



48th Annual **ICAAC***/**IDSA** 46th Annual Meeting

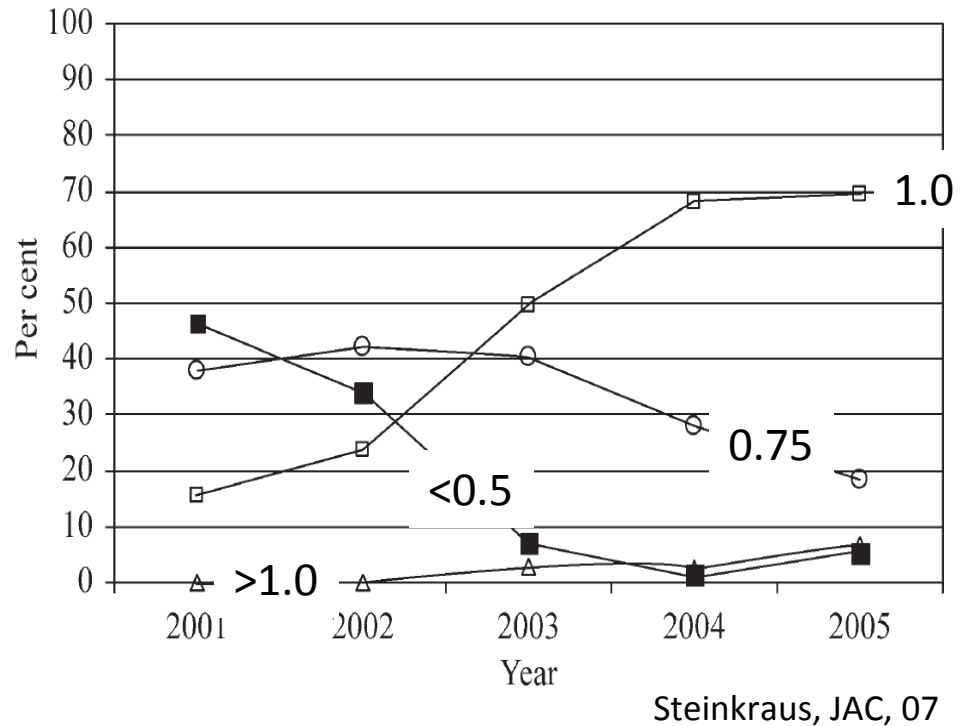
Washington, DC ~ October 25-28, 2008

A Joint Meeting of ASM and IDSA

Staphylococcus aureus

Vancomycin MIC creep in *S. aureus* : published data

- Studies reporting vanco MIC creep with MRSA produced conflicting results mostly due to MIC statistic used
- Some studies reporting vanco susceptibility changes in single centres over time period '00–'05
- More favourable outcome if vanco MIC <0.5



Vancomycin MIC creep in *S. aureus* : epidemiology

- MIC Creep Analysis in a Longitudinal Collection of Community-Associated (CA) and Nosocomial-Associated (NA) MRSA (**LOLANS et al**)
- **Methods:** 295 clinical MRSA (collected during 1990-2000 and 2004-2007)
- **Results:** Six time periods were assessed (1990-1997, 1998-2000, 2004, 2005, 2006 and 2007). CA types account for the highest proportion of isolates (isols) in each period (44 - 76%). Overall, the V GM MIC rose (1.2-fold) from 1.25 to 1.48. In USA100, V GM MICs remained stable. In USA300/400, similar V GM MICs (1.13-1.21) were seen up to 2004, rising to 1.43 in 2005 ($p < 0.001$, 2005 v 1990-2000 and 2004), further increasing to 1.5 by 2007 ($p < 0.001$, 2006-2007 v 1990-2000 and 2004). Increases reflect a change in the percentage (%) of isols with an MIC = 1.5ug/ml (41.7% in 2004 to 81.6% in 2005 to 100% in 2007, $p < 0.001$). The overall D GM MIC showed no consistent upward trend, but varied (0.58-0.81) depending on the time period. The USA100 D GM MICs, however, were rather constant (0.56-0.61). Variation in the USA300/400 D GM MIC paralleled that in the overall D GM MIC, and a decline was seen in the % of isols with an MIC ≤ 0.75 ug/ml (100% in pre-2001 to 80-90% in 2004-2006 to 44.4% in 2007). The overall L GM MIC increased (1.6-fold) through 2006, but declined 1.4-fold in 2007; there was no consistent trend for clonal types. No striking increase appeared in the overall QD GM MIC, but the USA100 QD GM MIC increased from 0.28 to 0.4.
- **Conclusions:** Gradual upward MIC creep occurred in CA MRSA and played a key role in overall MRSA GM MICs for V and D.

Vancomycin MIC creep in *S. aureus* : epidemiology

- Vancomycin MIC Creep Occurs in *S. aureus* Without Regard for Methicillin Susceptibility (**PALAVECINO et al**)
- Single university hospital USA

Year	No. strains	Number (%) of <i>S aureus</i> tested and VAN MICs			No. MSSA/MRSA with MIC ≥ 2 $\mu\text{g/ml}$
		≤ 0.5 $\mu\text{g/ml}$	1 $\mu\text{g/ml}$	≥ 2 $\mu\text{g/ml}$	
2002	2375	1829 (77)	539 (23)	7 (0.3)	4/3
2003	2409	1248 (51)	1154 (48)	7 (0.3)	6/1
2004	2774	964 (35)	1774 (64)	32 (1)	18/14
2008	690	6 (1)	440 (64)	244 (35)	102/142

- **Conclusions:** shift in the VAN MIC distribution from 2002-2004 to 2008 both in MSSA and MRSA

Vancomycin MIC creep in *S. aureus* : methodological aspects

- Differences in Vancomycin MICs with Methicillin-Resistant *Staphylococcus aureus* (MRSA) Isolates Based Upon Susceptibility Test Method (**PRAKASH et al**)
- Methods** 101 MRSA isolates recovered between 2002 and 2006 from bacteremic patients with MICs in the range of 0.5 to 2 µg/mL tested by the CLSI broth microdilution and agar dilution methods and by E tests using two different brands of Mueller-Hinton agar plates (BBL, Remel).

