WASHINGTON STATE UNIVERSITY

*World Class. Face to Face.*

# A One-Health Perspective on Antibiotic Resistance in Tanzania


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NIH National Institutes of Health *Turning Discovery Into Health*

BILL & MELINDA GATES *foundation*

USDA

WASHINGTON STATE UNIVERSITY COLLEGE OF VETERINARY MEDICINE

PAUL G. ALLEN SCHOOL FOR GLOBAL ANIMAL HEALTH

BBSRC *bioscience for the future*

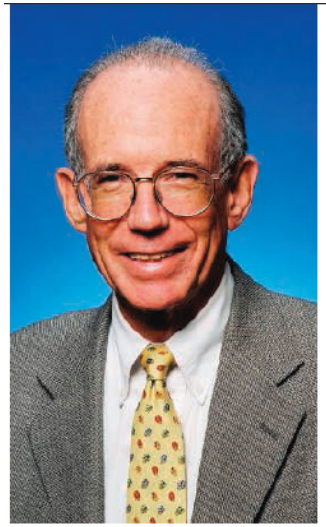
NSF

# CDC report

- 18 AMR agents of concern
- >2 million infections
- ≈23,000 deaths
- $35 billion excess costs
- Antibiotics are most commonly prescribed drugs
- But up to 50% of these prescriptions are not needed
- FDA Guidance to Industry #213

SCIENCE VOL 342 15 NOVEMBER 2013

EDITORIAL



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# Time to Deal with Antibiotics

ANTIBIOTIC DRUGS—PENICILLIN, TETRACYCLINE, AND THEIR MORE MODERN SUCCESSORS—HAVE been critical elements in the world's efforts to sustain health and deal with human diseases. Unfortunately, the vital role of these drugs has been critically compromised by the prevalence of dangerous infections that antibiotics can no longer control, because bacteria are resistant to them. Even nations with strong health care systems, respected medical centers, and fine hospitals are experiencing a growing epidemic of infections that they now simply cannot cure. Here in the United States, such infections kill nearly 23,000 people each year, according to the Centers for Disease Control and Prevention's (CDC's) report *Antibiotic Resistance Threats in the United States, 2013*. Farming practices are largely to blame for the rise of antibiotic-resistant strains, and at last there is hope for reform.

"Farming practices are largely to blame for the rise in antibiotic-resistant strains, and at last there is hope for reform"

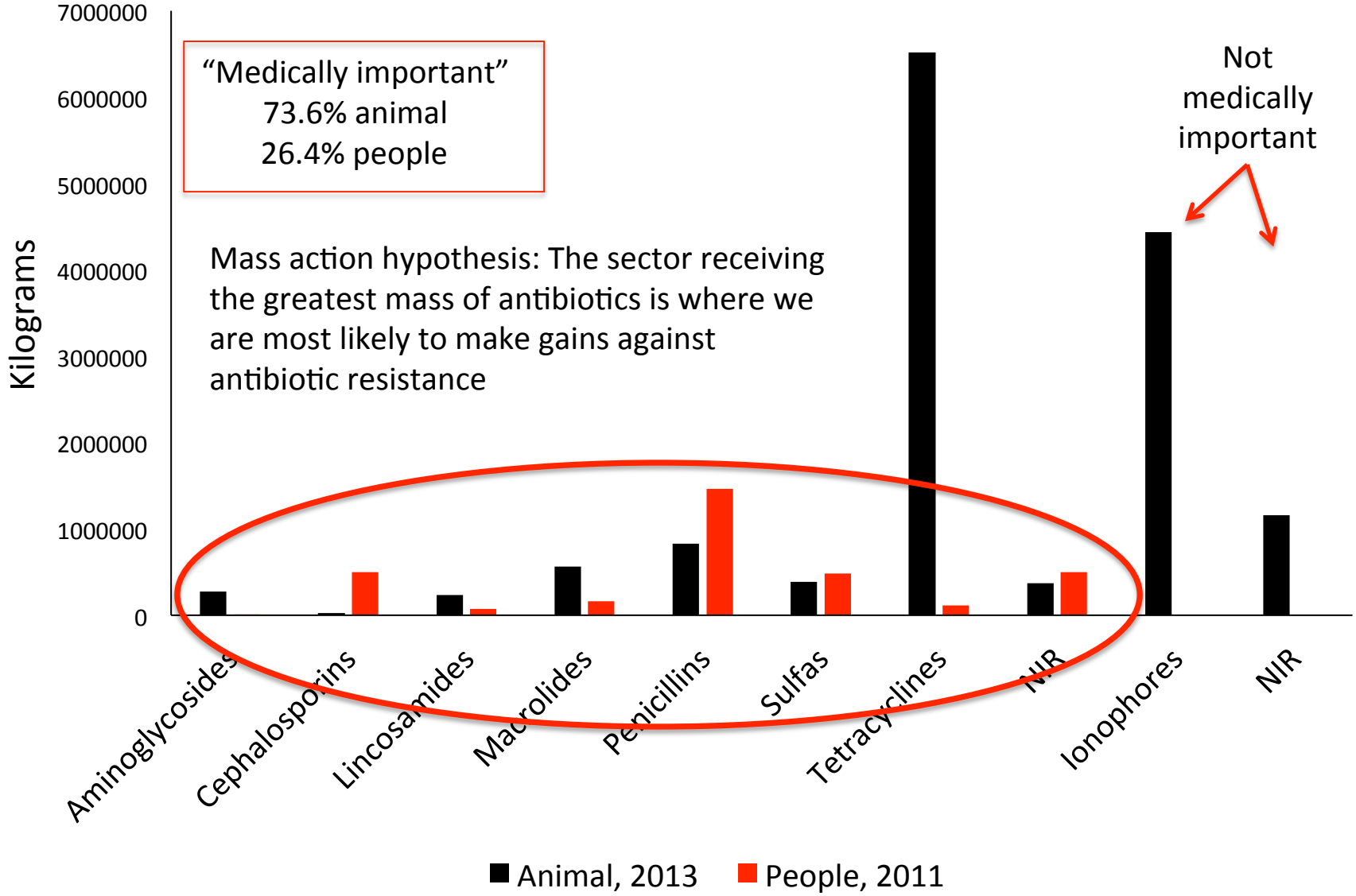
# Farming practices are largely to blame?

| Agent | Human | Animal | Both | Caveats |
|---|---|---|---|---|
| *Clostridium difficile* | X | | | X |
| Carbapenem-resistant Enterobacteriaceae | X | | | X |
| Drug resistant *Neisseria gonorrhoeae* | X | | | |
| Multidrug resistant *Acinetobacter* | X | | | |
| Drug-resistant *Campylobacter* | | **X** | | |
| Fluconzaole-resistant Candida | X | | | |
| ESBLS producing Enterobacteriaceae | | | X | |
| Vancomycin-resistant *Enterococcus* | | | X | |
| Multidrug resistant *Pseudomonas aeruginosa* | X | | | |
| Drug-resistant non-typhoidal *Salmonella* | | **X** | | |
| Drug-resistant *Salmonella* Typhi | X | | | |
| Drug-resistant *Shigella* | X | | | X |
| Methicillin-resistant *Staphylococcus aureus* | X | | | X |
| Drug-resistant *Streptococcus pneumoniae* | X | | | |
| Drug-resistant Tuberculosis | X | | | |
| Vancomycin-resistant *Staphylococcus aureus* | X | | | |
| Erythromycin-resistant Group A Streptococcus | X | | | |
| Clindamycin-resistant Group B Streptococcus | X | | | |

Note: Threat levels = urgent, serious, concerning

Note: *Campylobacter*, *Salmonella*, and ESBLS = 7.5% of deaths

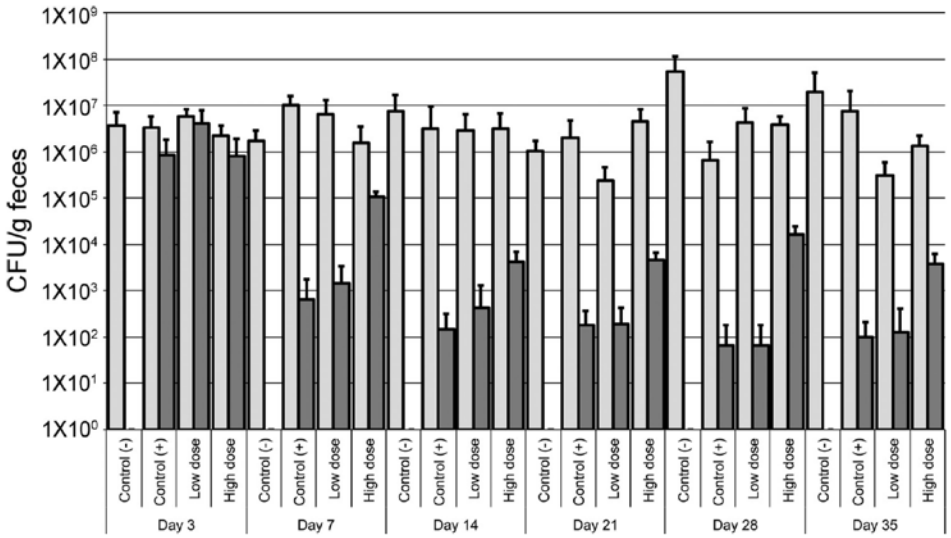
# US Domestic Antibiotic Sales




FDA 2012, FDA 2015

AEM
Journals.ASM.org

# *In Vivo* Transmission of an IncA/C Plasmid in *Escherichia coli* Depends on Tetracycline Concentration, and Acquisition of the Plasmid Results in a Variable Cost of Fitness



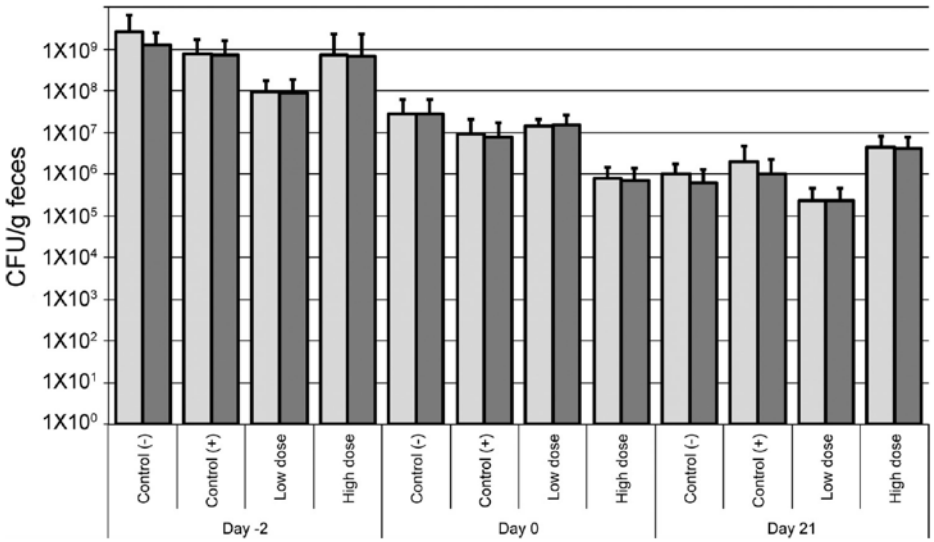
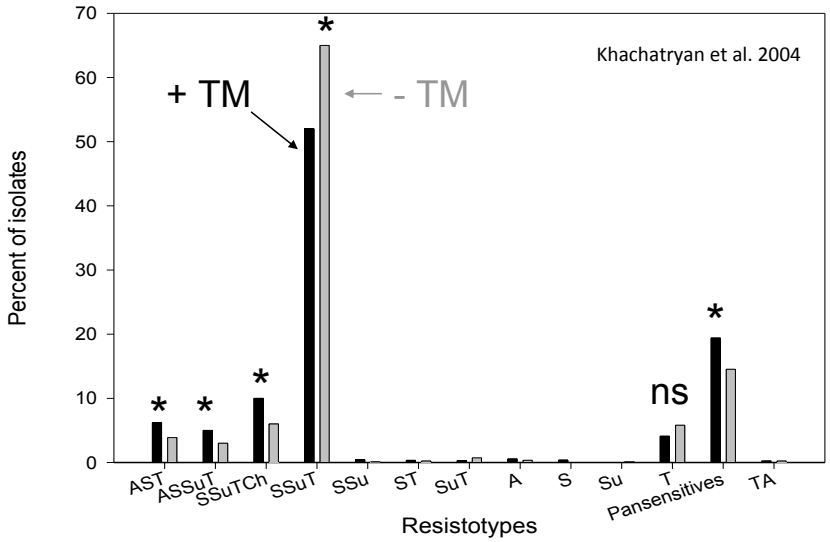
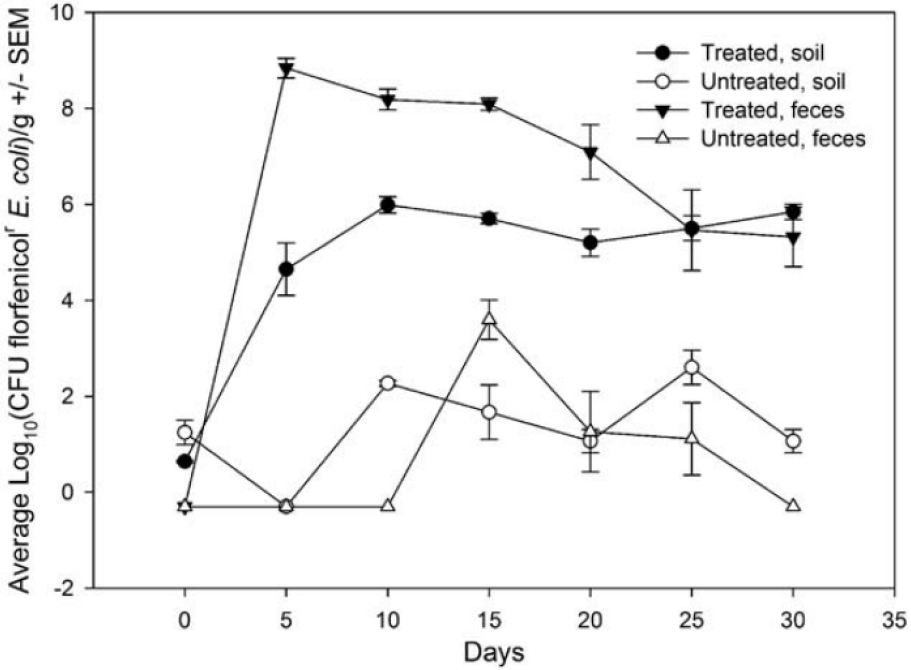



