

VACCINATION TO REDUCE AMR BURDEN – HOW SHOULD WE USE EXISTING VACCINES? WHAT VACCINES MIGHT WE SEEK TO DEVELOP?

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STRATEGIC FRAMEWORK FOR VACCINES TO REDUCE AMR

- Impact on both AMR burden and antibiotic use may be demonstrable for existing vaccines designed to target AMR bacterial pathogens – e.g. **PCV** impact on AMR in pneumococci (data will be shown in this presentation); impact on AMR of **Hib**; **cholera**; ***Neisseria meningitidis***; **TB** (? any published data to date). New conjugate vaccines to reduce disease, antibiotic use and AMR in **typhoid** fever, **NTS** and **GBS**.
- Impact on antibiotic use of existing viral vaccines (**measles, flu, rotavirus**) – some flu data are published on this; future viral vaccines (**RSV**) may impact antibiotic use
- New human vaccines should be developed to combat the key current AMR ESKAPE pathogens (***Enterococcus faecalis***; ***Staphylococcus aureus***; ***Klebsiella pneumoniae***; ***Acinetobacter baumannii***; ***Pseudomonas aeruginosa***; ***Escherichia coli***). Short term protection against these pathogens in hospitalized patients and also short term protection for neonates allows the possibility to use monoclonal antibodies as well as novel ideas such as DNA vaccines encoding these antibodies. Maternal immunization could also protect neonates from AMR pathogens in the first 3 months of life.
- Animal vaccines have already proven the concept of impact on antibiotic use

COMPETING SELECTION OF PNEUMOCOCCAL CONJUGATE VACCINE AND ANTIBIOTIC USE ON ANTIMICROBIAL RESISTANCE

- Evidence of efficacy and effectiveness of PCV on resistance
- Impact of replacement and continuing selective pressure from antimicrobial use
- PCV given to children successfully eliminates 10 - 13 of 98 known pneumococcal serotypes including 90% of antibiotic resistant strains in vaccinated children, but also reduces resistance in adults by interruption of transmission of antibiotic resistant vaccine type strains
- Antibiotic use continues to select resistance in the remaining 85 - 88 serotypes
- Do replacement antibiotic-resistant strains emerge?

SOUTH AFRICA: VACCINE EFFICACY – RESISTANCE TO ANTIBIOTICS – ALL CHILDREN – INTENT TO TREAT ANALYSIS

	Cases in control group	Cases in vaccine group	Vaccine efficacy	95% confidence interval
Penicillin resistance	21	7	67	19 - 88
Cotrimoxazole resistance	32	14	56	16 - 78
Any resistance	39	17	56	21 - 77

In the cotrimoxazole group 29 and 13 were HIV +ve – VE 55%

Klugman et al, 2003, NEJM, 349,1341-8

CALIFORNIA: REDUCTION IN ANTIBIOTIC USE IN PCV7 TRIAL

“PCV reduced antibiotic prescriptions by **5.4%** (CI 4.0 to 6.7%) in all follow-up starting at Dose 1 and by **5.7%** (CI 4.2 to 7.2%) after the primary series in children followed per protocol.”

PCV reduced the subset of "**second line**" antibiotics by **12.6%** (CI 9.6 to 15.6%) in all follow-up time and by **13.3%** (CI 9.9 to 16.5%) in per protocol follow-up.

“From Dose 1 to age 3.5 years, PCV prevented a total of **35 antibiotic prescriptions per 100 children** vaccinated per protocol.”

