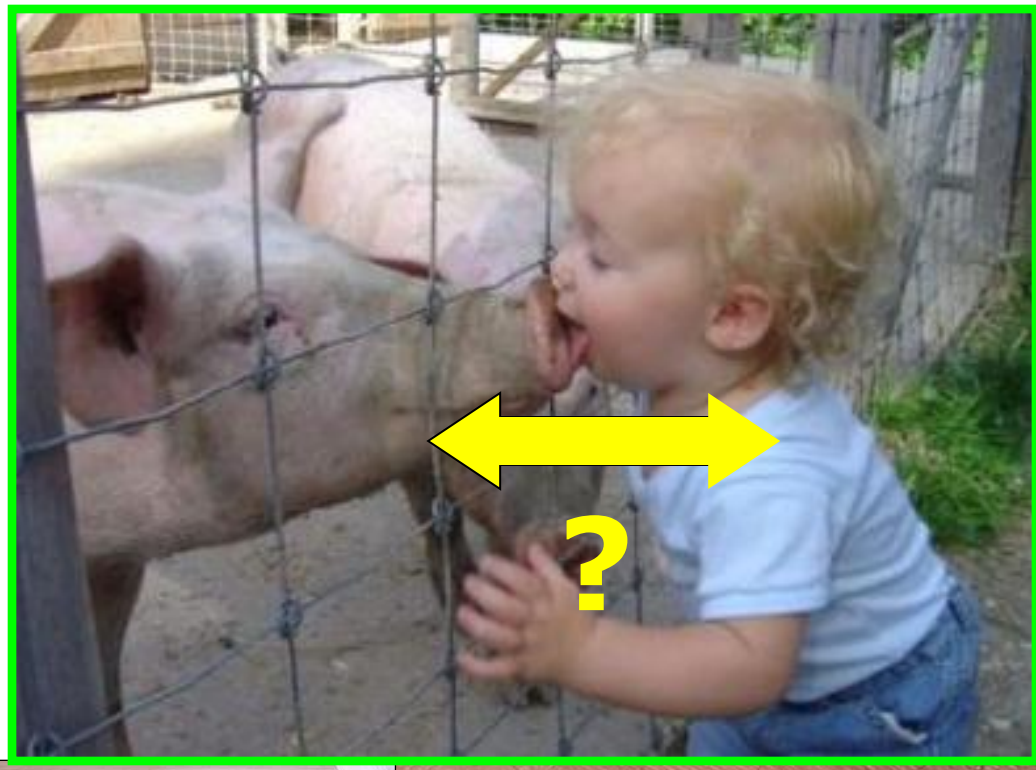
Livestock Associated MRSA

What is the appropriate level of concern?



Peter Davies BVSc, PhD
University of Minnesota

Questions: LA-MRSA

- What are the human health implications?
- Why/how did it emerge?
- What should be done about it?

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)
  - 81% (44 of 54) of farms positive
- All isolates a 'single clonal group'
  - MLST: ST 398
  - 3 closely related spa types
- Uniformly resistant to tetracycline
  - Use of tetracyclines may be selecting for MRSA?

MRSA in market hogs and swine veterinarians in the USA

(Funded by National Pork Board)

- MRSA prevalence in swine veterinarians
  - 150 attendees at 2008 AASV meeting
  - 5 of 8 isolates spa type t034
- MRSA prevalence in market hogs
  - 539 hogs from 45 herds (9 plants)
    - All pigs negative at 3 plants
  - 25% prevalence (pigs)
    - Diverse spa types and variability among plants
    - t034 spa type most common
    - Cross-contamination in lairage?

Multi-state study (IA-MN-OH)

(Funded by National Pork Board)

- 45 farms
  - 18 IA-IL (9 ABF – 9 conventional)
  - 18 MN (9 ABF – 9 conventional)
  - 9 OH-NC (3 ABF – 6 conventional)
- All 21 ABF farms negative
- 4 of 24 (16%) conventional farms positive
- All in IA – why?

EFSA farm prevalence study (dust samples)

Variability among countries – why?

MRSA from slaughter-age pigs in Canada

Weese et al. BMC Vet Res. 2011 7:41

Province	Herds	Herd prevalence
A	10	0
B	5	0
C	10	30% (3/10)
D	13	7.7% (1/13)
E	8	25% (2/8)

Variability among provinces?

Or uncertainty?

MSSA isolates in MN

- 92 isolates of MSSA characterized in MN pigs
  - PCR negative for mecA gene
  - Clustered on 4 farms (3 conv., 1 ABF)
- 65 (71%) of pig isolates were spa type t034
  - 1 isolate from human
- Need further characterization
  - Phenotypic and genotypic
  - *mec*A variants?

What are the risks?

- To whom?
- How?
- How often?
- How severe?

OP-ED COLUMNIST

Our Pigs, Our Food, Our Health

Nicholas D. Kristof/The New York Times

One of the many industrial hog farms outside Camden, Ind.

By NICHOLAS D. KRISTOF
Published: March 11, 2009

CAMDEN, Ind.

TWITTER
LINKEDIN

MISINFORM-ATION

PROFILE

Maryn McKenna

Maryn McKenna is

31 JULY 2010

Newsbreak: "Pig MRSA" ST398 involved in the death of a child?

Community dissemination of MRSA ST398

Cuny et al (2009)

- Study of German farming community where MRSA ST398 prevalent on pig farms
- Nasal swabs from
  - Pig farmers and family members
  - Swine vets and family members
  - 462 pupils (10 to 16 yo) in villages in the high density pig farming area

Nasal colonization with ST 398

Cuny et al (2009)

Group	N	Pct Pos
Pig farmers	113	86%
Farmer family members	116	4.3%
Swine Veterinarians	18	45%
Vet family members	44	9%
Schoolchildren*	462	0.007% (3)

***All 3 positive children lived on pig farms**

Communities in pig dense areas in Holland

(van Cleef 2010)

- 3 municipalities in Netherlands where livestock MRSA prevalent
- Adults completed questionnaire and nose swab (n = 583)
  - One of 534 persons without livestock-contact positive (0.2%)
  - 13 of 49 of farm residents/workers positive (26.5%)
- Conclusions:
  - High prevalence of livestock-associated MRSA in people with direct contact with farm animals.
  - Not spread into the wider community

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
  - Infection risk
  - Transmission 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'
- 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
  - One reported fatality with ST398 MSSA without 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)

Self reported disease in US swine farmers
Leedom Larson et al (2010)

- Mail survey
  - 135 (17.2%) surveys received from 783 pork producers actively farming hogs
- Five (3.7%) respondents reported a history of physician-diagnosed MRSA SSTI
  - Time period unclear (ever?)
- No bacteriological information or control group

Distribution of LA-MRSA and other MRSA clinical isolates in Europe

(van Cleef et al., 2011)

Sample source	No. (%) typed clinical isolates: MRSA ST398, n = 113	No. (%) typed clinical isolates: Other MRSA, n = 3,435	p value†
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 (1.3%)
  - None harbored the mecA gene.
- No cases of ST398 MRSA invasive disease

Public health risk of ST398 MRSA

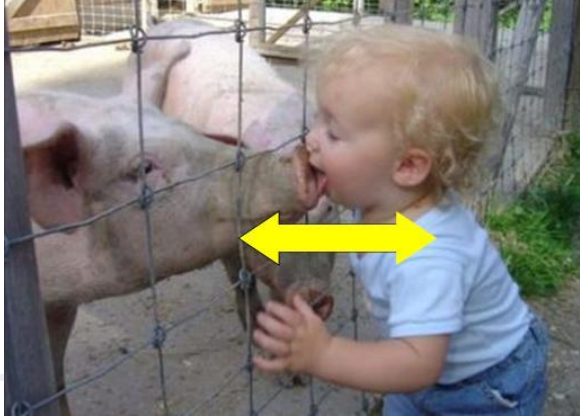
- Current evidence suggests low transmissiblity
- Current evidence suggests low pathogenicity?
  - Lack of reported fatalities (over 7 years)
  - Elevated infection risk in farm workers yet to be documented
  - Significantly less invasive disease in Europe
  - No reports of outbreaks

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
  - PVL 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 et al, EID June 2011

- t571 ST398 MSSA detected in 9 families from the Dominican Republic living in Manhattan
  - with no apparent contact with livestock (Bhat et al., 2007)
- t571 the sole MSSA spa type in Dutch study of ST398 clinical isolates, including 3 cases of nosocomial bacteremia
  - with no apparent livestock contact (van Belkum et al., 2008)
- t571 the predominant (11%) MSSA type at a Beijing hospital
  - Livestock contact unlikely (Chen et al 2010)
- Recent case report of t571 MSSA from Colombia
  - With no apparent livestock contact (Jimenez et al 2011)

Emergence of unusual bloodstream infections associated with pig-borne-like *Staphylococcus aureus* ST398 in France. (van de Marquet et al., 2011)

- Study of t571 MSSA strains from cases of bloodstream infections in France
- The 30 isolates differed from pig-borne strains
- Isolates shared similarities with strains from humans in China and virulent USA300 strains
- Epidemiologic diversity in ST398 lineage

Human origin for avian pathogenic *Staphylococcus aureus* (Lowder and Fitzgerald 2010)

- Traced origin of *S. aureus* CC5 causing morbidity in the broiler industry.
- Evidence that it evolved from a single human to poultry host jump followed by extensive genetic diversification
  - Acquisition of novel mobile genetic elements
  - Loss of virulence gene function
- "Loss of function of genes involved in human disease suggests that the clone may now be attenuated for virulence in humans"

Evolutionary genomics of *S. aureus* reveals insights into the origin and molecular basis of ruminant host adaptation (Guinane et al, 2010)

- Evidence that CC113 clone of *S. aureus* resulted from a human to ruminant host jump followed by adaptive genome diversification.
- Whole-genome sequencing
  - Molecular evidence for host adaptation
  - Gene decay and diversification of proteins involved in host-pathogen interactions
- Interspecies transmission leads to genetic adapation and changes in virulence and transmissibility?

Diversity of genome of human and LA ST398 MRSA strains (Hallin et al., 2011)

- 'LA-MRSA strains represent a homogenous lineage distinct from co-local HA- and CA-MRSA strains
  - characterized by a lack of human-associated virulence and adhesion determinants
- Absence of detectable enterotoxin gene among ST398 LA-MRSA strains from a wide host range is reassuring regarding their foodborne pathogenic potential.'

LA-MRSA: Implications

- Not good news for swine/livestock industries
- Priority to understand occupational risks
- Preventive measures in industry
  - Personal hygiene
  - Showers (soaps, towels)
  - Clothing
- Wound treatment, covering
- Awareness and medical treatment

The role of antimicrobial use?

- Tetracycline resistance
  - MRSA emergence in horses
- Long term use of beta lactams in food animals
- 'Therapeutic' vs. 'non-therapeutic' uses
- Role of antimicrobial growth promotants
  - Most are not beta lactams
- Newer injectable products
  - Long acting cephalosporins

Selective pressures (Aarestrup 2010)

- Tetracyclines
  - MSSA in pigs also tetracycline resistant
- Zinc
  - 74% of ST398 MRSA in DK had high MIC to zinc
  - All 60 MSSA strains had low MIC to zinc
- Widespread use of zinc since AGP ban
  - Prevention of enteric disease in weaned pigs
  - Used on most DK swine herds
- Law of unintended consequences?

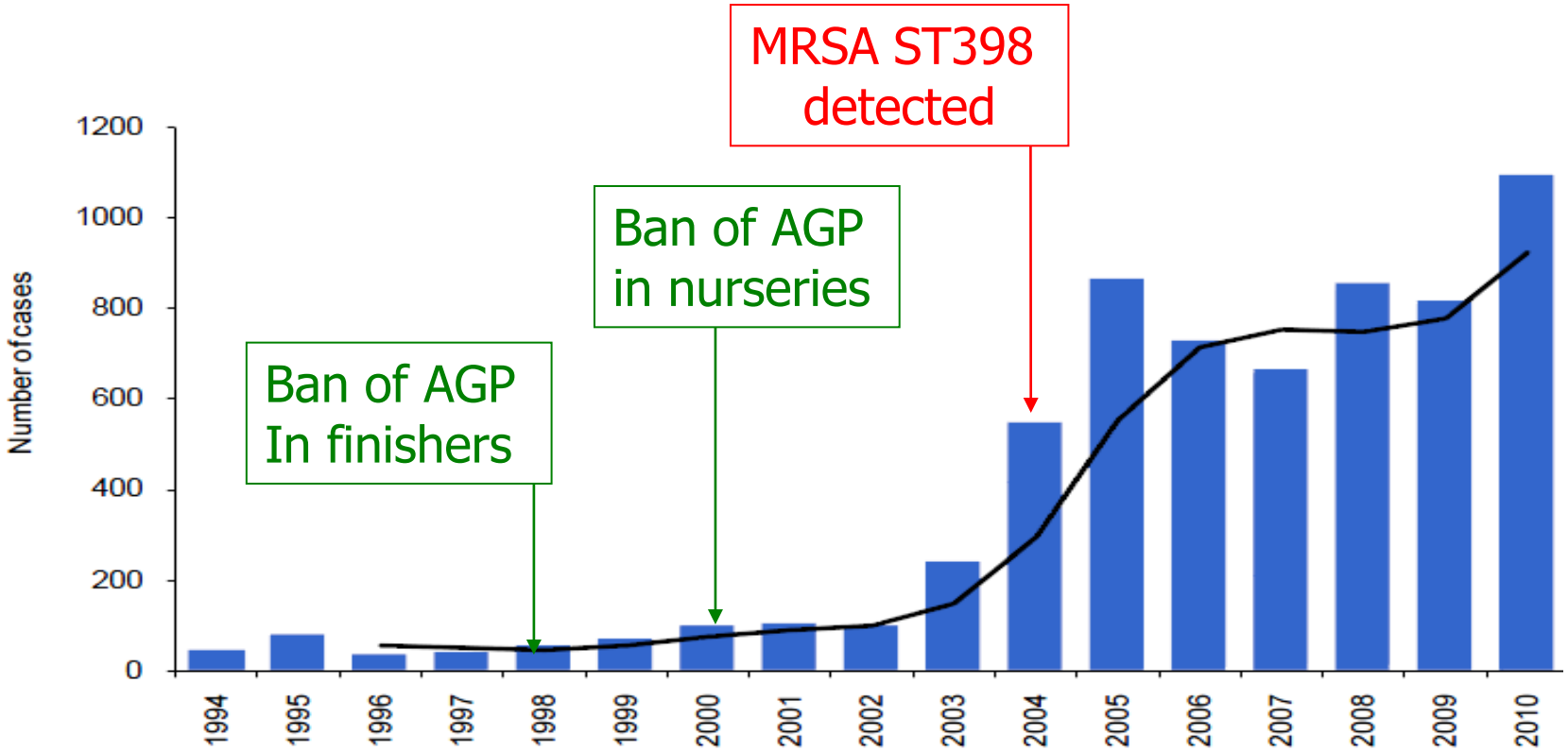
Zinc resistance of *Staphylococcus aureus* of animal origin is strongly associated with methicillin resistance

Lina M. Cavaco [1,*], Henrik Hasman [1], Frank M. Aarestrup [1]

- Global strain collection
  - MRSA and MSSA
  - Swine and veal isolates
- Study showed that zinc resistance and the czrC gene widespread among CC398 MRSA
- Suggests use of zinc in feed might have contributed to the emergence of MRSA.

Growth promotants as the evil

MRSA cases in Denmark (all types)



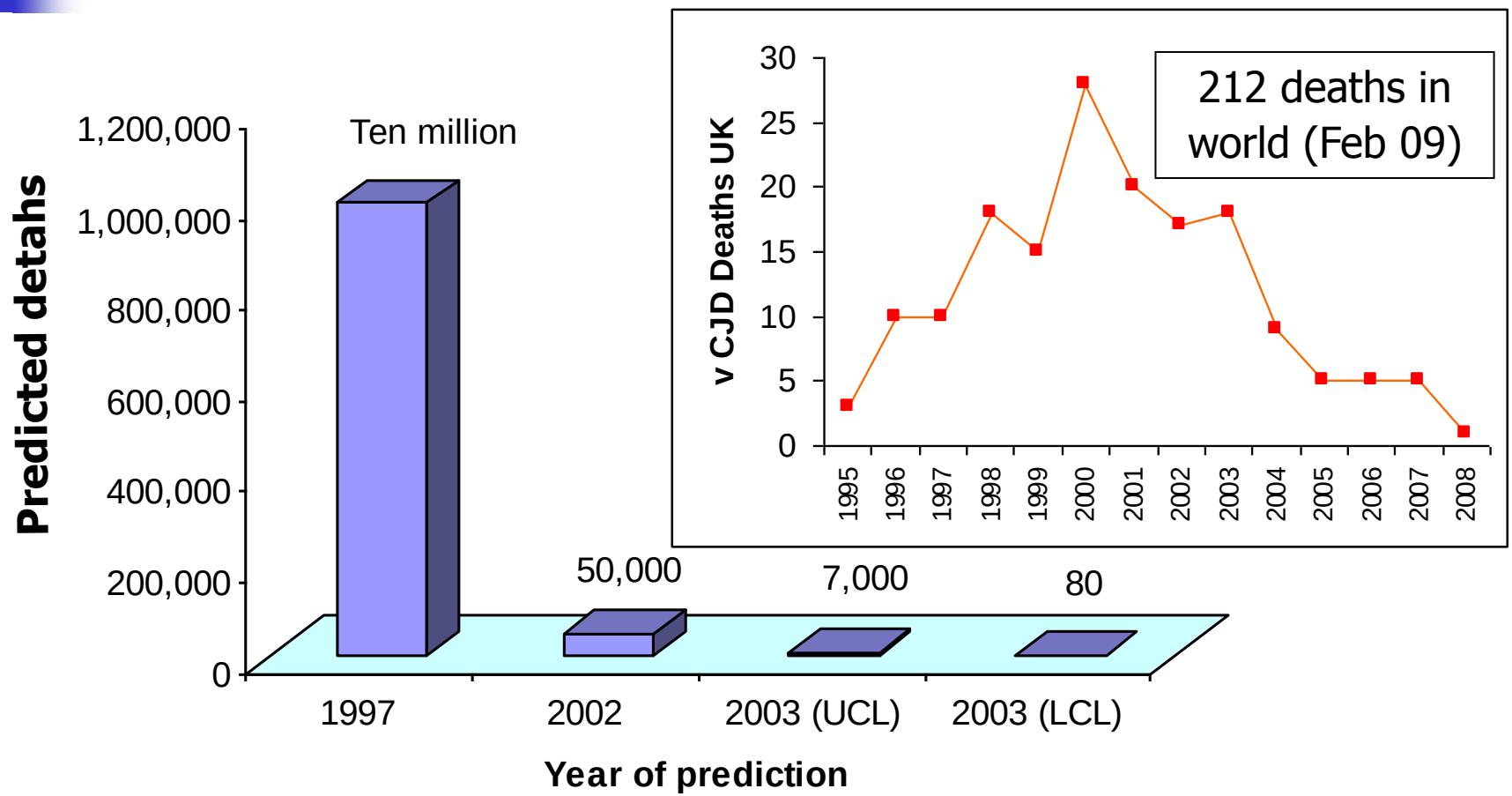
DANMAP 2010

The rest of the story……

- Understanding LA-MRSA is embryonic
- Naïve perceptions of complex epidemiology
  - All MRSA found in livestock are ST398
  - Livestock are the only reservoirs of ST398
- ST398 isolates of diverse genotype and geographic origin may also be epidemiologically distinct
- Requires systematic investigation of *S. aureus* epidemiology in animals and humans.
- Occupational health and public relations concerns
  - Not yet a public health concern!

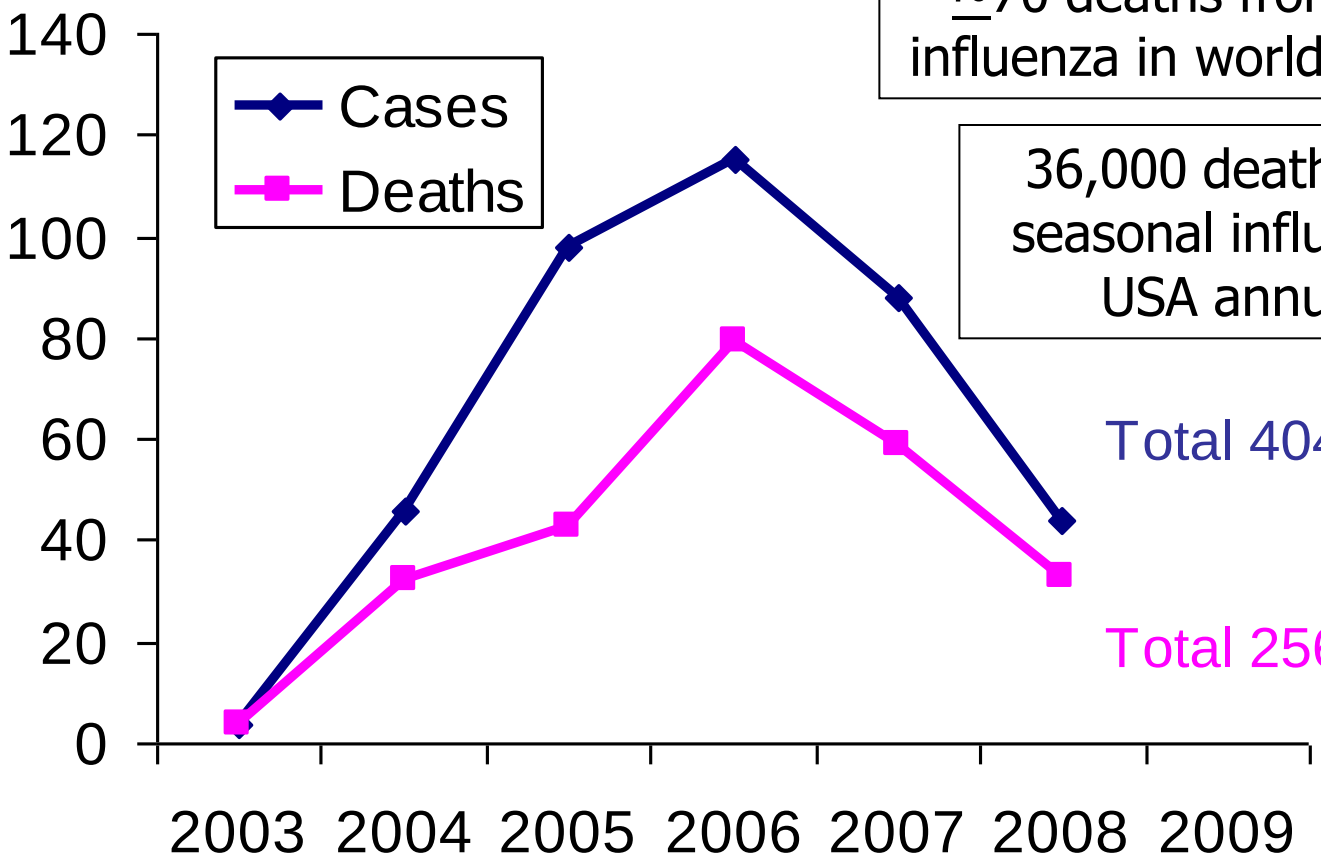
Panic and Prediction

Predicted of size of vCJD epidemic



Reported deaths from H5N1 influenza

WHO



~70 deaths from H5N1 influenza in world annually

36,000 deaths from seasonal influenza in USA annually

Total 404

Total 256

Staphylococcal foodborne disease

- Common foodborne disease
  - Ingestion of preformed toxins in food
  - Only rare reports of MRSA involvement
  - All livestock associated ST398 investigated have been negative for enterotoxins
- Antimicrobials not indicated
  - Resistance of isolates irrelevant
- MRSA in meat relevant only due to exposure risk from food handling

MRSA prevalence in Dutch meat

de Boer et al (2009)

Meat type	*n*	Number (%) positive
Beef	395	42 (10.6)
Veal	257	39 (15.2)
Pork	309	33 (10.7)
Lamb/mutton	324	20 (6.2)
Chicken		
– Total	520	83 (16.0)
– NL+ other EU countries	302	
– Import (non-EU countries)	162	
– Biological	56	
Turkey	116	41 (35.3)
Fowl	118	4 (3.4)
Game	178	4 (2.2)
Total	2217	264 (11.9)

Most isolates ST398

MRSA in meat: what are the implications?

De Boer et al (2009)

- High prevalence of MRSA in raw meats not shown to contribute to the dissemination MRSA to humans.
- MRSA numbers so low that risk of colonization is slight.
- Conditions for growth of *S. aureus* in raw meats are poor.

MRSA in meat – what are the implications?

- VWA Risk Assessment Bureau (Holland)
  - Foodstuffs play a negligible role, in the spread of MRSA.
- Weese and van Duijkeren (2009)
  - Evidence implicating food as the source of infection appears to be tenuous.
  - Clinical relevance of MRSA contamination of food, … is currently unclear
- DANMAP 2010
  - Frequent occurrence of MRSA in meat combined with no/very few cases in urban areas makes it safe to conclude that there is very little if any risk for meat being a risk for contracting MRSA CC398.