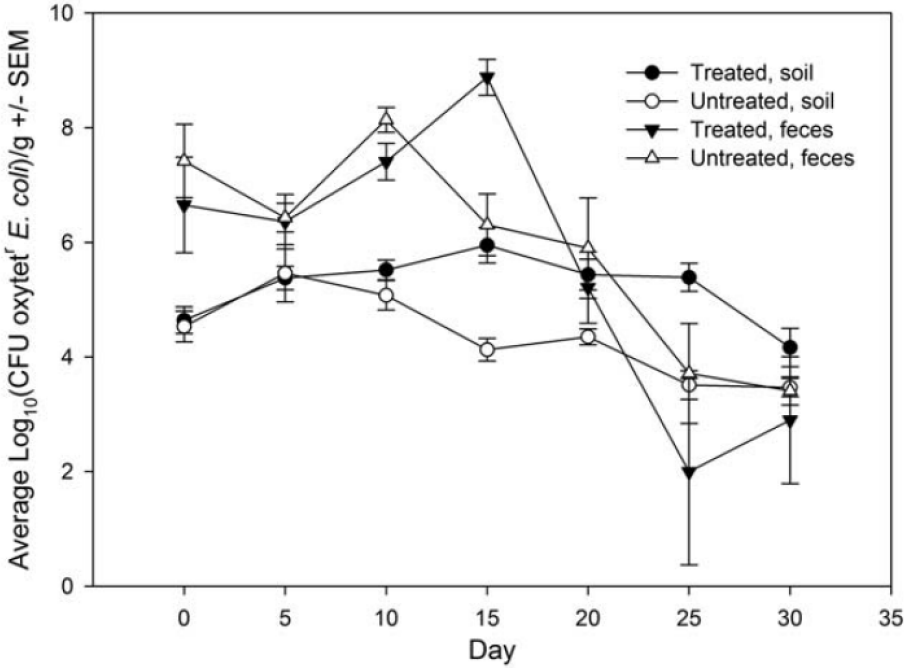

TABLE 2 Experimental design for controlled pig studies

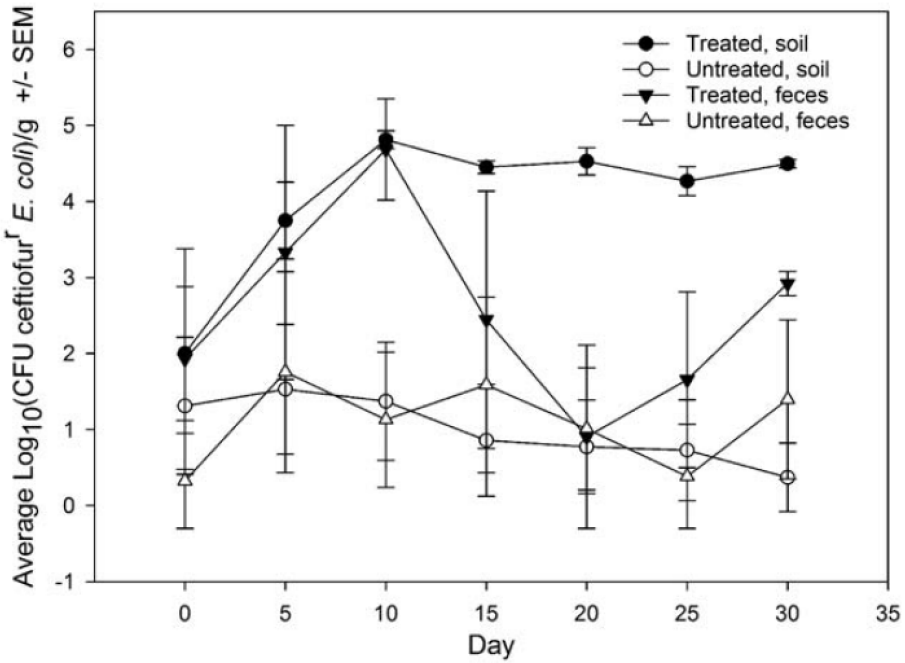
| Group | No. of pigs | Challenge | Treatment[a] | Room |
|---|---|---|---|---|
| 1 | 5 | None | None | 1 |
| 2 | 5 | *E. coli* PFEC(pAR060302:rfp) | None | 2 |
| 3 | 5 | *E. coli* PFEC(pAR060302:rfp) | CTC, 50 g/ton (low dose) | 3 |
| 4 | 5 | *E. coli* PFEC(pAR060302:rfp) | CTC, 350 g/ton (high dose) | 4 |

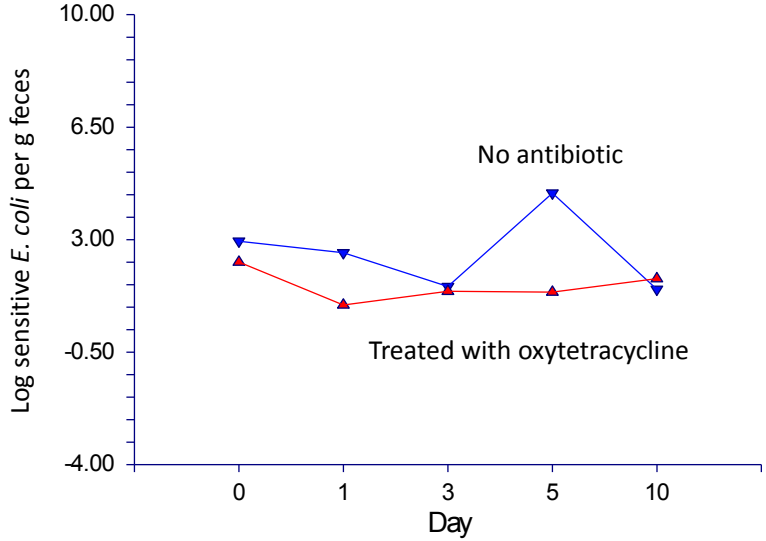
[a] High-dose treatment involved 350 g/ton of chlortetracycline (CTC) for 7 days, followed by 50 g/ton of CTC for 14 days, which was then repeated.






