Vaccines and other biologics for prevention and treatment of healthcare-associated infections

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ACIP Meeting

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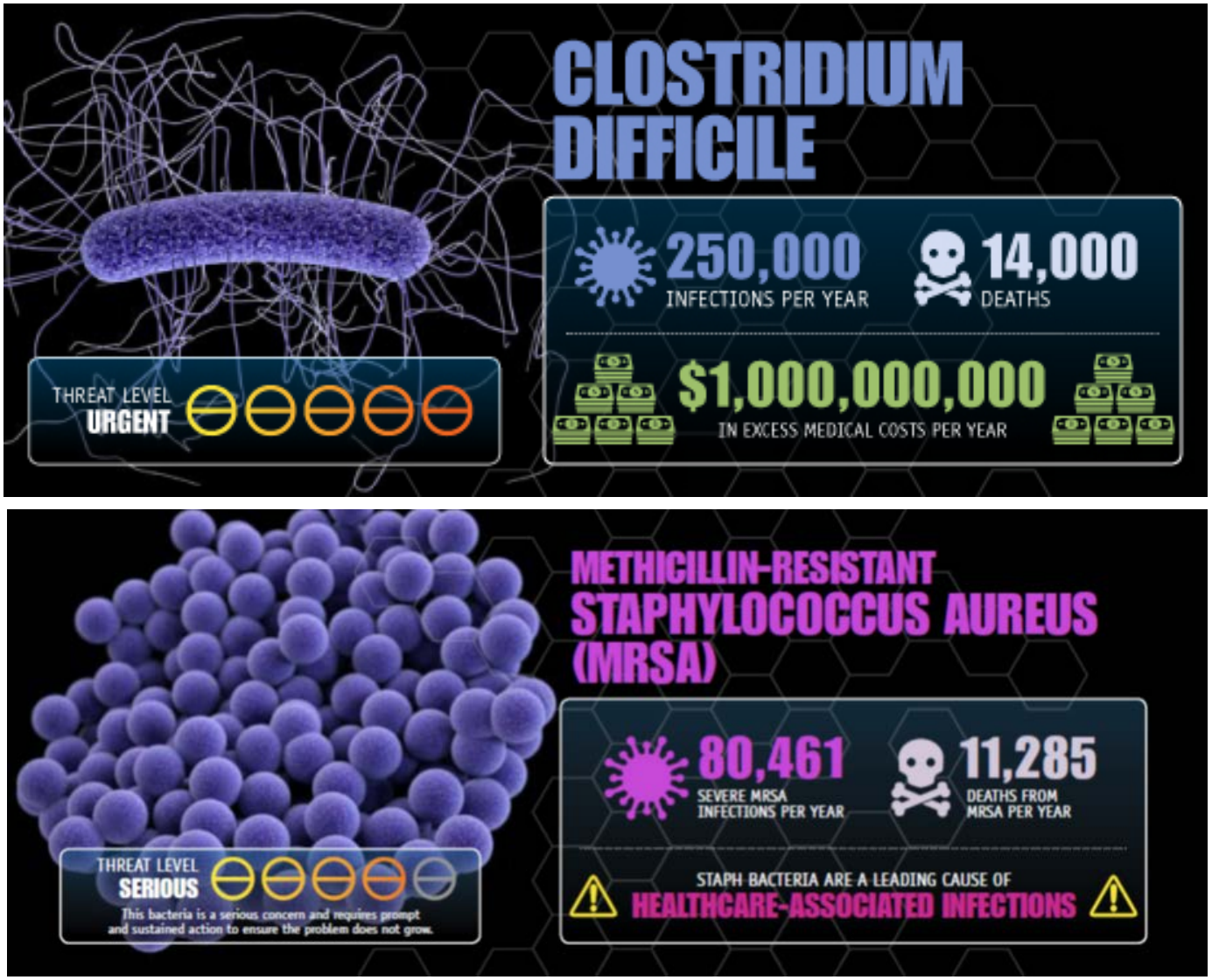
Outline

