Emergence of Livestock Associated MRSA

Occupational and public health consequences

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Methicillin resistant *S. aureus* (MRSA) ‘Changing paradigms’

- Major problem of chronically ill in institutions
  - Resistance linked to antimicrobial use in hospitals
  - Not a concern for broader community
- 1990s : global emergence of CA-MRSA
  - Different ‘clones’ distinct from ‘hospital’ strains
  - No epidemiologic role of animal reservoirs
- 2004...: detection/emergence of ‘LA-MRSA’
MRSA in animals – publication rate

- Cattle
- Cat, Dog
- Horse
- Pig, Sheep

Years: 70s, 80s, 90s, 95, 96, 97, 98, 99, 00, 01, 02, 03, 04, 05, 06, 07

N: 0, 2, 4, 6, 8, 10, 12

2010 >50
Holland – an issue emerges!

- Very low MRSA prevalence
  - ‘Search and destroy’ policy
  - Intensive screening and typing with sma1 PFGE

- 2004: 6mo girl screened before for surgery for a congenital heart defect
  - MRSA isolate not typable with Sma1 PFGE

- 2 other screening isolates not typable by Sma1 PFGE
  - All 3 ‘cases’ epidemiologically linked to pigs

- Studies of MRSA prevalence in pigs, farmers and pork
**S. aureus** subtyping methods

- PFGE
- MLST
- SCC\textit{mec} typing (I – X)
- Spa typing
  - Ridom
  - egenomics

‘Livestock associated’

- Sma1 Untypable
  - ST398 (CC398) III, IV, V
- t034, t011, t108
- 539, ..........................
National survey of slaughter pigs in Holland
- 39% of 540 pigs positive (nasal swabs)

All isolates a ‘single clonal group’
- Nontypable (NT) by sma1 PFGE
- MLST: ST 398
- 3 closely related spa types predominant (t011, t108, t1254, ...)

Uniformly resistant to tetracycline
- Use of tetracyclines may be selecting for MRSA?

Matthew 7:7 - “Seek and ye shall find”

MRSA in market hogs (de Neeling et al, 2006)
Colonization of farm workers

- **ST398** also isolated from pig farmers (Voss et al. 2005)
  - 23% of farmers positive on nasal swab
  - 760x general population prevalence
- Dutch health authorities changed MRSA screening procedures
  - People exposed to pigs and calves considered high risk
  - Isolated and screened before hospital admission
- **ST398 MRSA** isolated from pork (van Loo et al., 2007)

Matthew 7:7 - “Seek and ye shall find”
MRSA in livestock: An epidemic waiting to happen? (Wulf and Voss, 2008)

- Not just a “Dutch” problem
- May become an important source of community acquired MRSA
- Epidemiology different to ‘classic MRSA strains’
- Inter-human spread is possible
- Probably ‘just a matter of time until an outbreak’
ST398 (livestock associated) MRSA

Generally accepted facts

- Common occurrence of LA-MRSA in livestock
  - Pigs, cattle, avian, horse, ..?
  - Many countries – particularly pigs

- High prevalence of MRSA in livestock farmers, veterinarians, slaughter plant workers
  - 20-40% in farmers (vs. ~ 0.5 - 2% in population)
  - Mainly LA-MRSA

- Negligible risk of exposure in other groups
Livestock Associated MRSA

- ST398 MRSA found in pigs in many countries including USA
  - Also other animals (cattle, horse, poultry, dog)
- Not just ST398
  - ST9 (t899, t337) in Asia, Italy, Spain, USA
  - ST5 (2/tunk.) in North America (US, Canada)
  - ST49 in Switzerland, ST1 in Denmark
  - Etc..
Consistent observation: occupational exposure to animals increases risk of MRSA positive culture
- Farmers, veterinarians, abattoir workers

Colonization vs. contamination
- Duration of ‘colonization’
- Role of regular animal contact

Consequences of colonization
- Transmission risk
- Disease risk
Duration of colonization

- Research workers (short term exposure) \textit{van Cleef et al (2011)}
  - 33 of 199 exposures led to positive culture on farm
  - Only 1 of 33 retested positive after 24 hours

- Evidence suggests most short term exposure leads to short term ‘colonization’
  - But farmers are regularly exposed

- Veal farmers in Holland \textit{Graveland et al (2011)}
  - Rapid decline in prevalence during absence of animal contact
  - LA-MRSA poor persistent colonizers in most humans.
Transmission of ST398 MRSA among people

- Studies of transmission in Dutch hospitals (Bootsma, 2010)
  - ST398 is 5.9 times less transmissible than non-ST398 MRSA in Dutch hospitals’
  - ‘Spreading capacity per admission insufficient to lead to an epidemic’
- ‘Nosocomial transmission of ST398 MRSA is 72% less likely than non-ST398 MRSA strains’
  