Fireman et al, PIDJ 2003; 22:10-16

FINLAND: REDUCTION IN ANTIMICROBIAL PRESCRIBING - PCV10

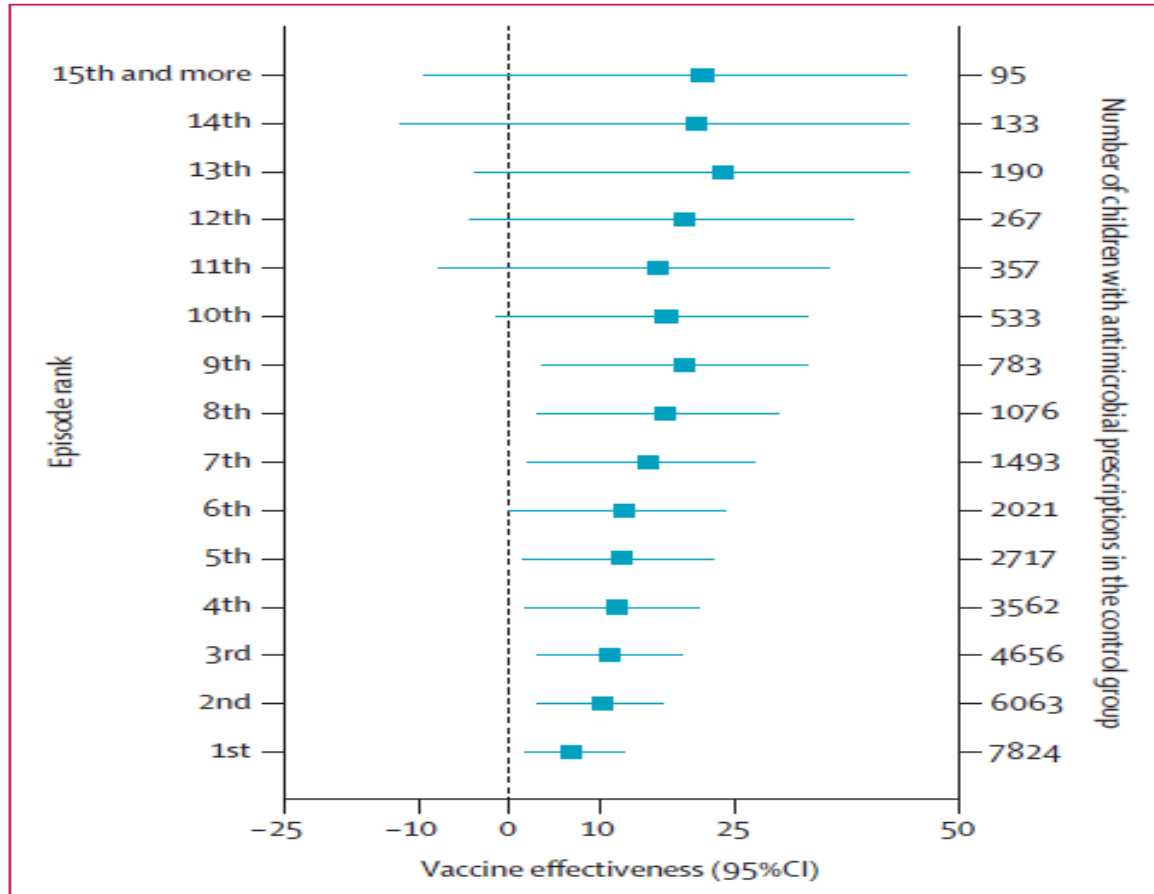


Figure 4: Vaccine effectiveness against outpatient purchases of antimicrobials recommended for acute otitis media by purchase episode rank in infants

20 327 participants in the PHiD-CV10 group and 10 200 in the control group.

Palmu et al, Lancet Infect Dis 2014; 14: 205-12

FINLAND: REDUCTION IN ANTIMICROBIAL RESISTANCE AMONG CHILDREN

Study of the antimicrobial susceptibility of invasive and non-invasive *Streptococcus pneumoniae* (pneumococcus) isolated in the Helsinki Metropolitan Area during 2009-2014 in children and in adults.

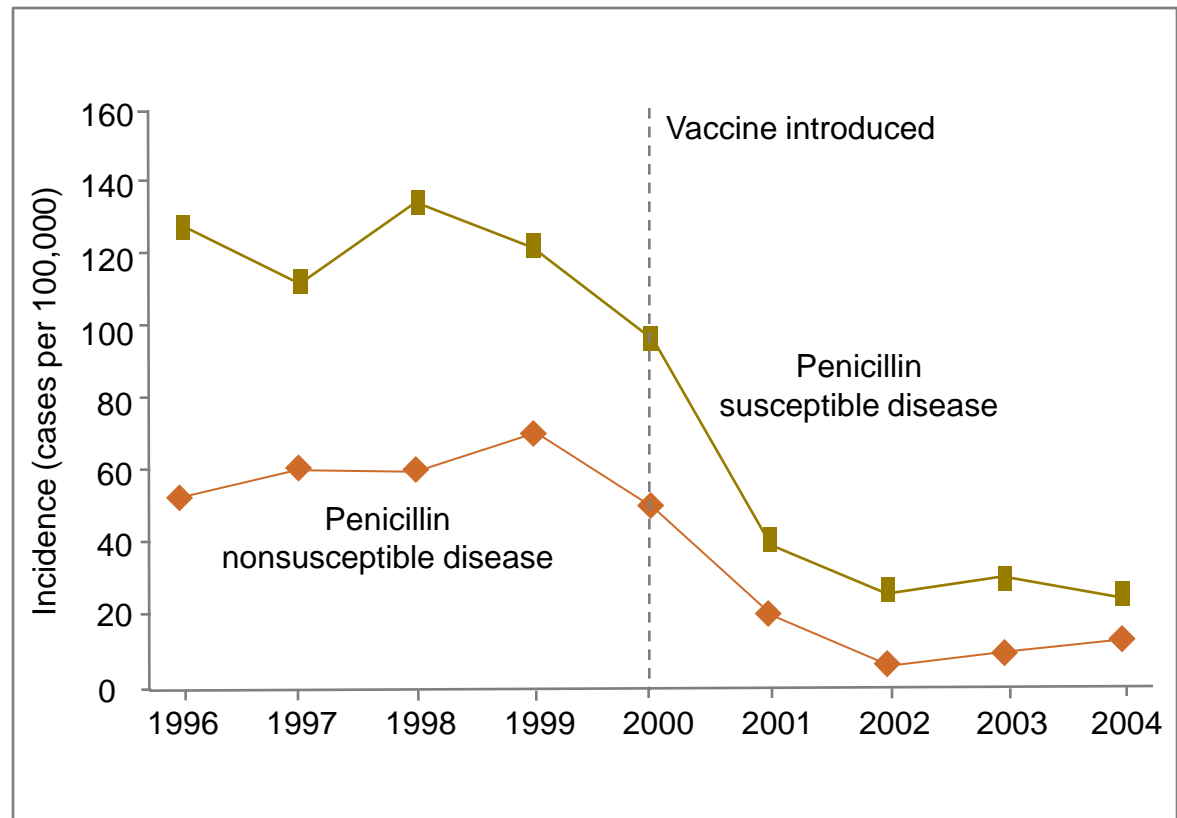
The invasive isolate numbers recovered from patients aged <5 years old declined from 33/228 (15%) in 2009 to 8/208 (4%) in 2014 ($p < 0.001$) and non-invasive isolate numbers declined during the same time period from 221/595 (37%) to 119/432 (28%) ($p < 0.001$).

