Il ruolo dei vaccini nella prevenzione delle patologie delle vie aeree.

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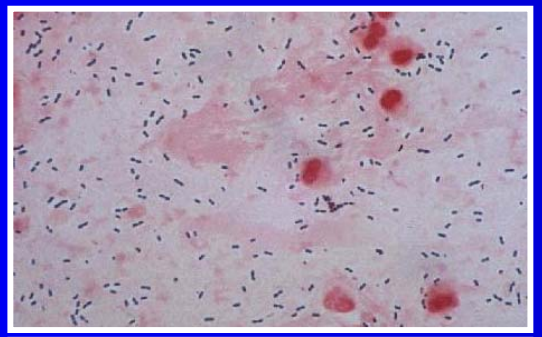
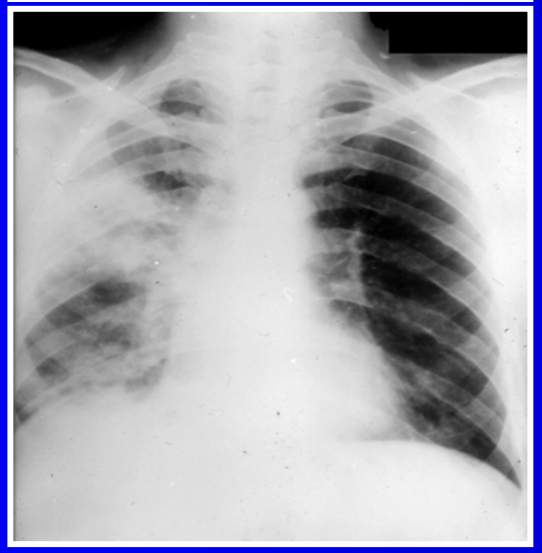
Genoa, Italy.

Outline:

- Pneumococcal vaccination:
  - caracteristics of the vaccine
  - effectiveness
  - cost-effectiveness
- Influenza vaccination in asthma and allergy:
  - safety
  - effectiveness
  - influence of corticosteroid therapy.

Streptococcus pneumoniae infections.





- *Streptococcus pneumoniae* is a ubiquitous human bacterial pathogen representing the leading cause of pneumonia and meningitis in all age groups.
- This is particularly true in infancy and old age, with associated significant mortality.

Kim Mulholland, Pediatr Pulmonol, 2003; 36

Control of pneumococcal diseases by vaccination.

accination with 23-valent
neumococcal capsular polysaccaride
CP) has been promoted for the past
) years but its true value in providing
urable protection in individuals
quiring it most is in greatest doubt.

he introduction of the protein-
onjugated pneumococcal
olysaccharide vaccine provides new
pportunity for prevention exist.

General indications:

- Childhood & advanced age.
- Immunodeficiencies
- Chronic renal diseases
- Chronic heart diseases
- Chronic lung diseases
- Chronic liver diseases
- Diabetes mellitus
- Severe splenic dysfuncti

Pneumococcal vaccination with capsula polysaccaride vaccine (PPV) or protein conjugated polysaccaride vaccine (CPV

T-independent mechanism, resulting in the production of oligoclonal populations of short-lived, terminally differentiated Ig producing cells

T-dependent mechanism, resulting in the clonal expansion of long-lived memory B-cells populations.

trial of 9-valent pneumococcal conjuga accine in children with and those witho HIV infection.

First Episodes of Invasive Pneumococcal Disease.*

Variable	Vaccinated Group	Control Group	P Value
	no. of episodes		
HIV-negative children			
Invasive pneumococcal disease	11	19	0.2
Vaccine-serotype pneumococci	3	17	0.003
Non–vaccine-serotype pneumococci	4	1	0.38
Vaccine-related–serotype pneumococci	4	1	0.38
HIV-positive children			
Invasive pneumococcal disease	22	47	0.004
Vaccine-serotype pneumococci	9	26	0.006
Non–vaccine-serotype pneumococci	9	8	1
Vaccine-related–serotype pneumococci	6	16	0.05

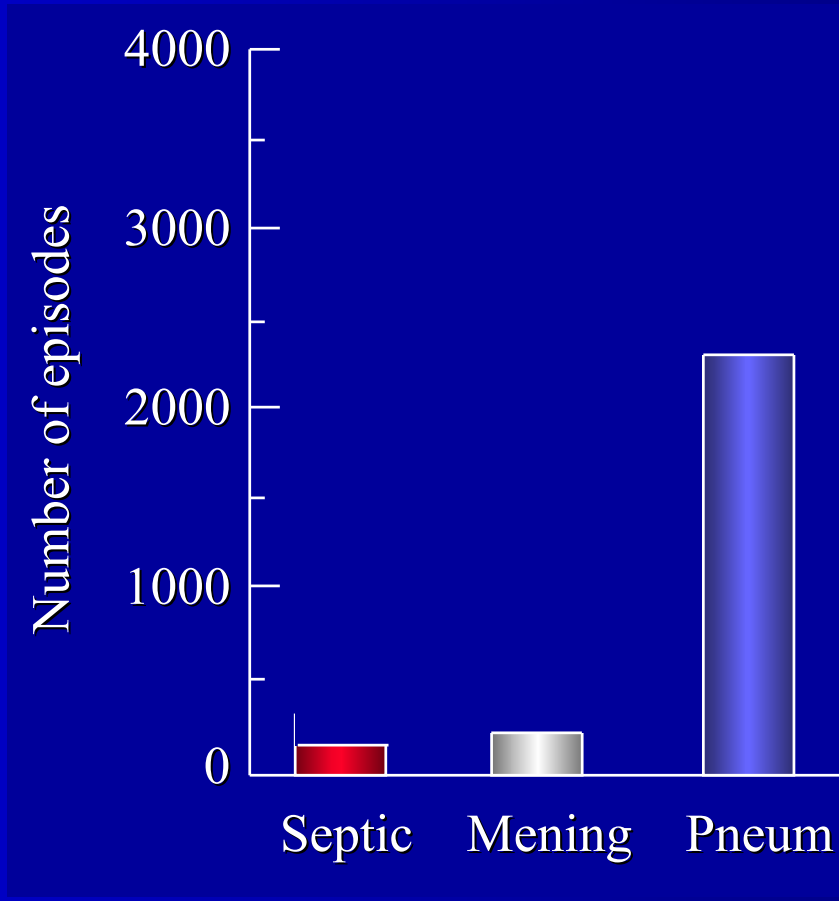
Klugman KP et al. N Engl J Med 2003;349:

ow many episodes of hospital care mig be prevented by widespread uptake of pneumococcal conjugate vaccine?

n 1999 in U.K. in children 3 m to 5rs ld, 134 episodes of septicaemia, 245 of aeningitis, and 216 of pneumonia due to neumococci were reported.

pisodes of "unspecified" disease espectively 68, 36 and 2548) were robably pneumococcal in origin.

8% cases of pneumococcal epticaemia, 76% of meningitis, and 6% of pneumonia may be preventable nnually by means of pneumococcal onjugate vaccination 22.



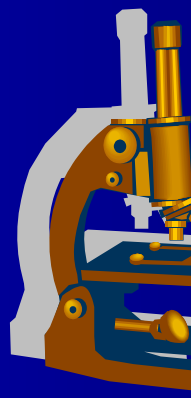
McIntosh ED. Arch Dis Child 2003; 88;

The cost-effectiveness of pneumococca conjugate vaccination in Australia.

Results: For a birth cohort of 250,000, the gross cost of vaccination is $ 78.6 million. Subtracting treatment cost savings, the net cost (discounted) is $ 61.7 million.

Vaccination prevents 13.7 deaths: the discounted cost per death avoided is $ 5.0 million, giving a break-even vaccine price of $ 15.40 per dose, instead of $ 90.00.