App. 1 log difference; *P*=0.08, n=5 calves each group

Liu et al. 2016

# Dose matters…

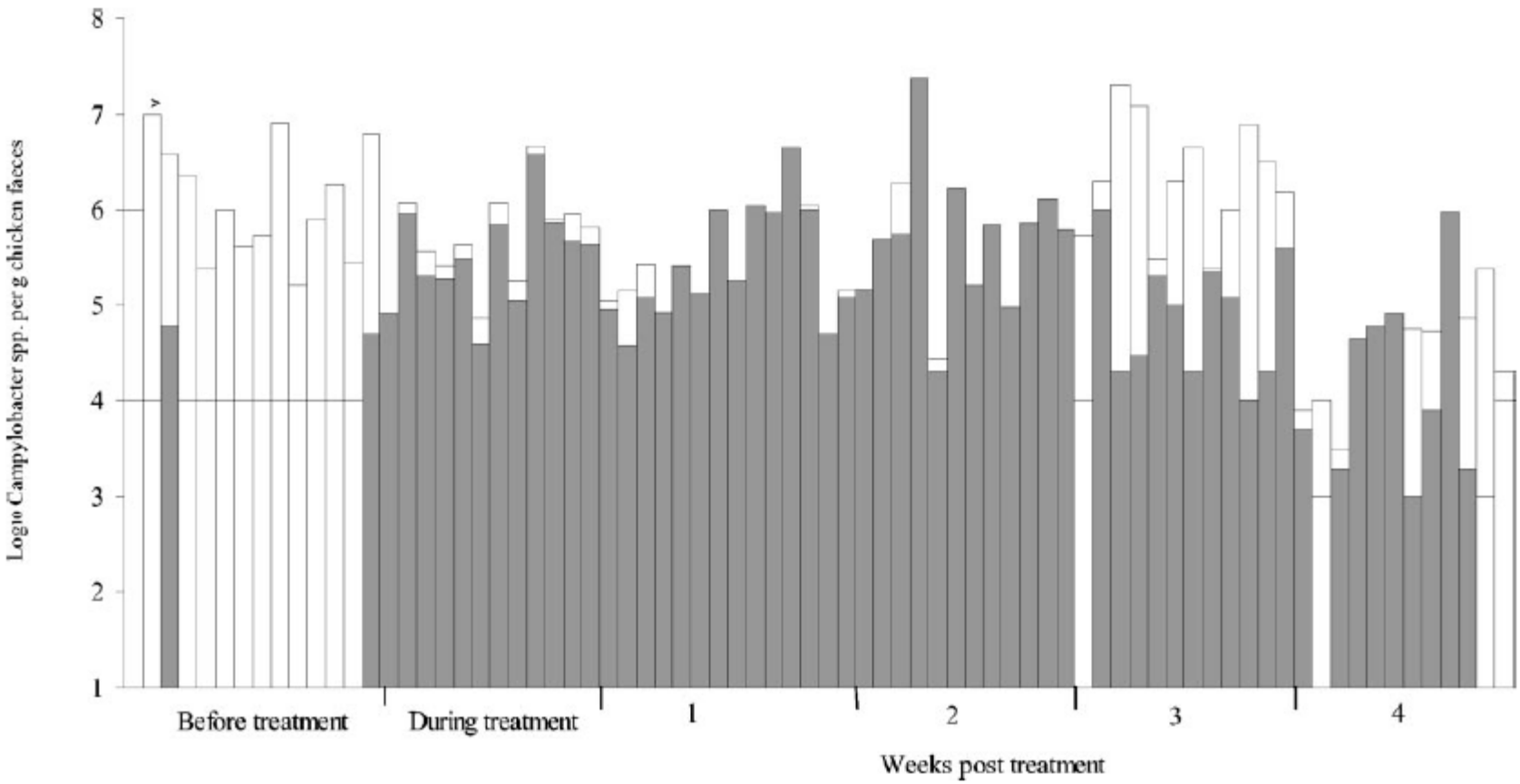


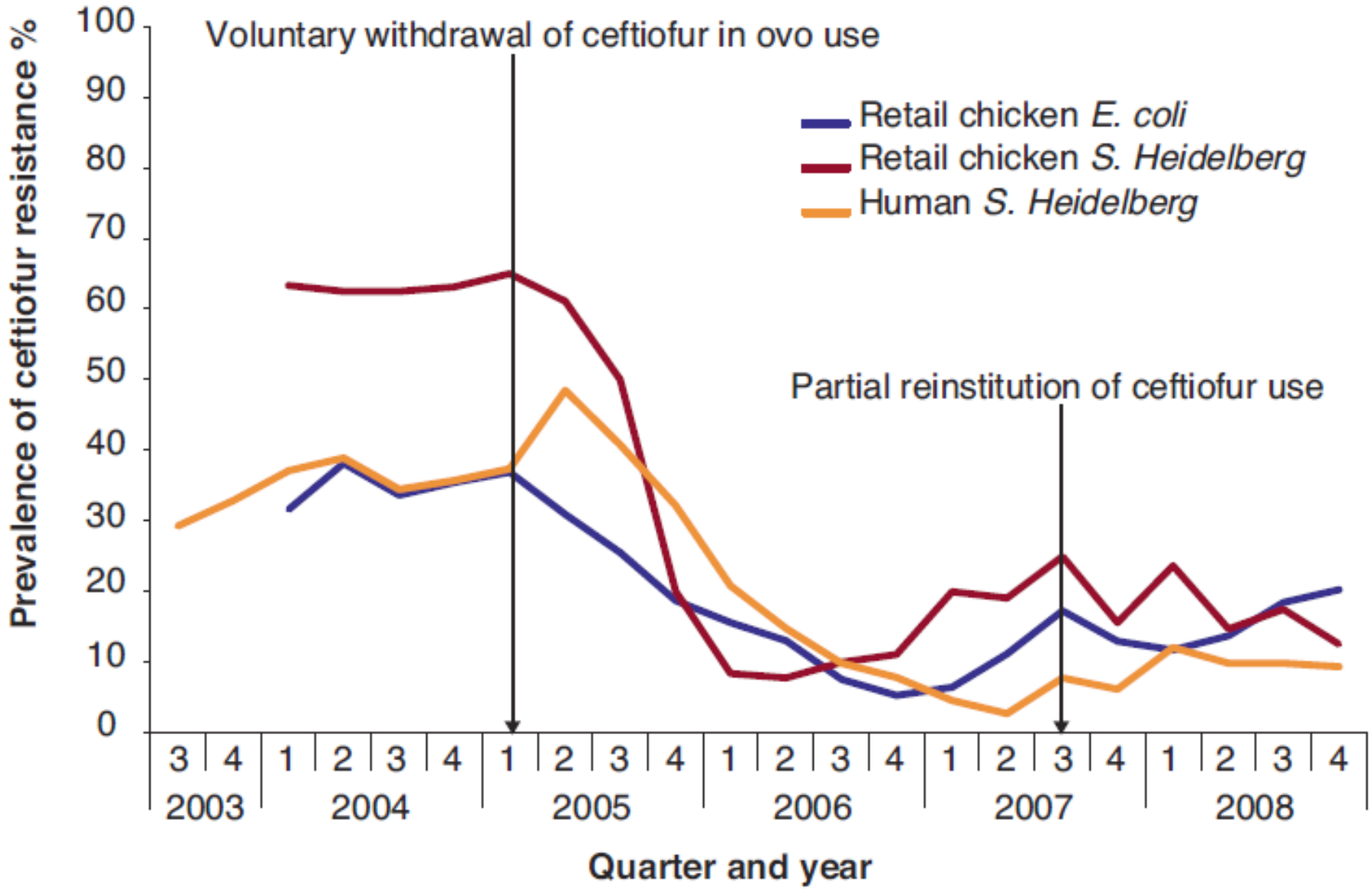

FIG. 2. Numbers of *Campylobacter* spp. in chicken feces collected before, during, and after fluoroquinolone treatment on a free-range commercial chicken farm (flock 5). Each bar represents an individual freshly voided fecal sample. Shading indicates the numbers of ciprofloxacin-resistant *Campylobacter* spp. estimated by replica plating onto Iso-Sensitest agar containing 1 μg of ciprofloxacin per ml, 10 μg of amphotericin B per ml, and 32 μg of cefoperazone per ml (see text). The detection limit for the numbers of resistant strains varied between the samples and is illustrated as a horizontal line through each bar. The > symbol over a bar denotes that the total number of campylobacters exceeded the detection limit indicated by the top of the bar.

Humphrey et al. 2005 AAC

# DANMAP

- 2000-2012 ban on growth promotion practices
- Swine population increased 28%
- Therapeutic use of antibiotics increased 80%
- 2007-2012 – MDR *Salmonella* Typhimurium isolations increased 40-60%; mirrors sporadic cases
- 2003-2012 – increases in resistance of clinical isolates of *E. coli* and *Streptococcus pneumoniae*

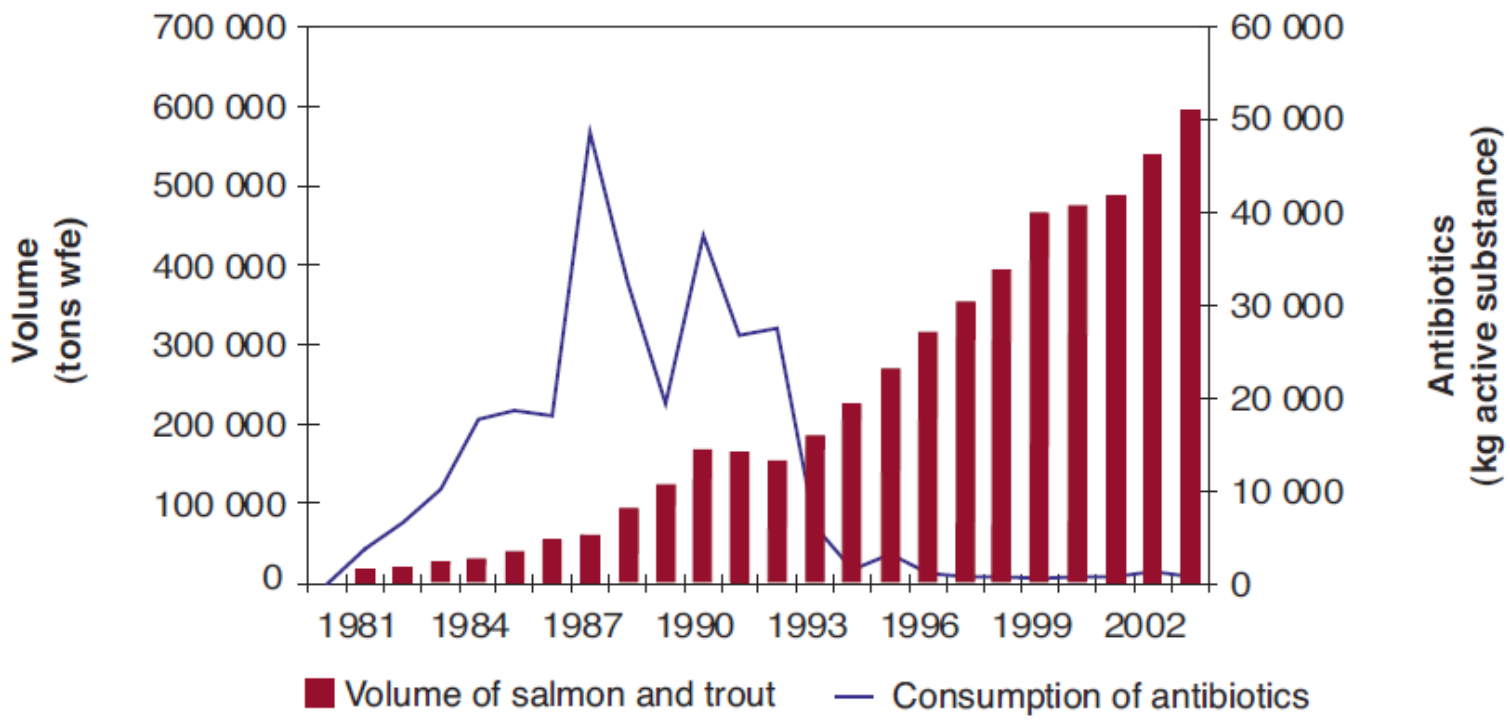
www.danmap.org




Dutil et al. 2010 EID

# Controlling incidence of disease limits the demand for antibiotics

**Figure 4.6 Reduction in antimicrobial use after the introduction of vaccination in aquaculture**




WHO 2012

# USDA-AFRI FY 2015 RFA

## Animal Health and Production of Animal Products

- Total program funds = $27 million, to be divided between:

**Food for thought:**

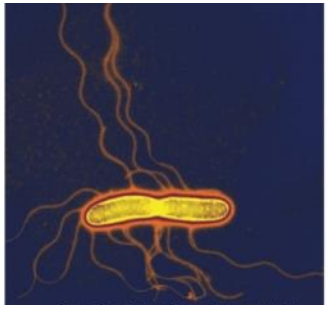
- **NIH biomedical funding $24 billion**
- **USDA funding for animal health < 0.09%**

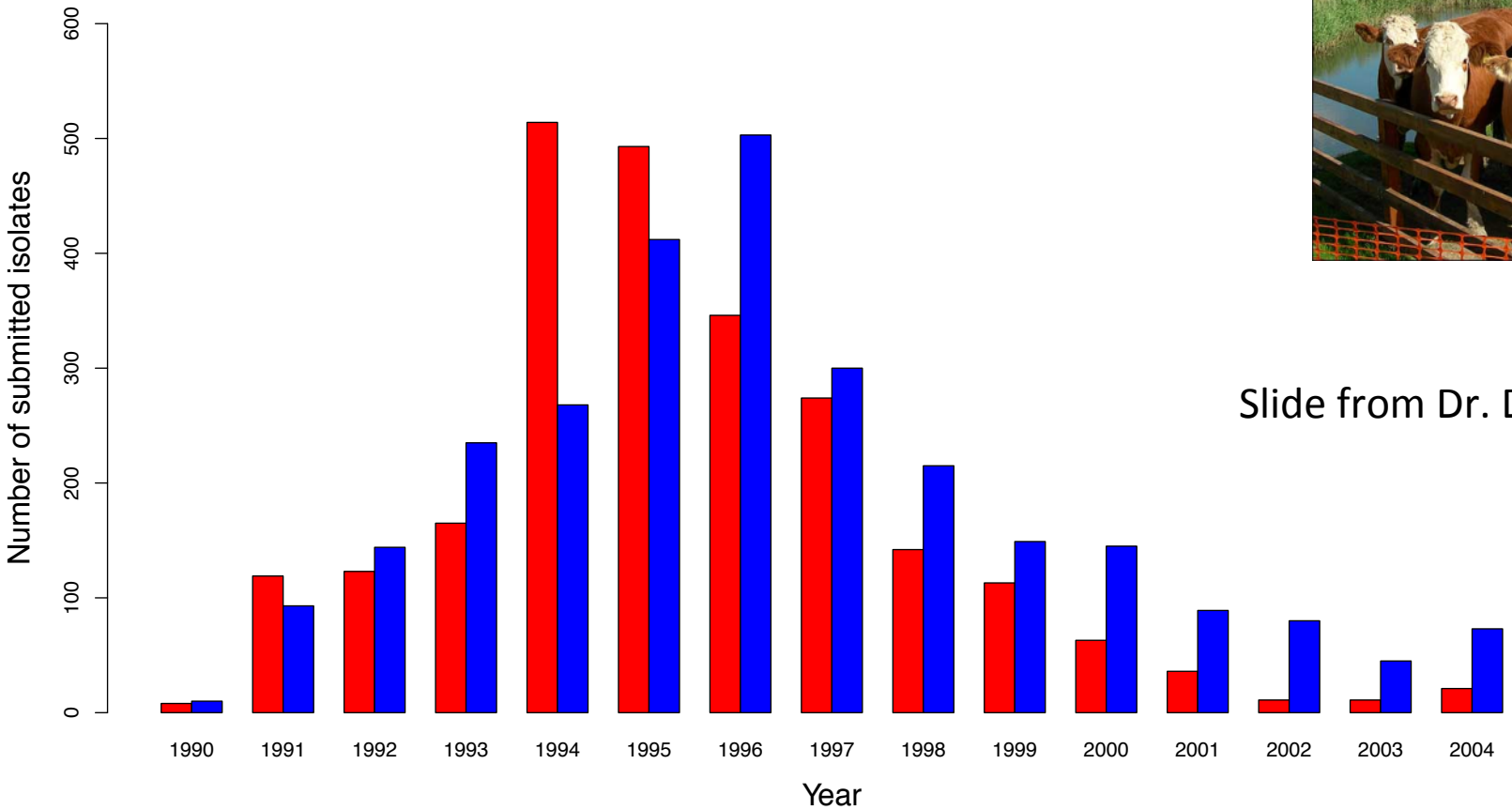
  - Animal health and disease ($11 million total)
  - Tools & resources – animal breeding, genetics & genomics
  - Tools & resources – veterinary immune reagents

