Antibiotic Resistant Threat Report
Methods Review

Healthcare associated infection pathogens

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion
Outline

- 2013 Antibiotic Threats Report
  - Overview of previous methodology
- 2019 Antibiotic Resistance Threats Report
  - Updated methods for burden estimates using electronic health data
- Attributable Mortality and Costs
  - Updated methods for estimates
- Conclusions
Data Source Considerations for 2019 AR Threat Report

- No single surveillance system exists for antibiotic resistant healthcare-associated infections, making national estimates for total burden of infections difficult
- For 2013 Threat Report, DHQP relied on two major data sources
  - CDC Healthcare Associated Infection Prevalence Survey (2011)
    - Carbapenem-Resistant Enterobacteriaceae
    - Multidrug-Resistant *Acinetobacter*
    - Fluconazole-Resistant *Candida*
    - Extended Spectrum B-lactamase producing Enterobacteriaceae (ESBLs)
    - Vancomycin-Resistant *Enterococcus* (VRE)
    - Multidrug-Resistant *Pseudomonas aeruginosa*
  - Emerging Infections Program Active Bacterial Core Surveillance (2011)
    - *Clostridium difficile* infections
    - Invasive MRSA infections
Data Source Considerations for 2019 AR Threat Report (continued)

- CDC HAI Prevalence Survey
  - Advantages
    - Probably best overall estimate for hospital-onset healthcare-associated infections (not necessarily antibiotic resistant infections)
  - Disadvantages
    - Does not capture all community-onset infections (only those meeting NHSN definitions, no community-associated infections)
    - Burdensome, hard to replicate over time
    - Not primarily designed to produce pathogen-specific AR burden estimates
      - Resistance data from NHSN were used
      - cell sizes are small (estimates imprecise)

- Emerging Infections Program Active Bacterial Core Surveillance
  - Advantages
    - Population based, complete capture of both community-onset and hospital-onset healthcare-associated infections
  - Disadvantages
    - Limited healthcare-associated infections under surveillance (*Clostridium difficile*, *Invasive MRSA*)
    - Fewer EIP sites reporting invasive MRSA compared to 2013, captures only MRSA infections involving sterile sites
Data Source Considerations for 2019 AR Threat Report (continued)

- **Electronic Health Record data from large sample of US hospitals**
  - **Advantages**
    - Can estimate burden from both non-sterile and sterile body sites
    - Large sample sizes and more precise estimates compared to other surveillance systems
    - Easy to produce serial estimates and trends
    - Can make estimates for community-onset events (among hospitalized patients)
  - **Disadvantages**
    - Not a statistical sample of hospitals
      - But accompanying administrative data can be used to apply weighted extrapolations to derive national estimates
    - Not all positive cultures represent true infection, difficult to apply detailed epidemiologic definitions of infection to these data
      - One could argue, however, that all positive cultures represent contribution to epidemiologic “burden”
2013 Threat Report: Mortality Estimates

- For most healthcare associated pathogens the number of associated deaths was calculated using an overall estimate of attributable mortality of 6.5%
  - Estimated by Roberts et al (CID, 2009)
methicillin-resistant *Staphylococcus aureus* (MRSA)
carbapenem-resistant *Enterobacteriaceae* (CRE)
extended-spectrum cephalosporin resistance in *Enterobacteriaceae* suggestive of extended-spectrum β-lactamase (ESBL)-production,
carbapenem-resistant *Acinetobacter* species (CRAsp),
vancocycin-resistant *Enterococcus* (VRE),
multidrug-resistant (MDR) *Pseudomonas aeruginosa*. 
AR Threats Burden Estimation

- Estimate annual number of incident cases from 2012 – 2017 among inpatients in US Acute Care Hospitals using three electronic health databases:
  - Premier Healthcare Database¹
  - Cerner Health Facts²
  - BD Insights Research Database³

- Data from dynamic cohort of hospitals
  - 7.4 million discharges annually
  - Represents ~20% of US discharges annually

- Pathogens estimated using this methodology: MRSA, CRE, ESBLs, VRE, carbapenem-resistant Acinetobacter, MDR Pseudomonas, Drug-resistant Candida*


*Drug-resistant Candida refers to Candida species that are resistant to at least one antifungal drug in the azole or echinocandin classes.
General Analytic Plan

- Develop definitions for incident cases that can be applied to the datasets
- Generate hospital specific annual burden
- Apply weighted extrapolations to derive national estimates of annual burden of cases
- Apply pathogen-specific estimates of attributable mortality to derive annual burden of deaths
- Apply pathogen-specific estimates of attributable costs to derive annual burden of costs
Case Definitions

- Positive incident clinical cultures for specimen of interest with accompanying susceptibility testing results indicating resistance
  - Isolates from patients having no culture yielding the same resistance phenotype of interest in the previous 14 days were counted as an incident case
  - CRE, ESBL definitions accounted for cascade reporting
  - Excluded likely surveillance cultures
Case Definitions

