Environmental chemicals, *Staphylococcus aureus*, and antimicrobial resistance

NAS Workshop
January 14, 2019

Meghan F. Davis, DVM, MPH, PhD  
Assistant Professor  
Department of Environmental Health & Engineering, JHSPH  
Department of Molecular & Comparative Pathobiology, JHSOM  
mdavis65@jhu.edu

Elizabeth Matsui; Meredith McCormack; Lesliam Quiros Alcala; Shanna Ludwig; Jonathan Shahbazian
Outline

• Motivation: How infectious diseases and environmental stressors interact

• Case example: *Staphylococcus aureus*
  – Antimicrobial resistance
  – Infection outcomes
  – Asthma outcomes
The Environmental Health Paradigm

*How exposures cause disease and how we can reduce exposure or response to prevent disease (improve the health of the public)*
Toxicology

- Exposure
  - Internal dose
    - Biologically effective dose
      - Early biological effects
        - Altered structure and function
          - Clinical disease
A place for infectious disease in exposure assessment

Rethinking how microbes fit into the environmental health paradigm

Drug-resistant Pathogens

Infectious dose

Infected cells; agent replication

Antimicrobial drugs & disinfectants

Environment

Animals

Food

Dust

Soil

Air

Water

Environment

Environment

Infxn

Death

Acute dz

Chronic dz

Recovery

Example: Methicillin-resistant *S. aureus* in home dust

- *S. aureus* colonizes a third of the U.S. population
  - Colonization is a risk factor for later infection
- Home contamination rates range from 40 – 100% (reservoir)
S. aureus nasal colonization & the environmental reservoir
S. aureus nasal colonization & the environmental reservoir
S. aureus nasal colonization & the environmental reservoir
MRSA contamination in homes of people with recent infxn

Risk factors for **multidrug resistance**:
- Human or pet use of antimicrobial drugs
- Use of disinfectants on EPA list of MRSA-cidal products
- Rural residence

**FIG 1** Percentage of sites contaminated with MRSA at the enrollment visit (baseline) and the 3-month visit. Samples were collected from eight standardized locations in the common room, kitchen, and bedroom (BR) of each household.

Example: host adaptation of *S. aureus* CC398

- Origin as a methicillin-susceptible *S. aureus* (MSSA) colonizing humans
- Jump to livestock associated with:
  - methicillin-resistance gene acquisition
  - tetracycline-resistance gene acquisition
- Putative selection pressure from tetracycline use in livestock
- Potential association with zinc
  - Zinc supplementation of livestock feed

Example: Lead and *S. aureus* colonization

**Scenario 1:** Prior Pb exposure in human host prevents colonization by susceptible strains (MSSA)

**Scenario 2:** MRSA strains selected by later Pb exposure in human host

**Scenario 3:** MRSA strains selected by later Pb exposure in the environment

Non-infectious roles of bacteria

- **Inflammation**
  - Innate immune response
  - **Endotoxin**: Gram-negative bacterial lipopolysaccharide (LPS)
  - **Enterotoxin**: Secreted proteins from *Staphylococcus aureus* and related bacteria (Gram-positive bacterium)
  - **Superantigens**: antigens that cause non-specific T-cell activation & cytokine release

Infectious Agent as Exposure

First Exposure

Acute disease

Second Exposure

Nth Exposure
Non-infectious roles of bacteria

- Inflammation
- Allergy
  - Th2-biased response
  - Typically requires prior exposure / sensitization (IgE)

Infectious Agent as Exposure

First Exposure \(\rightarrow\) Sensitization \(\rightarrow\) Second Exposure \(\rightarrow\) Exacerbation \(\rightarrow\) Nth Exposure

Worse disease
Example: Impacts of *S. aureus* on asthma may vary by age

<table>
<thead>
<tr>
<th>Outcomes, OR [95% CI]</th>
<th>Whole population</th>
<th>Age 6-30yo</th>
<th>Age 31-85yo</th>
<th>S. aureus-age int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>n=16,234</td>
<td>n=8,703</td>
<td>n=7,531</td>
<td></td>
</tr>
<tr>
<td><strong>Selected wheeze outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze in past yr</td>
<td>1.02 [0.87, 1.20]</td>
<td><strong>1.35 [1.06, 1.73]</strong>*</td>
<td>0.85 [0.68, 1.06]</td>
<td><em>p</em>&lt;0.006</td>
</tr>
<tr>
<td>Nocturnal wheeze</td>
<td>1.05 [0.84, 1.34]</td>
<td><strong>1.52 [1.15, 2.00]</strong>**</td>
<td>0.79 [0.53, 1.18]</td>
<td><strong>p</strong>=0.01</td>
</tr>
<tr>
<td>ER for wheeze</td>
<td><strong>1.28 [1.00, 1.62]</strong>*</td>
<td><strong>1.50 [1.10, 2.03]</strong>*</td>
<td>1.11 [0.70, 1.78]</td>
<td><em>p</em>=0.26</td>
</tr>
<tr>
<td>Meds for wheeze</td>
<td>0.93 [0.75, 1.14]</td>
<td><strong>1.52 [1.08, 2.14]</strong>*</td>
<td><strong>0.64 [0.48, 0.84]</strong>**</td>
<td><strong>p</strong>&lt;0.001</td>
</tr>
<tr>
<td><strong>Selected asthma outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma ever</td>
<td>1.07 [0.92, 1.23]</td>
<td>1.25 [0.99, 1.56]</td>
<td>0.92 [0.76, 1.11]</td>
<td><strong>p</strong>=0.04</td>
</tr>
<tr>
<td>ER for asthma</td>
<td>1.44 [0.89, 2.31]</td>
<td><strong>1.97 [1.05, 3.73]</strong>*</td>
<td>0.85 [0.37, 1.94]</td>
<td><em>p</em>=0.09</td>
</tr>
</tbody>
</table>

