Diabetic Foot Infections: Current Treatment & Delaying the "Post-antibiotic Era"

Benjamin A. Lipsky, MD, FACP, FIDSA, FRCP
Emeritus Professor of Medicine,
University of Washington
Visiting Professor, Teaching Associate,
Green Templeton College, University of Oxford

UW Medicine
SCHOOL OF MEDICINE

GREEN TEMPLETON COLLEGE

Epidemiology of Diabetic Foot Infections

Population having **diabetes**: ***12+%***

↓

Develop a **foot wound*:* ~25%**

↓

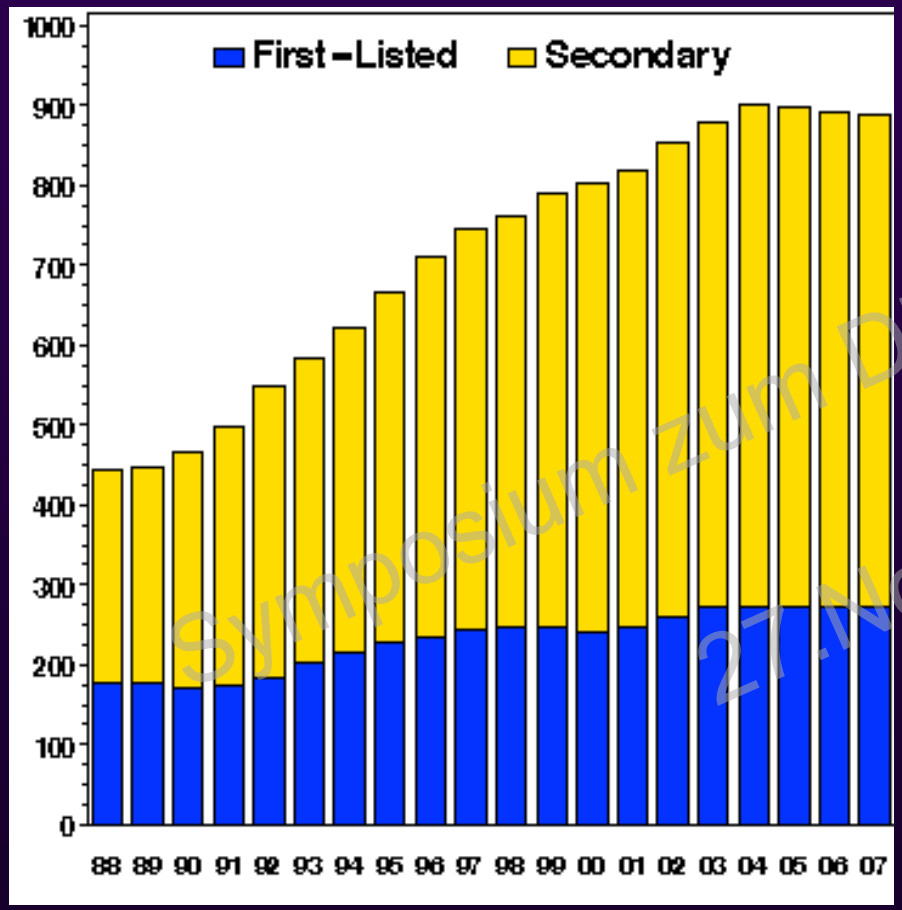
Wound **infected** at presentation: ***~55%***

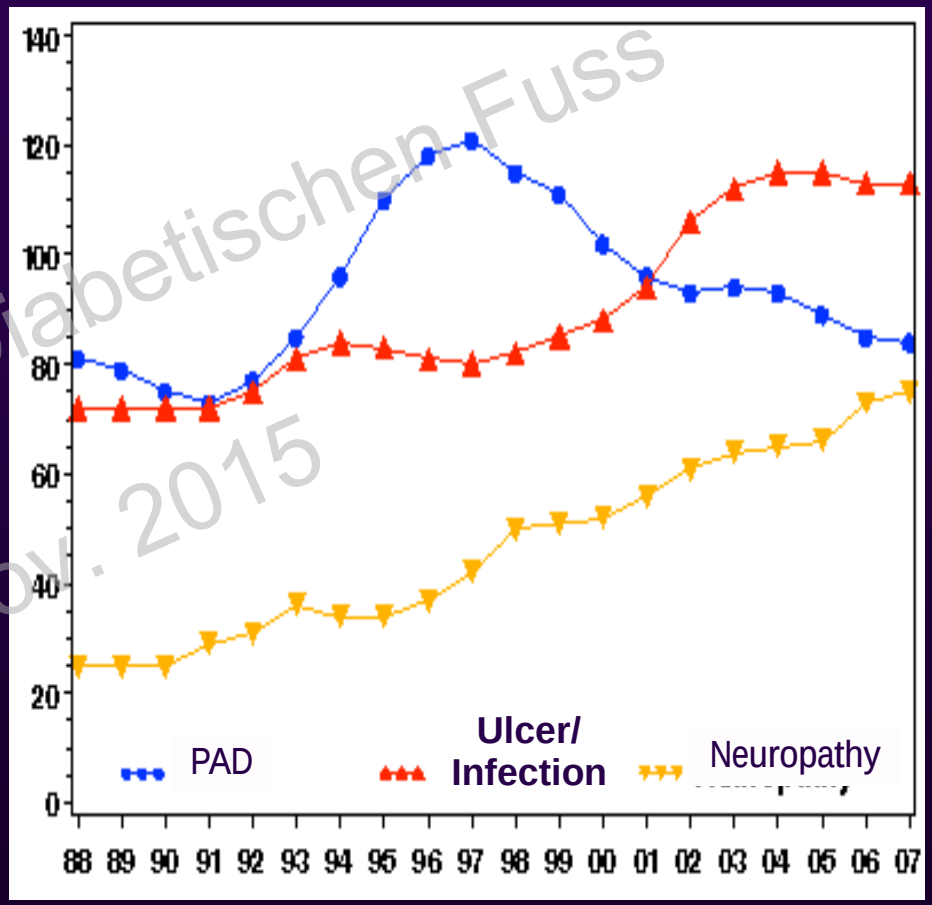
↓

Mild: ***35+%*** | **Moderate**: ***30-60%*** | **Severe**:***5-25%***

Lipsky et al, *Clin Infect Dis* 2012;54:132

Hospital Discharges for Diabetic LE Condition
In Thousands, USA 1988-2007





Number of hospital d/c for diabetic patients with peripheral arterial disease (PAD), ulcer/Inflammation/Infection, or neuropathy as 1st listed diagnosis

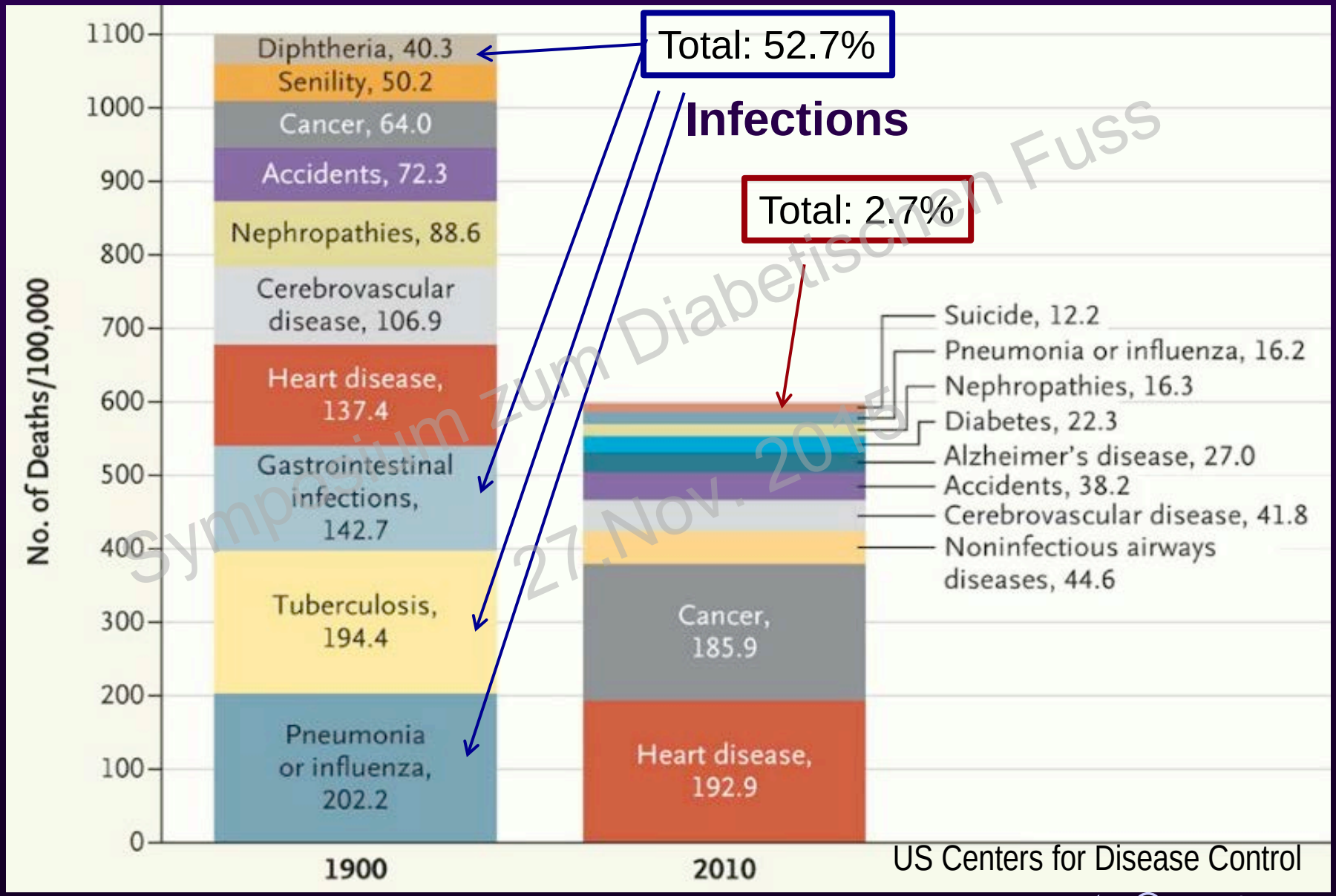
CDC, 2013: http://www.cdc.gov/diabetes/statistics

The "Post-Antibiotic" Era

A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill.

