



# ***Broad Spectrum Antimicrobials (BSA)***

**Joe Larsen, Ph.D.**  
**Branch Chief**

December 10, 2012



# BSA Program



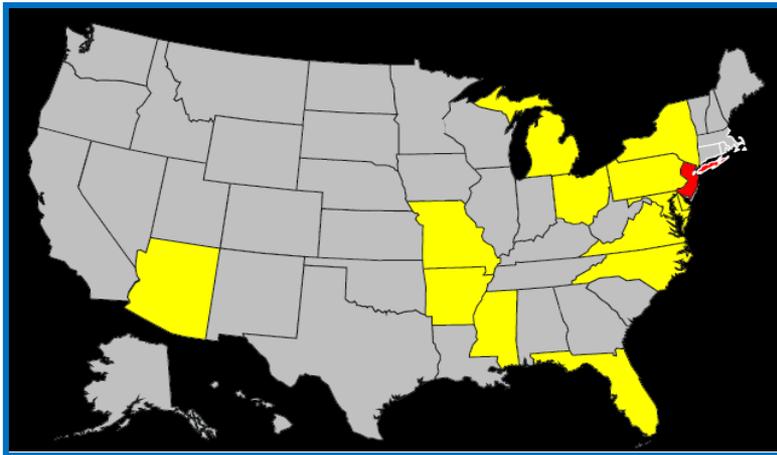
- Take Aways:
  - BSA program has adopted a strategy that concurrently addresses public health emergency preparedness and the public health threat of antimicrobial resistance
  - The emergence of multi and pan drug resistant (MDR/XDR) hospital and community acquired infections is an immediate public health crisis
  - Antimicrobial Resistance complicates the response to any public health emergency
  - Multi-Drug Resistant Organisms (MDROs) are bacterial threat agents



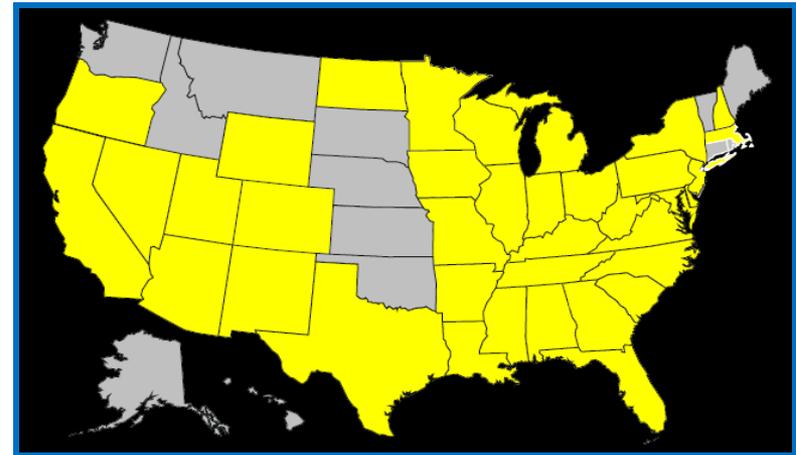
# Spread of Extreme Drug-Resistant *Klebsiella*



- 1996: Carbapenem-resistant *Klebsiella pneumoniae* carbapenemase (KPC) first isolated from patient in North Carolina
- 2000-2005: *Klebsiella* strain carrying the same NC KPC gene spreads throughout NYC hospitals
- 2005: KPC spreads globally to France, Colombia, Canada, China, Greece, Israel, England, Norway, Sweden, Poland, Finland, Brazil and Italy
- 2006-2011: KPC spreads from 14 to 37 States
- 2011-12: Outbreak at NIH hospital-7 dead



**2006**



**2011**

Source: CDC

FOUO/Procurement Sensitive-Not for Distribution

ASPR: Resilient People. Healthy Communities. A Nation Prepared.



