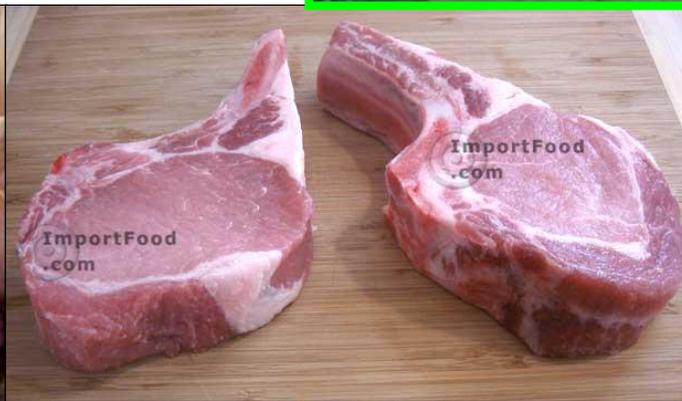
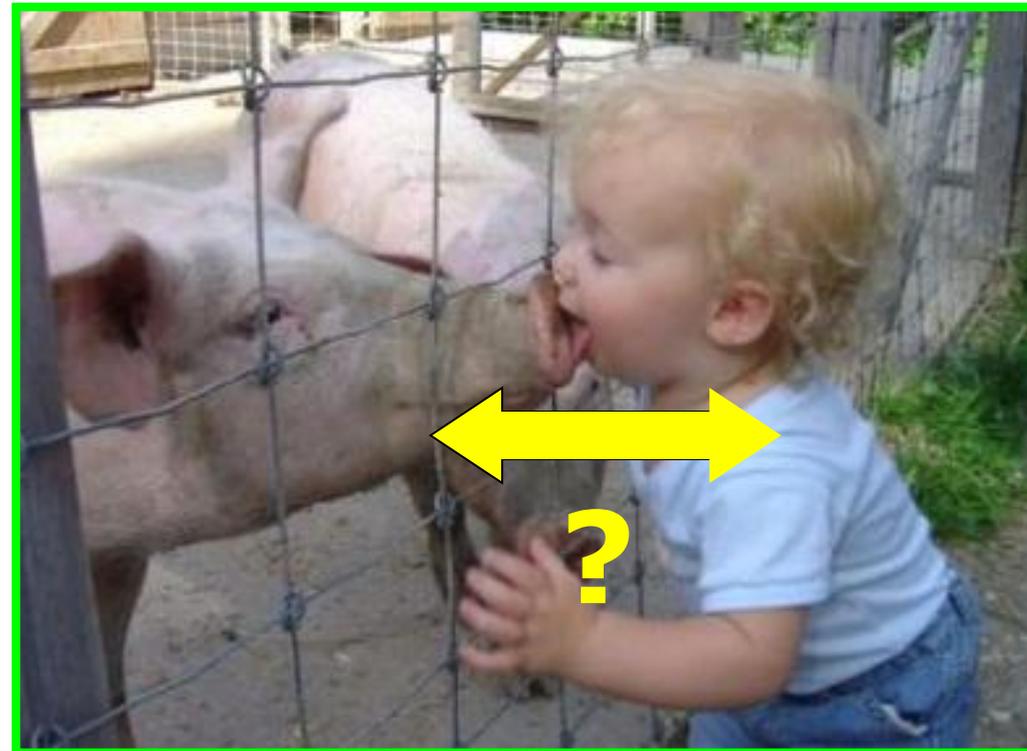
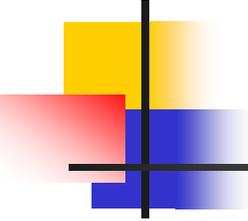