  Wassenberg (2011)
Burden of disease from ST398 MRSA

- Many reports don’t distinguish infection from colonization
- Small number of serious infections
  - Often no livestock association
  - 5 fatal cases in world in 8 years: 1 with livestock contact
- Retrospective study of human isolates in Canada
  - 5 ST398 out of 3,687 MRSA isolates
  - 4 skin/soft tissue infections (Golding et al 2010)
- CDC has examined >12,000 isolates in USA
  - ST398 not identified in a human clinical case (June 2011)
  - MN DOH – no ST398 among 7,000 isolates tested
Burden of disease from ST398 MRSA

- 89 papers/reports of ST398 associated clinical cases
- Data recorded
  - Numbers of isolates from screening vs. clinical infections
  - Clinical presentations
    - bacteremia; pneumonia; skin or soft tissue infection, etc.
  - Number of cases with invasive infections (not SSTI)
  - Fatalities
  - History of animal contact
Disease burden from ST398 MRSA
Cumulative data from 89 publications (n = 2,553 cases)

- 2,056 screening isolates
- 497 (19.5%) clinical
  - 203 unspecified
  - 125 ‘invasive’
  - 5 fatal
- Invasive disease
  - Many cases MSSA not MRSA
  - Livestock exposure very inconsistent
    - Yes:10%  No:26%  Unknown: 64%
Distribution of LA-MRSA and other MRSA clinical isolates in Europe  
(van Cleef et al., 2011)

<table>
<thead>
<tr>
<th>Sample source</th>
<th>No. (%) typed clinical isolates</th>
<th>MRSA ST398, n = 113</th>
<th>Other MRSA, n = 3,435</th>
<th>p value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>2 (1.8)</td>
<td>343 (10.0)</td>
<td><strong>0.004</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>20 (17.7)</td>
<td>451 (13.1)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Skin and wound</td>
<td>76 (67.3)</td>
<td>2,312 (67.3)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>6 (5.3)</td>
<td>173 (5.0)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (8.0)</td>
<td>156 (4.5)</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

*Only data from 9 national or regional laboratories in the 7 countries that reported clinical isolates and typed all these isolates were included.
Geographic distribution of *S. aureus* causing invasive infections in Europe
Grundmann et al 2010

- 357 laboratories serving 450 hospitals in 26 countries (2006-2007)
  - 2,890 MSSA and MRSA isolates from invasive infections
- ST 398 spa types (t011, t034, t571, t1255, and t2383) identified on 12 occasions
  - None harbored the mecA gene.
- No cases of ST398 MRSA invasive disease
DANMAP 2009 – 2011

- **DANMAP 2009**
  - 13% of slaughter pigs positive (ST398 MRSA)
  - 10 (0.7%) human ST398 bacteremia cases (all MSSA)

- **DANMAP 2010**
  - 16% of slaughter pigs positive
  - 11 (0.8%) human ST398 bacteremia cases (all MSSA)

- **DANMAP 2011**
  - 16% of slaughter pigs positive
  - 11 (0.7%) human ST398 bacteremia cases (all MSSA)
ST398 genomic studies and virulence

- > 30 known ‘virulence factors’ in *S. aureus*
  - Likely underpins the diversity in clinical expression

- Schijffelen (2010): full genome of ST398/t011 strain
  - Just 2 virulence factors found
  - ‘lack of virulence factors may explain the infrequency of serious clinical infections with ST398’

- Argudin (2011): 100 ‘non-human’ ST398
  - Many resistance determinants but few virulence factors
ST398 genomic studies and virulence

- Hallin (2011): 18 ST398 vs. other MRSA
  - ST398 strains lacked human-associated virulence and adhesion determinants
  - absence of enterotoxin genes indicates likely insignificance for foodborne disease

- Summary
  - Limited studies of ST398 genome
  - Consistently few known human virulence factors
Fatal ST398 infections

- 5 fatal cases reported
- 4 MSSA not MRSA
  - Spa type t571 (not common in swine)
  - No significant livestock contact
- One MRSA with livestock contact
  - Spa type t011 (common in swine)
  - 85yo man with lung carcinoma and COPD
- Higher burden from MSSA than MRSA?
Public health risk of ST398 MRSA

- Elevated occupational risk of infection not yet documented
- Current evidence suggests low transmissibility
  - No reports of outbreaks
- Current evidence suggests low virulence?
  - Significantly less invasive disease in Europe
  - Serious infections uncommon
  - General lack of virulence determinants
  - Few fatalities
Real-time PCR to distinguish ST398 from non LA-MRSA
(Meurs et al, Infection. 2012 Sep 1. [Epub ahead of print])

- Severe infections due to LA-MRSA and transmission between individuals is relatively rare.
- LA-MRSA may warrant less stringent containment measures than HA-MRSA in hospital settings
- Real-time PCR a reliable assay to detect ST398
  - Anticipate that use of PCR can prevent the unnecessary closing of hospital wards
  - May lead to substantial health care savings
Lethal pneumonia caused by an ST398 *S. aureus* strain

Rasigade et al (2010)

- **Observations**
  - Fatal necrotizing pneumonia in a previously healthy 14yo girl
  - ST 398 - spa type t571
  - Panton-Valentine Leukocidin positive
  - Tetracycline *susceptible*
  - Methicillin *susceptible* (MSSA)
  - No livestock contact

- **Inference**
  - “spread of *S. aureus* ST398 among livestock is a matter of increasing concern because strains of this sequence type were able to acquire PVL genes”
“One Health” means more than one inference

- ‘.. concern because strains ST398 strains were able to acquire PVL genes’  
  Rasigade et al (2010)

- But....
  - Livestock strains almost uniformly tetracycline resistant and PVL negative
  - Spa type t571 uncommon in animal isolates

- Could adaptation of ST398 to livestock hosts include loss of human virulence factors?

