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MRSA
clinical perspective

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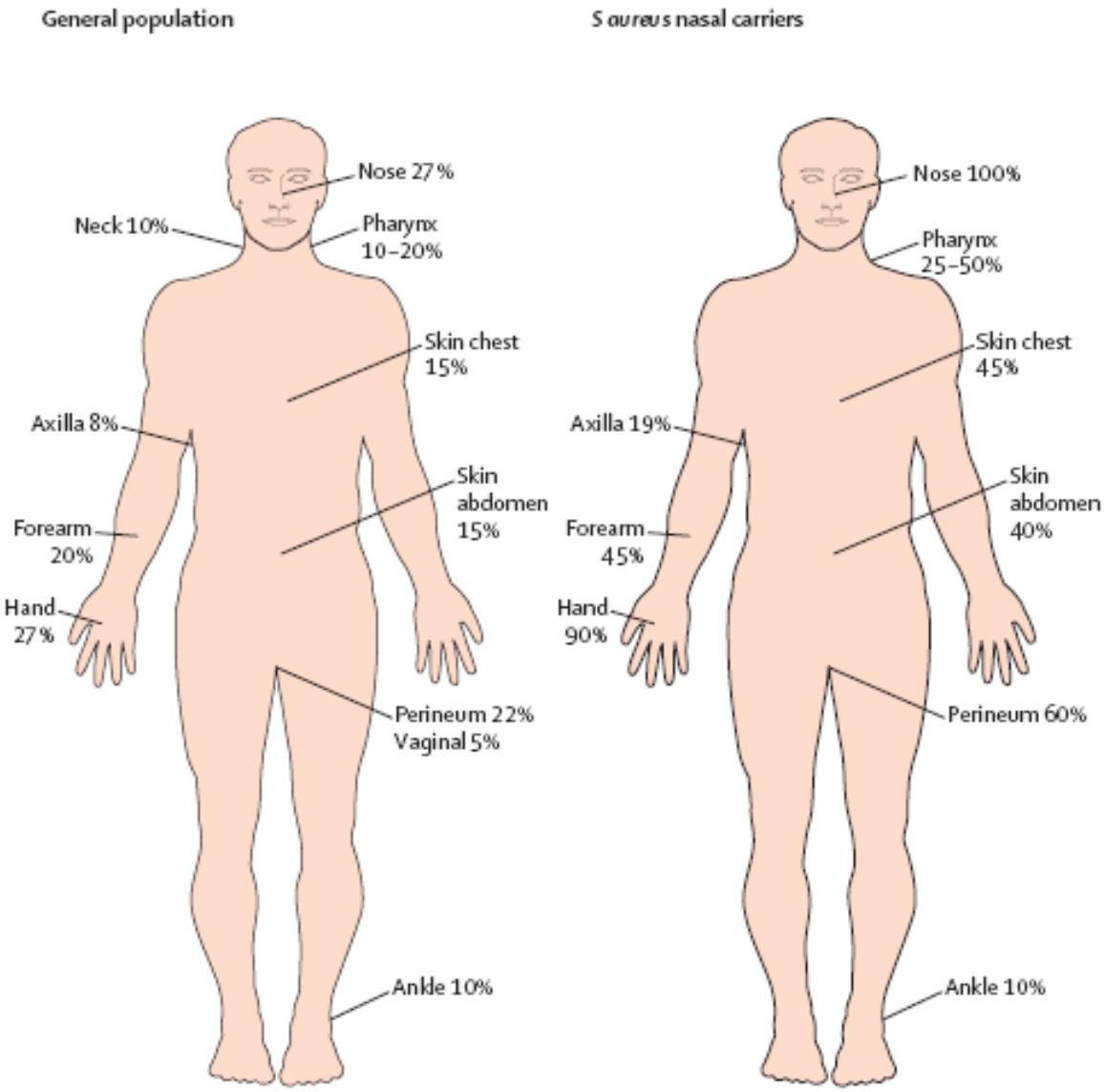
S. aureus

- *S. aureus* is one of the most common causes of human infections
- Presence
  - ubiquitary
    - *Staphylococcus aureus* is a normal inhabitant of the skin and mucous membranes in the nose of healthy humans
    - *S. aureus* also colonize animals
    - Can survive on surfaces and dust for months

Colonization

- Frequence of carriage
  - ~20 % permanent
  - ~ 30 % intermittent
  - ~ 50 % never

Colonization - where



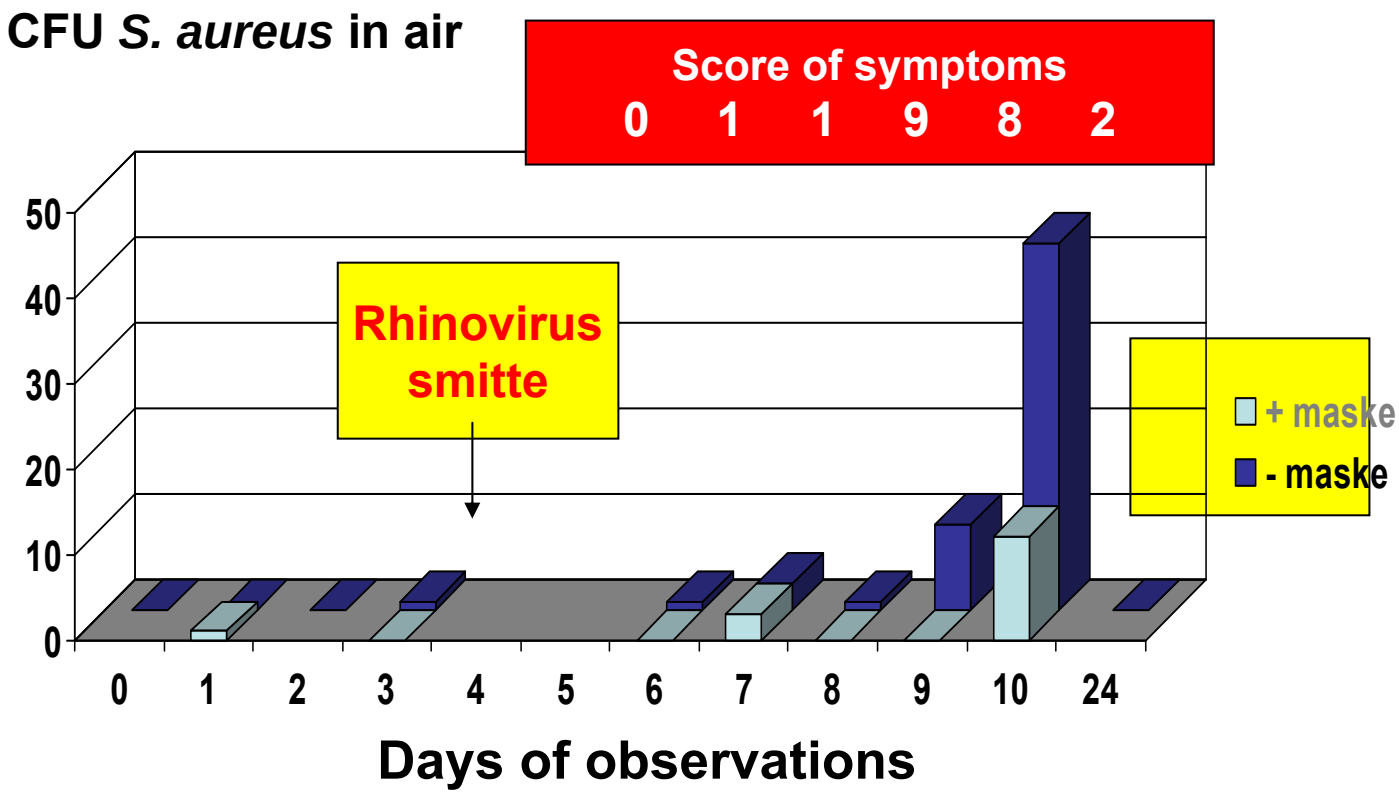
Wertheim, Lancet Inf Dis, 2005, 5, 751

Transmission

- Direct or indirect contact
  - Primarily HANDS!
- Prevention of transmission
  - Wash fingers!
    - Obs juvels especially rings
  - gloves

- (Droplet borne)