Number of isolates (%) with MIC (µg/mL) determined by:				
Vancomycin MIC (µg/mL)	Broth microdilution	Agar dilution	E test (Remel agar)	E test (BBL agar)
0.5	21 (20.8)	1 (1)	0 (0)	0 (0)
0.75			1 (1)	1 (1)
1	77 (76.2)	88 (87)	11 (10.9)	1 (1)
1.5			69 (68.3)	62 (61.4)
2	3 (2.97)	12 (11.9)	20 (19.8)	37 (36.6)
Modal MIC (µg/mL)	1		2	

- Conclusion** : Vancomycin MICs generated by the E test method were consistently higher than CLSI broth or agar dilution methods.

Vancomycin MIC creep in *S. aureus* : methodological aspects

- Lack of Heteroresistance among *Staphylococcus aureus* Isolates with Vancomycin MICs of 2 µg/mL by Automated Testing (**SATOLA et al**)
- **Methods:** 30 MRSA blood isolates collected at a tertiary care hospital from 3/26/08 - 7/6/08 with VA MICs of 2 µg/mL were evaluated. Initial susceptibility testing was done on the MicroScan® Walkaway® 96 (Siemens Healthcare Diagnostics, Inc., Deerfield, IL) identification/susceptibility system using the POS Combo29 microbroth dilution panel with the PROMPT™ inoculation method. Etest® (bioMérieux, Durham, NC) and reference broth microdilution MICs were determined using standard CLSI methods. PAP profiling was performed using BHI agar with VA ranging from 0.5 to 8 µg/mL, and SA strains ATCC 29213, Mu3, and Mu50 as controls; log₁₀ viable counts were plotted against VA concentrations to calculate area under the curve (AUC). Isolates with an AUC ≥ 0.9 compared to Mu3 (a hVISA strain) were defined as hVISA.
- **Results:** Vancomycin MICs for 30 invasive MRSA isolates were 2 µg/mL by MicroScan® but ranged from 1.0 to 1.5 µg/mL (mode = 1.5) by the standard Etest® protocol and 0.5 µg/mL to 1.0 µg/mL (mode = 1) by reference broth microdilution. By PAP-AUC, the mean ratio of test isolate to Mu3 was 0.50; none of the test isolates had AUC ratios ≥ 0.9, the threshold for the hVISA phenotype.
- **Conclusions:** SA isolates with MIC = 2 µg/mL by automated MicroScan® testing had lower MICs by Etest® and microbroth dilution and showed no evidence of heteroresistance to vancomycin by PAP. The susceptibility testing method must be considered when evaluating vancomycin treatment outcomes.

Vancomycin MIC creep in *S. aureus* : clinical aspects

- Relationship of MIC to Vancomycin on Outcome of Methicillin-Resistant *Staphylococcus aureus* Health Care-Associated and Hospital-Acquired Pneumonia (HAQUE et al)
- **Methods:** 2 yr retrospective study of consecutive patients hospitalized for therapy of MRSA HCAP or hospital acquired pneumonia (HAP) in 4 academic health care centers. MICs to vancomycin were done by Etest and heteroresistance by macrodilution Etest.
- **Results:** 132 patients were evaluated for 28 day all cause mortality. Underlying disease was similar in survivors vs. non survivors except: cardiac disease 22% vs. 42% (p=.016), diabetes 18% vs. 38% (p=.011). 28 day all cause mortality increased as MICs to vancomycin increased: mortality at 28 days for MIC 0.75 mcg/ml: 0% (n=0), MIC 1.0 mcg/ml: 13% (n=4), MIC 1.5 mcg/ml: 34% (n=24), MIC 2.0 mcg/ml: 50% (n=13), MIC 3.0 mcg/ml: 100% (n=1) (p=0.013). 26 isolates were USA 300; 88% (n=23) survived. Rates of mortality amongst vancomycin heteroresistant isolates were 30% vs. 33% for non heteroresistant isolates (p=NS). Rates of mortality amongst mean vancomycin trough <10 mcg/ml were 38% (n=6), vancomycin trough 10-14.9 mcg/ml: 14% (n=5), vancomycin trough 15-20 mcg/ml: 45% (n=18) (p=0.012). AUC/MIC in patients alive at 28 days was 367.6, non survivors 285.0 (p=NS).
- **Conclusion:** These data suggest that patients with an increasing MIC to vancomycin within the susceptible range have higher 28 day mortality in MRSA pneumonia. It is important to obtain MICs to vancomycin when using it for HAP and HCAP.