- Prevention of healthcare associated infections – challenges and opportunities
- Potential role for vaccines
- Specific vaccines undergoing later phase human trials
  - *Staphylococcus aureus* (SA4Ag/Pfizer)
  - *Clostridium difficile* (toxoid/Pfizer)
- Monoclonal antibody - bezlotoxumab – Zinplava (Merck)
- Ongoing and potential CDC and public health contributions to HAI vaccine development, evaluation, program implementation

Antibiotic Resistance Threat Report, 2013: Common, Potentially Vaccine Preventable HAIs



CDC: Antibiotic Resistance Threats in the United States, 2013

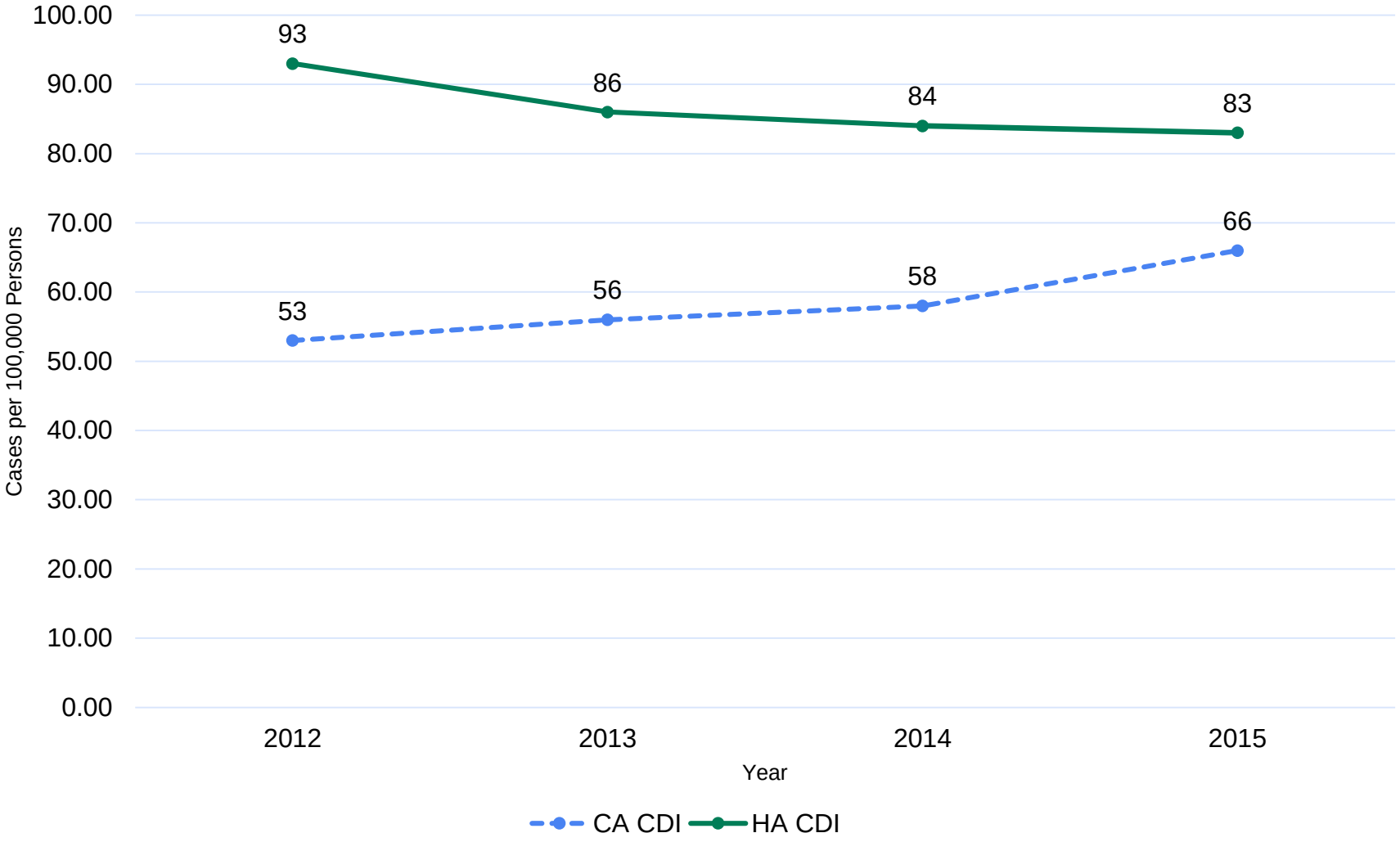
National Action Plan to Prevent Healthcare-Associated Infections: Progress and Targets for 2020

