Antimicrobial Resistance: A Global Challenge

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Overview

History
Responses
Challenges
Factors
Global Problem for Individual Patients
BACTERIAL RESISTANCE: A VIEW OF THE DECADES

• 1940s: Unbridled optimism
  - Penicillin: “wonder drug”

• 1950s: Disenchantment
  - Pen-resistant staphylococci
  - Emergence of gram-negative bacteria

• 1960s: Guarded optimism
  - Semisynthetic anti-staph penicillins
  - Cephalosporins
  - Aminoglycosides
• **1970s: New Disenchantments**
  - $\beta$-lactamase + pathogens (GC, *E. coli*, *S. typhi*)
  - Emergence of MRSA

• **1980s: Renewed optimism**
  - Extended spectrum cephalosporins
  - Carbapenems
  - Fluoroquinolones
  - Resurrection/purification of vancomycin

• **Early 1990s: Gloom**
  - Multiresistant enterococci: susceptible to nothing
  - Nothing promising on the horizon

(Adapted from T. Eichoff, M.D.)
September, 1994
Early 1990’s: VRE, VISA, MDR Pneumococci

Once again, the pharmaceutical (vaccine) industry came through (albeit with old compounds)

Quinu/Dalfo (1999)*

Linezolid (2000)  
(Prevnar 7: 2000)

Daptomycin (2003)  
(Prevnar 13: 2010)

... subsequently, for MRSA:

Ceftaroline/ceftobiprole  
Telavancin  
Dalbavancin  
Oritavancin  
Tedizolid

* FDA dates
MEDICAL DISPATCH
SUPERBUGS
The new generation of resistant infections is almost impossible to treat.

By Jerome Groopman

Resurgence of the Gram-negatives

Acinetobacter

2008
ESBLs

Porin/efflux mutants

CREs

KPC, IMI, SME, VIM, IMP, etc.

NDM

MCR-1 (& 2)
We knew for years ...

Finally, others agree
• United Nations:
  – On 21 September 2016, the UN General Assembly is convening a one-day high-level meeting at the UN Headquarters in New York on “Antimicrobial Resistance”

  – ... only the 4th time in the UN’s history that its General Assembly—a global deliberative body that primarily grapples with issues like war and economics — has held a meeting to tackle a health topic. (The other three were HIV, noncommunicable diseases and Ebola.)
Wellcome Trust report

The Wellcome Trust today (9/9/16) released a report to inform the United Nations General Assembly's High-level Meeting on AMR

- Based on an international summit of researchers, policymakers and multilateral institutions in London in April 2016

- Responsibly reducing agricultural use of antibiotics
- Improving surveillance systems for antibiotic use and resistance in people and animals
- Strengthening public health systems so antibiotics can be used optimally
One of the most potent threats to global economic prosperity is too little discussed. Resistance to antibiotics, ... , is already well established and well recognized by specialists as a problem -- but it doesn't yet frighten the public. It should.”


(this was before the 11/’15 report of colistin-R due to mcr-1)
The studies concluded that —

... without action to check antimicrobial resistance, superbugs would, by 2050, “cause the deaths of 10 million people a year — more than now die of cancer — and cost the global economy $60 trillion to $100 trillion ...”.

... 6 yr of USA GNP or ... (BBC News) 35 years w/o the UK contribution to the global economy
O’Neill report:

Reduce unnecessary use through better testing

Track spread of resistance

A global "innovation fund" of around $2 bn to support new ideas

A reappraisal of existing drugs

Train a new generation of scientists in the field
Mail Online
Aug. 29

Florida millionaire releases surveillance video of his ex-fiancée 'beating herself'

Indestructible strain of E.coli 'has reached the US', researchers warn

University of Cincinnati is accused of condoning 'rape culture' after students hang

Shocking moment female Lyft passenger threatens to humiliate 'f*****g idiot' driv

2 days before the usual ID/CDC “Alerts”

2 days before the usual ID/CDC “Alerts”

(mBio, Aug. 30)
"no publicity is bad publicity"