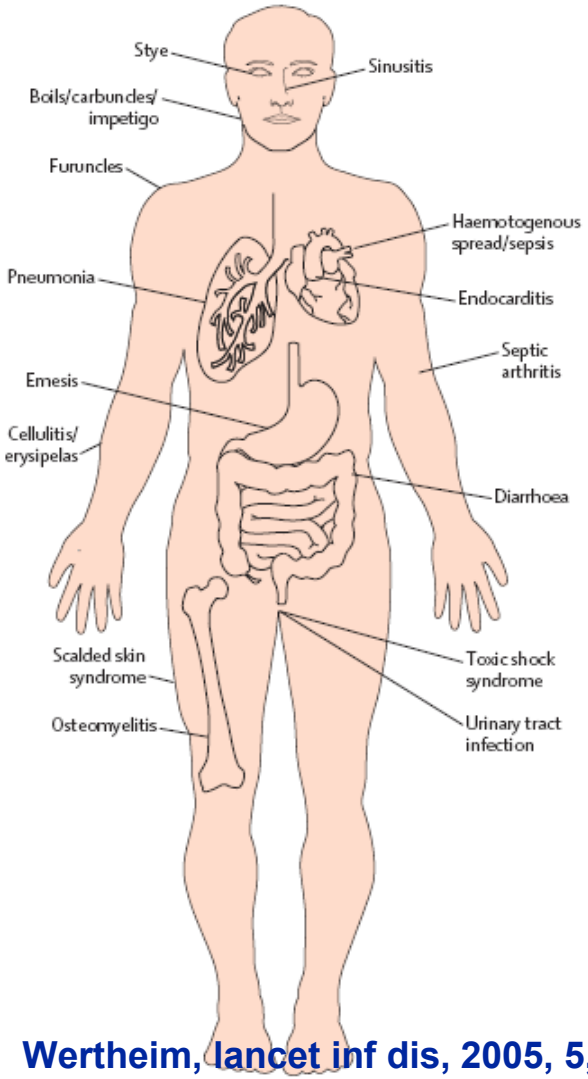
Common cold can make a carrier a transmitter!



Sherertz et al. Ann Intern Med 1996;124:539-47

Infections

- Skin and soft tissue
  - Impetigo, foruncolosis (abscesses), breast infections, **Wound infections**
- Invasive diseases
  - IV- cath. infections, pneumonia, bacteremia, endocarditis, osteomyelitis, meningitis (especially as a complication to neurosurgery)
- Toxic diseases
  - Toxic shock syndrome
  - Food poisoning



Wertheim, lancet inf dis, 2005, 5, 751

Patogeneses

- *S. aureus has a wide range of pathogenic factors*
  - Adhesins
    - MSCRAMMs (microbial surface components recognizing adhesion matrix molecules)
      - Protein A, fibrinogen- and collagen binding proteins
  - Virulence factors
    - Toxins
      - TSST, eta,etb, enterotoxins, PVL
    - Hemolysins

      $\alpha, \beta, \delta, \gamma$
    - Extracellular enzymes
      - Coagulase, proteases, lipases, hyeleronidase

From colonization to infection

- Intact skin / mucus membranes are very effective barriers against infections with *S. aureus*!!
  - wounds
  - Virus infections ie. in the respiratory tract

- **CAN lead to infection**

Infection

- Source
  - Colonizing strain
    - 80% (42-100%) is caused by the strain colonizing the person prior to the infection

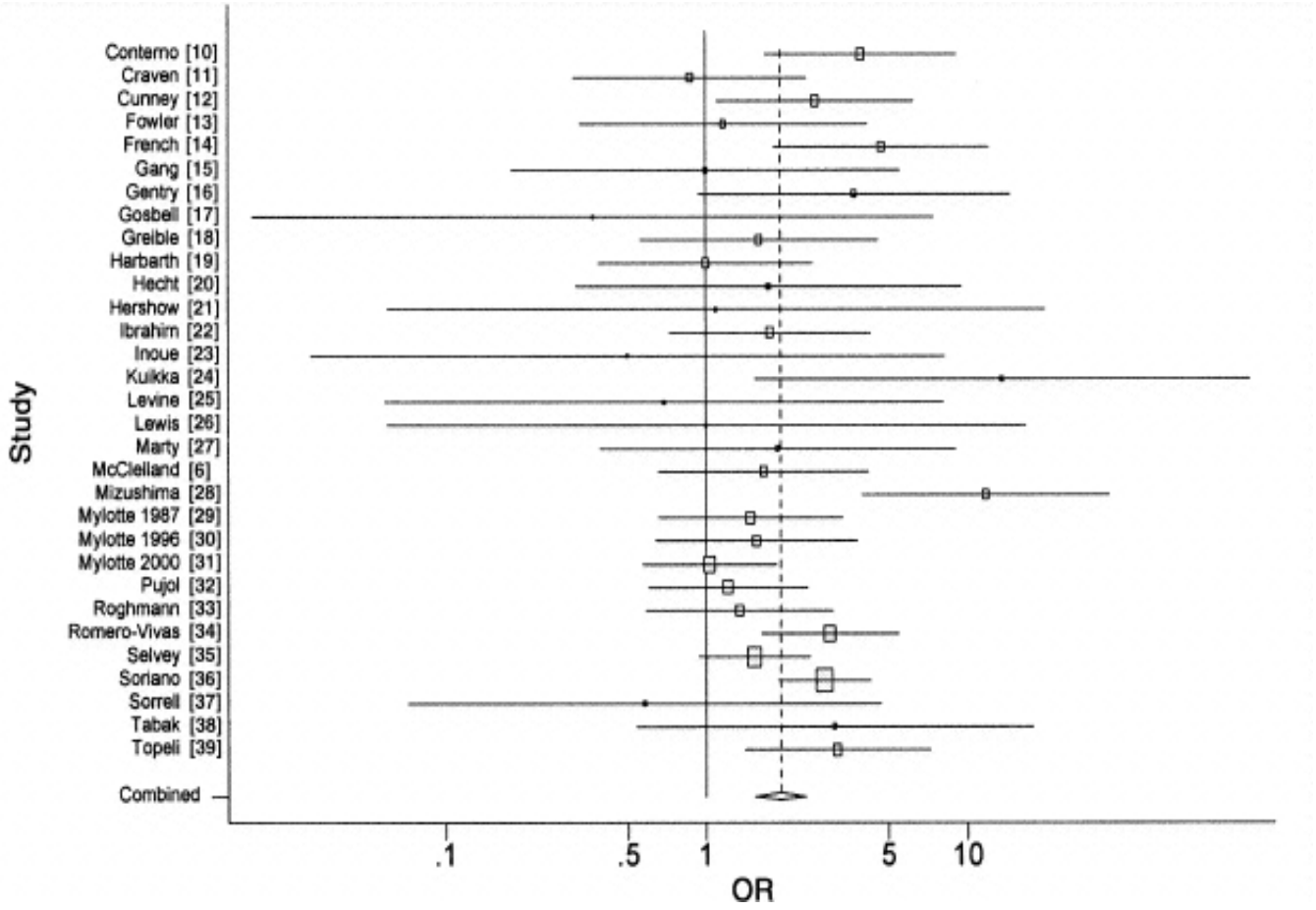
Wertheim, Lancet Inf Dis, 2005, 5, 751

  - Transmission
    - Patient to patient
    - Personnel to patient
    - Patient to personnel

Why is MRSA a problem I

- MRSA is resistant to the most potent group of anti – staphylococcal antibiotics
  - i.e. β-lactam antibiotics
- Often resistant to other classes of antibiotics too
- MRSA infections have increased morbidity and mortality

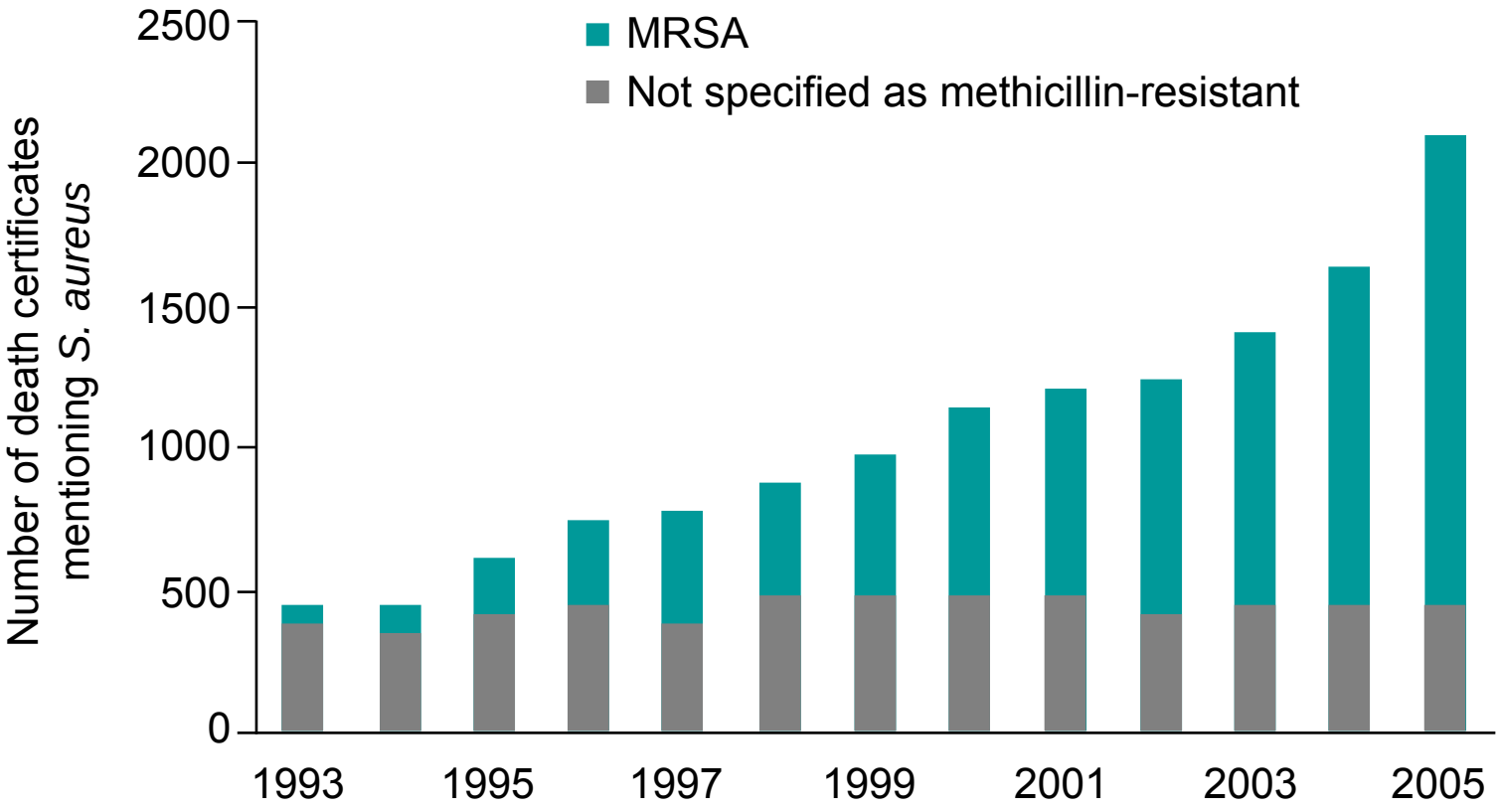
Mortality of bacteremia caused by MRSA as compared to MSSA