-- Dr. Margaret Chan, OBE, MD, DSc
Director-General, World Health Organization

Causes of Death in US: 1900 vs 2010

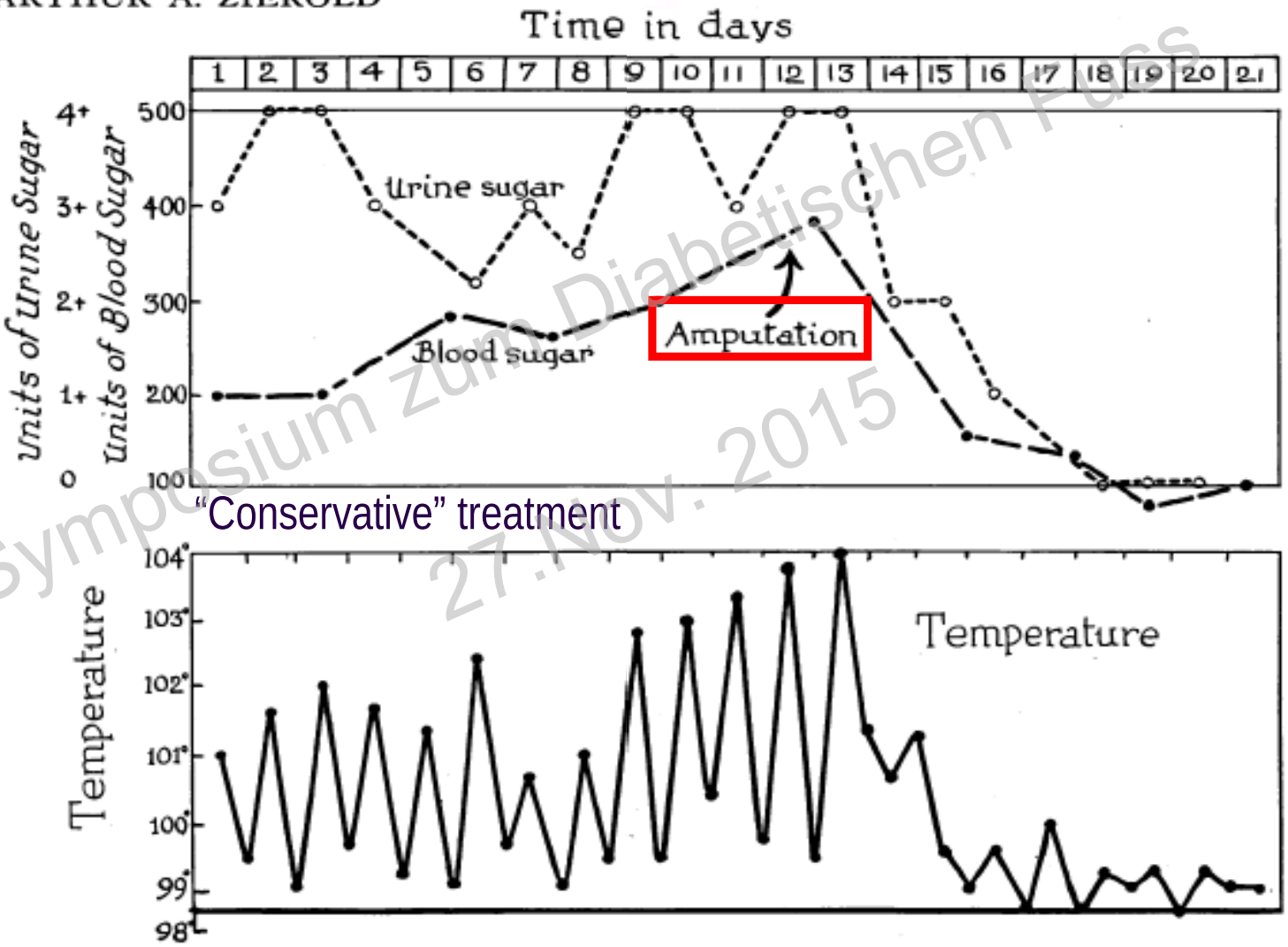


Diabetic Foot Infection: the Pre-Antibiotic Era

Volume 110 Number 4 Annals of Surgery October, 1939

ARTHUR A. ZIEROLD

DIABETIC GANGRENE



Diabetic Foot Infection in the Pre-Antibiotic Era

Deaths after operation on lower extremities, n=806

Cause of Death	No. of Cases	% of Deaths	% All Patients
Infection	42	50	5.2
Cardio-renal	37	44	4.6
Miscellaneous	5	6	0.6
Total	84	100	10.4

Zierold, AA, *Ann Surg* Oct 1939

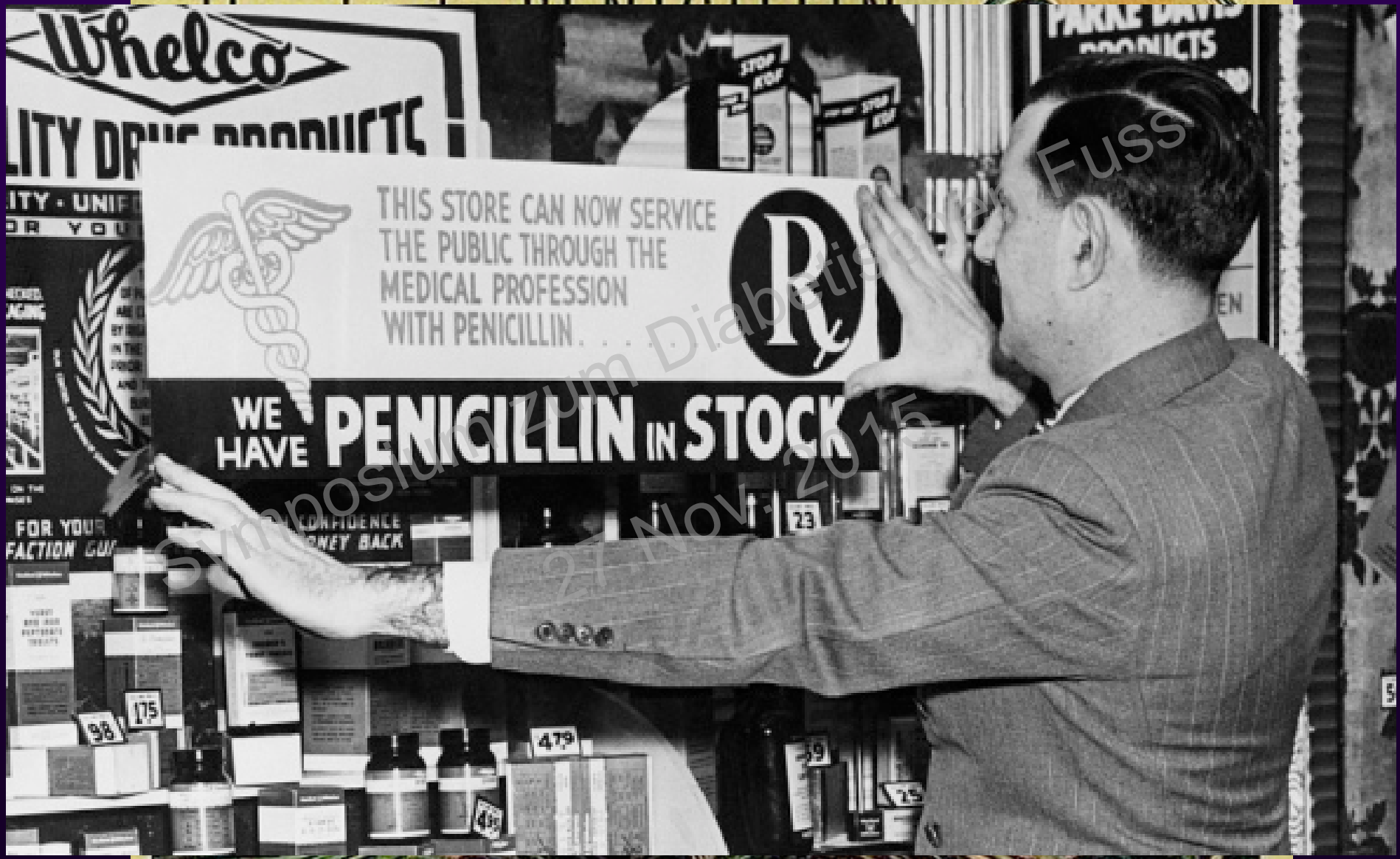
Effect of Antibiotics on **Major Amputation*** & **Mortality** Rates for Diabetic Gangrene

Reference	*Before* Penicillin		*After* Penicillin	
	Amputation	Mortality	Amputation	Mortality
Regan et al, 1949	99/140 (70.7%)	12/136 (8.8%)	36/122 (29.5%)	5/122 (4.1%)
McKittrick** 1946	680/1036 (65.6%)	101/1036 (9.7%)	80/229 (34.9%)	6/229 (2.6%)