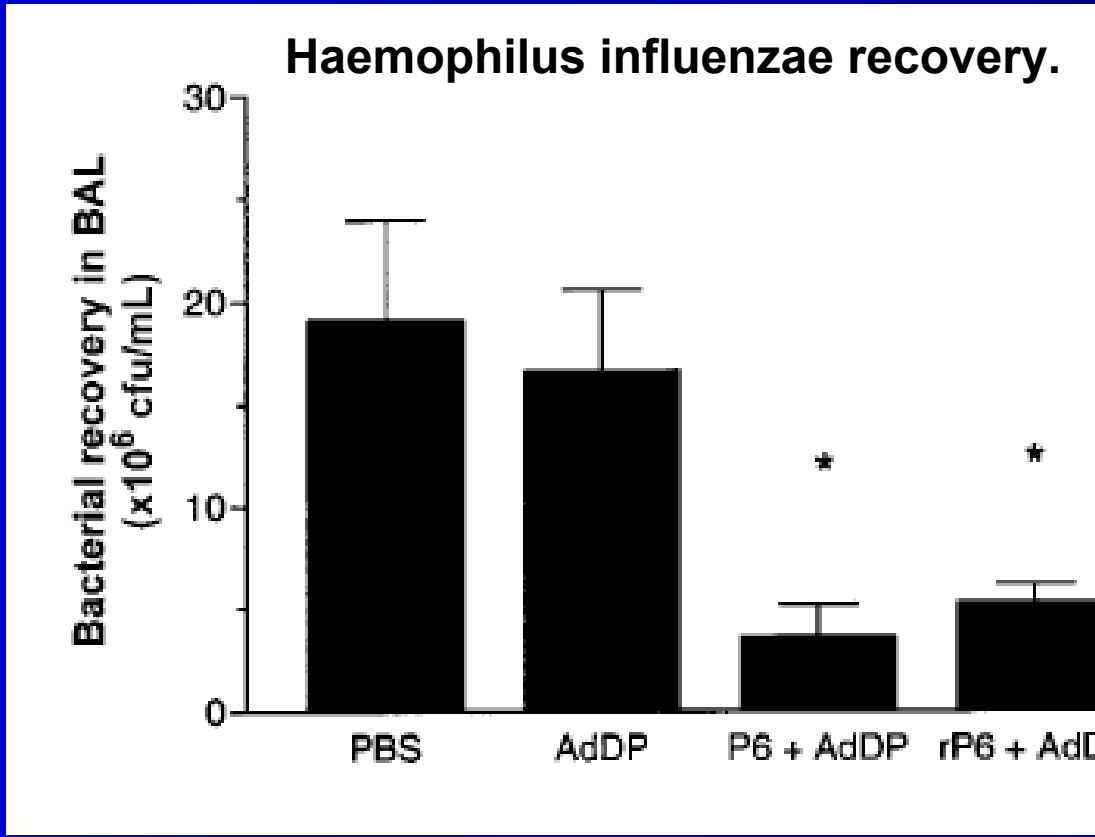
Conclusion: The importance of PCV7 to cost-effectiveness in resource rich and resource poor settings warrants further studies.



Butler JR et al. Vaccine. 2004; 22: 11

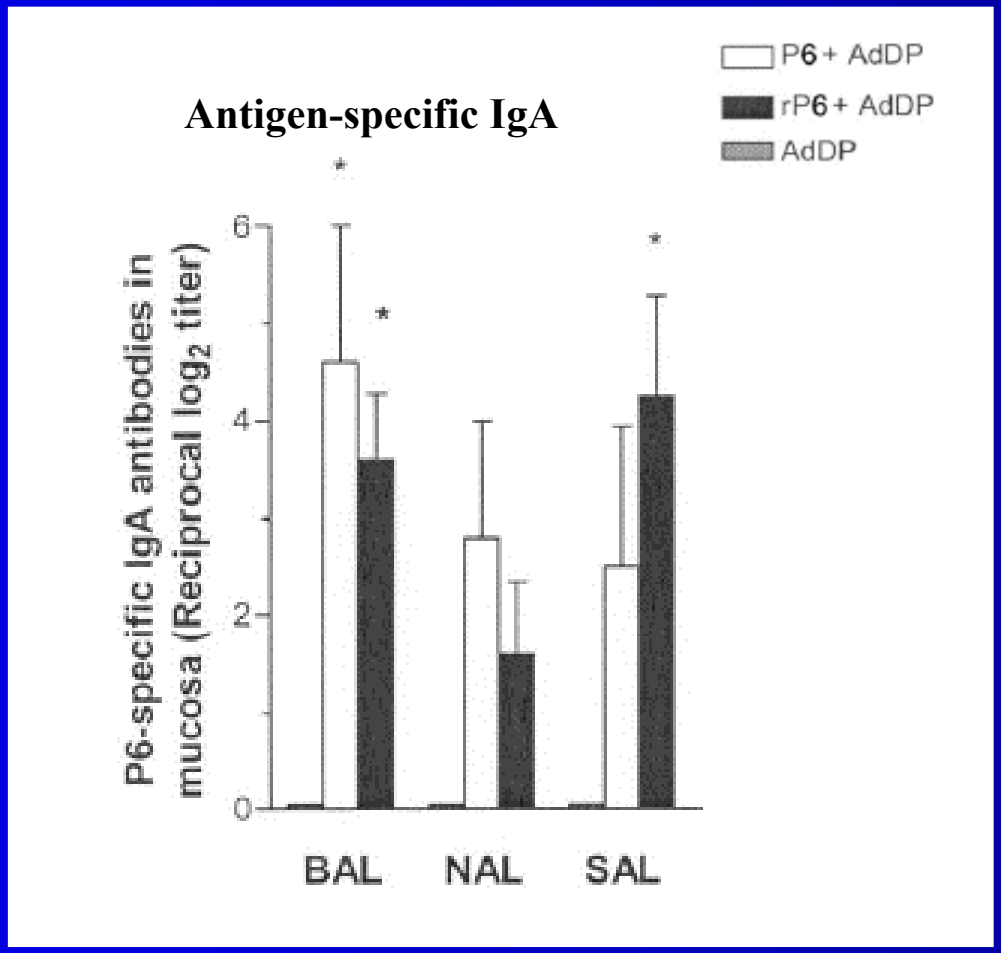
Intranasal vacination with recombinant roteins and adjuvant against *Haemophilus influenzae* in mice.

ranasal vaccination
recombinant P6
mophilus influenzae (*H.i.*)
ein and
mantylamide dipeptide
DP) as mucosal
vant confers efficient
ection against otitis
ia and lung infection
H.i. in mice.



Bertot GM et al. Journal Infect Dis 2004; 189:1

Intranasal vaccination with rP6 protein and AdDP induce efficient production IgA abs against *Haemophilus influenzae* in mice.

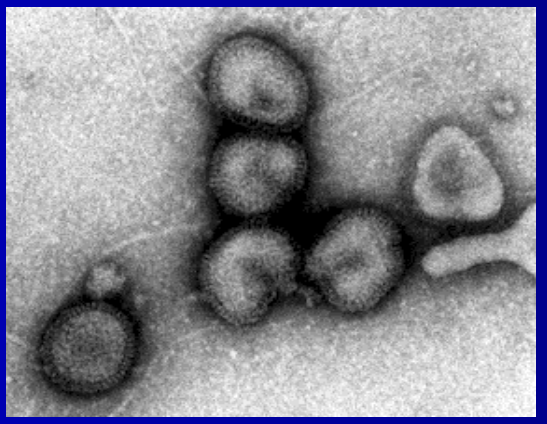


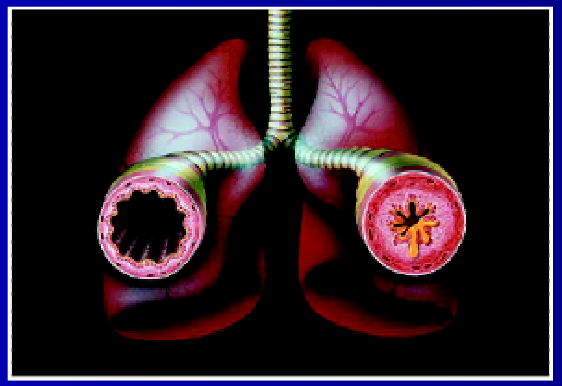
Influenza

Annual influenza vaccination is *recommended* for children at high risk of complications from influenza due to underlying medical conditions, and *encouraged* for all children aged 6 to 23 months when feasible.

In 2000 in U.S.A. approximately 5.2 to 10.0 million children aged 6 months through 17 years (7.4%-14.2%) had high-risk conditions indicated for influenza vaccination.