At the same time, the proportion of penicillin non-susceptible non-invasive isolates in this age group decreased from 25% (56/220) to 13% (15/119) ($p = 0.001$) and multidrug-resistant isolates from 22% (49/220) to 6% (7/119) ($p < 0.001$), respectively.

Among patients aged ≥ 5 years old, the isolate numbers did not show a similar decreasing trend compared to the younger group and, further, the number of non-PCV10 serotype isolates increased in invasive cases.

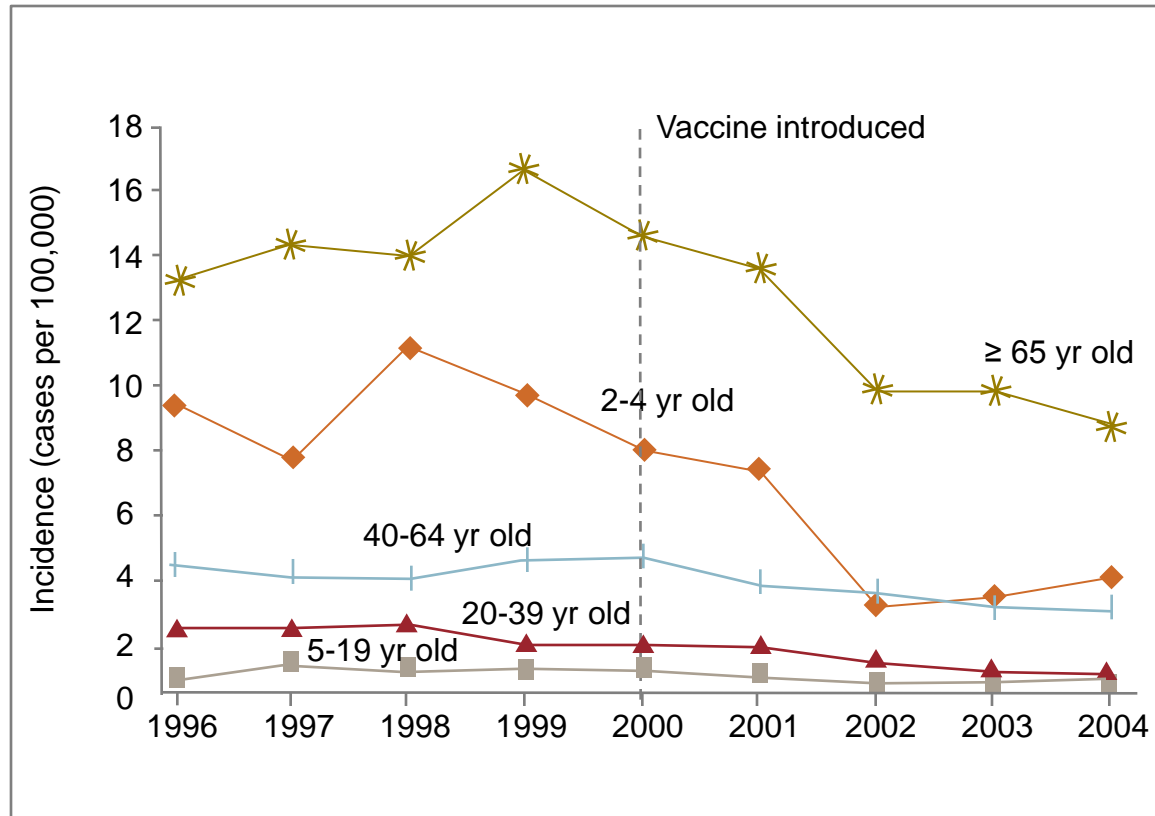
Sihvonen et al, Eur J Clin Microbiol Infect Dis. 2017 Jun 13, epub ahead of print