Emergence of Livestock Associated MRSA

*Occupational and public
health consequences*

Peter Davies BVSc, PhD
University of Minnesota



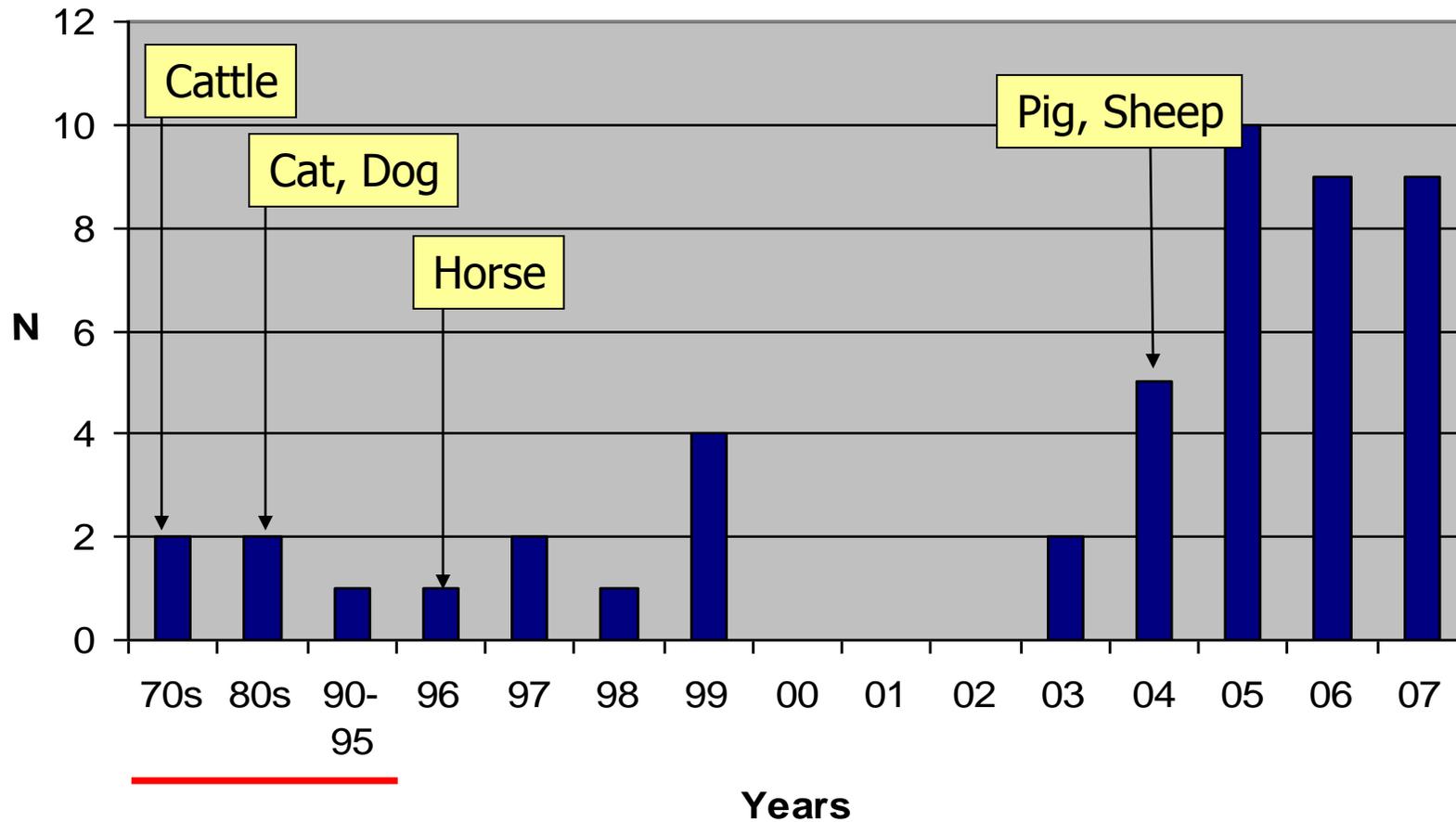


Methicillin resistant *S. aureus* (MRSA)

