Anti-infective Drugs Advisory Committee Meeting

November 18-20, 2008

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Meeting Objectives

- November 18:
  - Establish the treatment effect (M1) of antibacterial drugs for skin infections
  - Derive an NI margin (M2) based on clinical judgment of an acceptable loss of efficacy
  - Discuss trial design elements for skin and skin structure infections
- November 19 am:
  - Discuss NDA 22-110 Telavancin
- November 19 pm:
  - Discuss NDA 22-153 Oritavancin
- November 20 am:
  - Discuss NDA 22-269 Iclaprim

Introduction

- cSSSI: infected ulcers, burns, major abscesses and infections of deeper soft tissues
- uSSSI: simple abscesses, impetiginous lesions, furuncles, and cellulitis
- Guidance for Industry (draft): Uncomplicated and Complicated Skin and Skin Structure Infections-Developing Antimicrobial Drugs for Treatment
  - http://www.fda.gov/cder/guidance/2566dft.pdf

Epidemiology of SSSIs

- Majority caused by Gram positive organisms
  - *Staphylococcus aureus* (methicillin susceptible and resistant strains), *Streptococcus pyogenes,* and *Streptococcus agalactiae*
  - Some cSSSI associated with GNR and anaerobes
- Community-associated MRSA and SSSIs
  - MRSA isolated from 59% (range 15-74%) of adults presenting to ERs in 11 U.S. cities (Moran et al. NEJM 2006;355:666-74)
- Active Bacterial Core surveillance
  - 85% of invasive MRSA infections were healthcare-associated and 14% were community-associated (Klevens RM. JAMA 2007;298(15):1763-1771)

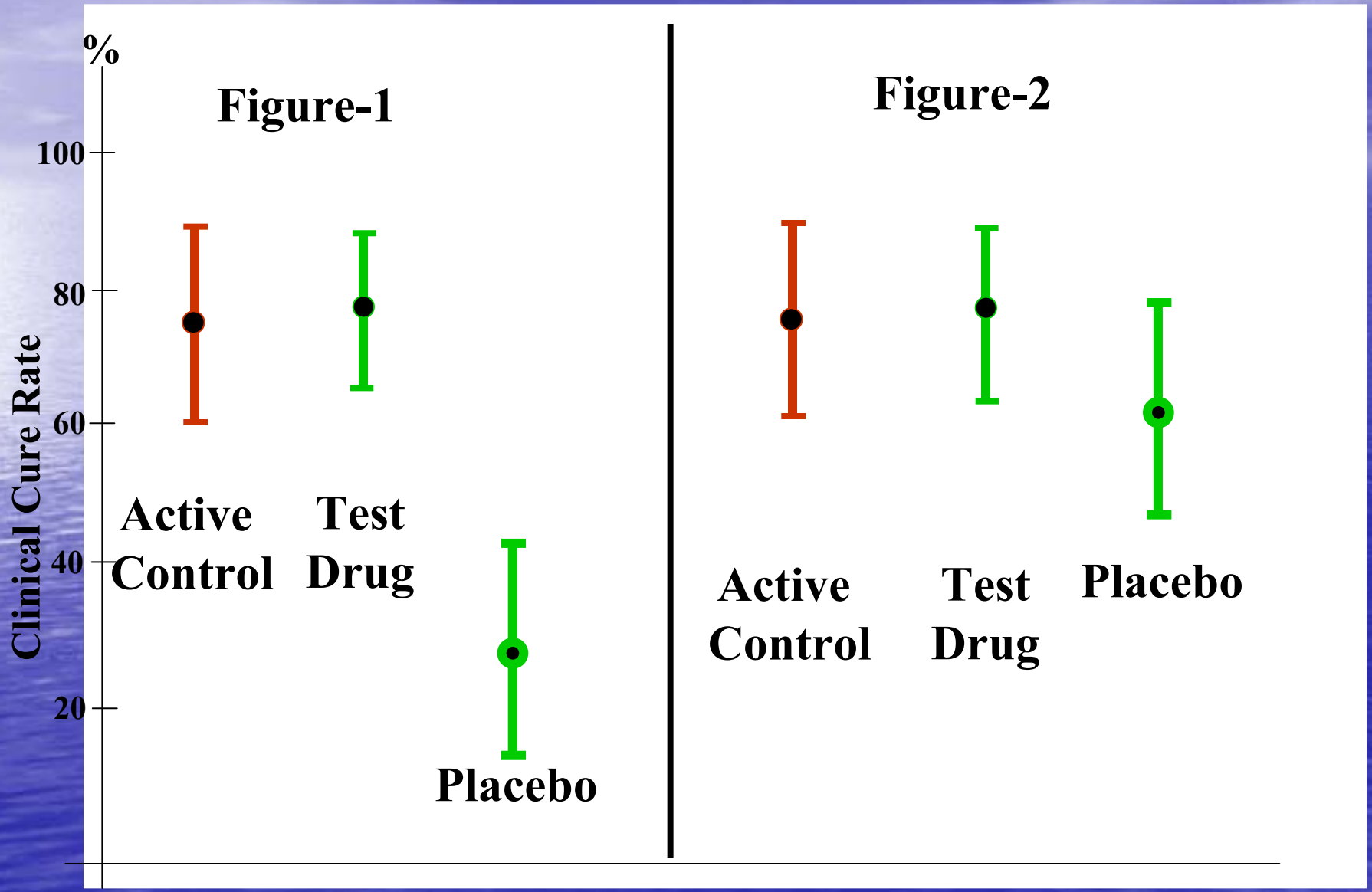
Regulatory Framework

- FD&C Act Amendment 1962 effectiveness requirement for substantial evidence
  - “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

Regulatory Framework

- 21 CFR 314.126 Adequate and well-controlled studies:
  - “the purpose of conducting clinical investigations is to distinguish the effect of the drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation”
  - “the study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect”

Active Controls and Noninferiority



Regulatory Framework

- Food and Drug Modernization Act 1997 section 115(a)
  - "data from one adequate and well-controlled clinical investigation and confirmatory evidence" may constitute *substantial evidence*
- Generally in cases where*:
  - Single multicenter trial of excellent design
  - Highly reliable and statistically strong evidence of important clinical benefit (e.g. survival)
  - Other pertinent info available (studies of other doses, regimens, dosage forms, other stages of disease, other populations, or different endpoints)

**See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products at http://www.fda.gov/cder/guidance/1397fnl.pdf*

Overview of Agenda and Issues

- November 18, 2008 all-day
  - Presentations to review evidence of treatment effect of antibacterial drugs for skin infections and NI margin justification by
    - FDA, Theravance, Targanta, Arpida and the Infectious Diseases Society of America
  - Issues for committee discussion:
    - acceptability of NI trials,
    - appropriate margins and endpoints,
    - timing of assessments,
    - and infection types for inclusion in new trials

Overview of Agenda and Issues

- November 19, 2008 a.m.
  - NDA 22-110 telavancin (TLV): Theravance and FDA presentations
  - Two phase 3 studies (0017 and 0018): randomized, double-blind, active-controlled, parallel group, multicenter and multinational studies of TLV 10 mg/kg IV q 24h vs. vancomycin 1 g IV q 12 h
  - Issues for committee discussion:
    - evidence of safety and effectiveness,
    - implications of animal repro/tox data for use in pregnant women and women of childbearing potential,
    - need for any risk management

Overview of Agenda and Issues

- November 19, 2008 p.m.
  - NDA 22-153 oritavancin (ORI): Targanta and FDA presentations
  - Two studies (ARRI and ARRD): randomized, double-blind, multicenter studies of
    - 200 mg ORI IV q 24 h vs. 15 mg/kg vancomycin IV q 12 h (study ARRI)
    - ORI 1.5 mg/kg IV q 24 h vs. ORI 3.0 mg/kg IV q 24 h vs. vancomycin 15 mg/kg IV q 12 h (study ARRD)
  - Issues for committee discussion:
    - evidence of safety and effectiveness considering primary endpoint and confidence intervals,
    - outcomes in patients with MRSA
    - weight-based dosing regimen in study ARRD

Overview of Agenda and Issues

- November 20, 2008 a.m.
  - NDA 22-269 iclaprim: Arpida and FDA presentations
  - Two phase 3 studies (ASSIST-1 and ASSIST-2): randomized, investigator-blinded, multi-center, active-controlled trials of iclaprim 0.8 mg/kg IV q 12 h vs. linezolid 600 mg IV q 12 h
  - Issues for committee discussion:
    - evidence of safety and effectiveness,
    - any possible limitations of the use of iclaprim considering comparative outcomes of iclaprim and linezolid,
    - any specific clinical situations where iclaprim might be used

Acknowledgements

- NI margin background working group: Sumati Nambiar, Thamban Valappil, Janice Pohlman, Alfred Sorbello, Scott Komo
- Review teams and other FDA staff for NDAs 22-110, 22-153 and 22-269
- FDA Advisors and Consultants Staff

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OAD RUNNERS
RUNNER'S
Foot Loc

Approach to determining non-inferiority margin in cSSSI

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Anti-Infective Advisory Committee Meeting
November 18, 2008

Outline

- Regulatory background
- Contemporary cSSSI trials
- Review historical studies used to estimate treatment effect of antibacterials in skin and skin structure infections
- Discuss uncertainties in the estimate of the treatment effect

Regulatory Background

- Most recent registrational trials for cSSSI and uSSSI have been non-inferiority trials; NI margin varied from 10-15%.
- Several discussions on the use of active-controlled non-inferiority trials as basis for approval of antimicrobials
  - Draft Guidance for Industry Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval (October 2007)
  - Sponsors are being asked to provide evidence to justify the proposed noninferiority margin for all indications

Regulatory Background

- Several antibacterials approved for cSSSI
  - Quinupristin/dalfopristin, linezolid, ertapenem, daptomycin, tigecycline, meropenem, moxifloxacin
  - Linezolid, daptomycin, tigecycline approved for cSSSI due to MRSA
- Several older antibacterials approved for SSSI, not differentiated as uncomplicated or complicated
  - Imipenem, ticarcillin-clavulanate, ampicillin-sulbactam, ceftriaxone

Contemporary cSSSI trials

- Disease definition:
  - Includes infections involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses
  - Excludes necrotizing fasciitis, secondarily infected dermatoses, and infections involving prosthetic materials.
- Active comparators: Vancomycin, linezolid, semi-synthetic penicillins (SSP), imipenem, piperacillin-tazobactam, amoxicillin/clavulanate.
  - concomitant aztreonam and metronidazole
  - oral switch after a period of parenteral therapy

Contemporary cSSSI trials

- Surgical interventions and local therapies allowed in the protocol have varied across studies.
  - Bedside surgical procedures versus planned surgical procedures
- Treatment duration: 7-14 days
- Primary endpoint: Clinical response of cure or failure based on resolution or improvement of signs and symptoms and the need for further antibacterial therapy as assessed by the investigator.
- Timing of assessment: 7-14 days after end of therapy.

Approach to estimation of NI margin

- Estimate antibacterial treatment effect
  - cSSSI
  - Uncomplicated skin and skin structure infections (uSSSI)
- Assess constancy of the treatment effect
  - Factors such as disease, patient populations, micro-organisms, endpoints, timing of assessment
- Estimate M1, the effect of active comparator over placebo accounting for uncertainties (discounting)
- Determination of M2 (NI margin) based on clinical judgment to preserve a fraction of M1

Methodology

- Literature search conducted to identify historical studies.
- For quantifying treatment effect:
  - Used data primarily from comparative studies to avoid cross study comparisons between treatment arm and control arm.
  - Endpoint assessed was relatively well defined and was not limited to mortality alone.
  - Timing of endpoint assessment was specified.
  - Proportions cured (n/N) at a specified time point were available.
  - Studies with only microbiologic endpoints were excluded.
- Natural history studies and single arm studies were used as supportive data.

Antibacterial Treatment Effect in Skin and Skin Structure Infections

- Natural history studies
- Placebo-controlled studies
  - cSSSI
    - None identified
  - uSSSI (primarily impetigo, superficial abscesses)
- Treated versus standard of care (non-antimicrobial therapy)
  - Erysipelas
  - Hand infections
- Case series of penicillin or sulfonamide-treated patients

Natural History Studies

Natural history studies: Necrotizing fasciitis

- Provides one of the earliest descriptions of untreated streptococcal gangrene.
  - 20 cases described; 7 had bacteremia.
- Some patients recovered with wound care alone; more severe ones progressed to systemic symptoms and often death.
- Treatment consisted of incision and drainage, excision of gangrenous skin, hot water soaks, etc.
- Outcome:
  - 15/20 recovered completely; 4/20 (20%) died; outcome unknown in 1.
  - Recovery occurred over a prolonged time period. Average time of grafting was 50 days.