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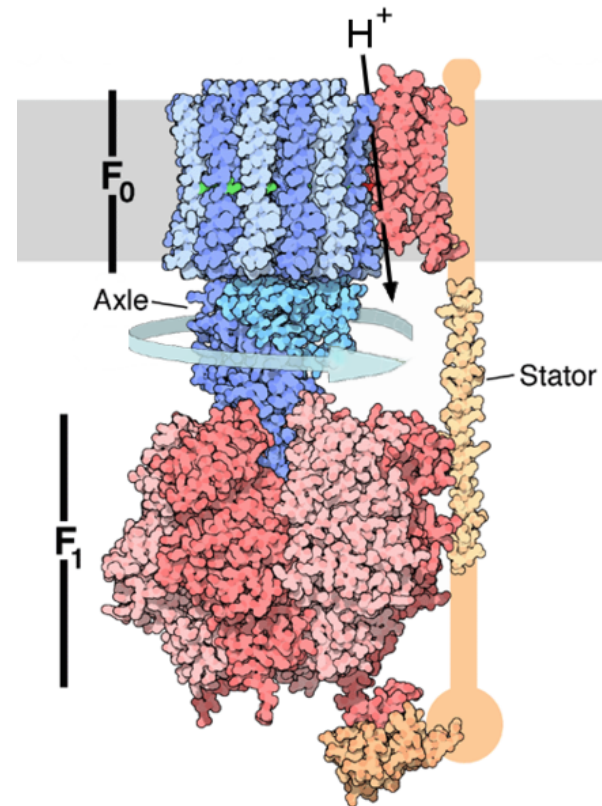
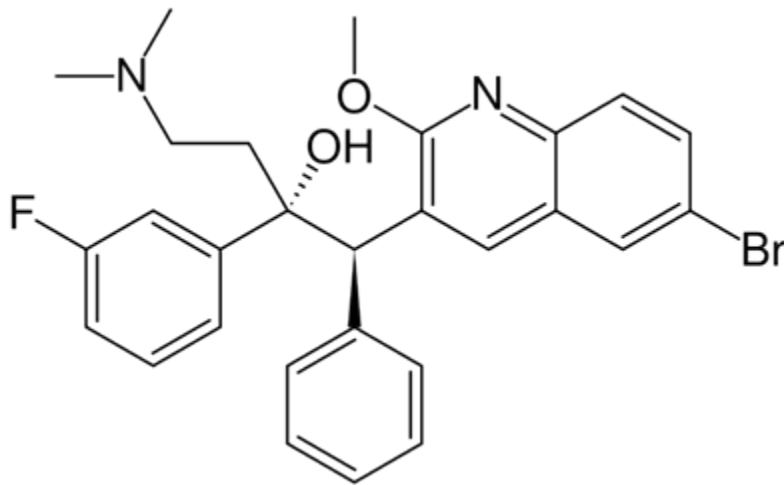
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Tuberculosis

Diarylquinolines for tuberculosis

TMC207 (R207910)

- Described first at 2004 ICAAC
- broad antimycobacterial spectrum
- Inhibits mycobacterial ATPsynthase c subunit



Diarylquinolines for tuberculosis

- published data:
 - Mechanism of action
 - good in vitro activity on drug-sensitive /resistant Mtb (MIC: 0.03) and dormant Mtb
 - Excellent activity in murine tuberculosis as 1st line and in combination with 2nd line drugs
 - Pharmacokinetic/tolerance phase IIb open label in treatment-naive patients

Diarylquinolines for tuberculosis

- New data:
 - In vitro :
 - Activity of TMC207 Against *Mycobacterium avium* In Vitro
 - Mouse model :
 - Early and Late Bactericidal Activity in Murine Tb
 - Sterilizing Activity of a Second Line Regimen Including TMC207 in Murine Tb
 - Activity of TMC207 Against *Mycobacterium avium* in Murine Tb
 - Clinical trial :
 - Interim Analysis of a Double-Blind, Placebo-Controlled Study with TMC207 in Patients with Multi-Drug Resistant (MDR) Tuberculosis

Diarylquinolines for tuberculosis

- Activity of TMC207 Against *Mycobacterium avium* In Vitro and in the Mouse Model (LOUNIS et al),
- **Methods:**
 - activity of TMC207 (TMC) against *M. avium* in vitro and in the C57Bl/6J mouse model in monotherapy or in combination with clarithromycin (CLA) and/or amikacin (AMK).
- **Results:**
 - in vitro, TMC207 displayed a bacteriostatic activity against *M. avium* strain 101 with an MIC of 0.01 and an MBC of >128 mg/l
 - in vivo, all treated mice were still culture positive after 4 months of treatment. Regimens including AMK had the greatest bactericidal activity (-4.5 log₁₀ CFU), followed by CLA (-2.99 log₁₀ CFU) and TMC (-1.4 log₁₀ CFU)
- **Conclusions:**
 - Despite having a similar MIC, the in vivo efficacy of TMC207 against *M. avium* is much less dramatic compared to the efficacy against *Mycobacterium tuberculosis*, underlining the importance of a bactericidal rather than a bacteriostatic activity.

Diarylquinolines for tuberculosis

- Sterilizing Activity of 2nd Line Regimen Including TMC207 (J) in Murine Tuberculosis (IBRAHIM et al)
- **Background:** WHO recommends combining amikacin (A), ethionamide (Et), moxifloxacin (M), and pyrazinamide (Z) for TB patients who cannot receive rifampin (R) and isoniazid (H). 9 months treatment is needed in mice to achieve culture negativity with this regimen.
- **Methods:** Positive controls were 6 months daily RHZ (WHO standard regimen), 6 months AEtMZ, and 4 months of JRZ (best J containing regimen in a previous study, Ibrahim 47th ICAAC). Test regimens were 4 and 6 months of JMZ, and 6 months JAEtMZ. Culture negativity of lungs was assessed at the end of treatment. Relapse rates were assessed 3 months after treatment end.
- **Results:** Culture negativity was obtained after 4 months for JRZ and JMZ regimens, and after 6 months for RHZ, AEtMZ and JAEtMZ.
- **Conclusion:** sterilizing activity of the 4-month JRZ regimen was confirmed. The JMZ regimen, omitting both R and H, was as effective after 6 months as the standard RHZ regimen. Adding TMC207 to AEtMZ improved the efficacy of this second line regimen. Both JMZ and JAEtMZ may shorten treatment duration of MDR-TB.

