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

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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

**Clostridium Difficile**
- **250,000 Infections per Year**
- **14,000 Deaths**
- **$1,000,000,000 in Excess Medical Costs per Year**

**Methicillin-Resistant Staphylococcus Aureus (MRSA)**
- **80,461 Severe MRSA Infections per Year**
- **11,285 Deaths from MRSA per Year**


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

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**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

- **Cdifffense** (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)*

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<tr>
<th>Vaccine or Biologic</th>
<th>Target</th>
<th>HAI (s)</th>
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<tr>
<td>NVD3a (NovaDigm)</td>
<td><em>Candida</em> agglutinin and <em>S. aureus</em> adhesion protein</td>
<td>Vulvovaginal candidiasis Surgical site infection</td>
</tr>
<tr>
<td>VLA84 (Valneva)</td>
<td><em>C. difficile</em></td>
<td>Primary prevention</td>
</tr>
<tr>
<td>Antibody (multiple companies)</td>
<td><em>S. aureus</em></td>
<td>Infection, pneumonia</td>
</tr>
<tr>
<td>Antibody (multiple companies)</td>
<td><em>P. aeruginosa</em></td>
<td>Pneumonia</td>
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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
Expansion of HAI research, evaluation and infrastructure support in states

State-based HAI Prevention Activities

CDC PREVENTION EPICENTERS PROGRAM
DISCOVERING NEW WAYS TO PROTECT PATIENTS

Locations

University of Utah
University of Iowa
Rush University Medical Center
Harvard Pilgrim Health Care and University of California, Irvine
University of Illinois at Chicago
Cook County Health & Hospital System

Harvard Pilgrim Health Care and University of California, Irvine
University of Pennsylvania
The Johns Hopkins University
University of Maryland, Baltimore
University of Maryland, Baltimore

Washington University
Emory University
Duke University and University of North Carolina

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

Emerging Infections Program
Healthcare-Associated Infections/Community Interface

Over 17,000 healthcare facilities reporting

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

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)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.