Meleney FL. Archives of Surgery 1924

Natural history studies: Streptococcal bacteremia

- Report of 246 patients with hemolytic streptococcal bacteremia.
- Overall mortality was 72%
- 61/246 (~25%) had cellulitis/erysipelas
- 49/61 (80%) died

Keefer CS. Ingelfinger FJ, Spink WW. Archives of Intern Med 1937
; Re-published Rev Infect Dis Sept 1986

Natural history studies: *S. aureus* bacteremia

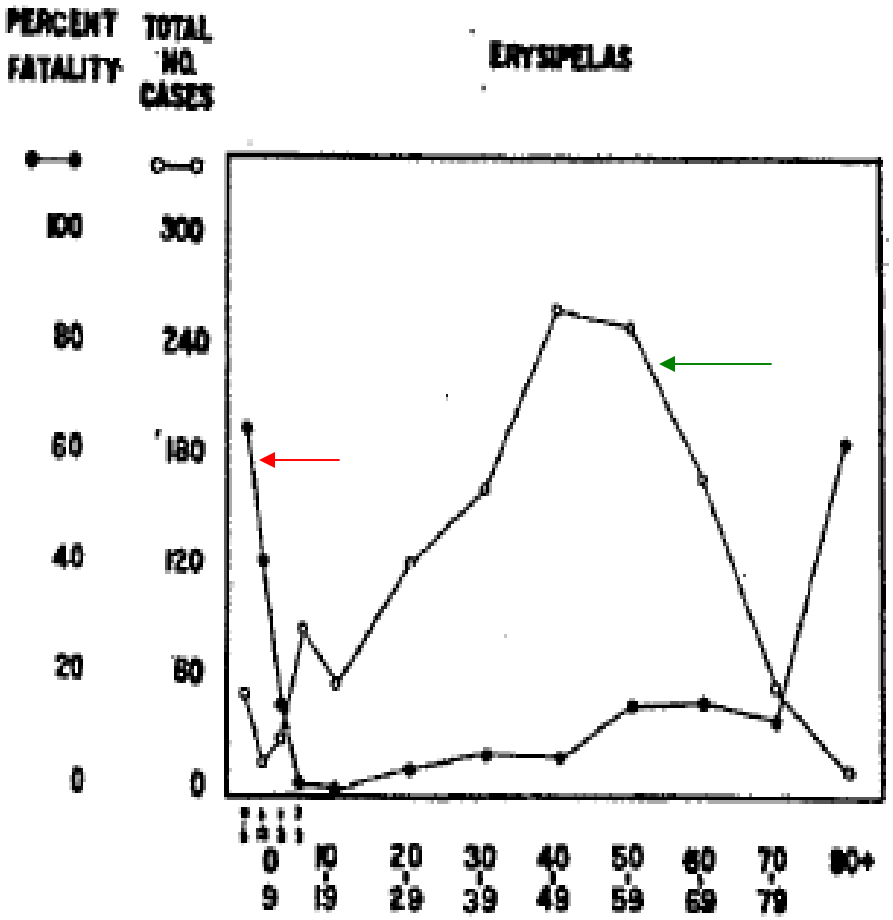
- 122 cases of *S. aureus* bacteremia at Boston city Hospital; 22 recovered.
- Portal of entry was skin in 57 (46.7%)
  - Boils and carbuncles, infected wounds, others
- Mortality:
  - 63/75 (84%) patients who received only general care
  - 33/42 (78.6%) received general care plus sulfonamides
  - 4/4 treated with antitoxin

Skinner and Keefer Archives Internal Medicine Nov 1941

Treated vs. standard of care (Non-Antimicrobial)

Erysipelas

- Although not always a severe disease, it can be associated with mortality in the more severe cases especially at the extremes of age.



Keefer CS. NEJM 1938

Studies in erysipelas

- Study of 312 cases (Feb 1936-May 1936) that assessed treatment with Prontosil, a synthetic antibacterial that was later shown to be a prodrug of sulphanilamide.
- Methods:
  - First 161 cases were allocated to 3 groups in order of admission; Group 1 UV light only, Group 2 Prontosil only and Group 3 UV light plus Prontosil.
  - The second 151 cases were allocated to 3 groups; first two were same as above and the third was treated with scarlet fever antitoxin.
- Patient characteristics:
  - Authors state that duration of disease before admission to hospital, age of the patient, severity of the infection, and associated diseases were similar in the groups.
  - All groups were treated under similar conditions (wards, nursing staff).
- Treatments were given during the acute stage only; each case was reviewed daily.

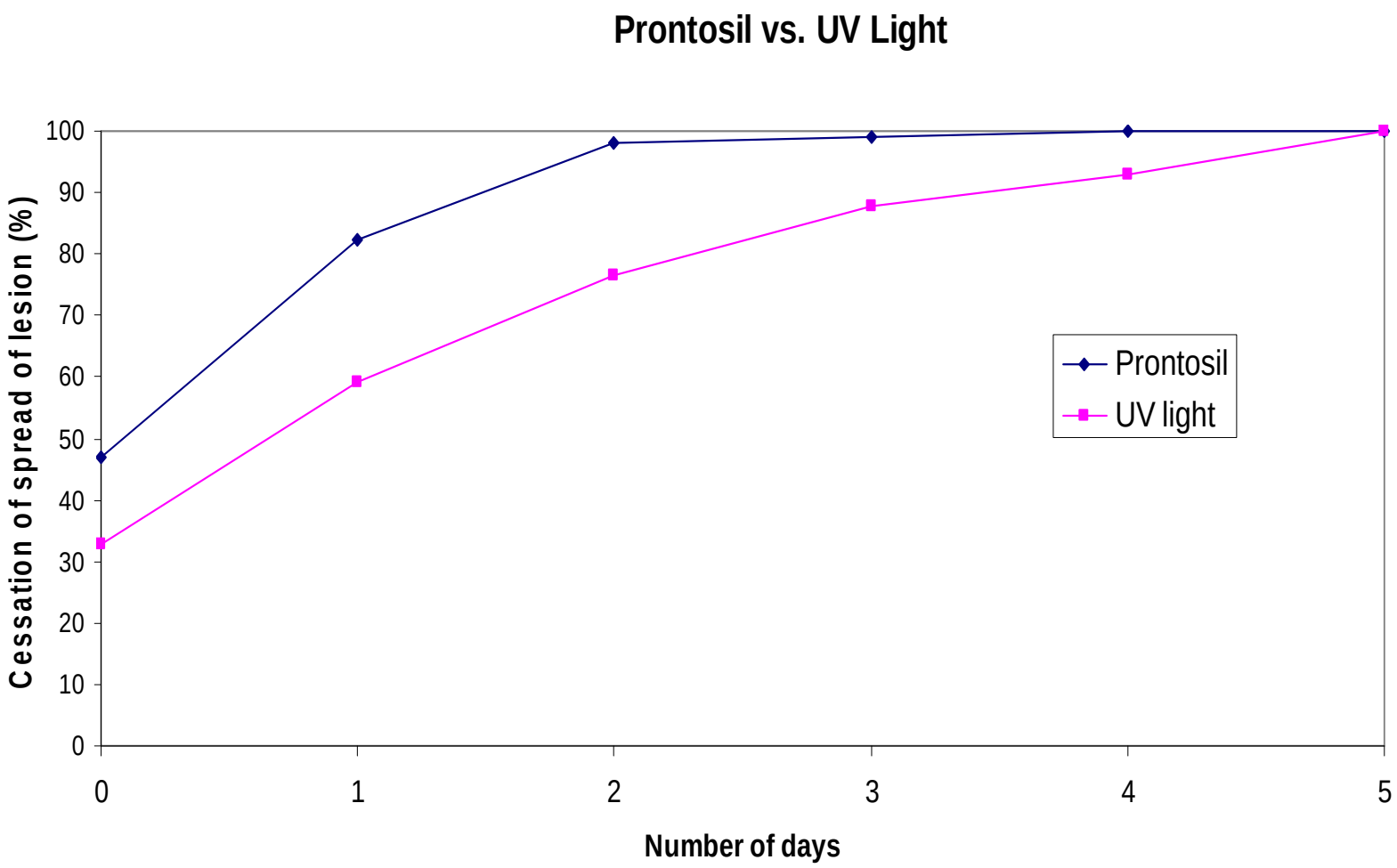
Snodgrass WR and Anderson T BMJ July 1937

Outcomes at 48 hours

Endpoint	Prontosil n=106	UV light n=104	Treatment difference (95% CI)
Cessation of spread of lesion	100/102 (98.0%)	75/98 (76.5%)	21.5% (11.7%, 31.3%)*
	100/106 (94.3%)	75/104 (72.1%)	22.2% (11.6, 32.9)
Resolution of pyrexia	70/92 (76.1%)	43/89 (48.3%)	27.8% (13.1%, 42.4%)*
	70/96 (72.9%)	43/95 (45.3%)	27.7% (13.2, 42.1)

* Excludes fatal cases n=10

Snodgrass and Anderson T BMJ, July 1937


Prontosil vs. UV Light
Cessation of spread of lesion (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
Number of days
Prontosil
UV light

Studies in erysipelas

- The three main objectives of this study were:
  - To study the therapeutic benefits of sulphanilamide in erysipelas
  - To study the effects of a larger and more prolonged dose of sulphanilamide
  - To study the effects of varying dosage of sulphanilamide in the first 12 hours.
- Cases were assigned to two treatment groups (sulphanilamide or UV light) in the order of admission
  - 270 cases were enrolled, 135 in each group
  - 1, 2, or 3 grams of sulphanilamide were given at 4 hourly intervals till temperature became normal, followed by 0.75 grams three times a day till discharge
- Authors state that the two treatment groups were similar in terms of patient characteristics and were treated under similar conditions.

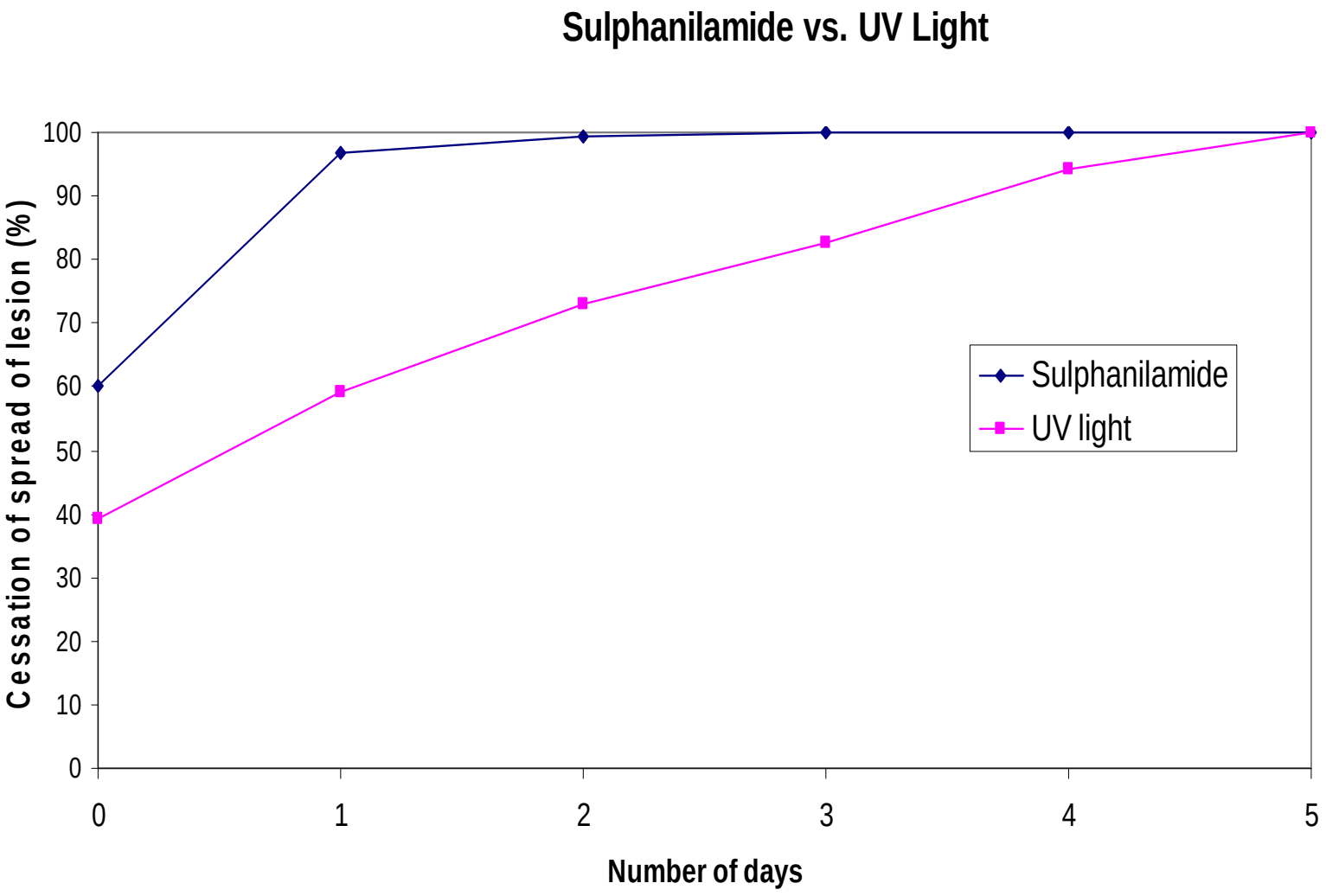
Snodgrass WR and Anderson T, BMJ Dec 1937