Measure	Data Source	Baseline Years	2013 Target	Progress By 2014	Targets for 2020
Reduce central-line associated bloodstream infections (CLABSI) in ICU and ward-located patients	CDC/NHSN	2006-2008	50% reduction or .50 SIR	50% reduction or .50 SIR	**50% reduction** from 2015 baseline
Reduce catheter-associated urinary tract infections (CAUTI) in ICU and ward-located patients	CDC/NHSN	2009	25% reduction or .75 SIR	No change	**25% reduction** from 2015 baseline
Reduce the incidence of invasive healthcare-associated methicillin-resistant Staphylococcus aureus (MRSA) infections	CDC/EIP/ABC	2007-2008	50% reduction	36% reduction	**50% reduction** from 2015 baseline
Reduce facility-onset methicillin-resistant Staphylococcus aureus (MRSA) infections in facility-wide healthcare	CDC/NHSN	2010-2011	25% reduction or .75 SIR	13% reduction or .87 SIR	**50% reduction** from 2015 baseline
Reduce facility-onset Clostridium difficile infections in facility-wide healthcare	CDC/NHSN	2010-2011	30% reduction or .70 SIR	8% reduction or .92 SIR	**30% reduction** from 2015 baseline
Reduce the rate of Clostridium difficile hospitalizations	AHRQ/HCUP	2008	30% reduction	18% increase	**30% reduction** from 2015 baseline
Reduce Surgical Site Infection (SSI) admission and readmission	CDC/NHSN	2006-2008	25% reduction or .75 SIR	18% reduction or .82 SIR (2012)	**30% reduction** from 2015 baseline

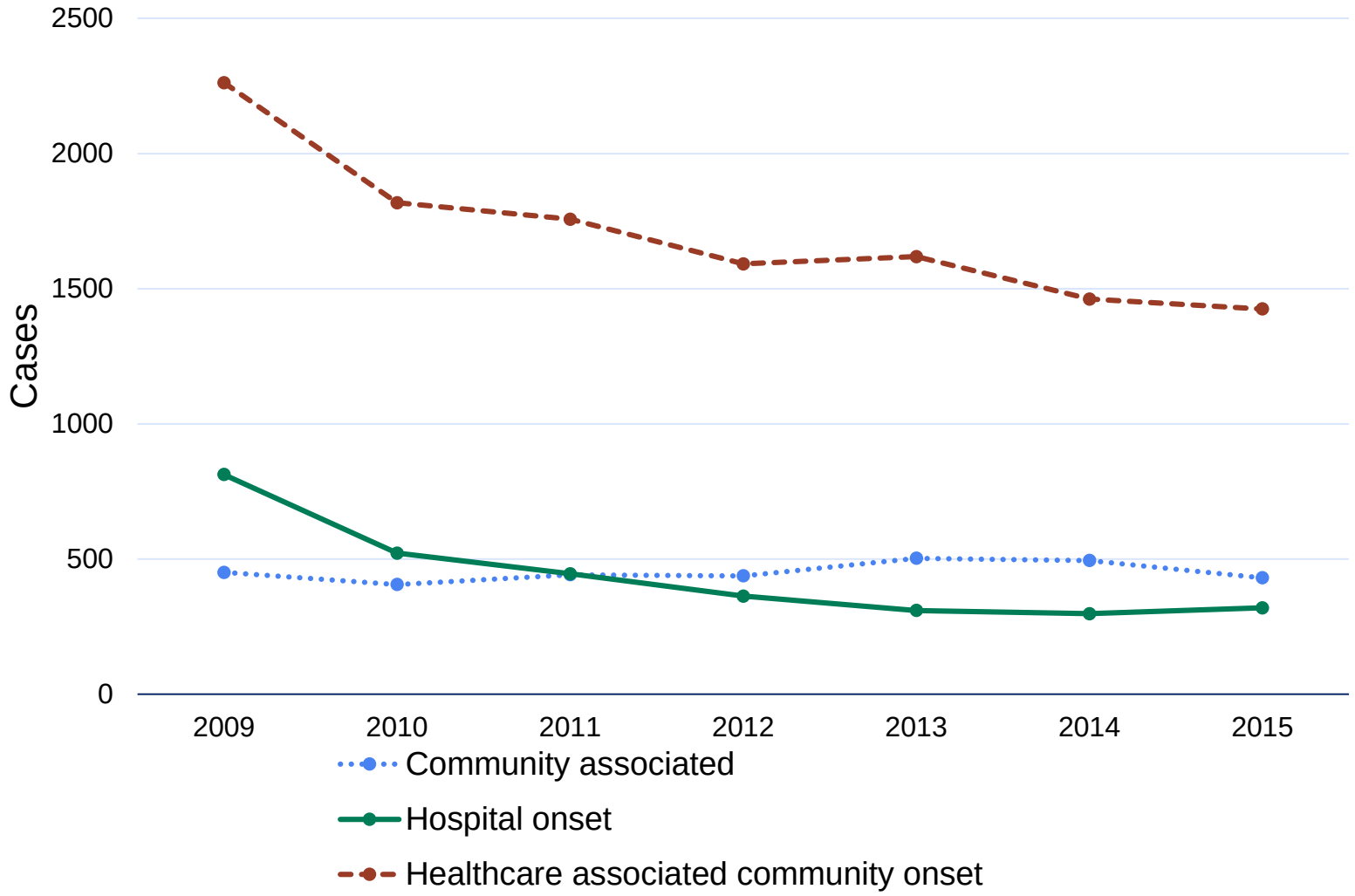
SIR – Standardized Infection Ratio: method for measuring progress in HAI reduction. The SIR compares the actual number of healthcare-associated infections to the predicted number of infections. The predicted number of infections is a risk-adjusted estimate that is determined using national baseline data.