Asthma accounted for the majority of conditions.





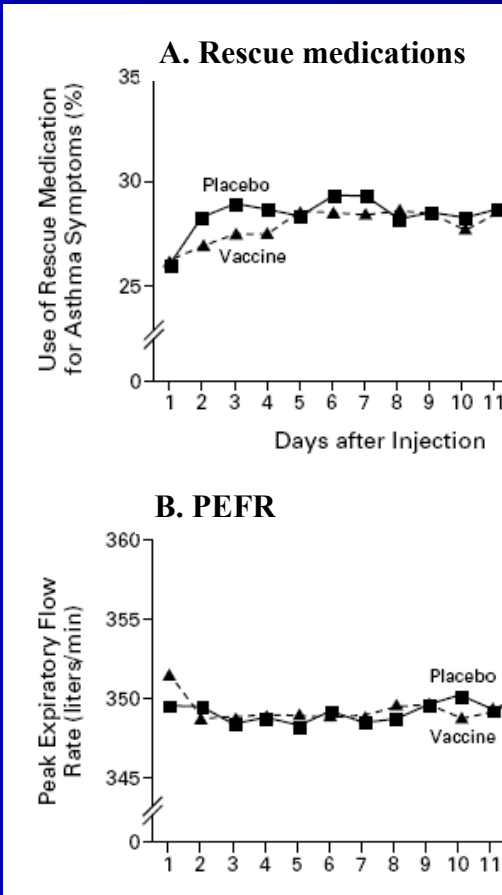
Erhart L M et al. J Pediatr. 2004; 144

he safety of inactivates influenza vacci in adults and children with asthma.

Methods. Trial in 2032 pts with asthma (3 to 64 yrs) to investigate the safety of the inactivated trivalent split-virus influenza vaccine.

Results. In two week period the frequency of exacerbations of asthma was similar after the influenza vaccination and after placebo injection (28.8 % and 27.7 %).

Conclusions. The inactivated influenza vaccine is safe to administer to adults and children with asthma, including those with severe asthma. Given the morbidity of influenza, all those with asthma should receive the vaccine annually.



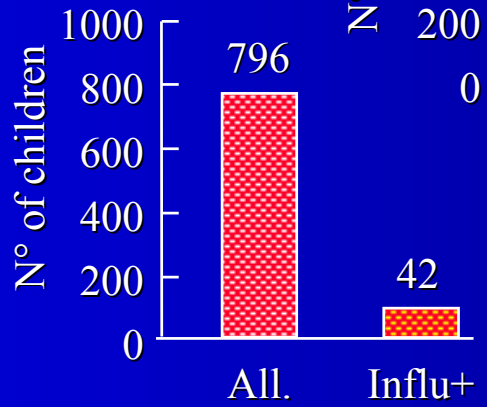
NEJM 2001; 345: 15

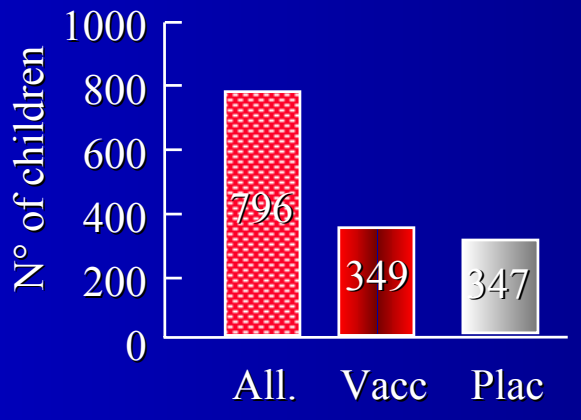
Effectiveness of influenza vaccination i children with asthma.

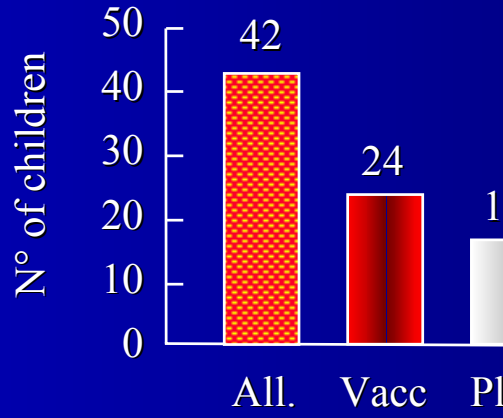
udy design. 796 children had renteral vaccination with ctivated vaccine or placebo and lowed from November to April 1 the next year.

sults. Influenza-related asthma acerbations were of similar severity both groups; however they lasted days shorter in the vaccine group = 0.06).

nclusions. Influenza vaccination l not result in a significant luction of the number, severity, or ration of asthma exacerbations used by influenza.







Bueving HJ et al. AJRCCM 2004; 169: 4

ffect of corticosteroid therapy on immun response to influenza vaccination in children and adults with asthma.

294 patients with asthma [group 1: high-medium-doses of ICS or ora CS ; group 2: not receiving CS or low-dose ICS] were randomized to receive placebo or inactivated trivalent split-virus influenza vaccine.

Serologic responses to each influenza vaccine antigen were significantly *higher in vaccine* than in placebo recipients and were *similar among influenza vaccine groups 1 and 2*.

Post hoc subgroup analyses demonstrated an *attenuated response* to influenza B antigen in subjects receiving high-dose ICS compared with subjects who were steroid-naive ($P<.05$).

Hanania NA, et al. JACI 2004; 113:

Egg allergy poses as a challenge in influenza vaccination programs.

fluenza vaccines are derived from
e extra embryonic fluid of chicken
nbryos inoculated with specific
pes of influenza virus.

ne vaccines typically contain
easurable quantities of egg protein
ergens, such as ovomucoid-
albumin.

dverse allergic reactions have been
en in patients (including children)
th egg allergy injected with
activated influenza vaccines.

	Egg protein (ovomucoid-ovalbumin) content (µg		
Year	Fluvirin (Evans)	Fluogen (Parke Davis)	FluShield
2001-2002	0.06	Not done	29.5
2000-2001	Not done	Not done	38.4
1999-2000	Undetectable	Not done	Not
1998-1999	0.8, 0.05	Not done	1
1997-1998	Not done	Not done	6.5
1996-1997	Not done	0.02	1
1995-1996	Not done	1.2	Not
1994-1995	0.01	0.1	2

Zeiger RS. JACI 2002;110:

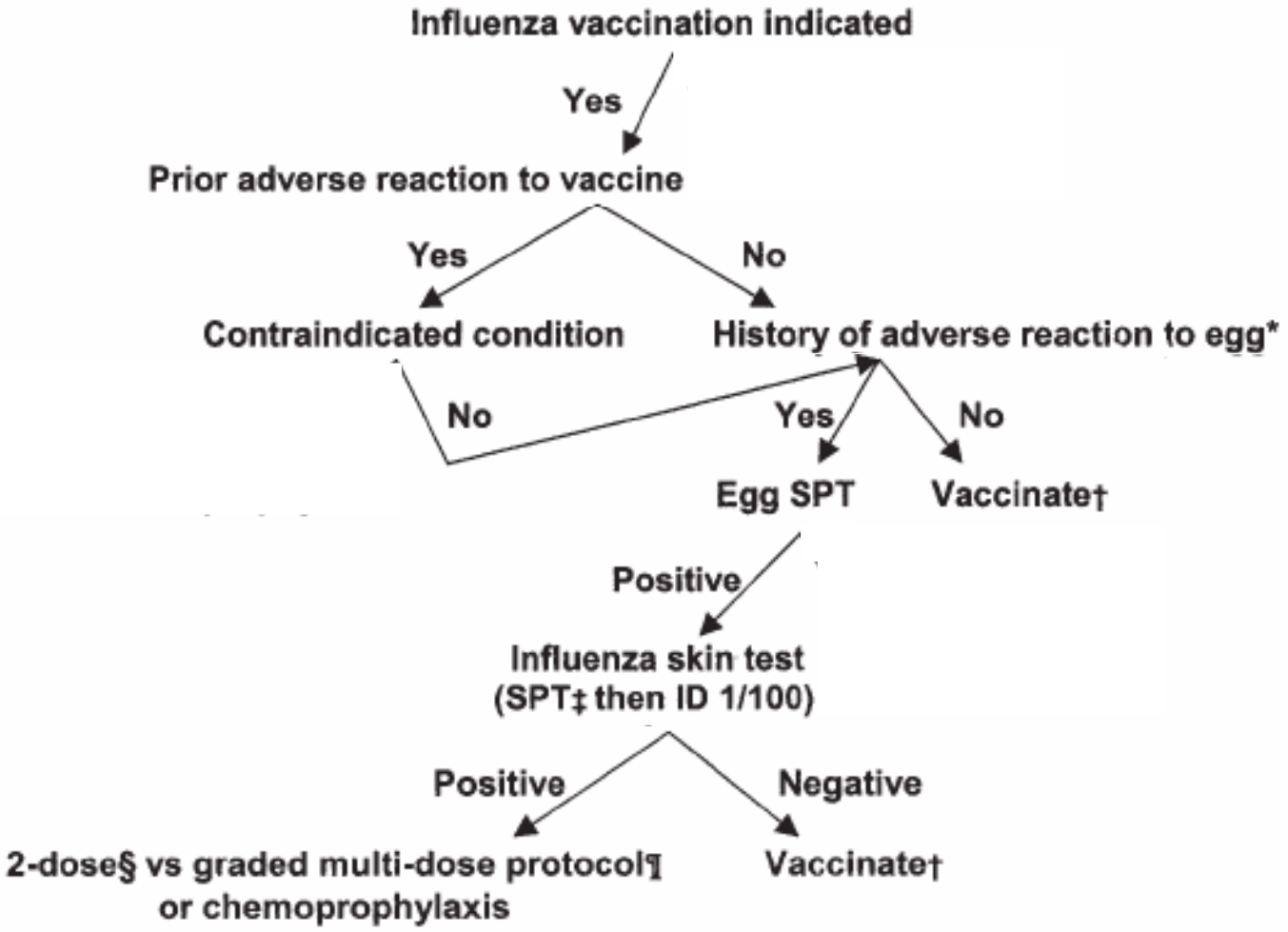
The Red Boock

Children with severe anaphylactic reactions to chicken or egg protein (generalized urticaria, hypotension, or manifestations upper or lower airway obstruction) can experience, on rare occasions, a similar type of reaction to killed influenza vaccines.

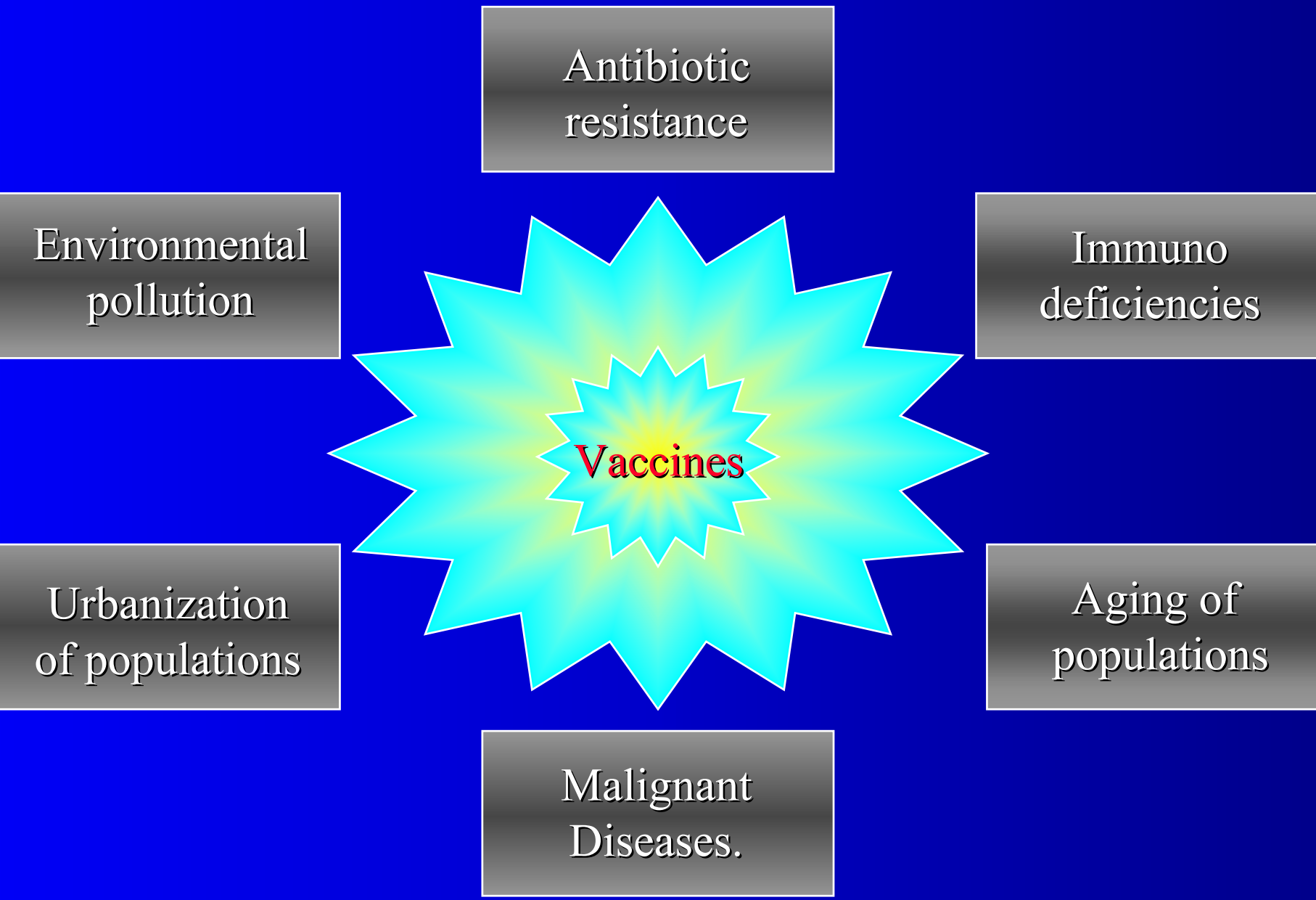
Although influenza vaccine has been administered safely to such children after skin testing and even desensitization, these children *generally* should not receive influenza vaccine becau of their risk of reactions, the likely need for yearly vaccinatio and the availability of chemoprophylaxis against influenza infection.

Red Book: report of the Committee on Infectious Diseases. 25th ed.

Influenza vaccination in egg allergy: a practical protocol.



Zeiger RS. JACI 2002;110:


Antibiotic resistance
Environmental pollution
Immuno deficiencies
Vaccines
Urbanization of populations
Aging of populations
Malignant Diseases.

Egg protein content in various lots of influenza vaccines.

	Egg protein (ovomucoid-ovalbumin) content (μg/mL)*		
Year	Fluvirin (Evans)	Fluogen (Parke Davis)	FluShield (Wyeth)
2001-2002	0.06	Not done	29.5, 33.1
2000-2001	Not done	Not done	38.4, 42.4
1999-2000	Undetectable	Not done	Not done
1998-1999	0.8, 0.05	Not done	10.9
1997-1998	Not done	Not done	6.5, 8.3
1996-1997	Not done	0.02	1.0
1995-1996	Not done	1.2	Not done
1994-1995	0.01	0.1	27.2