USA: CHILDREN LESS THAN TWO YEARS OF AGE



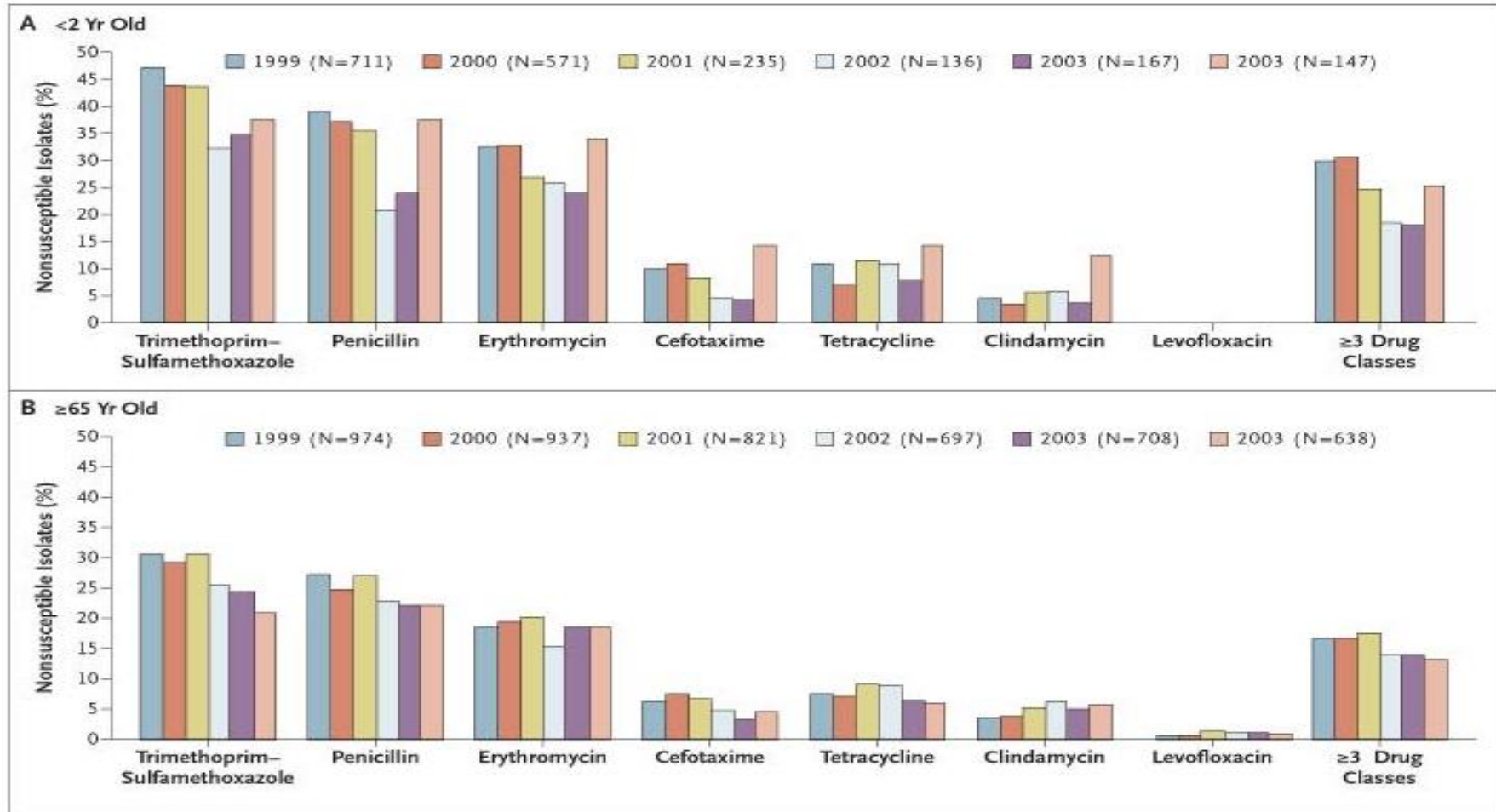
Kyaw et al, NEJM, 2006,354,1455-63

USA: PENICILLIN RESISTANCE IN CHILDREN OVER TWO AND ADULTS



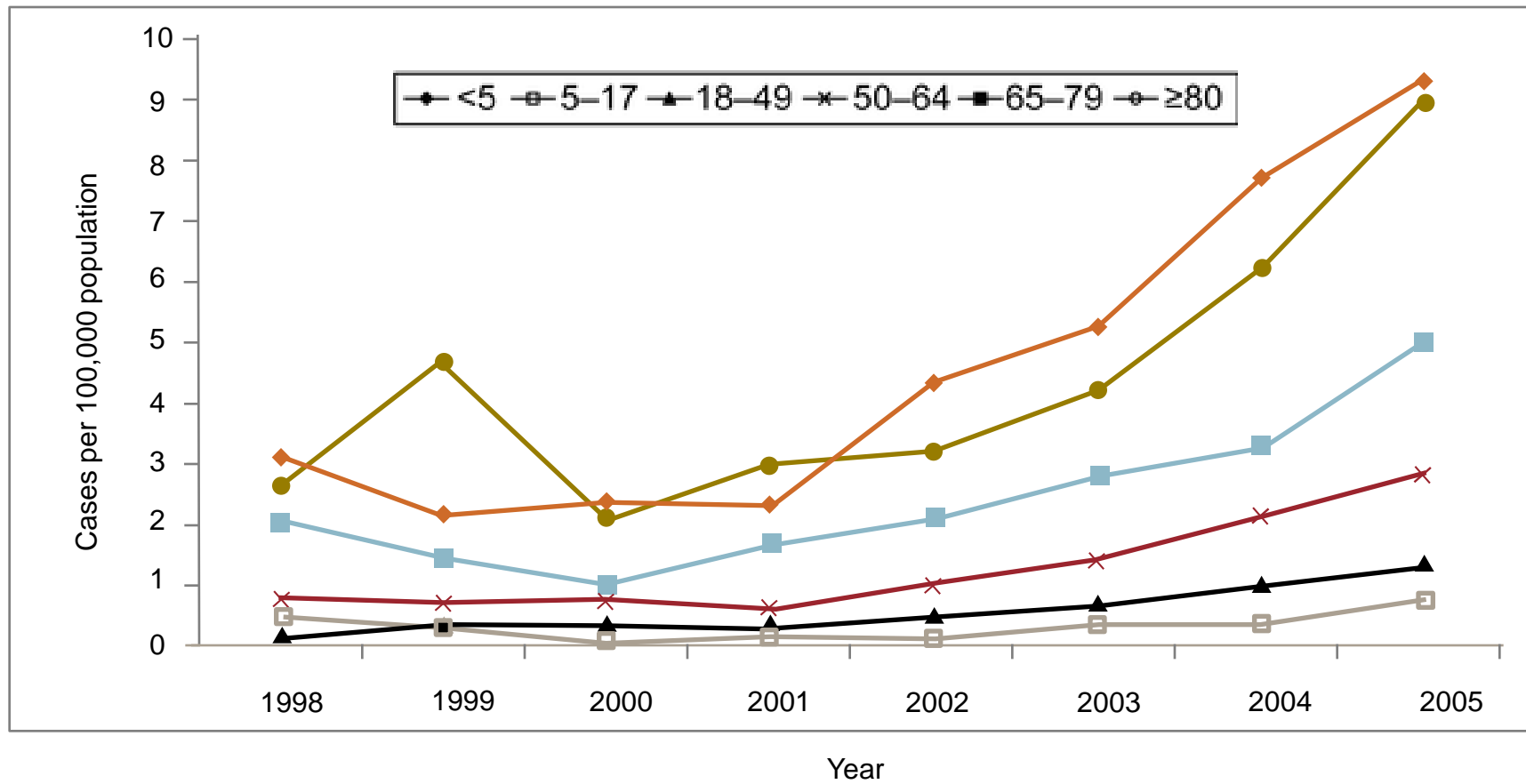
Kyaw et al, NEJM, 2006,354,1455-63

USA: EFFECT OF INTRODUCTION OF PCV-7 ON DRUG-RESISTANT *S. PNEUMONIAE*



Kyaw et al. *N Engl J Med.* 2006; 354:1455–63

USA: SEROTYPE 19A



Moore et al, JID, 2008, 197(7):1016-1027

