Reinvigorating the Oral Antibacterial Drug Development Pipeline

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Reinvigorating the Oral Antibacterial Drug Development Pipeline

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CDER/FDA

The Brookings Institution

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Need for oral antibacterial drugs

- Treat less severe infections in an outpatient setting
- Step-down therapy for severe infections after a period of intravenous therapy
- Safe and effective oral therapies can minimize hospital stay, use of central lines/PICC lines for IV drug administration and its associated complications
- Pediatric population: Need for age appropriate formulations in children

Recent approvals

- ## Intravenous formulation only
  - Doripenem: Complicated urinary tract infections and complicated intra-abdominal infections
  - Ceftaroline: Acute Bacterial Skin and Skin Structure Infections (ABSSSI), community acquired bacterial pneumonia
  - Oritavancin and dalbavancin: ABSSSI

- ## Intravenous and oral formulations
  - Tedizolid: ABSSSI

- ## Oral formulation only
  - Fidaxomicin: *Clostridium difficile* diarrhea (CDAD)
  - Bedaquiline: MDRTB when an effective treatment regimen cannot otherwise be provided

Oral antibacterial drugs and GAIN

- Qualified Infectious Disease Product (QIDP): 62 QIDP designations granted so far
- QIDP designations not limited to antibacterial drugs with intravenous formulation only
- Fast track status also given to both oral and intravenous formulations

Potential development scenarios

- Oral therapy alone for serious infections
- Oral therapy alone for less serious infections
- Step-down oral therapy as follow on to IV therapy for more serious infections

Oral formulation alone

- *Clostridium difficile* associated diarrhea
- Gonorrhea, Chlamydia
- Uncomplicated UTI
- Community acquired bacterial pneumonia
- Other respiratory tract infections- Acute bacterial sinusitis, acute bacterial otitis media
- Bacterial vaginosis

Intravenous formulation alone

- Serious infections: cIAI, hospital acquired/ventilator associated bacterial pneumonia (HABP/VABP)
- Use of nonstudy oral antibacterial drug as step-down therapy can confound assessment of both efficacy and safety
  - Assessment at end of IV therapy if the test of cure visit occurs at some time point after completion of therapy
  - Often requires a minimum duration of IV therapy with investigational drug to better assess safety

Intravenous and oral formulation

- Oral formulation can be studied as step-down therapy for serious infections or for less serious infections
- Endpoint assessment will not be confounded by nonstudy drugs
- Minimize need for hospitalization for IV therapy
- Minimum duration of IV therapy will not be needed unless there are specific safety reasons
  – Excipients used in the formulation
  – Tolerability issues

Transition from IV to oral

- Important characteristics assessed to determine acceptability of an oral formulation:
  - Pharmacokinetic characteristics:
    - Expect differences in Tmax, Cmax
    - Absolute bioavailability
    - Food effect
    - Substrate of gut enzymes (e.g. CYP3A4) and transporters (e.g. P-gp, BCRP)
  - Pharmacokinetic/Pharmacodynamic considerations:
    - Relevant PK/PD index be similar between IV and PO

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Oral antibacterial drugs: Unmet need

- Gonorrhea: Unmet need due to increasing resistance to available therapies

- Uncomplicated UTI: Increasing incidence of UTI due to multidrug-resistant Gram-negative bacteria not covered by available oral therapies

- *Clostridium difficile* associated diarrhea

- Osteomyelitis: Need for long term therapy; oral options needed

- Mycobacterial infections: Tuberculosis, NTM

Streamlined development programs

- Gonorrhea: Allow for a single trial along with trial at another body site; would need reasonable safety data especially with regard to tolerability

- UTI: Single trial in uncomplicated UTI with oral formulation and one trial in cUTI with the IV formulation (with or without oral step-down)

- CABP: One trial with IV formulation in more severe CABP and one trial with the oral formulation in less severe CABP

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm401620.pdf

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Benefit risk considerations

- Greater uncertainty could be acceptable for patient populations with serious disease that do not have other treatment options (21 CFR 312.80, subpart E)

- More difficult for less serious infections, unless there is an unmet need, e.g. gonorrhea

- Clinical use setting will be different for oral antibacterial drugs compared to IV antibacterial drugs
  - Achieving limited use for an oral antibacterial drug can be challenging

- Stewardship is important for both limited use and general use population
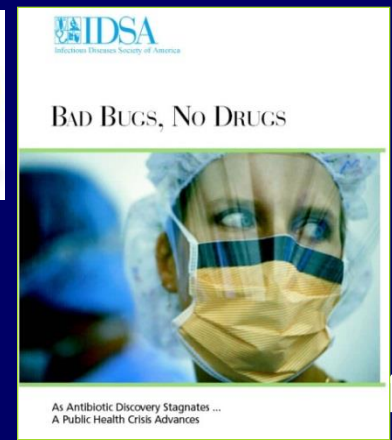
Thank You

Challenges with Oral Antibiotic Development: Clinical Perspective

Helen W. Boucher MD FACP FIDSA

Tufts Medical Center, Tufts University School of Medicine

On behalf of the Infectious Diseases Society of America

Unmet Need

- **Any antimicrobials to treat Gram-negative infections**

- **Better antimicrobials to treat Gram-positive infections**

- **Robust and sustainable pipeline of anti-infective drugs to provide for our patients now and in future generations**

WHY?

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Lives Devastated/Lost Due to Antibiotic Resistant Infections

Premature Death

Rebecca Lohsen (17 yr)--Dead

Mariana Bridi da Costa (22 yr)--Dead

Carlos Don (12 yr)--Dead

Ricky Lannetti (21 yr)--Dead

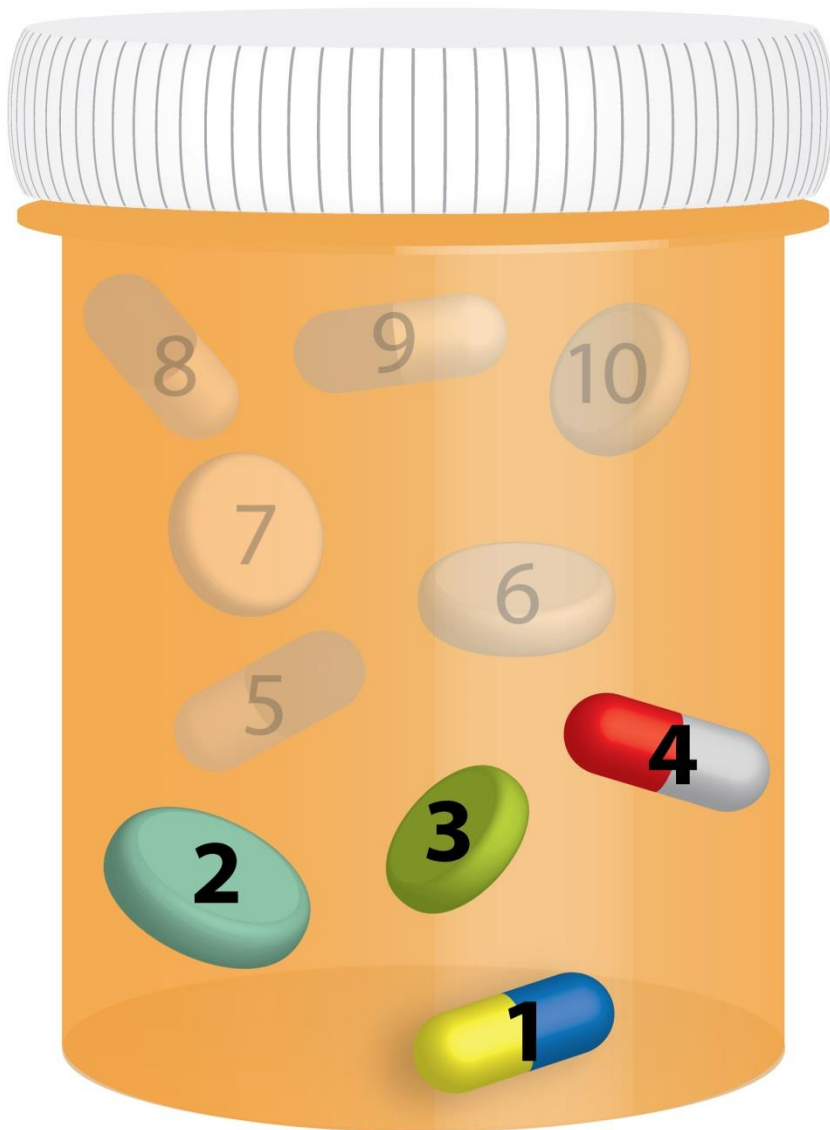## Life-altering Disability

Tom Dukes: colostomy, lost 8" colon

Addie Rereich, 11yo
Double lung transplant
Stroke, nearly blind
$6 million hospital bill

Status of the 10 x '20 Initiative

Bad Bugs Need Drugs

10 x '20

Ten new **ANTIBIOTICS** by 2020

4 oritavancin
The Medicines Company; Approved: August 6, 2014

3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014

2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014

1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010

Case

47 year old female school teacher presents with pain upon urination, lower abdominal pain

- Started on standard oral therapy - ciprofloxacin

Two days later she comes back and appears ill with ongoing new chills, nausea and back pain

- High fever, exam notable for new right flank tenderness
- Urine shows signs of infection
- Labs: elevated white blood cells with left shift

Therapy advanced to guideline therapy for pyelonephritis; she looked well enough to go home

- One dose IV ceftriaxone, then oral bactrim

Case continued… Two days later

Substantially worse, acutely ill, high fever, low BP, requires hospitalization for intravenous hydration as unable to eat or drink; 2 episodes of vomiting

— **Exam – T 38.7, BP 90/60, elevated HR, ill appearing, mild distress due to pain; worsening right flank tenderness**

— **Despite antibiotic therapy, urine culture grows > 100,000/mL *K. pneumoniae***

— ***K. pneumoniae* identified as ESBL+**

  — **Resistant to ciprofloxacin, ceftriaxone, TMP/SMX**

- **Admitted to hospital and treated with imi/meropenem**

  — **Drugs of choice for ESBLs**

Lessons from this case

- **Infections caused by resistant pathogens are serious and not entirely uncommon**
- **This could happen to you**

What if there were an oral option?