- Could some ST398 variants persist in people without any role of livestock?
More of the story
Davies P.R. et al, EID June 2011

- **t571 ST398 MSSA**
  - Detected in 9 families from the Dominican Republic living in Manhattan, NY (Bhat et al., 2007)
  - Only MSSA spa type in Dutch study of ST398 clinical isolates including 3 cases of nosocomial bacteremia (van Belkum et al., 2008)
  - Predominant MSSA type at Beijing hospital (Chen et al 2010, Zhao et al 2012)
  - Case report of from Colombia (Jimenez et al 2011)
- All with no apparent livestock contact
- 30% of ST398 bacteremia cases in 89 publications reviewed were **t571 MSSA**
‘Animal independent’ ST398 clinical infections in NY city (Uhlemann et al, 2012)

- Studied:
  - 161 outpatient MRSA isolates
  - 160 non-invasive MSSA cases
  - 160 bloodstream MSSA isolates

- No ST398 among outpatient MRSA cases
- ST398 t571: 5% of non-invasive MSSA; 2.5% of MSSA bacteremias
- Only reported ST398 infections in USA are t571 MSSA without known livestock contact
- “Clinically important clone that differs significantly at the genome level from its livestock associated counterpart”
Understanding of LA-MRSA and ST398 *S. aureus* is embryonic

- Naïve perceptions of complex epidemiology
  - All MRSA found in livestock are ST398
  - Livestock are the only reservoirs of ST398
- ST398 not associated with livestock may be a larger public health concern (though burden remains very small)
- ST398 (livestock associated) is an occupational risk
- Need systematic research of *S. aureus* in animals and humans
  - Need to understand *S. aureus* ecology not just MRSA
Ongoing studies

- Ecology of *S. aureus* on swine farms (NPB)
  - Intensive sampling of pigs on 2 farms
- Longitudinal study of *S. aureus* and MRSA colonization and infection in swine veterinarians
  - NIOSH (UMASH center)
  - 67 swine veterinarians
Pilot study of *S. aureus* ecology in pigs

- 2 farms: conventional (convenience)
  - 2 cohorts per farm
  - Sows – suckling – nursery – finishing
- Nose – tonsil – skin (axilla) – feces – (vagina)
- *S. aureus* prevalent in all anatomical sites
  - Nose, tonsil and skin highest (59 – 66%)
  - No MRSA detected
- Multiple spa types on both farms
  - Multiple spa types within pigs
*S. aureus* spa types (*n* = 537) in pigs on 2 farms in MN

- ST398: 197
- ST9: 153
- ST5: 27
- ST9: 17
- ST9: 13
- ST9: 8
- ST398: 3
- ST9: 2
- ST9: 1

90%
**S. aureus** colonization and infection in swine veterinarians

- Regularly exposed to varied swine populations
- Cross-sectional study for MRSA in 2008 (NPB)
- Longitudinal study 2012-2014 (NIOSH)
  - Nasal swabs collected monthly from 67 swine vets
  - Survey of pig contact and clinical infections
  - S. aureus and MRSA
Pilot study 2008: swine veterinarians

- 113 veterinarians (87 from USA, 26 international) and 37 students at AASV
- 8 individuals positive
  - 7 veterinarians, 1 student
- 5 of 8 isolates spa type $539/t034$ (ST398)
  - Three US vets from 3 states (2 Canadian)
- Other spa types:
  - $2/t_{\text{unknown}}$ (ST 5)
  - 7 (student), 963 (retired swine veterinarian)
**S. aureus** and MRSA in swine vets: 2012

- **US population**
  - SA: 30%  MRSA: 1.5%

- **Swine vets - July 2012:**
  - SA: 64.6  MRSA: 10.8%

- **Swine vets - August 2012:**
  - SA: 62.7  MRSA: 7.5%

- **Swine vets - September 2012:**
  - SA: 63.2%  MRSA: 10.3%

- Prevalence comparable to 2008 (P = 0.38)
Spa types in US swine veterinarians (Jul-Aug 2012)

65%
Summary – preliminary results

- Livestock associated *S. aureus*
  - Diverse and likely precede LA-MRSA
- Occupational exposure very common
  - Most transient contamination
  - Possibly permanent colonization in some people
  - Awaiting information on infection risk!
- Major LA-MRSA variants (ST398, ST9, ST5)
  - MSSA variants possibly widespread in pigs in the USA
  - MRSA variants appear less common