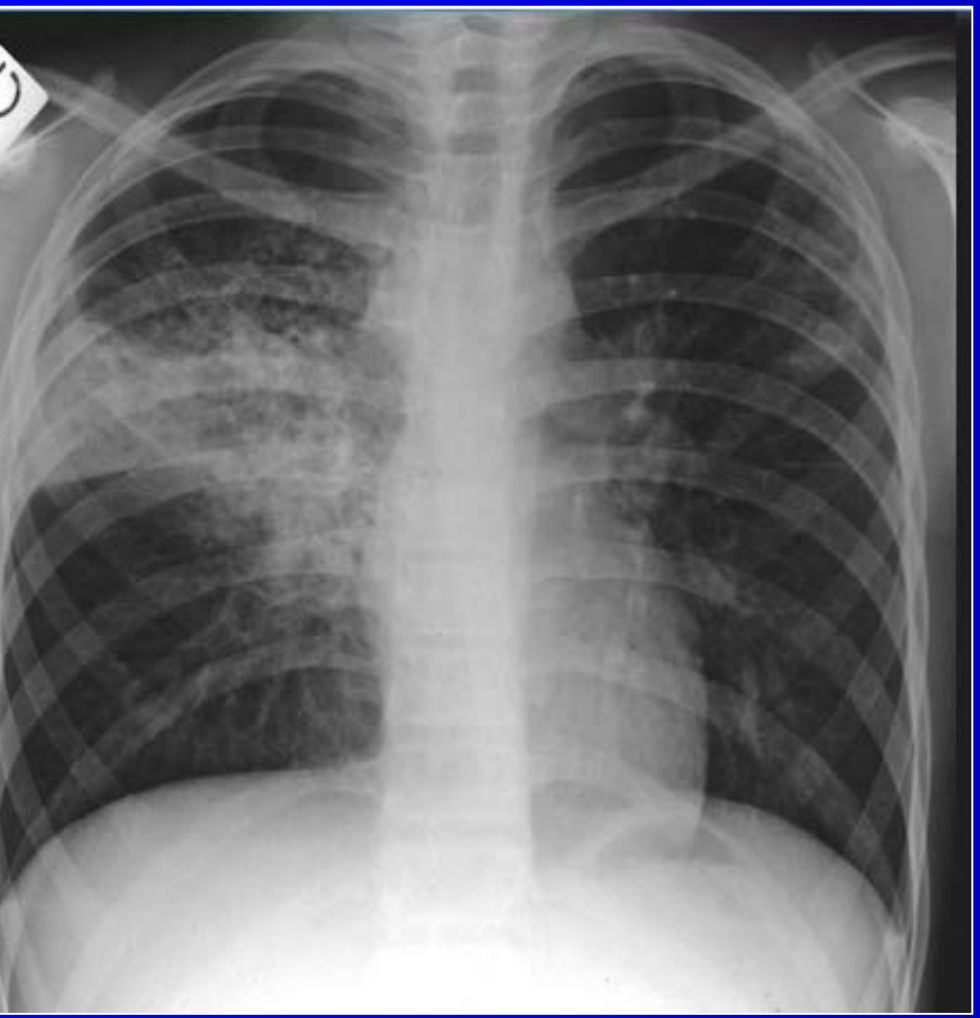
Zeiger RS. JACI 2002;110:

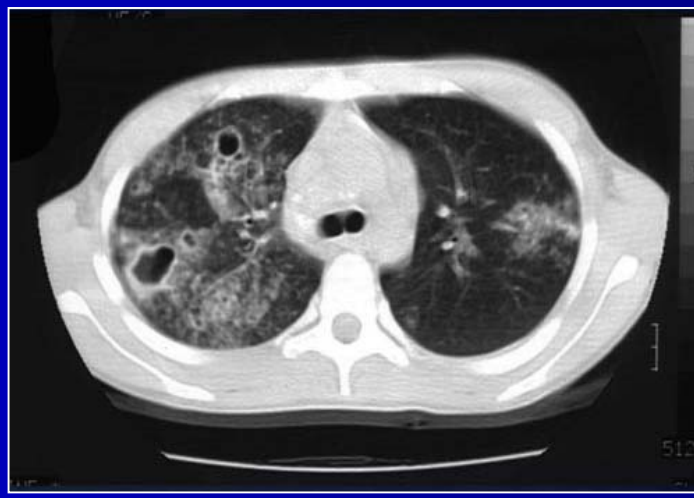
Influenza vaccination coverage level at a cystic fibrosis center: out of 335 pts, 256 received the vccine.

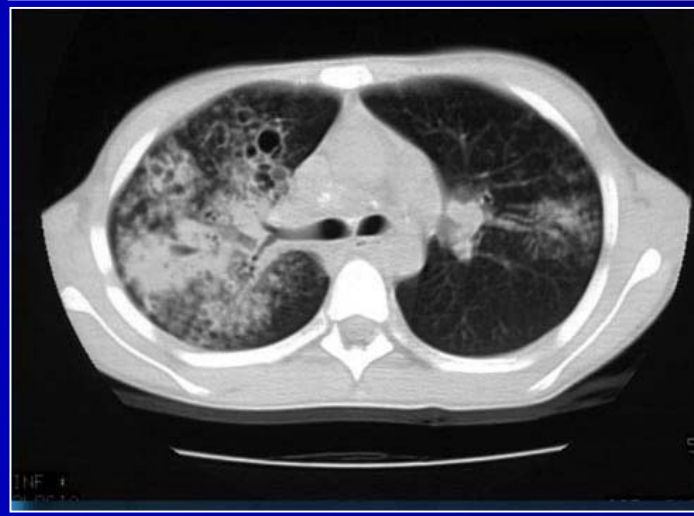
Reason	Number of Patients (<18 Years Old)	Number of Patients (≥18 Years Old)
Forgot	8	8
Too busy	5	7
Too healthy	7	4
Worried about side effects	6	2
Too sick at the time	5	3
Too expensive or not covered by insurance	3	2
Does not work for me	3	0
Afraid of needles	1	1
Allergic to eggs	0	1
Other or several reasons	9	4
Total	47	32

Marshall BC et al. Pediatrics 2002; 1

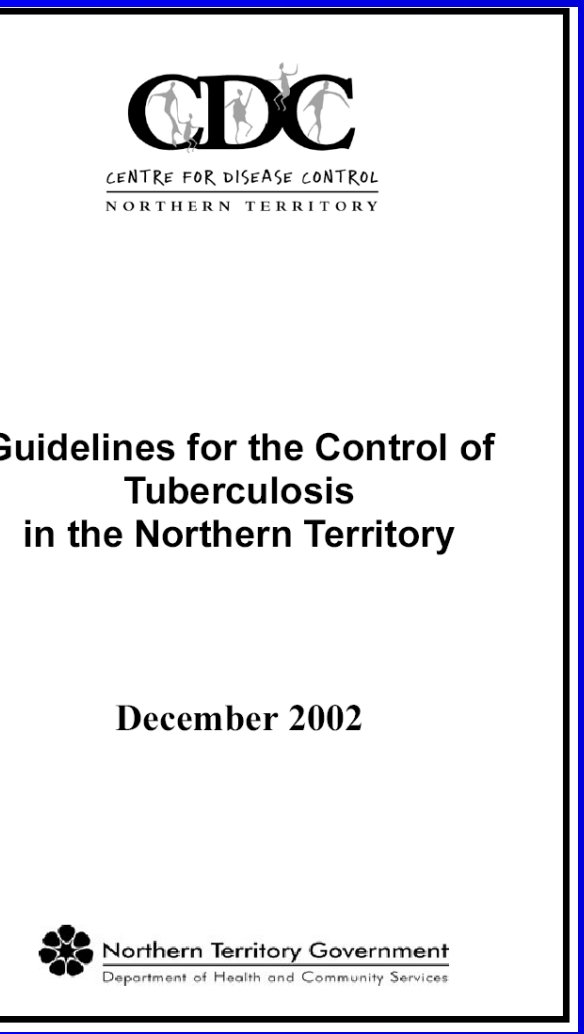
Pulmonary tuberculosis.







Open questions in TB control.



- Indications for Mantoux test.
- Role of BCG vaccination.
- How to distinguish Mantoux reactions caused by BCG from thos caused by natural mycobacterial infections.
- Positive Mantoux Test Cutoffs.
- Boosted reactions to Mantoux.

BCG vaccination.

BCG is a suspension of live attenuated *M. bovis* and remains the only vaccine available for TB.

The aim of BCG vaccination is not to prevent transmission o MTB but rather to prevent progression of infection to diseas Its main role is in preventing meningeal and disseminated (miliary) TB in young children for whom its efficacy is greater than 80%.