Number of relapsing mice / total mice, 3 months after treatment completion		
Regimen	4 mo	6 mo
2RHZ+4RH		3/27
2JRZ+2JR	3/19	
2JMZ+4JM	8/20	2/19
2AEtMZ+4EtM		11/19
2JAEtMZ+4JEtM		5/18

Diarylquinolines for tuberculosis

- Early and Late Bactericidal Activity of TMC207 in Murine Tuberculosis (IBRAHIM et al)
- **Background:** In an early bactericidal activity (EBA) study in humans, J at 400mg/day did not demonstrate activity before day 4, while rifampin (R) and isoniazid (H) did. We evaluated the EBA of J in murine TB. In a second experiment, we evaluated the late bactericidal activity (LBA) of J by measuring its ability to kill bacilli persisting after initial intensive phase of one month with WHO standard regimen.
- **Methods:** In the EBA study, mice were treated with H, pyrazinamide (Z) or J for up to 2 months. In the LBA study, mice were treated with RHZ combination for 1 month followed by 2 months of monotherapy with H, R, Moxifloxacin (M) or J.
- **Results:** In the EBA study, the bactericidal activity of J started after 4 days (- 1.3 log₁₀ CFU), while H did not demonstrate efficacy until after 2 weeks. J was not significantly more active than H in the first week of treatment. In the LBA study, 2 months of J monotherapy was able to reach 100% culture-negativity, compared to 50% for rifampin, 38% for moxifloxacin and 12% for isoniazid.
- **Conclusion:** results of mouse EBA study are consistent with those of earlier in vitro data in that the activity of TMC207 starts after 4 days of treatment.
During the continuation phase of treatment, J has bactericidal activity superior to that of existing antituberculous drugs.

Diarylquinolines for tuberculosis

- Interim Analysis of a Double-Blind, Placebo-Controlled Study with TMC207 in Patients with Multi-Drug Resistant (MDR) Tuberculosis (**DIACON et al**)
- **Methods :**
 - phase IIB trial in 47 patients with newly diagnosed MDR TB
 - 5-drug MDR regimen (KAN+OFX+ETA+TER+PZA) plus either placebo (n=24) or TMC207 (n=23) for 8 weeks and then continued with the MDR regimen
- **Results:**
 - no serious adverse events
 - 47.5% of (KAN+OFX+ETA+TER+PZA) plus TMC207 treated patients became culture negative versus 8.7% treated with (KAN+OFX+ETA+TER+PZA) plus placebo (p=0.003) within 8 weeks.

New diagnostics for tuberculosis

- Continued need for rapid, cheap detection methods of new tuberculosis cases, detection of cases of latent tuberculosis
 - Interferon- γ -release assays (IGRA's- Quantiferon-TB, T-SPOT) as alternatives to tuberculin skin test (TST)
 - Published meta-analysis (Pal, Ann intern Med 08):
 - IGRA 's have excellent specificity unaffected by BCG vaccination (contrary to TST)
 - IGRA's (and TST) have variable sensitivity (test, population dependent)

New diagnostics for tuberculosis

- Accuracy of QuantiFERON-TB Gold Test vs. Tuberculin Skin Test to Detect Latent Tuberculosis Infection in HIV Positive Individuals in Iran (**MARDANI et al**)
 - cross-sectional study in 50 HIV + patients in Tehran in 2007
 - patients had neither history of previous TB nor were currently affected by active TB, all had BCG vaccination
 - Of 14 positive TSTs, 12 had positive QFT, 1 was TST positive but QFT negative, 1 was QFT indeterminate
 - Of 36 negative TSTs, 18 had negative QFTs, 8 had positive tests and 10 indeterminate results
 - Agreement between TST and QFT was 76.9%
- TSPOT.TB: Spotting TB in HIV Patients (**SATTAH et al**)
 - Ongoing, prospective cohort study with 34 HIV+ patients : 8 with active TB, 12 with previously treated pulmonary TB, 9 with NTM infections, 2 LTBI and 3 TB suspects.
 - T-SPOT.TB positive in 8 of 8 HIV+ patients with confirmed active TB disease (TST : negative in 4 of 6, 3 of 8 smear negative) regardless of CD4 T cell counts
 - T-SPOT.TB was negative in 7 of 9 patients with NTM infections

New diagnostics for tuberculosis

- QuantiFERON-TB Gold In Tube for Diagnosis of *Mycobacterium tuberculosis* Infection in Children with Household Tuberculosis Contact (KASAMBIRA et al)
 - Results from interim analysis of 40 adult cases and 60 pediatric contacts (median age : 5.6 yrs; 95% vaccinated with BCG; 10% HIV-positive)
 - TB is common among S. African children who live with adults with active TB. 12% of children had indeterminate QGIT results; agreement between QGIT and TST was moderate (73%)
- Cost-Effectiveness of QuantiFERON-TB Test versus Intradermoreaction in the Diagnosis of Latent Tuberculosis Infection Around a Case of Active Tuberculosis (S. DEUFFIC-BURBAN et al)
 - decision analysis model to compare the strategies for 15,000 BCG-vaccinated French adults in close contact with a TB case each year, and who do not have TB disease
 - in France, for the diagnosis of LTBI after close contact with a TB case, the TST strategy is less cost-effective than the QFT strategy. QFT strategy was found to be associated with higher costs compared to TST/QFT strategy. It was however more effective and reasonably cost-effective

