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)

2019 Antibiotic Resistance Threats Report using Electronic Health Data

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),
vancomycin-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 Database[1]
  - Cerner Health Facts[2]
  - BD Insights Research Database[3]
- **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***

1. Premier Applied Sciences. Premier healthcare database white paper: data that informs and performs. Charlotte, NC: Premier Applies Sciences; 2018. https://learn.premierinc.com/white-papers/premier-healthcare-database-whitepaper
2. DeShazo JP, Hoffman MA. A comparison of a multistate inpatient EHR database to the HCUP Nationwide Inpatient Sample. BMC Health Serv Res 2015;15:384. 3.
3. Becton, Dickinson and Company, Franklin Lakes, NJ

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 and Costs Methods

In collaboration with Rich Nelson, PhD

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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

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY JULY 2017, VOL. 38, NO. 7

ORIGINAL ARTICLE

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

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EPIDEMIOLOGY AND SURVEILLANCE

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

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Reducing Time-dependent Bias in Estimates of the Attributable Cost of Health Care–associated Methicillin-resistant *Staphylococcus aureus* Infections

A Comparison of Three Estimation Strategies

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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

2019 AR Threat Report

- 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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Extra Slides

Case Definitions

Pathogen	Organisms Included in Definition	Antibiotics Included in Definition	Definition of Resistance Phenotype	Denominator for Calculating Proportion of Isolates with Resistant Phenotype
Methicillin-resistant *Staphylococcus aureus* (MRSA)	*Staphylococcus aureus*	methicillin, oxacillin, cefoxitin	Any isolate that tested (R) to at least 1 of these: methicillin, oxacillin, cefoxitin	Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to: methicillin, oxacillin, cefoxitin
Vancomycin-resistant *Enterococcus* (VRE)	*Enterococcus* spp.	vancomycin	Any isolate that tested (R) to vancomycin	Any isolate that tested (S, I, R) to vancomycin
Carbapenem-resistant *Enterobacteriaceae* (CRE)	*E. coli, Klebsiella* spp., *Enterobacter* spp.	imipenem, meropenem, doripenem, ertapenem, ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan	Any isolate with at least 1 resistant result (R) to imipenem, meropenem, doripenem, ertapnem	*Any isolate with at least 1 non-susceptible or susceptible result (S, I, R) to imipenem, meropenem, doripenem, ertapnem **OR** same isolate with at least 2 reported susceptible (S) results to: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan
Extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*	*E. coli, Klebsiella* spp. *(not Klebsiella aerogenes)*	cefotaxime, ceftriaxone, ceftazidime, cefepime, ampicillin, piperacillin, aztreonam, cefazolin	Any isolate with at least 1 non-susceptible, result (I or R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime	**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
Carbapenem-resistant *Acinetobacter* (CRAsp)	*Acinetobacter* spp.	imipenem, meropenem, doripenem	Any isolate with at least 1 non-susceptible result (I or R) to: imipenem, meropenem, doripenem	Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to at least 1 drug in the medication categories
Multidrug-resistant (MDR) *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	1. Extended-spectrum cephalosporins (cefepime, ceftazidime), 2. Fluoroquinolones (ciprofloaxacin, levofloxacin), 3. Aminoglycosides (amikacin, gentamicin, tobramycin), 4. Carbapenems (imipenem, meropenem, doripenem), 5. Piperacillin Group (piperacillin, piperacillin/tazobactam)	Any isolate that tested either (I) or (R) to at least 1 drug in at least 3 of the medication categories	Any with at least 1 susceptible or non-susceptible result (S, I, R) to at least 1 drug in the medication categories