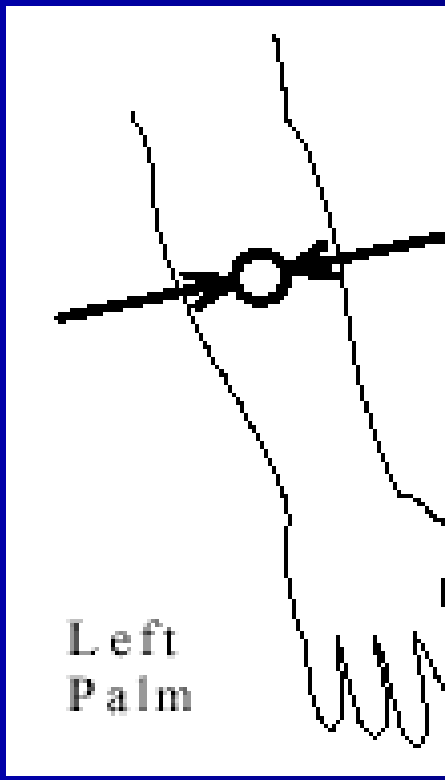
It is not recommended for routine vaccination of adults but may have benefits over a Mantoux screening policy in healt workers expected to be exposed to multi-drug resistant TB.

Effect of BCG vaccination on Mantoux testing.

Most people vaccinated with BCG will develop a Mantoux reaction $\geq$ 10 mm within 8-12 wks of vaccination: this reaction does not correlate with effectiveness of the vaccine.

The degree of persistence of this response is influenced by the age at vaccination: if BCG is given in the 1st yr of life, it is unlikely to cause Mantoux reactions of $\geq$ 10 mm after the age of 2 or 3 yrs.

Those vaccinated later in childhood are more likely to have persistent responses but the majority of these will be < 10 mm within 10 years of vaccination.



ow to distinguish Mantoux reactions caused by BCG from those caused by natural infections?

he most important factor influencing the probability that a uberculin reaction represents true infection with MTB rather han the effect of BCG is the prevalence of LTBI in the opulation sub-group being tested.

ome authorities recommend that BCG vaccination status be gnored when performing the Mantoux test if the patient is in a igh risk group for TB infection or if the vaccine was given in nfancy.

n these instances the likelihood of true infection with MTB elative to a false-positive reaction is increased.

Risk factors for TB infection in children i contact with infectious TB cases in the Gambia, West Africa.

n a highly endemic country with high BCG vaccination overage, TB infection in children who were in contact with ndividual with infectious TB was directly related to the inten f exposure to the individual with TB.

Nutritional status and presence of a BCG scar were not ndependent risk factors for TST positivity in this population.

A positive TST in a child reflects most probably TB infection ather than previous BCG vaccination.

Lienhardt C et al. Pediatrics 2003; 111:608

Should France continue to use BCG?

the context of the decrease of tuberculosis incidence, a re-assessment o
e French BCG vaccination policy has been undertaken.

ata from several countries having discontinued primovaccination confir
e effectiveness of BCG vaccination on childhood tuberculosis, mainly o
tra-pulmonary cases.

se on these data and on the estimation carried out by the National Instit
r Public Health Surveillance of the impact of the discontinuation in Fra
BCG re-vaccination and primovaccination, it was decided to discontinu
e policy of re-vaccination and of routine tuberculin testing.

multidisciplinary expertise aimed at studying the relevancy, the feasibil
d the acceptability of various options of reducing the target-population
imovaccination is on-going.

Levy-Bruhl D. Rev Prat. 2004; 54

Neonatal BCG vaccine and response to tuberculin test in children in contact with tuberculosis patients in Recife, Brazil.

his case-control study analyses the association between the tuberculin esponse (TT) and the neonatal BCG vaccine in 330 children under 15 w re home contacts of tuberculosis patients.

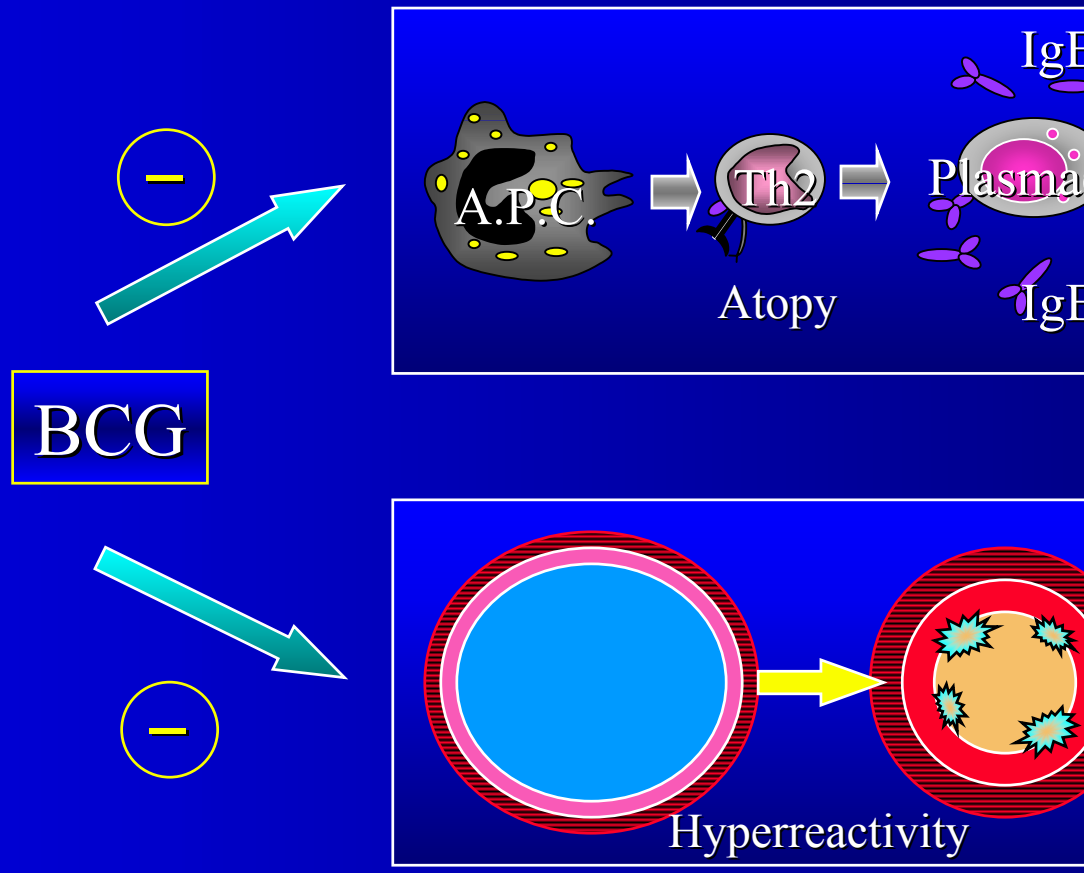
he multivariate analysis showed that being exposed to a patient with ulmonary lesions with cavities (OR = 3.14; CI: 1.59-6.20; p = 0.000), a ositive sputum smear (OR = 3.65; CI: 1.52-8.78; p = 0.002) or a positiv ulture (OR = 4.42; CI: 1.39-14.1; p = 0.005), being under five (OR = 0.4 I: 0.22-0.99; p = 0.045) are independently associated with a positive TT

he fact that a prior BCG scar is not associated with a positive response e TT indicates the need to re-open discussion of the guidelines which e many poor countries where tuberculosis is still a serious public health roblem.