New diagnostics for tuberculosis

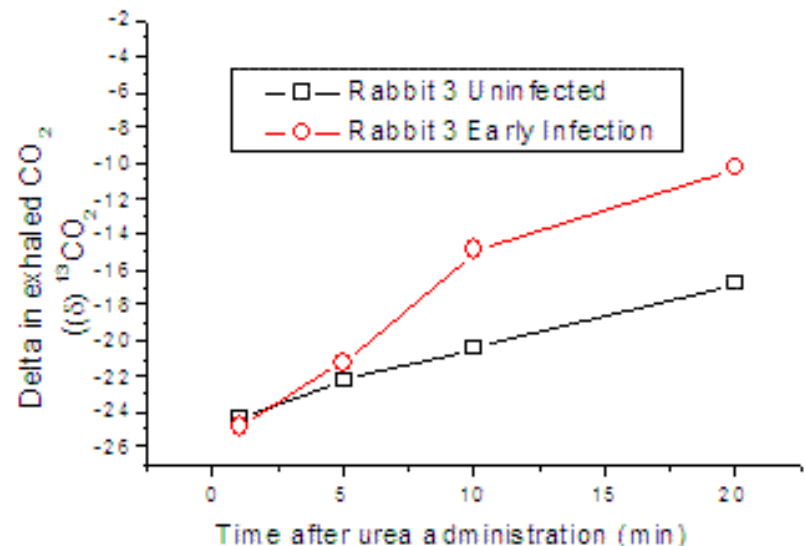
- Urea Breath Testing as a Rapid Diagnostic in the Testing of *M. tuberculosis* (JASSAL et al)

- **Methods:**

- Rabbits infected with *M. bovis*
- Instillation 20-35mg of [¹³C]-urea
- Exhaled air analyzed prior to and during, infection

- **Results:**

- No adverse effects
- increase in ¹³CO₂ both early and late in disease within 10 to 20 minutes of administration



New diagnostics for tuberculosis

- Clinical Evaluation of a Rapid Serologic Immunochromatographic Method in the Diagnosis of *Mycobacterium tuberculosis* (**BANJOKO**)
- **Background:** There is currently no single diagnostic method which can detect all tuberculosis (TB) cases. Therefore diagnosis can take several days and weeks and involve expensive, invasive and complex procedures.
- **Methods:** 100 clinically diagnosed tuberculosis patients (Test) attending Jericho Chest Clinic, Ibadan, Nigeria and 100 tuberculosis free healthy individuals (Control) were recruited for the study after ethical clearance and patients' consent were obtained. Rapid serological test based on immobilized antigens embedded on immunochromatographic strips obtainable from (AMRAD, Australia) were performed on all test and control subjects. Controls were selected using clinical examination and X ray while the TB patients were confirmed positive using chest X-ray, smear microscopy and microbial culture.
- **Results:** Sensitivity, specificity, negative predictive and positive predictive values of this serological method respectively were 78.0%, 94.0%, 81.0% and 92.9%.
- **Conclusions:** This result underscores the need to include serological method as a routine in the diagnosis and management of tuberculosis at the point of care particularly in poor resource settings and developing economies.



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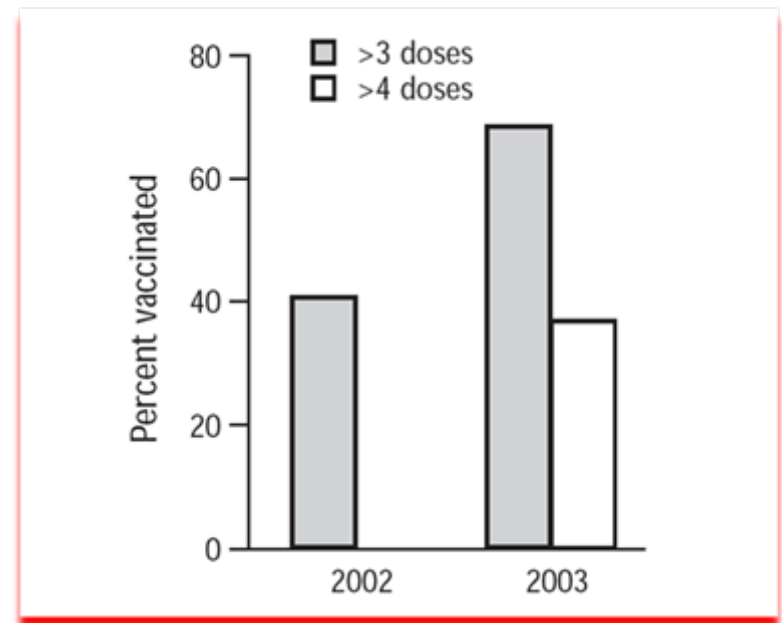
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Streptococcus pneumoniae

Effects of the introduction of PCV-7

- USA: feb 2000 – licensed for children up to 5 yrs – recommendation for use in all children < 2 yrs
- Included are : 4, 6B, 9V, 14, 18C, 19F and 23F
- PCV-7 Vaccination in 19 to 35 months-old