* Above or below knee amputation

** *Sulfonamides used 1940-1944*

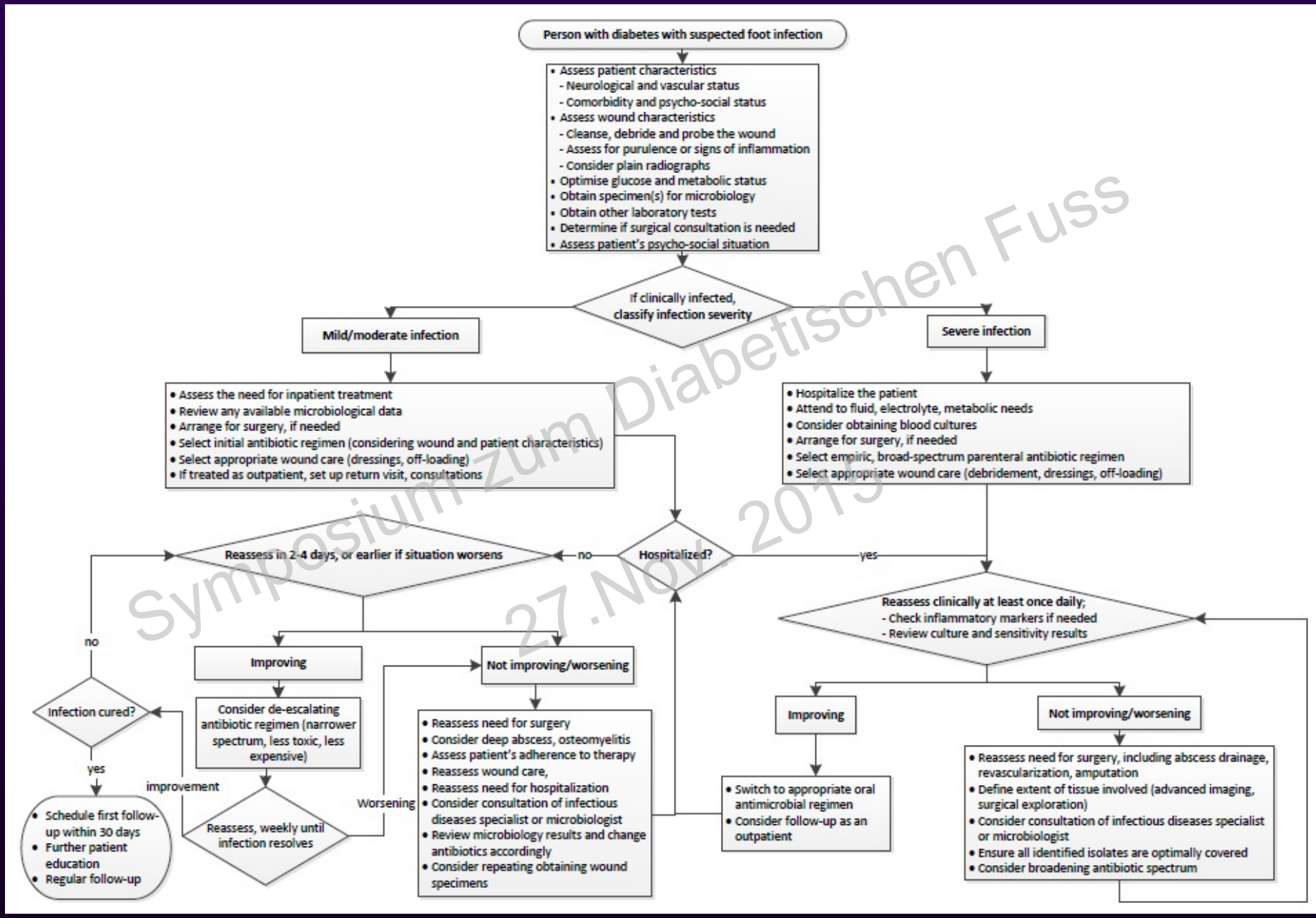
Pushkin R, Lipsky BA (in preparation)



History of Diabetic Foot Infection: Introduction of Antibiotic Therapy

- After introduction of insulin (1922) next major advance in treating DFI was antibiotic therapy
  - Allowed more conservative surgery (lower LEA level)
  - Made primary suturing safer option (better scar)
  - Reduced mortality of major surgery by almost half
- No other major advances for >30 years
  - DFI "forgotten step-child" until early 1980s
  - Related to concept: "ischemia + infection = gangrene" with neglect of role of neuropathy

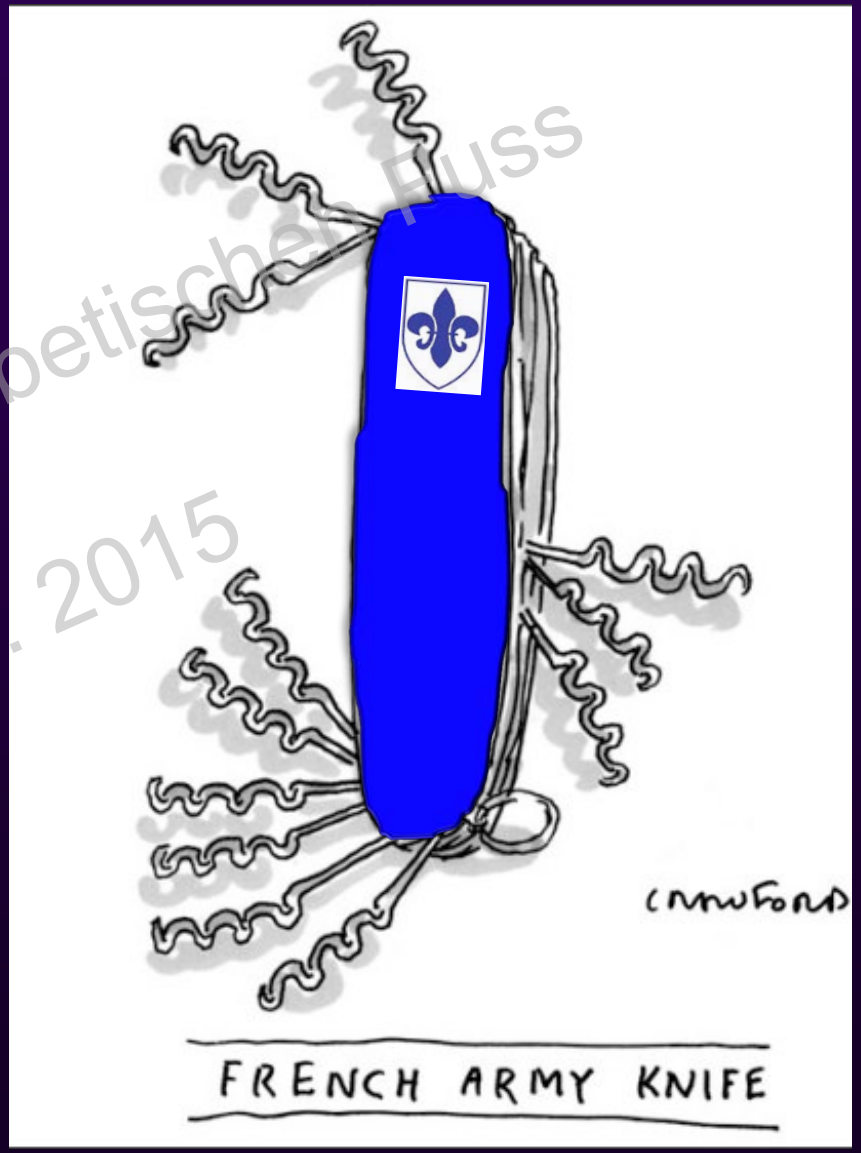
Connor H, *Diabetes Metab Res Rev* 2008;24(Suppl 1): S7



Lipsky et al, IWGDF DFI Guidance 2015

Inter- (*vs* **Multi-**) Disciplinary Team is Key

Swiss Army Knife



Oral Antibiotics for Diabetic Foot Infections

Drug	Renal dosing?	MRSA activity?	**Class**
Diclox/Fluclox-acillin	No	No	Penicillin (semi-synthetic)
Amoxicillin/clavulanate†	Yes	No	β-lactam/β-lact inhibitor
Cephalexin†	Yes	No	Cephalosporin (1st gen)
Cefdinir	Yes	No	Cephalosporin (2nd gen)
Cipro/Levo/Moxi-floxacin†	Yes	No	Fluoroquinolones
Clindamycin†	No	+/-	Lincosamide
TMP/SMX §	Yes	+	Folate inhibitors
Doxycycline §	No	+	Tetracycline
Linezolid §	No	+	Oxazolidinone

† Used in published trials of treatment of diabetic foot infections.
§ Active against community-associated methicillin-resistant *S. aureus*

Kosinski M, Lipsky BA. *Expert Rev Anti Infect Ther* 2010;8:1293

IV Antibiotics for Diabetic Foot Infections

Drug	Class	MRSA?	*B.frag*?	Renal?
Ampicillin/sulbactam	β-L/β-LI	No	Yes	Yes
Piperacillin/tazobactam	β-L/β-LI (*Pseudo*)	No	Yes	Yes
Gentamicin	Aminoglycoside	No	No	Yes
Imi/Mero-penem	Carbapenem (grp 2)	No	Yes	Yes
Ertapenem‡	Carbapenem (grp 1)	No	Yes	Yes
Levo/Cipro/Moxi-floxacin	Quinolone	No	Yes	No
Clindamycin	Lincosamide	Some	Yes	No
Tigecycline¶	Glycylcycline	Yes	Yes	No
Vancomycin¶#	Glycopeptide	Yes	No	Yes
Linezolid‡¶#	Oxazolidinone	Yes	No	No
Daptomycin¶‡	Cyclic lipopeptide	Yes	No	Yes
Ceftaroline	Cephalosporin (5 g)	Yes	No	No

Kosinski M, Lipsky BA. *Expert Rev Anti Infect Ther* 2010;8:1293

Systematic Review Treatment DFI: IWGDF 2015

Same search as 2011, reviewed August 2010-August 2014
Only 7 new papers, for a total of 40 (37 RCTs; 3 cohort)

- *Moxifloxacin* (IV/po) non-infer. to pip/tazo (IV, amox/clav po)
- *Tigecycline* significantly inferior to ertapenem ± vanco for SSTI & DFO, with higher adverse event rate
- *Gentamicin-collagen sponge* as adjunctive therapy did not improve outcomes at day 7, but did at test of cure
- *DeMarco* formula (procaine + polyvinylpyrrolidone) as adjunctive therapy in DFI w/PAD ↓ LE amputations
- *Microcyn* (superoxidized sol'n) at least as effective as levofloxacin for mild DFU infections
- Antibiotic therapy alone for *osteomyelitis* provides similar outcomes to surgical therapy (2 studies)