'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

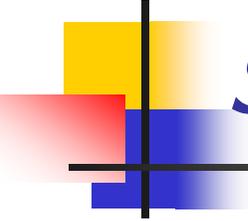


2010
>50

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*mec* typing (I – X)
- Spa typing
 - Ridom
 - egenomics

'Livestock associated'

Sma1 Untypable

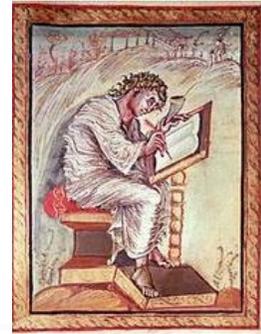
ST398 (CC398)

III, IV, V

t034, t011, t108.....

539,

Matthew 7:7 - "Seek and ye shall find"



MRSA in market hogs (de Neeling et al, 2006)

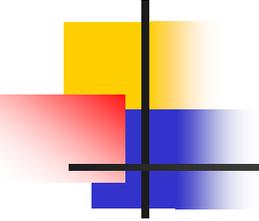
- National survey of slaughter pigs in Holland
 - 39% of 540 pigs positive (nasal swabs)
- All isolates a 'single clonal group'
 - Nontypable (NT) by sma1 PFGE
 - MLST: ST 398
 - 3 closely related spa types predominant (t011, t108, t1254,...)
- Uniformly resistant to tetracycline
 - Use of tetracyclines may be selecting for MRSA?

Matthew 7:7 - "Seek and ye shall find"



Colonization of farm workers

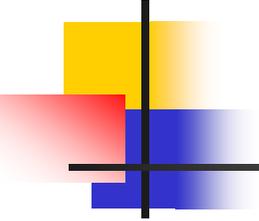
- ST398 also isolated from pig farmers (*Voss et al 2005*)
 - 23% of farmers positive on nasal swab
 - 760x general population prevalence
- Dutch health authorities changed MRSA screening procedures
 - People exposed to pigs and calves considered high risk
 - Isolated and screened before hospital admission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



MRSA in livestock: An epidemic waiting to happen?

(Wulf and Voss, 2008)

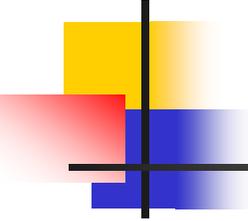
- Not just a “Dutch” problem
- May become an important source of community acquired MRSA
- Epidemiology different to ‘classic MRSA strains’
- Inter-human spread is possible
- Probably ‘just a matter of time until an outbreak’



ST398 (livestock associated) MRSA

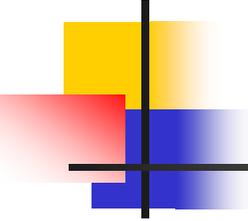
Generally accepted facts

- 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. \simeq 0.5 - 2% in population)
 - Mainly LA-MRSA
- Negligible risk of exposure in other groups



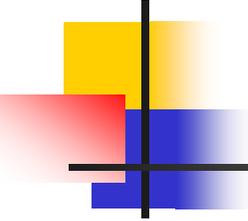
Livestock Associated MRSA

- 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..



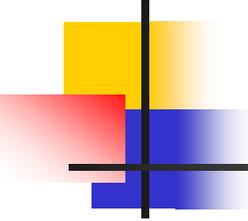
Occupational exposure!

- 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

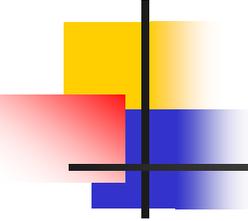
- Research workers (short term exposure) *van Cleef et al (2011)*
 - 33 of 199 exposures led to positive culture on farm
 - Only 1 of 33 retested positive after 24 hours
- Evidence suggests most short term exposure leads to short term 'colonization'
 - But farmers are regularly exposed
- Veal farmers in Holland *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