Source: https://health.gov/hcq/prevent-hai-measures.asp

Crude incidence of community-associated (CA) and healthcare-associated (HA) CDI, Emerging Infections Program, 2012-2015



Temporal changes in MRSA bloodstream infections, Emerging Infections Program surveillance area, 2009-2015 (6 sites)



Role for vaccines: complementary to existing strategies to combat healthcare-associated infections and antimicrobial resistance

- Cannot prevent every infection with infection control or antibiotic stewardship
- Vaccines are a proven successful strategy
  - Direct and indirect disease prevention (e.g., pneumococcal vaccines)
  - Effective regardless of mechanism or prevalence of antibiotic resistance
- Potential to reduce antibiotic use
  - Reducing overall vaccine preventable bacterial infections
  - Reduce broad spectrum use aimed at highly resistant strains
  - Indirect effect for vaccines directed against other drivers of antibiotic use (influenza, RSV, GBS)
- Reducing number of infections would reduce exposure of the pathogen to antibiotics
- Potential to reduce opportunities for exchange of resistance elements among bacteria, including cross species.

Increasing interest in vaccines to address AR and HAIs

- **Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR)** 2014:
  - "Develop a transatlantic strategy to facilitate vaccine development for HAIs"
- **National Vaccine Advisory Committee (NVAC)** 2016:
  - "…incentives proposed to stimulate antibiotic development must also be evaluated for their utility to accelerate the development of vaccines…"
- **Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria** (Vaccine Incentives Workgroup, 2017)
  - "Provide additional funding for the development of new product pipelines for vaccines that prevent viral or bacterial syndromes that drive antibiotic use"
  - "Optimize the interactions among sponsors, regulatory agencies (such as FDA), and use policy committees (e.g., the ACIP)"
  - "Incentivize the uptake of vaccines by influencing behavior, such as reimbursement to ensure 'first-dollar coverage'"

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

HAI vaccine development: technical challenges

- Natural infection typically does not protect against subsequent infection
- Often no established immune correlate of protection
  - Demonstrating antibody response might not be sufficient
- Animal models not predictive
- Need for multiple antigens, complex toxins
- Human trials require large at-risk populations

