# Initial Antibiotic Administration for Pneumonia Inpatients

*Is Timing Everything?*

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# Today's Outline

- The measure
- The evidence
- Issues and controversy
- What's changing
- How to affect practice

# Antibiotic within 4 hours*

- *Numerator*
  - Number of pneumonia patients who receive their first antibiotic dose within 4 hours of hospital arrival
- *Denominator*
  - Pneumonia patients 18 years and older (ICD-9 codes)
- *Key Exclusions*
  - Transfers from another acute care facility, no working diagnosis of pneumonia on admission, patients receiving comfort care only, patients who do not receive antibiotics within 36 hours of arrival, patients who receive antibiotics within 24 hours prior to arrival, patients in clinical trials

# Kahn et al, 1990

- Setting: 297 hospitals in 5 states
- Patients: adults
- Design: retrospective record review
- Outcome: mortality 30 days after admission
- Findings: Care that included antibiotics within 4 hours associated with 5.4% lower mortality
- Issues: Retrospective, limited adjustment, timing not focus

*JAMA*. 1990; 264:1969-1973.

# McGarvey and Harper, 1993

- Setting: 3 hospitals in PA
- Patients: 870 adults, mean age 80 y
- Design: pre/post-intervention package with 4-hr administration
- Outcome: inpatient mortality, LOS
- Findings: Care including antibiotics within 4 hours associated with 3.4% lower mortality, 1.3 day LOS reduction
- Issues: No adjustment, timing not focus

*QRB Quality Review Bulletin*. 1993; 19:124-30.

# Meehan et al, 1997

- **Setting:** 3555 hospitals in US; 1994-95
- **Patients:** random sample 14,069 aged > 65y, pneumonia by principal ICD-9 code, admit DX, and CXR. CAP only.
- **Design:** retrospective cohort, medical record review, severity adjusted
- **Outcome:** mortality 30 d following admission

*JAMA*. 1997; 278: 2080-84.

# Meehan, et al

## *Findings*

**Antibiotic administration within 8 hours associated with lower 30-day mortality among all patients:**

**Severity-adjusted odds ratio = 0.85; 95% confidence interval, 0.75 – 0.96.**

***JAMA*. 1997; 278: 2080-84.**

# Meehan, et al
## *Findings*

When limited to patients *without* pre-hospital antibiotics (75%), association at 8 hours stronger:

adjusted OR = 0.78; 95% CI, 0.67 – 0.89.

*JAMA*. 1997; 278: 2080-84.

# Dedier et al. 2001

- **Setting:** 38 academic hospitals, 1997-98
- **Patients:** 1,062 adults, age 18-98y
- **Design:** Retrospective medical record review, adjusted
- **Outcome:** inpatient mortality, LOS, clinical stability by 48 hours
- **Findings:** 8 hour administration not associated with outcome
- **Issues:** Retrospective, patient/hospital characteristics, and low power study

*Arch Intern Med*. 2001; 161: 2099-2104.

# Battleman, et al, 2002

- **Setting:** 7 hospitals, 1998
- **Patients:** 609 adults, mean age 67 y
- **Design:** Retrospective review, adjusted
- **Outcome:** Long length of stay (LLOS) $\geq$ 9d
- **Findings:** Mean time to dose in ED 3.5h
  OR = 1.75 per 8h; CI, 1.34-2.29
- **Issues:** Retrospective, adjustment

*Arch Intern Med.* 2002; 162: 682-688.

# Silber et al, 2003

- Setting: 1 hospital, 1999-2000
- Patients: 409 adults, age 21+ y
- Design: Prospective observational
- Outcome: Time to clinical stability (TCS)
- Findings: 4 hour administration not associated with shorter TCS
- Issues: Power, adjustment ?, exclusions, did not address mortality

*Chest* 2003; 124: 1798-1804.

# Houck, et al. 2004

- **Setting:** 3732 hospitals in US; 1998-99
- **Patients:** random sample 13,371 patients aged>65y; principal ICD9 code 48X; 038.X or 518.81 plus 48X; admit DX, (+) CXR, CAP, immunocompetent.
- **Design:** retrospective, medical record data, adjusted (PORT Pneumonia severity index (PSI), ICU, region, race, care process)

*Arch Intern Med*. 2004; 164: 637-44.

