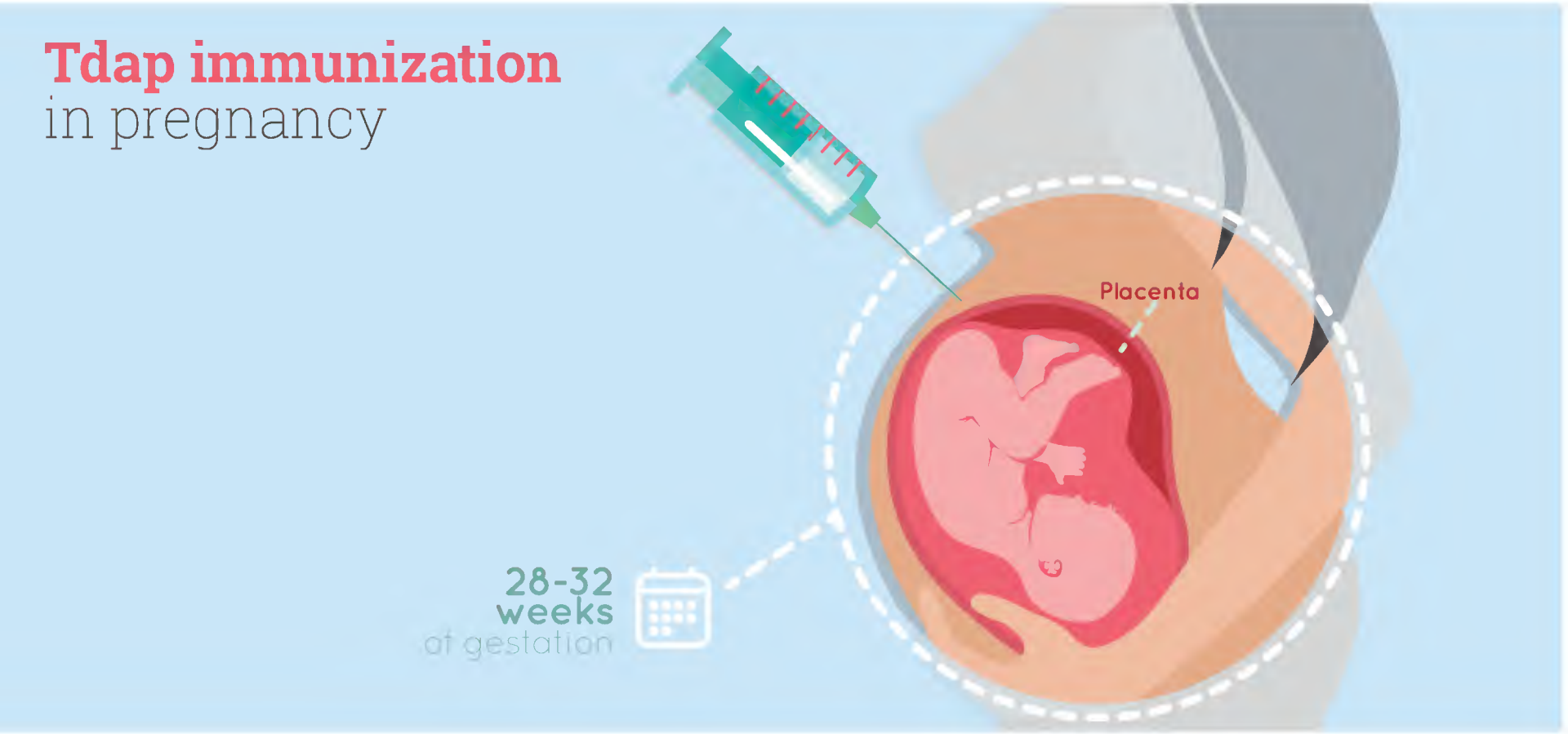
Sanchez-Schmitz G, Levy O., 2011

Pertussis: identified source of infection in 1306 infants from 7 US States (2006-2013)