Preventing recurrent *Clostridium difficile* infection with bezlotoxumab (Zinplava/Merck)

- Human monoclonal antibody
- Approved indication (2017): Prevention of recurrent infection for adult patients at risk
  - Administered as IV dose during treatment
  - Binds to *C. difficile* toxin B
  - No impact on initial clinical cure
  - Trial data: reduced risk of recurrence 38% during 12 week follow up
- Partial protection with bezlotoxumab suggests that protective immunity against CDI is possible
- Other monoclonals directed against Gram-negative bacteria and *S. aureus* infections in development*

*Source: clinicaltrials.gov

Candidate Vaccines

Investigational *Clostridium difficile* vaccine (Pfizer)

- Neutralizing antibodies against toxins are sufficient to prevent *C. difficile* infection
- Bivalent vaccine: Toxins A and B
  - Genetically engineered and detoxified; alum adjuvant
  - Induces high levels of neutralizing antibodies:
    - Neutralize toxins from >95% of clinically relevant *C. difficile* strains globally
    - Established responses following 0/1/6 month schedule in Phase 2 study in humans
- Status: Phase 3 trial (16,000 patients)
  - Safety, tolerability, and efficacy in adults ≥50 years of age

Previous investigational *Clostridium difficile* vaccine

- *Cdiffense* (Sanofi)
  - Antigen: purified full length toxin A and B, formalin inactivated, alum adjuvant
  - Immunogenic in healthy volunteers
  - Phase IIb/III trial: Low efficacy, development discontinued (2017)

Investigational *Staphylococcus aureus* vaccine SA4Ag (Pfizer)

- Highly conserved antigens :
  - Capsular polysaccharides CP5 and CP8 conjugated to the carrier protein CRM197
  - Mutated recombinant clumping factor A (rmClfA, lacks plasma fibrinogen-binding activity)
  - Manganese transporter protein C (MntC)
- Rapid, robust humoral immune response, lasting >6 months
- Opsonophagocytic bacterial killing responses
- Status: Phase 2b/3 trial (single preoperative dose) in elective spinal fusion surgery
  - 6000 subjects 18 to 85 years of age
- 9.7 million spinal procedures projected to occur 2021-2030
  - *S. aureus* causes ~50% of orthopedic surgical site infections

Previous investigational *S. aureus* vaccines

- StaphVAX (Nabi)
  - Antigen: capsular polysaccharides CP5 and CP8 conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A.
  - Protective in animal challenge models and immunogenic in healthy volunteers
  - Phase IIb/III trial in patients with ESRD
    - Safe, but low efficacy (development discontinued)
- V710 (Merck)
  - Antigen: iron surface determinant B (IsdB)
  - Protective in animal challenge models and immunogenic in healthy volunteers
  - Phase IIb/III trial in cardiothoracic surgery
    - Low efficacy
    - Increased mortality among patients who developed *S. aureus* infections (causality uncertain)
    - Development discontinued

Additional vaccines and antibodies against HAIs under development (stage 2)*

Vaccine or Biologic	Target	HAI (s)
NVD3a (NovaDigm)	*Candida* agglutinin and *S. aureus* adhesion protein	Vulvovaginal candidiasis Surgical site infection
VLA84 (Valneva)	*C. difficile*	Primary prevention
Antibody (multiple companies)	*S. aureus*	Infection, pneumonia
Antibody (multiple companies)	*P. aeruginosa*	Pneumonia

*Source: Pew Trust 2017. http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development