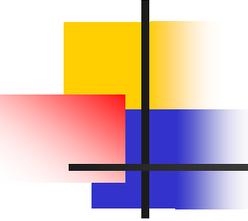
- Studies of transmission in Dutch hospitals (*Bootsma, 2010*)
 - ST398 is 5.9 times less transmissible than non-ST398 MRSA in Dutch hospitals'
 - 'Spreading capacity per admission insufficient to lead to an epidemic'
- 'Nosocomial transmission of ST398 MRSA is 72% less likely than non-ST398 MRSA strains'

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'

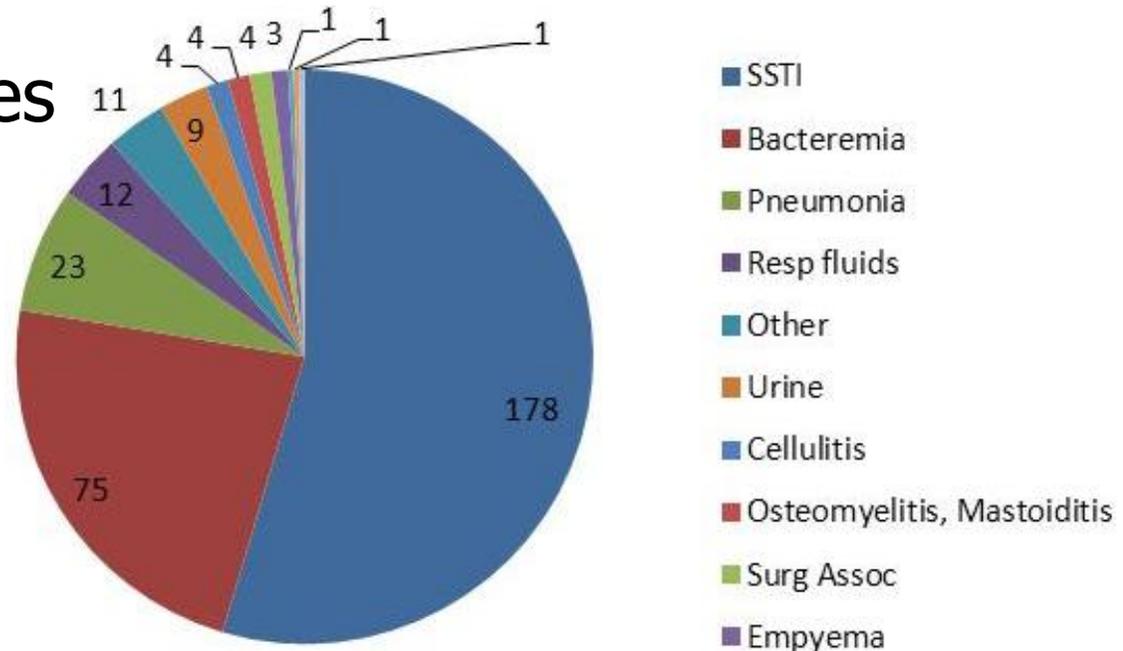
- 5 fatal

- 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)

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

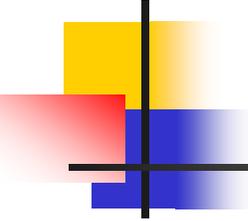
*Only data from 9 national or regional laboratories in the 7 countries that reported clinical isolates and typed all these isolates were included.

Geographic distribution of *S. aureus* causing invasive infections in Europe

Grundmann et al 2010

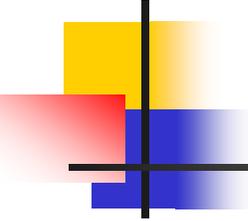


- 357 laboratories serving 450 hospitals in 26 countries (2006-2007)
 - 2,890 MSSA and MRSA isolates from invasive infections
- ST 398 spa types (t011, t034, t571, t1255, and t2383) identified on 12 occasions
 - None harbored the mecA gene.
- **No cases** of ST398 MRSA invasive disease