Effects of the introduction of PCV-7

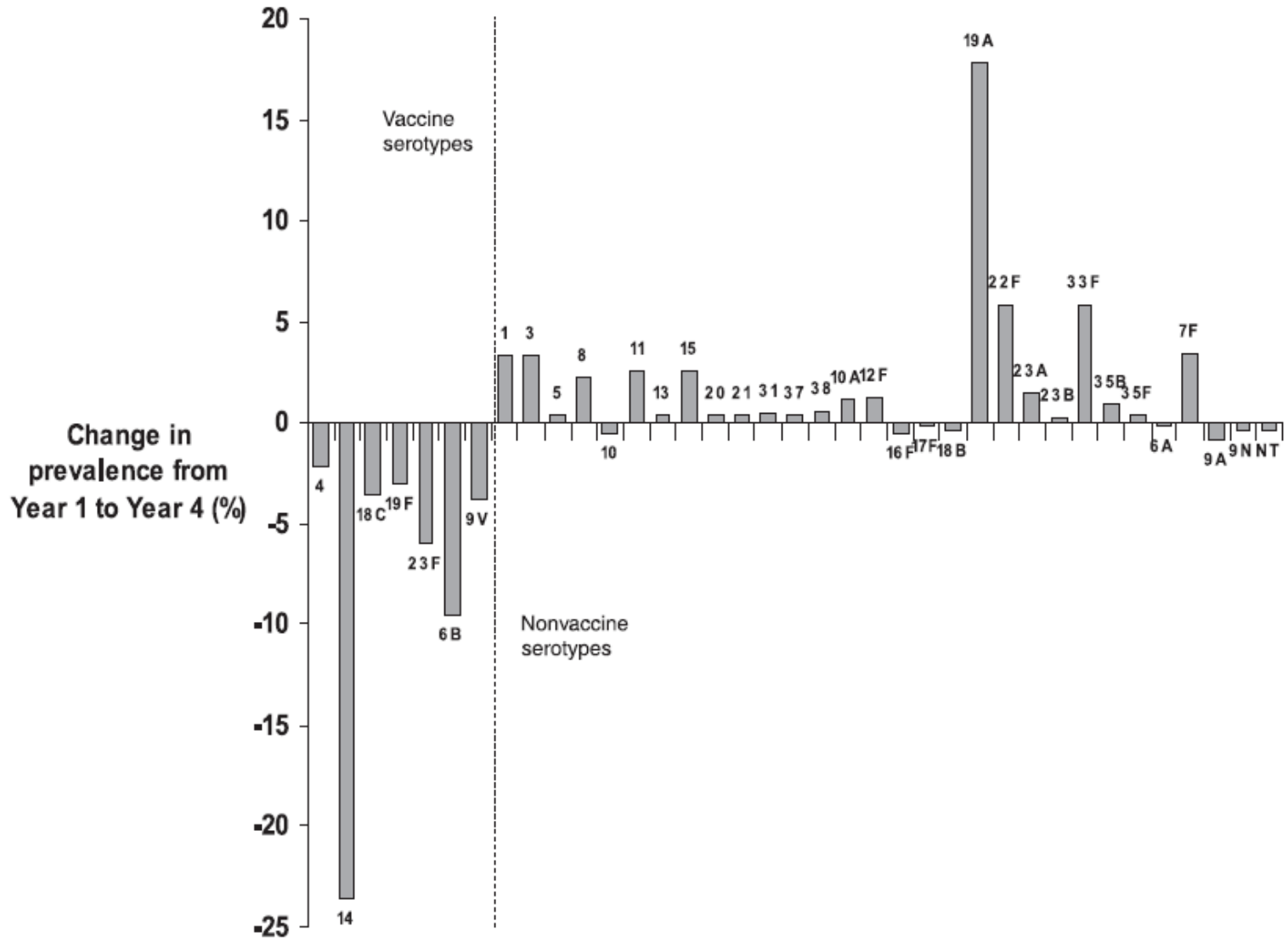
- **No impact on overall nasopharyngeal carriage rate in children but:**
 - reduction of vaccine-type strains / increase of non-vaccine-type strains / reduced carriage of V-types in siblings of vaccinees
 - Most resistant pneumococci encapsulated by serotypes included in PCV-7
 - Early reports: reduction of carriage of AB resistant strains
 - Later reports: no change in carriage AB-resistant strains but AB-resistant V-types replaced by AB-resistant NV-types

Effects of the introduction of PCV-7

- **Effect on disease-related pathogens in children**
 - Serotype switch to NV-types
 - PCV-7 coverage decreases : '00-'01: 65.5% → '03-'04: 27%
 - Increased AB-resistance in NV-types
 - Decrease in overall (V + NV-types) resistance mainly due to elimination resistant V-types
 - Increased resistance in respiratory (colonising/ non-invasive) NV-types
 - Particularly increased Ery –resistance in 19A

Serotype prevalence children 0-14 yrs

PROTEKT US: '00-'01 vs '03-'04 – blood isolates



% resistance NV- types - PROTEKT US

	blood		Non-blood	
	'00-'01	'03-'04	'00-'01	'03-'04
Pen-R	12.5	7.6	12.7	16.7
Pen-I	15.4	23.8	20.1	31.5
Ery	20.6	22.4	21.2	31.6
MDR	20.6	16.7	24.6	31.6

Effects of the introduction of PCV-7

- **Impact on invasive pneumococcal disease - USA**
 - Statistically significant declines in incidence of IPD in young children, children and adults
 - major impact of vaccine (70% of V-type prevented IPD) via effect on pneumococcal transmission (herd- immunity)
 - Increase in IPD by NV-types in certain age-groups/disease syndromes but small compared to overall disease reduction

Effects of the introduction of PCV-7: changes in *S pneumoniae* epidemiology

- Resurgence of Penicillin and Erythromycin Resistance 7 Years After the Conjugate Pneumococcal Vaccine Introduction (**MERA et al**)
- **Methods:** 56,693 isolates from '96-'07 surveillance database (Eurofins Medinet)
- **Results:**
 - Pen and ery resistance increased since 1996 and peaked in 2001 (24.8% and 38.6% respectively). Subsequently they declined to their lowest level in 2004 (16% and 31.7% respectively). There was a rebound to 18.2% for pen and 37.1% for ery in 2007.
 - shape of the curve is much steeper for children < 5 years old, with deeper troughs and larger rebounds
 - The decline in resistance was more marked in the New England and the Pacific census regions, and the rebound more pronounced in the South Atlantic region.
 - Blood and nasopharyngeal isolates had significantly flatter curves, otitis media isolates had very pronounced rebounds
- **Conclusions:** The rebound in resistance levels was consistently observed across all factors, but was more marked in the South Atlantic census region, children and otitis media isolates. The effect of the vaccine on lowering rates of resistance has begun to wane as the non-vaccine serotypes slowly acquire resistance.