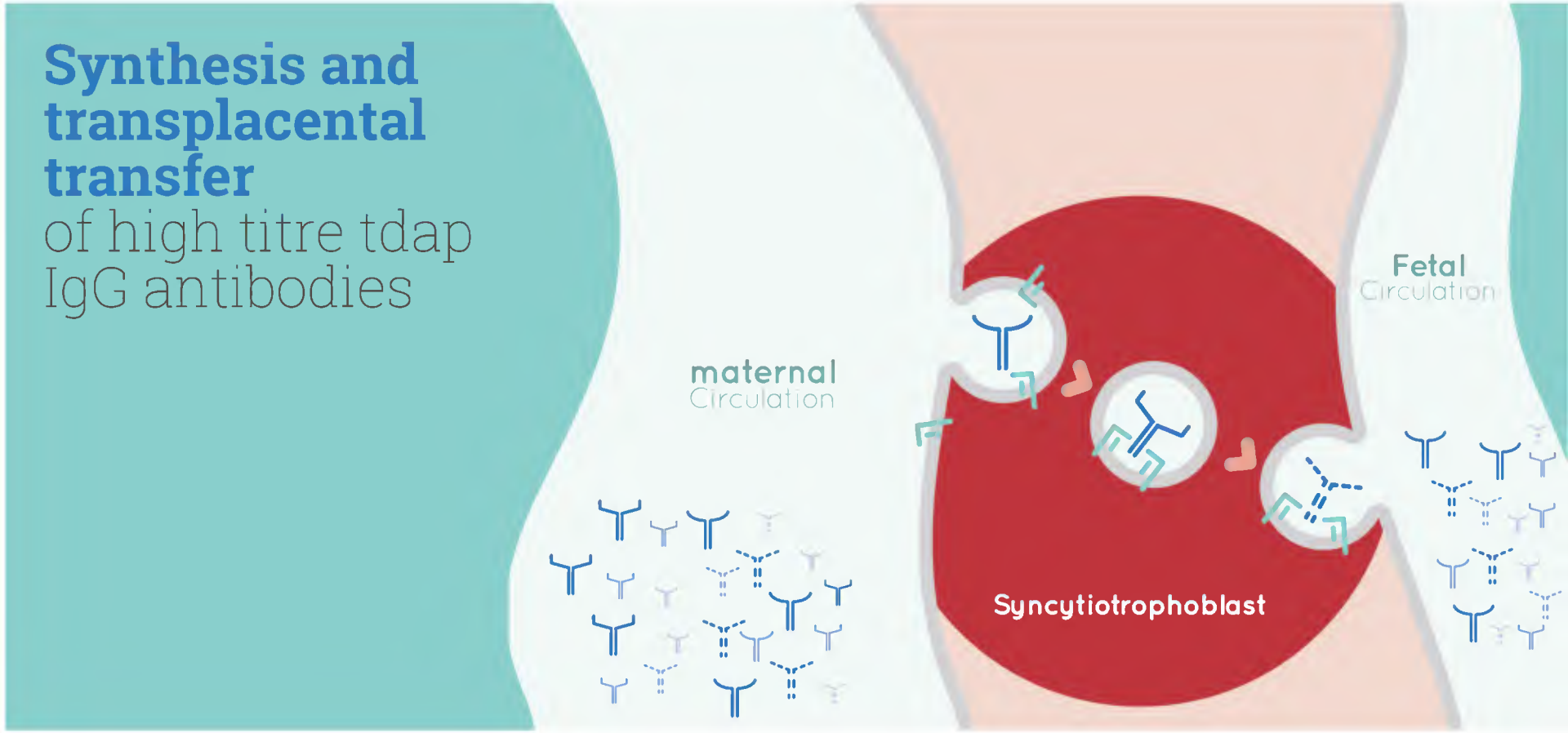


Skoff T. H. et al., 2015

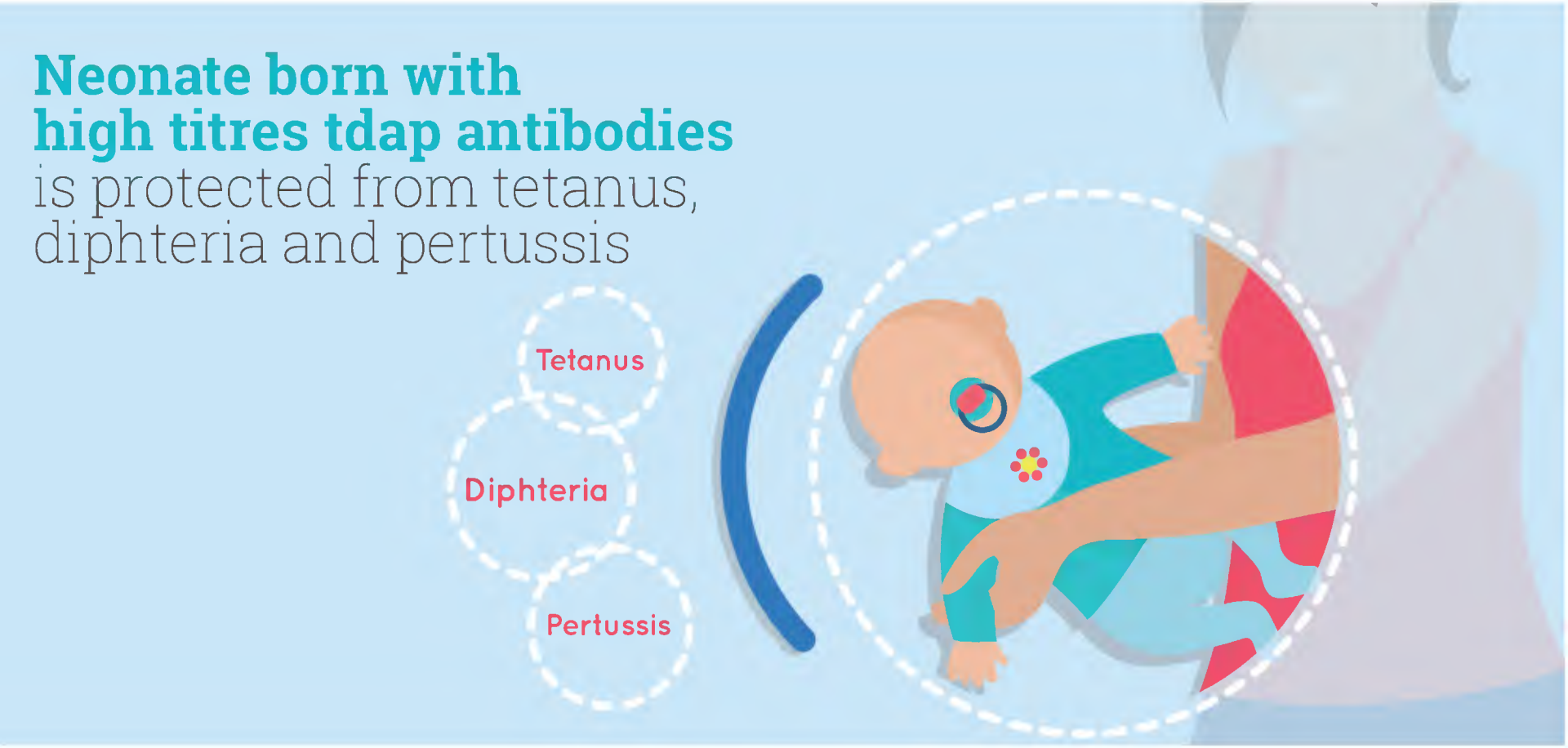
Tdap immunization