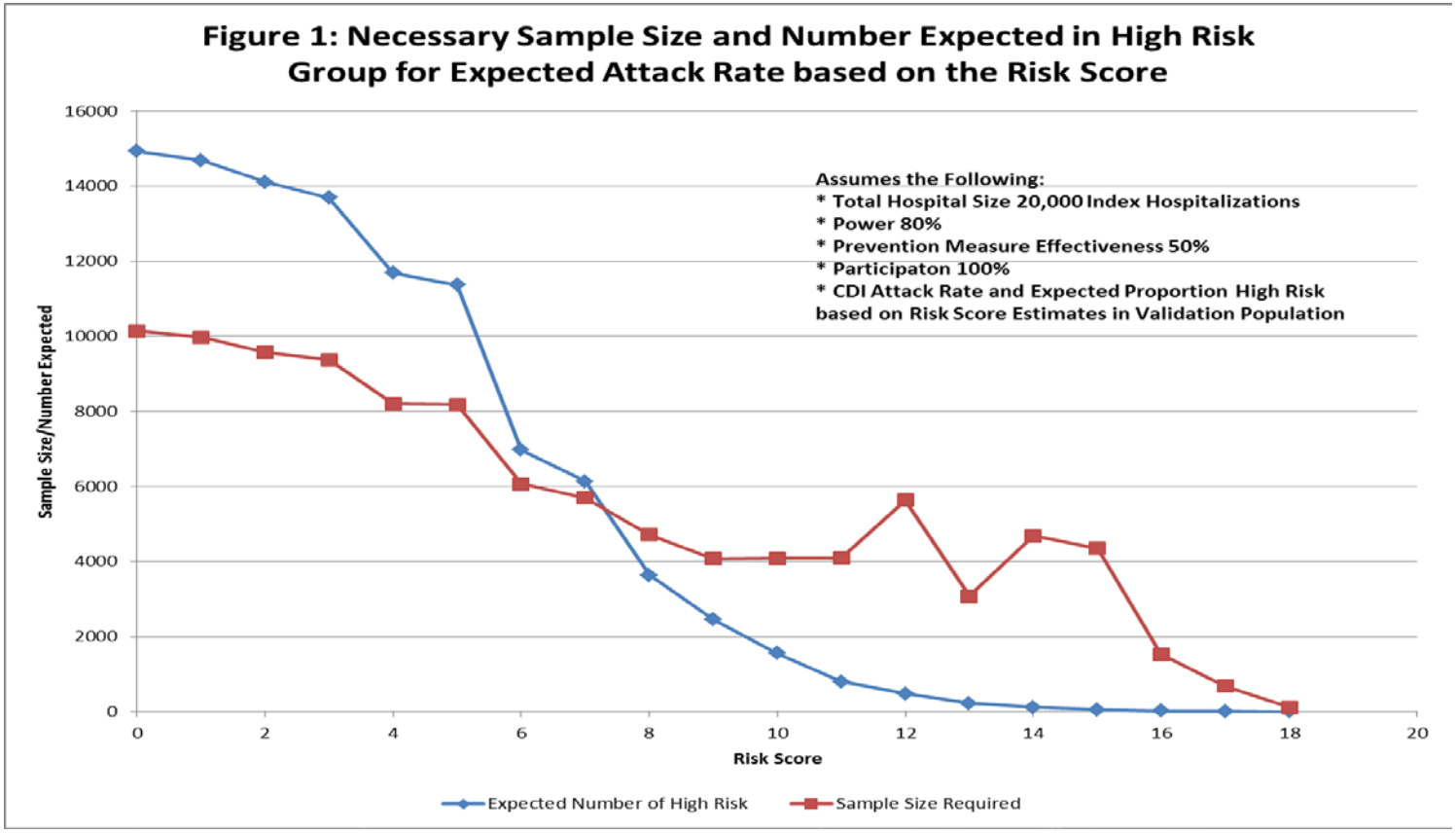
Programmatic challenges presented by HAI vaccines

- Delivery models based on universal, age-based vaccination will often not apply
- Approved indication will often be narrow (e.g., elective orthopedic surgery, post antibiotic, limited age group, chronic disease risk factors, etc.)
- Vaccination programs will rely on settings that are less experienced with delivering vaccinations (e.g., outpatient surgery, transitions of care, etc.)
- Immunogenicity might be reduced among persons at risk
- Unknown potential for interaction between other treatments (e.g., monoclonals, polypharmacy) and vaccines
- Economic analyses needed