# Houck, et al

## *Patients on Pre-hospital Antibiotics*

Among patients *with* pre-hospital antibiotics (n=4,438), 4 hour delivery not associated with 30-d mortality:

adjusted OR = 1.18; 95% CI, 0.97-1.45

*Arch Intern Med*. 2004; 164: 337-44.

# Outcomes by Time to First Antibiotic Administration*

| Time to First Dose | In-hospital Mortality % (95% CI) | 30-d Mortality % (95% CI) | LOS Above the Median (5 d), % (95% CI) |
|---|---|---|---|
| 0 – 2 hours | 7.4 (6.6-8.3) | 12.5 (11.5-13.7) | 43.6 (41.9-45.2) |
| > 2 – 4 hours | 6.3 (5.6-7.0) | 10.9 (10.0-11.8) | 41.0 (39.6-42.4) |
| > 4 – 6 hours | 6.9 (6.0-8.1) | 11.7 (10.4-13.0) | 42.9 (40.9-45.0) |
| > 6 – 8 hours | 7.2 (5.8-8.9) | 13.0 (11.0-15.1) | 46.1 (43.1-49.1) |
| > 8 hours | 8.0 (6.9-9.3) | 13.8 (12.3-15.5) | 47.2 (45.0-49.5) |

*Arch Intern Med.* 2004; 164: 337-44.

*Patients who were on antibiotics prior to admission are excluded from this analysis.

# First Dose Timing and Outcomes

| Timing of First Dose<br>Group 1 vs Group 2 | Group 1 Mortality % | Group 2 Mortality % | Adjusted Odds Ratio aOR (95% CI) | P value |
|---|---|---|---|---|
| ≤ 1 hour vs > 1 hour | 12.9 | 12.0 | 0.99 (.81-1.21) | 0.906 |
| ≤ 2 hours vs > 2 hours | 12.5 | 11.9 | 0.94 (.83-1.06) | 0.322 |
| ≤ 3 hours vs > 3 hours | 11.7 | 12.3 | 0.88 (.79-.99) | 0.030 |
| ≤ 4 hours vs > 4 hours | 11.6 | 12.7 | 0.85 (.76-.95) | 0.005 |
| ≤ 5 hours vs > 5 hours | 11.6 | 13.0 | 0.86 (.76-.97) | 0.017 |
| ≤ 6 hours vs > 6 hours | 11.6 | 13.5 | 0.84 (.73-.95) | 0.008 |
| ≤ 7 hours vs > 7 hours | 11.7 | 13.5 | 0.87 (.76-1.01) | 0.060 |
| ≤ 8 hours vs > 8 hours | 11.7 | 13.8 | 0.85 (.73-.99) | 0.040 |
| ≤ 9 hours vs > 9 hours | 11.8 | 13.8 | 0.86 (.73-1.02) | 0.075 |
| ≤ 10 hours vs > 10 hours | 11.9 | 13.4 | 0.91 (.76-1.09) | 0.327 |

Using multivariate logistic regression [the model included the timing of antibiotic first dose, PSI score, ICU admission, US census region, race/ethnicity, other processes of care (oxygenation assessment, performance of blood cultures, and antibiotic selection)]. Patients who were on antibiotics prior to admission are excluded from this analysis. (Houck PM, Bratzler DW, et al. *Arch Intern Med*. 2004.)

# First Dose Timing and Outcomes

| Outcome | Within 4 hours % | After 4 hours % | Adjusted Odds Ratio aOR (95% CI) | P value |
|---|---|---|---|---|
| 30-day mortality | 11.6 | 12.7 | 0.85 (.76-.95) | 0.005 |
| In-hospital mortality | 6.8 | 7.4 | 0.85 (.74-.98) | 0.029 |
| Length of stay > 5 days | 42.1 | 45.1 | 0.90 (.83-.96) | 0.003 |
| 30-day readmission | 13.1 | 13.9 | 0.95 (.85-1.06) | 0.344 |

Using multivariate logistic regression [the model included the timing of antibiotic first dose, PSI score, ICU admission, US census region, race/ethnicity, other processes of care (oxygenation assessment, performance of blood cultures, and antibiotic selection)].