— **An oral carbapenem?**

— **Oral drugs in other classes that might address gram-negative challenge?**

- **Benefits**

— **Avoidance of hospitalization**

- **Decreased morbidity: IV catheters, risk of sepsis**
- **Less time away from work/study**

— **Potentially lower cost of drug and care**

Oral Faropenem Daxolate

- **Broad spectrum oral carbapenem**
- **Full development completed**
  - **Phase II-III program completed by Bayer; NDA filed by Replidyne**
    - **Dose likely too low**
- **2006 Non-approvable letter; further trials recommended**
- **Dose optimized**
- **Regulatory issues – changing landscape**
  - **E.g., placebo for sinusitis, AECB**
- **Development discontinued**

Where are we now?
Oral Antibacterial Agents in Phase 3 Development

Gram-Positive

Gram-Negative

Drug name (Company)	Potential Indications
Solithromycin (Cempra)	CABP, GC
Eravacycline (Tetraphase)	cIAI, cUTI
Delafloxacin (Melinta)	ABSSSI, CABP, GC

60% likely to make it to FDA approval

Systemically available antibacterials
Drugs in development for C. difficle colitis not presented

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Antibacterials in Phase 2 Development
Oral Formulations (N=9)

Drug Name (Company)	Class	Active vs Gram-negative Pathogens	Potential Indications
Debio 1452 (Debiopharm Group)	Fabl Inhibitor	No	ABSSSI
CG-400549 (CrystalGenomics)	Fabl Inhibitor	No	ABSSSI
Radezolid (Melinta)	Oxazolidinone	Yes	ABSSSI, CABP
TAKSTA (fusidic acid, Cempra)	Fusidane	No	PJI
Nemonoxacin (TiaGen Biotech)	Quinolone	Yes	CABP, DFI, ABSSSI
Finafloxacin (MerLion Pharmaceuticals)	Fluoroquinolone	Yes	cUTI, cIAI, ABSSSI
Avarofloxacin (Furiex/Actavis)	Fluoroquinolone	Yes	CABP/ABSSSI
Zalbofloxacin (Dong Wha Pharma)	Fluoroquinolone	No	CABP
GSK2140944 (GSK)	Type 2 topoisomerase inhibitor	No	ABSSSI, Resp infection, CABP

Some have acitvity vs gram-negative pathogens, few or none are active vs CRE, ESBLs

Additional Unmet Needs

- **Oral therapy for respiratory infections**
  - **Otitis media, pharyngitis**
  - **CABP (outpatient)**
- **STDs including resistant Gonorrhea infection**
- **Step down therapy**
  - **bloodstream infection, endocarditis, osteomyelitis**

Robust and sustainable pipeline of anti-infective drugs to provide for our patients now and in future generations

Thank You!

- **Organizers and co-presenters**
- **Antimicrobial Resistance Committee, IDSA**
- **Amanda Jezek, IDSA**
- **John Billington, IDSA**

Disclosures

— **Consultant/advisor to:**

- **Merck, Wellcome Trust, Theravance**
- **Innovative Medicines Initiative of the European Medicines Agency**

— **Adjudication Committee – NIH**

Oral Antimicrobials:
Challenges in Developing Agents to Address Unmet Needs

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Senior Vice President and Chief Scientific Officer (Rempex)
Head, Health Sciences R&D, Infectious Disease Global Innovation Group
The Medicines Company
San Diego, CA

MN Dudley: Disclosure

- This is one perspective (not for all of industry, nor my employer)

- > 30 yrs in drug development in academic clinical and research practice, and R&D in industrial setting

- My thoughts reflect recent development experience with 4 antiinfective drug products over last 3 years, as well as oversight of R&D programs for oral, inhaled and IV agents

- Thanks to many …(Scott Hecker)

Oral Antibiotic Therapy of Infections Previously Managed with IV Antibiotics Became Possible with Fluoroquinolones

- Oral antimicrobial therapy for pathogens frequently encountered in inpatient setting became possible with fluoroquinolones in late 1980s.
  - Remarkable change in paradigm for treatment of many infections that facilitated earlier discharge, reduction of IV drug use (oral or IV$\rightarrow$ oral switch therapy)
  - Rapid rise in resistance in gram-negative pathogens to fluoroquinolones over the past decade has reduced the utility
    - UTIs in some areas of world are managed in outpatient setting with IV carbapenems in infusion centers

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

What's Next?
CRE is Moving to Settings Other Than Large Metropolitan Hospitals

Epidemiology in long-term acute care hospitals in Chicago[1]

- Median duration of colonization 16 months

- High risk of transmission

Community-Associated (CA) CRE[2]

- CA CRE vs. HCA CRE

  · CA cases younger, less ill, with fewer co-morbidities

  · CA-CRE cases were cUTIs

1. Haverkate et. al., ID Week 2014.
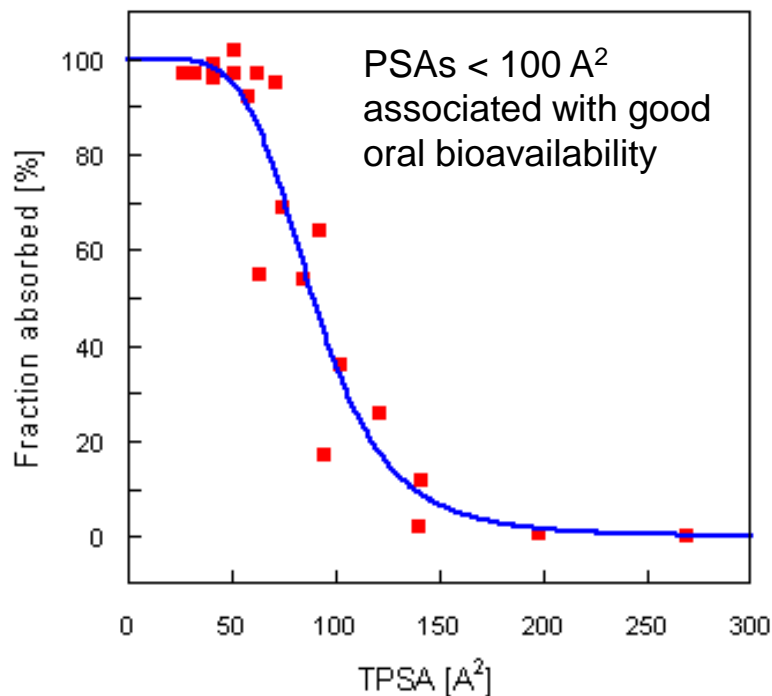2. 2. CDC Emerging Infection Program, ID Week 2014.

Scientific Considerations for Discovery and Development of Oral Antibiotics

- Antimicrobial potency in vitro and good PK properties often are orthogonal
  - Oral bioavailability even more challenging: size, polar surface area often properties that reduce drug uptake and/or target affinity
- Preclinical in vitro and in vivo models critical for understanding the PK and absorption
  - Lots of drugs can show bioavailability and efficacy in screening models in mice
    - Best to screen PK properties in higher species rather than rely on efficacy read-outs in mouse models of infection (false positives)
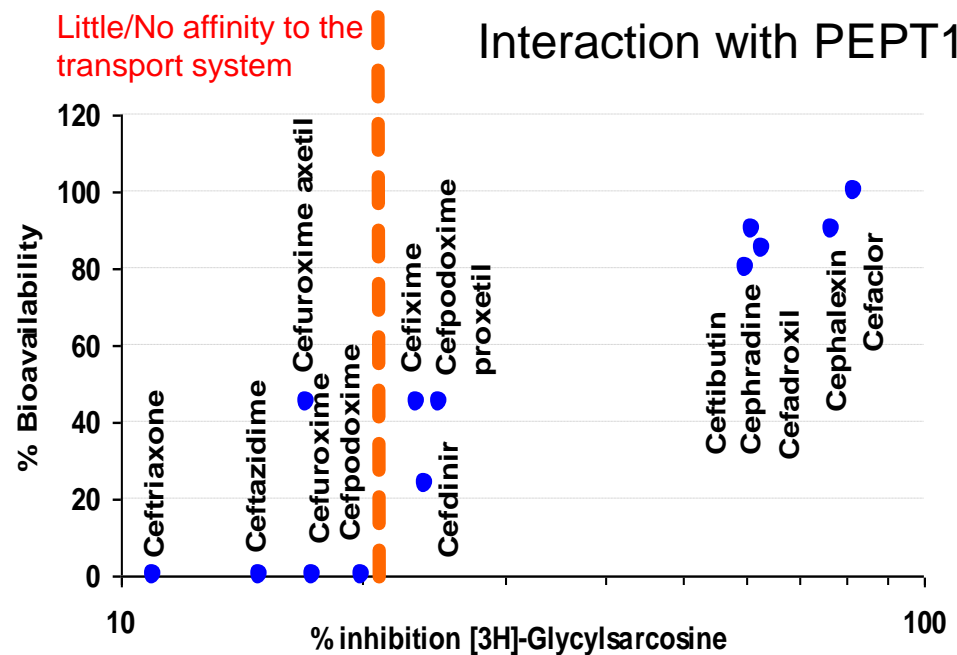
"You Can't Always Get What You Want…"

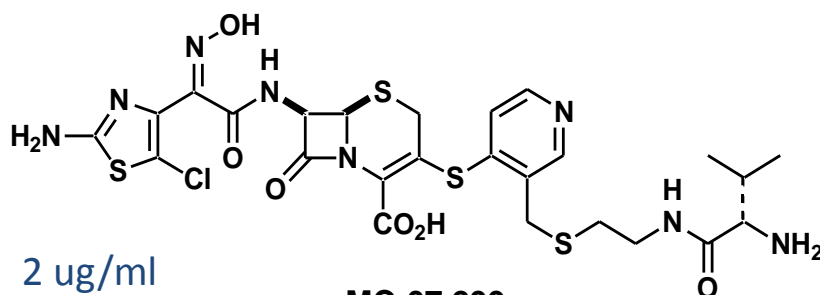# Oral anti-MRSA Cephalosporin Discovery Program (ca. 2001)

Polar Surface Area (tPSA) and Oral Bioavailability

PSAs < 100 A^2 associated with good oral bioavailability

Topological PSA: fragment-based method for rapid calculation
http://www.daylight.com/meetings/emug00/Ertl/index.html

Inhibition of [3H]-Glycylsarcosine Substrate Indicates a Substrate for a Peptide Transporter

Little/No affinity to the transport system

Interaction with PEPT1

Bretshneider et al. 1999, Pharm. Res. 16:55-61.

MIC90 vs. MRSA: 2 ug/ml

MC-07,299

^{3}H-Gly-Sar inhibition: 64%

Mouse Sepsis 20 mg/kg PO, survival: 4/10

Oral absorption (rat PK): ~0% !!

