The perspective of industry: non-inferiority trials for CAP

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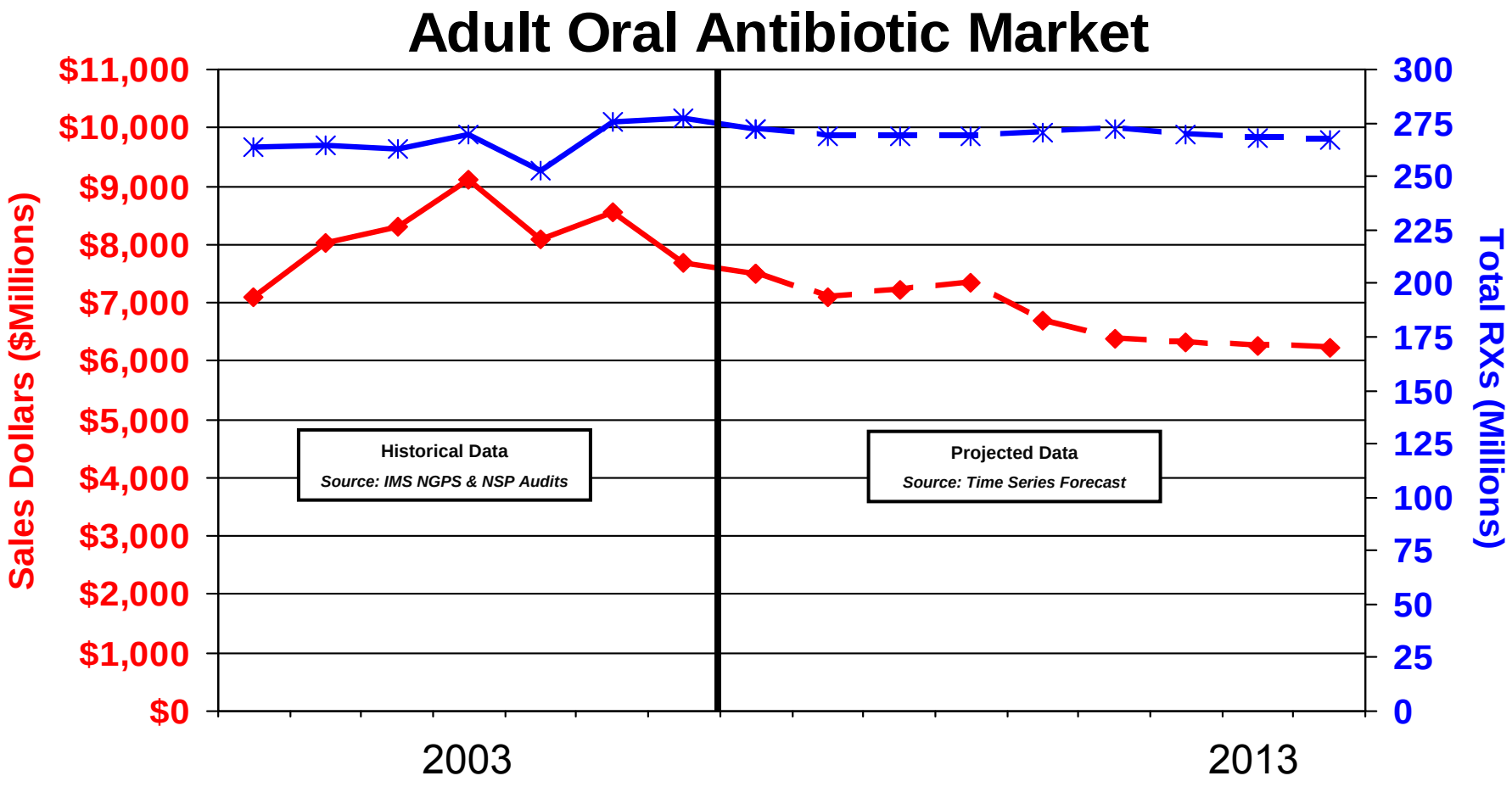
Previous lives include Bayer1986-2000 and Oscient 2003-2006