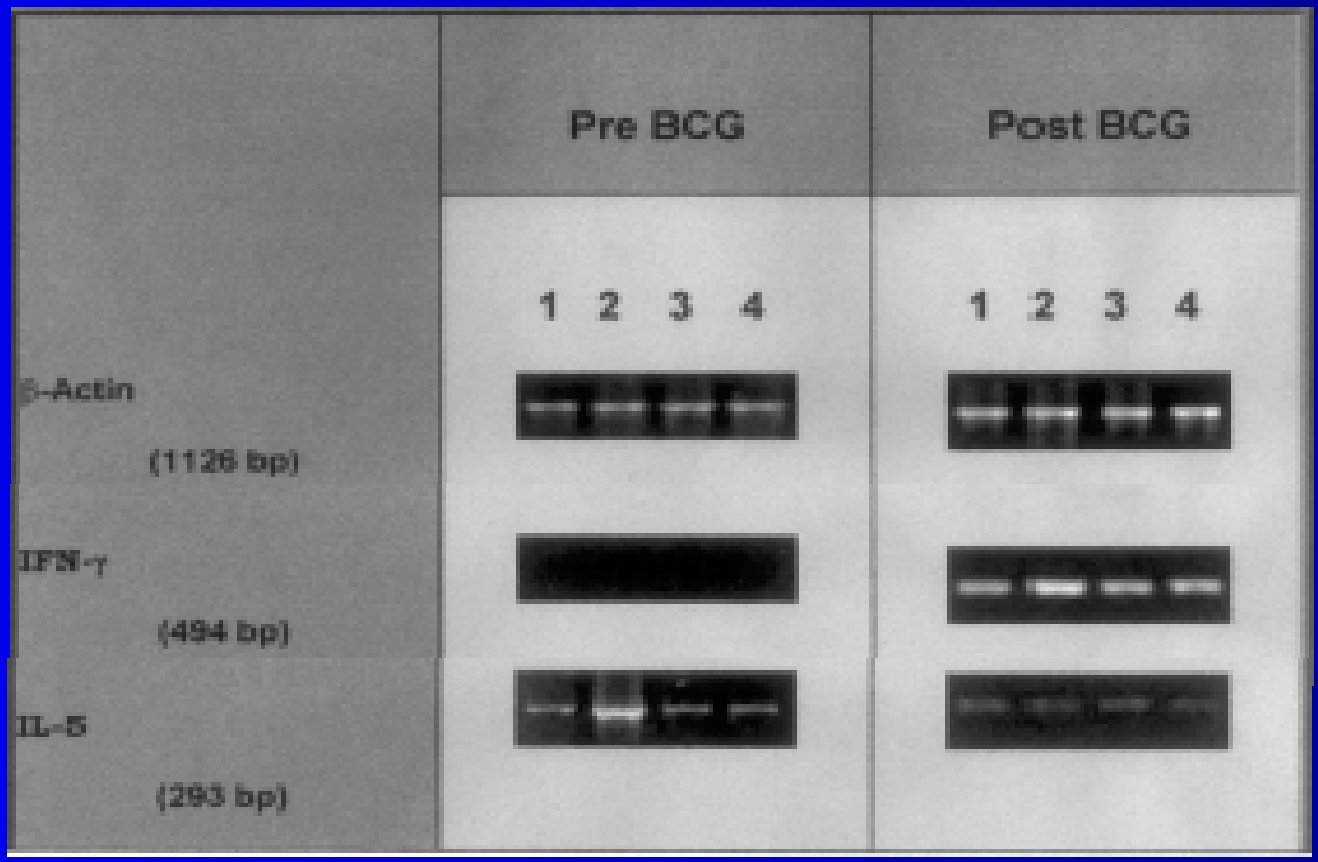
Militao de Albuquerque Mde F et al. J Trop Pediatr. 2004; 5

BCG vaccination, atopy and asthma

has been proposed that
rly age at BCG
ccination may
mulate a "Th_1- type"
mune response, with
otection against the
velopment of allergy
d its clinical
nifestations.



Effect of BCG vaccination on cytokine mRNA expression in atopic children with asthma.



Ozera A. et al. Immunology Letters 2003; 86

Age at BCG vaccination and risk of atopy.

	Cases/all (%)	OR (95% CI)
BCG vaccination		
Yes‡		
Age		
0–7 d	9/36 (25.0)	0.83 (0.38–1.79)
8 d–1 mth	14/39 (35.9)	1.39 (0.71–2.73)
2–5 mth	6/18 (33.3)	1.24 (0.46–3.36)
6–11 mth	17/59 (28.8)	1.01 (0.56–1.81)
1 y	10/37 (27.0)	0.92 (0.44–1.94)
2 y	15/45 (33.3)	1.24 (0.65–2.36)
3–4 y	17/69 (24.6)	0.81 (0.46–1.44)
5–6 y	53/228 (23.2)	0.75 (0.53–1.07)
7 y	206/718 (28.7)	1 (reference)
8 y	56/241 (23.2)	0.75 (0.54–1.06)
9–15 y	32/128 (25.0)	0.83 (0.54–1.28)
Unspecified¶	11/35 (31.4)	1.14 (0.55–2.37)

Bager p et al. Clin Exp Allergy 2003; 33:1512

Age at BCG vaccination and risk of allergic rhinitis and asthma.

	Allergic rhinitis		Asthma	
	Cases/all (%)	OR (95% CI)	Cases/all (%)	OR (95% CI)
BCG vaccination				
Yes†				
Age (years)				
0	24/144 (16.7)	1.35 (0.82–2.20)	15/144 (10.4)	1.61 (0.87–2.95)
1–2	11/82 (13.4)	1.04 (0.53–2.04)	7/82 (8.5)	1.29 (0.56–2.95)
3–6	36/291 (12.4)	0.95 (0.63–1.43)	23/291 (7.9)	1.19 (0.71–1.99)
7	92/711 (12.9)	1 (reference)	48/711 (6.8)	1 (reference)
8–15	42/365 (11.5)	0.87 (0.59–1.29)	25/365 (6.8)	1.02 (1.62–1.68)
Unspecified§	5/29 (17.2)	1.40 (0.52–3.77)	7/29 (24.1)	4.39 (1.79–10.8)

Bager p et al. Clin Exp Allergy 2003; 33:1512

hird generation, purified fusion protein (PFP accine to prevent severe respiratory syncyt virus (RSV) infections.

A phase II, multi-center, adjuvant-controlled trial was performed in RSV seropositive children with cystic fibrosis (CF); 151 received the adjuvant-control and 143 received the vaccine.

At enrollment, RSV-specific, serum antibodies were comparable between both groups. At post-vaccination and end-of-study, RSV-specific, neutralizing antibody (Nt Ab) and binding antibody (Bd Ab) the fusion (F) protein were significantly higher in PFP-3 vaccinees.

After 28 days post-vaccination, Nt Ab and Bd Ab to F protein titers declined slowly at rates of 0.23 and 0.37 log2 per month, respectively.

The PFP-3 vaccine-induced a robust immune response that lasted throughout the RSV season.

Piedra PA et al. Vaccine. 2003; 21: 24

Vaccination of cystic fibrosis patients against *seudomonas aeruginosa* reduces the proportion patients infected and delays time to infection.

Background. Cystic fibrosis (CF) almost always leads to chronic airway nfection with Pseudomonas aeruginosa.

Methods: In 1989-1990, 30 young children with CF, mean age 7 years, w o prior history of infection with P. aeruginosa, were vaccinated against eruginosa with a polyvalent conjugate vaccine.

Conclusions: Regular vaccination of young CF patients for a period of 1 ears with a polyvalent conjugate vaccine reduced the frequency of chro nfection with P. aeruginosa. This was associated with better preservatio ung function. Vaccinated patients gained more weight during the study eriod, a possible indication of an improved overall health status.

Lang AB et al. Pediatr Infect Dis J. 2004; 23: 5

The cost-effectiveness of pneumococca conjugate vaccination in Australia.

ackground: Pneumococcal conjugate vaccine, 7 valent (PCV7) is the m ostly vaccine considered for publicly funded programs. In mid 2001, ustralia funded PCV7 for high-risk groups only (indigenous children a hildren with certain underlying medical conditions).

Methods: The incidence of invasive pneumococcal disease (IPD), non- acteraemic pneumonia and otitis media was estimated.

esults: For a birth cohort of 250,000, the gross cost of vaccination is $ illion. Subtracting treatment cost savings, the net cost (discounted) is $ 1.7 million. Vaccination prevents 13.7 deaths. The discounted cost per eath avoided is $ 5.0 million, per life-year saved $ 230,130, giving a bre ven vaccine price of $ 15.40 per dose instead of $ 90.00.

onclusion: The impact of PCV7 against non-bacteraemic pneumonia is oorly defined, but its importance to cost-effectiveness in resource rich a esource poor settings warrants further studies.