PK-PD Considerations for Oral Antibiotics

- Dose mass can be limiting
- Potency and doses of oral antibiotics
  - Oral daily doses in 400 mg -2 g range
  - For systemic infections:
    - MIC <= 1 ug/ml
  - UTIs:
    - MICs up to 8? 16 ?
- High concentrations in urine can ease potency, PK requirements for treatment of UTIs
- Slow clearance/long half-life, oral absorption can help terminal half-life for beta-lactams to be longer ("flip-flop" PK model)
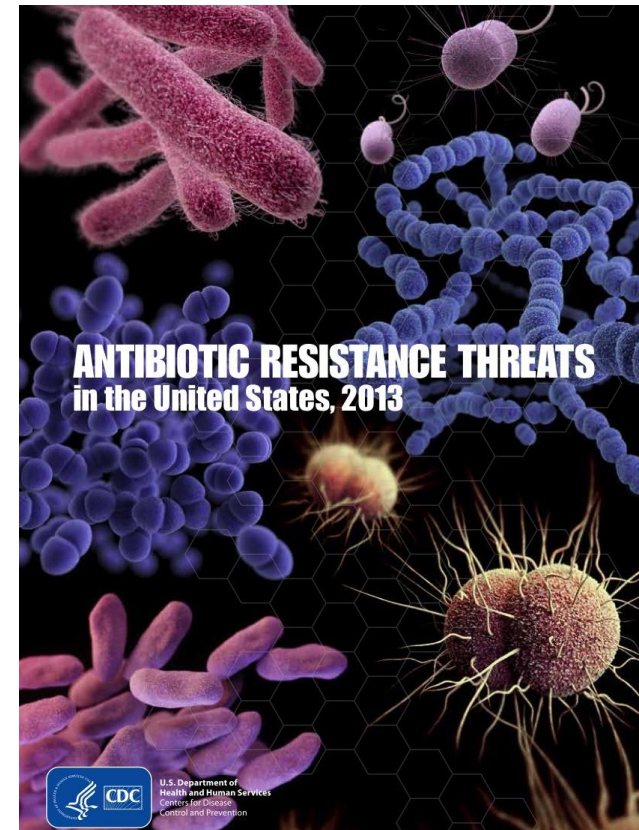
Incentives

- Many are similar considerations for IV agents
- Value based:
    - Does the new therapy address a threat pathogen/unmet need?
    - Does the new therapy preserve or open up different care pathways that are beneficial to the health care system?

Clinical Trials, Labeling and Stewardship

- Oral antimicrobials with activity vs. threat pathogens need to be managed carefully by stewardship programs

- Does indication-only based labeling without reference to specific pathogens (with resistance threat) promote use?

  – Importance of labeling: *"…for use in patients with suspected infection due to "XX" where existing agents are limited or not appropriate…"*

What Antimicrobial Resistance Threat Pathogens Can Be Addressed With Oral Antimicrobial Therapy?

- UTIs and Acute Pyelonephritis
  - Enterobacteriaceae
    - ESBL-producers (ceph resistant)
    - Carbapenem-resistant Enterobacteriaceae
  - *Pseudomonas aeruginosa*
  - VRE
- Gastroenteritis
  - *Shigella*
  - *Salmonella* (non-typhoidal)
  - *Campylobacter*
- STD
  - *Neisseria gonorrhoeae*
- Pneumonia
  - *S. pneumoniae*
- ABSSSIs and Diabetic Foot Infections
  - MRSA
  - Resistant gram-negatives

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Summary

- Oral antibiotic R&D is challenging
    - Extra level of complexity and costs to get candidates
- Value is both unmet need but also management of infections outside health care setting
- Appropriate guidance through labeling and stewardship practice is important to assist in preserving their usefulness

Challenges with oral antibacterials

A developer's personal perspective

John H. Rex, MD
SVP & Head of Infection Global Medicines Development, AstraZeneca
Non-Executive Director & Consultant, F2G Pharmaceuticals

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Slides happily shared – just drop me a note

What makes a chemical a drug?

What are the requirements for it to be given by mouth? By vein?

IV? PO? Why one, the other, or both?

- For IV drugs, it's mostly about solubility

- For oral drugs, it's much more complex. It must
  - Be stable in various solid forms
    - Bulk powder (must flow) and oral dosage form
  - Dissolve at the right time in the gut
  - Be appropriately transported across the gut wall (in the right direction!) while also having the right properties to reach the site of action

- Rules of thumb for oral drugs: Lipinski's rule of 5[1]
  - Molecular weight < 500, logP < 5, limits on H-bond acceptors, H-bond donors, and polar surface area
  - 90% of oral drugs meet Lipinski's rule

LogP is a measure of water vs. lipid affinity. Also of note is BCS (Biopharmaceutical Classification System), a system that uses solubility and permeability to create 4 categories for candidate oral compounds.

Antibacterials don't follow Lipinski's rules
Compared to drugs in other therapy areas...

- **Gram-Positive Antibacterial Agents**
  - *much* higher average mol. weight
  - less lipophilic (lower logP)
  - greater polar surface area
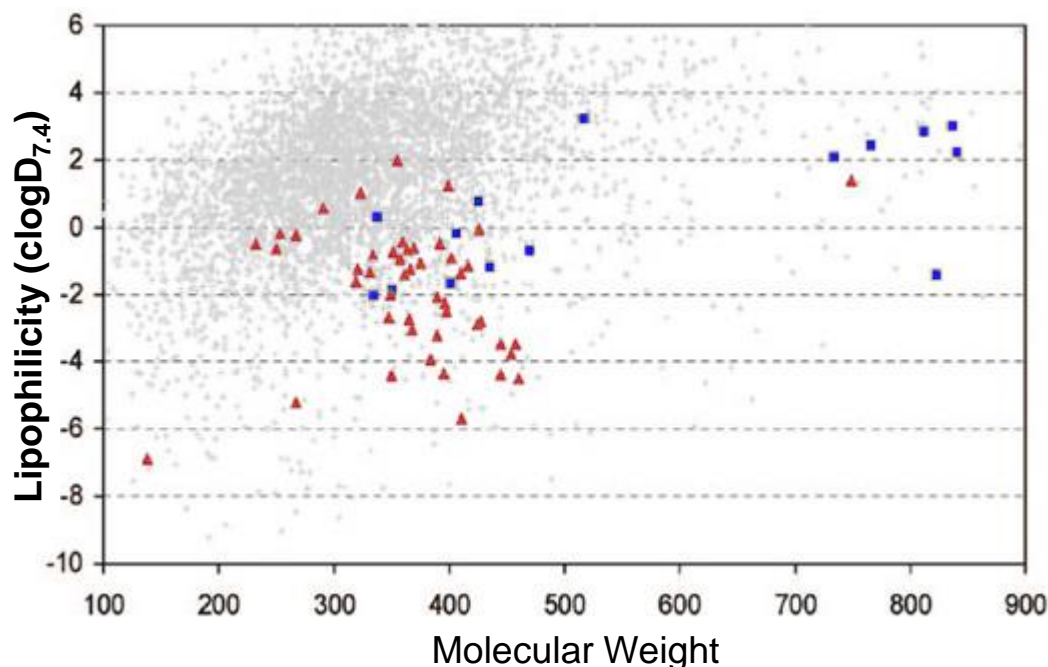 - more H-bond acceptors
  - more H-bond donors

- **Gram-Negative Antibacterial Agents**
  - higher average MW, *but average <600*
  - *much* less lipophilic (*much* lower logP)
  - greater polar surface area
  - more H-bond acceptors
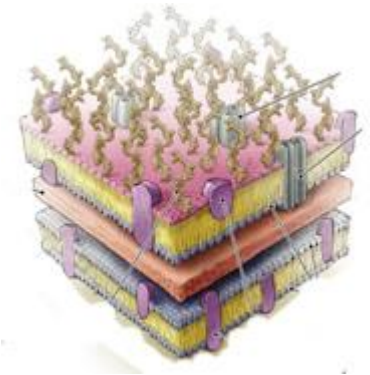 - more H-bond donors

Visually, it looks like this
■ : General compounds
■ : Gram-positive PO drugs
▲ : Gram-negative PO drugs

O'Shea, R.; Moser, H. E. *J. Med. Chem.*
2008, *51,* 2871-2878

Getting into the blood is just the first step – the drug must now enter the target microbe

- Outer membrane penetration is more likely[1] with
  - small, hydrophilic, polar, charged, zwitterionic, divalent cation chelators
  - This is all you need for Gram-positives

- For inner membrane penetration[1]
  - permeable, lipophilic, uncharged
  - Unless the target is in the periplasmic space between the outer and inner membranes, must cross this membrane as well for Gram-negatives

Opposites!

- Compounds that can do all this are rare indeed!

[1]The compound doesn't have to have all of these properties, but having some subset of them makes activity more likely. Refs: Nikaido, H. Microbiol. Mol. Biol. Rev. 2003, 67, 593-656 and Silver, L. L. Expert Opin. Drug Discov. 2008, 3, 487-500

Developing oral antibacterials

How might we do this?