Pathogen sequence data

# *Salmonella* Typhimurium DT104

Humans ⇌ Livestock

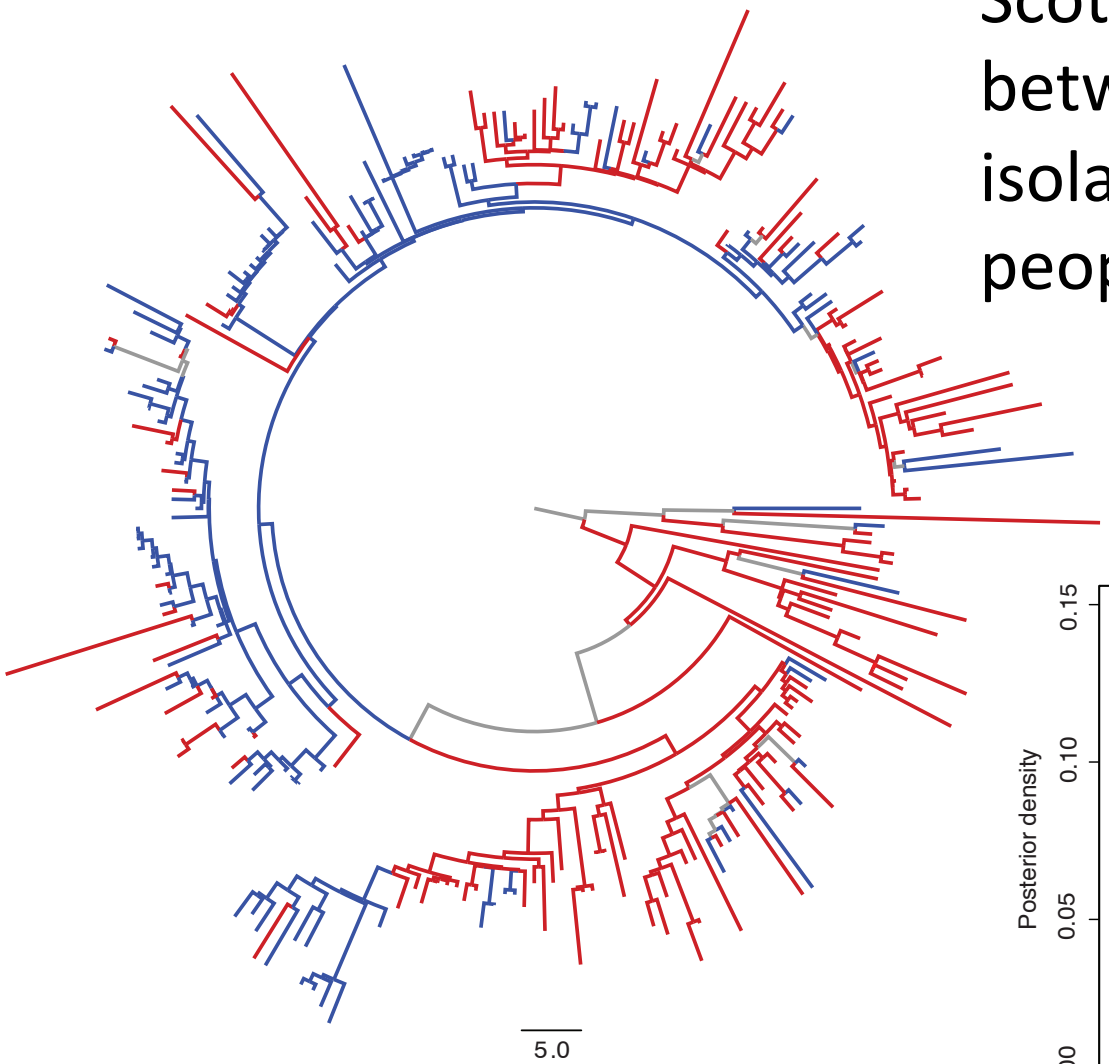


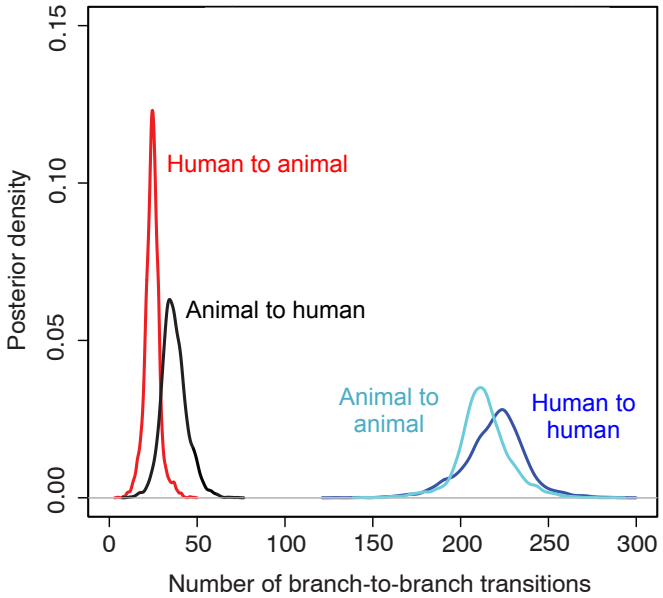



Slide from Dr. Dan Haydon

Mather, A.E., Matthews, L., Mellor, D.J., Reeve, R., Denwood, M.J., Boerlin, P., Reid-Smith, R.J., Brown, D.J., Coia, J.E., Browning, L.M., Haydon, D.T., & Reid, S.W.J. (2012). An ecological approach to assessing the epidemiology of antimicrobial resistance in animal and human populations. *Proceedings of the Royal Society B: Biological Sciences.* 279, 1630-1639.

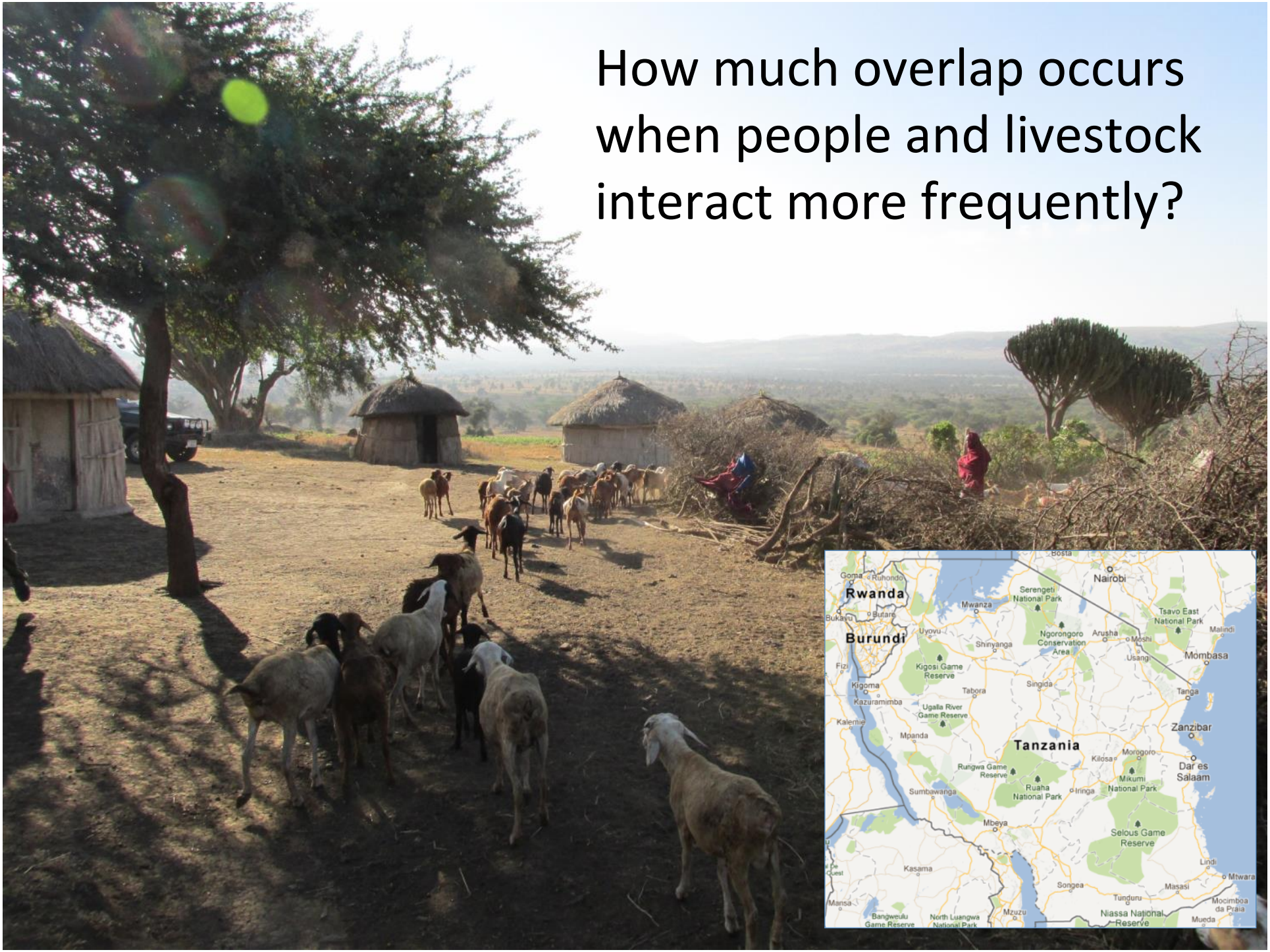
# Scotland: Limited overlap between *Salmonella* isolates from cattle and people

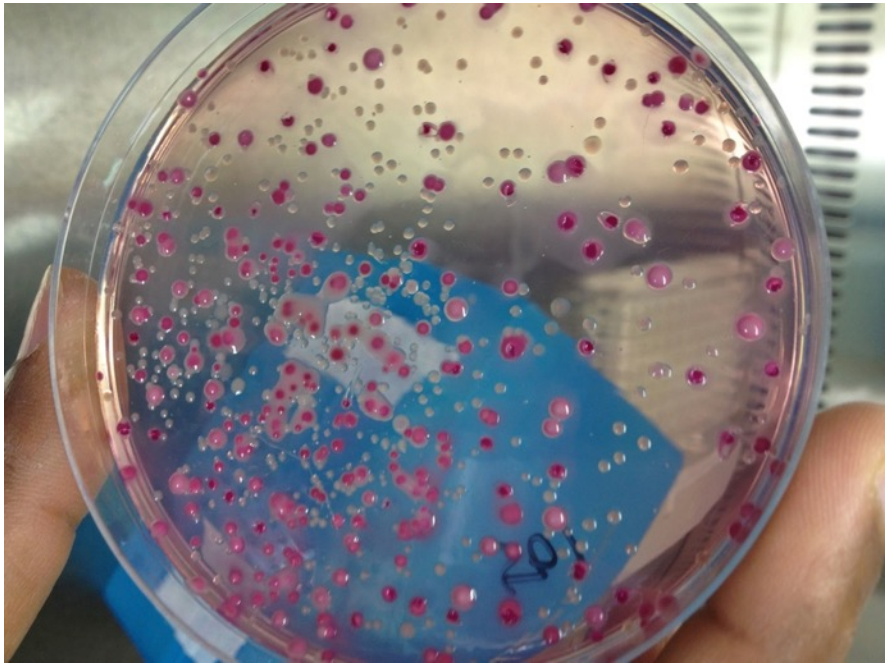



Mather, et al. 2012. *Proc Royal Soc B: Biol Sci.* 279:1630-39; Mather et al. 2013. *Science* 341:1514-17; Afema et al. 2014. Zoonosis Public Health doi: 10.1111/zph.12172