Houck PM, Bratzler DW, et al. *Arch Intern Med.* 2004.

# First Dose Timing and Outcomes

## *Stratified by Risk Classes**

| PSI Risk Classes II and III | Within 4 hours % | After 4 hours % | Adjusted Odds Ratio aOR (95% CI) | *P* value |
|---|---|---|---|---|
| 30-day mortality | 2.1 | 3.4 | 0.62 (.42-.93) | 0.02 |
| In-hospital mortality | 0.9 | 1.2 | 0.77 (.42- 1.44) | 0.42 |
| Length of stay > 5 days | 31.2 | 35.3 | 0.86 (.75-.99) | 0.03 |
| 30-day readmission | 9.4 | 10.9 | 0.87 (.70-1.07) | 0.19 |

* multivariate logistic regression: PSI score, ICU admission, census region, race/ethnicity, processes of care (oxygenation assessment, performance of blood cultures, and antibiotic selection. Patients without pre-hospital antibiotics

*Arch Intern Med*. 2004; 164: 337-44.

# First Dose Timing and Outcomes

## *Stratified by Risk Classes**

| PSI Risk Classes IV and V | Within 4 hours % | After 4 hours % | Adjusted Odds Ratio aOR (95% CI) | *P* value |
| --- | --- | --- | --- | --- |
| 30-day mortality | 15.5 | 16.5 | 0.87 (0.78-0.98) | 0.03 |
| In-hospital mortality | 9.2 | 9.9 | 0.86 (0.74- 1.00) | 0.04 |
| Length of stay > 5 days | 46.5 | 49.2 | 0.92 (0.84-1.00) | 0.04 |
| 30-day readmission | 14.7 | 15.2 | 0.99 (0.88-1.12) | 0.89 |

* multivariate logistic regression: PSI score, ICU admission, census region, race/ethnicity, processes of care (oxygenation assessment, performance of blood cultures, and antibiotic selection.

*Arch Intern Med*. 2004; 164: 337-44.

# Singer ME, et al. ICAAC 2005

- **Setting:** US Hospitals, 7/2002 – 10/2003
- **Patients:** adults aged >18 y, ICD9 code, CXR +, antibiotics within 8 hours, Non-SNF, no
  prior antibiotics, immunocompetent
- **Design:** Retrospective, JCAHO record abstraction,
  PSI/ICU adjustment
- **Outcome:** inpatient mortality, LOS
- **Findings:** administration within 4 hours associated with reduced mortality compared with 4-8 hours
- **Issues:** Retrospective, inpatient mortality only

Singer ME, Krishnaswamy J, Bonomo RA. [Abstract] The American Society for Microbiology's 45th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC™).

# Is 4 hours better than 8 hours?

- Antibiotic administration within 4 hours (vs. within 8 hours) associated with:
  - 31.7%* reduction in mortality in the elderly.
  - 12.5%* reduction in length of stay exceeding the median in the non-elderly
  - 7.4%* reduction in length of stay exceeding the median in the elderly
- Those receiving antibiotics in 4-6 hours were similar to those receiving antibiotics in 6-8 hours.

Singer ME, Krishnaswamy J, Bonomo RA. [Abstract] The American Society for Microbiology's 45th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC™).

# Is 4 hours better than 8 hours?

- Antibiotic administration within 4 hours of admission should be the standard of care for elderly adults with community-acquired pneumonia initially treated as inpatients. This is less clear for non-elderly adults.
- Antibiotics within 6 hours is an unsatisfactory compromise.

Singer ME, Krishnaswamy J, Bonomo RA. [Abstract] The American Society for Microbiology's 45th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC™).