in pregnancy



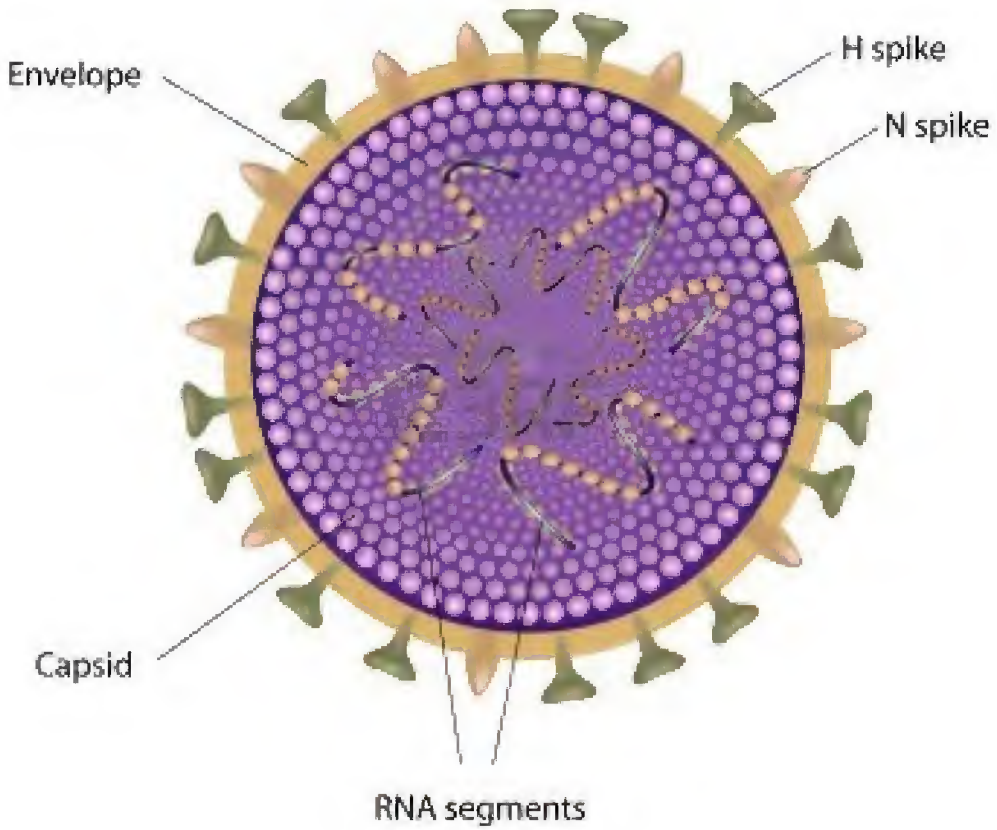
Synthesis and transplacental transfer of high titre tdap IgG antibodies