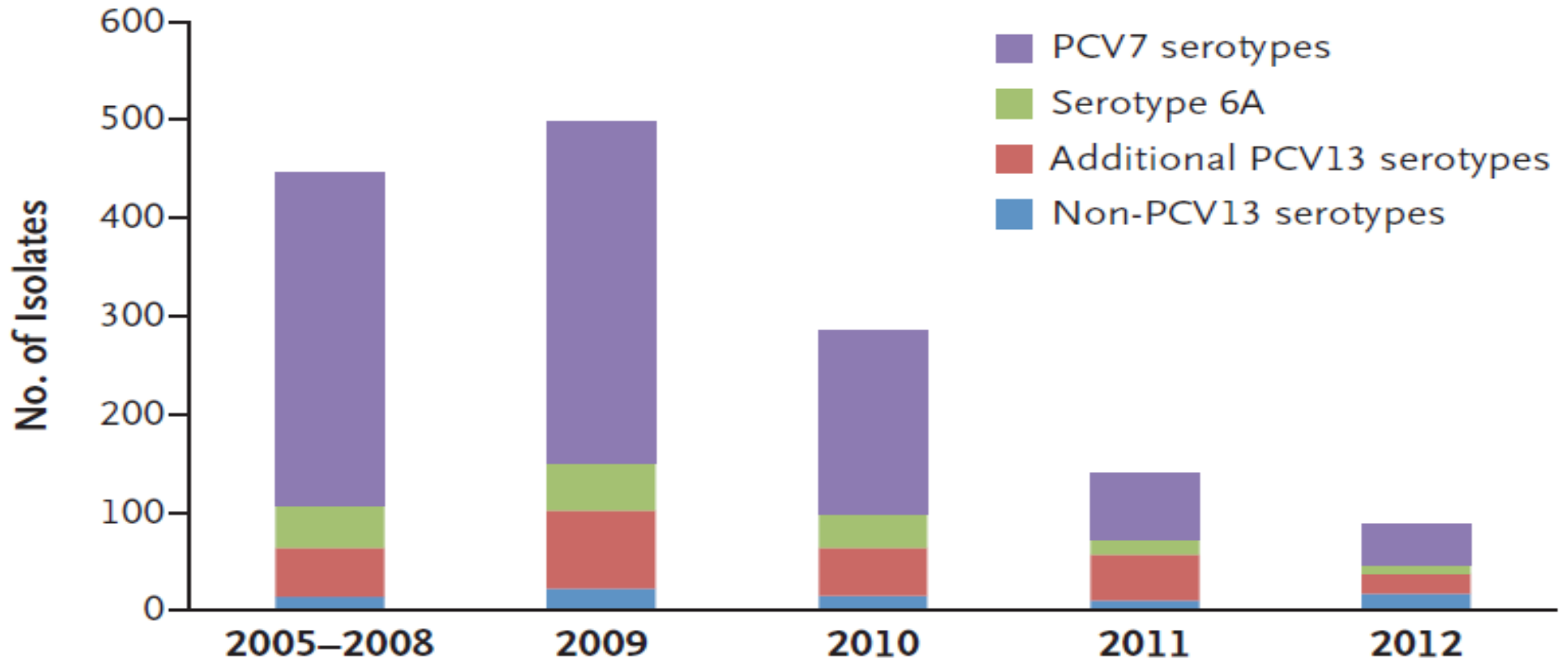
USA: EMERGENCE OF ANTIBIOTIC – RESISTANT SEROTYPE 15A

No.(%) of isolates per year									
Serotype, characteristic	1999	2000 ^a	2001	2002 ^a	2003	2004 ^a	2005	2006	2007
15A									
Patient age, years									
0-4	0	0	0	0	2	1	1	6	12
≥5	8	7	5	22	12	34	62	78	105
Susceptibility to penicillin									
Susceptible	6 (75.0)	3 (42.9)	2 (40.0)	9 (40.9)	4 (28.6)	5 (14.3)	8 (12.7)	11 (13.1)	18 (15.4)
Intermediate resistance	2 (25.0)	4 (57.1)	3 (60.0)	13 (59.1)	10 (71.4)	30 (85.7)	55 (87.3)	72 (85.7)	98 (83.8)
Resistance	0	0	0	0	0	0	0	1 (1.2)	1 (0.8)

a. The surveillance area expanded in 2000, 2002, and 2004. The distribution of penicillin-nonsusceptible isolates over time did not change when the analysis was repeated to include only the continuously participating surveillance areas.