Peters et al, *Diab Metab Res Rev* 2015 (epub Nov)

Systemic Antibiotics for Treating DFI: Cochrane

- 941 references reviewed; 20 included in analysis
- No antibiotic agent/regimen had higher rate of clinical resolution of infection or other end-points than comparator
- Only 1 trial (hi quality) identified significant difference: rate of infection resolution higher & adverse events lower with ertapenem (± vancomycin if MRSA) than tigecycline
- Differences in safety profile of agents in some studies
- Quality of evidence low: limitations in design, hi diversity in antibiotics, duration of treatments, outcome assess. time
- Future studies: standardize infection severity criteria; define outcome measures; establish duration of treatment; report both short- & long-term outcomes

Selva Olid, Lipsky, et al. *Cochrane Database SR* 2015;9: CD009061

Cochrane SR/MA of Topical Therapy DFI: Underway

Topical antimicrobial agents for preventing and treating foot infections in people with diabetes

Review information

Review type: Intervention

Review number: 146

Authors

Benjamin A Lipsky[1], Christopher Hoey[2], Mario Cruciani[3], Carlo Mengoli[4]

[1]Medicine, University of Washington, Seattle, Washington, USA

[2]Pharmacy Service, VA Puget Sound, Seattle, WA, USA

[3]Center of Community Medicine and Infectious Diseases Service, ULSS 20 Verona, Verona, Italy

[4]Department of Histology, Microbiology and Medical Biotechnology, Università di Padova, PADOVA, Italy

Citation example: Lipsky BA, Hoey C, Cruciani M, Mengoli C. Topical antimicrobial agents for preventing and treating foot infections in people with diabetes. Cochrane Database of Systematic Reviews 2014 , Issue 3 . Art. No.: CD011038. DOI: 10.1002/14651858.CD011038 .

Contact person

Carlo Mengoli

Associate Professor of Infectious Diseases
Department of Histology, Microbiology and Medical Biotechnology
Università di Padova

Lipsky et al, *Cochrane Database of Systematic Reviews* (registered)

Factors Influencing Choice Antibiotic Rx DFI

Infection related
- Clinical severity of infection
- Antibiotic therapy w/n 3 mos
- Presence of bone infection

Patient related
- Allergy to any antibiotics
- Immunological impairment
- Patient treatment preferences
- Patient adherence to therapy
- Renal or hepatic insufficiency
- Impaired GI absorption
- Peripheral arterial disease
- Hi risk MDROs, unusual bugs

Pathogen related
- Likelihood of non-GPC
- H/O MDRO coloniztn/infxn
- Local abx resistance rates

Drug related
- Safety profile (freq., severity)
- Drug interactions potential
- Frequency of dosing
- Formulary availability
- Cost (acquisitn, administrtn)
- Approval for indication
- ⇧ risk *C. diff* or abx resist.
- Published efficacy data

Lipsky et al, IWGDF Guidance DFI, *Diab Met Res Rev* 2015 (Nov)

Selecting Empiric Antibiotic Regimen for DFI

Severity	*Additional Factors*	*Pathogens*	*Potential Regimens*
Mild	No complications	GPC	S-S penicillin; 1st gen. cephalosporin
	ß -lactam allergy	GPC	Clinda[mycin];FQ; T/S; macro[lide];doxy[cycline]
	Recent antibiotics	GPC + GNR	ß -Lact-ß-L-ase-1; T/S; Fluroquinolone
	Hi risk MRSA	MRSA	Linezolid; T/S ; doxy[cyc]; ?macrolide; FQ
Mod[erate]/ Severe	No complication	GPC ± GNR	ß -L-ase 1; 2nd/3rd gen cephalosporin
	Recent antibiotics	GPC ± GNR	ß -L-ase 2; 3 g ceph, grp 1 carbapen[em]
	Water exposure, warm climate	GNR (*Pseudomonas*)	ß -Lase-2; S-S pen+ceftazidime, S-S pen+cipro, grp 2 carbapenem
	Isch[emia]/ necr[osis]/ gas	GPC ± GNR ± anaerobes	ß -L-ase 1 or 2; grp 1/2 carbpn 2/3 g ceph+clinda or metronidazole
	MRSA risks	MRSA	Glycopeptides; linezolid;daptomycin; fusidic [acid]; T/S (±rif[ampin])*; doxy; FQ
	Risk resistant GNR	ESBL, XDR	Grp 2/3 carbapenem; FQ; amino[glycoside]; colistin; tigecycline; minocycline

Lipsky et al, IWGDF 2015 Guidance on DFI

Antimicrobial Therapy of DFI by Clinical Situation

Type Infection	Route	Location	Duration
Soft tissue			
- Mild	Oral (? Topical)	Outpatient all	1-2 weeks
- Moderate/ - Severe	Oral (± init. IV) IV, switch po	Outpatient most Inpatient all	2-3 weeks

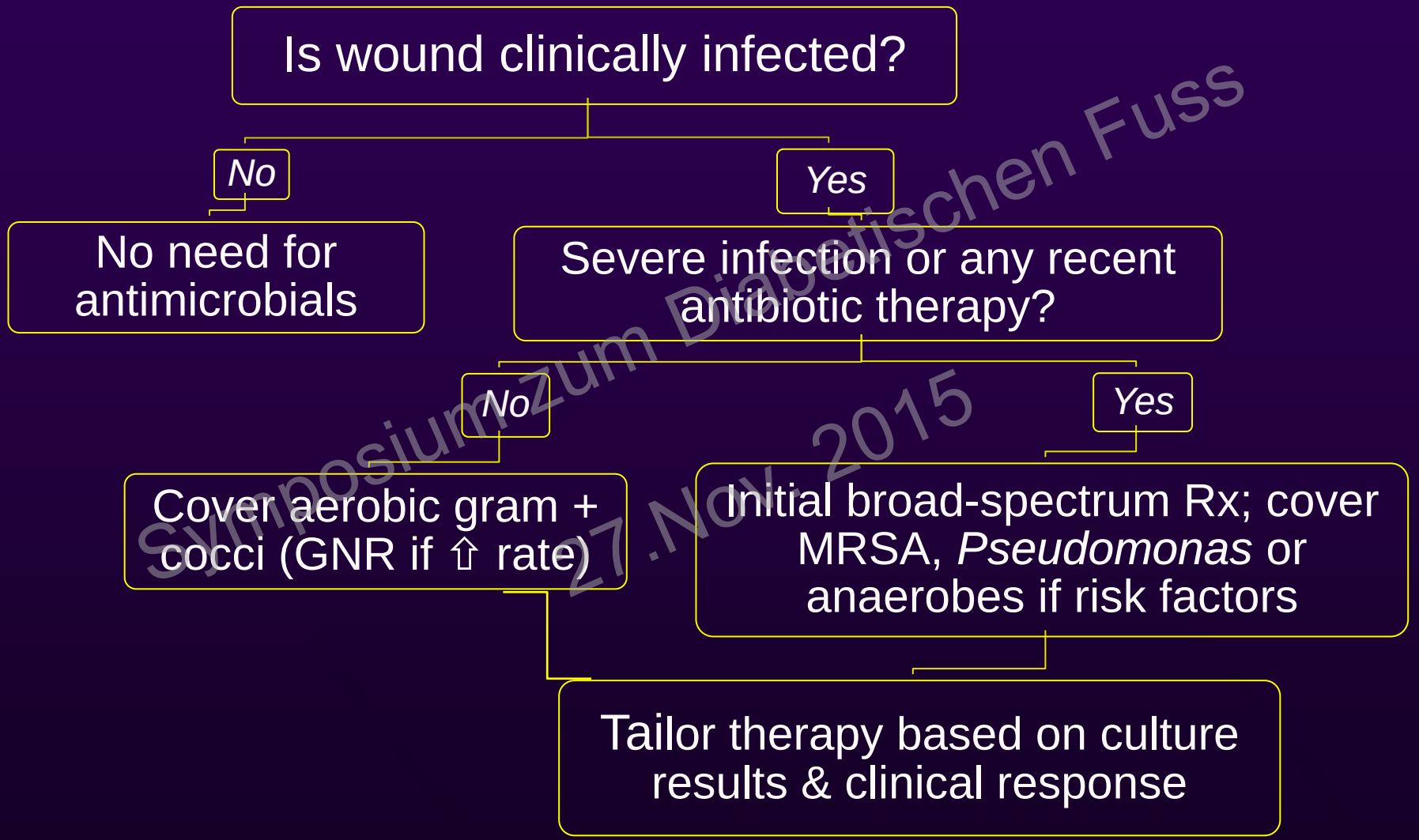
Lipsky et al, IDSA Guidelines, *Clin Inf Dis* 2004;39:885

Antimicrobial Therapy of DFI by Clinical Situation

Type Infection	Route	Location	Duration
Soft tissue			
- Mild	Oral (? Topical)	Outpatient all	1-2 weeks
- Moderate/ - Severe	Oral (± init. IV) IV, switch po	Outpatient most Inpatient all	2-3 weeks
Bone			
- Resected	IV or oral	Inpatient→ outpt	< 1 week
- Debrided	IV or oral	Inpatient→ outpt	4-6 weeks
- No surgery	IV, then oral	Outpatient	≥ 3 months