January 16th many concerns……

- **Global drug development**
  - US vs EU (EU does not want ANY placebo trials)
  - Acceptability of comparators-not all drugs viewed the same
  - Statistical evaluations and guidance- inconsistent between authorities
  - Indications required
    - CAP as an ‘anchor’ for RTI
- **Commercial aspects in today’s environment**
  - CAP represents the smallest opportunity in RTI and yet is fundamental to clinical programs
  - Research investment goes beyond clinical studies
    - Tufts Institute estimates drug development costs to be $800mio
    - Clinical trials may be 30% of this sum

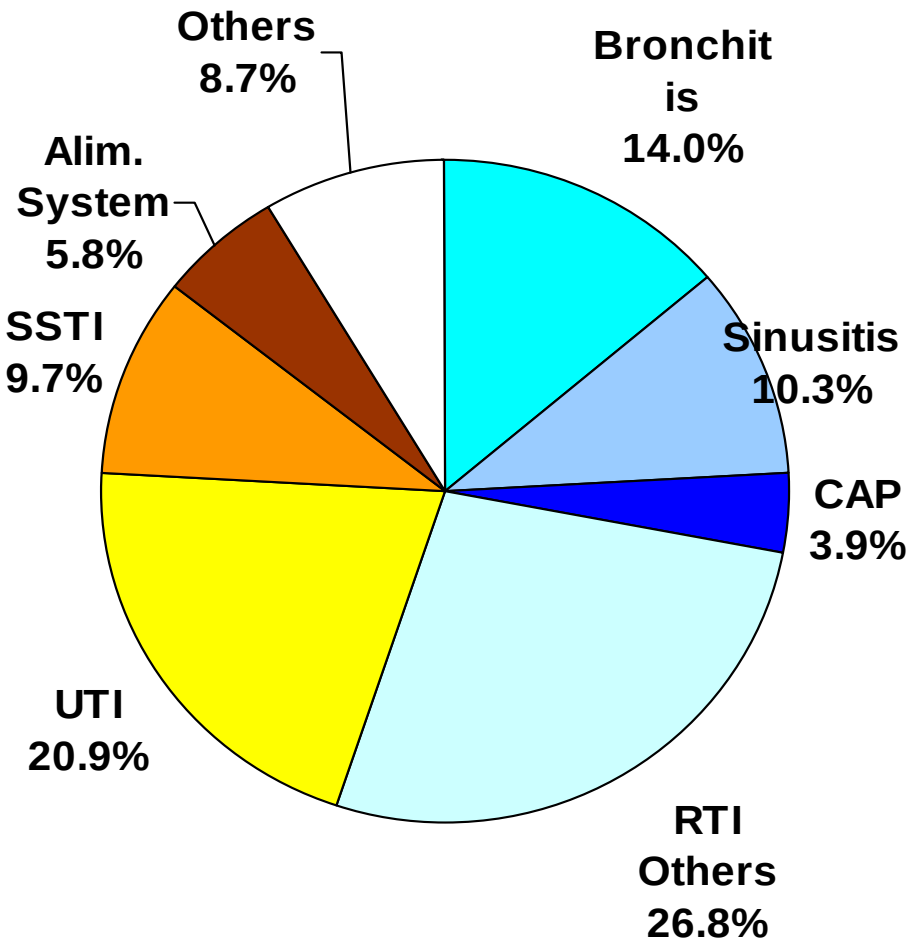
Historical and Projected Sales & Prescription Trends



<u>30% reduction in commercial opportunity over 10 years</u>

Antibiotic Rx Market by Indications - 2005

Oral Market: 399,8 mio Rx globally; IV market much smaller



Challenges

- **Ethical issues**
  - Resistance considerations for comparator drugs
  - Placebo controls?
- **Implications on drug development**
  - Feasibility using clinical response alone?
- **Appropriate endpoints and tools**
  - How & when to assess efficacy
  - Safety
  - Time-based endpoints
  - Bacteriological
  - **Patient-based assessments**

Proportion reporting moderate to severe symptoms during resolution of pneumonia

			Percentage by time from diagnosis		
Symptom	**Pre-pneumonia**	**Day 0**	**Day 7**	**Day 30**	**Day 90**
Fatigue	**10**	**79**	**48**	**28**	**20**
Cough	**7**	**80**	**51**	**23**	**13**
Dyspnea	**2**	**41**	**15**	**7**	**6**
Sputum	**3**	**39**	**23**	**12**	**8**
Pleuritic chest pain	**1**	**38**	**11**	**5**	**2**

What about day 0- 7???