▪ Cultures were categorized as sterile or non-sterile sites
  – Counted only the sterile culture for resistant isolates from both a sterile and non-sterile site collected within 14 days

▪ Epidemiologic classification
  – Community Onset (CO): culture immediately preceding admission or within the first three days of hospitalization
  – Hospital Onset (HO): culture obtained on day four of hospitalization or later
National Burden Estimates

- Iterative Proportional Fitting (raking) methodology used to match the distribution of discharges and hospitals to the American Hospital Association (AHA) annual survey for each year
  - Bed Size
  - US Census Division
  - Urban/Rural designation
  - Teaching Status

- Weighted means survey procedure to produce national estimates
Pathogen Specific Estimates Produced Annually 2012 - 2017

- Number of cases with confidence intervals
- Proportion of isolates displaying resistant phenotype (%R)
- Attributable mortality
- Attributable costs by pathogen

Similar to the previous report, these estimates were combined with estimates of non-healthcare associated pathogens also included in the report to calculate an aggregate burden for total infections, deaths, costs
Rates and Trends

- Trends in rates (national estimates per 1,000 discharges) from 2012 – 2017 were assessed for each pathogen
  - Modeled using multivariable logistic model incorporating a survey design with the corresponding weights and clustered by hospital
  - Adjusted for hospital characteristics, month of discharge, proportion of patients in specific age categories, and data source
  - Annual trends estimated using a log-linear (continuous) variable and a linear combination of five independent (categorical) variables
Validating the Estimates

- Estimated burden for each electronic health data system individually and found very similar results
- Sub-analysis of consistent reporters similar to full analysis
- National estimates appear consistent with other sources
  - EIP burden and trend estimates for MRSA, Candidemia, Carbapenem-resistant Acinetobacter, all very similar
  - Prevalence and trend estimates consistent with data published by external groups
- Percent-resistant (%r) is consistent with estimates from National Healthcare Safety Network (within 0-5%, unpublished data)
Attributable Mortality Background

- Few studies assess the mortality attributable to an MDRO
  - Limited in scope (1-2 hospitals), specific pathogens, or focused on hospital onset infections
  - More reports of associated mortality (i.e., the number of deaths immediately following a hospitalization with HAI or MDRO).
    - Because many HAIs/MDROs occur in older, sicker, populations this may overestimate the attributable mortality
  - Rarely account for time-dependent bias

- Relative risks are more commonly reported
  - Without further assumptions and details, these can not be used to calculate burden of mortality in a population
Previous Work at the Veterans Affairs Hospitals

Attributable Mortality of Healthcare-Associated Infections Due to Multidrug-Resistant Gram-Negative Bacteria and Methicillin-Resistant *Staphylococcus Aureus*

Richard E. Nelson, PhD,1,2 Rachel B. Slayton, PhD;7 Vanessa W. Stevens, PhD,1,2 Makoto M. Jones, MD,1,2 Karim Khader, PhD,1,2 Michael A. Rubin, MD, PhD;1,2 John A. Jernigan, MD;1 Matthew H. Samore, MD1,2

Attributable Cost and Length of Stay Associated with Nosocomial Gram-Negative Bacterial Cultures

Richard E. Nelson,8,9 Vanessa W. Stevens,8,9 Makoto Jones,8,9 Karim Khader,8,9 Martin L. Schweizer,1,4 EB N. Porencewich,4,5 Michael A. Rubin,6 Matthew H. Samore,6

Reducing Time-dependent Bias in Estimates of the Attributable Cost of Healthcare-associated Methicillin-resistant *Staphylococcus Aureus* Infections

A Comparison of Three Estimation Strategies

Richard E. Nelson, PhD,* † Matthew H. Samore, MD,* † Makoto Jones, MD,* † Tom Greene, PhD,† Vanessa W. Stevens, PhD,* † Chuan-Fen Liu, PhD,‡ Nicholas Graves, PhD,¶ Martin F. Evans, MD,§§ and Michael A. Rubin, MD, PhD,* †
Estimating deaths for the 2019 AR Threats Report

1. Estimated attributable mortality using risk differences in VA data for each pathogen
   – Cohort study using EHR data from entire VA health system
   – Exposure density sampling on each day of an inpatient stay: Matched each case with up to 10 controls using culture date and length of stay for cases
   – Multivariable Poisson regression models with clustered standard errors by patient
     • Adjusted for patient/hospitalization characteristics
     • Effect measure: adjusted absolute difference in probability of death
       – Generated 30 and 90 day mortality estimates (includes post-discharge deaths)
   – Separate estimates for CO and HO infections
Attributable Mortality: Comparisons using Premier Healthcare Data

- Because the VA patient population over-represents adult males, we confirmed these findings using the Premier Healthcare Data
  - Repeated analysis using cases identified in the Premier Health Dataset
    - Compared **In-Hospital** Mortality at 30 and 90 days
  - VA and Premier results very highly correlated (r=0.93)
    - Strongly suggests no unmeasured confounding factors that differ between VA and non-VA patient populations
    - mortality estimates derived from the VA cohort are not meaningfully different than those derived from the non-VA cohort
  - VA data preferable because includes post-discharge mortality
Data sources for Attributable Costs