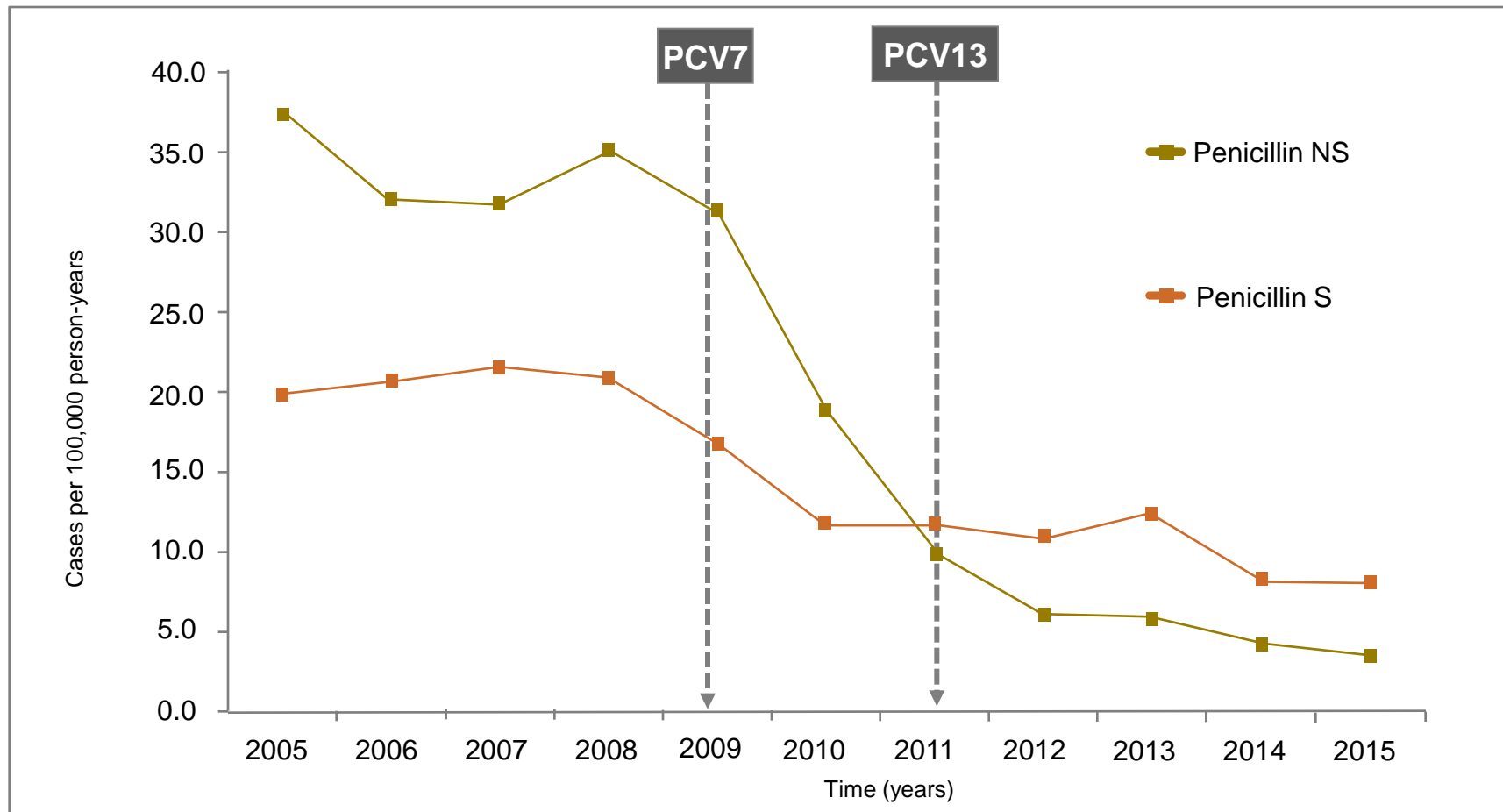
Gertz R E et al. J Infect Dis. 2010;201:770-775

SOUTH AFRICA: IMPACT OF PCV7 (2009) AND PCV13 (2011) ON PENICILLIN INTERMEDIATE AND RESISTANT STRAINS IN IPD < 2 YRS OLD



Von Gottberg et al, NEJM, 2014, 371, 1889 - 1899

SOUTH AFRICA: RATES OF DISEASE CAUSED BY PENICILLIN-SUSCEPTIBLE AND NONSUSCEPTIBLE PNEUMOCOCCAL ISOLATES AMONG CHILDREN <2 YEARS



*PCV7 and PCV13 were introduced in 2009 and 2011, respectively
A von Gottberg, unpublished data.*

INFLUENZA VACCINE IMPACT ON ANTIBIOTIC USE

TABLE 1. Influenza-Related Morbidity in Influenza Vaccinated and Unvaccinated Children With a History of rAOM During the 6-Month Study Period

	Vaccinated Children (n = 90)	Controls (n = 90)	Vaccine Effectiveness* (%)	P
No. patients with at least one AOM episode (%)	49 (54.4)	74 (82.2)	33.8	<0.001
Mean number of AOM episodes ± SD	0.94 ± 1.12	2.08 ± 1.52	54.8	0.03
Mean number of AOM episodes without perforation ± SD	0.39 ± 0.66	1.32 ± 1.49	70.5	<0.001
Mean number of AOM episodes with perforation ± SD	0.56 ± 0.96	0.76 ± 1.18	26.6	0.05
Mean duration of bilateral OME ± SD, mo	13.5 ± 8.24	15.97 ± 6.52	15.5	0.03
Mean duration of unilateral OME ± SD, months	3.00 ± 4.14	1.91 ± 3.79	57.1	0.06
No. of patients with at least one RTI (%)	65 (72.2)	73 (81.1)	10.9	0.16
Mean number of RTI episodes ± SD	1.46 ± 1.32	1.58 ± 1.25	7.6	0.52
Mean number of days with fever ± SD	4.11 ± 4.08	4.53 ± 1.93	9.2	0.37
Mean number of antibiotic courses ± SD	1.47 ± 1.26	2.59 ± 1.72	13.2	<0.001
No. patients on antibiotic prophylaxis (%)	5 (5.5)	11 (12.2)	54.5	0.11
No. days lost from school ± SD	6.62 ± 6.15	7.84 ± 3.24	15.6	0.10

P values were calculated using the χ^2 or Fisher exact test, the *t* test, or Wilcoxon test, as appropriate.