Metlay JP et al J Gen Intern Med 1997;12:423-430.
Measuring symptomatic and functional recovery in patients with CAP.

Primary endpoint: clinical success at test of cure

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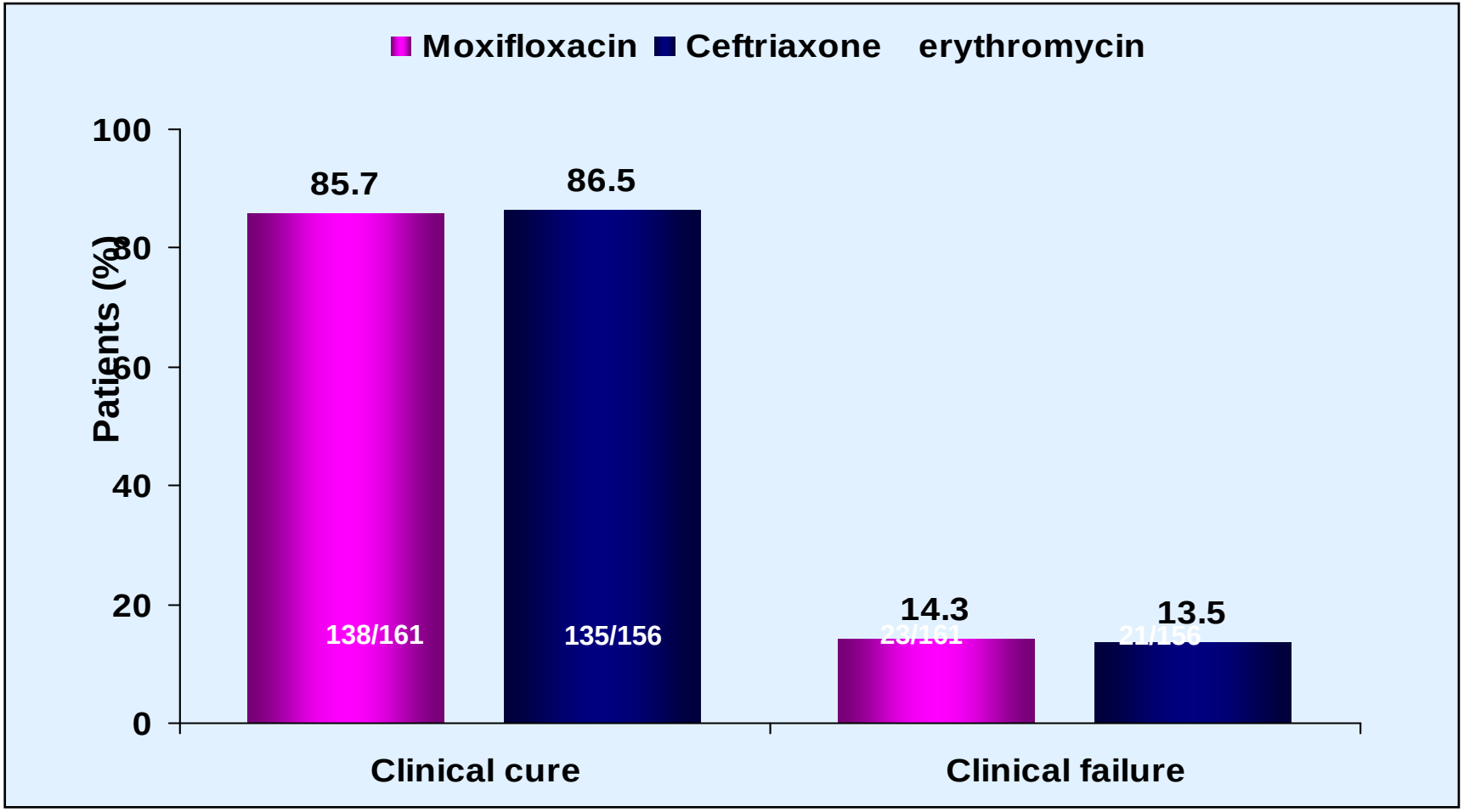
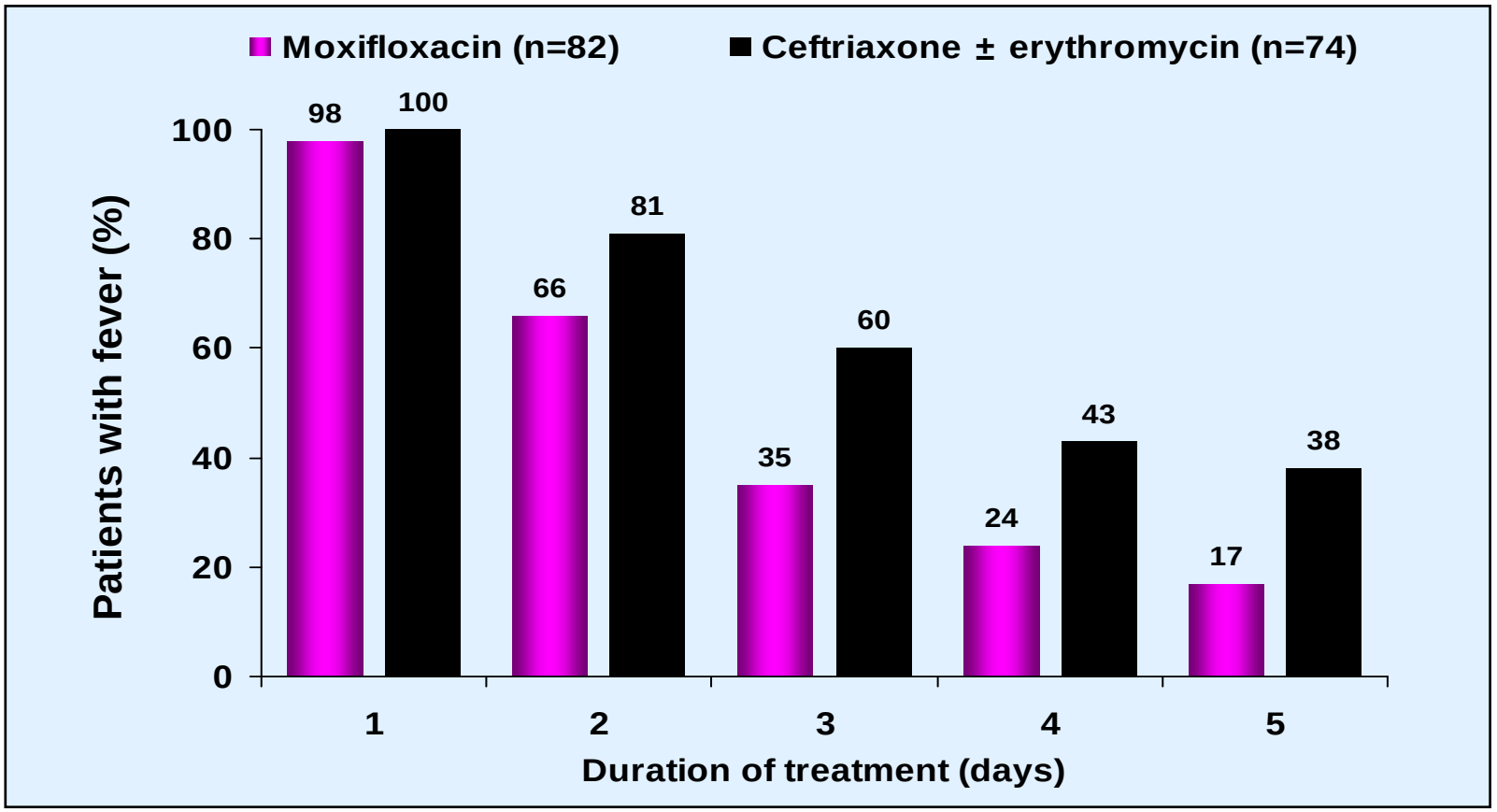


Plain vanilla is the flavor but there maybe a hidden tasty streak if you look properly!