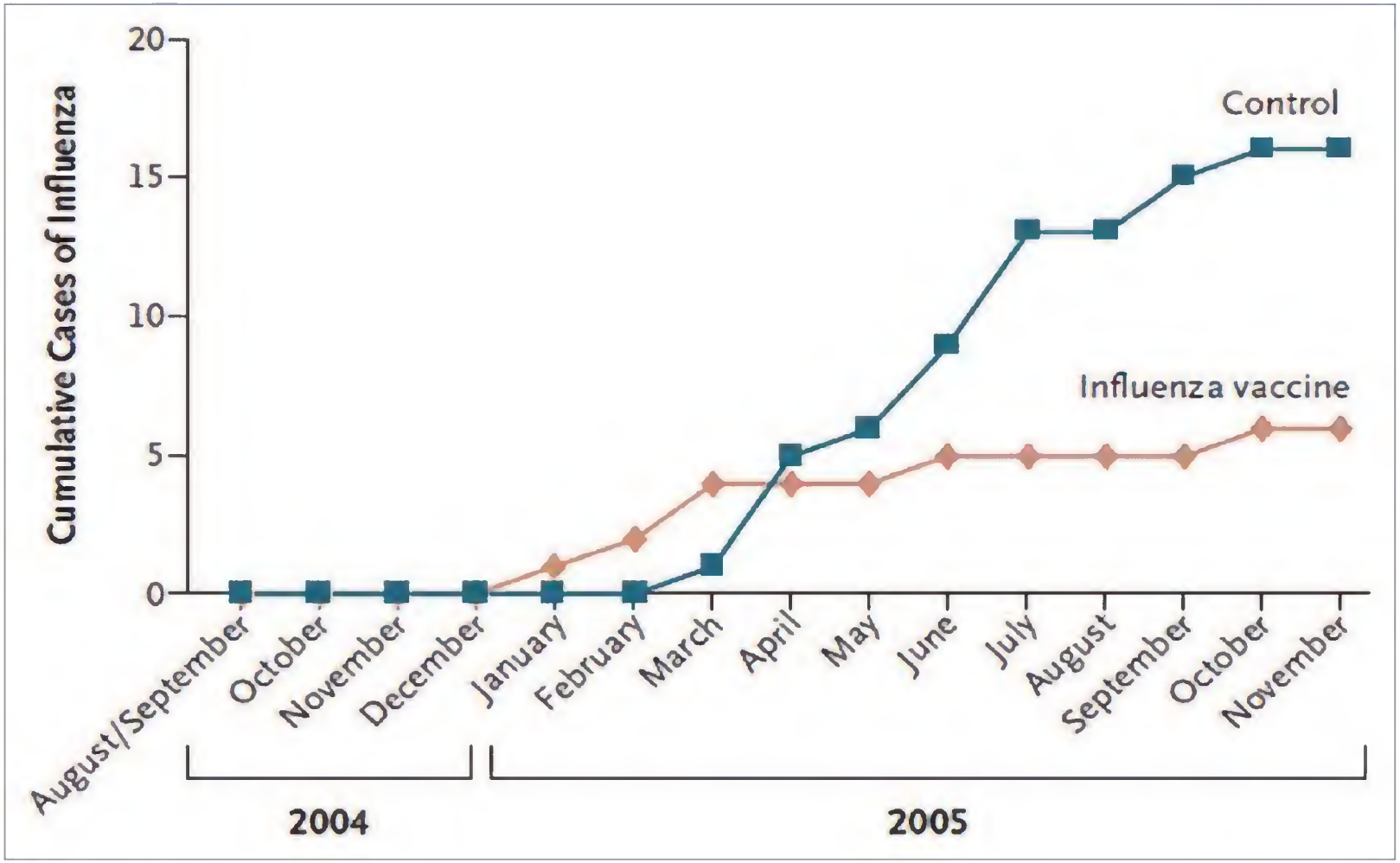
Neonate born with high titres tdap antibodies is protected from tetanus, diphteria and pertussis