*Vaccine effectiveness = 1 minus attack rate (defined as the event rate divided by the total population) among vaccinated children divided by the attack rate among controls.³⁰

RTI indicates respiratory tract infection; SD, standard deviation.

INFLUENZA VACCINE IMPACT ON ANTIBIOTIC USE

Methods

Phase III, observer-blind, multinational trial in 5 independent cohorts of healthy children 6-35 months (n=12,018) randomized 1:1 to IIV4 (15 µg hemagglutinin /strain) or control during 5 influenza seasons (2011-2014).

Surveillance for PCR confirmed influenza-like episodes (ILE) from 14 days post-vaccine till end of flu season

Results

Overall incidence of RT-PCR confirmed influenza in the whole studied cohorts was 5.9% and 11.5% in the IIV4 and control groups respectively (total vaccinated cohort).

Compared to control, IIV4 resulted in risk reductions of 47% [95% confidence interval (CI): 39%-54%] in general medical visits, 79% [95%CI 53%-91%] in emergency room visits, **50% [95%CI 40%-58%] in antibiotic use**, 54% [95%CI 25%-72%] in parental work absence, and 55% [37%-68%] in missed day care associated with influenza.

Conclusions

Use of IIV4 in healthy young children reduced healthcare utilization, antibiotic use, and parental and child absenteeism.

MEASLES VACCINE COULD PREVENT ANTIBIOTIC USE AND ANTIBIOTIC PROPHYLAXIS

	Co-trimoxazole (n=46)	Placebo (n=38)	Odds ratio† (95% CI)
Main outcome measures			
Pneumonia after inclusion	1 (2)	6 (16)	0.08 (0 to 0.56)§
Admitted to hospital with measles after inclusion	0 (0)	3 (8)	0 (0 to 1.03)
Other outcome measures			
Diarrhoea after inclusion	3 (7)	5 (13)	0.27 (0.04 to 1.39)§
Severe fever after inclusion	6 (13)	11 (29)	0.32 (0.10 to 1.07)
Oral thrush after inclusion	0 (0)	3 (8)	0 (0 to 1.03)
Stomatitis after inclusion	4 (9)	7 (18)	0.37 (0.09 to 1.50)
Conjunctivitis after inclusion	12 (26)	17 (45)	0.36 (0.14 to 0.96)*
Otitis media after inclusion	1 (2)	2 (5)	0.38 (0.02 to 4.42)§

*P<0.05.

†Controlled for age group.

SOME OBSERVATIONS FROM A HUMAN ID DOC ON ANIMAL VACCINES FOR AMR!

- Proof of concept in fish was shown in the reductions in use of antibiotics in salmon farming in Norway after introduction of vaccines for Vibriosis (*Vibrio anguillarum*) and Furunculosis (*Aeromonas salmonicida*). Current vaccines are in development for catfish farming.
- Proof of concept in chickens was demonstrated at this meeting by the remarkable reciprocal relationship between expenditure of Purdue Farms on vaccines (multiple vaccines including live Eimeria coccidial vaccines) versus use of antibiotics; including the concept of maternal immunization (Presentation by Bruce Stewart Brown)
- David Sjeklocha suggested that the lack of vertical integration of cattle farming constrains “preconditioning” with vaccines but more data in this area could certainly show impact on antibiotic free beef in the future
- In consultation with my GF colleagues in the Agriculture group we are supporting vaccine development for Contagious Bovine Pleuropneumonia (*Mycoplasma mycoides subsp mycoides*), Contagious Caprine Pleuropneumonia (*Mycoplasma capricolum subsp. capripneumoniae*), Brucella, bovine TB and East Coast Fever (as an alternative to infection and treatment with tetracyclines)
- My conclusion is that vaccines are an essential part of controlling antibiotic use (and therefore AMR) in animals

CONCLUSIONS

- Antibiotic use drives resistance to multiple antibiotic classes
- Vaccines may reduce resistance but continued use drives resistance in residual strains
- PCV has reduced the burden of antibiotic resistant pneumococcal disease globally
- Replacement disease has eroded some of these gains by the selection of resistance in replacement strains
- Influenza vaccination can reduce antibiotic use for otitis media which is the leading indication for antibiotics in children
- Measles vaccine prevents both antibiotic use for pneumonia complications and the need for antibiotic prophylaxis
- There is a need to consider the development of vaccines and monoclonal antibodies to prevent the ESKAPE AMR pathogens
- Vaccines should be a critical component of managing AMR in both humans and animals