Welte *et al*. *Clin Infect Dis* 2005; **41**: 1697–705

Speed of defervescence

Defervescence for moxifloxacin (median 3 days) vs ceftriaxone+/- erythromycin (median 4 days; $p<0.003$)



Fever: body temperature >38.5°C

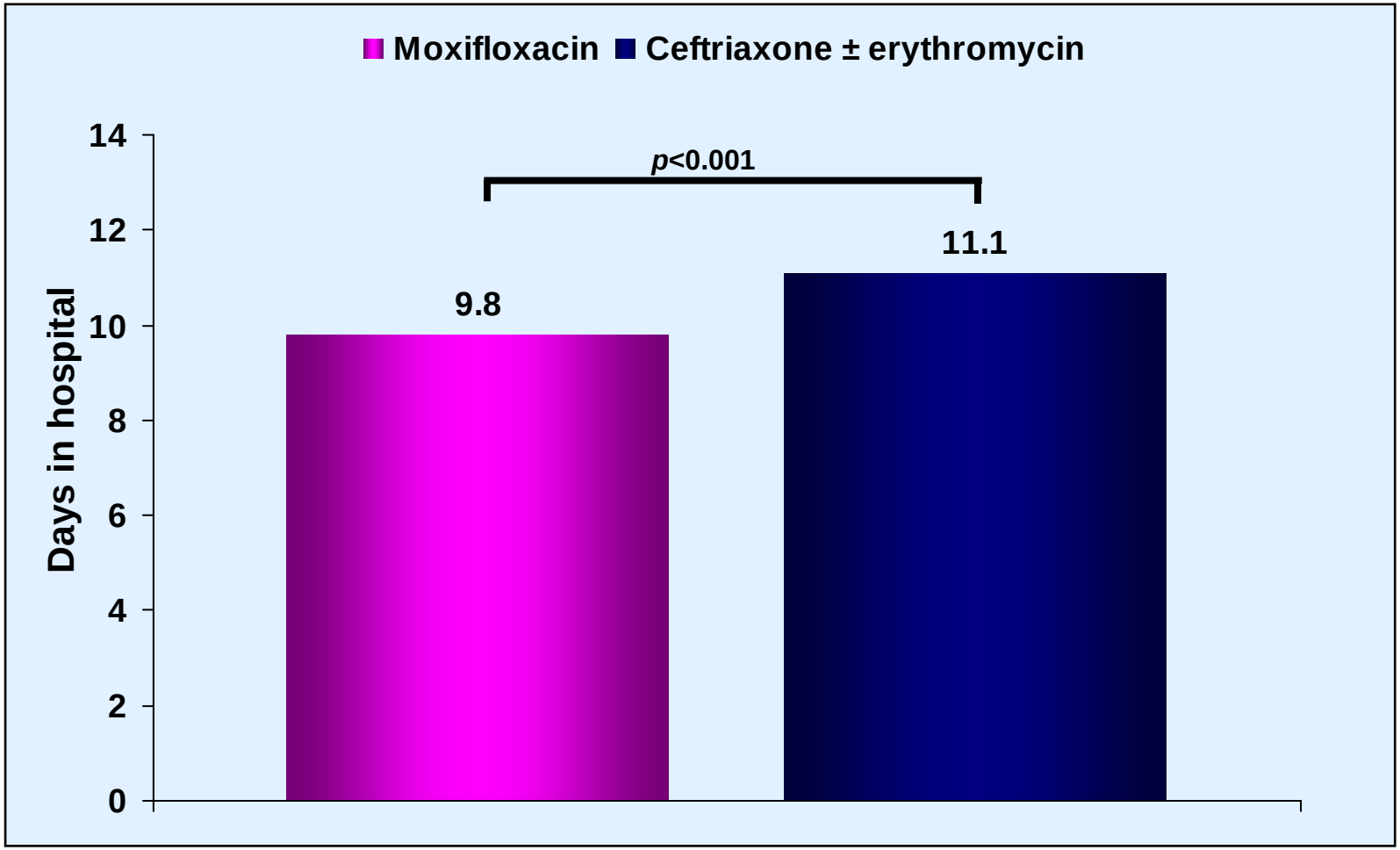
Welte *et al*. *Clin Infect Dis* 2005; **41**: 1697–705