Influenza Virus

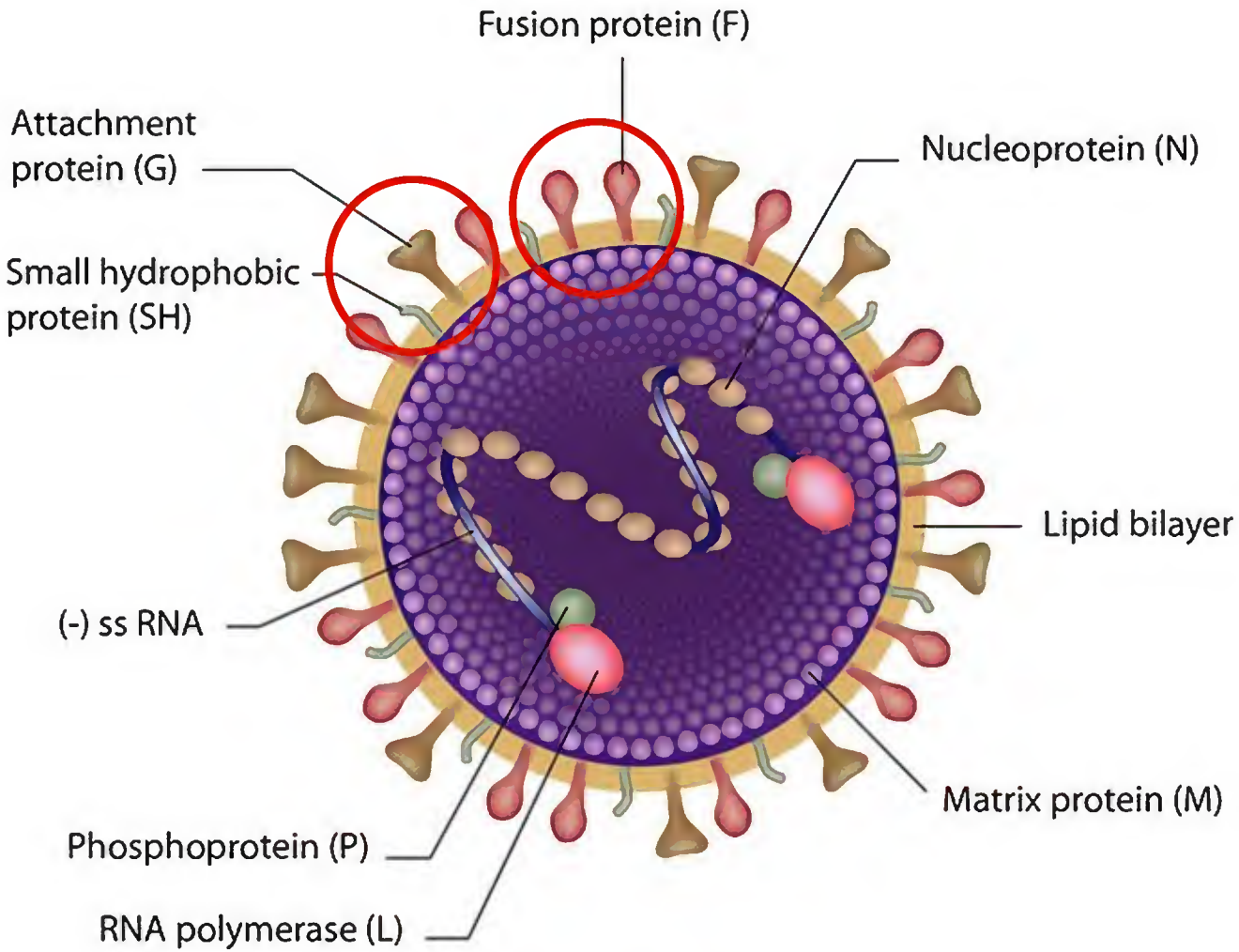


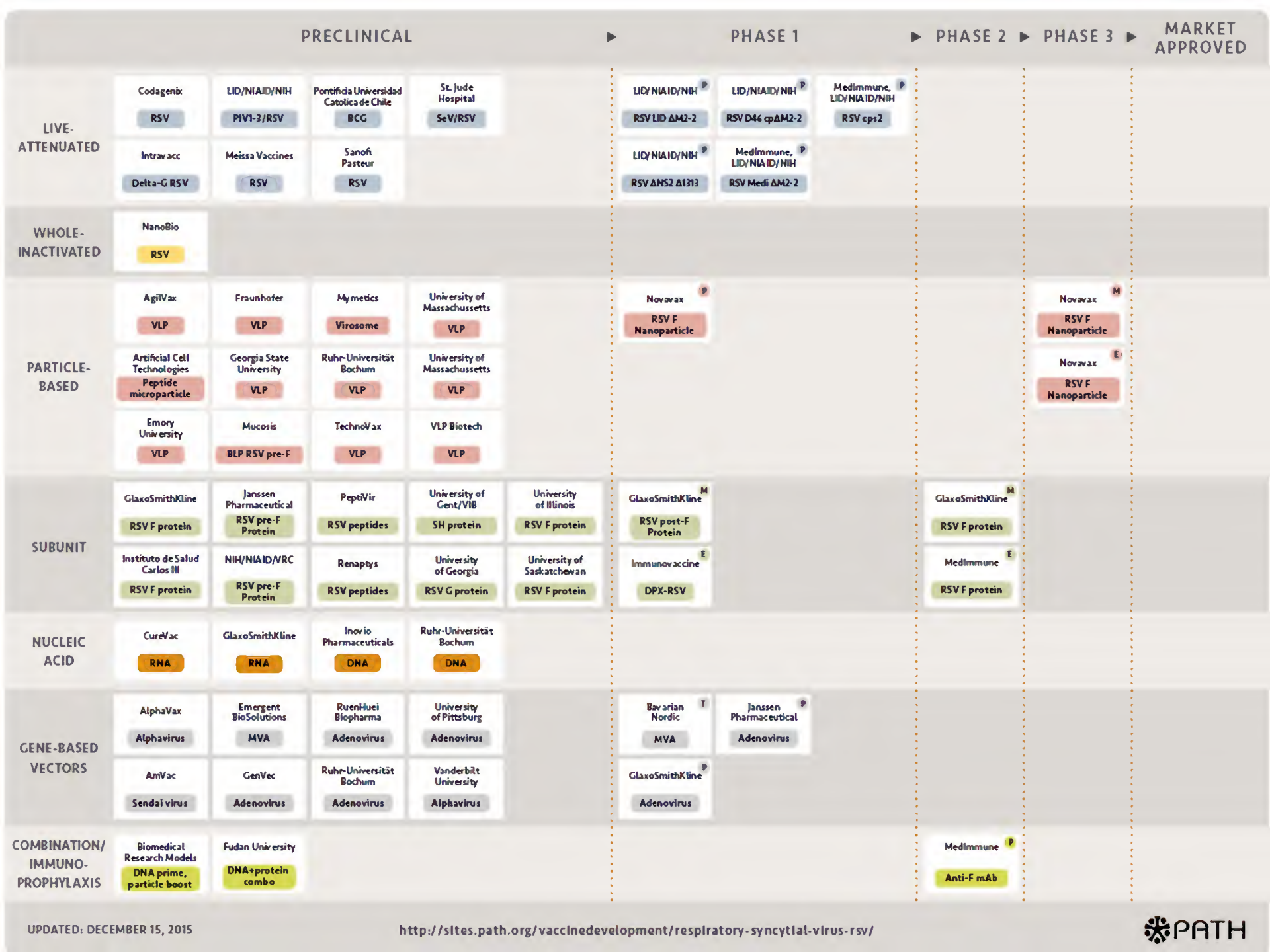
Laboratory-proven influenza in infants of pregnancy-vaccinated mothers