Men’s secret body hang-ups

... body hang-ups

... man boobs,
sweaty armpits

"f….g idiot" Lyft driver

... indestructible E. coli

University of Cincinnati is accused of condoning rape culture after students hang...
Bad, but not yet ‘indestructible’
\( mcr-1 \) with \( bla_{NDM} \) (carbapenemase)

- The stored \( E. coli \) strain was from a urine sample collected in August 2014 (earliest to date in the US)
- ... from man, aged 76 years, who had emigrated from India \( \sim 1 \) yr prior but not traveled since
- The isolate was R to colistin (\( mcr-1 \)) and all beta-lactams except aztreonam (\( bla_{NDM}, \) \( bla_{OXA-1} \)) and fluoroquinolones, but S to amikacin, gentamicin, nitrofurantoin, tigecycline, and trimethoprim-sulfamethoxazole.
- Seems not to have spread

Mediavilla JR et al., mBio 2016

Prior reports of \( mcr-1 \) with \( bla_{NDM} \)
Why Is AMR So Challenging (and so frightening)?

#1. We don’t have enough new antibiotics (or antibiotics in the pipeline) for patients in need

#2. We can’t stop most resistance from developing

#3. We don’t do a good job at preventing spread, once resistance has developed.

What would it take?

- Precautions like with Ebola?
  - Sanitation/sewers/potable water in lower resource countries. Ex. the discovery of KPC just off the shores of Rio as the world gathered ...
Why Is AMR So challenging?

#4. We don’t do a good job at reducing use, which is a huge factor in increasing numbers of R bacteria

“MEETING THE ENEMY... AND IT IS US”

_E. faecium_: found in only 25% of normal adults and at low concentrations ($10^5$ CFU/gm; variable)

In hematologic malignancy pts., following the use of broad spectrum antibiotics, _E. faecium_ can become the predominant organism (e.g., 30% vs. 0.01% normally), often $>10^9$ CFU VR _E. faecium/gm of stool_ (Suppola. CID 23:694, 1996),

- Increased the risk of VRE bacteremia 9-fold

  Taur/Pamer. CID 55:907, 2012

- More in the gut increases the likelihood of spread.
Effect of TMP or TMP/SMX for Prevention of Travelers’ Diarrhea on TMP-R of Fecal GNB

“Collateral damage”/”innocent bystander effect”

Geometric Mean CFU of Total (---) GNB and TMP-Resistant (- - -) GNB

> 5 log_{10} increase in TMP-R E. coli

Why Is AMR So challenging?

... but, even if we could decrease use, we don’t know how much use needs to be decreased (... since even appropriate use selects for AMR)

How to balance use & need (crops in low resource countries, sick patients)

#5. We don’t diagnose the cause or susceptibility quickly enough (increasing # of courses of Abx started and increasing their duration)

Best way to reduce Abx use is to reduce need e.g., pneumococcal vaccine, clean water, rapid diagnostics
Urgent Resistance Threats
Carbapenem-resistant Enterobacteriaceae (CRE)
Drug-resistant *Neisseria gonorrhoeae*

**Serious Threats**
Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant *Candida* (a fungus)
Enterobacteriaceae (ESBLs)
Vancomycin-resistant *Enterococcus* (VRE)
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant Non-typhoidal *Salmonella*
Drug-resistant *Salmonella Typhi*
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Drug-resistant *Streptococcus pneumoniae*
Drug-resistant tuberculosis
IMPACT OF RESISTANT BACTERIA IN DIFFERENT SETTINGS

Highly Industrialized Countries

- Hospitals
  - Staphylococci (methicillin/multi-resistant)
  - Enterococci (vancomycin/multi-resistant)
  - GN bacilli (resistant to new beta lactams)

- Pneumococci (penicillin/multi-resistant)

Less Industrialized Countries

- Community
  - Enteric pathogens (multi-resistant)
    - H. influenzae (chloramphenicol/ampicillin resistant)
  - STDs (penicillin/tetracycline resistant GC and H. ducreyi)

Tb (multi-resistant)

1990s slide

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ESCMID Online Lecture Library
IMPACT OF RESISTANT BACTERIA IN DIFFERENT SETTINGS