The role of oral drugs

- We often think of oral drugs as being for less severe infections
  - Higher doses can be given IV
  - IV guarantees systemic delivery
- But, oral drugs are used for severe infections
  - TB, Pneumocystis pneumonia
  - And they are invaluable as follow-on for severe infections
- But, there is a real challenge with the first step of initial registration…

Oral drug development challenge

- Because we generally must use active comparator non-inferiority designs in antibacterial development[1]
  - We must limit our studies to infections with consistently poor outcomes with placebo therapy
  - This, in turn, requires us to study severe infections
- Patients with severe infections
  - Need rapid attainment of high blood levels
  - May have reduced gut function / drug absorption
  - May hence require initial IV therapy
- But, for a clear demonstration of efficacy
  - Test agent should be the first & only therapy given

[1]Nambiar et al. Clin Pharm Ther 96:147-149, 2014

This leads to two scenarios…

- Easy: IV and PO possible for a given molecule
  - Requires: Similar efficacious levels with both
  - Studies can start IV and switch to PO
  - Can study even the most severe infections
  - Effect of test agent IV then PO is easily assessed
- Hard: only PO possible for a given molecule
  - Need setting where initial PO therapy is possible
  - *OR* a setting where initial IV therapy is obviously non-curative and additional therapy is needed to prevent relapse

Development possibilities

- Initial oral therapy possible
  - Upper respiratory infections (otitis media, etc.)
  - Less severe CABP
  - Less severe skin infections
  - UTI and less severe pyelonephritis
  - STDs (*N. gonorrhoeae*, *Chlamydia*)
  - *C. difficile*; Other gastroenteritis pathogens
  - Biothreat agents by animal rule
  - Tuberculosis

- Initial IV therapy definitely not curative
  - Osteomyelitis
  - Endocarditis

Development possibilities

- Initial oral therapy possible
  - ~~Upper respiratory infections~~
  - Less severe CABP
  - Less severe skin infections
  - UTI and less severe pyelonephritis
  - STDs (*N. gonorrhoeae*, *Chlamydia*)
  - ~~C. difficile;~~ Other gastroenteritis pathogens
  - ~~Biothreat agents by animal rule~~
  - ~~Tuberculosis~~

> Placebo effect size is too large, superiority designs are unreliable, unmet need is not high

> Special cases

- Initial IV therapy definitely not curative
  - ~~Osteomyelitis~~
  - ~~Endocarditis~~

> Lengthy trials, must have extensive safety data to support lengthy therapy, no easy way to do a small Phase 2 for dose selection

Plausible pathways considered

- Less severe CABP (but sufficiently severe to be convincing)
  - May be hard to find adequate severity patients who can take PO
  - Only studies respiratory pathogens: *S. pneumoniae* and *H. influenzae*
- Less severe skin infections (but sufficiently severe to be convincing)
  - May be hard to find adequate severity patients who can take PO
  - Does permit study of S. aureus, including MRSA
- UTI and less severe pyelonephritis
  - Studies Gram-negatives, but mostly limited to *E. coli*
  - Entirely plausible and a significant (and growing) unmet need
  - Requires drug to be cleared into urine; High urine levels augment effect and lead to reduced confidence about efficacy at other sites
- STDs (*N. gonorrhoeae*, *Chlamydia*)
  - Plausible and useful, but therapy is always brief (often just a single dose), efficacy will not generalize to other settings and pathogens,
- Gastroenteritis pathogens (*Salmonella, Shigella, E. coli*)
  - Plausible, studies Gram-negatives, but limited generalization

Economics

- Traditionally, oral drugs require a very different approach to sales & marketing via a (usually large) primary care marketing team
  - The sales & marketing team's size is loosely proportional to the number of physicians who use the agent
- These drugs would, however, be different – if approved on small datasets for patients with limited treatment options, a model in which volume of use is separated from innovation reward is really required
  - We're working hard on concept, but such models are not yet reality. It's going to take time.

Personal view

- When you look at all the hurdles, it is amazing that we have any antibacterials, IV or PO!

- We (AZ) chose some years ago to focus on serious infections

- That, in turn, led us to put less emphasis on oral-only drugs as development candidates

Reinvigorating the Oral Antibacterial Drug Development Pipeline

Brookings Institution • Washington, DC
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Oral Antibiotics
Study Designs

John H. Powers, MD

Associate Clinical Professor of Medicine

George Washington University School of Medicine

Define Unmet Medical Need
Relates to Study Objectives

- **Serious and life threatening diseases**
  - **Many infections for which oral drugs used as primary therapy not serious and life threatening**
  - **Unclear evidence of benefit – URIs**
  - **Clear evidence of benefit - uUTI (but not serious)**

- **Study settings**
  - **Primary oral therapy – can this be for serious/life threatening as reliance often based on tradition**
  - **Follow-on therapy after IV treatment –**
    - **Acute (e.g. skin infections, CABP**
    - **Chronic - TB, osteomyelitis, endocarditis?**
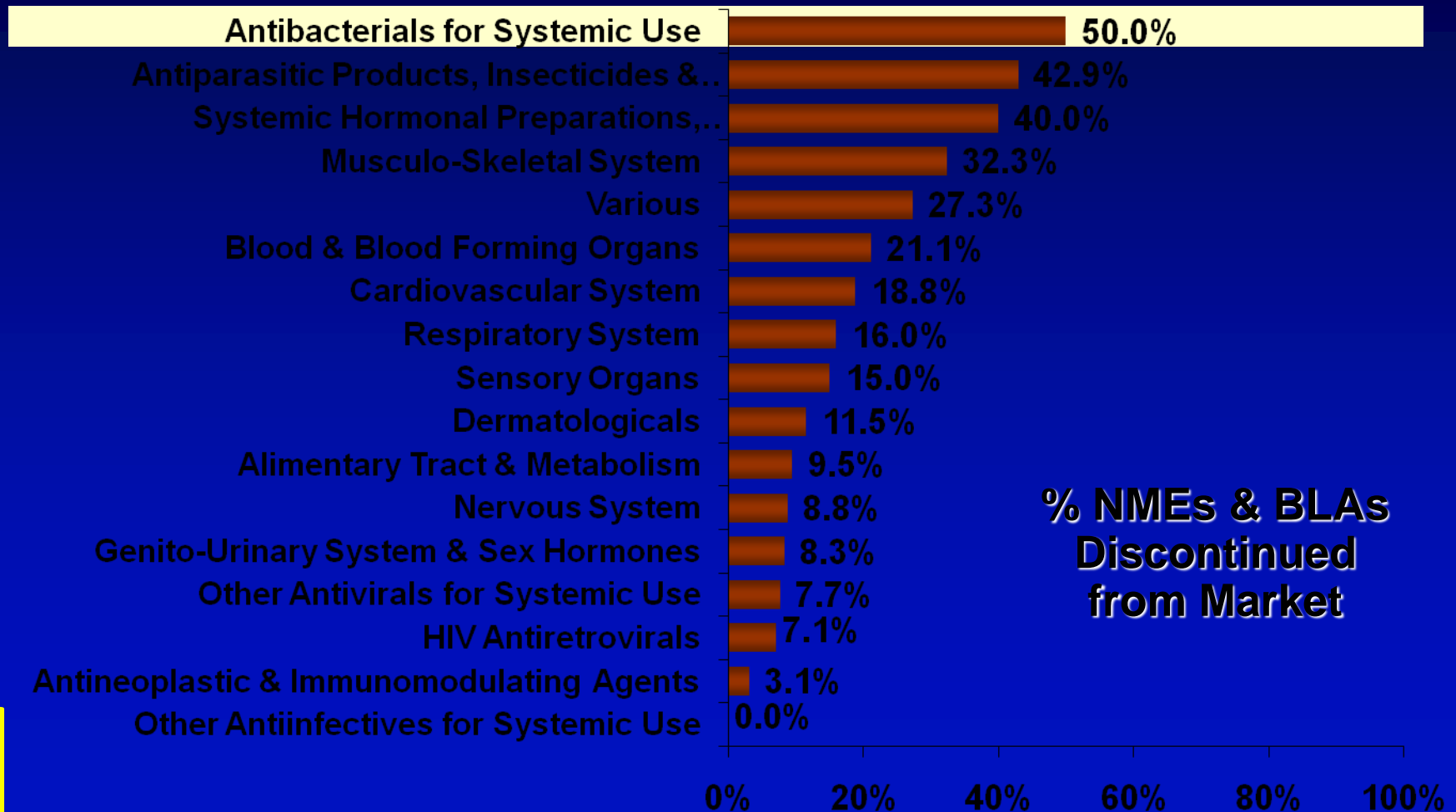
Research Questions and Study Design

- **Improved effectiveness = setting of antibiotic resistance**
  - **Superiority trial (enrollment diagnostics)**

- **Decreased harms – not relevant unless effective first**
  - **Does not have to be non-inferiority if use different endpoints**
  - **Examples of harms in recent literature (Fralick et al BMJ 2014) makes assurance of efficacy primary concern**

- **Improved convenience – should result in improved effectiveness or decreased harms**

- **Decreased overall costs – often not a regulatory question but clearly of important to payers**