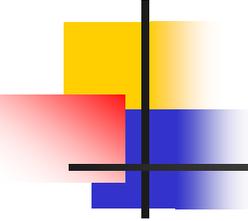
DANMAP 2009 - 2011

- 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)



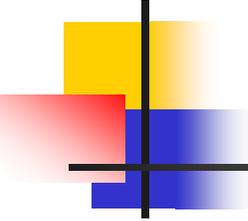
ST398 genomic studies and virulence

- > 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



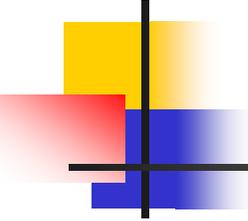
ST398 genomic studies and virulence

- 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?



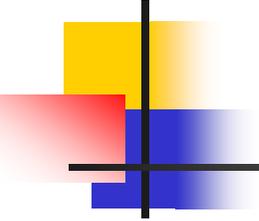
Public health risk of ST398 MRSA

- 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)

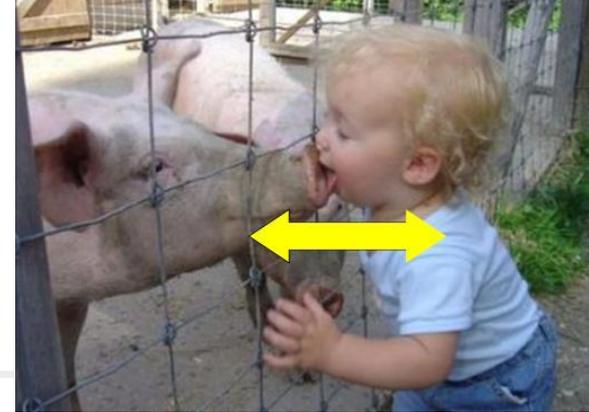
■ Observations

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

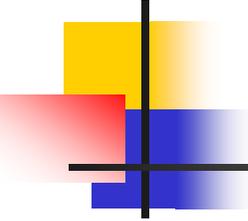
■ Inference

- “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



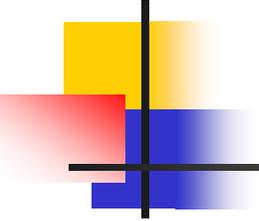
- ‘.. concern because strains ST398 strains were able to acquire PVL genes’
Rasigade et al (2010)
- But....
 - Livestock strains almost uniformly tetracycline resistant and PVL negative
 - Spa type t571 uncommon in animal isolates
- Could adaptation of ST398 to livestock hosts include loss of human virulence factors?
- Could some ST398 variants persist in people without any role of livestock?



More of the story

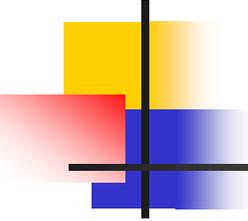
Davies P.R. et al, EID June 2011

- **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



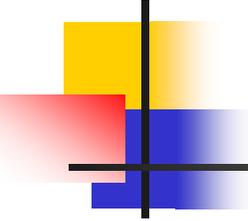
'Animal independent' ST398 clinical infections in NY city (Uhlemann et al, 2012)

- 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”



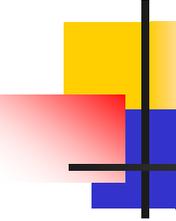
Understanding of LA-MRSA and ST398 *S. aureus* is embryonic