Highly Industrialized Countries

Hospitals
- Staphylococci (methicillin/multi-resistant)
- Enterococci (vancomycin/multi-resistant)
- GN bacilli (resistant to COLISTIN & ALL beta lactams)

Community
- Tb (multi-resistant)
- Enteric pathogens (multi-resistant)
- STDs (penicillin/tetracycline resistant GC and H. ducreyi)
- Pneumococci (Pen/MDR)
- H. influenzae (chl/amp R)

Less Industrialized/Recently Advanced Economies

Hospitals
- Staphylococci (methicillin/multi-resistant)
- Enterococci (vancomycin/multi-resistant)
- GN bacilli (resistant to COLISTIN & ALL beta lactams)

Community
- Tb (multi-resistant)
- Enteric pathogens (multi-resistant)
- STDs (penicillin/tetracycline resistant GC and H. ducreyi)
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G 2.9a
COMMON FEATURES OF SETTINGS WITH HIGH LEVELS OF ANTIMICROBIAL RESISTANCE

- Heavy Use *
- Ease of Spread

** Factors over which we have some control **

* The focus of the WHO, the UN, Wellcome Trust reports
PLIGHT OF LESS DEVELOPED COUNTRIES

These countries often have the double burden of:

- A high frequency of bacterial diseases in the community and poor diagnostics (thus, a high need for and use of (empiric/OTC) antibiotics)

- A high frequency of spread of pathogens as well as resistant “commensals”, thus –

  - a high frequency of antibiotic resistance -
Pathogens and Rflora often go hand-in-hand
Consequences and Gradations in Severity of Antimicrobial Resistance

- Inconvenient
- Toxic
- Costly
- Fatal
Consequences and Gradations in Severity of Antimicrobial Resistance

• **Inconvenient:**
  – Recommendations for gonorrhea for combination therapy incl. an IM shot
  – Having to have an IV or even hospitalization for a UTI (vs. oral TMP/SMX or a FQ)

• **Toxic:**
  – Using/adding an aminoglycoside or colistin;
  – Use of multiple agents with each drugs AEs/drug interactions
Consequences ... Severity of AMR

• Costly:
  – A shot for GC. IV/IM for a UTI
  – TB: huge stack of $$$ for MDR tb vs. a few coins
  – Infections with resistant organisms cause more and longer hospitalizations and Rx
    • incorrect initial Rx eg, early days of CA-MRSA
    • alternatives may be less effective
  – To avoid incorrect Rx, **empiric use** of newer (more $$), more toxic, and/or Abx combo
    – **Cont’d use** of initial empiric expensive agents until (or even when) Dx is made (“pt. doing well”)

• Fatal
A FEW EXAMPLES

We tend to think of AMR in terms of % and numbers and new genes, but if not for the individual infected patient with a need, it wouldn’t really matter.

*mcr-1* has been around a long time but we weren’t checking and wouldn’t have cared 10+ years ago because there wasn’t a need to use in patients.
1948 Case: Enterococcal Endocarditis

34 yr old American woman hospitalized in March, 1948 in Germany for
- congestive heart failure (valve damage)
- embolus from valve to the R arm (no pulse)
- blood grew “‘streptococci’ with higher MICs than with staph or other strep”.

Given penicillin X 3 mo. but blood still positive

In July: cerebral embolus (stroke) from vegetation

Given streptomycin monotherapy (resulted in a rash).

Given tetracycline (12 gm/d!!!) Nausea, vomiting
Fever, worsening CHF, hepatosplenomegaly, AFib
Multiple heart murmurs, edema to sacrum.
Blood continued + for “Streptococcus faecalis”.

Empirically given penicillin (6 MU/d) + streptomycin*
but stopped after 1 week for severe rash, … BUT

**** BC ON Pen + Sm WERE FINALLY NEGATIVE ****

One week later, off therapy, BC again +, and she expired 10 mo. after initial diagnosis.
Ex. of … fatal.

Keep this scenario in mind

Advice Call – 2-3 years ago

Liver transplant, complications, multiple abdominal wash-outs, renal failure, VRE peritonitis, bacteremia, probable endocarditis.

Linezolid-R at onset. Amp R. HLR to Gent.

3 wks of Dapto and 1 wk of Synercid. More + cultures (blood, peritoneal, pleural fluid) but now organism was highly Dapto-R (still Lnz-R).

“Failing Dapto + Amp + Tige”

Awaiting liver re-transplant plus kidney but “not until infection is cleared”
Consequences and Gradations in Severity of Antimicrobial Resistance

- Inconvenient
- Toxic
- Costly
- Fatal/Disabling

A THREAT TO MODERN MEDICINE
WHY IS RESISTANCE GLOBAL?

1. Biology of Development of Resistance
   a. Spontaneous mutants occur everywhere
      e.g., Tb, Cipro-R *E. coli*
   b. Acquired resistance genes pre-exist somewhere, maybe everywhere, before being seen by “us”, and probably did not cross into “human bacteria” just once. E.g.,
      - The *van* operons in enterococci (soil Bacillus species).
WHY IS RESISTANCE GLOBAL?

( b. Acquired resistance genes …)

Consider *mcr-1*: first report Nov., 2015. Since then:

- **Found in collections dating back to 1980’s** (China), 2005 (EU), Dutch travelers’ samples (2011-12), USA (2014).

- **Identified on 5 of 7 continents** (even sea gulls in Ushuaia, Arg.)

- **Identified in many species** (*E. coli, Klebsiella, Enterobacter, Shigella, Salmonella*). Transfers to and stable in Pseudomonas

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      “human bacteria” just once. E.g.,
      • The *van operons* in enterococci (soil Bacillus
        species).

   c. Birds of a feather flock
      together/resistance begets resistance
Once resistance develops ...
... “bacteria don't need passports”

2. Spread: One World/One Medicine/One Health

a. Community:

1. Returning travelers with TMP$^R$, ESBLs, NDM, Mcr-1 fecal E. coli and enteric pathogens
   - More often after diarrhea or Abx use

1. Food/livestock: VRE, Mcr-1 (not just salmonella, cryptosporidia, cyclospora …)

a. Hospitals: Cipro$^R$ Salmonella; NDM, Mcr-1
. . . bacteria don't need passports

- Traced to a patient hospitalized in Manila prior to transfer to Oregon in 1994.
- Isolate identical to a Cipro-R Salmonella ser. Schwarzengrund detected in 1995 in NY from a patient also hospitalized in the same Manila hospital in 1994 as the Oregon case.
Settings Influencing Resistance

One World/One Health

Day Care

lower resource/newly advanced economies (spread within)

Tertiary Hospitals

Community Hospitals

Community (Outpatients)

Nursing Homes

Enterics (pathogens, fecal TMP, ESBL, NDM)

GC, Tb

CipR Salmonella, NDM

Animal feedlots, fecally contaminated food (salmonella, VRE, mcr-1)

< 2 yr old with 0157:H7 E. coli with mcr-1>

(TMP-R E. coli Pen-R Pneumo)
Challenge #1 of AMR: Not enough new Abx/Abx in the pipeline ... the challenge for the individual patient and the “unmet clinical need”

WHY NO NEW DRUGS?

There are 3 big problems

– Discovery is hard
– Development is hard
– Economics are poor

From Rex JH - 2014-09-06 ICAAC Keynote - New tools & pathways for antibacterials
(... WHY NO NEW DRUGS?)

– **Discovery is hard**
  - Low-hanging fruit has been picked
  - Multiple differences with Abx vs. other drugs and bacteria are different from euk cells

– **Development is hard and expensive**
  - Regulatory issues, breakpoint issues
  - Relatively few patients with MDR infections (more rapid Dx might help identify them), they are very sick, often no active comparator, already on multiple Abx. Need new paradigms for trials and new reg’s
(... WHY NO NEW DRUGS?)