Outcomes at 48 hours

Endpoint	Sulphanilamide n=135	UV light n=135	Treatment difference (95% CI)
Cessation of spread of lesion	129/130 (99.2%) 129/135 (95.6%)	89/122 (73.0%) 89/135 (65.9%)	26.3% (17.5%, 35.1%)* 29.6 % (20.2%, 39.1%)
Resolution of pyrexia	94/125 (75.2%) 94/130 (72.3%)	53/112 (47.3%) 53/125 (42.4%)	27.9% (15.1%, 40.7%)* 30.0% (17.5%, 42.3%)

*Excludes fatal cases (n=6) and 12 “failed” UV cases

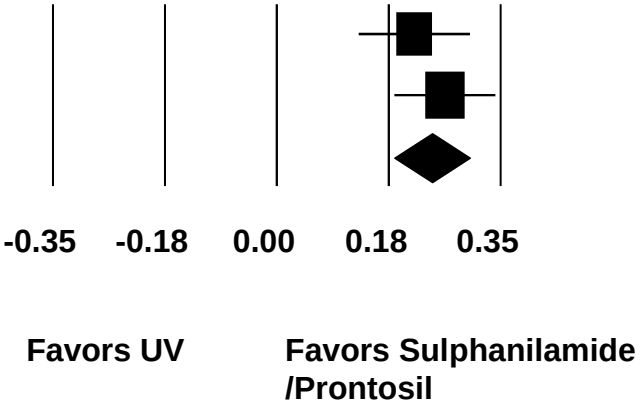
Snodgrass WR and Anderson T, BMJ Dec 1937


Sulphanilamide vs. UV Light
Cessation of spread of lesion (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
Number of days
Sulphanilamide
UV light

Cessation of spread of lesion at 48 hours

Drug	Statistics for each study			
	Risk difference	Standard error	Lower limit	Upper limit
Prontosil	0.215	0.045	0.127	0.303
Sulphanilamide	0.263	0.041	0.183	0.343
Random	0.241	0.030	0.182	0.300

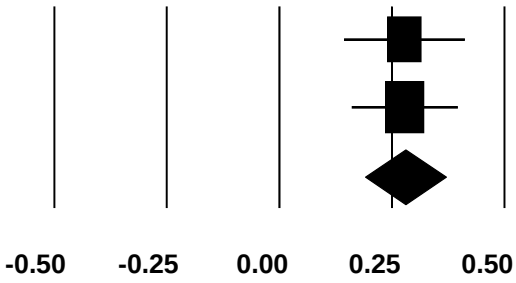
Risk difference and 95% CI



Resolution of fever at 48 hours

Drug	Statistics for each study			
	Risk difference	Standard error	Lower limit	Upper limit
Prontosil	0.278	0.069	0.142	0.413
Sulphanilamide	0.279	0.061	0.159	0.398
Random	0.278	0.046	0.189	0.368

Risk difference and 95% CI



Favors UV **Favors Sulphanilamide /Prontosil**

Other erysipelas studies

- Several historical studies compared UV light therapy to other topical therapies.
- In most studies, patients treated with UV light had better outcomes compared to those treated with various local therapies (ichthyol, glycerine, iodine, magnesium sulfate) or antitoxin.
  - Mortality was lower in UV light-treated cases.
  - Time to resolution of local signs or fever was shorter in UV-light treated patients.
- Unable to quantify the treatment effect as proportion of patients who had complete resolution of signs and symptoms at a fixed time point was not reported.

Ude WH. JAMA 1930; Sutherland DS. The Medical Officer 1935

Treatment effect in erysipelas

- Based on the two meta-analysis shown, the treatment effect of sulfonamides over UV light for clinical endpoints assessed at 48 hours was:
  - Cessation of spread of lesion: 24.1% (95% CI, 18.2%, 30.0%).
  - Resolution of fever: 27.8% (95% CI, 18.9%, 36.8%).
- It appears that UV light had beneficial effect compared to various local therapies.
- Treatment effect of sulfonamides over placebo is likely to be greater than the effect of sulfonamides over UV light.

Hand Infections

- Alternate cases were assigned to penicillin therapy.
  - Cases were treated with topical penicillin (3 received oral sulphonamides).
  - Controls received various local applications and in the more severe cases received oral sulphonamides.
- Surgical methods were same in both groups; same surgical team operated on both groups.
  - Controls: Wounds were packed with paraffin gauze at operation and later with eusol preparations.
  - Penicillin group: Wounds were powdered with the calcium salt of penicillin and packed with gauze soaked in penicillin paste. Dressings were repeated daily for minimum of 5 days.
- Cases were followed daily in the acute phase; long term follow up ~ 6 months.
- Group A Streptococci and *Staphylococcus aureus* were the most commonly identified organisms.

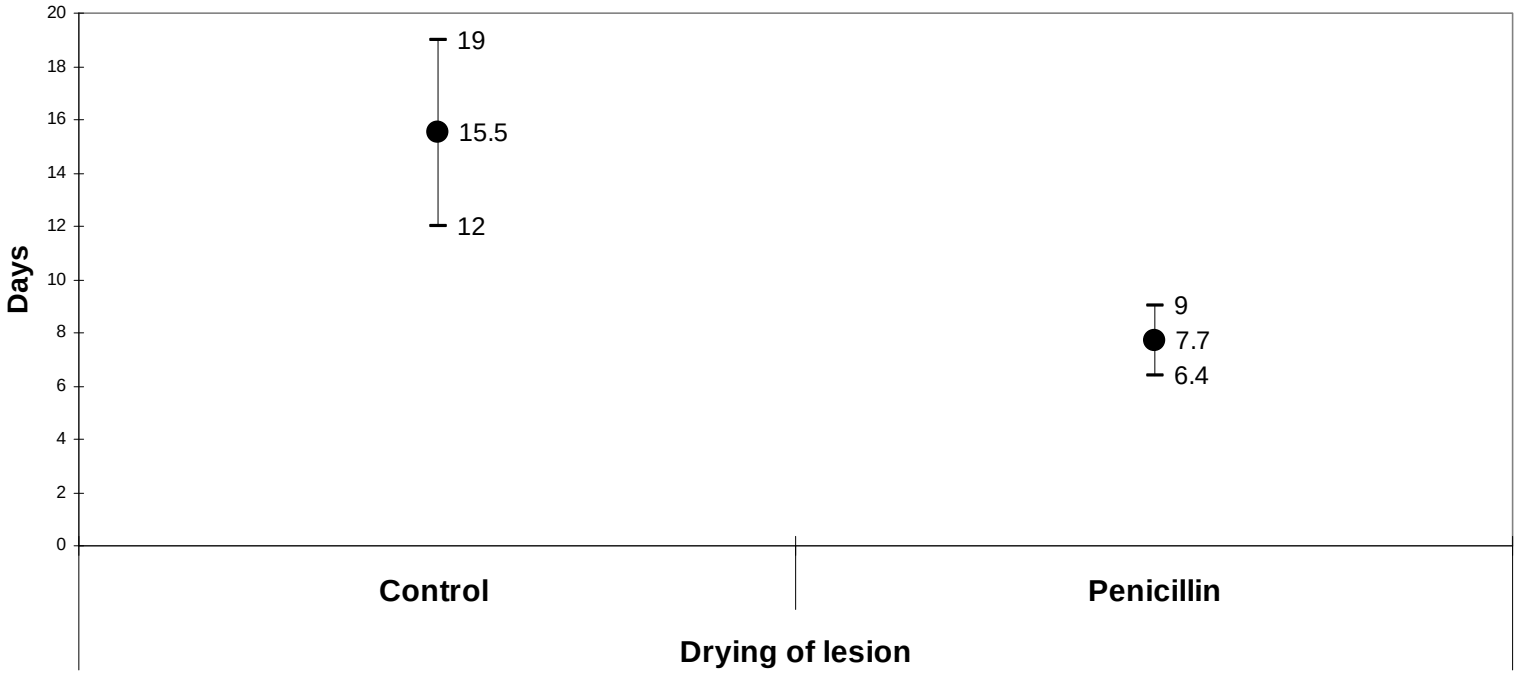
Florey ME, Williams REO. Lancet 1944

Infection types

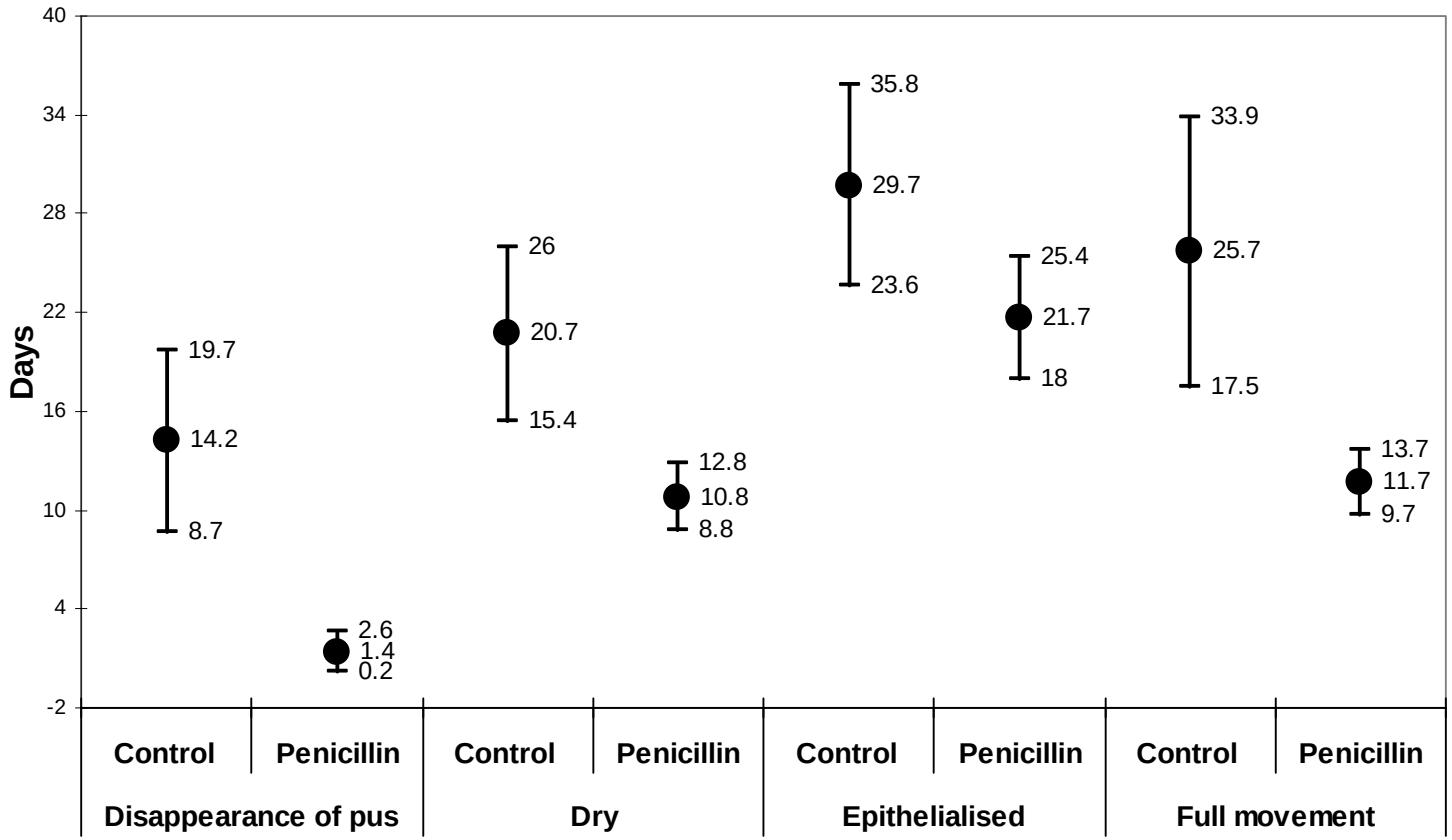
Site of infection	Control (n=102)	Penicillin-treated (n=110)
Paronychia	26	26
Pulp Infection	27	28
Web-space infection	9	9
Tendon Sheath infection	11	11
Abscesses	12	12
Others*	17	24