Example – CMS Review Dalbavancin

- **"With these limitations [noninferiority] in using efficacy data to establish substantial clinical improvement, the applicant suggested that the outpatient treatment, elimination of central lines and avoidance of hospitalization all may improve safety, avoid treatment associated infections and improve patient satisfaction, and that these factors demonstrate substantial clinical improvement. While the factors mentioned *may* be true, the applicant did not present any evidence to support its assertions."**
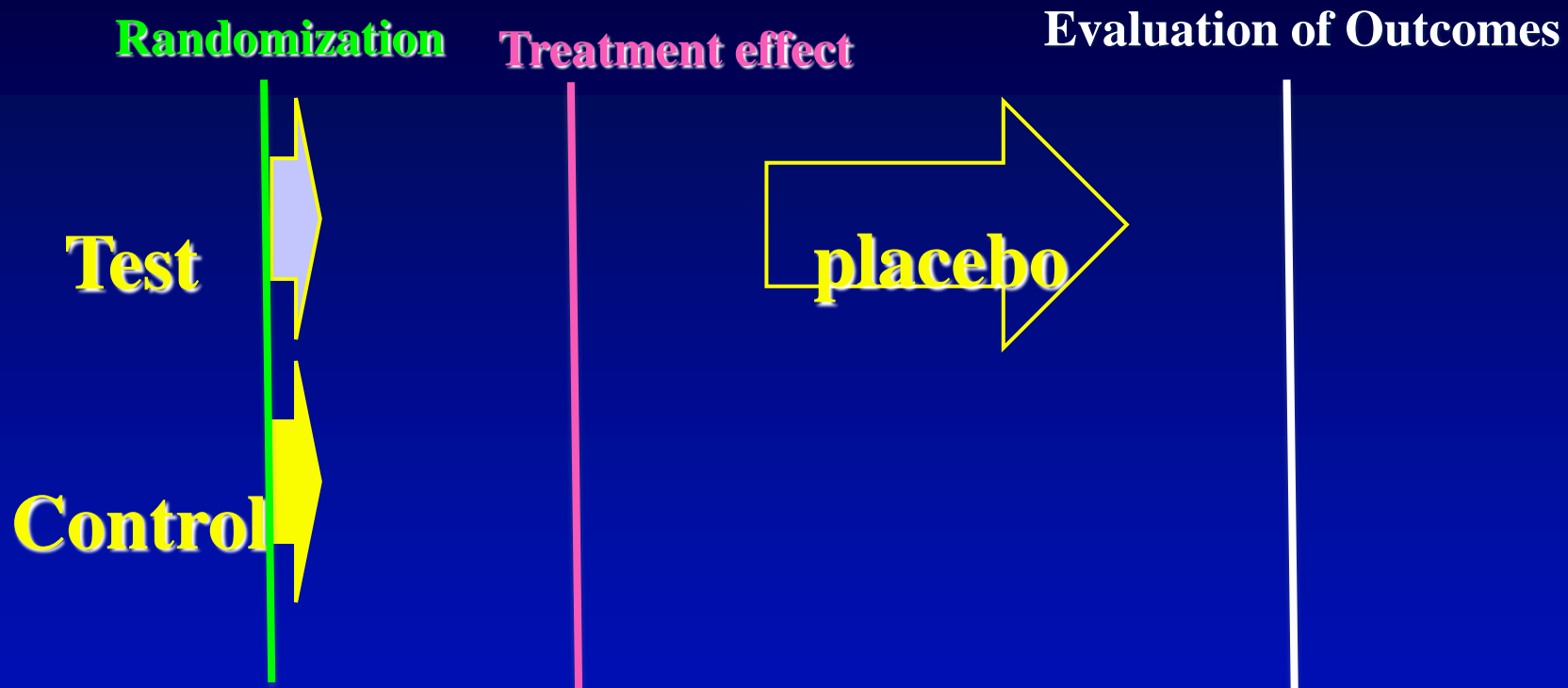
Discontinued NMEs and BLAs. Approved by FDA (1980-1999)
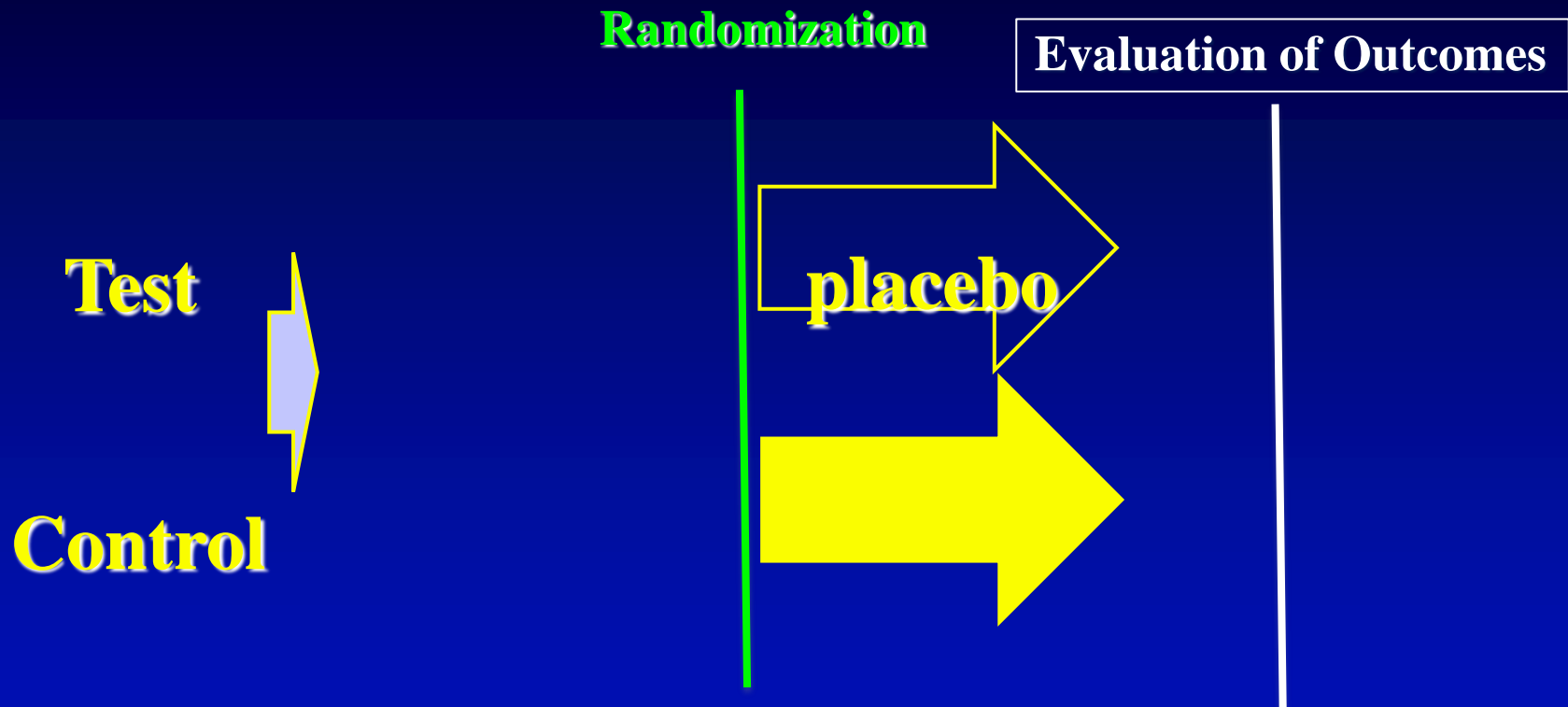## Outterson K et al J Law Medicine and Ethics 2013

Category	%
Antibacterials for Systemic Use	50.0%
Antiparasitic Products, Insecticides &..	42.9%
Systemic Hormonal Preparations,..	40.0%
Musculo-Skeletal System	32.3%
Various	27.3%
Blood & Blood Forming Organs	21.1%
Cardiovascular System	18.8%
Respiratory System	16.0%
Sensory Organs	15.0%
Dermatologicals	11.5%
Alimentary Tract & Metabolism	9.5%
Nervous System	8.8%
Genito-Urinary System & Sex Hormones	8.3%
Other Antivirals for Systemic Use	7.7%
HIV Antiretrovirals	7.1%
Antineoplastic & Immunomodulating Agents	3.1%
Other Antiinfectives for Systemic Use	0.0%

% NMEs & BLAs Discontinued from Market

0% 20% 40% 60% 80% 100%

Follow-On Drugs
Trial 1 - Non-inferiority trial fixed durations

Randomization   **Treatment effect**   Evaluation of Outcomes

Test

placebo

Control

For acute diseases (skin, CABP) don't know what benefit is of additional intervention to design NI

2.Comparison with a Control
Trial 2 - Superiority trial fixed durations

Randomization

Evaluation of Outcomes

Test

Control

placebo

2. Comparison with a Control
Study 4 – Superiority trial "optimized" duration

Randomization trigger

Evaluation of Outcomes

Test

placebo

Control

"Trigger" can be lab test, PRO or combination (PRO becomes "PRI")

Outcomes Assessments
What and How to Measure

- **Short term acute diseases - measure direct patient benefit with Patient Reported Outcomes (PROs)**

- **Surrogate endpoints (microbiological) – what direct benefit is surrogate a substitute for?**
  - **No formal evaluation e.g. GC**
  - **Poor correlation of micro and symptoms**
  - **Surrogate reserved for serious and life threatening with added benefit over available (21CFR214.500)**

- **PRO decreases misclassification bias**
  - **Decreases sample size**
  - **Electronic administration decreases missing data**

Outcome Assessments
How to Analyze

- **Use of ordinal (categories) endpoint analysis**
  - **Example of RADAR (Response Adjusted for Days of Antibiotic Risk stewardship studies)**
  - **Ordinal patient level analysis of categories:**
    - **Benefit: No Harm**
    - **Benefit: Harm**
    - **No benefit: No Harm**
    - **No Benefit: Harm**

- **Determine how to select patients with benefit: no harm**

- **More thoroughly analyze benefits and harms in superiority trial design**

Reinvigorating the Oral Antibacterial Drug Development Pipeline

Strategies to Support Oral Antibacterial Drug Development

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The Brookings Institution ● Washington, DC
Thursday, November 20, 2014

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Disclaimer

The information provided is the sole perspective of Christine C. Ginocchio and does not reflect the views of bioMerieux

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Potential Uses

- **Screening of patients with specific clinical syndromes for targeted microorganisms prior to, or concomitant with, study enrollment**

- **Enrichment of study population with patients with less common infections**

- **Smaller clinical trials since more patients enrolled would have a "proven" microbial etiology of their illness**

- **Identify risk for clinical failure or for adverse events**

- **Better trial outcome as a truly targeted therapy**

- **Post clearance for rapid screening: targeted therapy**

Use of Pre-existing Tests

- **A clinical trial of a novel antimicrobial agent with activity against both MRSA and MSSA in skin and skin structure infections**

- **May want a rapid test (1 hour or less) to screen wound specimens from potential patients to identify those specifically with MRSA infections**

- **Studies on new gram negative agents for LRTI – large syndromic panels already developed for diagnostic applications**

- **Such a strategy usually goes smoothly when the diagnostic test already exists**

Trial Developed Tests

- **Despite considerable synergy between pharmaceutical and diagnostics companies that could share the costs of both development and clinical trials, such synergies are few**

- **Pharmaceutical companies may seek a diagnostic partner to develop a test for a limited panel of infectious agents or often a single pathogen in a body site or organ, where multiple pathogens may be the etiologic agent of disease**

- **Pharmaceutical companies want a limited financial commitment for development**

- **Diagnostic companies want to develop "syndromic" products (ie, one that detects multiple infectious agents) with broad clinical utility and marketability**

- **Tests and drugs: independent**

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"Companion Diagnostics"

- **When the test and the drug are linked together as part of the clinical trial and ultimately for prescribing**

- **FDA clearance for both drug and test**

- **Financially beneficial for both (trial costs)**

- **Can limit scope of drug and test usage**
  - **Drug: Can't use without diagnostic to ensure infection, test may not be available on site or available 24/7. What about in out patient setting, cost, equipment, POC etc.?**
  - **Test: use limited to screening for agent treated by specific drug, significantly raising test cost and decreasing manufacturer revenue**
  - **What if: Drug failure – product success (or visa versa)?**
  - **One can delay other's time to FDA clearance/approval**

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Test Acceptance

- **Scope of diagnosis: single or multiple targets**

- **Performance: acceptable standards for positive and negative predictive values that would translate to changes in patient management and will vary based by disease**

- **Turnaround time will also determine the utility and uptake of diagnostic tests**

- **Some "time-sensitive" diagnoses require immediate specific targeted therapy to avoid sequelae of the diseases or relative toxicity of empiric treatment**

- **These tests are best performed near the patient as either POC tests (need for CLIA waiver?) or in rapid response laboratories (low to moderate complexity)**

Test Acceptance

- **Conversely, for diagnoses of diseases that progress at a slower rate, turnaround time is less urgent, permitting the use of tests performed in centralized laboratories**