# Waterer, et al. 2006

- **Setting:** 1 hospital, 11/98 – 7/2001
- **Patients:** 451 adults, mean age 58 y with 158 >65 y
- **Design:** Prospective cohort
- **Outcome:** “mortality”
- **Findings:** 4 hour administration not associated with reduced mortality. Altered mental status predicts mortality
- **Issues:** Power, population, adjustment, exclusions,

*Chest* 2006; 130: 11-15.

# Waterer, et al
## *Findings*

Among patients of all ages (n=451), time to first dose (TFD) >4 h not significantly associated with "mortality" when adjusted for "altered mental state":

adjusted OR = 1.85; 95% CI, 0.85 – 5.00.

Chest 2006; 130: 11-15

# Waterer, et al
## *Findings*

Among patients >65 years old (n=158), time to first dose (TFD) >4 h "approached" significant association with "mortality" in univariate analysis:

OR = 2.94, 95% CI, 0.92-9.43, p = 0.07

But NOT significantly associated when adjusted for "altered mental state":

P = 0.158, no OR reported

Chest 2006; 130:11-15

# ISSUE #1: "It's only retrospective data…we don't have a randomized trial"

We'll likely never have a pure timing RCT…ethical issues plus large=expensive, but…

# McGarvey and Harper, 1993

- Setting: 3 hospitals in PA
- Patients: 870 adults, mean age 80 y
- Design: pre/post-intervention package with 4-hr administration
- Outcome: inpatient mortality, LOS
- Findings: Care including antibiotics within 4 hours associated with 3.4% lower mortality, 1.3 day LOS reduction
- Issues: No adjustment, timing not focus

*QRB Quality Review Bulletin*. 1993; 19:124-30.

# Dean, et al. 2001

- Setting: Utah hospitals, 1993-1997
- Patients: 28661 admissions, age >65 y
- Design: Pre-post pneumonia guideline implementation; adjusted age, sex, rural
- Outcome: 30-day mortality
- Findings: Guideline implementation associated with reduced mortality (OR=0.69, p=0.04 for IHC patients; OR=0.81, p=0.08 for all
- Issues: adjustment, ecologic design, not limited to timing

*Am J Med 2001;110: 451-457.*

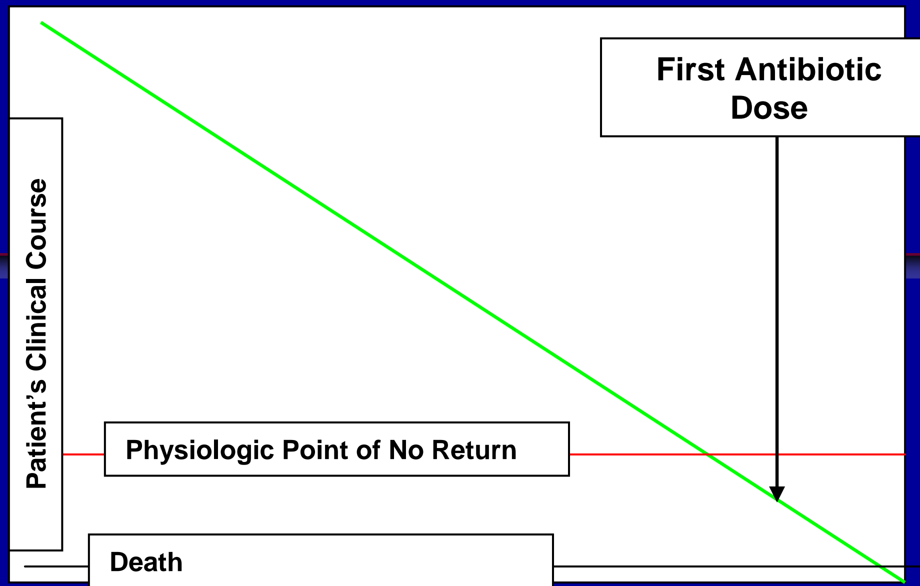
# ISSUE #2: "How can a few hours affect my patient? There is no biologic mechanism to explain this."