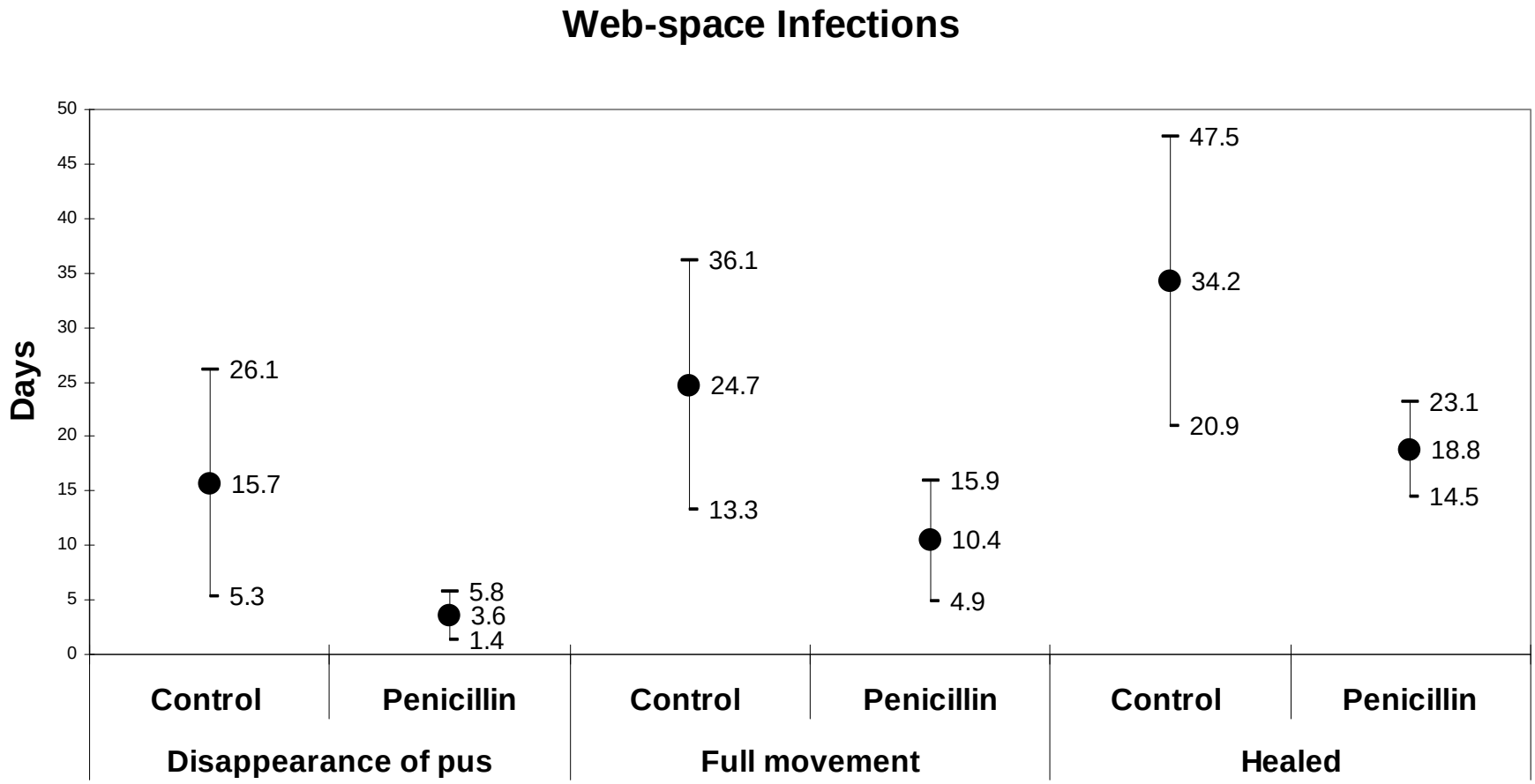
* Septic lacerations of hand, septic wounds, septic dermatitis

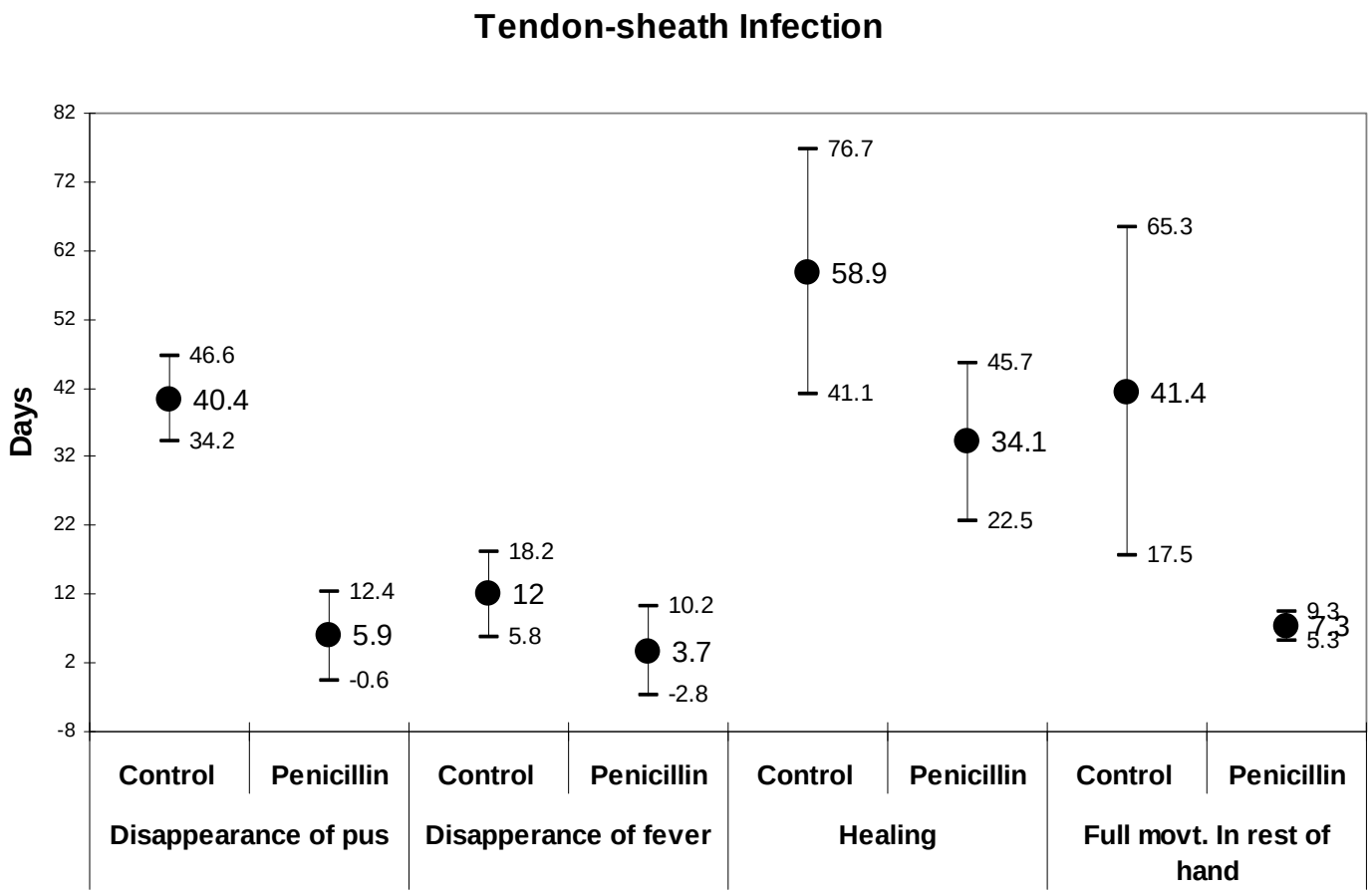
Paronychia


Days
20
18
16
14
12
10
8
6
4
2
0
19
15.5
12
9
7.7
6.4
Control
Penicillin
Drying of lesion

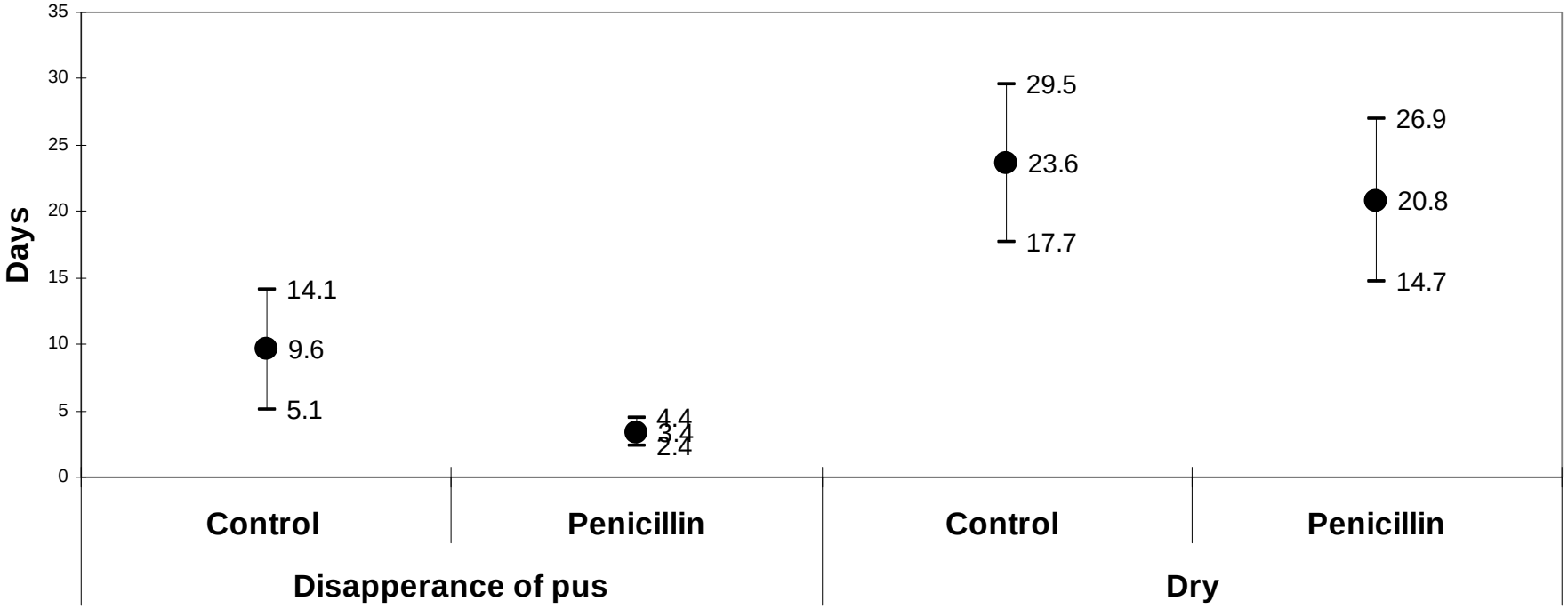
Simple Pulp Infections




Web-space Infections
Days
50
45
40
35
30
25
20
15
10
5
0
26.1
15.7
5.3
5.8
3.6
1.4
36.1
24.7
13.3
15.9
10.4
4.9
47.5
34.2
20.9
23.1
18.8
14.5
Control
Penicillin
Control
Penicillin
Control
Penicillin
Disappearance of pus
Full movement
Healed


Tendon-sheath Infection
Days
82
72
62
52
42
32
22
12
2
-8
46.6
40.4
34.2
12.4
5.9
-0.6
18.2
12
5.8
10.2
3.7
-2.8
76.7
58.9
41.1
45.7
34.1
22.5
65.3
41.4
17.5
9.3
7.3
5.3
Control
Penicillin
Control
Penicillin
Control
Penicillin
Control
Penicillin
Disappearance of pus
Disapperance of fever
Healing
Full movt. In rest of hand

Abscesses


Days
35
30
25
20
15
10
5
0
14.1
9.6
5.1
4.4
3.4
2.4
29.5
23.6
17.7
26.9
20.8
14.7
Control
Penicillin
Control
Penicillin
Disapperance of pus
Dry

Treatment Effect: Disappearance of pus

Infection type	Controls mean time, days (n)	Penicillin mean time, days (n)	Mean Difference, days (control-penicillin), (95% CI)
Pulp infection	14.2 (n= 21)	1.4 (n=22)	12.8 (7.2, 18.4)
Web-space infection	15.7 (n=9)	3.6 (n=9)	12.1 (1.5, 22.7)
Tendon sheath infections	40.4 (n=10)	5.9 (n=11)	34.5 (25.5, 43.5)
Abscesses	9.6 (n=12)	3.4 (12)	6.4 (1.6, 10.8)

Summary of treatment effect

- Overall, penicillin-treated patients had better clinical outcomes :
  - Pus had disappeared or was scanty within a week from surgery; in controls, it continued from 3-113 days.
  - Mean healing time was reduced
  - There was a great reduction in the number of dressings required and rapid return of mobility of the infected part.
  - Among pulp or tendon-sheath infections (35 penicillin-treated cases compared to 35 controls), working time saved by penicillin treatment was 1000 days.