Lipsky et al, IDSA Guidelines, *Clin Inf Dis* 2004;39:885

Simple Approach to Antibiotic Therapy for DFI

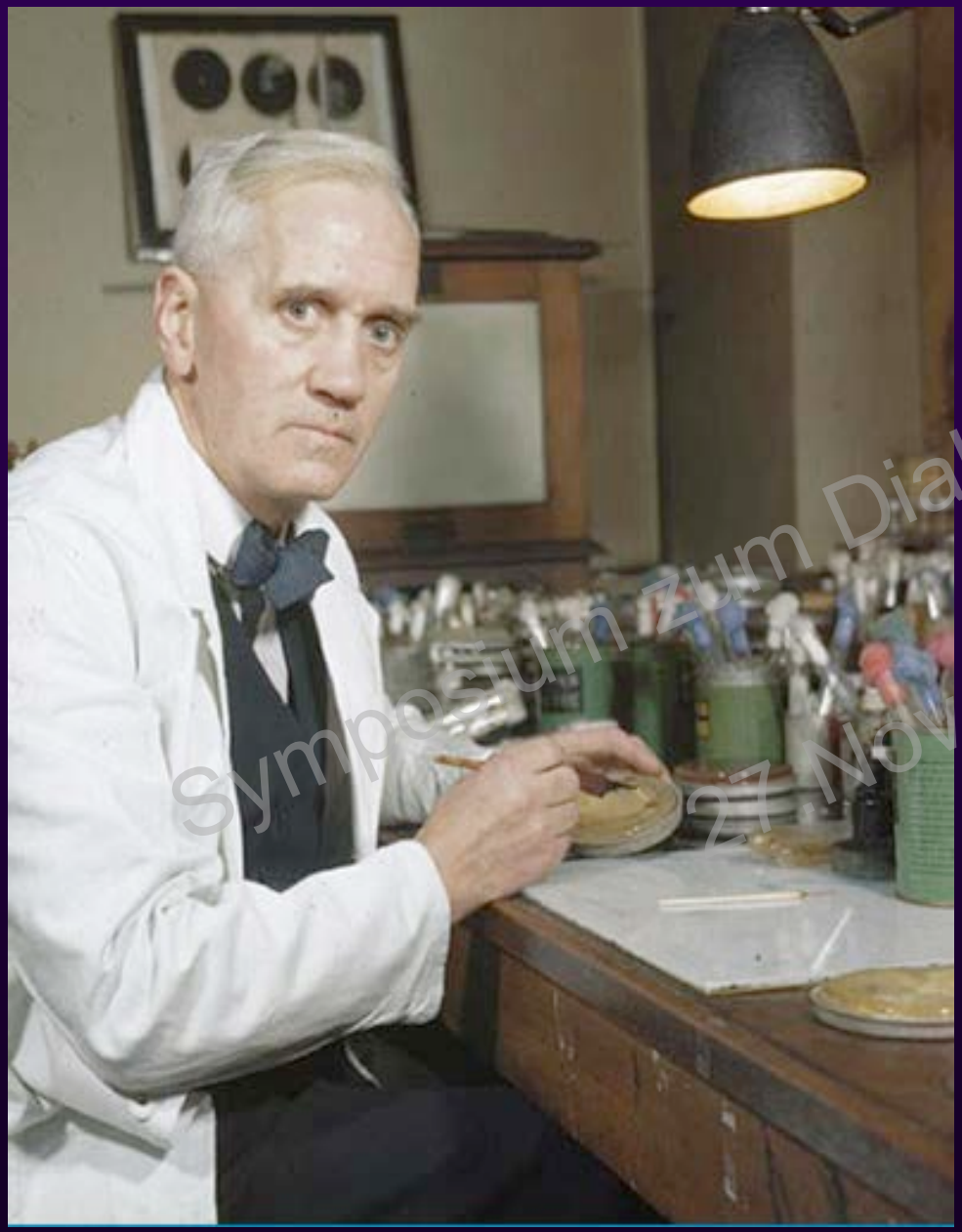


Adjunctive Therapies for Diabetic Foot Infection

- *Topical negative pressure wound therapy*
  - 1 paper (2 studies) *infxn/microbial-control*; low quality
- *Hyperbaric oxygen therapy*
  - No evidence that helps cure bone/ST infection
- *Granulocyte colony stimulating factors*
  - May ↓ need for surgery (incldng LEA) & hospital LOS
  - Does not hasten/improve cure of infection
- Rx with no proven value for curing infection
  - Advanced *dressings*; *silver* based treatments
- Larval (maggot) biotherapy may be helpful
- Early *surgery* ? reduce LEA (2 low quality studies)

Peters et al, Diab Metab Res Rev 2015 (November)

Antibiotic Treatment for Diabetic Foot Infection?



Antibiotic Resistance

"The thoughtless person playing with penicillin is morally responsible for the death of the man who succumbs to infection with a penicillin-resistant organism.
I hope this evil can be averted"

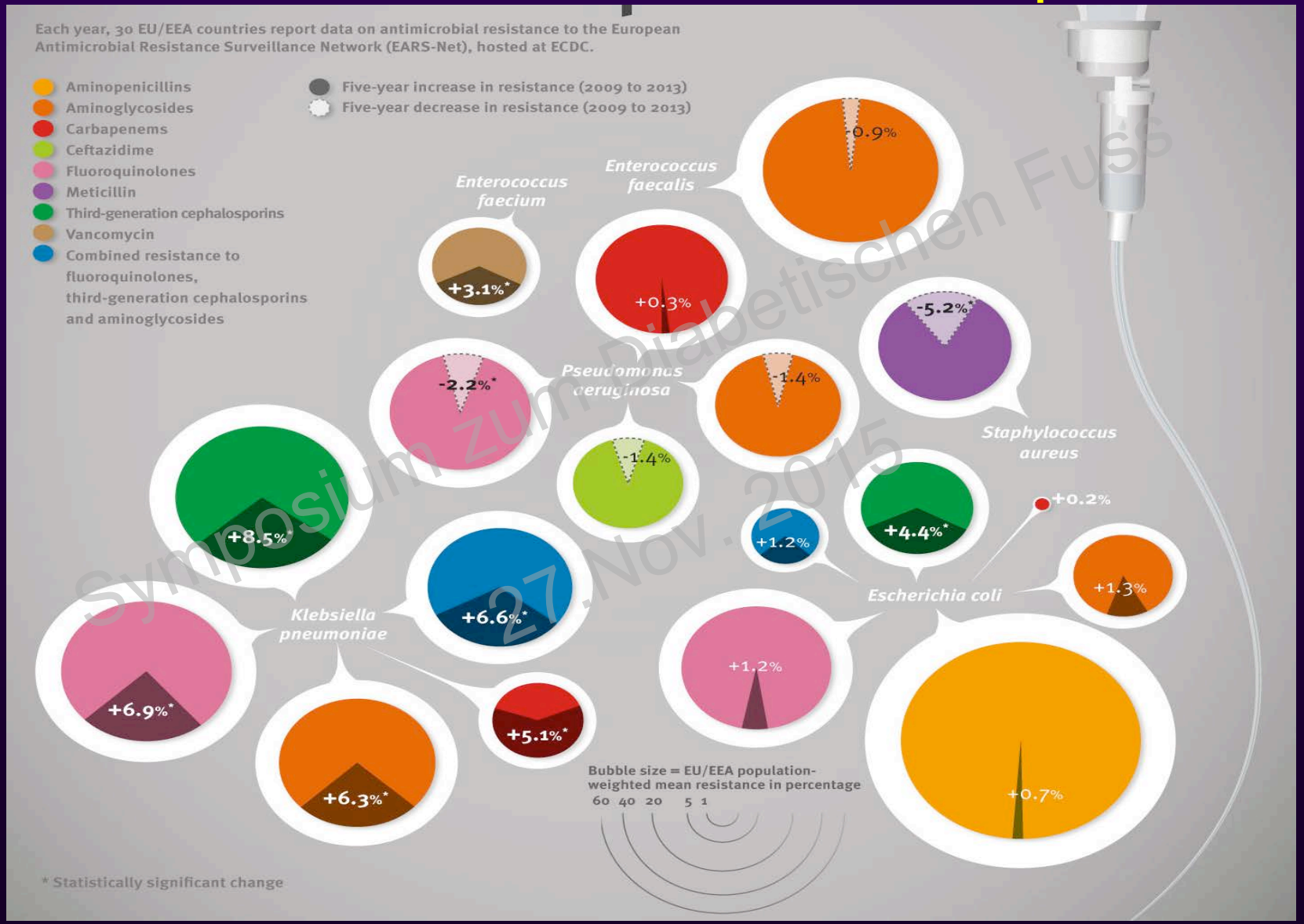
-- Alexander Fleming
NY Times 21 June 1945

Antibiotic Overuse→ Resistance

- In 2011 US healthcare providers prescribed 262.5 million courses of antibiotics (842/1000 persons!)
- CDC: 30%-50% of antibiotic use in hospitals is unnecessary or inappropriate
- Deaths directly caused by antibiotic-resistant bacteria
  - >23,000/ year in US (2 million illnesses)
  - 25,000/year in Europe
- *Antimicrobial stewardship* reduces: use of broad-spectrum agents, duration antibiotic therapy, length of hospital stay, readmissions