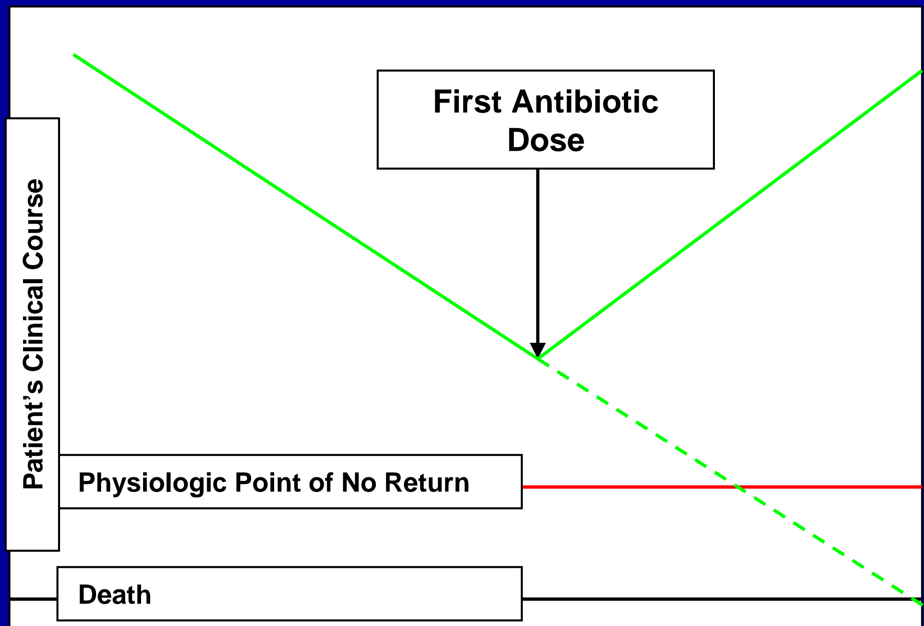
# ISSUE #2: "How can a few hours affect <u>MY</u> patient? There is no biologic mechanism to explain this."

Context? One patient at one hospital vs. 300,000 at 4,000 hospitals

# A Mechanism:
# Pneumonia Patient Outcome Subgroups

- Would survive, despite or without treatment
- No hope – die even with aggressive treatment
- Outcome depends on treatment




Time--------------→

# ISSUE #3: “It’s only a measure of better general care”

# Houck, et al

## *Patients on Pre-hospital Antibiotics*

Among patients *with* pre-hospital antibiotics (n=4,438), 4 hour delivery not associated with 30-d mortality:

adjusted OR = 1.18; 95% CI, 0.97-1.45

*Arch Intern Med*. 2004; 164: 337-44.

# Houck, et al, unpublished data

## *Patients <65 years old*

Among >2000 younger Medicare patients, 4 hour delivery not associated with 30-d mortality:

# ISSUE #4: "Results are internally inconsistent because of increased mortality among very early receivers"

# First Dose Timing and Outcomes

| Timing of First Dose Group 1 vs Group 2 | Group 1 Mortality % | Group 2 Mortality % | Adjusted Odds Ratio aOR (95% CI) | P value |
|---|---|---|---|---|
| ≤ 1 hour vs > 1 hour | 12.9 | 12.0 | 0.99 (.81-1.21) | 0.906 |
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# ISSUE #5: “The timing-outcome association is a result of confounding by….”

# Houck, et al

## *Confounding by Heart Failure??*

**Among patients with no evidence congestive heart failure (69%), 4 hour delivery associated with reduced 30-d mortality:**

**OR = 0.83; CI, 0.71-0.96**

# Houck, et al

## *Confounding by shock?*

Among patients with systolic BP > 90mm (n=13,325) , 4 hour delivery associated with reduced 30-d mortality:

OR = 0.86; (CI, 0.77-0.97)

# Waterer, et al

## *Confounding by mental status?*

Among patients >65 years old (n=158), time to first dose (TFD) >4 h "approached" significant association with "mortality" in univariate analysis:

OR = 2.94, 95% CI, 0.92-9.43, p = 0.07

But NOT significantly associated when adjusted for "altered mental state":

P = 0.158, no OR reported

Chest 2006; 130:11-15

# Houck, 2006

## *Confounding by mental status?*

- In 2004 Medicare database, altered MS essentially the same in <4h and >4h groups
- Logistic regression addressed mental status with no change in results
- Exclusion of patients with altered mental status did not substantially change result: 30-day mortality OR=0.74, p<0.001

Chest 2006; 130:1-3

# Controversy #1: “The measure is being applied to young patients”

# Controversy #1: “The measure is being applied to young patients”

True….and as the measure is being used, this is a mistake

# Controversy #2: "The measure is causing doctors to do bad things, like giving antibiotics without a pneumonia diagnosis"

Some evidence for this…why?