# Economic Impact of Antibiotic Resistance



## Mortality, LOS, and Extra Health Care Costs in Patients Infected with MDROs vs Patients Infected with Drug-Sensitive Bacteria

Drug Resistant Bacteria	Mortality (%)	LOS (Days)	Extra cost (US\$M)
ESBL <sup>+</sup> <i>K. pneumoniae</i>	15.2 vs 9.1	11 vs 7	44,359
MRSA	22.9 vs 19.8	30.6 vs 15.3	9,909
VRE	33.3 vs 11.1	17 vs 3	No Data
<i>A. baumannii</i>	57.5 vs 27.5	No Data	No Data
MDR <i>Acinetobacter</i> spp.	19.4 vs 4.5	13	60,913
MDR <i>A. baumannii</i>	No Data	36.8 vs 25.6	98,575
MDR <i>P. aeruginosa</i>	21 vs 12	20 vs 10	No Data

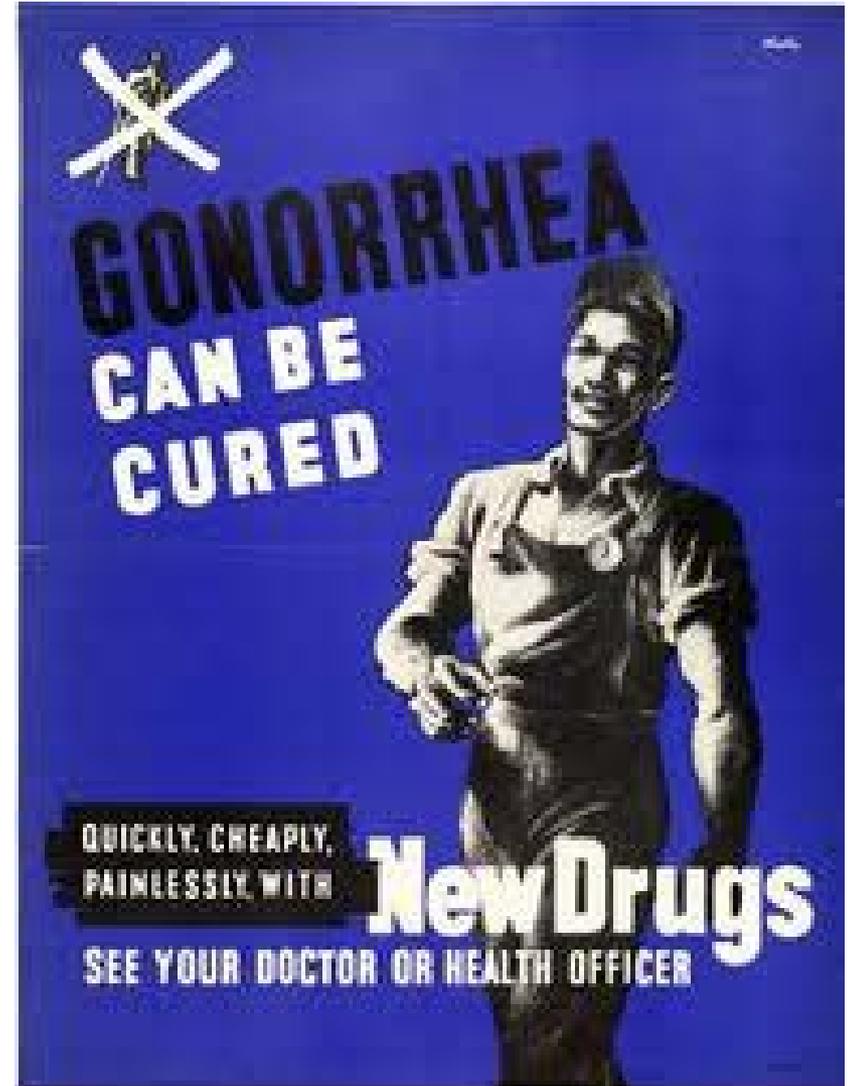
Source: *Expert Rev Anti Infect Ther.* 2008;6(4):523-539



# Timeline of a Pending Crisis: Emergence of MDR Community Acquired Bacterial Infections



- 2006: CDC alters TRT guidelines for gonorrhea to recommend oral fluoroquinolones
- 2009: GC Strain H041 isolated from Japanese sex worker, pan-resistant to FQs and cephalosporins
- 2010: CDC revised TRT guideline recommending oral cephalosporins due to resistance
- 2012: CDC revised TRT guidelines recommending cephalosporins by IM injection followed by oral macrolide/tetracyclines