OR: 1,93; 95% CI: 1,54 – 2,42

Cosgrove, CID 2003;36:53-59

Mortality related to MRSA and MSSA in England and Wales



National Statistics Online (available at http://www.statistics.gov.uk/CCI/nugget.asp?ID=1067; accessed 20 August 2008)

Why is MRSA a problem II

- MRSA infections are more expensive to treat
  - Infections vs no infections
    - All infections (Wernitz, CMI, 2005,466)
      - Prolonged stay in hospitals (14-28 days)
      - Additional costs (5000 - 29000 €)
  - Compared to MSSA infections
    - Bacteremia – (Cosgrove, ICHE,2005,166)
      - Prolonged stay in hospitals 2 days
      - Additional costs 7000 $
  - Prolonged rehabilitation

Why is MRSA a problem III

- Anti-MRSA antibiotics has to be administered empirically
  - Increased use of antibiotics will inevitably lead to increased resistance not only in staphylococci but also in other species.
    - Vancomycin resistant enterococci (VRE)
    - Vancomycin resistant MRSA
      - VISA (GISA)
      - VRSA (vanA positive)
        - » 9 isolates in USA

Heteroresistance

- **All** MRSA colonies have the *mecA* gene **but** the level of expression of the *mecA* is highly variable
  - **Heteroresistance**
  - Causes considerable problems when performing susceptibility testing

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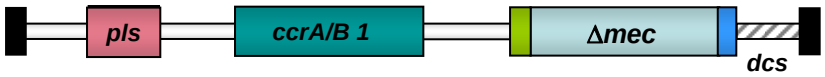
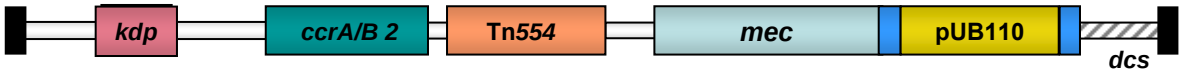
Evolution of MRSA

MRSA - Evolution

- 1. MRSA ”wave”
  - Almost monoclonal -
    - Archaic klon (ST250; CC 8; SCC*mec* I)
- 2. MRSA ”wave”
  - Acquisition of the *mecA* gene both in new cassettes and in new MSSA strains (rare event)
  - *SCCmec* I+ II + III
    - Dominated by few clones (CC8, CC5)
    - Hospital associated MRSA



SCC*mec* Type I (34 kb)



SCC*mec* Type II (52 kb)

SCC*mec* Type III (66 kb)

MRSA - Evolution

- 3. MRSA ”wave” – part 1
  - Acquisition of the new smaller SCC*mec* IV
    - New hospital associated MRSA clones (i.e. CC 22, CC 30, CC 45)
    - Transfer of SCC*mec* IV to CC 5 and CC8

SCC*mec* Type IV (20-24 kb)

- >90% of hospital acquired MRSA world wide belongs to only 5 clonal complexes
  - (CC 5, CC8, CC 22, CC 30, CC 45)

MRSA Evolution

- 3. MRSA ”wave” – part 2
  - Acquisition of the SCC*mec* IV into completely different lineages which can multiply and spread outside the hospital environment

Community acquired MRSA

  - 5 large lineages with CA-MRSA
    - CC 1, 8, 30, 59 and CC 80
- 4. MRSA “wave”
  - LA-MRSA
    - CC398

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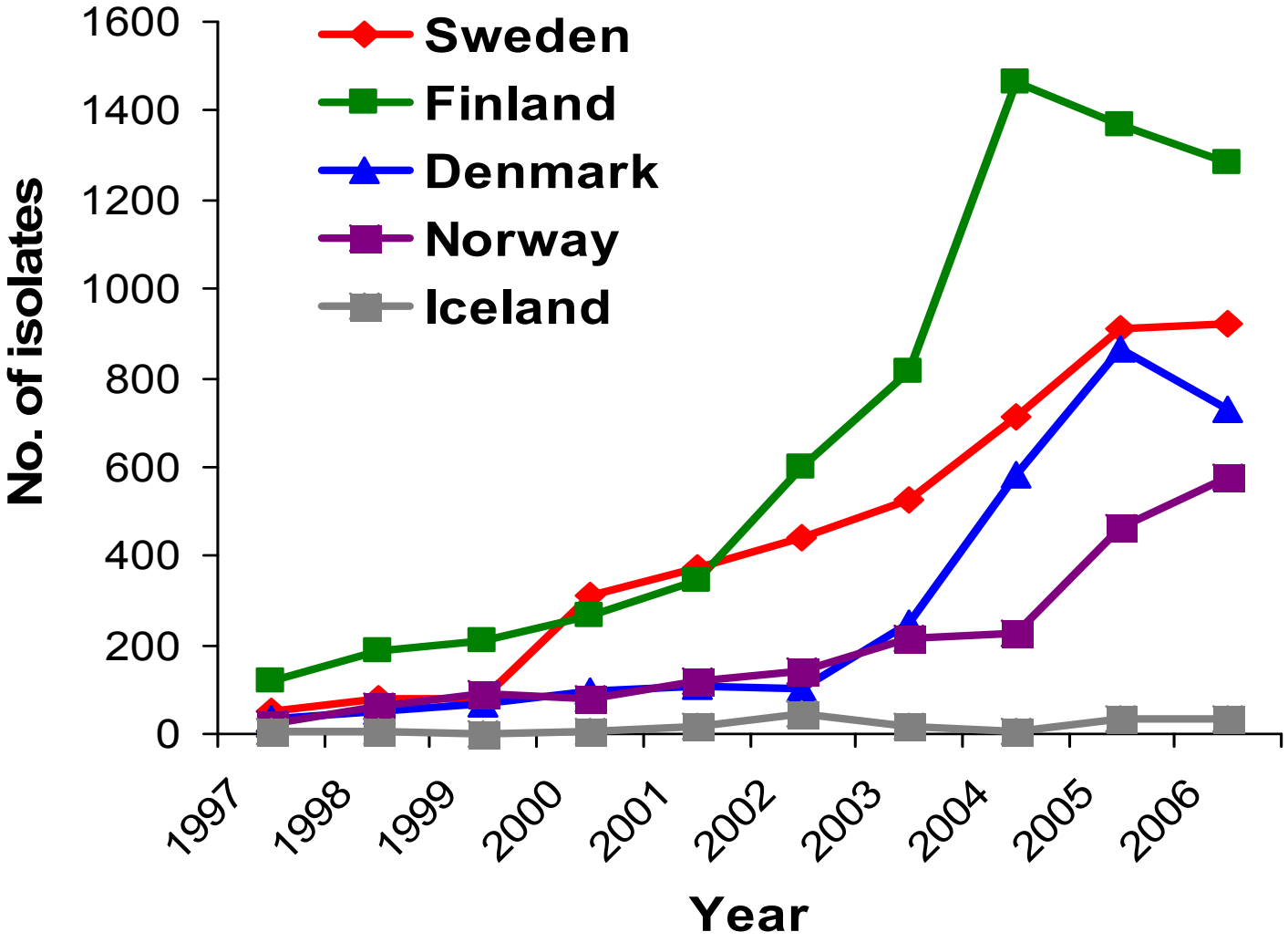
Epidemiology has changed