Zaman K. Et al, 2008

Respiratory Syncytial Virus




PRECLINICAL
PHASE 1
PHASE 2
PHASE 3
MARKET APPROVED
LIVE-ATTENUATED
Codagenix
RSV
LID/NIAID/NIH
PIV1-3/RSV
Pontificia Universidad Catolica de Chile
BCG
St. Jude Hospital
SeV/RSV
LID/NIAID/NIH P
RSV LID ΔM2-2
LID/NIAID/NIH P
RSV D46 cpΔM2-2
MedImmune, LID/NIAID/NIH P
RSV cps2
Intravacc
Delta-G RSV
Meissa Vaccines
RSV
Sanofi Pasteur
RSV
LID/NIAID/NIH P
RSV ΔNS2 Δ1313
MedImmune, LID/NIAID/NIH P
RSV MediΔM2-2
WHOLE-INACTIVATED
NanoBio
RSV
PARTICLE-BASED
AgiVax
VLP
Fraunhofer
VLP
Mymetics
Virosome
University of Massachussetts
VLP
Novavax P
RSV F Nanoparticle
Novavax M
RSV F Nanoparticle
Artificial Cell Technologies
Peptide microparticle
Georgia State University
VLP
Ruhr-Universität Bochum
VLP
University of Massachussetts
VLP
Novavax E
RSV F Nanoparticle
Emory University
VLP
Mucosis
BLP RSV pre-F
TechnoVax
VLP
VLP Biotech
VLP
SUBUNIT
GlaxoSmithKline
RSV F protein
Janssen Pharmaceutical
RSV pre-F Protein
PeptiVir
RSV peptides
University of Gent/VIB
SH protein
University of Illinois
RSV F protein
GlaxoSmithKline M
RSV post-F Protein
GlaxoSmithKline M
RSV F protein
Instituto de Salud Carlos III
RSV F protein
NIH/NIAID/VRC
RSV pre-F Protein
Renaptys
RSV peptides
University of Georgia
RSV G protein
University of Saskatchewan
RSV F protein
Immunovaccine E
DPX-RSV
MedImmune E
RSV F protein
NUCLEIC ACID
CureVac
RNA
GlaxoSmithKline
RNA
Inovio Pharmaceuticals
DNA
Ruhr-Universität Bochum
DNA
GENE-BASED VECTORS
AlphaVax
Alphavirus
Emergent BioSolutions
MVA
RuenHuei Biopharma
Adenovirus
University of Pittsburg
Adenovirus
Bavarian Nordic T
MVA
Janssen Pharmaceutical P
Adenovirus
AmVac
Sendai virus
GenVec
Adenovirus
Ruhr-Universität Bochum
Adenovirus
Vanderbilt University
Alphavirus
GlaxoSmithKline P
Adenovirus
COMBINATION/ IMMUNO-PROPHYLAXIS
Biomedical Research Models
DNA prime, particle boost
Fudan University
DNA+protein combo
MedImmune P
Anti-F mAb
UPDATED: DECEMBER 15, 2015
http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv/
PATH

A Study to Determine the Safety and Efficacy of the RSV F Vaccine to Protect Infants Via Maternal Immunization

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2017 by Novavax

Sponsor:
Novavax

Collaborator:
Bill and Melinda Gates Foundation

Information provided by (Responsible Party):
Novavax

ClinicalTrials.gov Identifier:
NCT02624947

First received: December 4, 2015
Last updated: January 23, 2017
Last verified: January 2017
History of Changes

Purpose

The purpose of this study is to determine the efficacy of maternal immunization with the RSV F vaccine against symptomatic RSV lower respiratory tract infection (LRTI) with hypoxemia through the first 90 days of life in infants.

Condition	Intervention	Phase
Respiratory Syncytial Virus Infections	Biological: RSV F vaccine with adjuvant Biological: Formulation buffer	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Participant, Investigator, Outcomes Assessor
Primary Purpose: Prevention

Official Title: A Phase 3, Randomized, Observer-Blind, Placebo-Controlled, Group-Sequential Study to Determine the Immunogenicity and Safety of a Respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine With Aluminum in Healthy Third-trimester Pregnant Women; and Safety and Efficacy of Maternally Transferred Antibodies in Preventing RSV Disease in Their Infants

Resource links provided by NLM:

healthcare

MDPI

Article

Knowledge, Attitude and Behaviours towards Recommended Vaccinations among Healthcare Workers

Giuseppe La Torre *, Stefania Scalingi, Veronica Garruto, Marco Siclari, Massimiliano Chiarini and Alice Mannocci