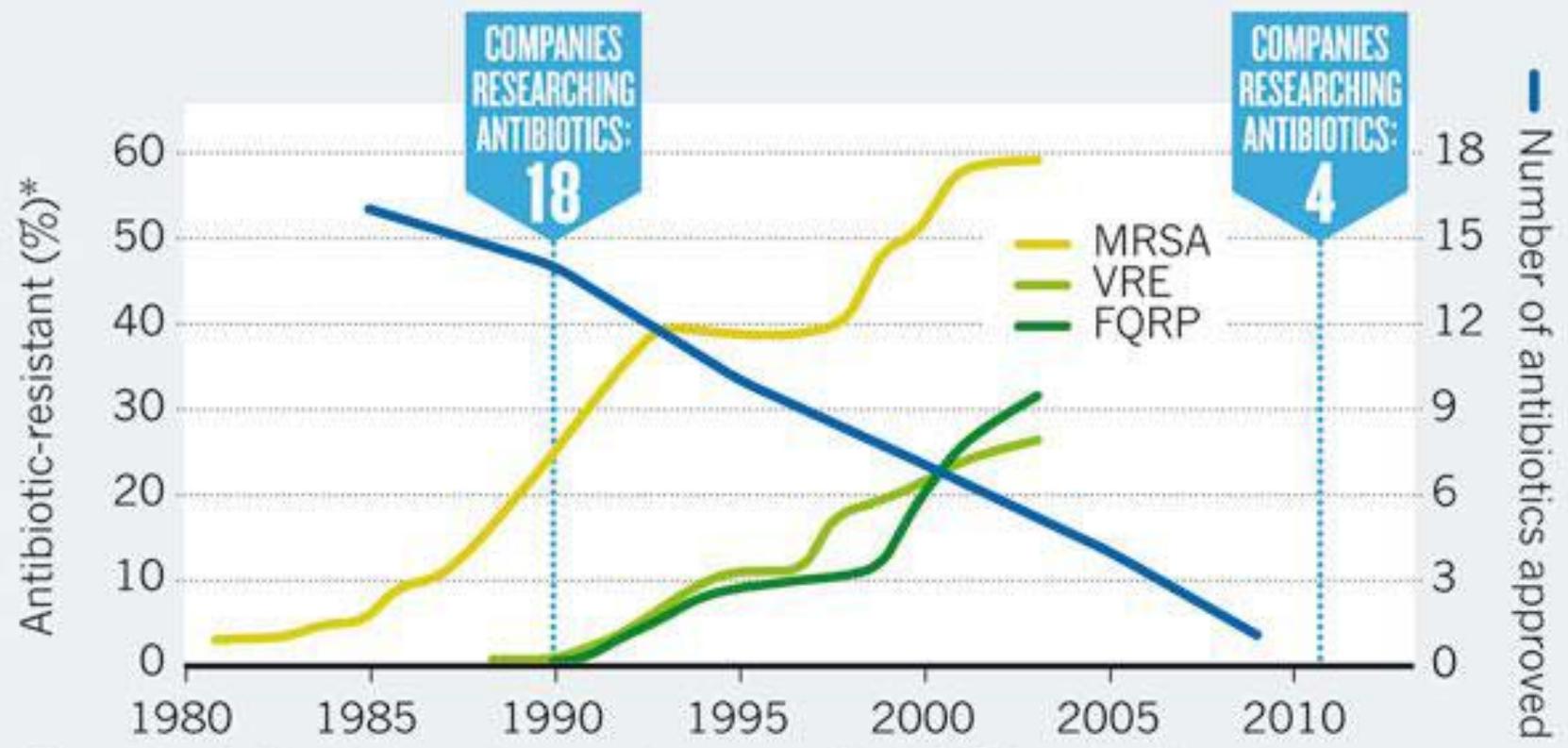


# Large Pharma has Abandoned Antibiotic Development



## A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



\*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

# Antibiotic Resistance Impacts Emergency Responsiveness

- 2005 Hurricane Katrina: 18% of hospitalized victims were infected with either Gram-positive MDR pathogens (MRSA and VRE) or Gram-negative MDR pathogens.
- 2009 H1N1 Pandemic: Bacterial co-infected patients had higher mortality, more frequently presented with shock, required mechanical ventilation, and had a longer duration of ICU care.
- 2010 Haiti Earthquake: 77% of sampled wound infections were polymicrobial, with 89% of infections involving Gram-negative pathogens.