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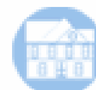

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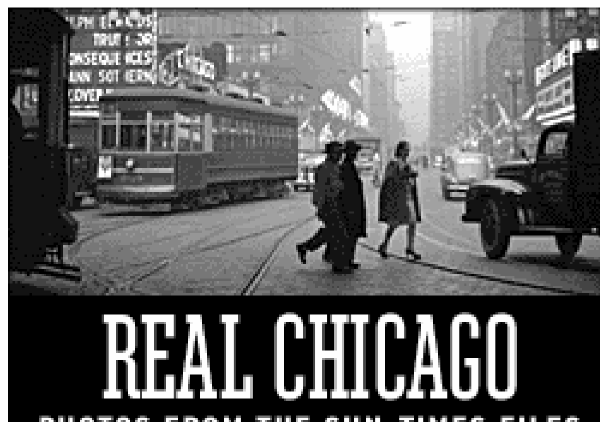
# Care lags for common killer

*March 6, 2006*

BY LORI RACKL **Health Reporter**

Pneumonia patients in the Chicago area often get hospital care that lags behind the rest of the nation, a Chicago Sun-Times analysis of government data shows.



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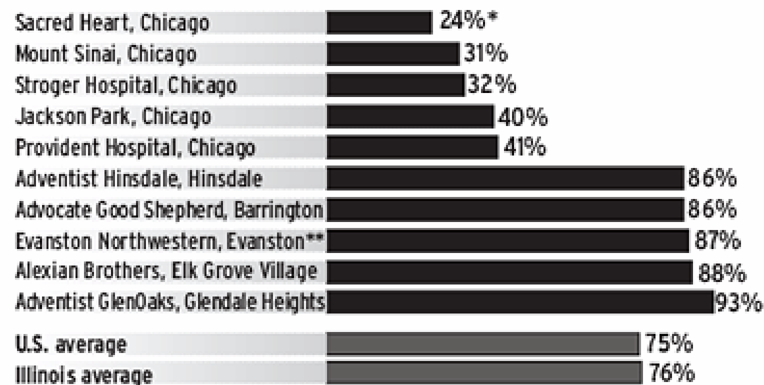
# THE BEST AND WORST OF CARE

Here's a look at local hospitals with the highest and lowest rates in following guidelines for pneumonia care:

## TIMELY ANTIBIOTICS

What percent of pneumonia patients got antibiotics within 4 hours of hospital arrival?

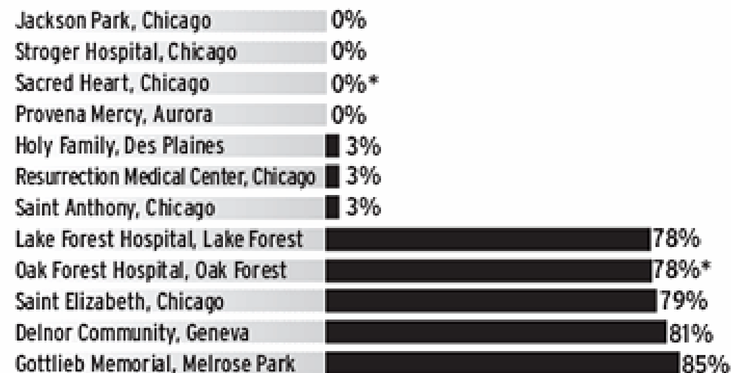
**Hospital**




## VACCINATION

What percent of eligible, older pneumonia patients were given the pneumococcal vaccine?