- **Another significant barrier to widespread uptake and use is the paucity of clinically applicable outcomes data to show that using the test in making treatment decisions is superior in terms of morbidity, mortality, or cost compared to empiric therapy**

- **Outcomes data with clinically relevant parameters (eg, clinical outcomes, complications, and mortality) are critical for providers to effectively use any assay**

- **Cost benefit versus traditional testing**

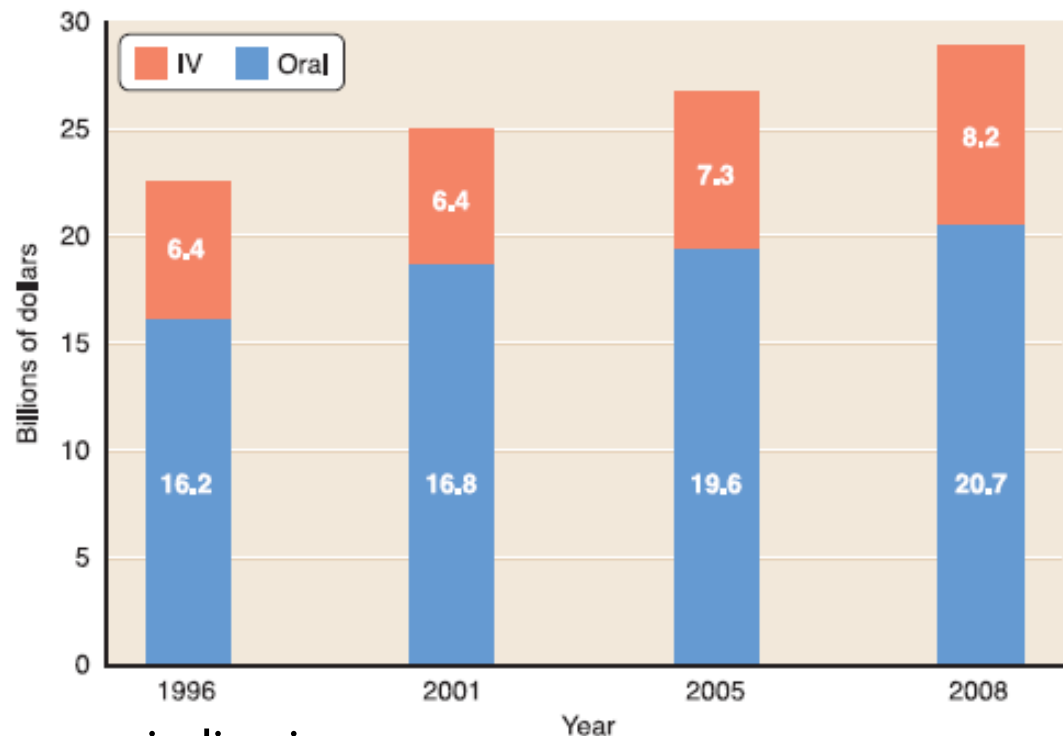# Strategies to Support Oral Drug Development

Michael Dunne, MD

Durata Therapeutics, Inc.

Comment presented are my own and not necessarily those of Durata Therapeutics

Strategies to Support Oral Antibacterial Drug Development

- Medical Need
  - ESBL gram negatives without oral options
  - Potential for Drug resistant *S. pneumoniae*
- Settings of Use
  - Respiratory
    - Otitis media
    - Bronchitis
    - Sinusitis
    - CAP
  - Skin infections
  - Genitourinary
    - UTI
    - STD's
    - Prostatitis
  - Gastrointestinal
  - Follow on from IV therapy indications

Shlaes DM *et al.* Antibiotic Discovery: State of the State. ASM News 2004; 70, 275

Strategies to Support Oral Antibacterial Drug Development

Advantages

- Market is significantly larger than intravenous therapies
- Studies are less expensive

Challenges

- Oral antibiotics are (perceived) for less severe infections
  - Risk/benefit ratio is less forgiving
  - Tolerability (nausea, etc.) is more important
- Generic pricing sets the floor
  - And generics have significant share of voice through third parties
  - Reluctance to accept marginal improvements in new oral therapies
    - Exactly what medical need has been addressed??
- Claims are not commercially attractive
  - No AECB
  - Sinusitis difficult
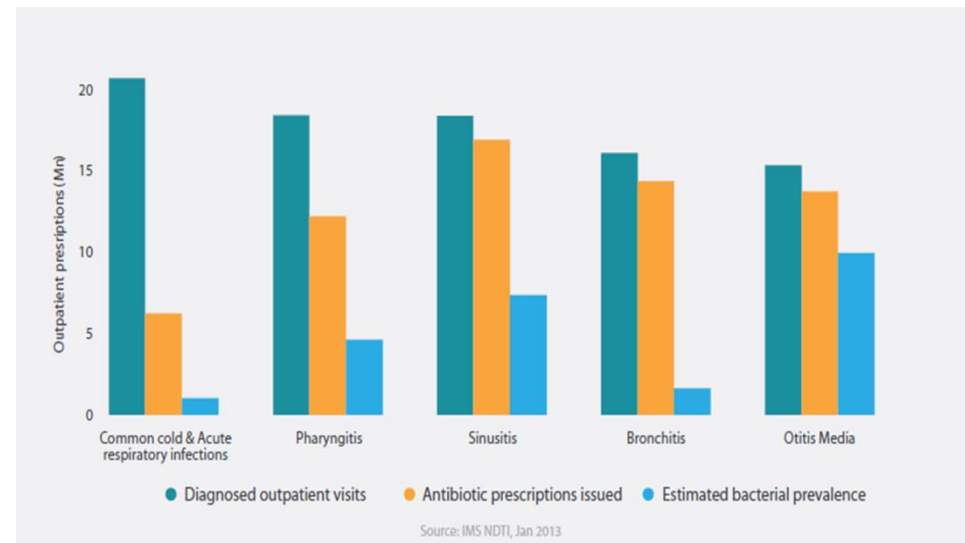 - Otitis media controversial

Oral Antibacterial Agents Non-inferiority Trial Design

- Appropriate to manage the ethical constraints of placebo controlled trials
- Require larger samples sizes to achieve 90% power
  - Less forgiving benefit/risk ratio requires more clarity on safety and tolerability
    - Superiority studies not more efficient if required sample size 'too small'
- Challenges the opportunity to qualify for NTAP payment
  - Non-inferiority not considered evidence of clinical improvement
    - Because superiority to standard of care is not established
  - Aren't antibiotics with improved *in vitro* spectrum <u>inherently</u> superior?

Oral Antibacterial Agents Diagnostics

- Advantages
  - Could distinguish between viral and bacterial respiratory infections
    - Allow for targeted use of antibiotics for sinusitis and bronchitis?
  - Identify pathogens sensitive to generics vs requiring new agents
    - Support value proposition and therefore appropriate pricing

- Challenges
  - Need sample material
    - ?prostatitis due to ESBL's
  - Must be established in clinical practice to be in a development program
    - Challenging for Drug development to drive Diagnostic development

Oral Antibiotic Agents
Payors and Incentives to R&D

- Diagnostic interventions (medical practice/tests) need to be better established
  - If the role for antibiotics is clear, reimbursement improves
  - If reimbursement improves, R&D will follow
  - ?Payor reimbursement incentives for better diagnostics?
- Better analytical tools to assess data collected from insurance and provider databases
  - Improve the ability to quantify value of the antibiotic
    - Better value justifies appropriate pricing and reimbursement
  - Would provide ongoing pricing incentives to support drug development
- Payors should accept that medical care in clinical trials is a covered service instead of being funded by clinical trial sponsors

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Oral Antibiotic Drug Development

Brookings 2014

Kevin Outterson

mko@bu.edu

Acknowledgements

- **Eastern Research Group Report for US DHHS**
  - **Chatham House Working Group on New Business Models for Abx**
    - **DRIVE-AB**
  - **Longitude Prize (rapid POC abx dx)**
- **CDC Antimicrobial Resistance Working Group**
  - **IDSA, ReACT, Brookings & Pew**

All comments today are entirely my own and do not necessarily reflect the position of anyone else

Overview

1. Oral v. IV

2. Threats

3. Pipeline

4. Economics

Overview

1. **Oral v. IV**

2. **Threats**

3. **Pipeline**

4. **Economics**

Fuzzy Boundaries

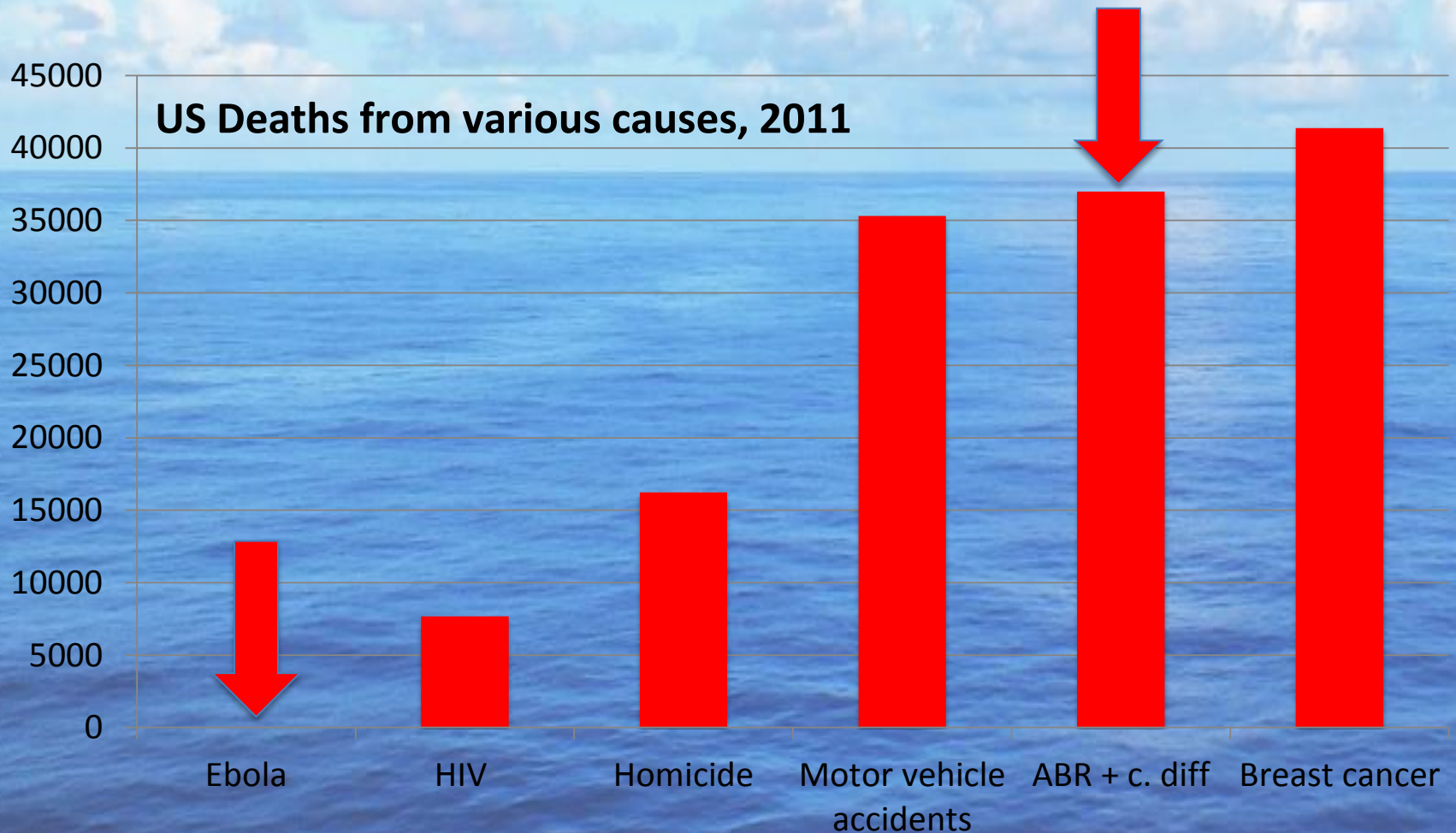|	Community	Inpatient
Oral	levofloxacin	levofloxacin, vancomycin
IV	OPAT	dalbavancin & oritavancin daptomycin, vancomycin