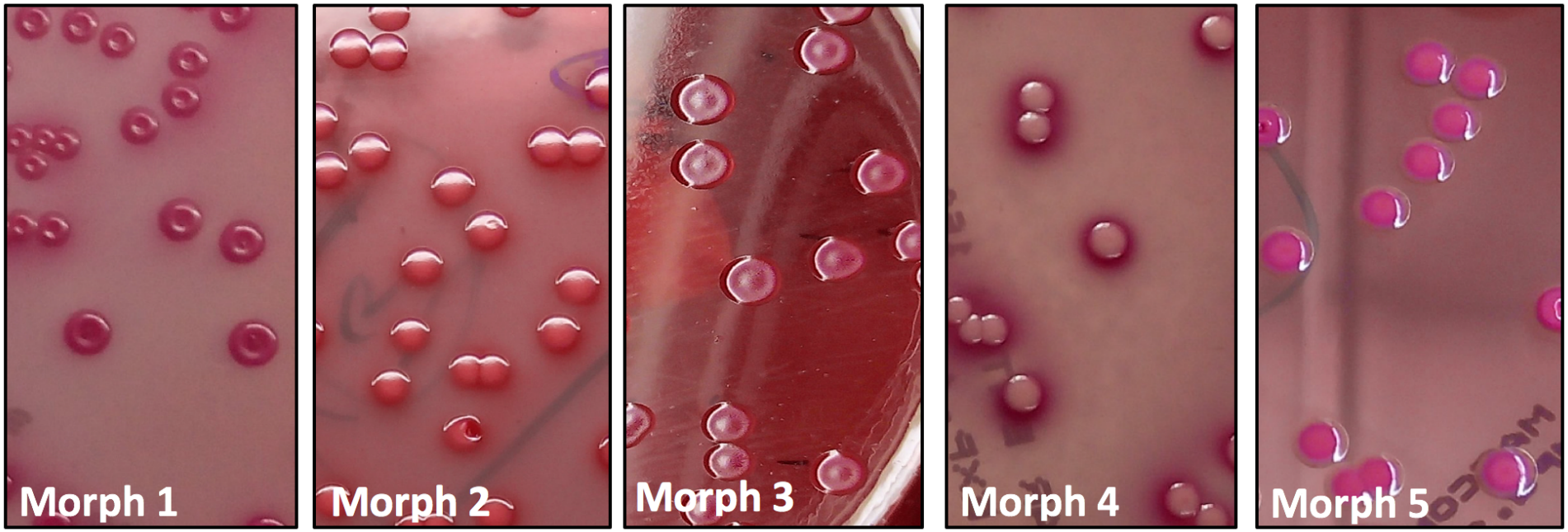
# How much overlap occurs when people and livestock interact more frequently?





**Nelson Mandela African Institution for Science and Technology**

# “Picking” *E. coli* from MacConkey agar plates

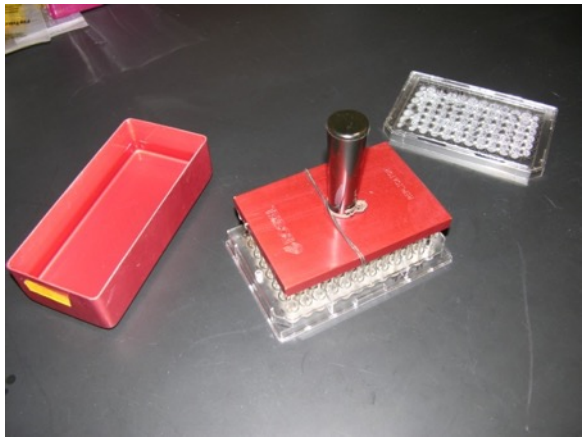


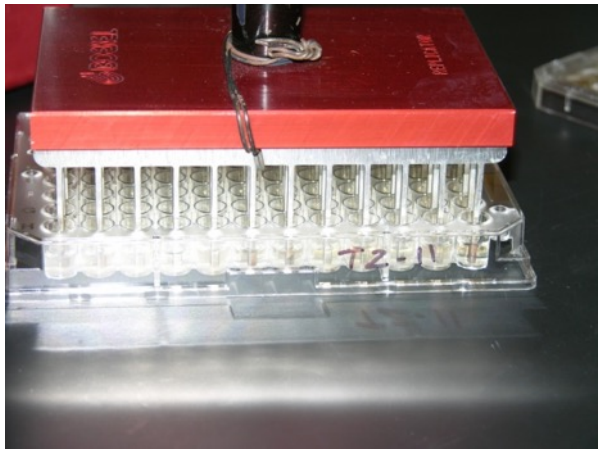

Validated by *uidA* PCR; >95% correct identification

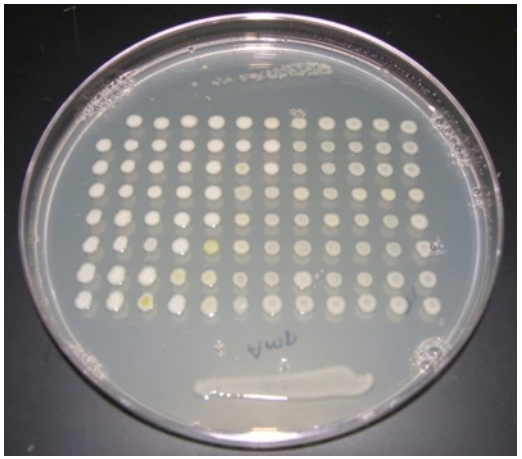
We have assumed that identification errors (*E. coli* or not) and phenotyping errors (resistant or not) are randomly distributed (i.e., no bias)

# Breakpoint assays

| | True prevalence | | |
|---|---|---|---|
| N | 1% | 0.1% | 0.01% |
| 48 | 0.38 | 0.05 | 0.005 |
| 100 | 0.63 | 0.10 | 0.01 |
| 300 | 0.95 | 0.26 | 0.03 |
| 35000 | 1.00 | 1.00 | 0.97 |







| Isolate | Plate | Row | Col | Amp | Chlor | Cipro | Kan | Tet | Sulfa |
|---|---|---|---|---|---|---|---|---|---|
| 362 | 5-10-13 | 3 | 3 | 1 | 1 | 1 | 1 | 0 | 0 |
| 363 | 5-10-13 | 3 | 4 | 1 | 0 | 0 | 1 | 1 | 1 |
| 364 | 5-10-13 | 3 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| 365 | 5-10-13 | 3 | 6 | 0 | 1 | 0 | 0 | 1 | 1 |
| 366 | 5-10-13 | 3 | 7 | 1 | 0 | 0 | 0 | 1 | 1 |

**Attributes of Study Villages (N=416 households).**

| Ethnicity | Site | *N* | Season | Year(s) |
|---|---|---|---|---|
| Maasai N=197 | Monduli | 34 | Wet&Dry | 13/15 |
| | Loibor Siret | 45 | Dry | 13/15 |
| | Terat | 23 | Wet | 13 |
| | Nadonjukin | 45 | Wet&Dry | 13/14/15 |
| | Loliondo | 20 | Dry | 13 |
| | Komolo | 30 | Dry | 15 |
| Arusha N=118 | Aremeru ward | 51 | Wet&Dry | 13/15 |
| | Loroi | 33 | Dry | 15 |
| | Meliot | 34 | Dry | 15 |
| Chagga N=101 | Masaera kati | 27 | Wet&Dry | 14 |
| | Masaera juu | 23 | Dry | 14 |
| | Mamsera chini | 25 | Dry | 14 |
| | Mamsera juu | 25 | Dry | 14 |

## Proportion of livestock owners and antibiotic use

| Variable | Chagga (n = 95) | Maasai (n = 203) | Arusha (n = 75) |
|---|---|---|---|
| Certified veterinarian | 0.96 | 0.36 | 0.45 |
| Veterinary drug shop | 0.04 | 0.58 | 0.37 |
| Traditional healers | 0.01 | 0.19 | 0.03 |
| No withdrawal | 0.04 | 0.93 | 0.28 |
| Self-report lay use of VA | 0.01 | 0.74 | 0.21 |
| Owns syringe for VA | 0.02 | 0.95 | 0.41 |

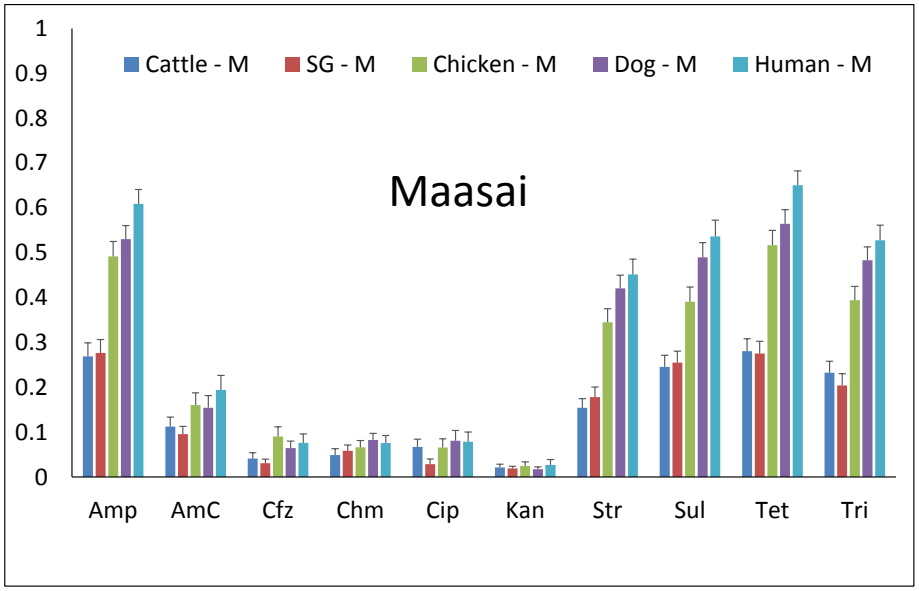
**Common livestock illnesses and frequency of antibiotic use for these presumptive diseases in Maasai households**

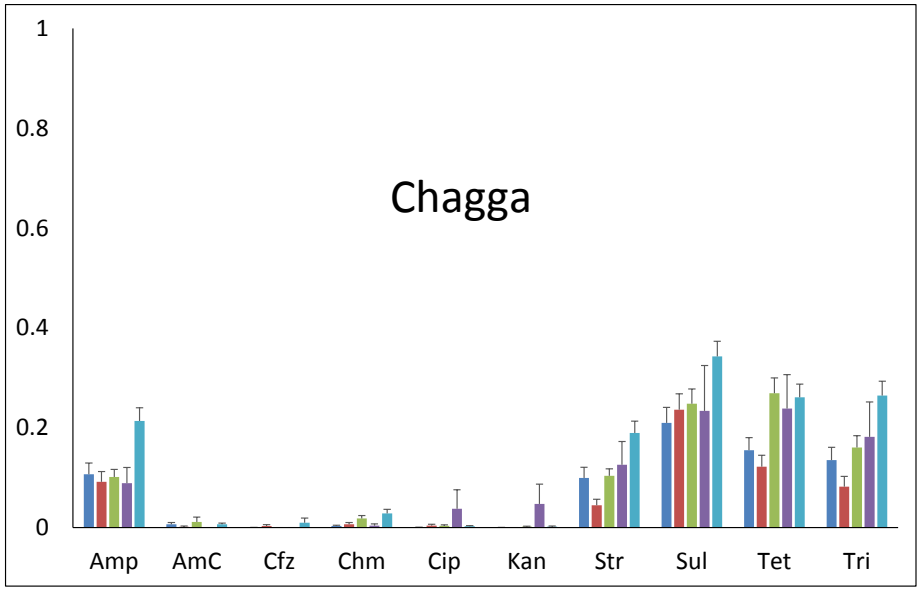
| Livestock illness | Freq | Prop | Treat |
|---|---|---|---|
| "*Endigana*" (East Coast Fever & Anaplasmosis) | 77 | 0.38 | VA |
| Pneumonia (CBPP or CCPP[a], possibly Pasteurellaceae) | 51 | 0.25 | VA |
| Foot and Mouth Disease (viral) | 33 | 0.16 | VA |
| Heartwater disease (*Ehrlichia ruminantium*) | 20 | 0.10 | VA |
| Trypanosomiasis (protozoa) | 11 | 0.05 | Antiprotazoal |
| Anthrax (*Bacillus anthracis*) | 9 | 0.04 | None[b] |
| Malignant Catarrhal Fever (viral) | 3 | 0.01 | None |
| Total | 204 | | |