Dependent variable	Measles	Mumps	Rubella	Varicella	Pertussis	Hepatitis B	Influenza	Tuberculosis
Which infectious diseases could be a risk for my health, if I am not vaccinated?	45.5	41.9	44.8	34	36.4	80	24	76
Is exposure to the disease a concrete risk factor for the patient's health?	52.5	46.9	50.4	46.1	49.2	70.9	46.2	79.2
Does the disease X vaccine pose a risk to my health?	8.4	8.8	8.4	8.6	7.4	11.4	14.7	14.9
Are the benefits of the disease X vaccine higher than the risks for me?	61.1	56.9	60.4	54.3	57.8	73.2	45.7	60.4
Will the disease X vaccine protect my patients?	61.8	57.8	62	56.7	56.4	70.1	54.1	60.8
For which disease have I been vaccinated?	62.7	55.9	57.8	40.3	48.7	82	28.5	42.4
For which disease is the National health system providing sufficient communication/information?	17.7	13.5	14.9	11.7	11.2	21.9	37.1	14.2
For which diseases do you believe a vaccination should be mandatory for health care workers?	38.4	37	40.3	33.8	39.8	77.8	40.3	64.8
For which diseases do you believe a vaccination should be mandatory for biomedical students?	38.2	35	38.9	33.5	38.7	75.7	36.6	62.9
For which diseases do you believe a vaccination should be highly recommended, like for health care workers and students?	39.6	37.1	40.8	34.9	41.5	71.5	46.8	60.9

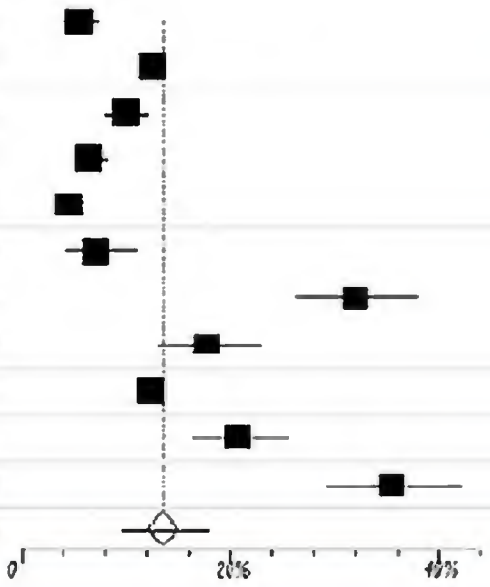
Human Vaccines 7:8, 728-733; July 2011; © 2011 Landes Bioscience

Prevalence of influenza vaccination among nurses and ancillary workers in Italy

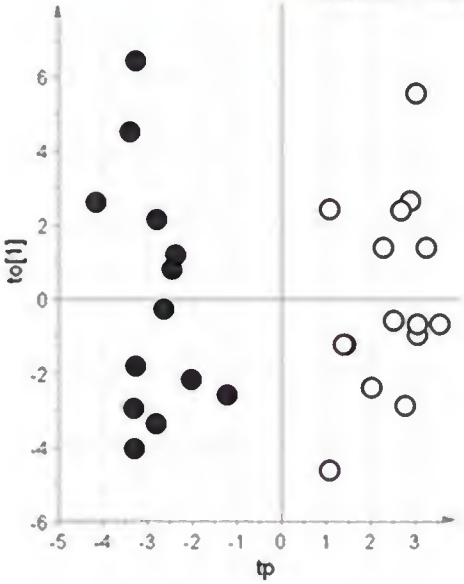
Systematic review and meta analysis

Giuseppe La Torre,[1,*] Alice Mannocci,[1] Paolo Ursillo,[1] Claudio Bontempi,[1] Alberto Firenze,[2] Maria Grazia Panico,[3] Antonella Sferrazza,[3] Chiara Ronga,[4] Adele D'Anna,[4] Emanuele Amodio,[5] Nino Romano[5] and Antonio Boccia[2]

Author	Year	Year of follow-up	Nurses n (vaccinates)	Nurses N (responders)	Prevalence of vaccinates in the responders sample(%)	Nurses 95% CI of prevalence (%) lower	upper
M.G. Panico	2011	2002-03	48	880	5,50	4,10	7,22
M.G. Panico	2011	2003-04	110	880	12,50	10,39	14,87
E. Amodio	2010	2005-06	86	867	9,90	7,93	12,08
E. Amodio	2010	2006-07	60	940	6,40	4,92	8,16
E. Amodio	2010	2007-08	39	890	4,40	3,15	5,96
M. Chittaro	2009	2004	18	254	7,10	4,26	10,98
M. Chittaro	2009	2005	81	254	31,90	26,21	38,01
M. Chittaro	2009	2006	45	254	17,70	13,21	22,96
S. Brusaferro	2004	1999-00	441	3618	12,20	11,15	13,31
S. Piffer	2000	1998	64	311	20,70	16,33	25,63
D.Ballada	1993	1990	81	227	35,50	29,28	42,10
total			1074	9375	13,47	9,58	17,90



CTRL vs RRI
(pre-treatment)
PLS-DA&(t-test, ROC)
Validation methods



CTRL vs RRI
(post-treatment)
PLS-DA&(t-test, ROC)
Validation methods