# MDROs are biological threat agents



Organism	Deaths Annually in U.S.	Mortality	Environmental Persistence	Drugs to TRT
MDRO, CRE- <i>Enterobacteraceae</i>	99,000	~50% for PDR- <i>Klebsiella pneumonia</i>	Yes	None
<i>Bacillus anthracis</i>	~0	~50%	Yes	Ciprofloxacin, Doxycycline
<i>Yersinia pestis</i>	~0	100% w/o TRT 11% w/TRT	Yes	Levofloxacin, Gentamicin, Doxycycline
<i>Burkholderia pseudomallei</i>	0	~50% w/o TRT	Yes	Ceftazadime, Co-trimoxazole



# BSA Program Strategy



- Revitalize the antibacterial pipeline through the support of public private partnerships targeting novel unprecedented and precedented classes of antibiotics
- Emphasize programs that address the immediate public health threat of MDR strains of hospital and community acquired pathogens
- Provide a biodefense capability to bridge the response between the first clinical case of threat agent infection to when mass dispensing of MCMs is initiated
- Enable the evaluation of products for all biothreat pathogens via the development of animal models and tools to support regulatory approval



# BSA Program



- Why invest in antimicrobials as a biodefense capability?
  - Commercial indications are a prerequisite to label expansion for biodefense
  - Supplements the public health emergency response until mass points of dispensing are established
  - Reduces the impact of drug resistance
  - Reduces life cycle management cost due to commercial availability



# BSA Priorities



## Biothreat

- *B. pseudomallei*
- *B. mallei*
- *F. tularensis*
- *Y. pestis*
- *B. anthracis*

## Antibiotic Resistance

- CRE
- Acinetobacter
- Pseudomonas
- MDR-GC
- ESBL
- MRSA
- VRE

## Drug Class

- **Unprecedented**
  - Novel Target
  - Novel Chemistry
- **Precedented**
  - Reduced AR
  - Improved Safety
  - Improved Dosing
  - Special Populations

In the known pipelines of the top 15 drug companies:

- Only five drug candidates, or 1.6% of the pipeline, were antibiotics
- Only four were active against Gram-negative bacteria
- Only two acted on new targets
- None had a novel mechanism of action



# Antivirals



- BARDA has both a TRT and PEP requirement for filoviruses; ~2M courses for Ebola or Marburg
  - Few candidate products in developmental pipeline
  - Combination of products likely required to treat disease
- BARDA has a requirement for 1.7M treatment courses of smallpox antiviral
  - For use in individuals presenting lesional disease
  - 2 programs currently ongoing
  - Aligns with IOM goal for 2 antiviral drugs with different MOA



# BSA Program



- Summary:
  - The BSA program will continue to support the development of novel antimicrobials for the treatment and prevention of biological threat agent infection while concurrently addressing the growing public health threat of antimicrobial resistance
  - Actively seek partnership opportunities with companies to bolster antimicrobial development and mitigate risk for biodefense drug development
  - Additional contract awards projected in FY13

# Interfacing with BARDA

- [www.phe.gov](http://www.phe.gov)
  - Program description, information, news, announcements
- [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)
  - Portal to BARDA
  - Register, request a meeting
  - Tech Watch
- [www.fedbizopps.gov](http://www.fedbizopps.gov)
  - Official announcements and detailed information about all government contract solicitations



**Technical POC for Research Area #3: Antimicrobial Drugs:**  
**Joe Larsen, Ph.D. Chief BSA Program**  
[joseph.larsen@hhs.gov](mailto:joseph.larsen@hhs.gov)      **202-260-0050**