*bold: p<0.05*

*p<0.05, **p<0.01, ***p<0.001*
Staphylococcal exposures in home dust are common

- Asthma Control Evaluation (ACE)
- Multicenter, randomized controlled trial (completed)
  - Part of the Inner City Asthma Consortium
- 12-20 year old inner city children with asthma, n=546

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sample</th>
<th>Any detection, n (%)</th>
<th>Median [25th, 75th%ile] gene copies per g dust</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em> (<em>femB</em>)</td>
<td>n=424</td>
<td>342 (81%)</td>
<td>15498 [3022, 46204]</td>
</tr>
<tr>
<td>SEA</td>
<td>n=424</td>
<td>264 (62%)</td>
<td>2681 [&lt;LOD, 13442]</td>
</tr>
<tr>
<td>SEB</td>
<td>n=424</td>
<td>153 (36%)</td>
<td>&lt;LOD [&lt;LOD, 3741]</td>
</tr>
<tr>
<td>SEC</td>
<td>n=415</td>
<td>149 (36%)</td>
<td>&lt;LOD &lt;LOD, 3205]</td>
</tr>
</tbody>
</table>
Adjusted associations between SA/SE and 2-wk symptoms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>S. aureus</th>
<th>SEA</th>
<th>SEB</th>
<th>SEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced activity (OR)</td>
<td>1.00</td>
<td>1.12 ***</td>
<td>1.09 ***</td>
<td>1.06 ***</td>
</tr>
<tr>
<td></td>
<td>[0.96, 1.05]</td>
<td>[1.07, 1.17]</td>
<td>[1.05, 1.13]</td>
<td>[1.03, 1.10]</td>
</tr>
<tr>
<td>Woken by asthma (OR)</td>
<td>1.00</td>
<td>1.04</td>
<td>1.03</td>
<td>1.07 **</td>
</tr>
<tr>
<td></td>
<td>[0.95, 1.07]</td>
<td>[0.98, 1.10]</td>
<td>[0.96, 1.09]</td>
<td>[1.02, 1.12]</td>
</tr>
<tr>
<td>Wheeze (OR)</td>
<td>0.97</td>
<td>1.01</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>[0.94, 1.00]</td>
<td>[0.98, 1.05]</td>
<td>[0.97, 1.03]</td>
<td>[0.95, 1.02]</td>
</tr>
<tr>
<td>ACT Score (β)</td>
<td>0.03</td>
<td>-0.08</td>
<td>-0.09</td>
<td>-0.07</td>
</tr>
<tr>
<td></td>
<td>[-0.10, 0.17]</td>
<td>[-0.22, 0.06]</td>
<td>[-0.22, 0.05]</td>
<td>[-0.20, 0.06]</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race/ethnicity, annual income ≤$15,000, smoking exposure, number of positive skin tests, and recommended treatment step; OR: odds ratio; Lower ACT score indicates worse asthma; 
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

Davis MF, Ludwig S, Brigham EP, McCormack MC, and Matsui EC. Effect of home exposure to *Staphylococcus aureus* on asthma in adolescents. *Journal of Allergy and Clinical Immunology* 2018. PMID: 28739287
Host factors may modify associations

Adolescent participants without a history of eczema had worse symptoms when exposed to home dust SEA.
Acknowledgments

- Elizabeth Matsui
- Meredith McCormack
- Lesliam Quiros Alcala
- Ebbing Lautenbach & the CURE trial
- Davis lab group: Dr. Shanna Ludwig, Dr. Kathryn Dalton, Jonathan Shahbazian, Isha Pandya, Jackie Ferguson, Jonathan Josephs-Spaulding, Andrea Christ, Kris Spicer, Isabel Jimenez-Bush, Ayanna Crear, Dr. Katie Sabella

- Fisher Center Discovery Program, Morris Animal Foundation, JH Center for a Livable Future, JH Innovation Award, NIH Office of the Director
- BREATHE Center
- Inner-City Asthma Consortium / Asthma Control Evaluation cohort