**Hospital**



# Drivers of undesired practice…

- Pay for performance (PFP)
- Public reporting of actual hospital-specific measure rates

Financial and competitive pressures make hospitals want to be “the best” and that means aiming for 100% compliance

# Why not always within 4 hours?

***The clinical diagnosis of pneumonia may not be clear at arrival.***

**"Diagnostic uncertainty" and clinical factors.**

| Clinical Factors | Diagnostic Uncertainty N=19 (%) | No Diagnostic Uncertainty N=59 (%) | P value |
|---|---|---|---|
| Rales | 12 (63.2 | 50 (84.7) | 0.043 |
| Fever | 7 (36.8) | 26 (44.1) | 0.579 |
| Oxygen desaturation (<92%) | 6 (31.6) | 39 (66.1) | 0.008 |
| Abnormal WBC | 12 (63.2) | 40 (67.8) | 0.709 |
| CXR infiltrate | 9 (47.4) | 50 (84.7) | <0.001 |

Metersky ML, et al. Chest 2006;130:16-21.

# Controversy #3: “Four hours is too hard…not a realistic target”

# Hospital Characteristics

## *and Antibiotic Administration Within 4 Hours of Arrival**

| Characteristic | No. of Hospitals | No. of Patients | Abx within 4 h % (95% CI) | *P* Value |
|---|---|---|---|---|
| No. of beds | | | | |
| >500 | 227 | 1378 | 53.3 (50.7-56.0) | Reference |
| 200-499 | 2192 | 4925 | 55.4 (53.9-56.7) | .19 |
| <200 | 937 | 7192 | 66.2 (65.1-67.3) | <.001 |
| Metropolitan area | | | | |
| >500,000 population | 1225 | 5087 | 57.2 (55.9-58.6) | <.001 |
| <500,000 population | 608 | 3125 | 56.9 (55.1-58.6) | <.001 |
| Non-metropolitan | 1523 | 5283 | 66.9 (65.6-68.2) | Reference |

*Patients without prehospital antibiotic treatment

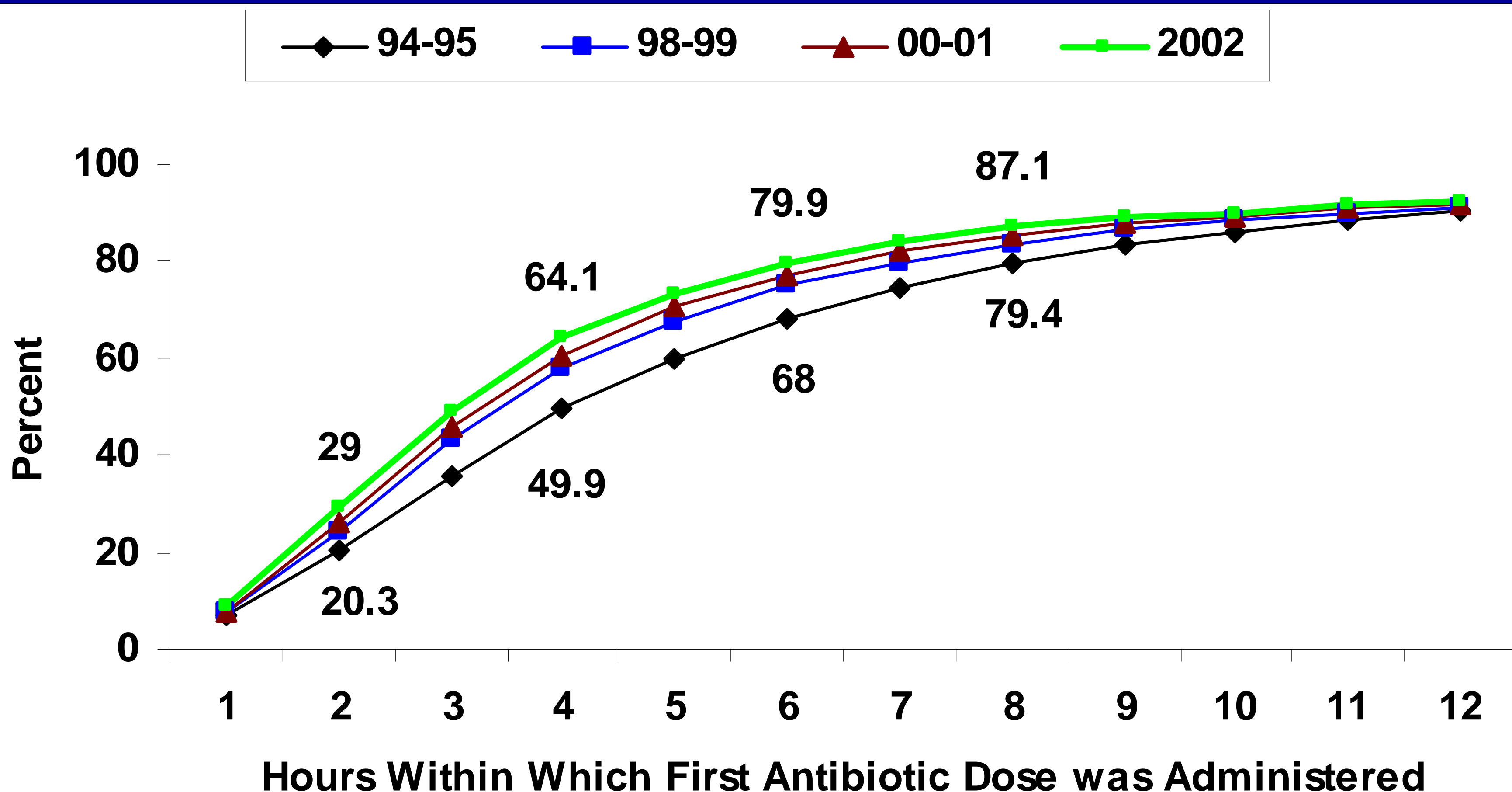
*Arch Intern Med*. 2004; 164: 337-44.