Case series

Sulfonamide-treated

- Long PH. JAMA 1937: 19 cases treated with para-amino-benzene sulfonamide and its derivatives:
  - 7 cases had SSSI; 6 recovered, one died (cellulitis and bacteremia)
- Keefer CS. NEJM 1938: 17 cases of streptococcal infections treated with sulfanilamide.
  - 9 cases of hemolytic streptococcal infection with bacteremia; 3 died; all 3 who had SSTI survived.
  - 8 cases of localized infection without bacteremia, 1 had cellulitis; there were no deaths.

Penicillin-treated

- Lyons C. JAMA 1943:
  - Penicillin was administered IV, IM or locally; 49/57 (86%) patients improved.
- Garrod LP BMJ 1943:
  - 171 cases of recent (3-12 day old) infected soft- tissue wounds.
  - All underwent immediate closure; penicillin was administered through tubes inserted at operation twice daily for 4 days.
  - 104/171 (60.8%) had complete union, 60/171 (35%) had subtotal union, i.e. healing by granulation and 7/171 (4%) failed.
- Meleney FL. Annals of Surgery 1946:
  - 744 cases of surgical infections treated with systemic or topical penicillin
  - 340 patients had SSSI
  - Overall cure rates was ~72%; higher in patients with cellulitis and furuncles compared to those with ulcers/ infected burn.

Cure rate by infection type

Diagnosis	Total	Cure %
Furuncle	26	92.3
Cellulitis	36	91.7
Carbuncle	28	82.2
Superficial abscess	32	81.3
Deep abscess	58	68.9
Infected wound	107	63
Ulcer	22	50
Infected burn	31	45.2
Total	340	71.8

Meleney FL. Annals of Surgery 1946

Penicillin case series

- Lockwood JS et al. Annals of Surgery 1944:
  - 440 medical and surgical cases treated with systemic penicillin.
  - Of the 57 cases of staphylococcic bacteremia, two thirds survived; source of bacteremia was not specified.
  - Only a few cases of boils/carbuncles were treated. Clinical improvement usually occurred 2-3 days after commencing therapy.
- Keefer CS JAMA 1943:
  - 500 cases of various types of infections, penicillin was administered IV, IM or locally.
  - 91 patients had *S. aureus* bacteremia; 34/91 (37%) died; 10 had SSSI and all recovered.
  - Of the 137 cases without bacteremia, 23 had cSSSI;19 recovered and 4 failed

uSSSI: Placebo-controlled studies

Placebo-controlled studies in uSSSI

- Impetigo
  - Studies assessing topical antibacterial therapies
    - Retapamulin vs. placebo
    - Mupirocin vs. placebo (Gould, Eells, 1986)
- Other superficial skin lesions
    - Erythromycin vs. placebo (Burnett 1962)
    - Cloxacillin vs. placebo (Eaglstein 1977)
    - Procaine penicillin vs. placebo (Bower 1984)
- Superficial abscesses
    - Cephalexin vs. placebo (Rajendran 2007)
    - Cephradine vs. placebo (Llera 1985)

Summary of treatment effect in impetigo

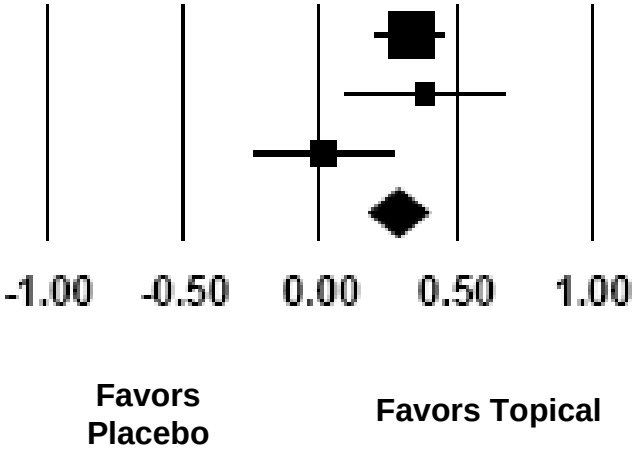
Study	Agent	Success rate Active drug	Success rate Control	Treatment difference, 95% CI
Retapamulin Phase 3 study	Retapamulin	119/139 (85.6%)	37/71 (52.1%)	33.5% (19.4%, 47.6%)
Gould (1986); subgroup with impetigo	Mupirocin	12/17 (70.6%)	7/22 (31.8%)	38.8% (4.4%, 73.1%)
Eells (1986)	Mupirocin	17/26 (65.4%)	16/25 (64%)	1.4% (-28.8%, 31.6%)

Treatment effect in impetigo

Meta Analysis

Study name	Statistics for each study			
	Risk difference	Standard error	Lower limit	Upper limit
Retapamulin	0.335	0.066	0.205	0.465
Gould	0.388	0.149	0.097	0.679
Eells	0.014	0.134	-0.249	0.276
	0.288	0.055	0.180	0.396

Risk difference and 95% CI



Summary of antibacterial treatment effect in SSSI

- Sulfonamides compared to UV light in erysipelas:
  - Endpoints were assessed at 48 hours.
    - Cessation of spread of lesion: 24.1% (95% CI, 18.2%, 30.0%)
    - Resolution of pyrexia: 27.8% (95% CI, 18.9%, 36.8%).
- Topical antibacterial therapies compared to placebo in impetigo:
  - Endpoint was assessed at end of therapy (7-9 days)
    - Resolution/improvement in signs and symptoms: 28.8% (95% CI, 18.0%, 39.6%).

Summary of antibacterial treatment effect in SSSI

- Systemic erythromycin compared to placebo in impetigo and other uSSSI:
  - Timing of assessment was not clear; if continual improvement did not occur, they were declared a failure
    - Resolution/improvement in signs and symptoms: 61.9% (95% CI, 43.5%, 80.3%).
- Cephalexin compared to placebo in addition to I&D in superficial skin abscesses:
  - Endpoint assessed at end of therapy, 7 days after I&D.
    - Resolution of signs and symptoms: -6.4% (95% CI, -16.4%, 3.8%)
- Natural history studies:
  - Mortality in untreated staphylococcal and streptococcal bacteremia (some had skin as portal of entry) was very high (70-80%); reduction in mortality was seen since introduction of antibacterials.

Constancy of treatment effect

- In cSSSI, as currently defined, it is likely that the treatment effect will at least be the same or greater than that seen in the studies of erysipelas or impetigo.
- Benefits of antibacterials were seen in several types of skin infections; similar infection types are enrolled in current cSSSI trials.
- *S. aureus* and *S. pyogenes* were the main organisms isolated in historical studies and are also the most common organisms identified in present trials.

Uncertainties in the estimate of treatment effect

- Endpoint:
  - In the erysipelas studies treatment effect was assessed at 48 hrs
    - Endpoint was cessation of spread and not resolution
    - In present trials, patients not improving by 48-72 hours classified as failure and switched to alternative therapy
  - In impetigo studies, treatment effect was assessed at end of therapy (7-9 days after start of therapy).
  - In patients with hand infections, by 1 week most penicillin treated patients were cured, while the control group remained symptomatic for much longer.

Uncertainties in the estimate of treatment effect

- Patient Populations:
  - Patients in present trials have more comorbidities such as obesity, diabetes mellitus and renal impairment
  - Ancillary care including wound management is likely to be superior in present trials
- Case definition: cSSSI represents a spectrum of diseases and not one clinical condition:
  - Cure rates higher in patients with cellulitis and lower in those with wound infections or ulcers
  - No treatment effect with antibacterials beyond I&D in superficial abscesses; applicability to deeper abscesses uncertain.

Uncertainties in the estimate of treatment effect

- Treatment effect could be an underestimate:
  - Treatment effect with present day antibacterials is likely to be higher.
  - Treatment effect with sulfonamides over placebo could be greater than that seen over UV light.
- Treatment effect could be an overestimate:
  - Cure rates for cessation of spread of lesion in erysipelas may not be directly applicable to all types of cSSSI
  - With improved supportive and wound care, treatment effect with antibacterials is difficult to discern

Conclusions

- In erysipelas, there is a treatment effect for the clinical endpoints of cessation of spread of lesion and resolution of fever assessed at 48 hours.
- In impetigo, there is a treatment effect for the clinical endpoint of cure based on resolution/improvement in signs and symptoms at the end of therapy (7-9 days after starting therapy).
- In superficial skin abscesses, there is no treatment effect with antibacterials beyond that achieved with I&D alone.
- Natural history studies and case series provide supportive evidence for antibacterial treatment effect in cSSSI.

Points to consider

- Can we assume that the treatment effect for cSSSI is at least as large as seen in erysipelas/uSSSI studies?
- Can we conclude that the historical treatment effect (M1) of antibacterial drugs in cSSSI is quantifiable based on the historical data presented given its limitations?
- If the treatment effect is quantifiable, how much of it should be discounted and how much should be preserved?

- "*Since the introduction of sulphanilamide as a remedy in streptococcal infections, we have a drug of utmost value in the general treatment of erysipelas…..*"

- *"Sulphanilamide may be prescribed at any stage of erysipelas, but of course the sooner it is given the sooner will it cut short the attack. In most cases it has a profound, sometimes dramatic effect: the temperature drops to normal in 48 hrs or less, the rash fades, and the patient feels better. Although left untreated, it will run its own course and disappear, the treatment is planned to shorten the course of the disease and add to the comfort of the patient".*

Hosford BMJ 1938

Non-Inferiority Margin for cSSSI: Issues and Considerations

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Anti-Infective Advisory Committee Meeting
November 18, 2008

Outline

- Objectives in a Non-Inferiority (NI) Trial
- Critical Elements
- Statistical Uncertainties
- Limitations of Meta-Analysis
- Discounting and Preservation
- Steps involved in the NI Margin Determination for cSSSI

Objectives in a NI Trial

Non-Inferiority trials are designed to:

- Determine whether the effect of a new treatment is not unacceptably worse compared to an active control treatment (based on a pre-specified NI margin).

AND

- Ensure that the control effect relative to placebo is consistent under the conditions of the trial.

Superiority and Non-Inferiority Trials

- Superiority trials provide direct evidence of treatment effect.
  - Objective is to demonstrate that the new drug is statistically superior to a placebo or to an active control
  - Superiority trials are always preferred, if possible.
- Non-inferiority trials provide indirect evidence of treatment effect.
  - Any new drug must be compared to an established active control that has demonstrated treatment effect <u>based on data external to the trial</u>.
  - Interpretation of the results can be misleading due to lack of assay sensitivity or constancy assumptions.

Primary NI Hypothesis

In a non-inferiority trial, the null hypothesis is that the degree of inferiority of the new drug (T) to the control (C), is greater than or equal to the margin, M.

H_0 : C - T ≥ M (T is inferior to C)
H_1 : C - T < M (T is not inferior to C)

(or H_0 : T - C ≤ -M; H_1 : T - C > -M)

Non-inferiority will be concluded if the lower bound of the two-sided 95% CI for the difference between C-T < M.

Components of NI Margin

M1: Active control treatment effect estimated from historical placebo-controlled studies (Statistical Margin).

M2: Clinically acceptable loss of efficacy for the new drug compared to the active control with respect to the primary endpoint;

$M2 < M1$.