Patient-reported relief from symptoms

- Compared to ceftriaxone ± erythromycin, moxifloxacin-treated patients reported a consistently faster improvement in signs and symptoms specific to community-acquired pneumonia
  - **Chest pain (*p*=0.021)**
  - **Weakness (*p*=0.015)**
  - **Sputum color (*p*=0.002)**
- Median time to feeling better:
  - Moxifloxacin: 3 days
  - Ceftriaxone ± erythromycin: 4 days

Welte *et al*. *Clin Infect Dis* 2005; **41**: 1697–705

Duration of hospitalization



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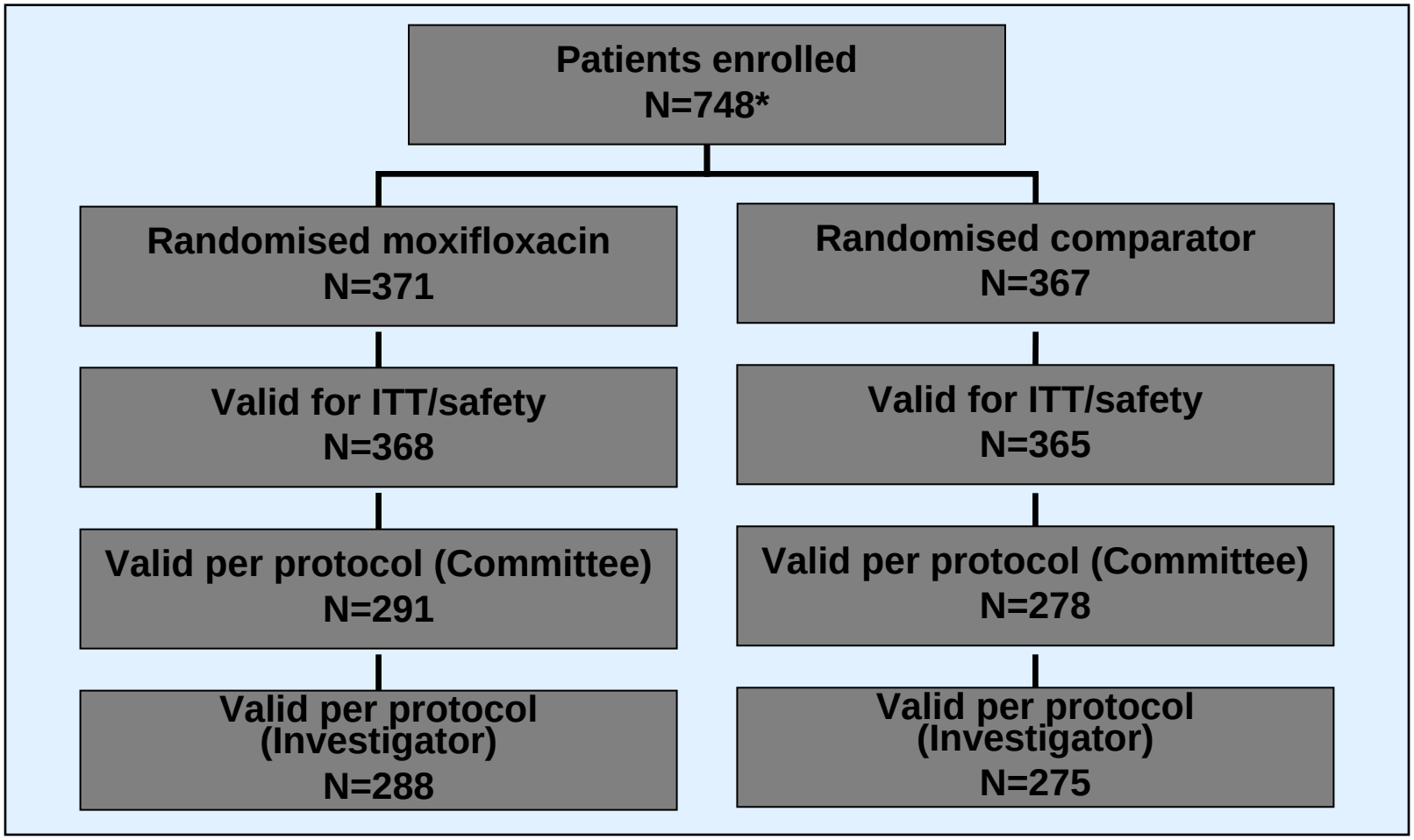
Methodological deficiencies need large number of patients