- 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

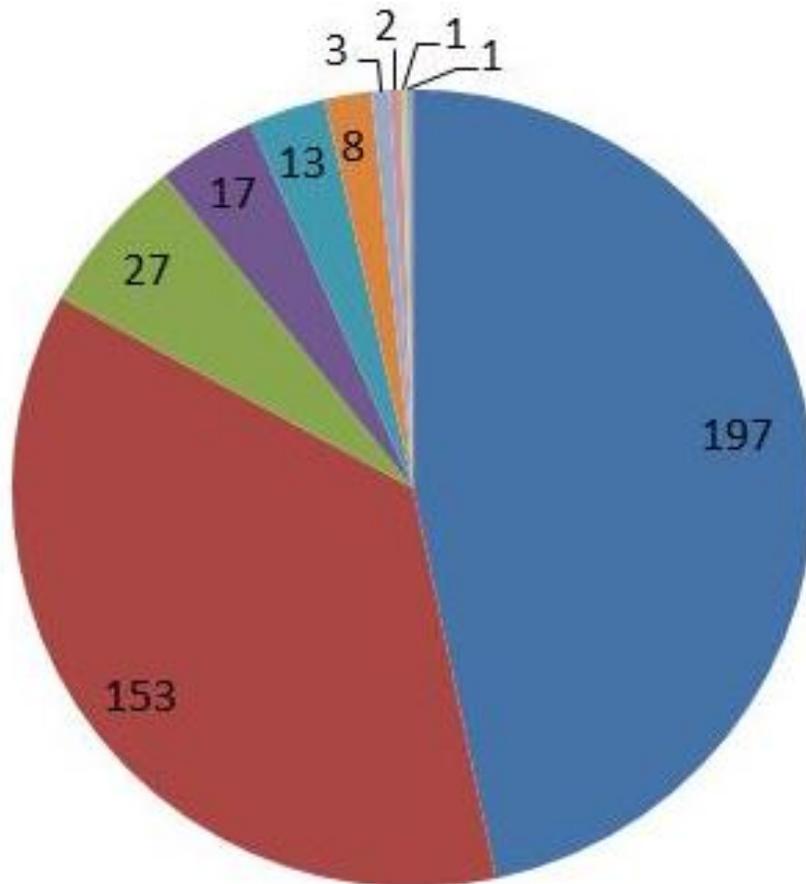
- Ecology of *S. aureus* on swine farms (NPB)
 - Intensive sampling of pigs on 2 farms
- Longitudinal study of *S. aureus* and MRSA colonization and infection in swine veterinarians
 - NIOSH (UMASH center)
 - 67 swine veterinarians



Pilot study of *S. aureus* ecology in pigs

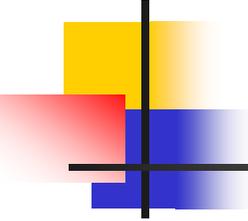
- 2 farms: conventional (convenience)
 - 2 cohorts per farm
 - Sows – suckling – nursery – finishing
- Nose – tonsil – skin (axilla) – feces – (vagina)
- *S. aureus* prevalent in all anatomical sites
 - Nose, tonsil and skin highest (59 – 66%)
 - No MRSA detected
- Multiple spa types on both farms
 -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

S. aureus spa types (n = 537) in pigs on 2 farms in MN



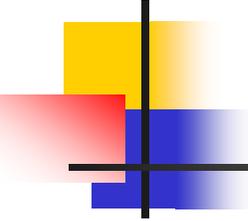
90%

539/t034	ST398
1435/t337	ST9
2/tunk	ST5
new/t3446	ST9
new/t2462	
109/t571	ST398
1064/t1255	
new/t5883	ST9
17/t216	
new/new	



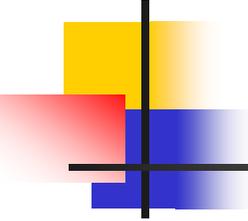
S. aureus colonization and infection in swine veterinarians