ICH-E10 "Choice of Control Group and Related Issues in Clinical Trials"

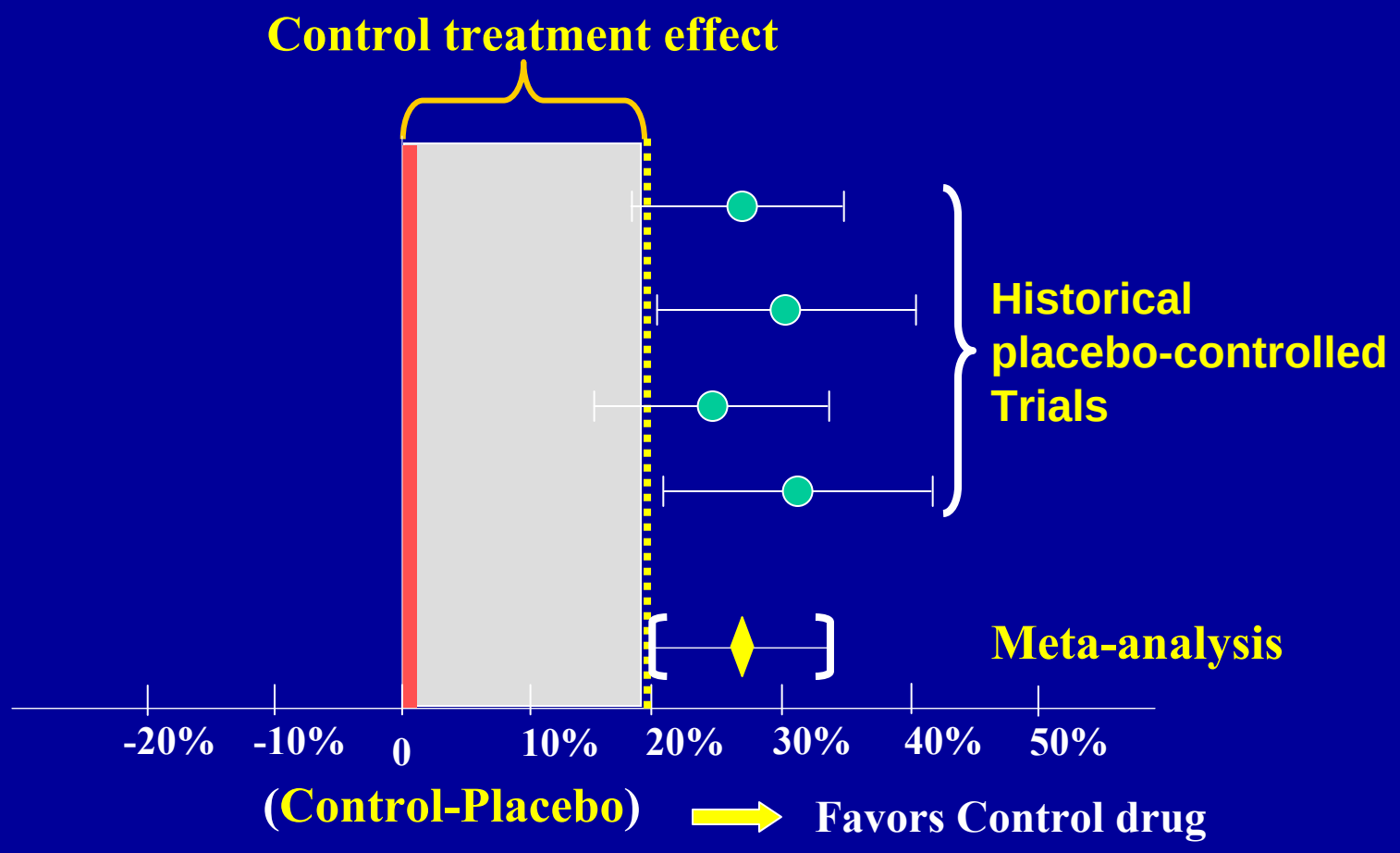
- "The non-inferiority trial design is appropriate and reliable only when the historical estimate of drug effect size can be well supported by reference to the results of previous studies of the control drug."

- A non-inferiority margin (M) is defined as "the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator".

- "The margin chosen for a non-inferiority trial cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo <u>in the setting of the planned trial"</u>.

When is it appropriate to consider non-inferiority trials?

Historical Treatment Effect (Point estimate, 95% CI)



Critical Elements for NI Trials

- Historical Evidence of Sensitivity to Drug Effect (HESDE)
- Assay sensitivity
- Constancy of the active control effect

Historical Evidence of Sensitivity to Drug Effects (HESDE)

- HESDE exists if an active control drug has reliably demonstrated a superior treatment effect compared to placebo or some other related drug(s) based on appropriately designed, and well conducted historical studies using a particular endpoint.

Assay Sensitivity

- Refers to the ability of the NI trial to distinguish an effective treatment from a less effective or ineffective treatment.
- Evaluating whether a trial will have assay sensitivity is based upon:
  - Historical Evidence of Sensitivity to Drug Effect (HESDE)
  - Similarity of the new NI trial to the historical trials
  - Quality and conduct of the new NI trial

Constancy of the Active Control Effect

- Refers to the similarity of the current NI trial to the historical studies.
- The conclusion that HESDE can be used for future NI trials is possible only if the NI trial is sufficiently similar to the historical studies with respect to all important study design features that might influence the effect size of the active control.
- The metric chosen to represent the treatment effect is an important factor to consider (e.g. Risk Difference, Relative Risk(RR), Odds Ratio, log(RR), or Hazard Ratios).

Statistical Uncertainties in NI Trials

- Lack of reliability, uncertainty in magnitude and lack of precision of the active control treatment effect.
- Validity of constancy assumption. Can we assume that the active control treatment effect in the NI trial and historical studies is similar?
- Poor trial design and conduct can introduce bias and has the potential to erroneously conclude non-inferiority.

Statistical Uncertainties contd…

- Non-compliance, misclassification of outcomes and informative missing values are problematic issues.
- Simulation studies have shown that misclassification of outcomes can inflate the overall type-I error rate in a non-inferiority trial.
- Confounding factors such as use of concomitant medications or adjunctive therapies can potentially bias the efficacy results.

Meta-Analysis in Estimating M1

- Used Meta analysis to obtain collective evidence of treatment effect from historical studies.
- Historical studies have several limitations that could impact the meta analysis results.

Limitations of Meta-Analysis in Estimating M1

- Tendency to over-estimate treatment effect due to publication bias
- Pooling effect size from studies in which the historical estimates may not be stable (e.g. observational studies or case series)
- Heterogeneity in treatment effects due to difference in disease characteristics, endpoints, and design features
- Analysis including small and large studies
- Limited data and lack of generalizability

Determination of M1 and M2 (or NI Margin)

- The historical active control treatment effect compared to placebo (M1), is derived using:
  - Two-sided 95% CIs for the treatment difference between the active control and placebo.
  - It is important to discount for all potential uncertainties.
- NI margin, M2 is derived based on preserving a fraction **(≥ 50%)** of the discounted M1 using clinical judgment.
- Substantial preservation of the treatment effect ensures that new drug is more effective than "placebo".

Discounting and Preservation of Active Control Treatment Effect

Discounting:

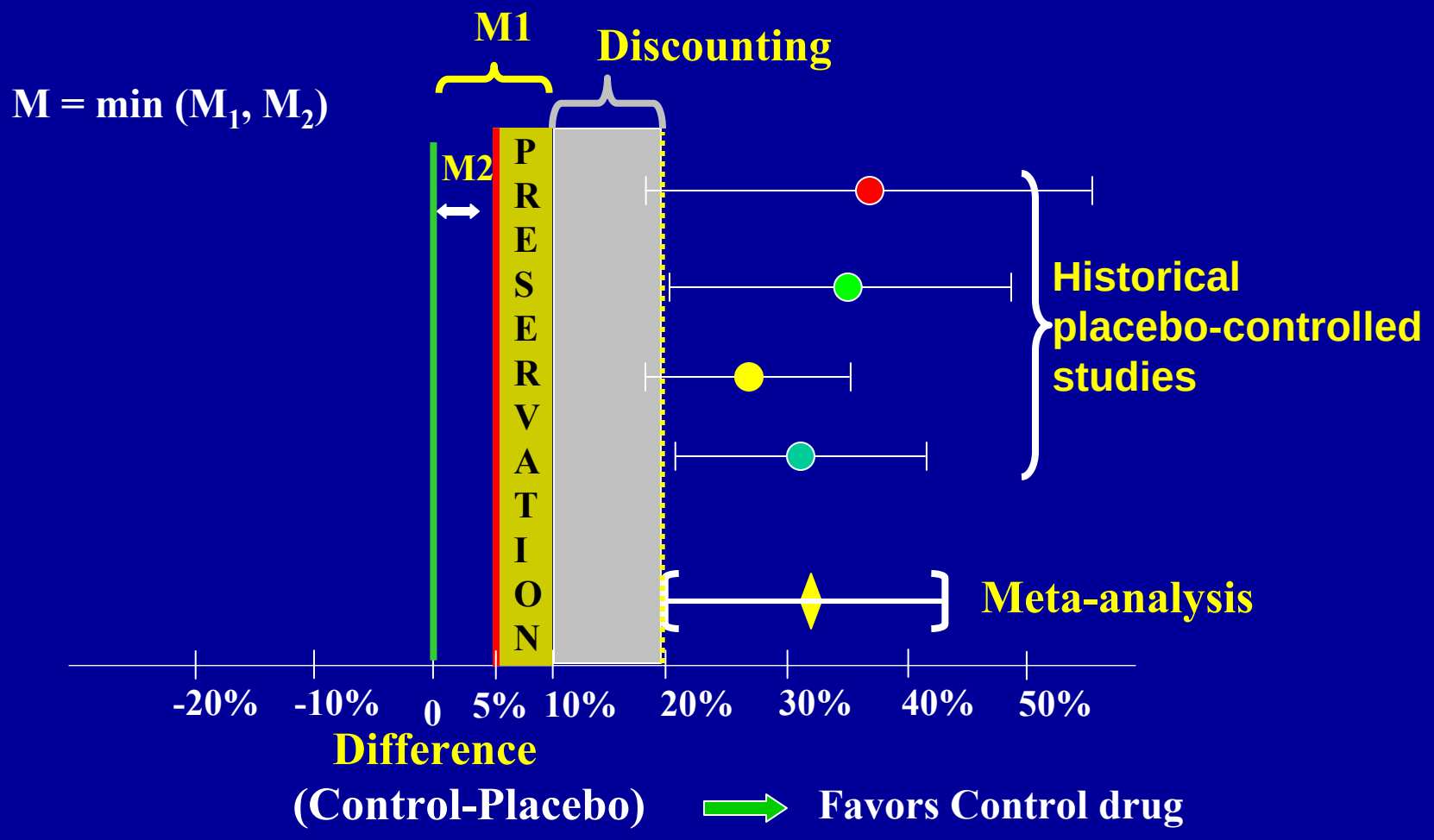
- Reduction in the magnitude of the active control treatment effect (M1) determined from the HESDE to account for the variability and statistical uncertainties.

Preservation:

- The proportion of the control effect preserved based on clinical judgment **(it can be ≥ 50%)**
- Higher rate of preservation is warranted when treatment failures result in irreversible outcome such as mortality.

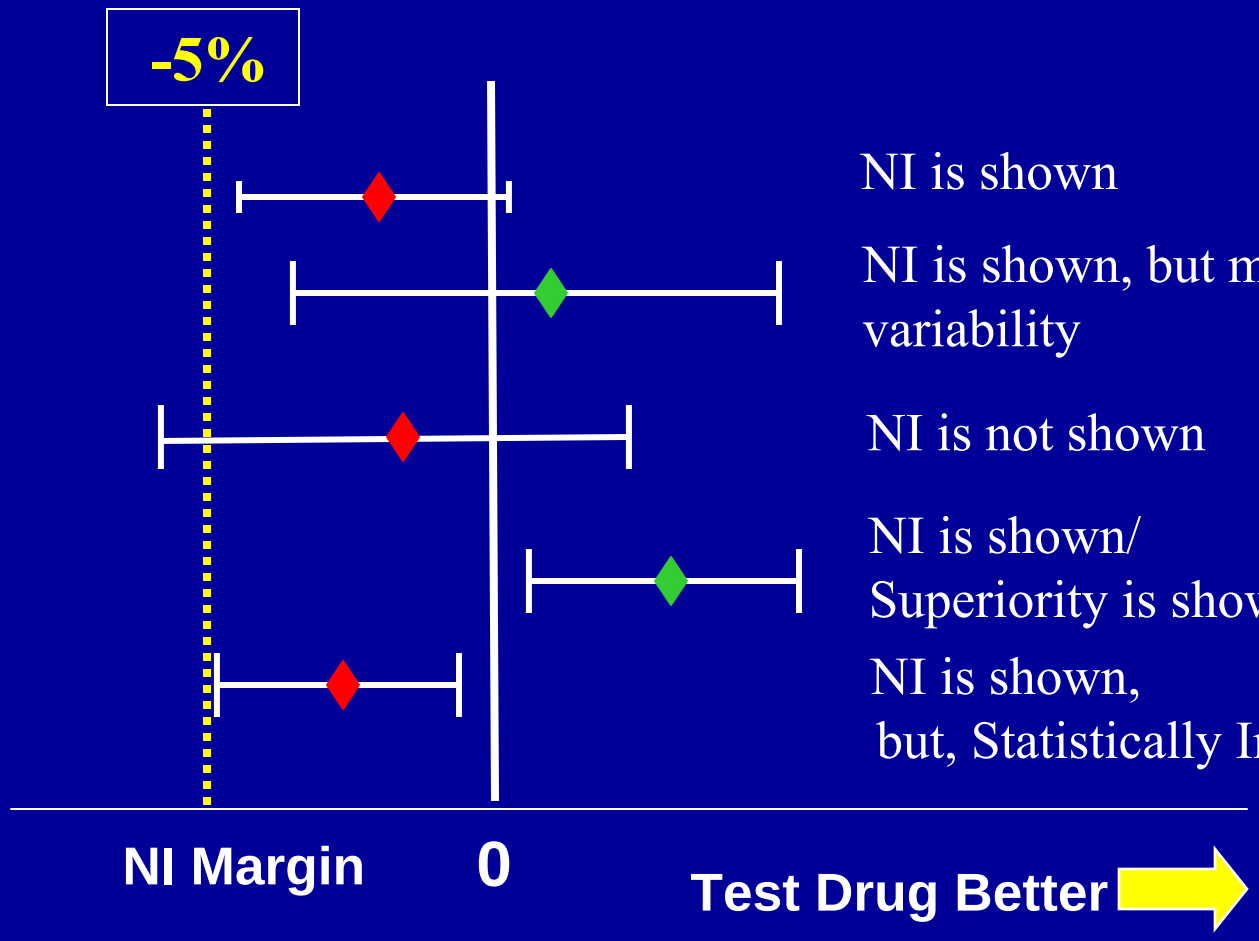
Example: Quantifying Active Control Effect