Hicks et al, *Clin Inf Dis* 2015;60:1308

Antibiotic Resistance in Europe



European Antibiotic Awareness Day Nov 16 2015

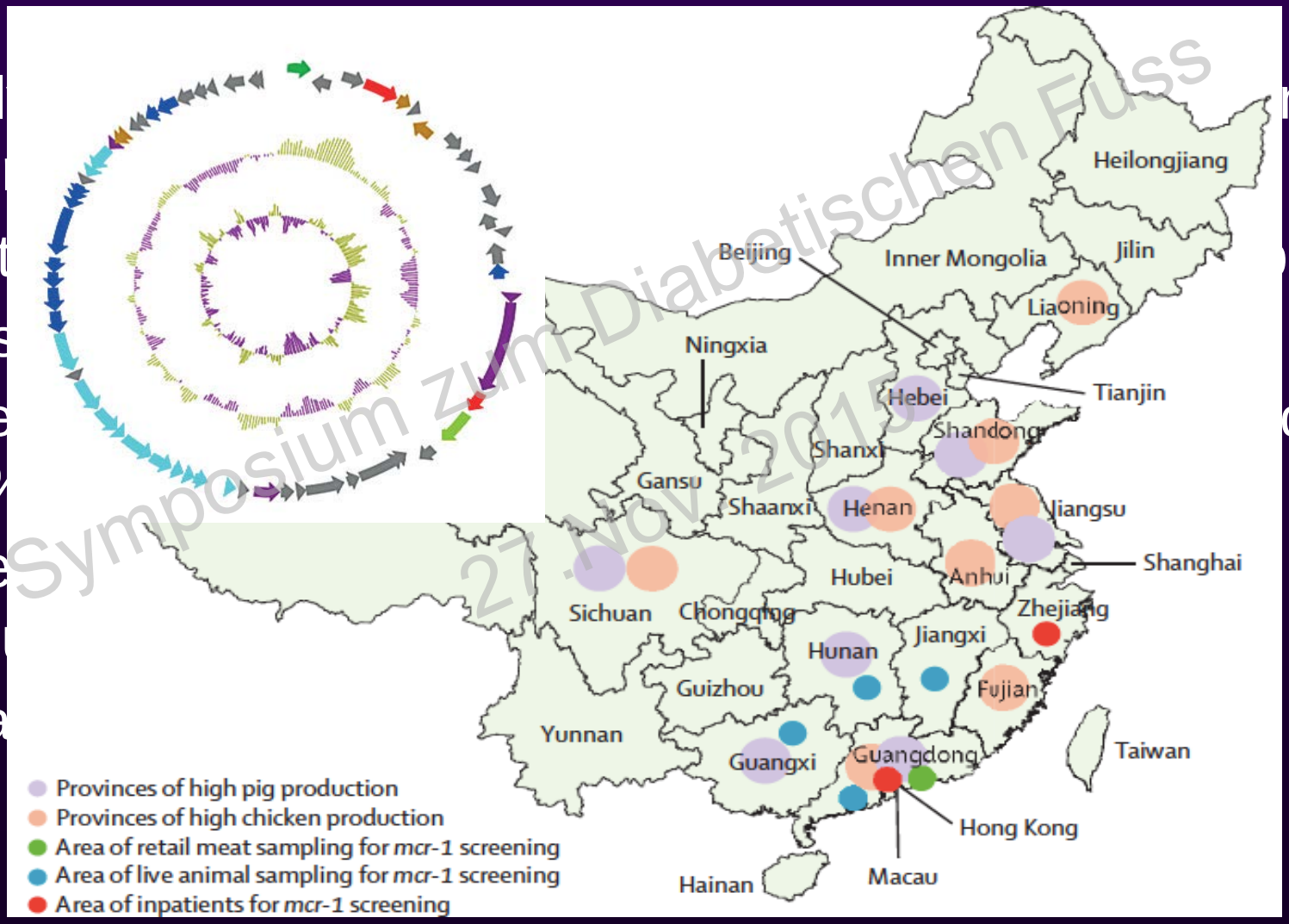
Antibiotic Resistance in Diabetic Foot Infections

- Brazil[1] 2015: hospitalized pts; 69% staphylococci or streptococci; 70% polymicrobial. Resistance:
  - *S. aureus*: 52% TMP/SMX; 67% erythromycin; 59% MRSA; 26% *VRSA* by disk (11% by MIC)
  - Streptococci: 100% cephalosporins, erythromycin
  - *Ps aerug*: 75% cefotax; 50% imipen; 25% polymixin
- Mexico[2] 2015; outpts; 42% *S. aureus*; 56% polymicrobial *S. aureus*: 88% MRSA; 10% *VRSA*
- Switzerland 2014: retrospective analysis 517 inpatients HUG 2008-14; MRSA 15%; ESBL colonization 5%

[1]Perim et al, *Rev Soc Bras Med Trop* 2015;48:546
[2]Cervantes-Garcia et al, *Int J Low Extrem Wounds* 2015;14:44
[3]Uçkay, et al. Oxford Bone Infection Conference, 2015

"A Major Breach of the Last Line of Defence": Plasmid-Mediated Colistin Resistance

- Pol … nts fo…
- Not … igs
- Res…
- The … d 1%
- Pre… mu…
- In a… to *K.*…



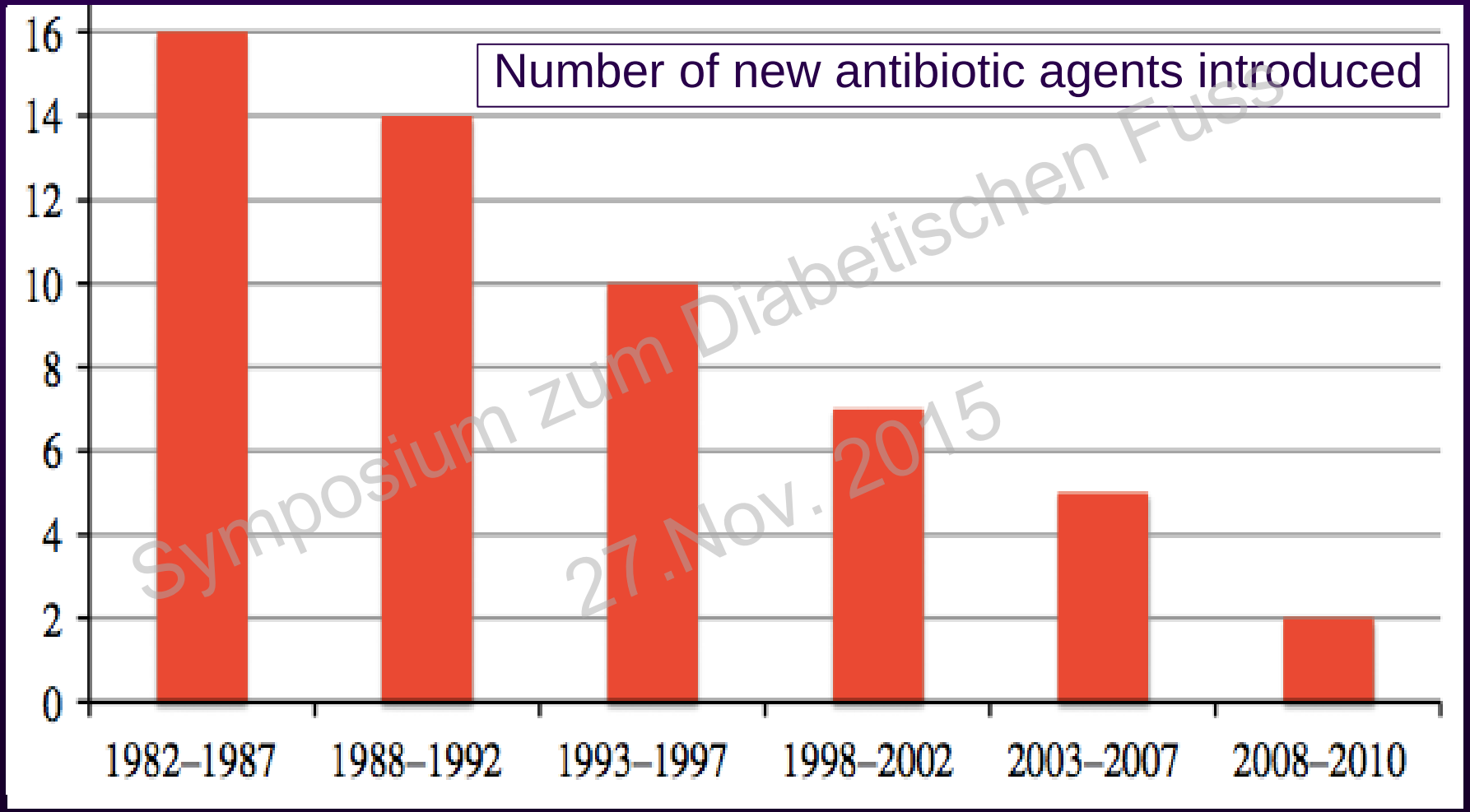
Liu et al, *Lancet Inf Dis* 2015 (epub 18 Nov)

A … by

Not only is there growing antibiotic resistance…

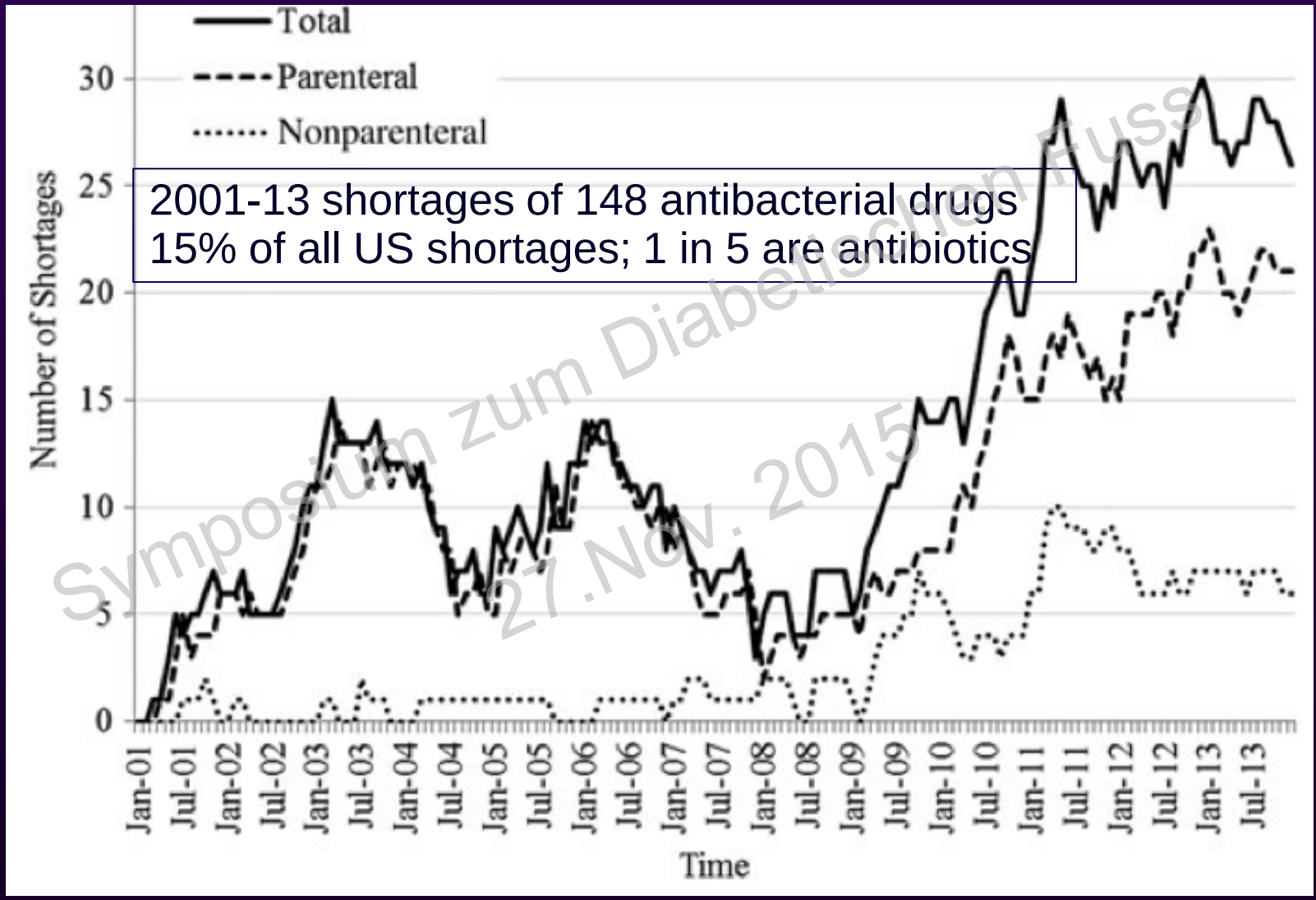
but there are few new agents being developed