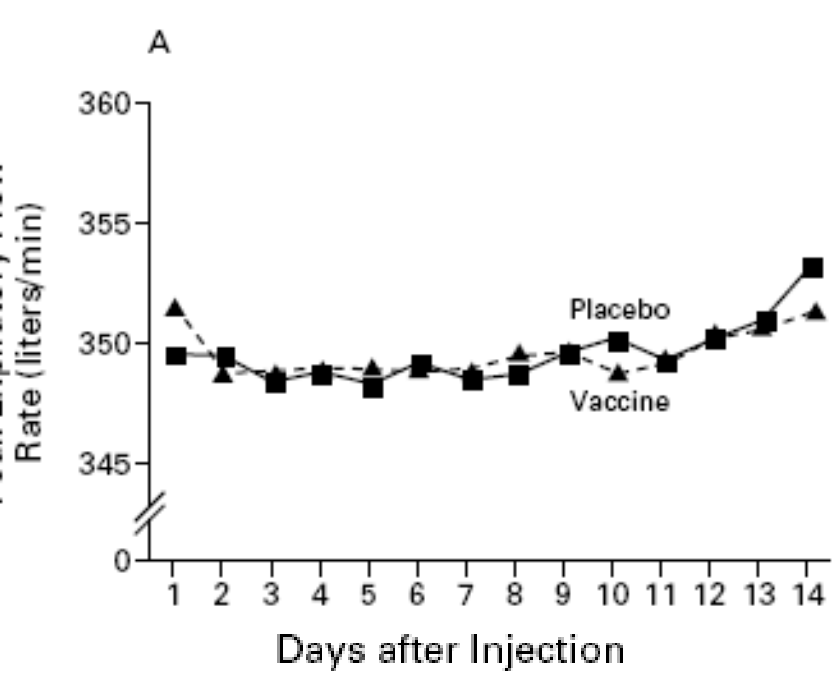
Butler JR et al. Vaccine. 2004; 22: 11

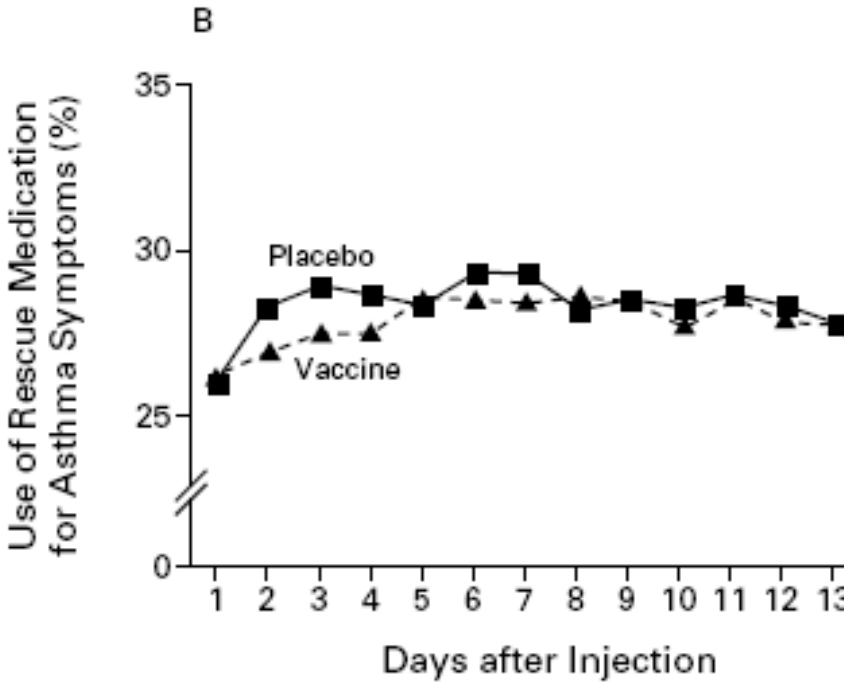
Prevalence of high-risk medical conditions in children aged 6 months to 17 years, United States, 2000.

	Population estimate (95% CI)
Asthma (ever)	8,918,000 (8,429,000–9,409,000)
Asthma (episode in past year)	3,994,000 (3,677,000–4,317,000)
Diabetes	190,000 (89,000–289,000)
Congenital heart disease	141,000 (80,000–208,000)
Other heart condition	789,000 (631,000–953,000)
Sickle cell anemia	162,000 (93,000–231,000)
Cystic fibrosis	7,000 (0–26,000)
One or more conditions (using ever asthma)	10,024,000 (9,502,000–10,546,000)
One or more conditions (using recent asthma episode)	5,192,000 (4,807,000–5,574,000)

Erhart J M et al. J Pediatr. 2004; 144

Daily Mean PEFR (A) and % patients who used rescue medication to control asthma (B) during th 2 wks after vaccine and placebo injections.





NEJM 2001; 345: 15

Clinical and immunological effects of nactivated influenza vaccine in childre with asthma.

Although annual influenza vaccinations are recommended by many authorities, some doctors may be reluctant to vaccinate asthmatic childr because of the risk of inducing bronchial reactivity and exacerbating the asthma.

In asthmatic children with stable asthma, influenza vaccine did not indu significant changes in PC20, FEV1, PEF variability, symptom scores an the Th1/Th2 ratio between day 1 pre-vaccination and day 14 post-vaccination.

Similar results of PEF variability and asthma symptom score were obtained when the analysis was restricted to the day 1 pre-vaccination a day 3 post-vaccination.

Chiu WJ et al. Pediatr Allergy Immunol. 2003; 14:

Pneumococcal vaccine for asthma: Cochrane Database.

Aim. To review trials to determine the efficacy of pneumococca vaccine in reducing mortality or morbidity from pneumococcal disease in asthmatics. Of the 3 papers retrieved, only 1 satisfied the inclusion criteria but its methodological quality was low.

Result. Comparisons in a sub-set of 30 asthmatic children, showed that pneumococcal vaccination decreased the incidence acute asthma exacerbations from 10 to 7 (per child per year).

Conclusion. This review found very limited evidence to support the routine use of pneumococcal vaccine in people with asthma. A randomised trial of vaccine efficacy in children and adults wi asthma is needed.

Sheikh A et al. Cochrane Database Syst Rev. 2002:CD

Effectiveness of influenza vaccination in children with asthma.

Absolute Numbers	Vaccine	Placebo	Ratio V/P (95% CI)	p
Number of episodes				
Influenza-related asthma exacerbations	24	18	1.33 (0.69 to 2.57)	0.39
Influenza-related URT episodes	20	18	1.11 (0.59 to 2.09)	0.75
All asthma exacerbations	1,156	1,155	1.00 (0.88 to 1.13)	0.99
All URT episodes	1,419	1,351	1.05 (0.94 to 1.17)	0.39
Percentage of children with episodes			Odds ratio V/P (95% CI)	
Influenza-related asthma exacerbations	5.8%	4.9%	1.19 (0.61 to 2.31)	0.61
Influenza-related URT episodes	5.5%	5.2%	1.06 (0.55 to 2.05)	0.87
All asthma exacerbations	85.5%	90.1%	0.65 (0.41 to 1.03)	0.06
All URT episodes	92.2%	92.7%	0.92 (0.52 to 1.62)	0.77
Duration of episodes (days) mean, SD			Difference V–P (95% CI)	
Influenza-related asthma exacerbations	9.2 (3.6)	11.2 (5.3)	−2.0 (−4.9 to 0.9)	0.19
Influenza-related URT episodes	8.1 (3.6)	8.0 (3.7)	0.1 (−2.3 to 2.4)	0.95
All asthma exacerbations	6.8 (5.0)	7.6 (5.0)	−0.7 (−1.3 to −0.1)	0.03
All URT episodes	6.5 (4.7)	6.6 (4.0)	−0.2 (−0.7 to 0.3)	0.54
Severity of episodes (symptom score)			Difference V–P (95% CI)	
Influenza-related asthma exacerbations	4.7 (2.7)	6.4 (3.1)	−1.7 (−3.5 to 0.1)	0.08
Influenza-related URT episodes	7.4 (2.7)	7.1 (3.7)	0.4 (−1.7 to 2.5)	0.72
All asthma exacerbations	3.0 (1.7)	3.1 (2.0)	−0.1 (−0.4 to 0.2)	0.42
All URT episodes	3.3 (1.7)	3.4 (2.2)	−0.0 (−0.3 to 0.2)	0.89
Percentage of days with symptoms			Difference V–P (95% CI)	
Asthma symptoms	26 (27)	27 (27)	−0.3 (−4.3 to 3.7)	0.87
URT symptoms	33 (29)	29 (26)	3.8 (−0.3 to 7.9)	0.07

Bueving HJ et al. AJRCCM 2004; 169: 4