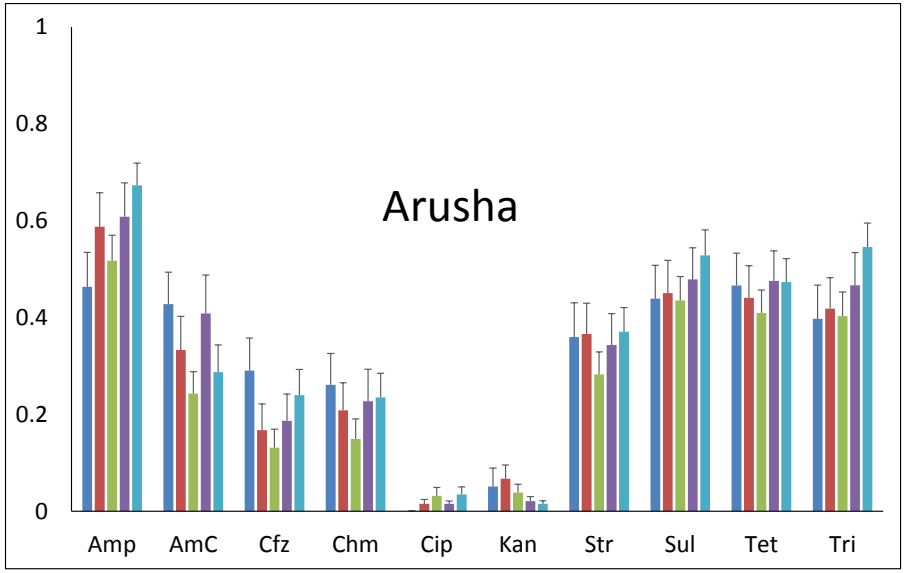
VA = veterinary antibiotics

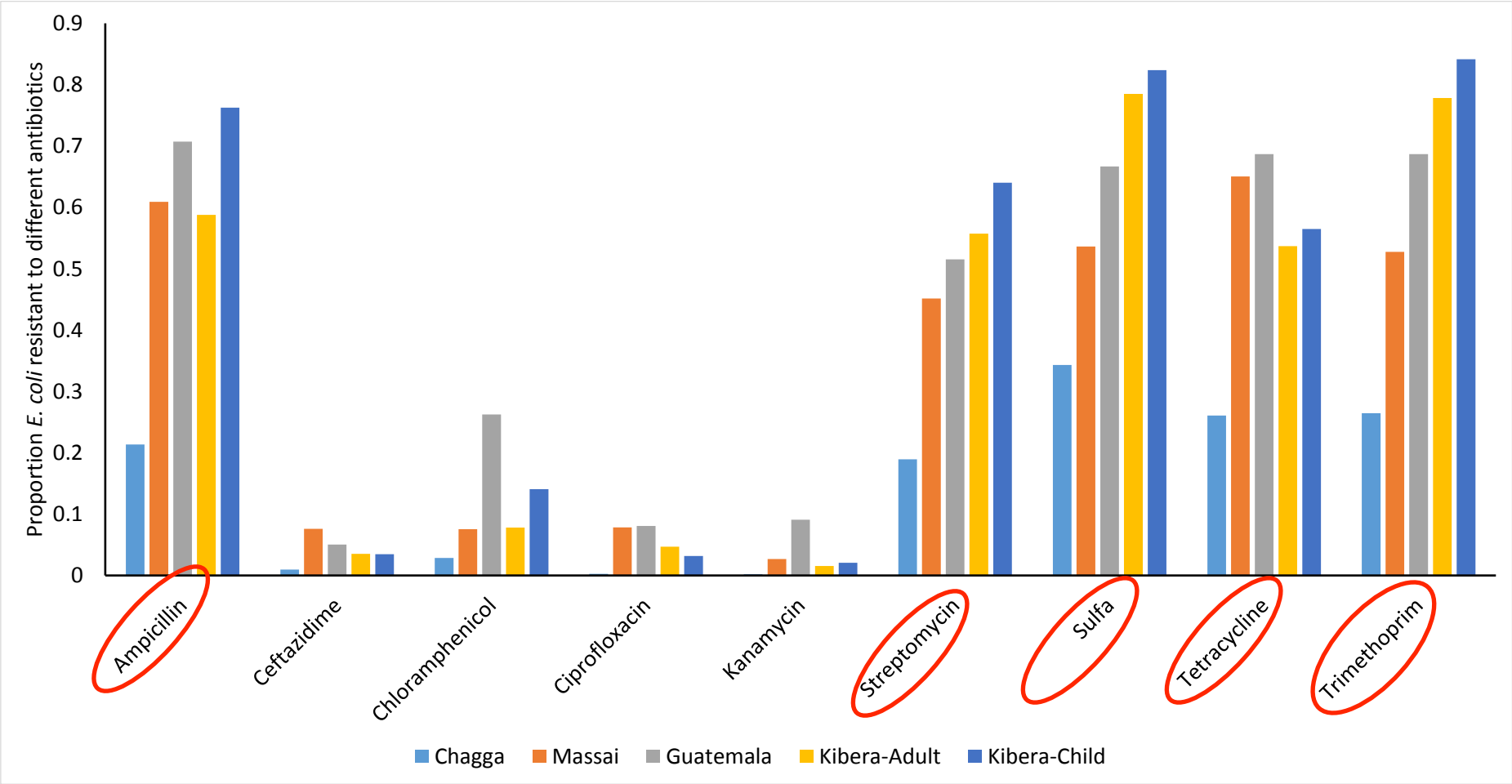
**Proportion of common veterinary antibiotics on hand in Maasai and Arusha homesteads**

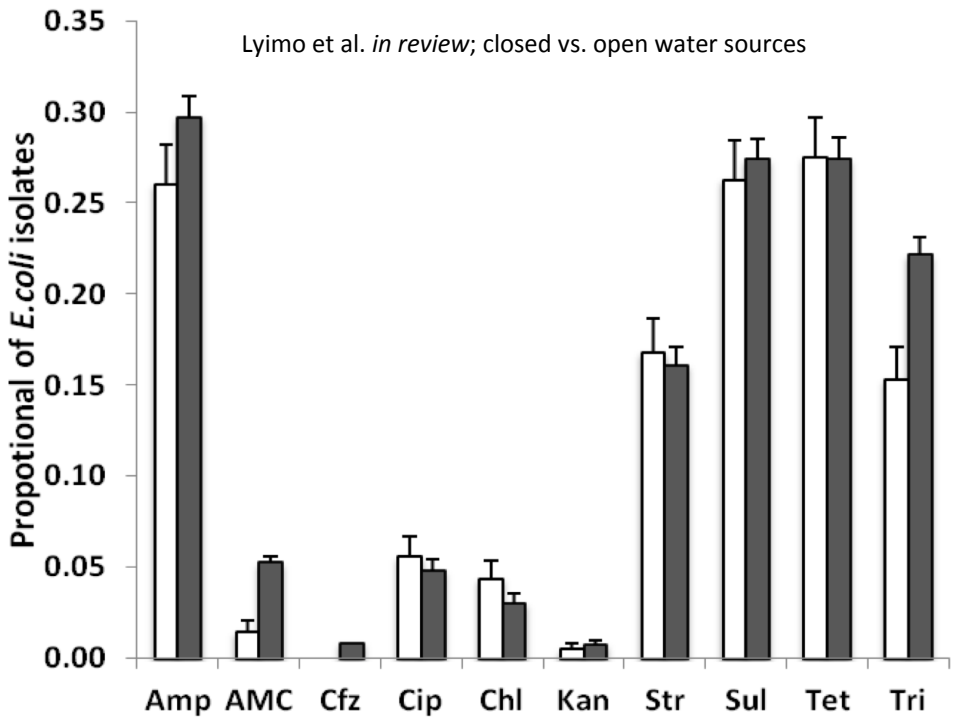
| Veterinary Antibiotics | Maasai | Arusha |
|---|---|---|
| Oxytetracycline | 0.80 | 0.15 |
| Penicillin & Streptomycin | 0.04 | 0.01 |
| Tylosin | 0.05 | 0.07 |
| Sulfonimides | 0.02 | 0.00 |

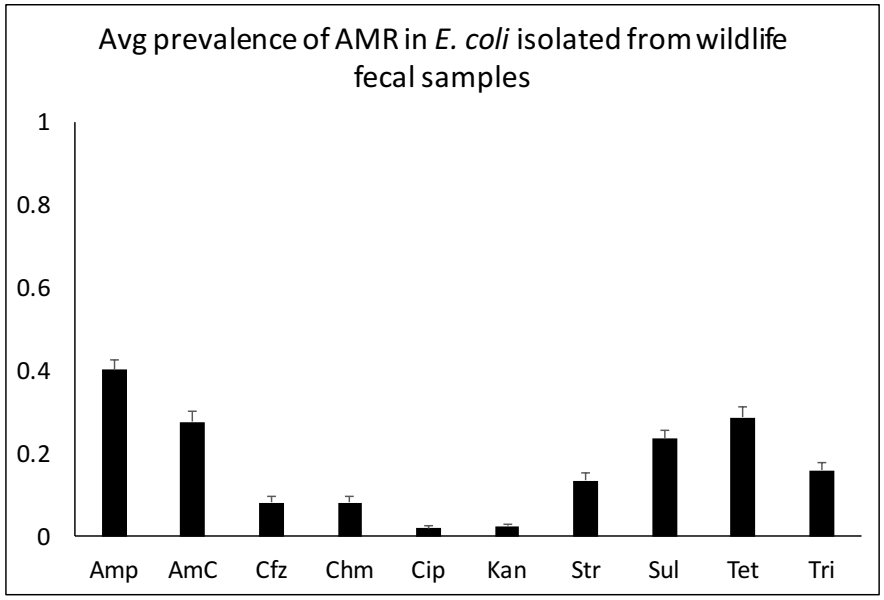

Maasai
Cattle - M
SG - M
Chicken - M
Dog - M
Human - M
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Amp
AmC
Cfz
Chm
Cip
Kan
Str
Sul
Tet
Tri

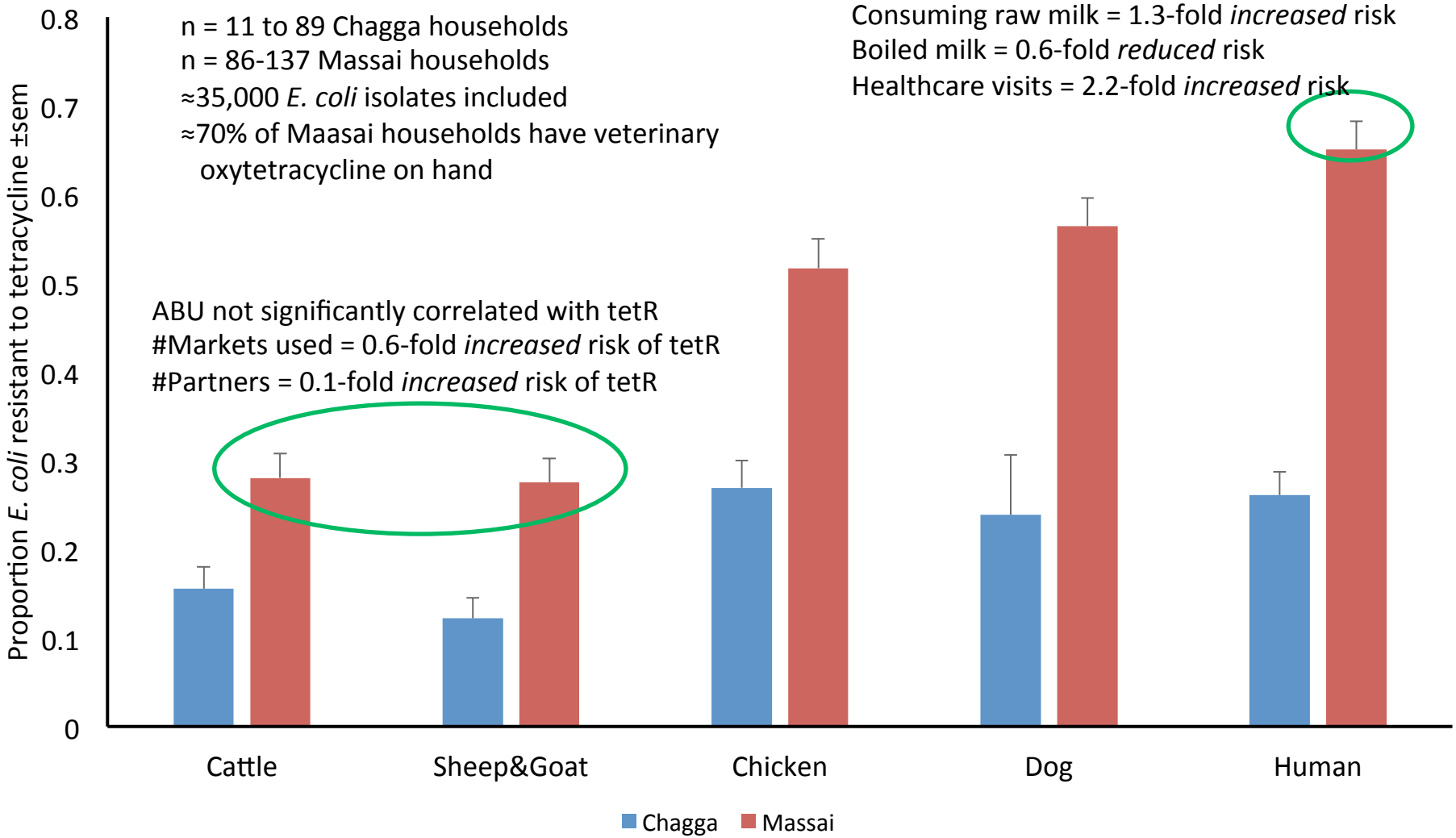

Chagga
1
0.8
0.6
0.4
0.2
0
Amp
AmC
Cfz
Chm
Cip
Kan
Str
Sul
Tet
Tri

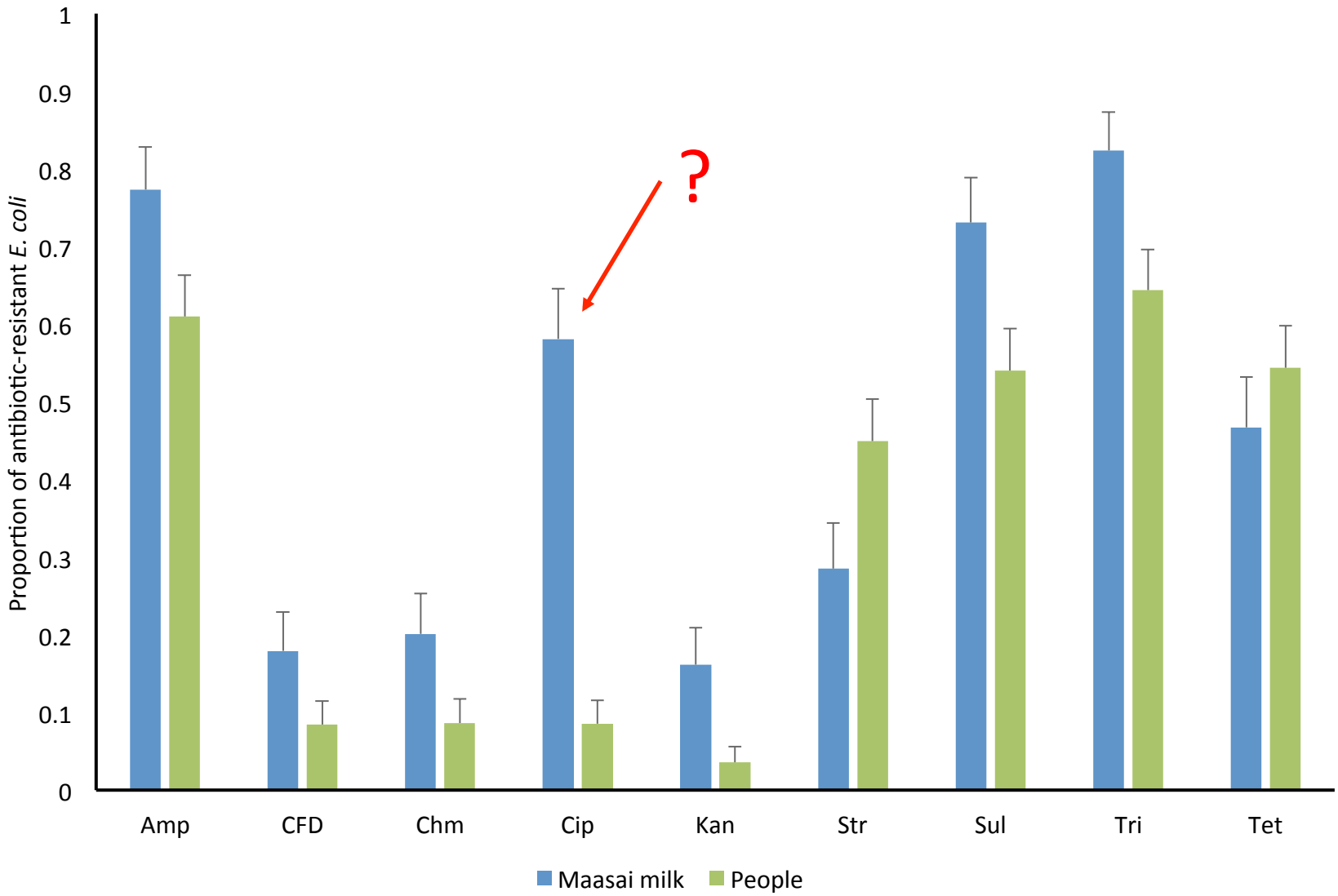

Arusha
1
0.8
0.6
0.4
0.2
0
Amp
AmC
Cfz
Chm
Cip
Kan
Str
Sul
Tet
Tri

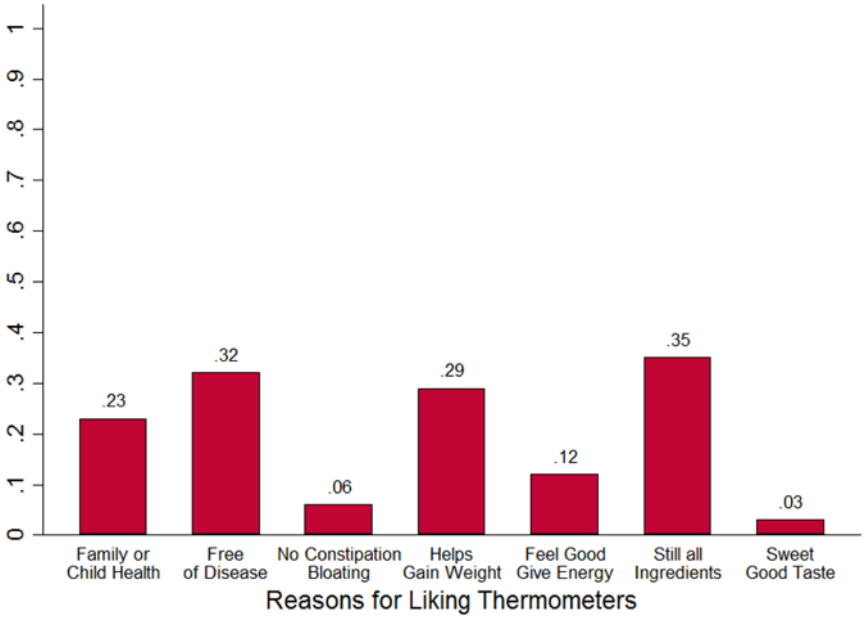

Proportion E. coli resistant to different antibiotics
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Ampicillin
Ceftazidime
Chloramphenicol
Ciprofloxacin
Kanamycin
Streptomycin
Sulfa
Tetracycline
Trimethoprim
Chagga
Massai
Guatemala
Kibera-Adult
Kibera-Child

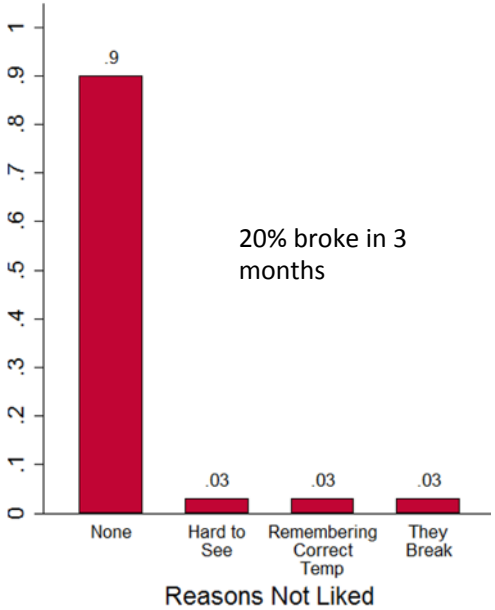

Lyimo et al. *in review*; closed vs. open water sources
Propotional of *E.coli* isolates
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Amp
AMC
Cfz
Cip
Chl
Kan
Str
Sul
Tet
Tri


Avg prevalence of AMR in *E. coli* isolated from wildlife fecal samples
1
0.8
0.6
0.4
0.2
0
Amp
AmC
Cfz
Chm
Cip
Kan
Str
Sul
Tet
Tri

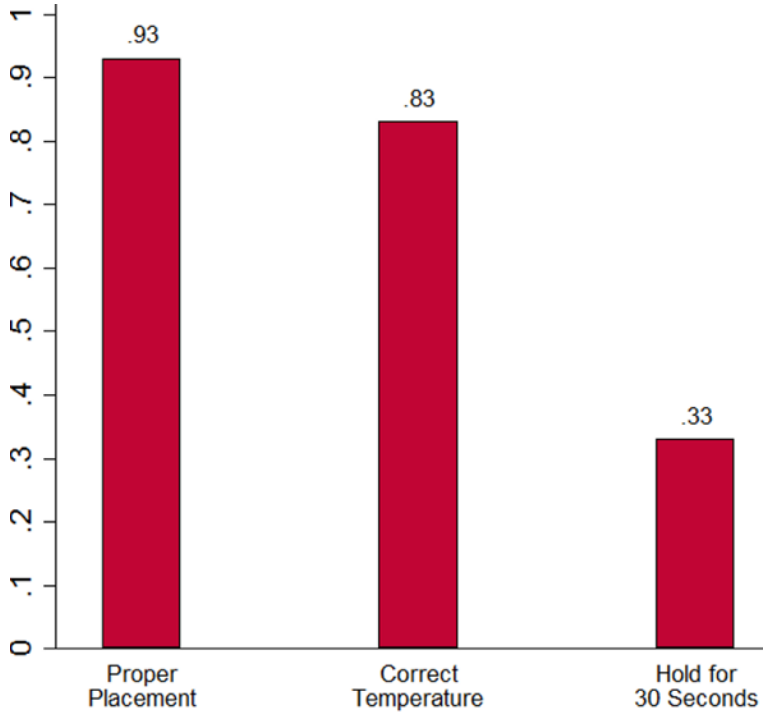

n = 11 to 89 Chagga households
n = 86-137 Massai households
≈35,000 E. coli isolates included
≈70% of Maasai households have veterinary oxytetracycline on hand
Consuming raw milk = 1.3-fold increased risk
Boiled milk = 0.6-fold reduced risk
Healthcare visits = 2.2-fold increased risk
ABU not significantly correlated with tetR
#Markets used = 0.6-fold increased risk of tetR
#Partners = 0.1-fold increased risk of tetR
Proportion E. coli resistant to tetracycline ±sem
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Cattle
Sheep&Goat
Chicken
Dog
Human
Chagga
Massai


1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Proportion of antibiotic-resistant E. coli
?
Amp
CFD
Chm
Cip
Kan
Str
Sul
Tri
Tet
Maasai milk
People




20% broke in 3 months



# Conclusions from TZ study

- There is no clear veterinary antibiotic-use signature, although the system is confounded
- Consumption of raw milk is an important risk factor and point of intervention
- The high prevalence of select resistance traits across all hosts tested is consistent with passive transmission from background reservoirs.

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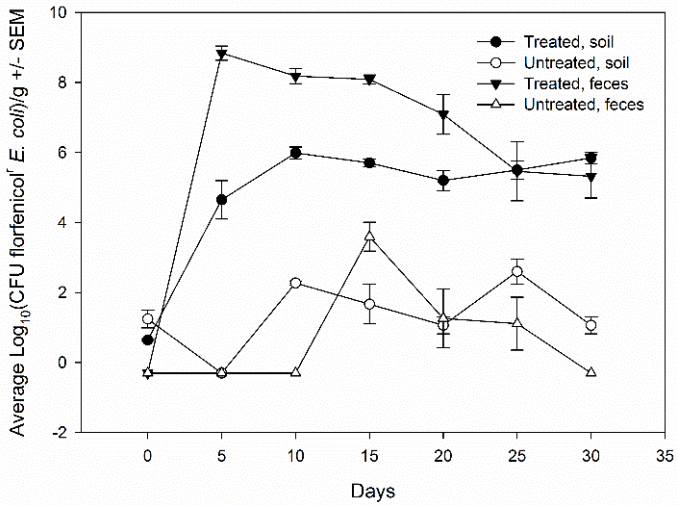
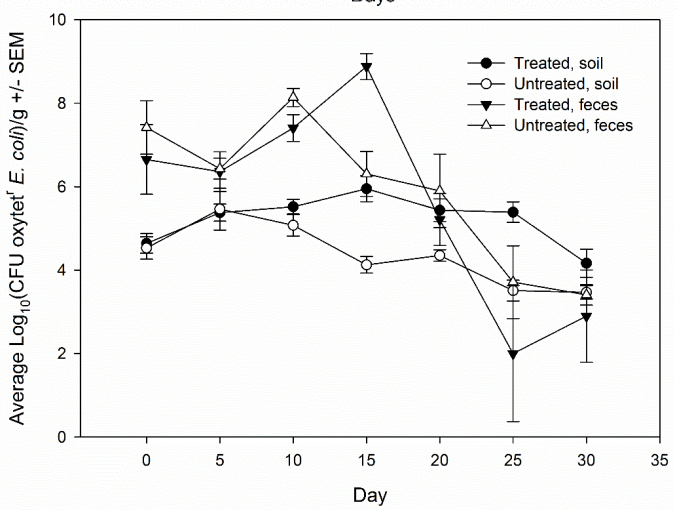
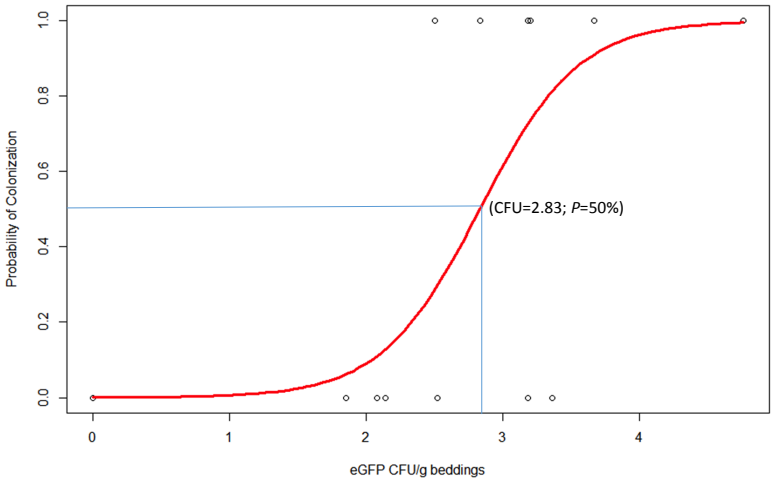
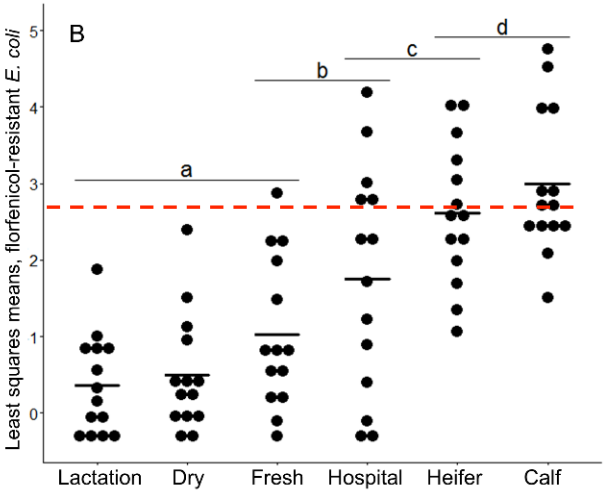
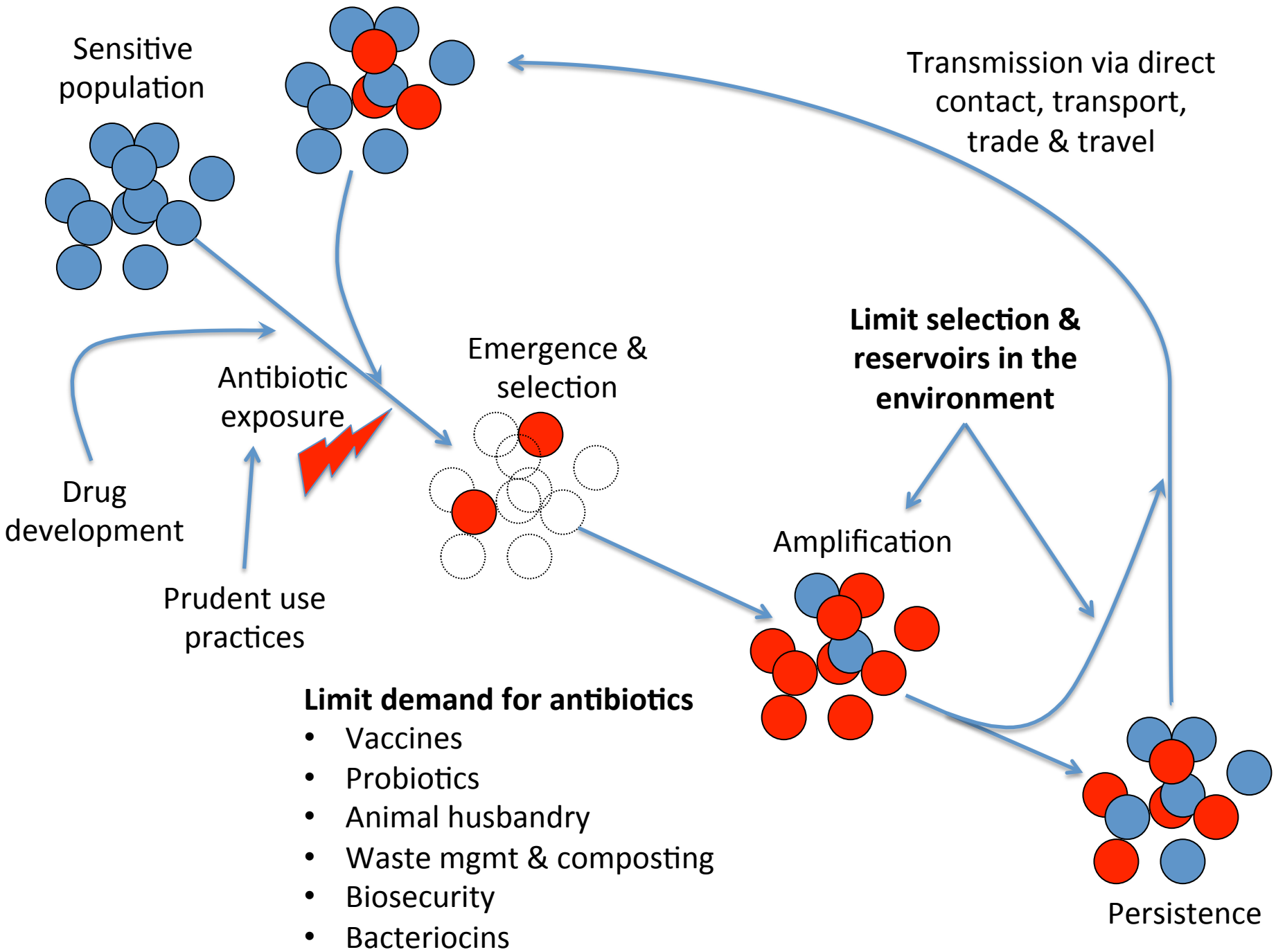
- National Pork Board

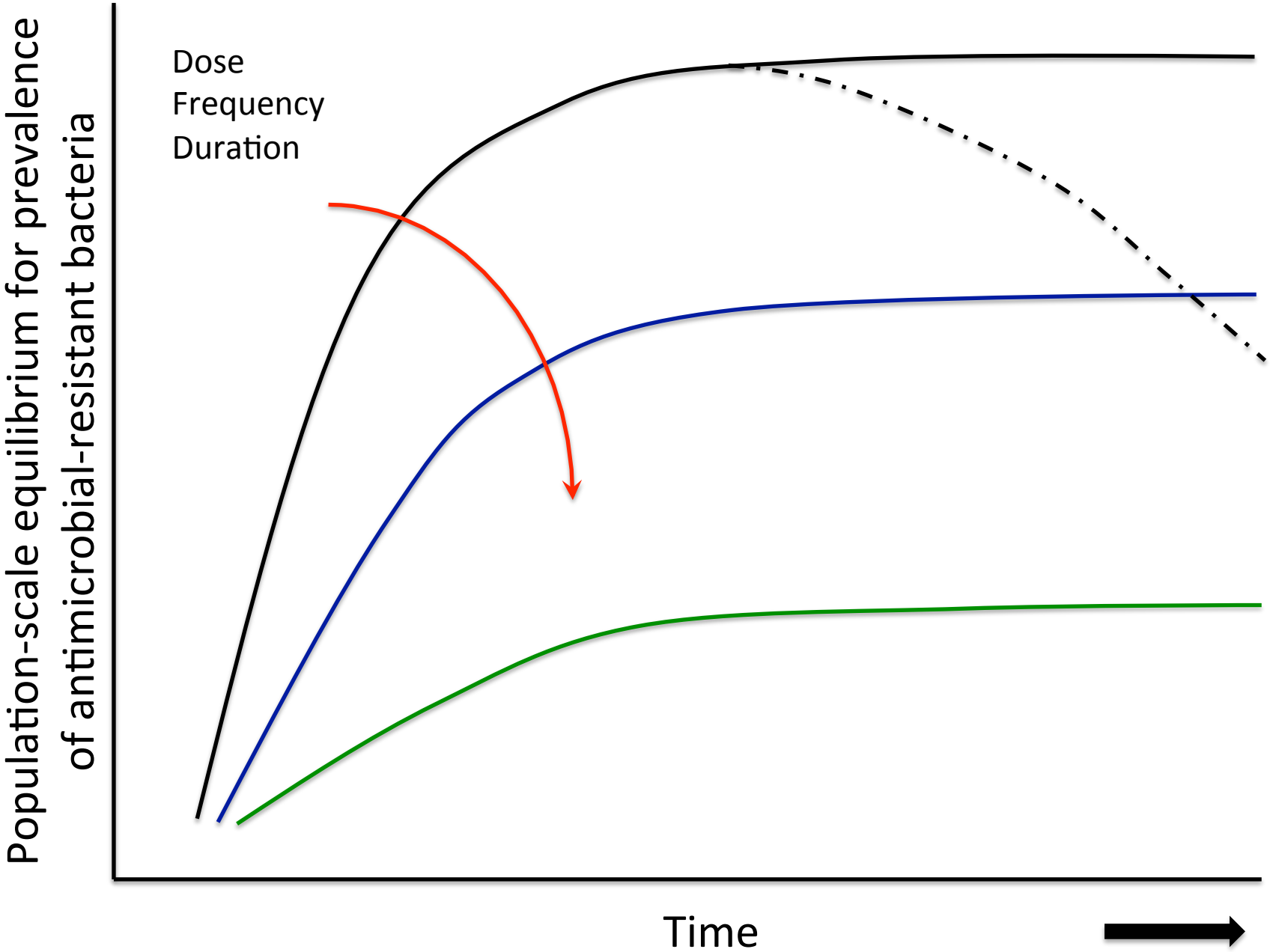

Treated, soil
Untreated, soil
Treated, feces
Untreated, feces
Average Log10(CFU florfenicolr E. coli)/g +/- SEM
Days


Treated, soil
Untreated, soil
Treated, feces
Untreated, feces
Average Log10(CFU oxytetr E. coli)/g +/- SEM
Day


(CFU=2.83; P=50%)
Probability of Colonization
eGFP CFU/g beddings


B
a
b
c
d
Least squares means, florfenicol-resistant E. coli
Lactation
Dry
Fresh
Hospital
Heifer
Calf


Sensitive population
Transmission via direct contact, transport, trade & travel
Antibiotic exposure
Emergence & selection
Limit selection & reservoirs in the environment
Drug development
Amplification
Prudent use practices
Limit demand for antibiotics
• Vaccines
• Probiotics
• Animal husbandry
• Waste mgmt & composting
• Biosecurity
• Bacteriocins
Persistence


Population-scale equilibrium for prevalence
of antimicrobial-resistant bacteria
Dose
Frequency
Duration
Time

# Next Up!

Dr. Katherine Haman

Veterinarian/Epidemiologist, Washington State Department of Fish and Wildlife