Overview

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A Serious Problem

US Deaths from various causes, 2011

Bar chart with y-axis labeled 0 to 45000 in increments of 5000. Categories: Ebola, HIV, Homicide, Motor vehicle accidents, ABR + c. diff, Breast cancer. Red arrows point down at Ebola (~13000) and ABR + c. diff (~37000).

Source: National Vital Statistics Report (NVSR) "Deaths: Final Data for 2011." Data for ABR + c. diff. is from CDC, Antibiotic Resistance Threats in the US, 2013; Ebola 2014, as of today.

NATIONAL SUMMARY DATA

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least **2,049,442** illnesses, **23,000** deaths

*bacteria and fungus included in this report

+

Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least **250,000** illnesses, **14,000** deaths

WHERE DO INFECTIONS HAPPEN?

Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.

CDC

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS239559

CDC Urgent Threats:

Drug-resistant *N. gonorrhoeae*

Clostridium difficile

Oral

CRE

IV

Overview

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IDSA

Bad Bugs Need Drugs

10 x '20

Ten new ANTIBIOTICS by 2020

FDA J01 NMEs 2010-14

1. ceftaroline fosamil (Oct. 29, 2010)
2. fidaxomicin (May 27, 2011)
3. dalbavancin (May 23, 2014)
4. tedizolid (June 20, 2014)
5. oritavancin (Aug. 5, 2014)
6. ceftolozane/tazobactam (soon)

ceftaroline fosamil

- **IV 2x daily**
- **Labeled for CABP & ABSSSI from susceptible G+ and G-bacteria (MRSA studied only in ABSSSI trial)**

fidaxomicin

- **Oral 2x daily for 10 days**
- **Labeled for CDAD**

dalbavancin

- IV 1000mg + 500mg a week later
- Labeled for ABSSI from susceptible G+ bacteria

tedizolid

- **Oral or IV, 1x daily for 6 days**
- **Labeled for ABSSSI from susceptible G+ bacteria & MRSA**

oritavancin

- **IV, 1200mg once**
- **Labeled for ABSSSI from susceptible G+ bacteria & MRSA**

ceftolozane/tazobactam

- **IV, 3x daily**
- **Phase 3 G- studies for CUTI, CIAI, HABP/VABP**
- **Addition of tazobactam as a beta lactamase inhibitor**
- **Commercial goal: 45mm d/t US & 30mm in EU; peak sales > $1bn**

Comparison

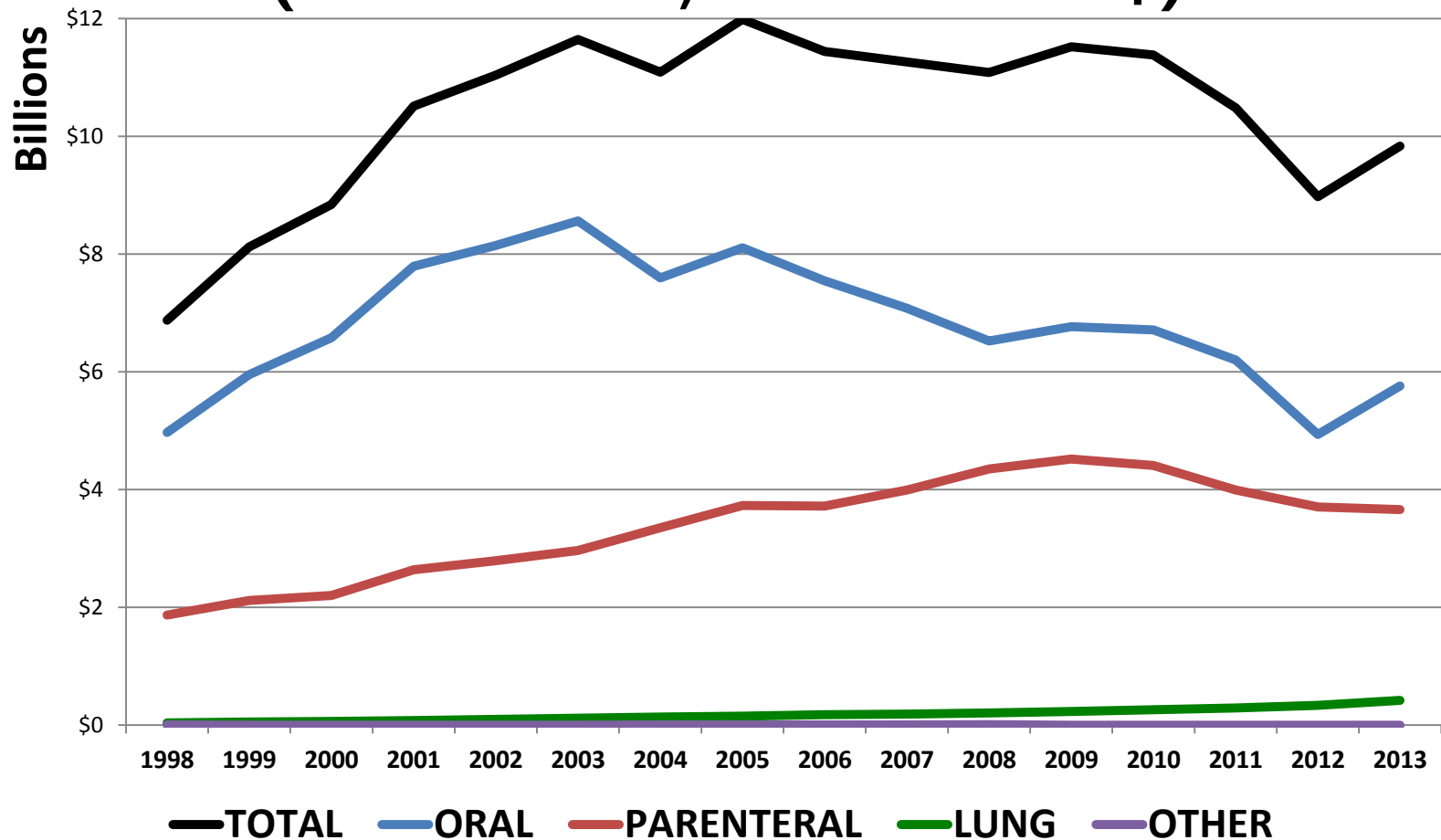|	Oral	IV
G+	fidaxomicin, tedizolid	ceftaroline fosamil, dalbavancin, tedizolid, oritavancin
G-		ceftaroline fosamil, ceftolozane/tazobactam

- **DR *N. gonorrhoeae***
- **CRE**
- ***Clostridium difficile***

Overview

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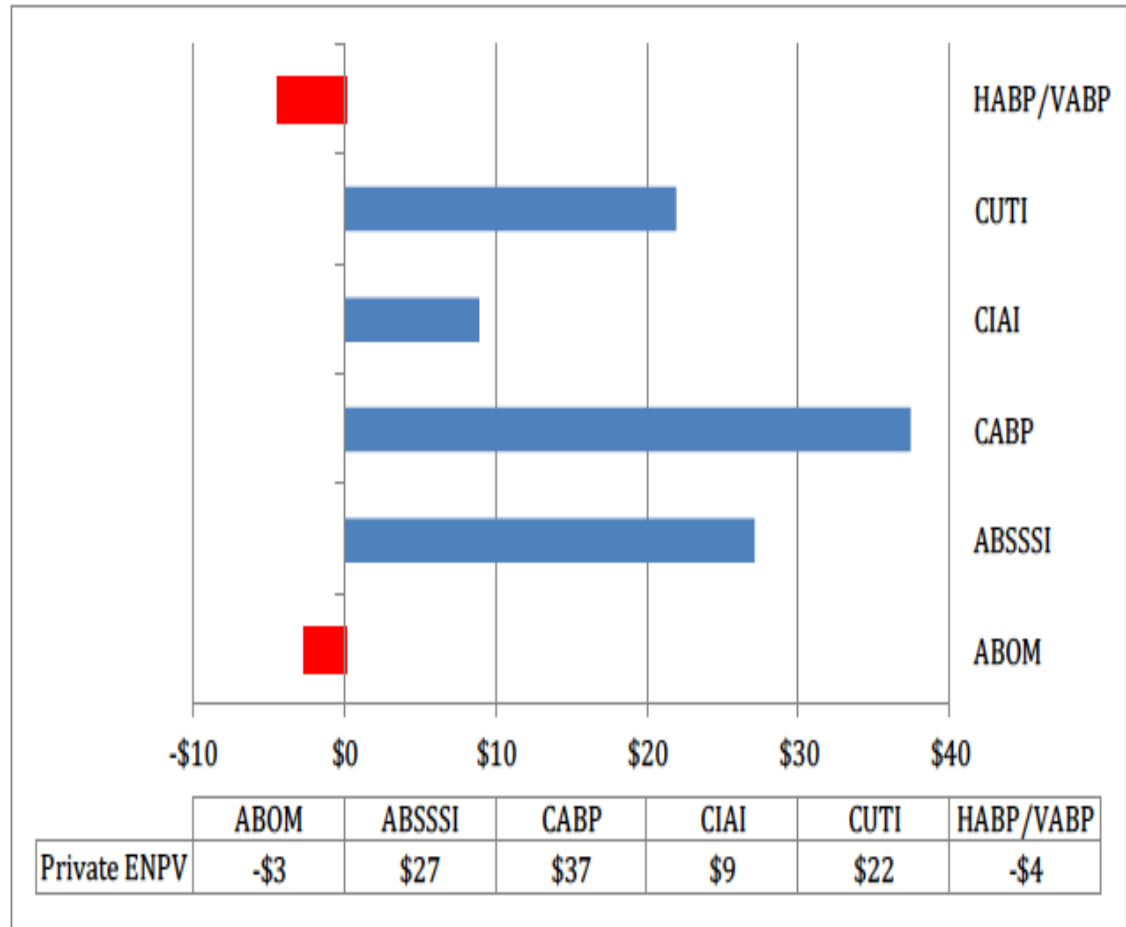
US J01 Sales