- Economics are poor
  - Short term use
  - ID docs/stewardship work to hold in reserve
  - Resistance may shorten the lifespan
  - Public thinks antimicrobials should be cheap (e.g., outcry over HepC drugs) although value for days of work and life restored is huge
  - Companies answer to stockholders
There’s no time to lose

*It takes 10-20 years to make a new antibiotic*


From Rex JH - 2014-09-06 ICAAC Keynote - New tools & pathways for antibacterials
Some examples of what we all* might face:

1. Healthy people get “MerSA” infection (of course, we have Abx but it’s still an example that many recognize)

1. We might develop a bad disease (diabetes, cancer, renal or other organ failure, auto-inflammatory disease, morbid obesity) or have a very premature infant (then, more likely colonized with AMR bugs; even a minor UTI may become a major issue)

1. We might be involved in an auto accident or suffer a gunshot wound or severe burn or get pneumonia … ICU or need a new hip or knee

* Including politicians, CEOs, your boss deciding on a new project, stockholders/investors
Some examples of what we all might face:

4. Sexually ‘adventurous’ here or abroad, might take anti-retrovirals prophylactically, but still get MDR GC (requiring a shot + pill) or, among MSM, MDR Shigella (T/S\(^R\), Cipro\(^R\), now with increasing Azithro MICs)

5. We might (travel ... and) pick up an AMR organism in our GI tract and then later develop a *UTI* with that organism or gallbladder or IA infection ... Cipro\(^R\) T/S\(^R\), ESBL, NDM, MCR-1 ... that requires IV or toxic Rx

6. Travellers’ diarrhea (shigella, campylobacter, salmonella) or typhoid unresponsive to the traditional TMP/SMX or Cipro.
Blood cultures yielded *E. faecium* with the following susceptibilities (MIC in μg/mL):

- Ampicillin  $\geq 32$ (R)  
- Daptomycin  16 (R)  
- Vancomycin  $\geq 32$ (R) 
- Linezolid  48 (R)  
- Genta synergy  (R) 
- Quin-Dalfo  0.38 (S) 
- Strepto synergy  S  
- Tetracycline  $\geq 16$ (R) 
- Tigecycline: 0.5 (S)

Not responding to Dapto + Ampi + Tige
Did not tolerate Q/D (“I’d rather die . . .”)
How about oritavancin + streptomycin?

Grossly off label but I couldn’t think of anything else
What Did I Know about Oritavancin?

- **Oritavancin** (also known as LY333328 in the late 1990’s, Orbactiv) is a novel semisynthetic lipoglycopeptide, ... multiple actions, forms dimers with much higher affinity than Vanco.
  - approved for adult patients with ABSTTI (due to susceptible isolates of ... including Vanco-S Efs

- **Older literature**
  - MICs generally unchanged by VanA or VanB
  - Bactericidal against enterococci ... but may be less so when Vanco-R genes are present
Effects of Vancomycin Resistance Genes on Orita *in vivo* (that’s all there is)

In rabbit endocarditis with *E. faecalis*: acquisition of VanA and B resistance did not reduce the effect of LY (Orita) (Saleh-Mghir/Fantin, AAC 43:115, 1999)

But, the addition of gentamicin to a less effective dose of Orita enhanced the *in vivo* effect against VSE and VRE and prevented emergence of resistant mutants (MICs 8-20 μg/ml, seen only with VanA VRE)

(Lefort/Fantin, AAC 44:3017-21, 2000)
How are we going to dose it?

Oritavancin approval is for a single 1200 mg dose for skin infections. Not metabolized, persists a long long time, not renally excreted ...

What dose would we use for endocarditis? Once/week? Twice? 3x/week? Is that safe?

One report of prolonged use twice weekly for VRE prosthetic valve endocarditis for over 10 weeks. Not really successful (had valve replaced) but was used once/week at first, probably too little; might have selected for less susceptible mutants. (Johnson JA. OFID, 2015)
State of the Art with MDR Bacteria:

Trial and error, relying on *in vitro* and, if we’re lucky, some animal model results to support our choice

Unknown, unapproved and even unexplored dosing

Unknown, unapproved and unexplored combinations

This is like the late 1940s and that early enterococcal endocarditis patient!
Antimicrobial Resistance: A Personal Challenge for Patients Around the World