(Point estimate, 95% CI)



Non-Inferiority Inference

Treatment Difference (Test Drug – Control)
95% Confidence Intervals



NI is shown	(1)
NI is shown, but more variability	(2)
NI is not shown	(3)
NI is shown/ Superiority is shown	(4)
NI is shown, but, Statistically Inferior	(5)

Steps involved in the NI margin Determination for cSSSI

NI margin Determination for cSSSI

- Estimate historical evidence of sensitivity to drug effect (HESDE) for:
  - Complicated skin and skin structure infections (cSSSI)
  - Uncomplicated skin and skin structure infections (uSSSI)
- Assess constancy of the treatment effect
  - Disease, patient population, micro-organisms
- M1 is estimated based on accounting for statistical uncertainties and variability.
- Finally, determine NI margin M2, based on clinical judgment of an acceptable loss of efficacy.

END

Treatment Effect of Antibiotics in Complicated SSSI (cSSSI): Analysis of Historical Data

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Consultant: Merck, Arpida, Advanced Life Sciences, Basilea, Astellas
Shareholder: NovaDigm Therapeutics, Inc.

This review conducted by the Antimicrobial Availability Task Force of the IDSA—NO FINANCIAL SUPPORT

- John Bartlett, MD (Chair)
- Helen Boucher, MD
- John Bradley, MD
- John Edwards Jr., MD
- David Gilbert, MD
- Robert Guidos, JD (IDSA Staff)
- W. Michael Scheld, MD
- Brad Spellberg, MD
- George Talbot, MD

Background & Goal

- Ongoing confusion about antibiotic (Abx) non-inferiority (NI) clinical trials
- Effect size vs. placebo of Abx for many infections not known because Abx became available before widespread use of placebo controlled trials (PCT)
- Need method to estimate Abx effect size for a disease with no PCT available

Why cSSSI?

- cSSSI: millions of cases per year, billions of dollars in expenditures
- MRSA has exacerbated the concern
- NDAs filed for several Abx for cSSSI
- Current antibiotics for cSSSI all have limitations

Methods

- Systematic literature review of PubMed, ScienceDirect, Google
- Searched
  - (cellulitis OR erysipelas), (wound AND infection), or (abscess OR carbuncle)
  - From years 1900-50—PCN active against most *S. aureus* through 1950
- Articles reviewed, further pertinent references identified

Methods

Cure defined as alive AND NO:

- Septic complications or
- Worsening infxn after Tx initiated or
- Persistence after completion of Tx or
- Persistence for ≥ 28 days on Tx or
- Relapse or recurrence or
- Failure to heal wounds/dehiscence or
- Failure of skin grafts or
- Amputation

Methods

- Weighted average cure rates and 95% confidence interval (CI) calculated for Abx or Non Abx

- Lower limit of Abx effect size = (lower limit 95% CI cure with Abx) - (upper limit 95% CI cure without Abx)

Results

- Full manuscript provided to FDA
- Time is short—cannot review all data
- Will not discuss sulfa—monotherapy sulfa irrelevant in modern era (for 40 years sulfa combined with dihydrofolate reductase inhibitor, e.g. TMP-SMX)
- In all our analyses, sulfa inferior to PCN

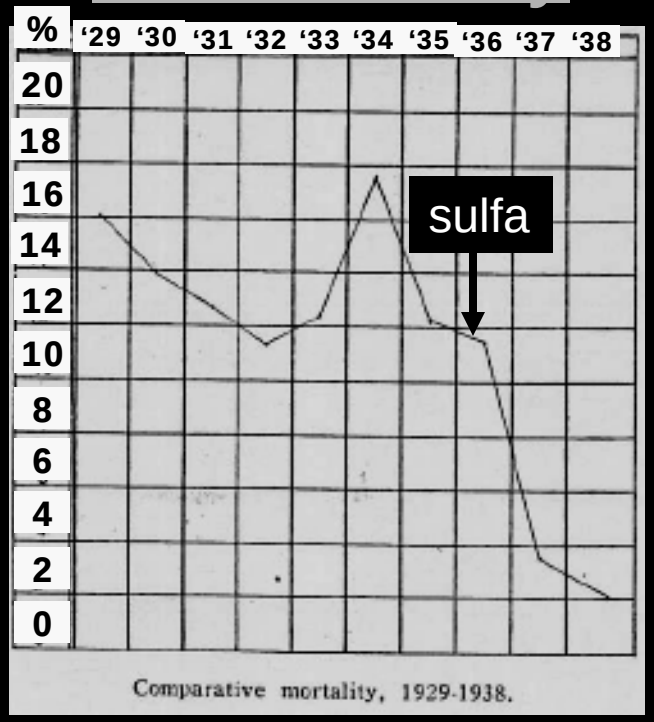
Literature Summary

- 90 peer reviewed publications from 1900-1950 included in weighted averages and CIs
- Described outcomes in >28,000 patients with cSSSI

Population Mortality Estimates

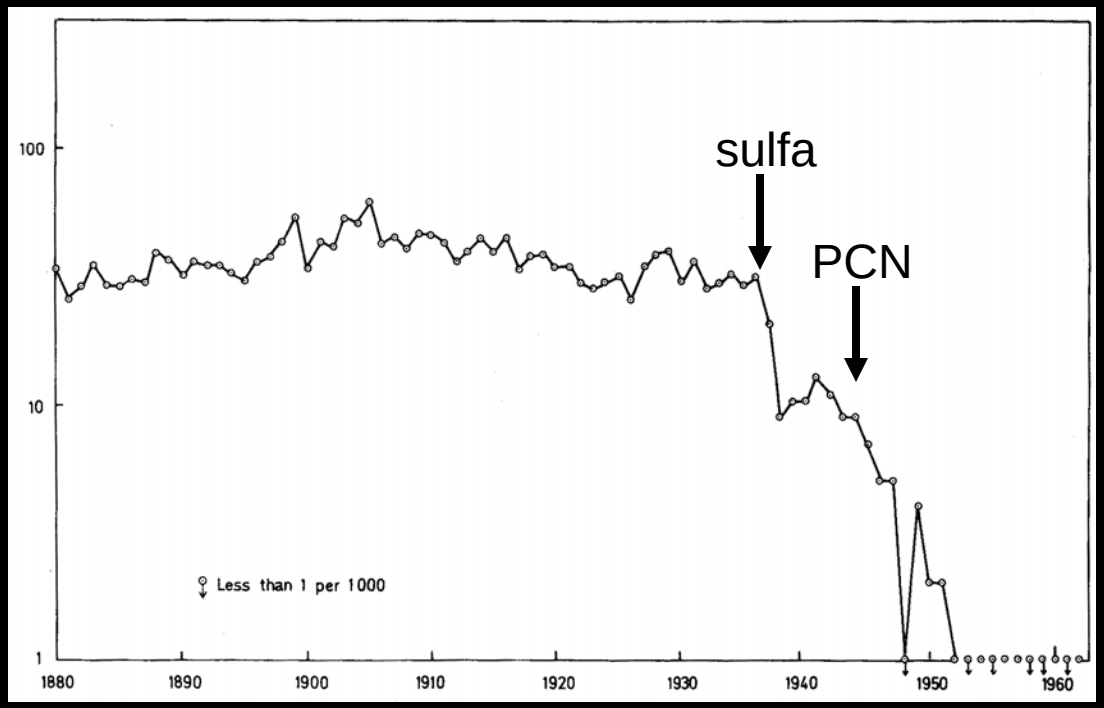
- 2 other studies reported population based mortality rates from erysipelas—not included in weighted averages

Cook County



Hoyne et al '39 JAMA

Norway National Registry



Madsen '73 Infection

Cellulitis/Erysipelas Cure Rates

- 37 studies reported quantitative results
- β-hemolytic strep predominant, *S. aureus* #2 pathogen when reported
- No difference in cure between: topical creams/ointments, UV Tx, X ray Tx, "vaccination", anti-toxin serum, bacteriophage, or autologous blood—these lumped together as "Non Abx"

Cellulitis/Erysipelas Cure Rates

Summary Cure Rate Non Abx vs. Systemic PCN

	Non Abx	PCN
Overall Cure	1520/2294	196/200
% (95% CI)	66% (64-68%)	98% (96-99%)
Abx Effect Size		32% (28-36%)
Lower Limit Abx Effect*		28%

*(lower limit of 95% CI of Abx cure rate) – (upper limit of 95% CI of Non Abx cure rate) = 96% - 68%

Cellulitis/Erysipelas Mortality

Summary Mortality Rates from 52 Studies

	Non Abx	PCN
Overall Mortality	2528/23657	1/325
% (95% CI)	11% (10 -11%)	0.3% (0-0.8%)
Abx Effect Size		-10% (-10 - -11%)

Wound/Ulcer Cure Rates

- 23 studies reported quantitative results for trauma, surgery, or combat wounds, or ulcer infections

- Most studies reported microbiology: *S. aureus* #1, strep #2 (most but not all β strep), rare GNR/anaerobes/*Enterococcus*

Wound/Ulcer Cure Rates

Summary Cure Rate Non Abx vs. PCN*		
	Non Abx	PCN
Overall Cure	160/449	1476/1775
% (95% CI)	36% (32-39%)	83% (81-85%)
Abx Effect Size		48% (42-53%)
Lower Limit Abx Effect†		42%

†(lower limit of 95% CI of Abx cure rate) – (upper limit of 95% CI of Non Abx cure rate) = 81% - 39%

*Blended topical, local, systemic Tx

Wound/Ulcer Cure Rates

- 7 studies identified which clearly reported cure rates only for systemic PCN, and not for topical or local PCN
- 97/109 pts cured: 89% (83-95%)
- Lower limit of Abx effect vs. Non Abx = 44%

Major Abscess Cure Rates

- 34 studies reported quantitative results
- *S. aureus* most common by far, much rarer strep
- Abscesses were “carbuncles” or “major abscesses”
- Furuncles excluded

Major Abscess Cure Rates

Summary Cure Rate Non Abx vs. Systemic PCN

	Non Abx	PCN
Overall Cure	254/336	282/293
% (95% CI)	76% (71-80%)	96% (94-98%)
Effect Size		21% (14-27%)
Lower Limit Abx Effect*		14%

*(lower limit of 95% CI of Abx cure rate) – (upper limit of 95% CI of Non Abx cure rate) = 94% - 80%

Major Abscess Cure Rates

- In contrast, cure for topical/local PCN was significantly lower: 58/69 pts cured = 84% (76-93%)

Modern Dose Escalation Data

- Phase II dalbavancin dose escalation study for cSSSI (Seltzer et al. '03 CID 37:1298-303)
- 41 pts randomized to 1 vs. 2 doses of dalbavancin for cSSSI

Study Population	2 Dose Cure Rate	1 Dose Cure Rate	Effect Size*
Clinically Evaluable	94%	62%	32%
Intention to Treat	91%	60%	31%