CDC and public health contributions to HAI vaccine development and evaluation

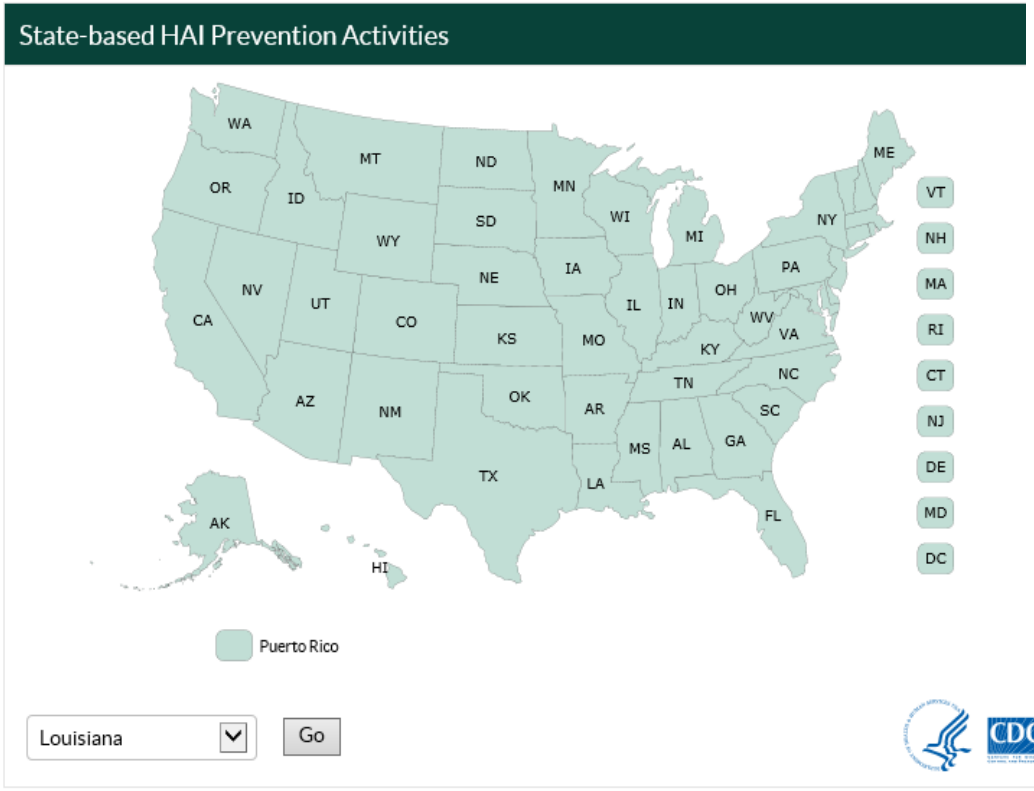
Epidemiologic studies helping to identify populations and settings for trials

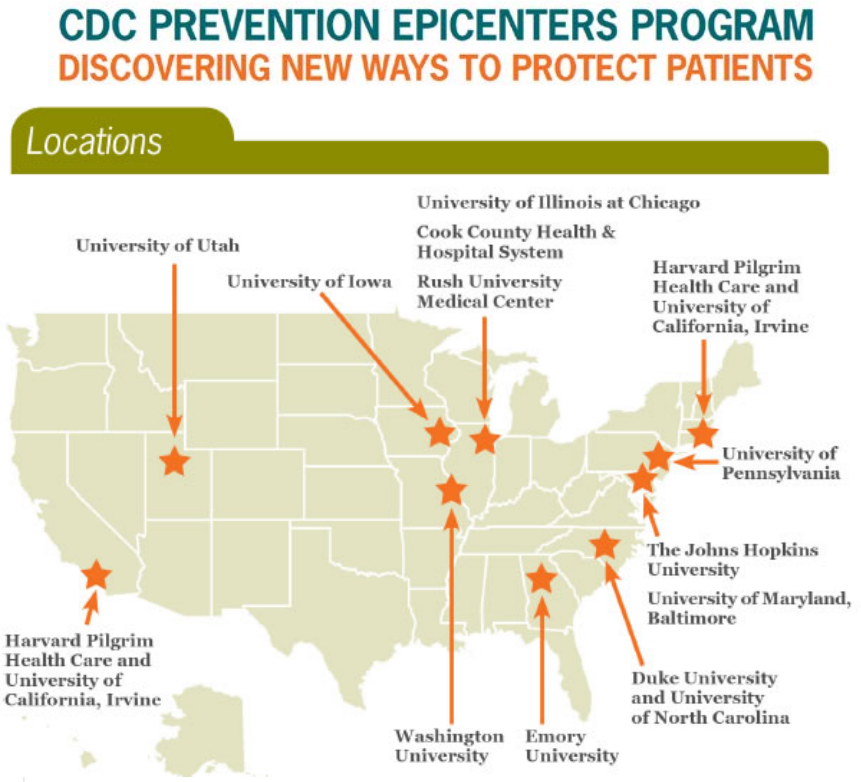
- Modeling potential impact of vaccination strategies
- Risk factor and healthcare encounter studies
- Linking data sources to follow patients across healthcare encounters