MRSA in the Nordic countries



SSAC MRSA WP
http://www.srga.org/SSAC/doc/2005/SSAC_MRSAreport_2004.pdf

Risk factors for MRSA

Traditional risk factors for nosocomial MRSA infection[1,2]

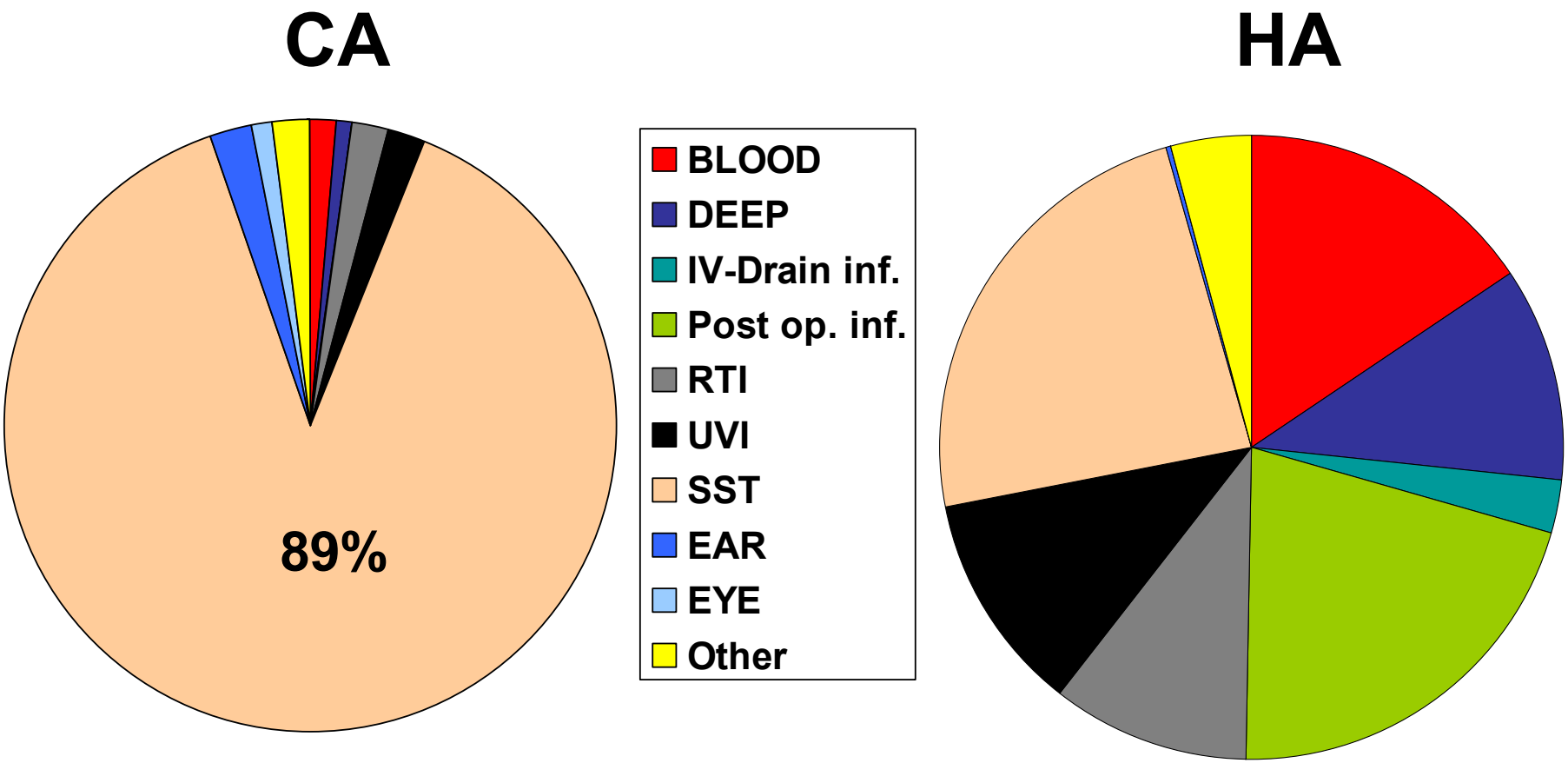
- Previous hospital stay
- Prolonged length of stay prior to infection
- Surgical procedure(s)
- Enteral feeding
- Previous antibiotic use
- Central venous catheter insertion

Risk factors for community-acquired (CA) MRSA[3]

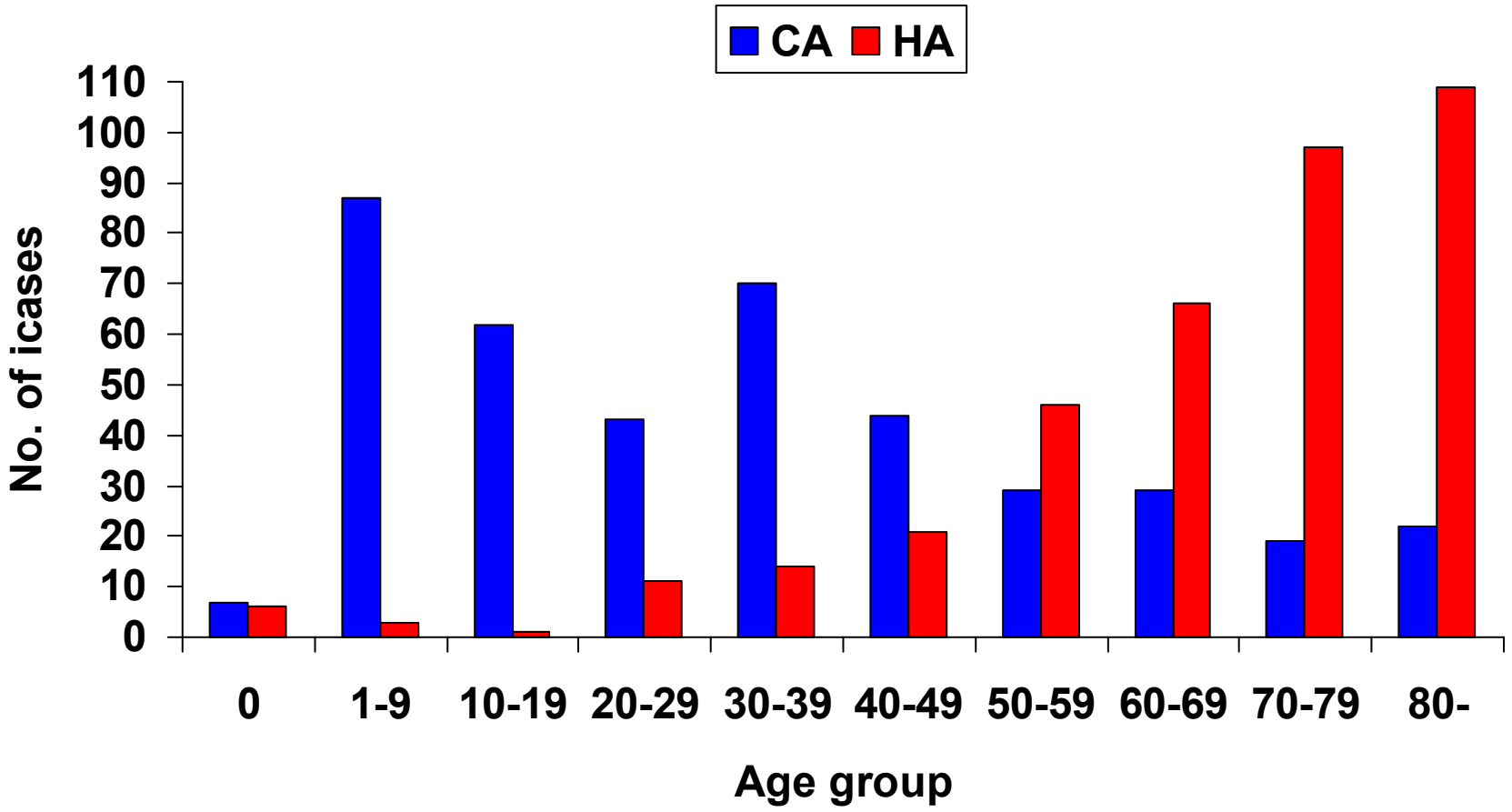
- History of colonization/infection with CA-MRSA
- Close contact with person colonized/infected with CA-MRSA
- Participation in contact sports
- Injection drug use
- Living in correctional facilities, residential homes or shelters
- Military personnel
- Men who have sex with men
- Adults ≥65 years; children <2 years
- Concurrent SSTI; recent influenza-like illness and/or severe pneumonia

1. Graffunder E, Venezia R. *J Antimicrob Chemother* 2002;49:999–1005
2. Oztoprak N *et al. Am J Infect Control* 2006;34:1–5
3. Boucher HW, Corey GR. *Clin Infect Dis* 2008;46:S344–S349

Type of infection



Infections vs age groups

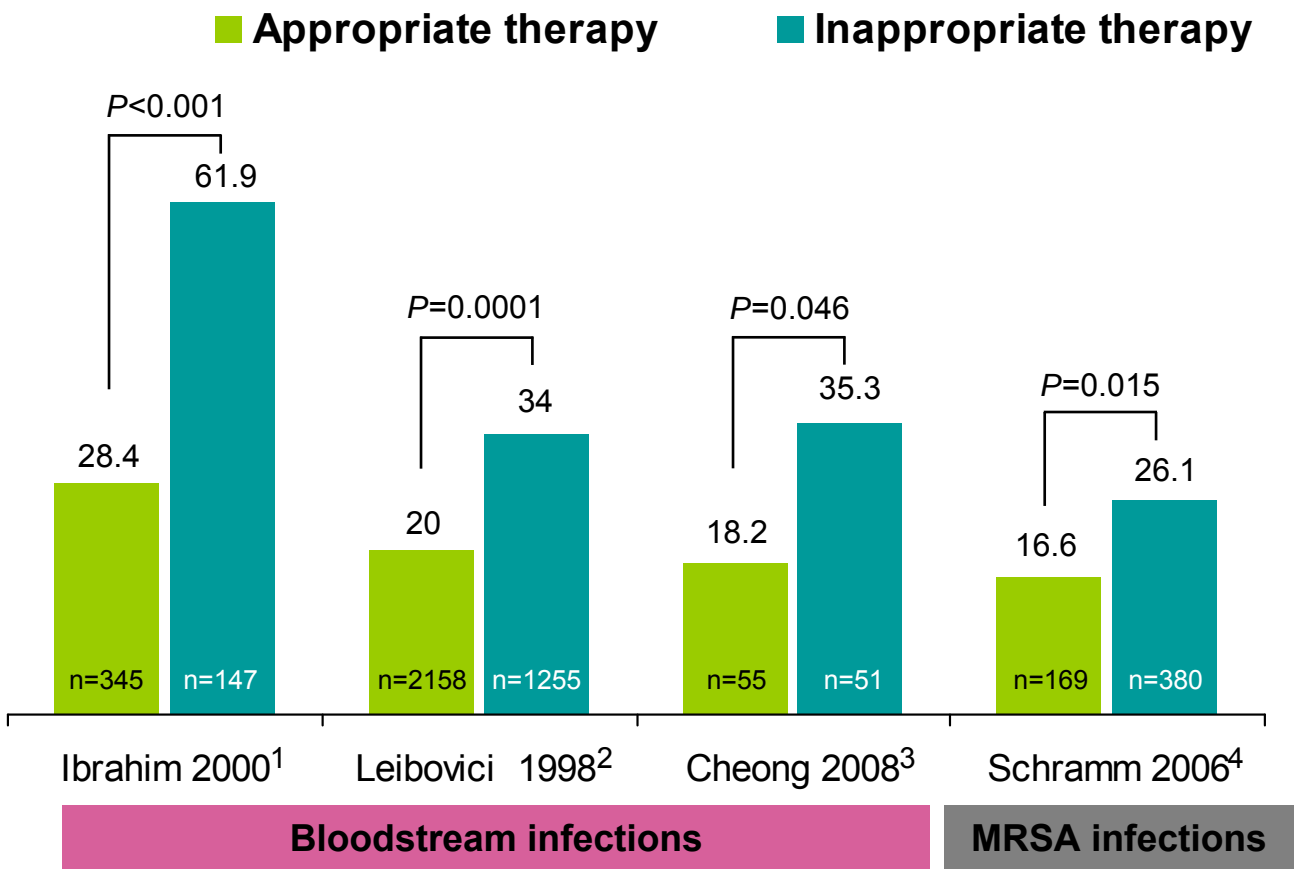


Optimal empiric therapy

- The most appropriate empiric regimen for clinically suspected *S. aureus* infection is determined by the likelihood that MRSA is the cause,[1] based on:
  - Local prevalence of MRSA
  - Patient's history of MRSA carriage or infection
  - Other risk factors for MRSA infection
- Appropriate initial antibiotic therapy is a vital factor in determining outcome[2,3]
  - Risk of mortality decreases when appropriate therapy is initiated quickly

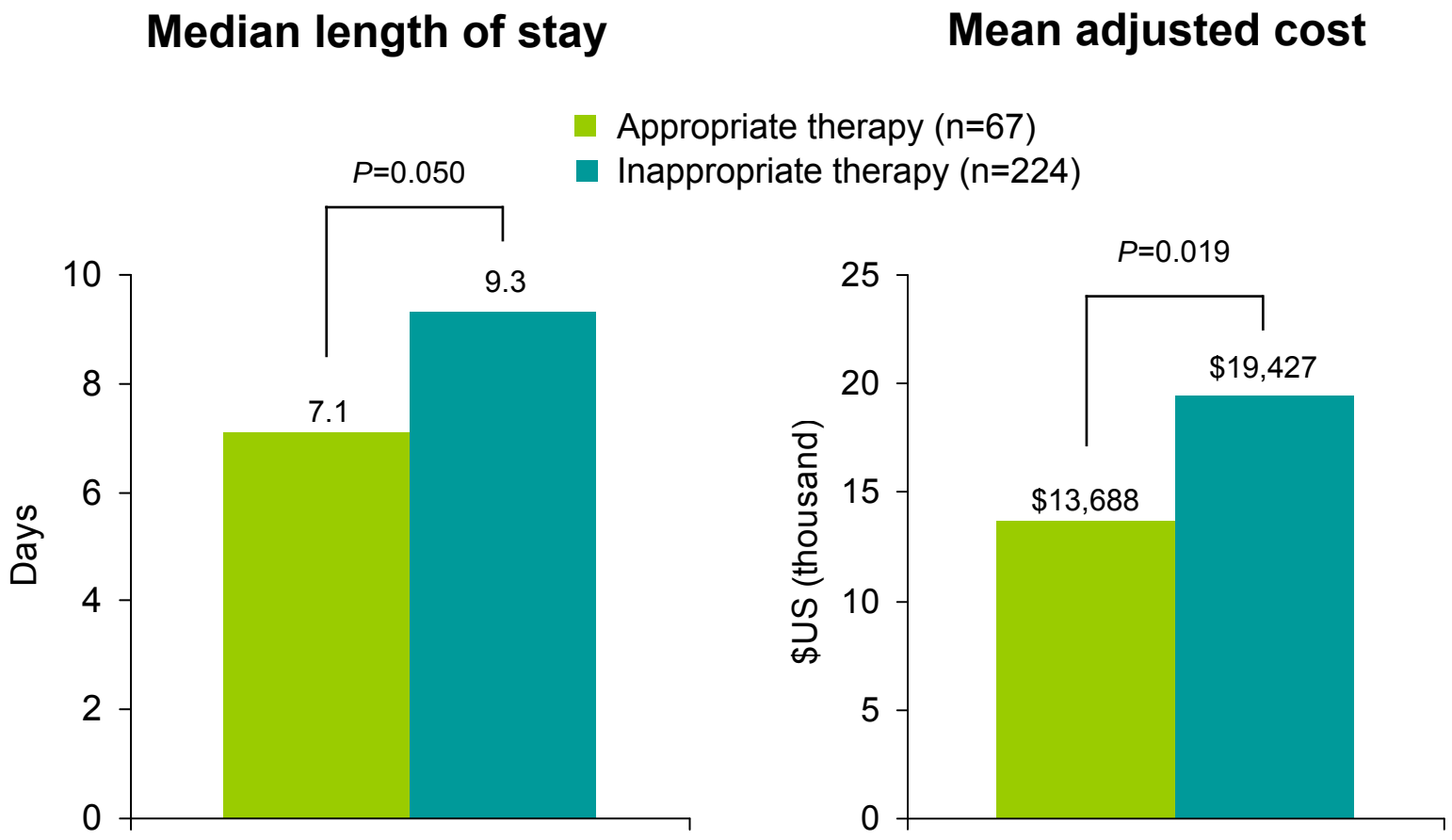
1. Mitchell DH, Howden BP. *Intern Med J* 2005;35:S17–S24
2. Ibrahim E *et al*. *Chest* 2000;118:146–155
3. Lodise T *et al. Clin Infect Dis* 2003;36:1418–1423

Inappropriate antibiotic therapy increases mortality rates by up to two-fold



1. Ibrahim E *et al*. *Chest* 2000;118:146–155
2. Leibovici L *et al*. *J Intern Med* 1998;244:379–386
3. Cheong HS *et al. Eur J Clin Microbiol Infect Dis* 2008; Epub ahead of print
4. Schramm GE *et al. Crit Care Med* 2006;34:2069–2074

Resource utilization and cost implications of inappropriate therapy



Data from a single hospital in the US (Jan 2002 to Dec 2004)

Shorr AF *et al*. *Crit Care Med* 2008;36:2335–2340

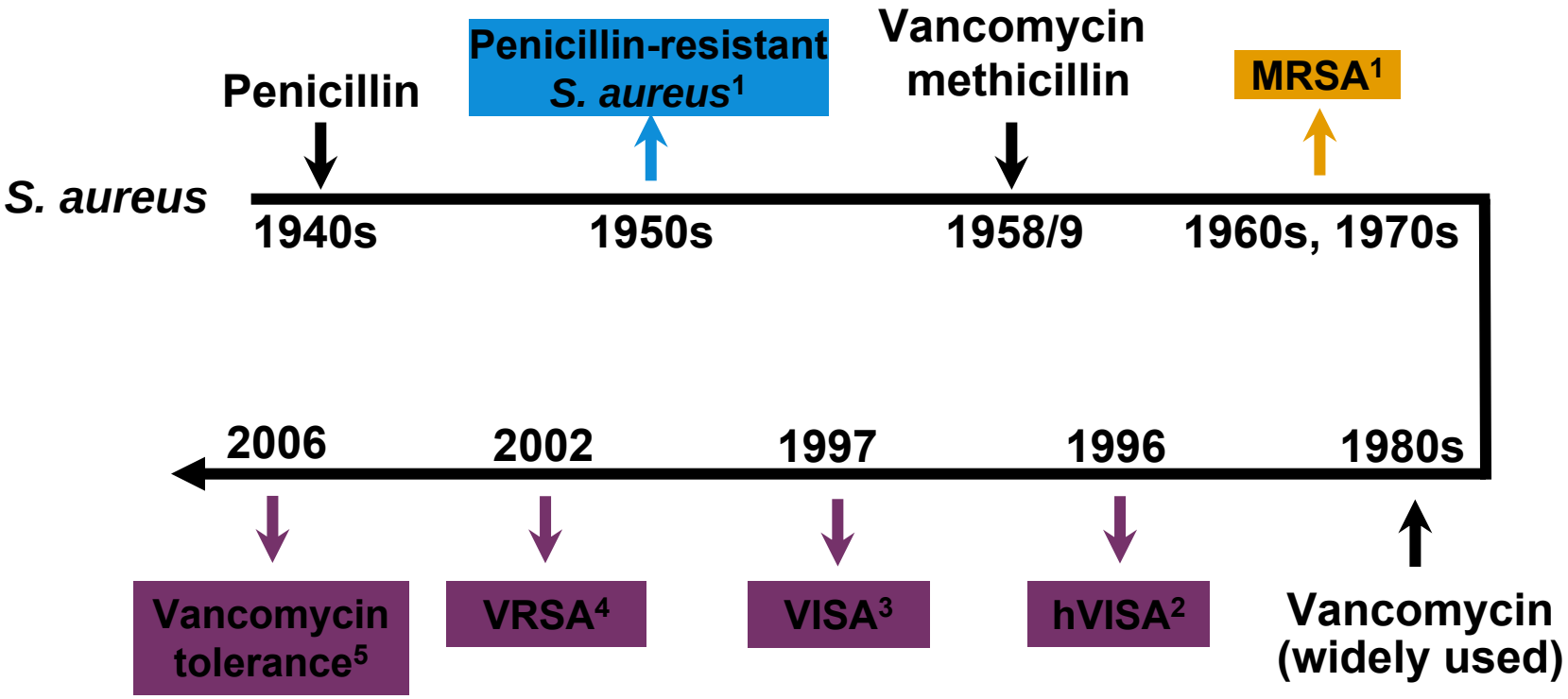
CO-MRSA bacteraemia

- CO-MRSA bacteraemia* is frequent
  - 61% of SAB cases were community onset in a recent large multicentre investigation from Australia and New Zealand[1]
    - 18% were MRSA
    - 27% of all MRSA cases had a typical CA-MRSA susceptibility profile
  - 24% of MRSA bacteraemia patients consulting a Taiwanese emergency department[2]
  - 39.7% in a multicentre study of invasive MRSA clones in France in 2006–2007[3]

*Community-onset infection: present on admission or diagnosed within the first 72 hours following admission[4]

1. Liao C-H *et al*. *Int J Antimicrob Agents* 2008; Epub ahead of print
2. Turnidge JD. *J Med Austr*; submitted for publication
3. Dauwalder O et al. *J Clin Microbiol* 2008; Epub ahead of print
4. Johnson LB *et al. Infect Control Hosp Epidemiol* 2003;24:431–435

Evolution of drug resistance in *S. aureus*



1. Liñares J. *Clin Microbiol Infect* 2001;7(Suppl 4):8–15
2. Hiramatsu K *et al*. Lancet 1997;350:1670–1673
3. MMWR *Morb Mortal Wkly Rep* 1997;46:624–625
4. MMWR *Morb Mortal Wkly Rep* 2002;51:565–567
5. Jones R. *Clin Infect Dis* 2006;42:S13–S24

Emergence of VISA and hVISA

- Almost exclusively seen in MRSA[1]
  - VISA: MIC 2–4 µg/ml[1]
    - Approximately 100 cases reported[2]
  - hVISA: MIC in susceptible range (<2 µg/ml) but subpopulations have vancomycin MIC ≥4 µg/ml[1]
    - Reported prevalence amongst *S. aureus* strains varies[3]
      - Meta-analysis of 14 studies calculated a prevalence of 1.67%
- Resistance mechanism not fully elucidated, but is thought to involve capture of vancomycin in the cell wall[4]

1. CLSI. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. MIA-A7, 2006
2. Tacconelli E, Cataldo MA. *Expert Opin Pharmacother* 2007;8:2505–2518
3. Liu C, Chambers HF. *Antimicrob Agents Chemother* 2003;47:3040–3045
4. Cui L *et al. Antimicrob Agents Chemother* 2006;50:428–438

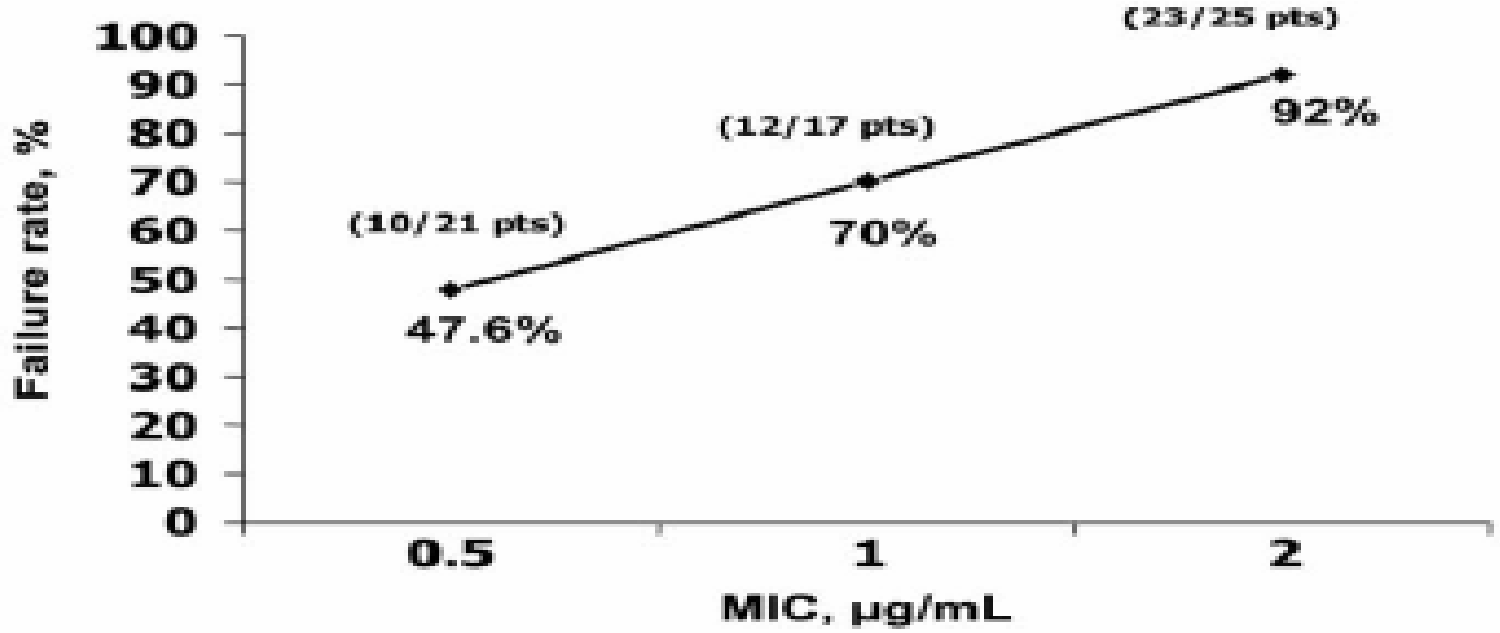
Emergence of VRSA

Date/ location	Strain	MIC (µg/ml)	Source	Previous exposure to vancomycin
Jun 2002; MI	USA100	1024	Catheter site and foot ulcer	6.5 weeks in previous 3 months
Sep 2002; PA	USA100	32	Foot ulcer	Sep 1997
Mar 2004; NY	USA800	64	Nephrostomy tube	Nov 2003
Feb 2005; MI	USA100	256	Foot ulcer	9 weeks in previous 3 months
Oct 2005; MI	USA100	512	Surgical site wound	8 weeks in previous 3 months
Dec 2005; MI	Not defined	1024	Foot ulcer	~10 years
Oct 2006; MI	USA100	512	Triceps wound	5 weeks in previous 3 months

MI, Michigan; PA, Pennsylvania; NY, New York

Sievert D *et al*. *Clin Infect Dis* 2008;46:668–673

Relationship of Vancomycin MIC to Clinical Failure Rates[a]



a. Moise-Broder et al. *Clin Infect Dis* 2004; 38: 1700-1705.

MRSA Treatment Options

- **FDA approved:**
  - Vancomycin
  - Linezolid
  - Daptomycin
  - Tigecycline
- **Other**
  - TMP/SMX
  - Clindamycin
  - Long-acting tetracyclines
  - Fusidic acid

- **Investigational agents:**
  - Telavancin
  - Dalbavancin
  - Oritavancin
  - Iclaprim
  - PBP-2a–targeted β-lactams (eg, ceftobiprole, ceftaroline)

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Bad Bugs, No Drugs

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

IDSA
Infectious Diseases Society of America

July 2004

Eradication treatment

- **Treatment principles:**
  - Eradication treatment was not commenced until infection was cleared and risk factors removed (if possible)
  - For community associated cases the whole household was treated simultaneously.
  - Topical treatment was first line treatment
    - mupirocin x3/day in the nares and chlorhexidine body and hair wash x1 daily for 5 days
  - Cleaning: Changing of towels and underwear daily, changing of linen and major cleaning of the environment was recommended on day 2 and 5
  - In case of failure, topical treatment was repeated with or without systemic antibiotics (two antibiotics, based on resistance pattern).
- Full follow up
  - ≥ 3 set of swabs; one at minimum 6 months after end of eradication treatment
- Success was defined as full follow up and continued negative at the 6 months control.

Urth, ISSSI 2008-P627

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Significance of an animal reservoir for human health

MRSA from pets and companion animals

- Even though the primary transmission route is from man to animal; animals do act as a reservoir for transmission back to humans
  - Ping pong transmission in families
  - Therapy/visiting pet dogs/cats
  - Veterinarians

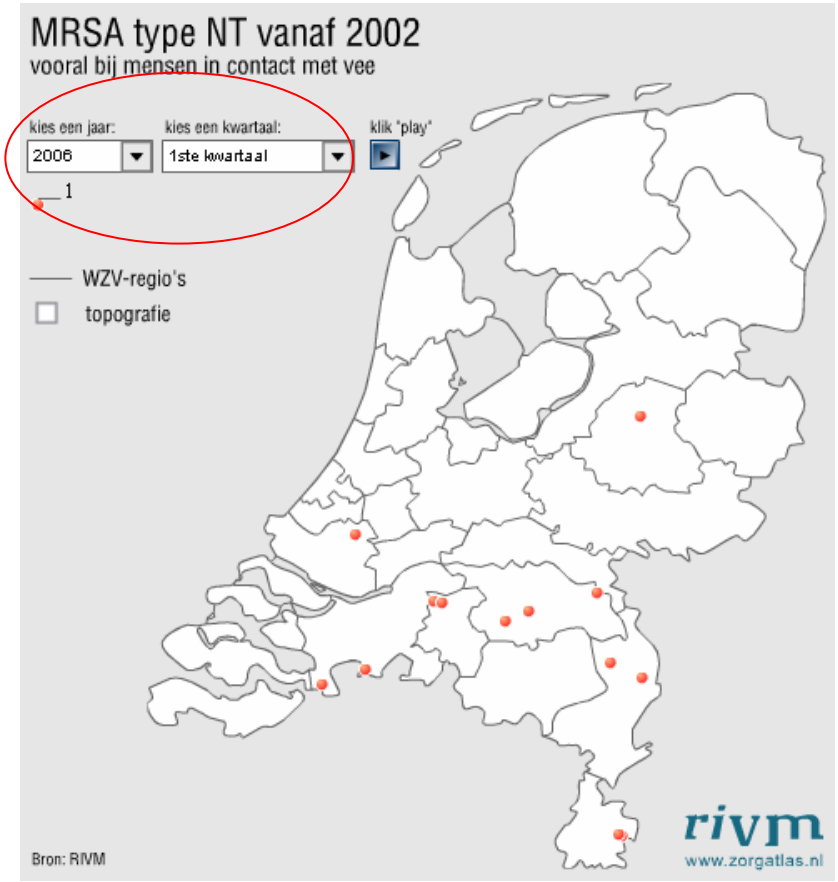
Manian, CID, 2003, 26; Enoch J Hosp Inf, 2004, 186; Loeffler, JAC, 2005, 692; Strommenger, JAC, 2006, 461; Moodley, JAC, 2006, 1118

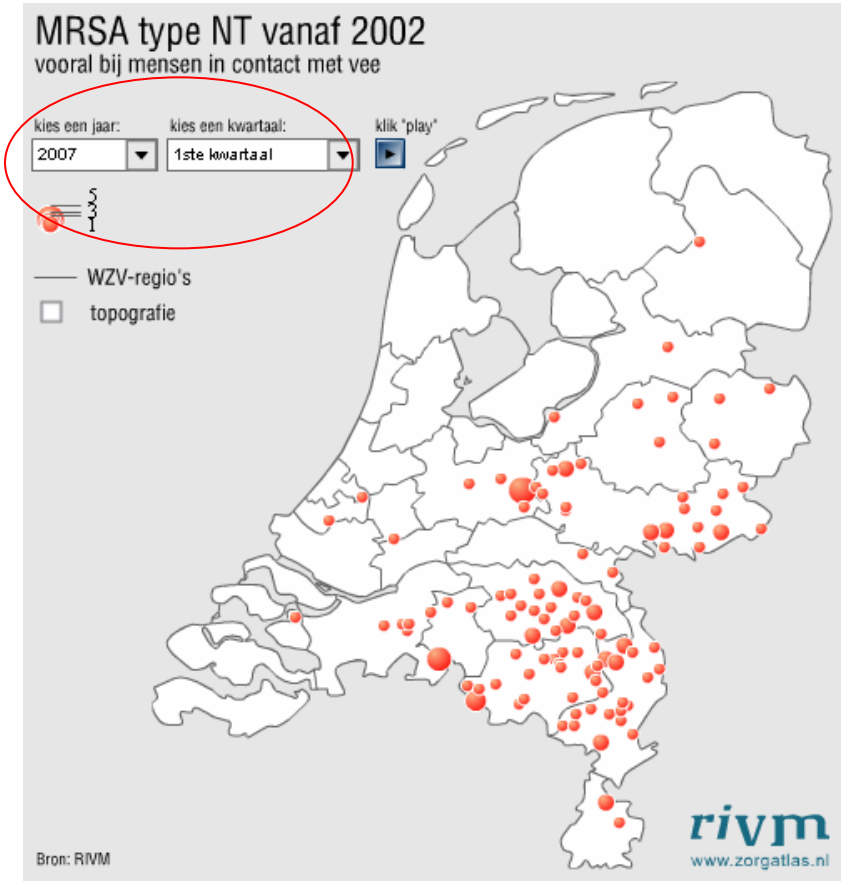
Risk of MRSA in contact with Production animals

- Farmers and families
  - Risk of carriage of MRSA in persons with direct contact to pigs and their households
    - 50 farms – 232 persons
      - 50 farmers, 13 employes
      - 169 household members
    - Intensive pig contact – 29%
      - Medium contact – 12%
      - Higher risks if contact with sows and finisher pigs
    - Living on a farm, but no direct contact – 2%
  - Slaughterhouse personnel – 1%
  - Animal Transport workers – 3-5%

Van Cleef, NVMM 2008

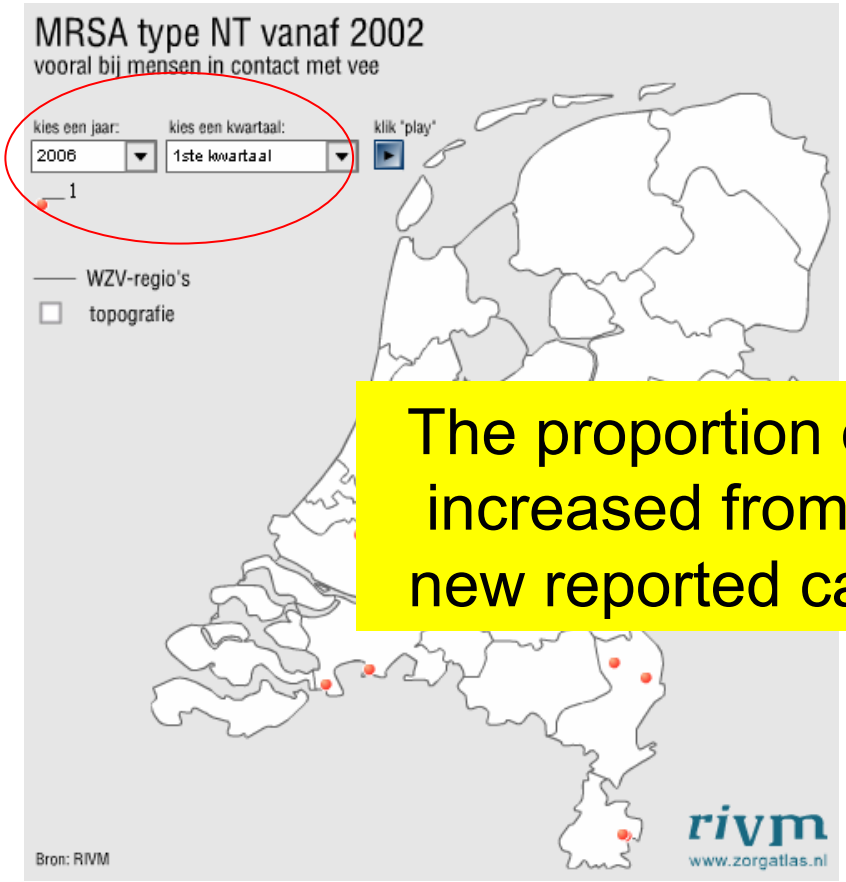
Development in the Netherlands

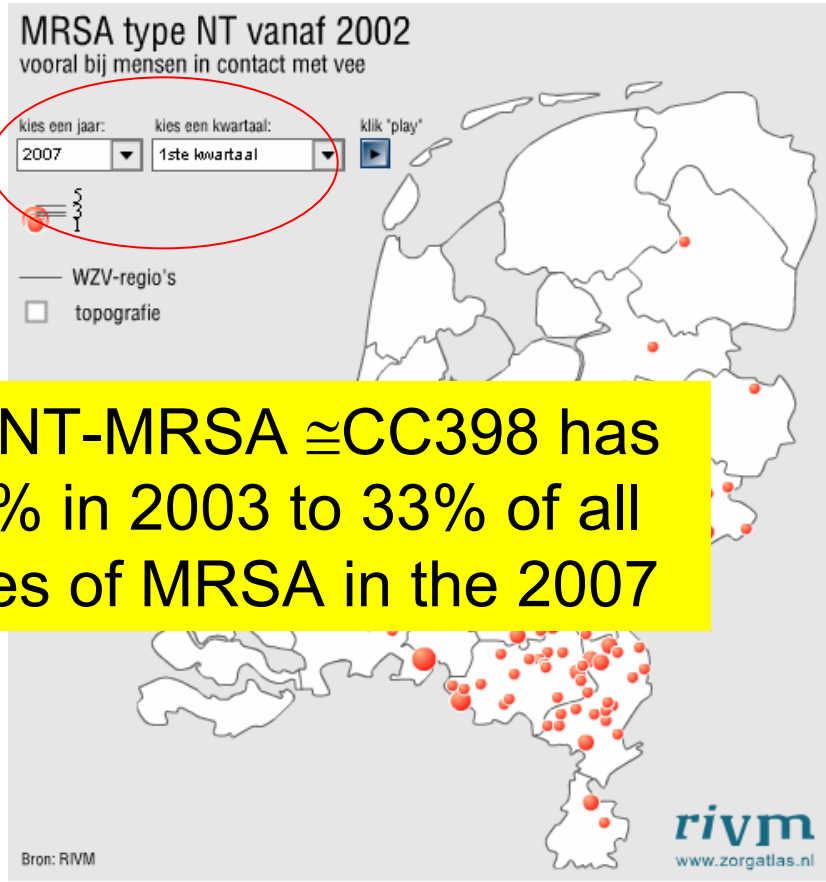




www.rivm.nl/vtv/object_mapo2168n21466.html

Development in the Netherlands





The proportion of NT-MRSA ≅CC398 has increased from 0% in 2003 to 33% of all new reported cases of MRSA in the 2007

www.rivm.nl/vtv/object_mapo2168n21466.html;
Voss, CMI, 2008, 519

Veterinarians – both production animals and small animals

- Veterinarians have proved in high risk of carriage of MRSA
  - At the IPVS conference in Copenhagen in 2007
    - 34/272 ~12.5% carried MRSA, 31 were ST398
  - The Netherlands
    - 7/142 veterinarians or -students ~ 4.6% (x150 the carriage rate in general population
  - Denmark
    - 9/674 veterinarians ~ 3.9%
  - UK
    - 20/274 equine veterinarians ~ 7.2%
    - 10 % of small animal practitioners
  - Canada
    - 26/257 equine veterinarians ~ 10.1%

Wulf, EID, 2006, 1939; Wulf, CMI, 2008, 29; Anderson, Vet microbiol, 2008, 410; Moodley, Scand J work Environ Health, 2008, 151.

General population
no known animal contact

- Reports are emerging
  - Denmark
    - Single cases/ families
      - 2 households with adopted children form China, PVL positve
  - Sweden
    - 2 cases, PVL positive
  - Scotland
    - 3 cases (P743-ISSSI 2008)
  - China
    - Survey for PVL positive MRSA among invasive diseases
      - 5 cases of ST398

Lewis, EID, 2008 Epub; Welinder-Olsson, EID, 2008, 1271; Yu, CMI, 2008,381

Clinical infections

- Give the same kind of infections as other MRSA i.e. resembles the picture of CA-MRSA
  - Majority is SSTI
    - 50% of cases in the Danish case control investigation had SSTI
  - Invasive infections are also reported
    - Bacteremia, Endocarditis, VAP, multiorgan failure
      - In fact it is not possible to publish clinical cases as case reports anymore

Lewis, EID, 2008, Epub; Ekkelkamp, Nedj Tijdschr Geneeskd, 2006, 2442; Witte EID, 2007, 255

CC398 and healthcare

- Outbreak at a Dutch hospital
  - 5 patients and 5 HCW found positive
  - One HCW lived on the grounds of a pigfarm but had no direct contact to the animals
- HCW in contact with pigs or field calves
  - MRSA Carriage rate of 1.7%
  - (0.15% in control group)

Wulf, Eurosuveillance, 2008, issue 9;
Wulf, J Hosp inf, 2008, Epub.

Conclusions of a survey for MRSA in meat in Holland

- MRSA was found in 2 out of 79 samples of meat
  - 1 CC398
  - 1 USA300 (ST8)
- *S. aureus* is frequently present in meat, usually in low amounts
  - 43% of samples
- Within butcheries and supermarkets there is a high clonal relationship between *S. aureus* strains indicating cross-contamination within the shop

Data from provided by Jan Kluytmans

MRSA on retail meat in Netherlands 2007

meat type	# sampled	# (%) mrsa positive
- turkey	83	26 (31)
- chicken (NL)	143	39 (27)
- veal	119	20 (17)
- pig	192	20 (10)
- cow	218	21 (10)
- lamb/sheep	161	9 (6)
- other fowl	95	4 (4)
- wild life	132	4 (3)
- chicken (import)	150	2 (1)
total	**1293**	**145 (11)***

*, < 10 cfu/g, 84% was ST 398

Unpublished data, Courtesy Henri Verbrugh on the behalf of SOM

Conclusion

- In pets and companion animals MRSA primarily seems to be a humaniosis
  - Do not presently seem to be of larger significance for the public in general
  - Nevertheless, they can act as reservoir for transmission/retransmission to humans
- The CC398, however, appear to be an "animal" *S. aureus* – and the reservoir could be infinite
  - Seems to colonize a variety of animal species
  - CC398 seems to have an extraordinary genetic diversity!

Conclusions

- Colonize and infect persons with close direct contact to the animals
  - The reservoir of MRSA in humans increases
  - Elimination of carriage in persons with daily animal contact is futile
  - Although clinical cases due to CC398 still is rare, the number of cases continues to increase
    - Includes cases of severe disease
    - May (will?) have consequence for choice of emperic treatment in the future

Conclusions

- Colonize and infect persons with close direct contact to the animals
  - The reservoir of MRSA in humans increases
  - Elimination of carriage in persons with daily animal contact is futile
  - Although clinical cases due to CC398 still is rare, the number of cases continues to increase
    - Includes cases of severe disease
    - May (will?) have consequence for choice of emperic treatment
- Pool for transmission of SCC*mec* to hitherto susceptible lineages