- 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

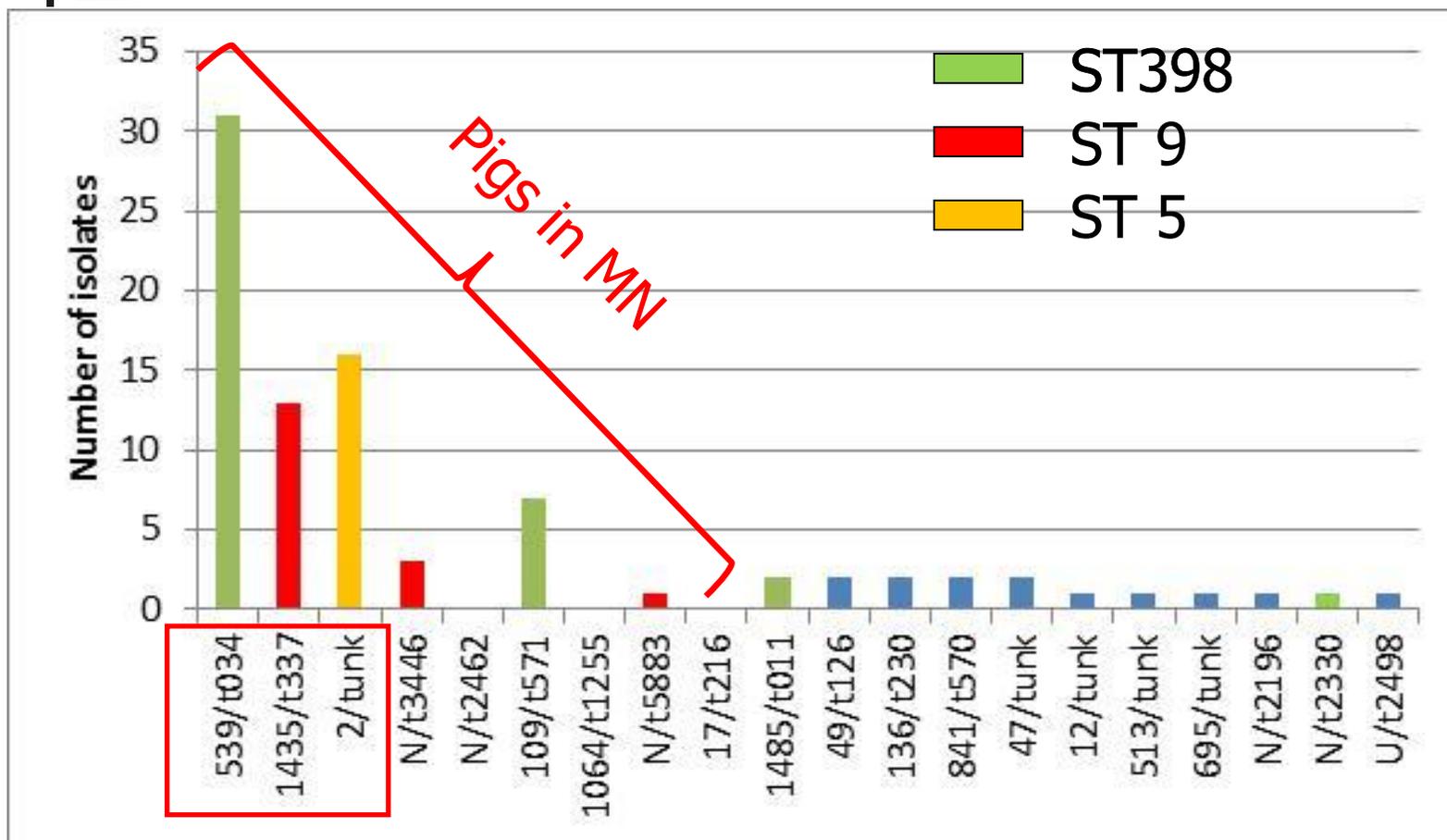
- 113 veterinarians (87 from USA, 26 international) and 37 students at AASV
- 8 individuals positive
 - 7 veterinarians, 1 student
- 5 of 8 isolates spa type **539/t034 (ST398)**
 - Three US vets from 3 states (2 Canadian)
- Other spa types:
 - **2/t_{unknown}** (ST 5)
 - 7 (student), 963 (retired swine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



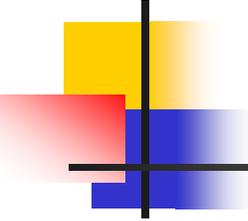
S. aureus and MRSA in swine vets: 2012

- 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