Lack of New Antibiotic Classes & Agents



Fischbach MA, Walsh CT, *Science* 2009;325:1089

And now…Antibiotic *Shortages*



Quadri et al, *Clin Infect Dis* 2015; 60:1737

Antibiotics Are Not Like Other Drugs

- Responsible for more lives saved than any other class of medications
- Used equally for humans and animals
- Allow life-saving procedures otherwise not possible
- The more they're used the less effective they are
- Use for 1 person can ↓ effectiveness for others
- All are destined to become ineffective over time; microbes have likely invented antibiotic mechanisms to protect against every biochemical target

Resistance already exists to drugs we've not invented!

Teixobactin: A New Antibiotic Resistant to Resistance

- First new class of antibiotic agent in 30 years
  - Isolated from soil; using new method of cultivation
  - From a GNR–; active on all Gm+ (but not Gm–)
  - Inhibits cell wall synthesis by binding to lipid II (→ peptidoglycan) & lipid III (→ teichoic acid)
  - Effective *in vitro* & in experimental animals; no AEs
  - Found no resistant mutants of *Staph aureus* or *M. tb*
- Properties suggest a path to developing antibiotics that are likely to be slow to develop resistance

Ling et al, *Nature* 2015 (epub 5 January)

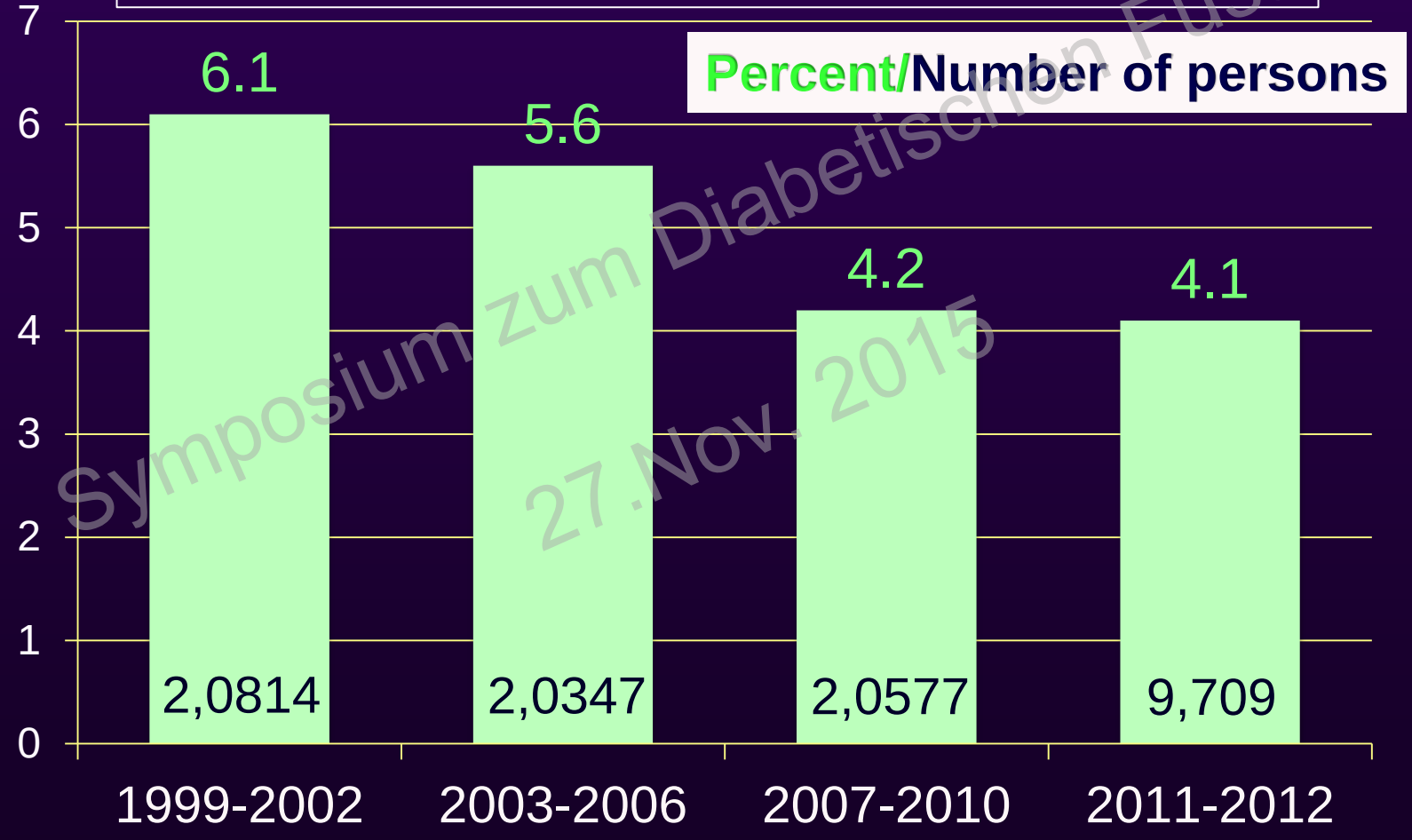
Nudging Appropriate Rx: "Antibiotic Judo"

- All physicians & most educated patients are aware of problem; education not the answer
- *Nudging* by public commitment: MD signed poster in exam room: (*If an antibiotic would do more harm than good, your doctor will explain this & offer better treatments*) ↓ inappropriate use by 20%
- Directly attack fear & uncertainty: root cause of dilemma
  - Develop & use rapid molecular dx tests bacterial vs non-bacterial (non-infectious) diseases
  - Financial incentives against unnecessary antibiotics
  - Antibiotic "non-prescription": why & what else to do

Meeker et al, & Spellberg B. *JAMA Intern Med* 2014; 174:425, 432
Carlet, *Clin Infect Dis* 2015; 60:1837

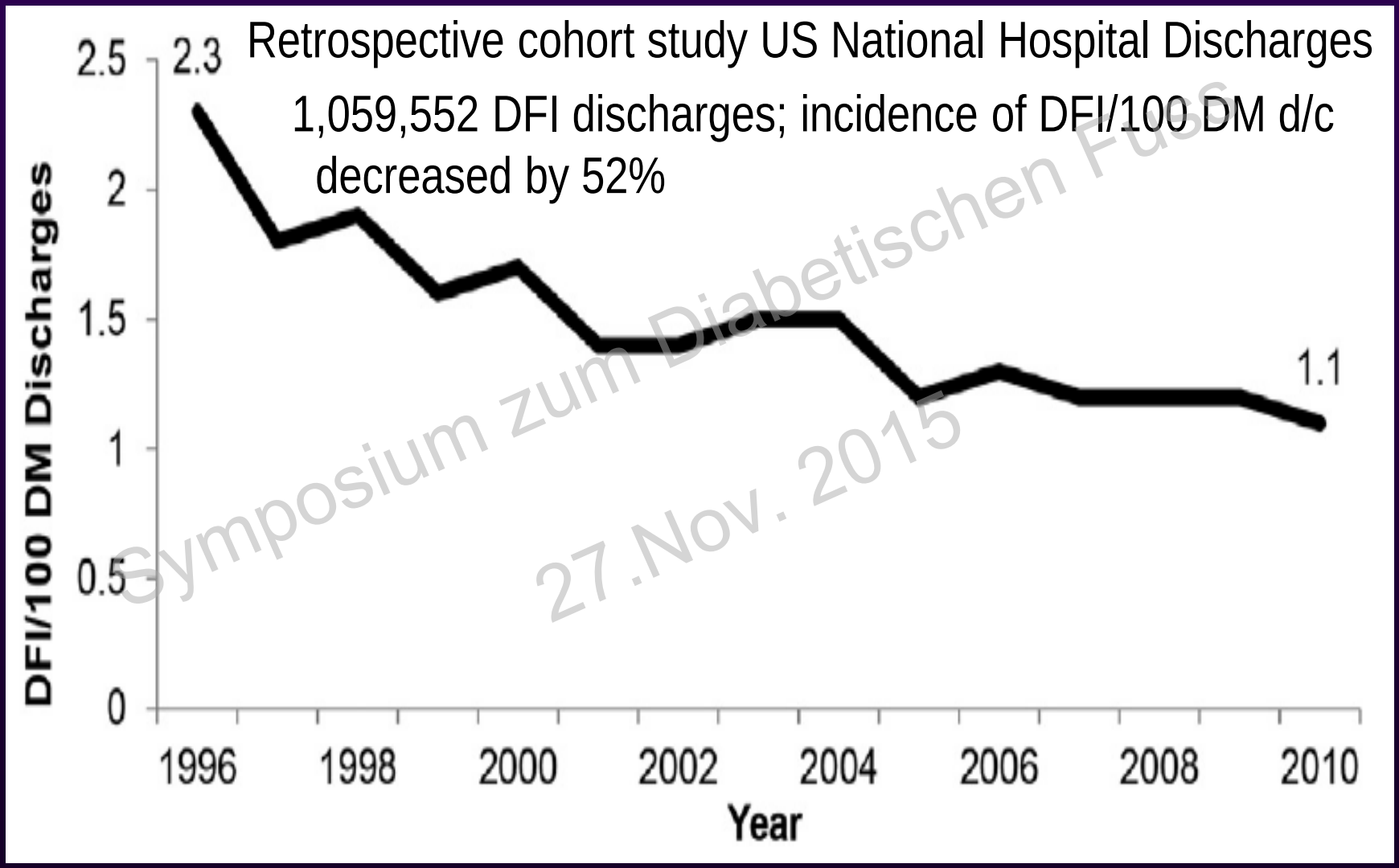
Trends in Use of Prescription Antibiotics (%): NHANES 1999-2012