*Minimum effect size, since 1 dose dalbavancin presumably superior to placebo

Summary of Analysis

- We found unambiguous, robust evidence of a large Abx treatment effect in cSSSI

- Lower limit Abx effect vs. Non Abx Tx:
  - 28% for cellulitis/erysipelas
  - 42% for wound/ulcer infections
  - 14% for major abscesses

Implications for NI Studies

- Overall effect size in a study depends on proportion (P) of patients with cellulitis/ erysipelas, wound/ulcer, or abscess
- Study effect size = $(P_{cellulitis/erysipelas} \times 0.28) + (P_{wound/ulcer} \times 0.42) + (P_{abscess} \times 0.14)$
- 28% effect size if P's evenly distributed
- If >1/3 wound/ulcer, effect size larger, if > 1/3 abscess, effect size smaller

Implications for NI Studies

- For a 28% effect size, <u>if</u> the goal is to preserve 50% effect size $\rightarrow$ 14% margin
- We are NOT advocating preserve 50% of effect size—this is highly conservative for cSSSI (low mortality with treatment)
- Preservation of 50% effect size arbitrary, not specified in ICH or FDA guidances
- Other statistical methods to derive margin from effect size merit exploration

Evidence of Robustness

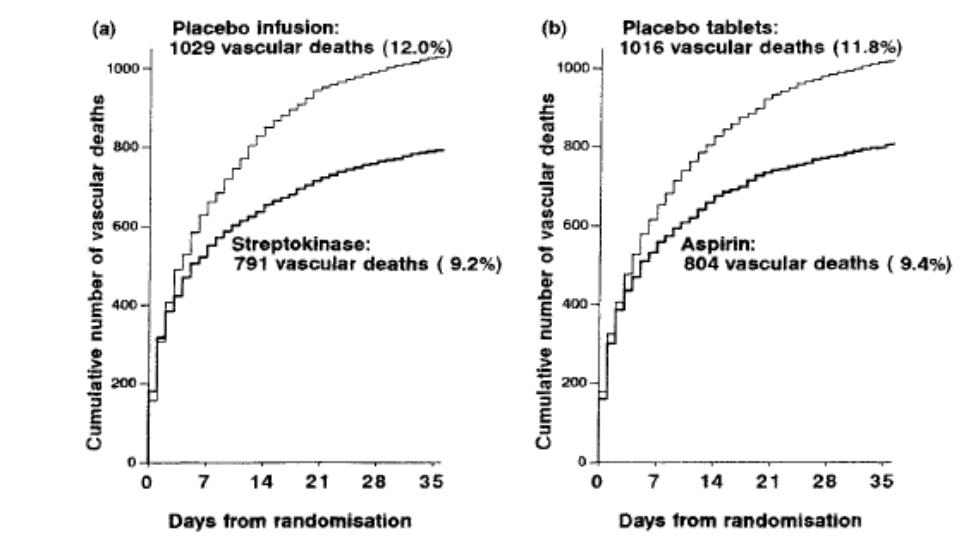
- Time to cure studies all show marked superiority of Abx vs. Non Abx
- Topical less effective than systemic Abx
- Modern dose escalation cSSSI study shows similar Abx effect size
- Data from impetigo (uSSSI) concordant
- Population-based studies show massive mortality benefit of Abx for cSSSI

Abx Mortality Benefits

Disease	Mortality No Tx	Mortality With Tx	NNT*
Cellulitis/Erysipelas	11%	<1%	10
Myocardial Infarction	12%	9%	30

*Number Needed to Treat to save a life

Mortality Myocardial Infarction: ISIS-2 (Lancet '88 2:349-360)



Mortality

- We’ve forgotten how deadly cSSSI were in the pre-Abx era, because Abx are so effective
- Importance of mortality is as evidence of the robustness of our analysis
- Mortality is <u>not</u> a viable endpoint for cSSSI because mortality rates are very low with Abx

Constancy Assumption

- Microbiology very similar
- Modern dalbavancin dose finding study
- Mortality rates with Abx similar to mortality rates in modern cSSSI studies

Limitation

Inclusion of single-armed studies

- No other data available, nor will other data become available in the future

- Placebo studies for cSSSI would be:
  - unethical based on evidence of Abx effect on cure and mortality (we're not talking about uSSSI!)
  - Not enrollable due to patient, primary physician, and IRB refusal

Limitation

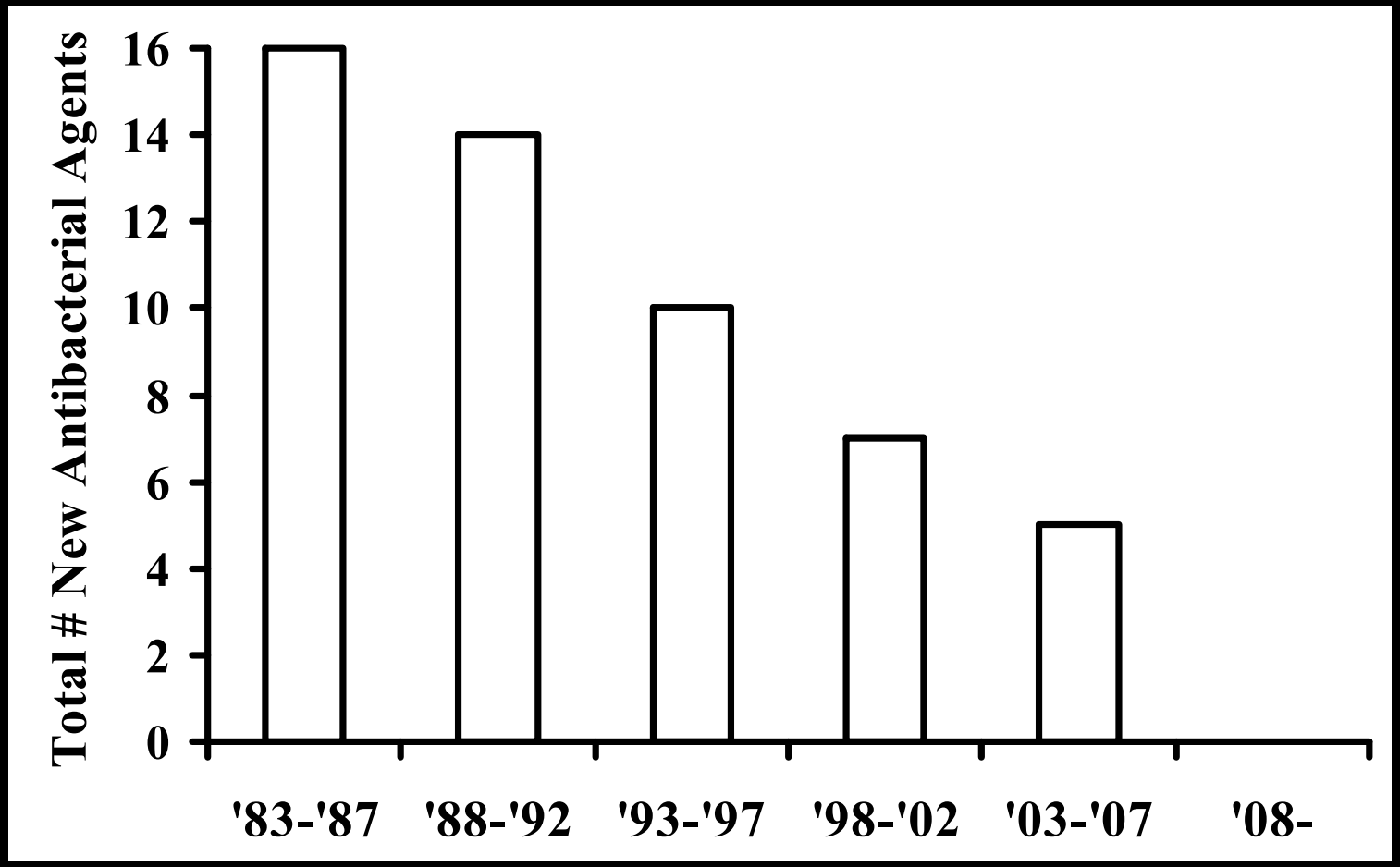
Inclusion of single-armed studies

- We are not going to get other/better data on this topic

"The perfect is the enemy of the good."
--Voltaire

We Need New Abx!

- Must weigh limitations vs. need



Unique Public Health Need

- Antibiotics are unique: drugs in no other class lose efficacy in a transmissable manner over time
- Therefore, the public health need for antibiotics is different than for any other class of drugs

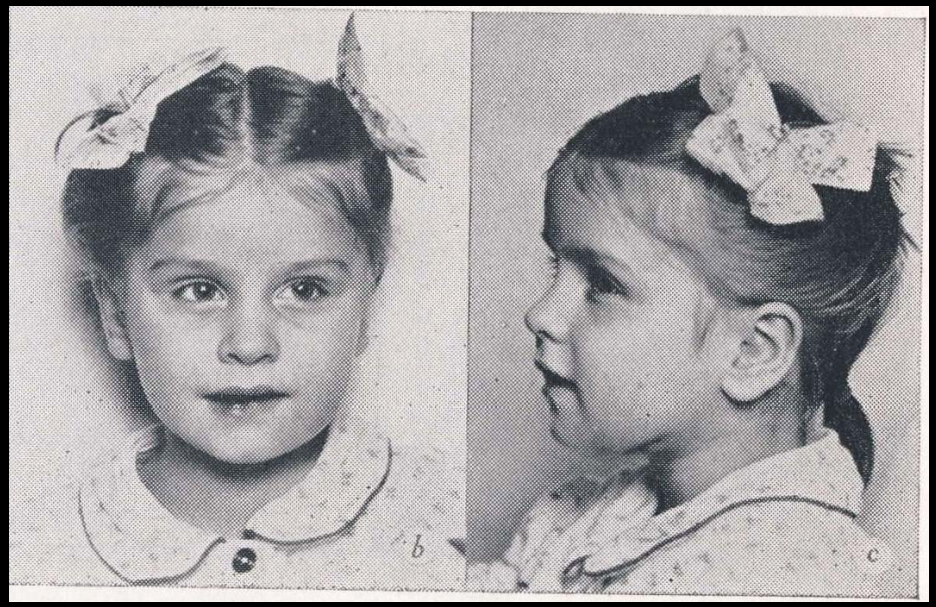
The “Dark” Ages

- 4 yo girl in excellent health suddenly developed facial cellulitis
- Spread relentlessly, fever to 104°F
- Could not sleep because her face and neck so swollen she could not swallow her own secretions
- Began gasping for breath

Herrell ’43 Proc Staff Meetings Mayo Clinic 18:65-76

The “Dark” Ages

- Pus from I&D grows *S. aureus*
- Pneumonia and bacteremia present
- Infection “almost universally fatal”
- PCN administered: 20,000-30,000 units per day



Conclusion

- ICH E10

"The determination of the margin in a non-inferiority trial is based on both statistical reasoning and <u>clinical judgment</u>"

Conclusion

- We believe data sufficient for NI margin justification for Abx for cSSSI based on
  - 1) magnitude of efficacy
  - 2) robustness of the data
  - 3) conservative calculations
  - 4) compliance with critical features of ICH and FDA guidance
  - 5) critical need for new Abx

Thank you!

Questions

AIDAC Meeting

November 18, 2008

Question 1

- Are non-inferiority trials acceptable for the indication of cSSSI? Please vote Yes/No.
  - If Yes, please discuss the following points and provide your rationale:
    - What margin is acceptable?
    - What is the appropriate primary endpoint?
    - What is the appropriate timing of assessment of the primary endpoint (e.g. on therapy, at the end of therapy, or at a fixed time point after completion of therapy)?
  - If No, please provide your rationale and advice you may have on alternative trial designs.

Question 2

- Please discuss if it is acceptable to justify a NI margin for cSSSI as a group or should it be justified by specific infection type, i.e. cellulitis, wound infections, or abscesses.
- If it is acceptable to study cSSSI as one group, should the number of infections of any one type be limited?
- Should patients with diabetic foot infections be studied in a separate clinical trial or should they be included in cSSSI trials?

Question 3

- Given that the data evaluated for determining treatment effect in skin infections includes data from various types of skin infections, are non-inferiority trials acceptable for the indication of uSSSI? Please vote Yes/No.
  - If Yes, please discuss the following points and provide your rationale:
    - What margin is acceptable?
    - What is the appropriate primary endpoint?
    - What is the appropriate timing of assessment of the primary endpoint (e.g. on therapy, at the end of therapy, or at a fixed time point after completion of therapy)?
  - If No, please provide your rationale and advice you may have on alternative trial designs.

Question 4

- Should uSSSI studies only enroll patients with infections such as impetigo, erysipelas, and cellulitis and exclude those with abscesses?