J Baggs, et al. Vaccine 2015;33:6241-9.

Expansion of HAI research, evaluation and infrastructure support in states



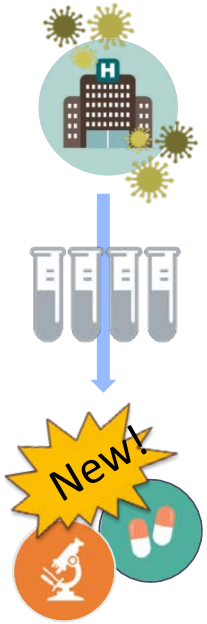


Emerging Infections Program

Healthcare-Associated Infections/Community Interface

Making diverse bacterial isolates available

CDC & FDA Antibiotic Resistance Isolate Bank



CDC uses bacteria samples (isolates) from health departments, labs, and outbreak and surveillance activities.

CDC analyzes and sequences the bacteria's resistance and makes the data and sample available.

Researchers can use the bacteria and data to challenge, develop new diagnostic tests and antibiotics.

Laboratorians can validate lab tests to improve patient care.

Specimen panels potentially useful for vaccine development

BY THE NUMBERS

CDC curated 14 panels from its 450,000+ isolate collection

55,000 isolates shared since July 2015

571 unique customers

637 orders processed

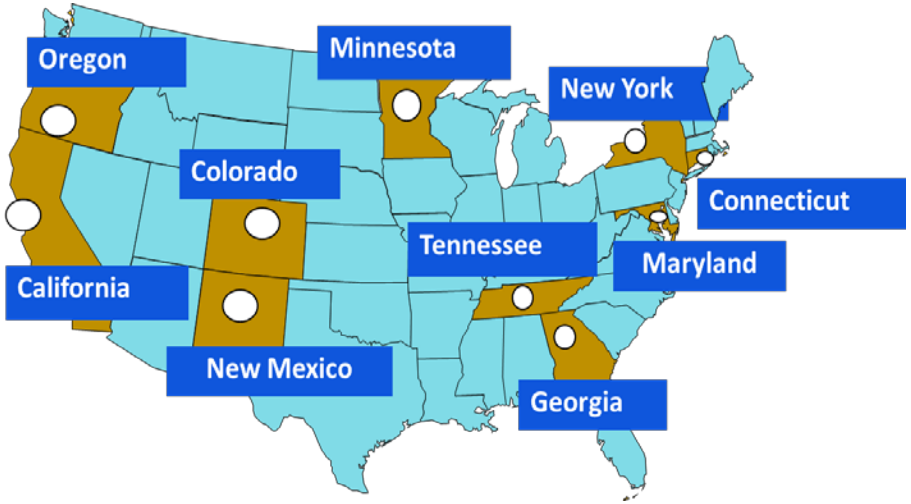
ARISOLATEBANK

Established large surveillance systems for post-approval effectiveness and safety assessments

Emerging Infections Program

Healthcare-Associated

Infections/Community Interface



Laboratory-confirmed infections occurring in a population based surveillance system, areas include 10-20 million persons total

NHSN
National Healthcare Safety Network

Over 17,000 healthcare facilities reporting

Immunization Safety Office (ISO)

HAI vaccines workgroup?

- 2-3 years in best case scenario from vaccine licensure
- HAI vaccines and HAI vaccine programs will be different in many respects from currently licensed vaccines in adult schedules
- Careful and deliberate discussion will be needed, and merits consideration of forming an HAI vaccines workgroup as early as later 2018

Questions/Discussion

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov