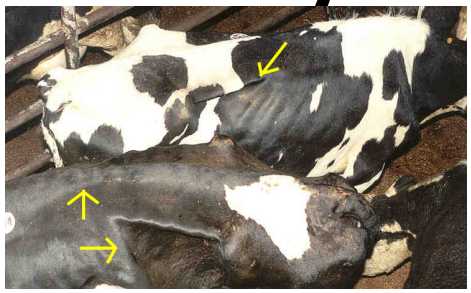
Impact of Antibiotic Use in Animal Agriculture and Influence on Resistance Controversy



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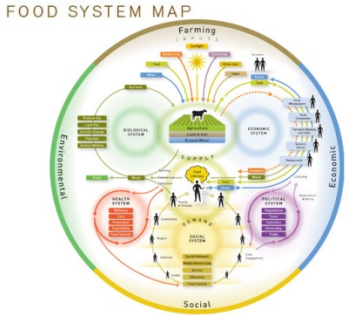
Get Smart
PSU Nov. 15*, 2016*



www.nourishlife.org

- **Animal Care and Therapeutics**
- **Preventative care vs. disease treatment**
- **Quality concerns**
- **Regulatory issues & food safety concerns**
  - **What does that mean for producers**
  - **What does that mean for consumers**
  - **What does it mean for animal well-being**
  - **Impact for markets and environment**

Time Magazine, March 19, 2014 p. 20

Briefing

Health

Three main assaults drive bacteria to mutate

1. Superpopular antibacterial soaps and sanitizers

2. The overprescription of antibiotics to treat infections

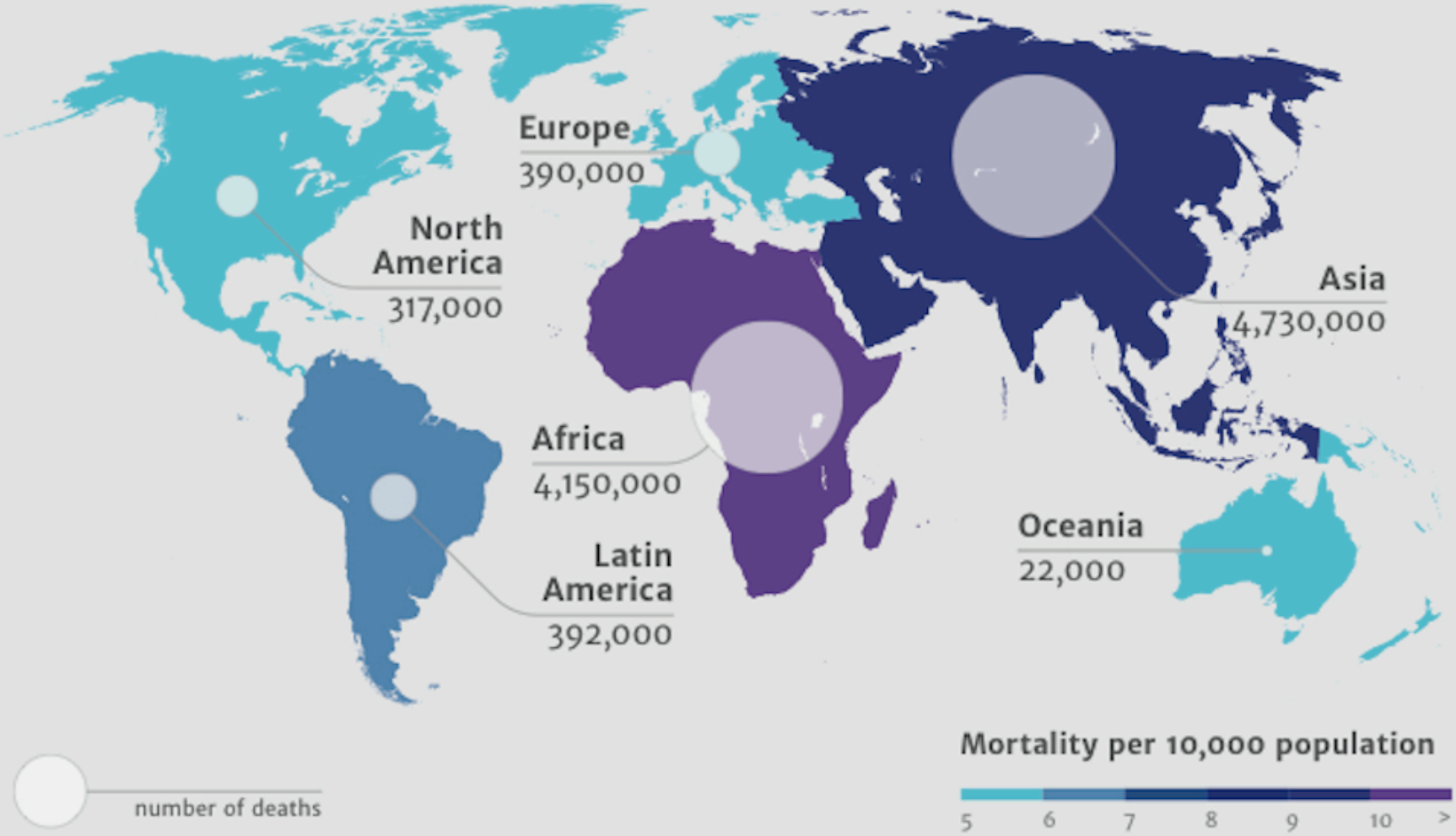
3. The rampant use of the drugs on livestock

The end result? Antibiotic-resistant superbugs

Man vs. Microbe We're losing the battle against bacteria. Can we win the war?

BY ALICE PARK

The Worried Well



Review Antibiotic Resistance, 2014

All Animal Ag Species- Care and Well-being Initiatives

- Address injured or ill animals
  - Treatment protocols
- Painful conditions
- Chronic conditions and euthanasia
- Relative economic value animals
- Routine care procedures of caretakers (+ training)
- Care and welfare of animals during transportation
- Prevention & keep well > treat when ill

Animal use and contribution to resistance?

- Animals consume and excrete antibiotics
  (~ 2 trillion lbs of manure generated in USA annually)
- Animals can transmit resistant bacteria in food
  - Food of animal origin as cause of food-borne infections:
    - *Salmonella*
    - *Campylobacter*
    - *Yersinia*
    - *E Coli 0157-H7*
- Transfer to human specific organisms (esp. seen in examples from pigs and chickens when sick).

Antibiotic by Route of Use

- ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS**1**
- ACTIVELY MARKETED IN 2014
- DOMESTIC SALES AND DISTRIBUTION DATA
- REPORTED BY MEDICAL IMPORTANCE AND ROUTE OF ADMINISTRATION

		Annual Totals (kg)	% Subtotal	% Grand Total
Medically Important	***Feed1***	**6,977,747**	**74%**	**45%**
Medically Important	***Injection1***	**341,790**	**4%**	**2%**
Medically Important3	***Intramammary***	**11,450**	**<1%**	**<1%**
Medically Important	***Oral5 or Topical1***	**104,082**	**1%**	**<1%**
Medically Important	***Water6***	**2,040,920**	**22%**	**13%**
Medically Important	***Subtotal***	***9,475,989***	***100%***	***62%***
Not Medically Important4	***All Routes7***	**5,882,221**		**38%**
	Grand Total	***15,358,210***		***100%***

NARMS 2014, p 44

Why use antibiotics in feed?

- Use at periods of higher stress: feed changes, transportation, weather changes
- Reduces shedding of food safety pathogens
  - Trade 1/53,000,000 illness due to resistance
  - Vs. 1/32, 900 illness due to greater food safety illness (additional 6,000 severe cases/yr)
- Lower carbon footprint
  - Average 13% greater gain/kg of feed
  - Saves 4-6% of input cost

Cox and Ricci, Envir Sci, 2007
Matthew, et al., Food Path Dis 2007

Antibiotics

Therapeutic vs. **Disease Prevention/control**

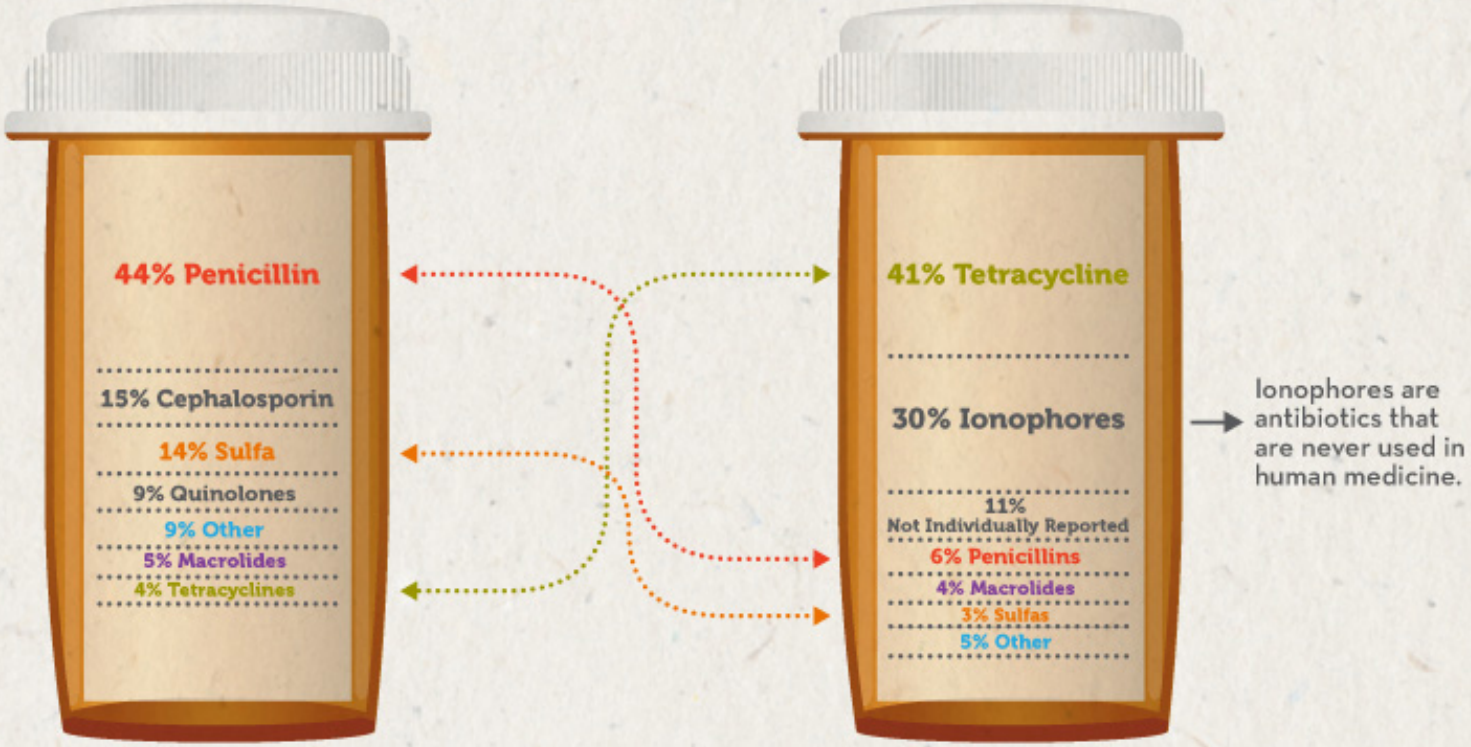
- Acutely ill animals
- Many fewer animals
- Higher doses (gm vs. mg)
- More handling
- Tissue residue
- New products & cost R&D
- Treat pain and suffering
- Stunted growth
- Higher cost/animal

- Keep healthy vs. sick
- Entire herd or flock
- Low dose, no residue
- Fewer food pathogens
- Older products, not normally for humans
- Avoid prevent pain/ suffering
- Lowers cost of production
- Improves efficiency (less manure, less acres)

http://www.nppc.org/issues/animal-health-safety/antimicrobials-antibiotics/

TOP ANTIBIOTICS USED IN HUMANS vs. ANIMALS

The top antibiotics used for food producing animals in 2011 were rarely used in humans, and vice versa.



SOURCE: FDA 2011 reports

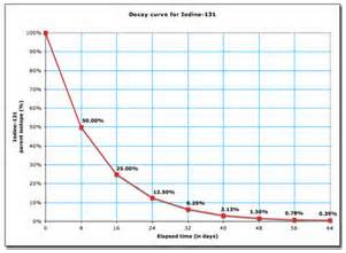
Wholly or partially funded by one or more Checkoff programs

Reduction of Residues and Resistance

- Judicious use programs
- Restrict extra label use
  - Diagnostics to inform science based protocols
  - Create written protocols for common conditions
  - Up to date and written VCPR and VFD
- Supervise use as much as possible on farms
- Extended withdrawal times
  - Physiological state of animal
  - Dose, depot and tissue location
- FARAD (www.farad.org)

Factors that can affect elimination of therapeutic product

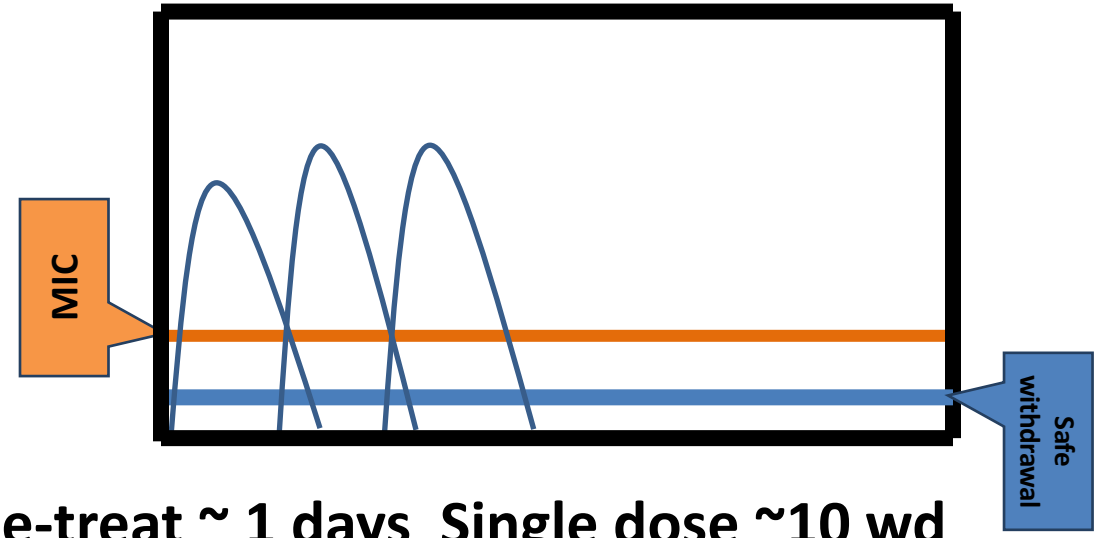
- Dose and size of depo
  - Rate of absorption
  - IV < IM <SQ (product moves depo to plasma)
  - Pharmokenetics
    - Overall health and status of animal
    - Target plus elimination organs
    - Special characteristics of product
  - Multiple doses or different doses
  - Dose in different site than designed



Extended WDT

- WDT is the time required after dosing for tissue concentrations to be depleted to or below specific safe concentration
- More closely associated to tissue depots vs. plasma depots
- Tissue with the slowest depletion determines the WDT for the species
  - 10 t ½ = 99.9% depletion, days usually rounded up (no fractions of days), physiological state, different tissue
  - In US safe concentration can be defined as the tolerance limit-law is zero for not approved compounds
- In Europe usually termed Maximum residue level

Normal Dose
Normal Kidney/Liver ~ Predictable Withdrawal

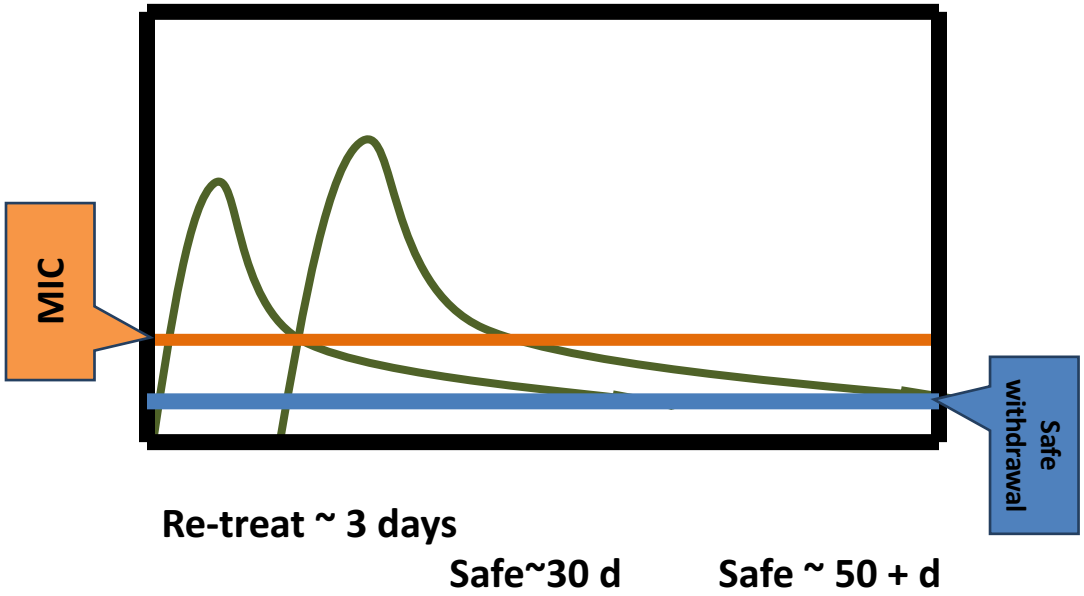


Re-treat ~ 1 days Single dose ~10 wd

Multiple doses - safe ~ + few d

- **Same dose but repeated**
- **Withdrawal (slightly extended)**
  - **(e.g., few d plus new dose)**
- **Milk withholding**
  - **Pretty predictable even if 1 ppb**

Extended Treatment or Compromised Kidney/Liver Very Long Withdrawal



- Same dose but repeated
- Withdrawal (can be greatly extended)
  - (e.g., not just 3 d plus new dose)
- Milk withholding
  - Very long if target is 1 ppb

Malaria Resistance and Lessons Learned

- *Read and Huijben, Evol. App., 2009*

Fallacies

- Drugs with long half lives are preferable
- De novo resistance mutations are main enemy
  - (vs. transportation around globe)
- Genetic trade offs alone determine costs of resistance to pathogen
  - (vs. in host ecology)
- Fixation of resistance is inevitable if drug pressure is maintained

Staphylococcus aureus

- **Samples submitted to ADL for mastitis or bulk tank milk culture (2008, 2013, 2014, 2015) examined for *S. aureus***
- ***S. aureus* isolates**
  - **163 isolates (n=115 QMS; n=48 BTM) from 77 farms**
    - **Small cell variant phenotype analysis**
    - **Antibiotic resistance**
      - **Amoxicillin + Clavulanic acid, Cefoxitin, Ciprofloxacin, Clindamycin, Erythromycin, Gentamicin, Oxacillin, Tetracycline, Vancomycin, Penicillin.**
    - **Enterotoxin genes: A, B, C, D, E, F, G, H, I, J, K, L, M, O, P, Q, R, TSST-1**
    - **Leukocidin genes: LukAB, LukED, LukMF**
    - **DNA Fingerprinting: Multi Locus Sequence Typing**

Jayarao, unpublished 2015

Antimicrobial Resistance

- **Sensitivity**
  - 130/163 = 80% of isolates sensitive to all ten antimicrobials examined.
  - BTM: 37/48 =77%
  - QMS: 93/115 = 81% **NO MRSA strain isolated from Pennsylvania dairy herds**

Antibiotic Resistance Profile	No of Isolates	No. of Farms
None	130	74
Clindamycin	1	1(QMS)
Cefoxitin	3	2 (BTM)
		1 (QMS)
Penicillin	7	1 (BTM)
		6 (QMS)
Tetracycline	5	5 (QMS)
Vancomycin	11	2 (BTM)
		3 (QMS)
		2 (BTM)
		3
Amoxicillin, Penicillin	1	1 (BTM)
Clindamycin, Erythromycin	2	1(QMS)
Oxacillin, Penicillin	1	1 (QMS)
Clindamycin, Erythromycin, Tetracycline, Penicillin	2	2 (BTM, QMS)

Jayarao, unpublished 2015

Prevalence of Antibiotic Resistance %

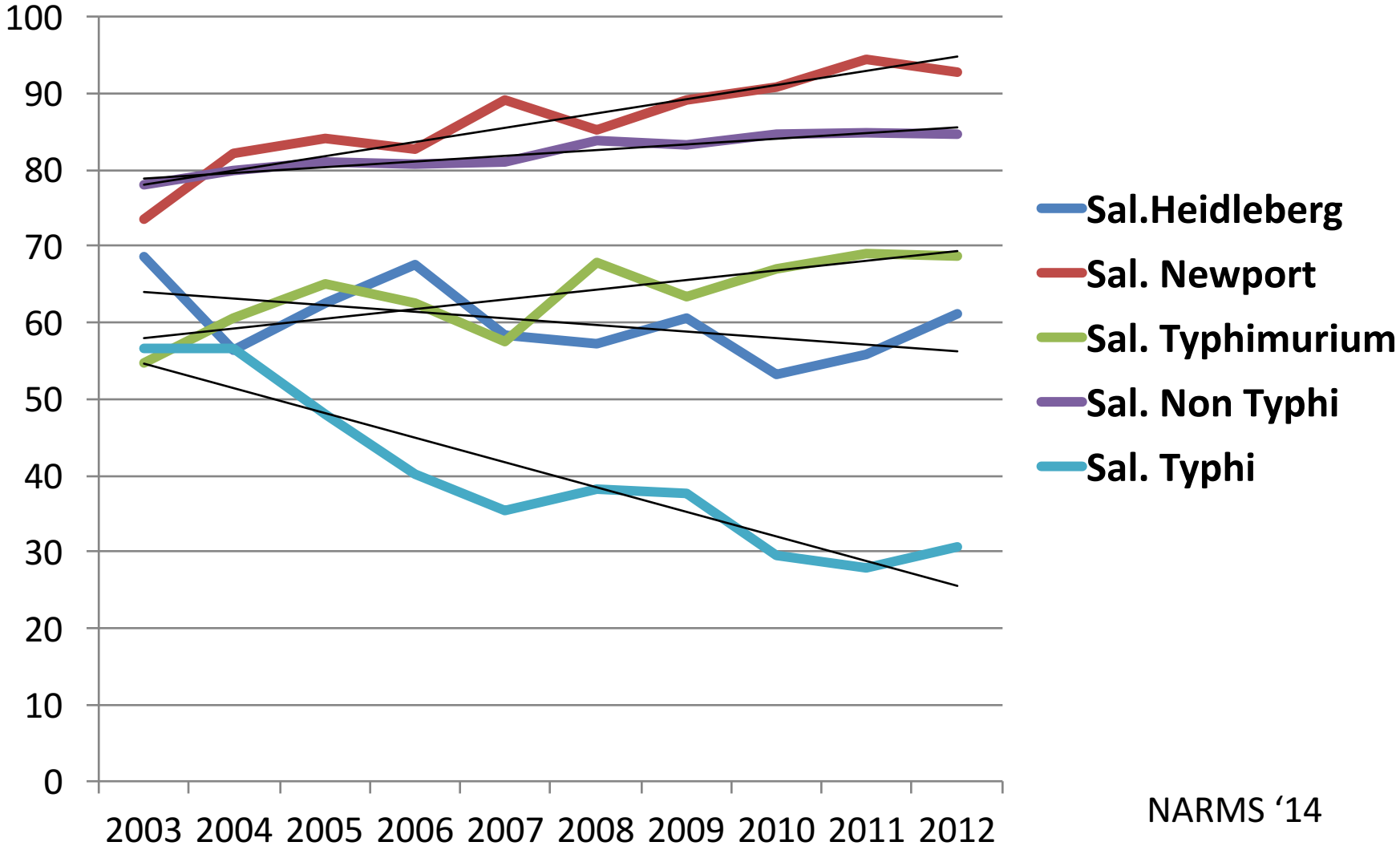
Antibiotic	Salmonella	E coli '07	Salmonella	E coli ' 08	Salmonella	E coli '09
	n=202	n=525	n=232	n=500	n=117	n=510
Amikacin	0	0	0	0	0	0
Amoxi/clav.	1.0	1.5	0	1.1	0	0.6
Ampicillin	1.5	2.1	0	2.2	0	1.6
Cefoxitin	1.0	1.5	0	1.3	0	0.4
Ceftiofur	1.0	0.8	0	1.1	0	0
Chloramphenicol	1.0	0.2	0	0.9	0	0.4
Kanamycin	0	3.8	0	4.8	1.7	3.3
Streptomycin	1.0	5.1	0.4	6.5	1.7	2.8
Sulfizoxazole	1.0	3.8	0	4.8	1.7	2.8
Tetracycline	1.0	13.1	0	9.8	1.7	7.8
Trim. /sulfa	0	1.0	0	1.5	0	1.2

Liu, in press 2016

Resistant *E. coli* isolates from Various Cattle Groups in PA

Antimicrobial Agents	Farm Prevalence (%)			
	Pre-weaned calves (n=77)	Post-weaned calves (n=75)	Dry cows (n=72)	Lact. cow (n=80)
AUG	40.3 (31)	14.7 (11)	0.0 (0)	5.0 (4)
AMP	57.1 (44)	33.3 (25)	1.4 (1)	12.5 (10)
AZI	2.6 (2)	1.3 (1)	0.0 (0)	0.0 (0)
FOX	37.7 (29)	13.3 (10)	0.0 (0)	5.0 (4)
TIO	31.2 (24)	12.0 (9)	0.0 (0)	5.0 (4)
AXO	36.4 (28)	13.3 (10)	0.0 (0)	6.3 (5)
CHL	29.9 (23)	18.7 (14)	1.4 (1)	1.3 (1)
CIP	1.3 (1)	1.3 (1)	0.0 (0)	0.0 (0)
GEN	13.0 (10)	5.3 (4)	0.0 (0)	0.0 (0)
NAL	7.8 (6)	4.0 (3)	0.0 (0)	0.0 (0)
STR	70.1 (54)	38.7 (29)	6.9 (5)	21.3 (17)
FIS	67.5 (52)	44.0 (33)	11.1 (8)	22.5 (18)
TET	81.8 (63)	69.3 (52)	26.4 (19)	40.0 (32)

No resistance detected



NARMS '14

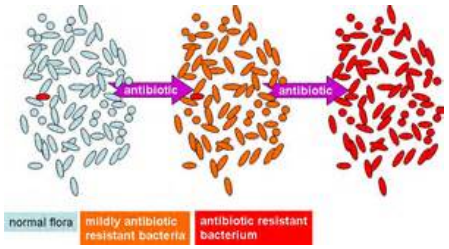
Malaria Resistance and Lessons Learned

- *White, et. al., Malaria Journal, 2009*

Resistance

- Greater: fast parasite growth and high burdens
- Recrudescence and multiple recrudescence are required for de novo selection of resistance
- Inadvertent treatment of asymptomatic parasitemia is unlikely source of resistance
- Strive for therapeutic levels in all patients
- Ill patients with hyperparasetemia very risky

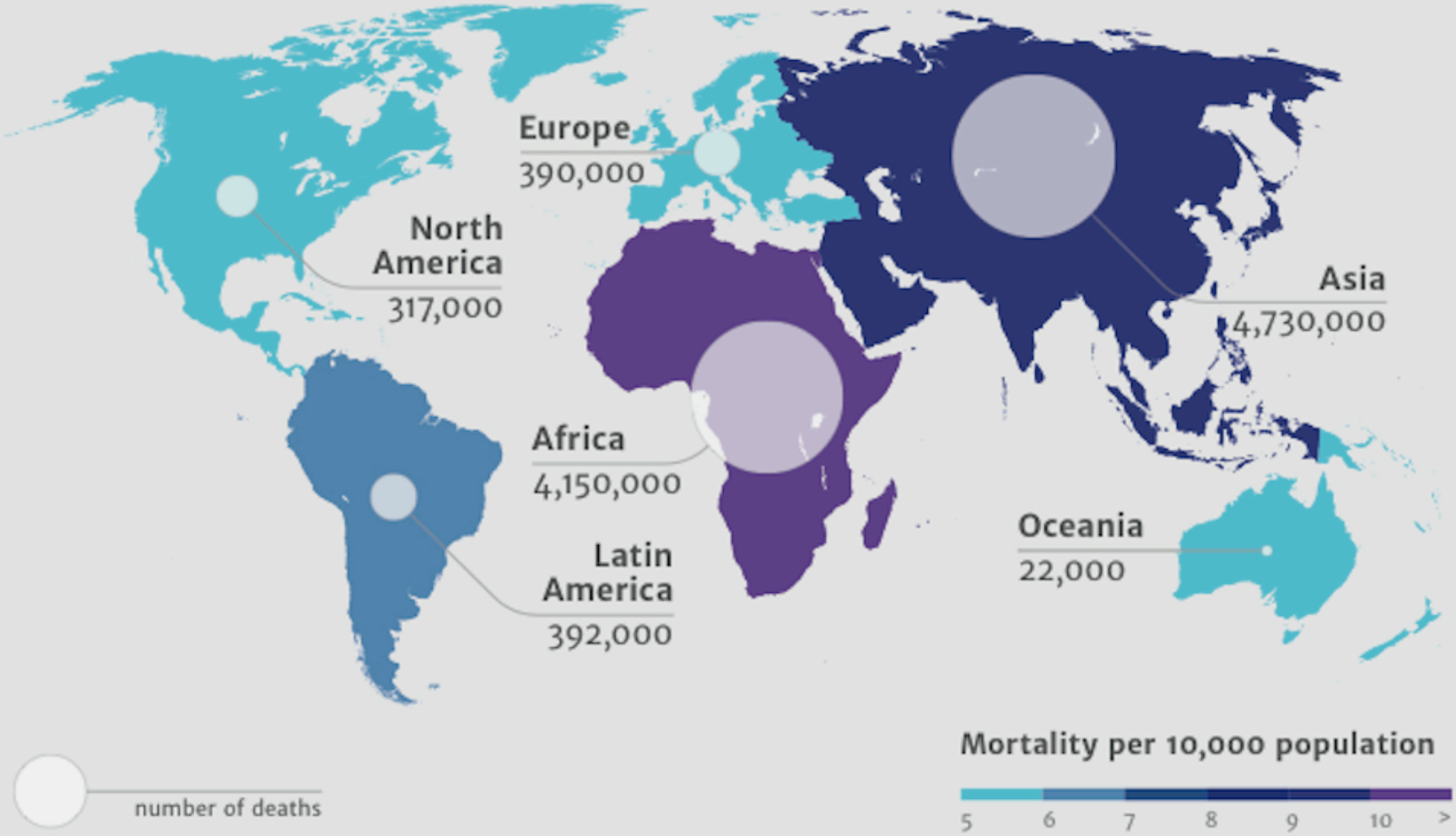
Antibiotic use the only cause or solution for AMR?



- Genes in environment
  - Co selection against metals
  - Allows for plasmids and integrons +cassettes to DNA
  - Co-resistance to heavy metals allows for maintenance of resistance (polluted countries)
  - Increased use of trace minerals to improve performance
- Heavy industrial impact = greater resistance

Berendonk, et.al, Nat Rev Micro, 2015
McAurther, et.al, Micro Ecol, 2015

The Worried Well



Review Antibiotic Resistance, 2014

Example: Imported Shrimp

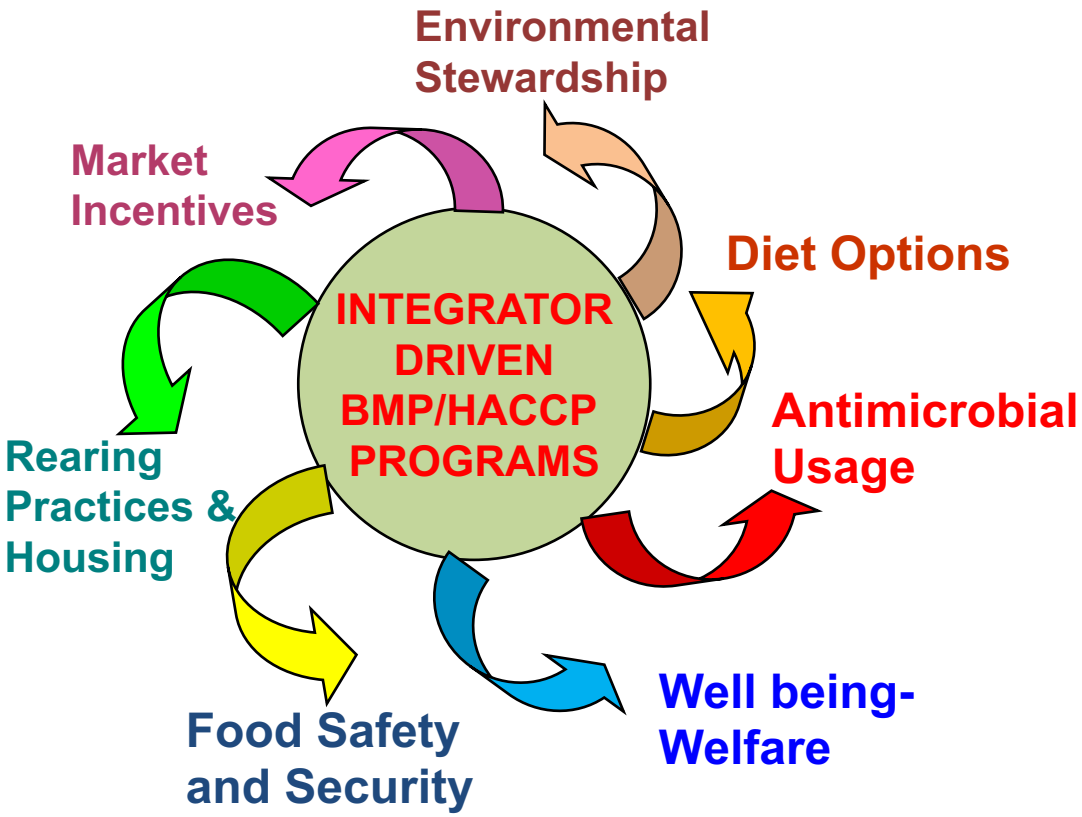
- ~ One hundred percent of Vietnamese shrimp farms use ciprofloxacin.
- Fluoroquinolone concentrations in sediments and surface waters may reach >4,000 µg/kg.
- All kinds of bacteria inhabit these ponds, including those present in the manure of terrestrial animals (such as chickens) that is fed to the shrimp

- "Where does this lead?"

http://cdn.intechopen.com/pdfs-wm/35141.pdf

Systems Approach

Advantages of US Food Supply vs. Production Forced Out of Country



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