Effects of the introduction of PCV-7: changes in S pneumoniae epidemiology

- *S. pneumoniae* Serotype 6C: A Recently Recognized Serotype (JACOBS et al)
- **Background:** There are now 91 pneumococcal serotypes since the recognition in 2007 of 6C, which cross-reacts serologically with 6A. Serotype 6C results from a change in the *wciN* gene region of the capsular locus of 6A.
- **Methods:** Isolates of serotype 6A in various collections were recovered. Serotype 6C was differentiated from 6A by multiplex PCR. Antimicrobial susceptibility was performed by CLSI broth microdilution, and PFGE was performed on selected isolates.
- **Results:** Sixty-one serotype 6C isolates were found: 31 of 102 Cleveland isolates collected 1979-2007, 19 of 39 pediatric isolates collected nationwide 2005-2006, and 11 isolates from Boston collected in 2006. The earliest isolate was recovered in 1989, with 4 recovered prior to 2000, the year of introduction of the conjugate pneumococcal vaccine, and the remainder thereafter. Sources of isolates included blood (5), lower respiratory (27), sinus (5), ear (3) and nasopharynx (19), recovered from 50 children and 11 adults. Pediatric isolates were found in all 6 major US regions. Antimicrobial susceptibility showed 22 isolates nonsusceptible to penicillin, macrolides and SXT, 6 with other resistance patterns, and 31 fully susceptible. PFGE of 26 isolates showed multiple patterns, with few clusters containing 2-5 related strains.
- **Conclusions:** This study documents the occurrence, nationwide distribution, and diversity of the recently recognized serotype 6C, with 57 of 61 isolates isolated after the introduction of the conjugate pneumococcal vaccine.

Effects of the introduction of PCV-7: changes in *S pneumoniae* epidemiology

- Emergence of *Streptococcus pneumoniae* Serotype 19A as Cause of Complicated Necrotizing Pneumonia in Children (**WOOTTON et al**)
- **Background:** We report 4 children admitted to our institution with complicated pneumonia due to the non-vaccine *S. pneumoniae* 19A during the winter 2007-2008. Severe necrotizing pneumonia caused by this serotype has not been previously reported in children.
- **Methods:** Retrospective review of children age 0-18 years admitted with pneumonia due to *S. pneumoniae* serotype 19A during the study period (September 1, 2007 - March 30, 2008) was conducted. Demographics, clinical features, therapy and outcomes were recorded. Antibiotic susceptibility profiles of isolates were summarized.
- **Results:** 4 children with 19 A *S. pneumoniae* pneumonia were identified. Mean age was 3.4 yrs (range 2.8-4.0). 3 (75%) were previously healthy; 1 (25%) had asthma. Chest radiograph finding included multi-lobar infiltrates (4), empyema (3) and pneumatoceles (2). 3 (75%) were admitted to the ICU and 3 (75%) intubated for mean duration 10.6 days (range 5-22 days). 3 (75%) required surgical drainage of empyema. Mean duration of stay was 19 days (range 11-28). *S. pneumoniae* was isolated from pleural fluid [3(75%)] and blood [3(75%)]. 3 (75%) of the 19A *S. pneumoniae* isolates had matching susceptibility profiles.
- **Conclusions:** Serotype 19A *S. pneumoniae* has emerged as a cause of complicated, necrotizing pneumonia in children; pneumatoceles, empyemas requiring surgical drainage and prolonged hospital stay were common features of these severe infections. Serotype 19A *S. pneumoniae* has not previously been reported as a cause of complicated pneumonia in children but should now be considered in the differential diagnosis.

Effects of the introduction of PCV-7: changes in S pneumoniae epidemiology

- A Dynamic Transmission Model of Invasive Pneumococcal Disease (IPD): Implications for Serotype 19A (T. VAN EFFELTERRE et al)
- **Background:** Introduction of pneumococcal conjugate vaccine (PCV7) in the US in 2000 has nearly eliminated PCV7-type IPD in <2 year-olds. In contrast, there has been a 3.5-fold increase in serotype 19A IPD, including a 7.6-fold increase in antibiotic non-susceptible 19A.
- **Methods:** We developed a dynamic compartmental model of pneumococcal transmission to evaluate the potential impact of vaccines with varying efficacy on serotype 19A IPD. The model uses published data on serotype-specific pneumococcal carriage and invasiveness to account for competition within the nasopharynx, the impact of antibiotic (Ab) use, and the likelihood of IPD. We validated the model using IPD serotype and resistance data since 1998 from CDC's Active Bacterial Core surveillance.
- **Results:** With no vaccine effect against 19A, the model projects that rates of 19A IPD in the US in 2020 will be twice the 2006 level. If a vaccine reduces 19A carriage by 20% but has no effect on IPD among carriers, the model predicts near elimination of 19A IPD within 10 years. Similarly, because some PCV7 types are more transmissible than 19A, reduction of PCV7-type colonization by 30% would virtually eliminate PCV7-serotype IPD within 10 years. In contrast, a vaccine with no effect on carriage and 20% efficacy against 19A IPD would only reduce 19A IPD incidence by 20%, adjusted for coverage. The model predicts that Ab-resistant 19A is ~30% less transmissible than susceptible 19A and that antibiotic use provides a selective advantage for resistant compared to susceptible strains.
- **Conclusions:** Vaccines with relatively small effects on carriage of 19A or PCV7 types could have a major impact on IPD incidence. Increases in 19A IPD cannot be attributed to introduction of PCV7 alone; antibiotic pressure acting on resistant 19A clones likely also played a role. Finally, the predicted fitness cost associated with 19A resistance suggests that a decrease in Ab use might slow the trend of rising 19A IPD.

Effects of the introduction of PCV-7: cost-effectiveness

- Long-Term Effect of 7-Valent Pneumococcal Conjugate Vaccine (PCV7) Use on Invasive Pneumococcal Disease (IPD) in the US (**WHITNEY et al**)
- **Methods:** We identified cases of laboratory-confirmed IPD through 8 U.S. sites continuously participating in Active Bacterial Core surveillance from 1998 through 2006. We calculated changes in age- and serotype-group specific IPD incidence rates in 2006 compared to 1998-1999 (before introduction) and estimated cases prevented in the U.S.
- **Results:** From 1998-1999 to 2006, IPD incidence declined from 24.4 per 100,000 in 1998-1999 to 13.5 per 100,000 in 2006 (-45%, 95%CI -47 to -42%). IPD rates caused by vaccine serotypes declined from 15.5 to 1.3 per 100,000 and were significantly lower (88%-100%) in 2006 for all age groups. IPD rates caused by serotype 19A and non-PCV7 serotypes increased from 0.8 to 2.7 per 100,000 and from 6.1 to 7.7 per 100,000, respectively, with significant increases observed among all age groups. During 2001-2006, an estimated 11,000 to 15,000 fewer cases of IPD occurred annually among children <5 years and 9,000 to 18,000 fewer cases occurred annually among persons ≥5 years in the U.S. Overall, >170,000 IPD cases and 10,000 deaths were prevented since PCV7 introduction.
- **Conclusions:** Marked public health benefits of PCV7 use in the U.S. remain evident 6 years after introduction. Increases in nonvaccine serotype IPD remain small relative to vaccine benefits.

Effects of the introduction of PCV-7: cost-effectiveness

- Cost-Effectiveness of PCV-7 : An update (**RAY et al**)
- **Methods:**
 - estimates, based on recently published data, of the reduction in hospitalized pneumonia among unvaccinated persons following PCV7 introduction, as well as revised estimates of treatment costs and pre-vaccine disease burden.
- **Results:**
 - Over 7 years, 20 million children were vaccinated. When only direct effects of PCV7 on otitis, pneumonia and invasive pneumococcal disease (IPD) were included, net cost of PCV7 was \$115 per child vaccinated, 58,000 cases of IPD were averted, and cost per life-year saved (LYS) was \$136,000. After incorporating estimated reductions in IPD for unvaccinated persons, net cost of PCV7 was \$68 per child vaccinated; 160,000 cases of IPD and 10,400 deaths were averted in all ages; and cost per LYS was \$9,300. When reported reductions in hospitalized pneumonia in unvaccinated persons aged 18-39 years were included, PCV7 was estimated to have saved \$14 per child vaccinated, and averted a total of 589,000 pneumonia hospitalizations and 18,000 deaths. When reported reductions in hospitalized pneumonia in unvaccinated persons of all ages were included, PCV7 was estimated to have saved \$366 per child vaccinated and averted 1.4 million pneumonia hospitalizations.
- **Conclusion:**
 - In the US, the presence of even modest indirect effects of PCV7 on pneumonia hospitalizations substantially improves the cost-effectiveness and may have resulted in overall cost savings.

Let the Sun Shine In: Temperature and UV Radiation Affect the Incidence of Pneumococcal Infection in Philadelphia

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- **Background:** *Streptococcus pneumoniae* is a common cause of severe illnesses including pneumonia, meningitis, and bacteremia. Although excess wintertime mortality related to pneumonia has been noted for over a century, the seasonal occurrence of invasive pneumococcal disease (IPD) has been described relatively recently and is poorly understood. Given concerns related to global climate change, we sought to investigate how environmental factors influence IPD occurrence. **Methods:** The investigation included 602 cases of IPD reported in Philadelphia County between 2002-2007. Poisson regression was used to identify associations between weekly weather patterns and disease incidence. To examine the relationship between acute environmental fluctuations and IPD occurrence, a case-crossover approach was employed. Both methods controlled for seasonal factors that could confound relationships between weather effects and disease occurrence. **Results:** IPD incidence was greatest in the wintertime, and spectral decomposition revealed a peak at 51.0 weeks, suggesting annual periodicity. Weekly incidence was found to be associated with cooling-degree temperature, (IRR per °C: 0.95, [95% CI 0.92-0.98]), and clear-sky UV index (IRR per W/m²: 0.74 [95% CI 0.60-0.92]). Case-crossover analysis suggested that occurrence was intransigent to daily fluctuations in temperature (OR: 1.01, [95% CI 0.96-1.06]), and numerous other environmental factors. **Conclusions:** We confirmed the wintertime predominance of IPD in a major urban center. Meteorological predictors of IPD in Philadelphia are extended periods of low UV radiation, and decreasing temperature above a threshold; these effects may explain its wintertime seasonality. In particular, increased summertime light exposure may reduce host susceptibility to pathogens, or the fitness of pathogens themselves