# What might be changed?

- Be skeptical, but with good power and design!
- Apply measure to population from which it was derived (i.e., <65 year olds)
- Appropriate inclusion/exclusion criteria
- Benchmark targets for PFP
- “rate-bands” for public reporting

# Changing Practice

# Timing of Antibiotic First Dose




Bratzler DW, Houck PM. Academy for Health Services Research and Policy. Washington, DC. June 24, 2002.

# Reliable Systems

## *Improving First Antibiotic Dose Timing*

- Identify the delays in the system
  - Triage to physician exam
  - Delays in diagnostic tests
  - Delays in availability and administration of antibiotics

# Reliable Systems

## *Improving First Antibiotic Dose Timing*

- Identify the delays in the system
  - Triage to physician exam
    - Protocols for nursing referral to x-ray
      - Patients presenting with certain combinations of symptoms (e.g., cough, fever, sputum production, shortness of breath, hypoxemia)
      - Recognizes the importance of documenting an infiltrate to confirm the diagnosis of pneumonia
      - May reduce diagnostic uncertainty
    - Delays in diagnostic tests

# Reliable Systems

## *Improving First Antibiotic Dose Timing*

- Identify the delays in the system
  - Delays in availability and administration of antibiotics
    - Have standard formulary antibiotics most commonly used for pneumonia available in the ED
    - Always initiate dose prior to patient leaving the emergency department

# Reliable Systems

## *Antibiotic Selection and Timing*

- Standard formulary antibiotics
  - Pre-printed order sheets for use in ED
  - Clinical pathways or protocols

# Conclusions

- Antibiotics within 4 hours:
  - Consistent association with better outcomes in large Medicare studies
  - Based on plausible mechanism
  - Can't rule out all confounding, but much
  - Timing measure is being misused
  - Application of measure must change
  - Is practical in most hospitals
  - Is much more common now

  - Prevent deaths in Medicare population

# A Final Thought…

"All scientific work is incomplete…is liable to be upset or modified by advancing knowledge. That does not confer on us a freedom to ignore the knowledge that we already have or to postpone the action that it appears to demand at a given time."

Sir Austin Bradford Hill. Proc R Soc Med 1965;58:295-300