P for trend <0.001; for all ages groups <60



Frenk et al, *J Antimicrob Chemother* 2015 (epub Oct 12)

Epidemiology DFI Hospitalizations USA: 1996-2010



Duhon et al. *Ame J Infect Contr* 2015 (in press 7 November)

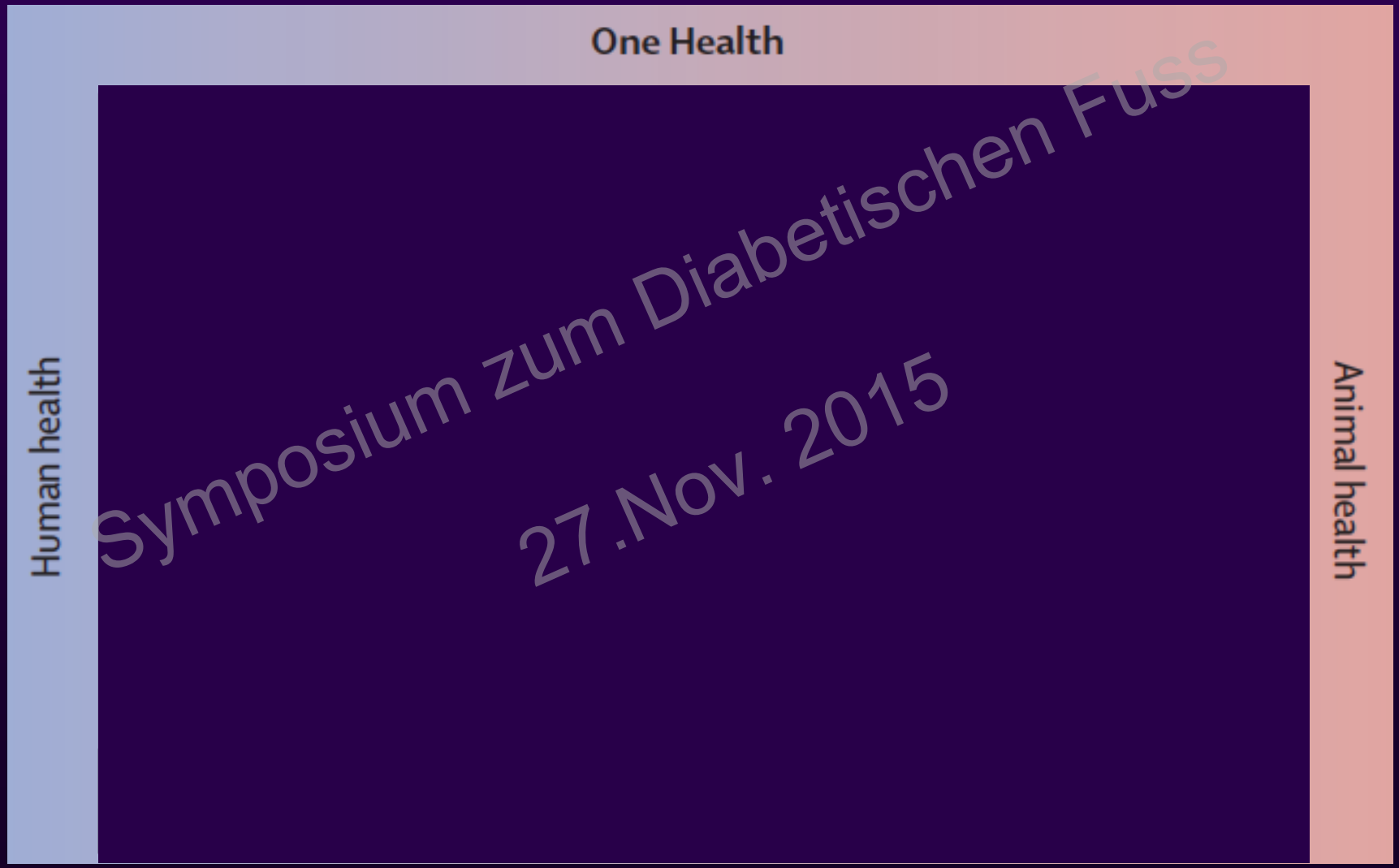
Bacteriophages: Specific Killers of Bacteria

- Discovered in 1915; first used clinically in 1920s
- Largely replaced by antibiotics, except in Eastern Europe (especially Poland, Georgia)
- Making a comeback as therapeutic agents for antibiotic-resistant microorganisms
- Effective against common DFI strains (planktonic & biofilm) including *S. aureus, Pseudomonas, Acinetobacter*


Bacteriophages φ29 & T2

Mendes et al, *J Med Microbiol* 2014;63:1055

Policy Framework for Sustainable Access to Effective Antimicrobials



Dar et al, *Lancet* 2015 (epub November 18)

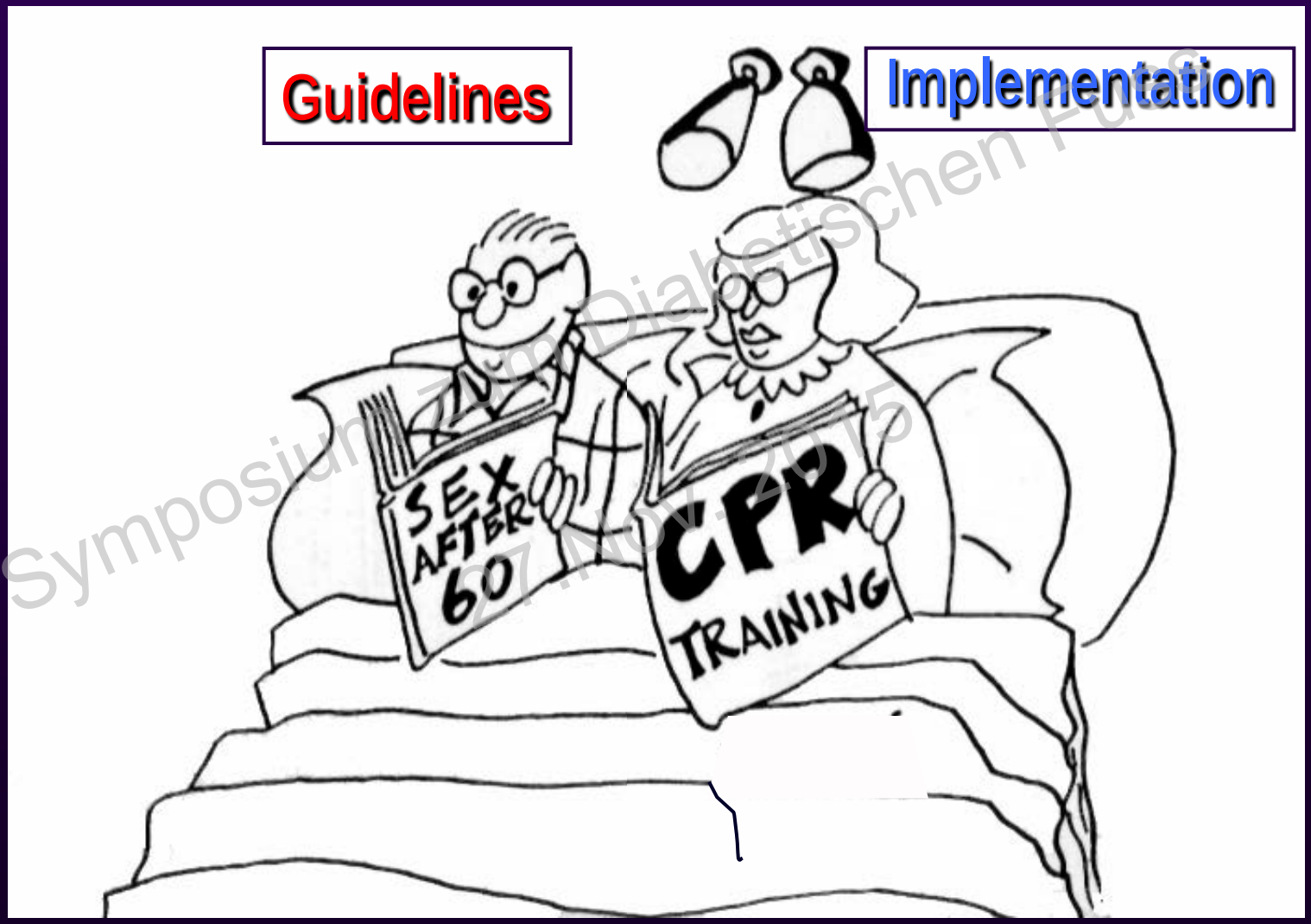
Targeting Optimal Antibiotic Rx: Think “ABX”

Appropriate *indication*

Be focused in *spectrum*

X cut treatment *duration*

Improving Prescribing for Diabetic Foot Infections



Thank You
Danke schön