- VA EHR data
- HERC Average Cost Information: *allows for application of VA cost information to a more general population*
  - Costs are assigned to each encounter based on the characteristics of that encounter (all patients with the same characteristics are assigned the same cost)
  - Average cost is computed by performing a cost regression using Medicare data for Veterans adjusting for LOS, DRG weight, whether patient died in hospital, age, gender, ICU stay, and number of diagnoses
  - Estimated coefficients from this model are applied to VA data to generate a predicted cost for each encounter
- estimates consistent with published literature (where available)
Summary
In 2017, MRSA, VRE, CRE, ESBL-producing Enterobacteriaceae, Carbapenem-resistant *Acinetobacter*, and MDR *P. aeruginosa* caused significant public health burden

- MRSA and ESBL infections account for the majority of the infections

Between 2012-2017:
- incidence decreased significantly for MRSA, VRE, CRAsp, and MDR *Pseudomonas*
- CRE incidence was unchanged.
- ESBL incidence increased significantly, driven entirely by increase in community-onset cases
Limitations

- Hospitals were de-identified so could contribute in multiple data systems.
  - Removed potential duplicate hospitals and conducted sensitivity analyses (no impact on conclusions)
- Clinical cultures are not necessarily infections
  - But do represent potential source for spread of resistant organisms
- Not able to account for previous healthcare exposures when determining epidemiologic class
  - Only categorized by timing of culture
- Estimate does not include burden of pathogens diagnosed outside of the hospital (outpatient and nursing home settings)
  - Most mortality should be captured using the hospitalized population
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- Alex Kallen
- Anthony Fiore
- Michael Craig
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Extra Slides
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Organisms Included in Definition</th>
<th>Antibiotics Included in Definition</th>
<th>Definition of Resistance Phenotype</th>
<th>Denominator for Calculating Proportion of Isolates with Resistant Phenotype</th>
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</thead>
<tbody>
<tr>
<td>Methicillin-resistant</td>
<td>Staphylococcus aureus (MRSA)</td>
<td>methicillin, oxacillin, cefoxitin</td>
<td>Any isolate that tested (R) to at least 1 of these: methicillin, oxacillin, cefoxitin</td>
<td>Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to: methicillin, oxacillin, cefoxitin</td>
</tr>
<tr>
<td>Vancomycin-resistant</td>
<td>Enterococcus spp.</td>
<td>vancomycin</td>
<td>Any isolate that tested (R) to vancomycin</td>
<td>Any isolate that tested (S, I, R) to vancomycin</td>
</tr>
<tr>
<td>Carbenem-resistant</td>
<td>E. coli, Klebsiella spp., Enterobacter spp. (CRE)</td>
<td>imipenem, meropenem, doripenem, ertapenem, ampicillin, amoxicillin/sublactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan</td>
<td>Any isolate with at least 1 resistant result (R) to imipenem, meropenem, doripenem, ertapenem</td>
<td>*Any isolate with at least 1 non-susceptible or susceptible result (S, I, R) to imipenem, meropenem, doripenem, ertapenem OR same isolate with at least 2 reported susceptible (S) results to: ampicillin, ampicillin/sublactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan</td>
</tr>
<tr>
<td>Extended-spectrum β-</td>
<td>E. coli, Klebsiella spp. (not Klebsiella aerogenes)</td>
<td>cefotaxime, ceftriaxone, ceftazidime, ceceplime, ampicillin, piperacillin, aztreonam, cefazolin</td>
<td>Any isolate with at least 1 non-susceptible, result (I or R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime</td>
<td>**Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime OR same isolate with at least 2 reported susceptible (S) results to: ampicillin, piperacillin, aztreonam, or cefazolin</td>
</tr>
<tr>
<td>Carbenem-resistant</td>
<td>Acinetobacter spp.</td>
<td>imipenem, meropenem, doripenem</td>
<td>Any isolate with at least 1 non-susceptible result (I or R) to: imipenem, meropenem, doripenem</td>
<td>Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to at least 1 drug in the medication categories</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR)</td>
<td>Pseudomonas aeruginosa</td>
<td>1. Extended-spectrum cephalosporins (cefepime, ceftazidime), 2. Fluoroquinolones (ciprofloxacin, levofloxacin), 3. Aminoglycosides (amikacin, gentamicin, tobramycin), 4. Carbapenems (imipenem, meropenem, doripenem), 5. Piperacillin Group (piperacillin, piperacillin/tazobactam)</td>
<td>Any isolate that tested either (I) or (R) to at least 1 drug in at least 3 of the medication categories</td>
<td>Any with at least 1 susceptible or non-susceptible result (S, I, R) to at least 1 drug in the medication categories</td>
</tr>
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