* 738 were stratified and then randomised

Torres *et al.* ECCMID 2006, Poster 1061
Read *et al.* ERS 2006, Poster 2083

If *S pneumoniae* accounts for >40% of moderate to severe CAP :why these data on baseline causative organisms?

	Moxifloxacin N=291 n/N (%)	Ceftriaxone + levofloxacin N=278 n/N (%)
Pneumococcal pneumonia[a]	**77 (26.5)**	**85 (30.6)**
Pneumonia due to intracellular organisms[b]	**41 (14.1)**	**45 (16.2)**
Pneumonia due to *Legionella pneumophila*	**10 (3.4)**	**12 (4.3)**
Gram-positive aerobic organisms*	**37 (12.7)**	**47 (16.9)**
Streptococcus pneumoniae	**32 (11.0)**	**45 (16.2)**
Staphylococcus aureus	**6 (2.1)**	**2 (0.7)**
Gram-negative aerobic organisms*	**20 (6.9)**	**10 (3.6)**
Haemophilus influenzae	**10 (3.4)**	**8 (2.9)**
Enterobacteriaceae	**10 (3.4)**	**2 (0.7)**
Other	**1 (0.3)**	**0 (0)**

[a]*S. Pneumoniae* cultured from respiratory/blood cultures **and/or positive urinary antigen testing**
[b]Acute and convalescent blood serology (*Chlamydophila pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae*) and urine antigen for *Legionella pneumophila.* Includes mixed infections i.e. infections due to a common bacterial pathogen and an intracellular CAP organism
*Microbiologically valid population

Read *et al.* ERS 2006, Poster 2083

Which population for analysis? The impact on sample size- the accountants perspective

- FDA prefers “co-primary “ analysis for NI trials
- CE population =85% of enrollees
- mITT 30-35% for typical pathogens
- Costs of these numbers
  - CE 10%Δ n= 432 **$23mio**
  - mITT 10%Δ n=1236 **$65mio**
  - 15%Δ n= 618 **$35 mio**
  - At least 2 studies required assuming comparators are globally accepted
  - **The ‘anchor’ of CAP costs >$70million alone.**

What have we learned about hospitalized CAP?

- Etiology is same as mild-moderate disease- CAP is a continuum
- New microbial diagnostics may make spotting the pneumococcus easier but will be these tests be universally available for trials (even in Primary Care)?
- Course of progression of disease is often **host driven** e.g. co-morbid conditions
- Incidence of CAP is likely to increase as population ages & co-morbidities rise but ROI issues still linger
- Clinical assessment alone is not enough to see ‘true differences’

Industry Perspective on CAP

- **Operational considerations**
  - Impact of real clinical practice varies by country
  - Etiology-can we do better in getting bacterially infected cases?
  - Patient sub-populations
- **Regulatory considerations**
  - Standard of care vs treatment guidelines
  - Study design-not globally acceptable despite ICH guidelines
  - Feasibility- IRB & timelines prohibitive
  - Niche indications- cipro or azithro for key infections aside from RTI
- **Financial considerations**
  - Diminishing commercial opportunity as we move to shorter courses with fewer tablets in an era of antibiotic stewardship

Clinicians need more options to manage increasingly challenging patients; these do NOT have to better but perhaps safer or better compliance.

<u>Antibiotics should be judged on totality of factors not just efficacy.</u>

Encouraging signs

- Came to the meeting fearing the worst
- We have heard more signs of compromise and willingness to reach appropriate decisions
- Still some way to go but…
- How can Industry contribute to establishing the “new science” without jeopardizing future antibiotic R& D?
- Perhaps the shiraz was too good last night but onto April 1 & 2 with some optimism and hope?