(1998-2013, constant US$)

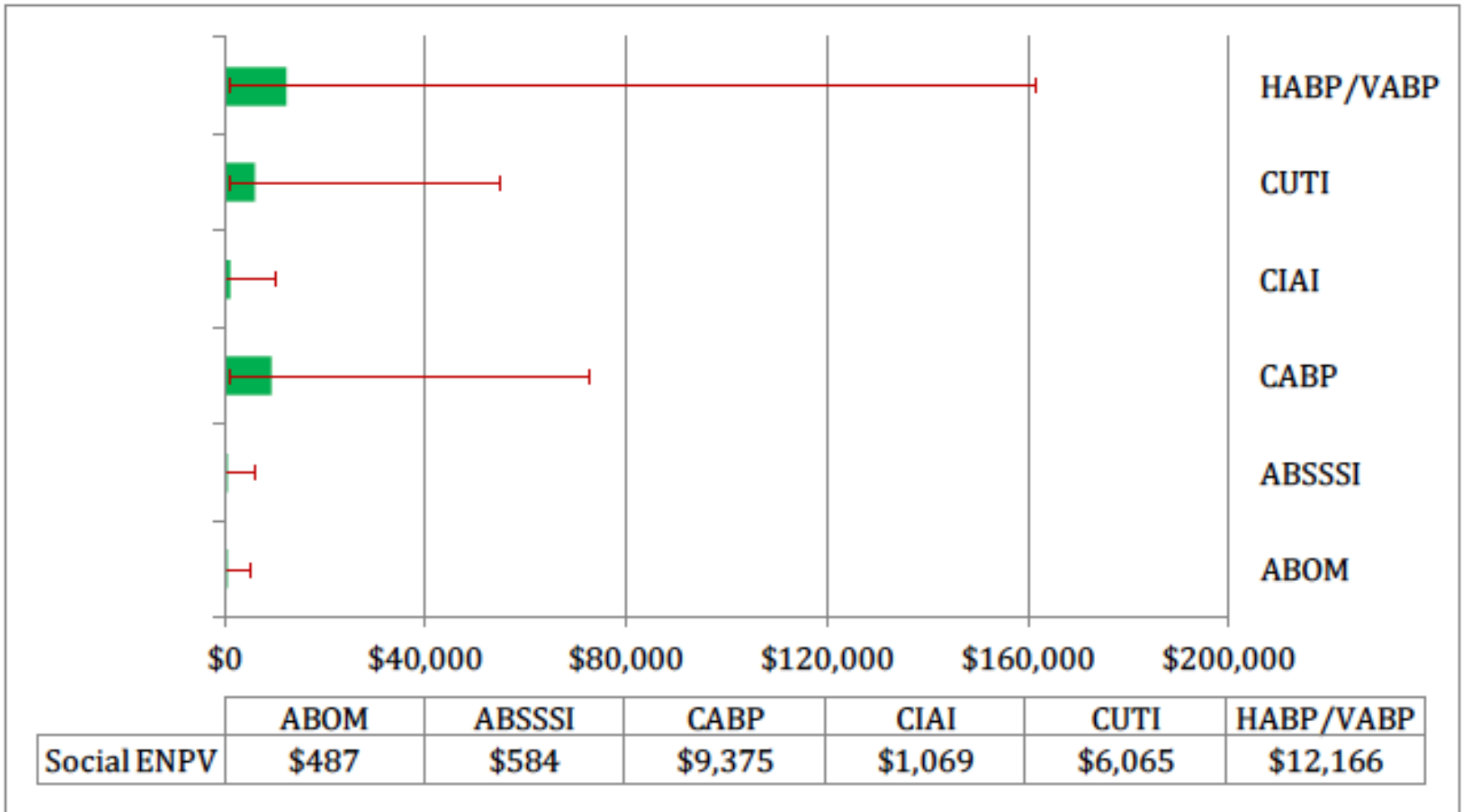Source: IMS US J01 usd_mnf (dollar sales at ex-mnf prices); St. Louis Fed GDP deflator, 2009=100

Private NPV

- Private NPV variable across indications
- CABP has the highest private NPV & HABP/VABP the lowest

Figure 3: Estimated Private ENPVs by Indication for a New Antibacterial Drug (in $ Million)

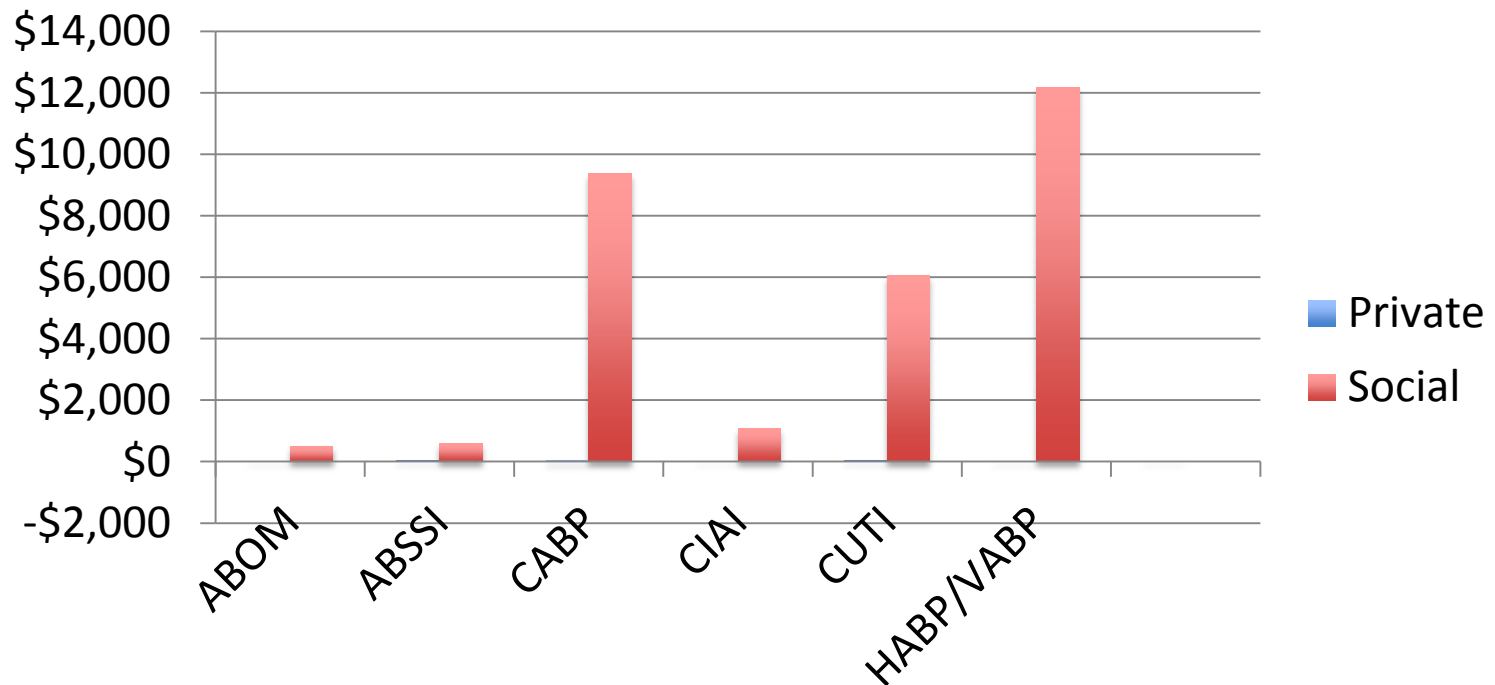|	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Private ENPV	-$3	$27	$37	$9	$22	-$4

ERG for DHHS 2014

Social NPV

Figure 6: Sensitivity of Estimated Social ENPVs by Indication for a New Antibacterial Drug (in $ Million) - Error Bars Represent 90% Confidence Bounds

	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Social ENPV	$487	$584	$9,375	$1,069	$6,065	$12,166

ERG for DHHS 2014

Annual US private and social ENPV by indication, in millions of US$

Adapted from ERG for DHHS 2014

Chatham House

Working Group on New Business Models for Antibiotics

Key delinkage elements

- Delink revenues from sales volume;
- Increase total incentives for antibiotics;
- Permit long-term coordination by stakeholders; and
- Preserve access without regard to ability to pay.

Kesselheim AS Outterson K. Health Affairs 2010; Yale J. Health Policy, Law & Ethics 2011; Chatham House 10.2.13

Functional elements

1) Structuring the reward
2) Geographic scope
3) Product scope
4) Financing
5) IP
6) Rationalizing antibiotic use

Source: Chatham House WG Report (pending, 2014)

Functional elements

1) Structuring the reward
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3) Product scope
4) **Financing**
5) IP
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Source: Chatham House WG Report (pending, 2014)

Financing

- $1.8bn = 0.5% 2013 US Rx

  0.006% 2013 US NHE

  $5.68 US per capita

- User fee on non-human uses (Hollis, NEJM 2013; Health Policy 2014)

Papers @
SSRN & Google Scholar

Blogging health policy @ TheIncidentalEconomist & @koutterson

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