Antibiotics and Food-Animals: Challenges and Opportunities

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Preserving the efficacy of antibiotics

Scales of investigation:
- Commensal & pathogenic bacteria
- People and animals
- Individuals and households
- Communities and hospitals
- Rural and urban

Current research:
- **AMR gene function & regulation**
- **Manipulating AMR fitness cost**
- **Alternatives to antibiotics**
- **Environmental fate of antibiotics**
- **Biofilms and wounds**
- **Epidemiology of AMR**
- **Testing interventions**

Intervention projects:
- Water sanitation/ infused iodine
- Pasteurization in rural East Africa

Where we work:
- Pacific Northwest, Tanzania, Kenya, Guatemala and Brazil

Funding, 2000-2018

NSF

USDA

DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA
DMRDP

NIH
National Institutes of Health

CDC
Centers for Disease Control and Prevention

Bill & Melinda Gates foundation

Funded by UK Government
Fleming Fund

BBSRC
bioscience for the future

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Framing the problem

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

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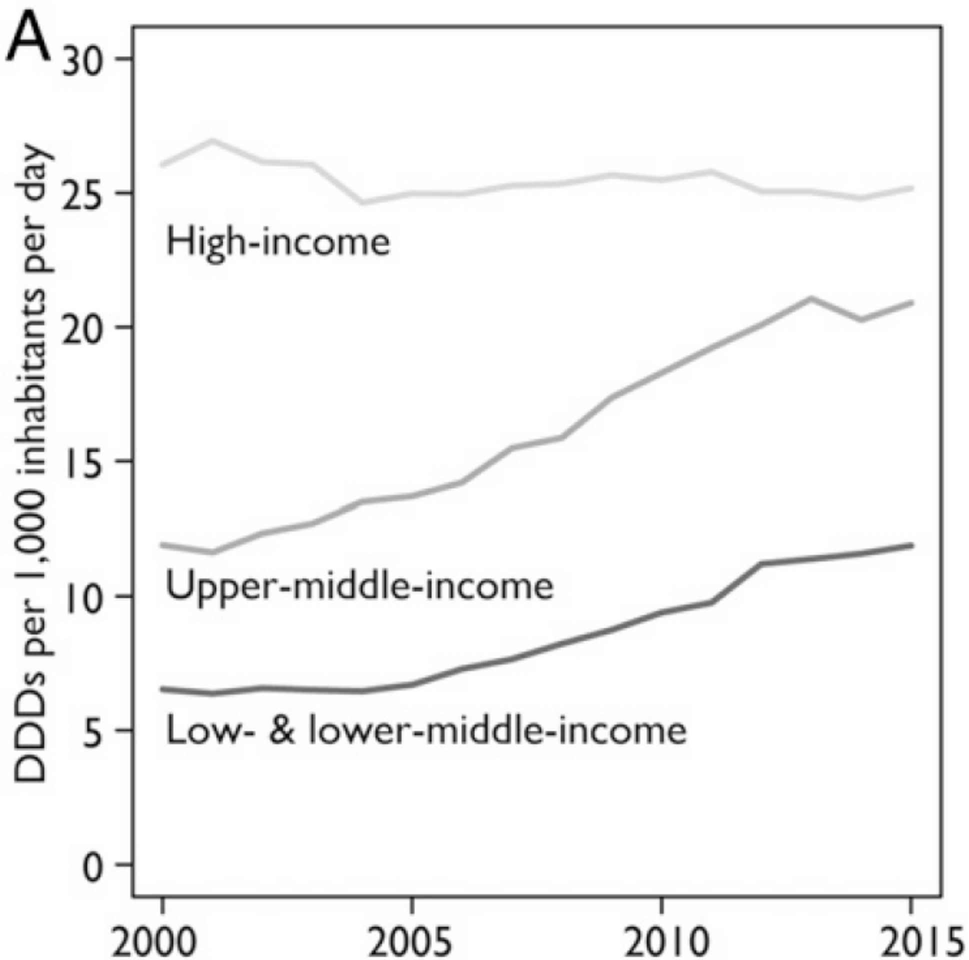
Framing the problem



Antibiotic use is ultimate driver, with pressure coming from both human and veterinary medical use

Ultimately, growth in demand for antibiotics is being driven by global demographics…

Klein et al. 2018. PNAS

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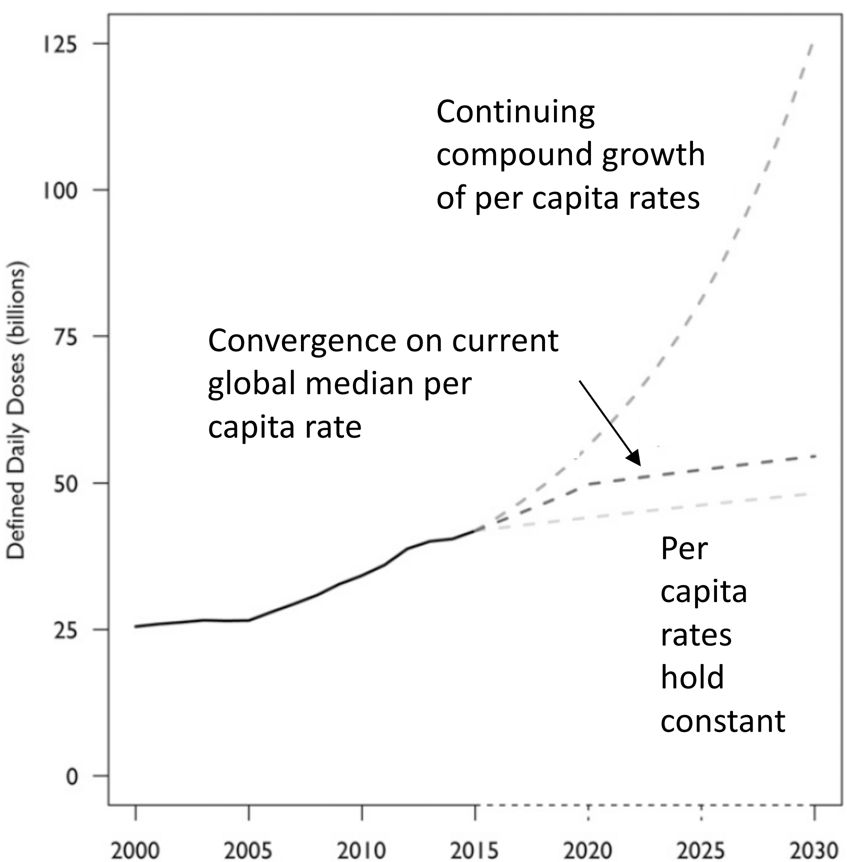
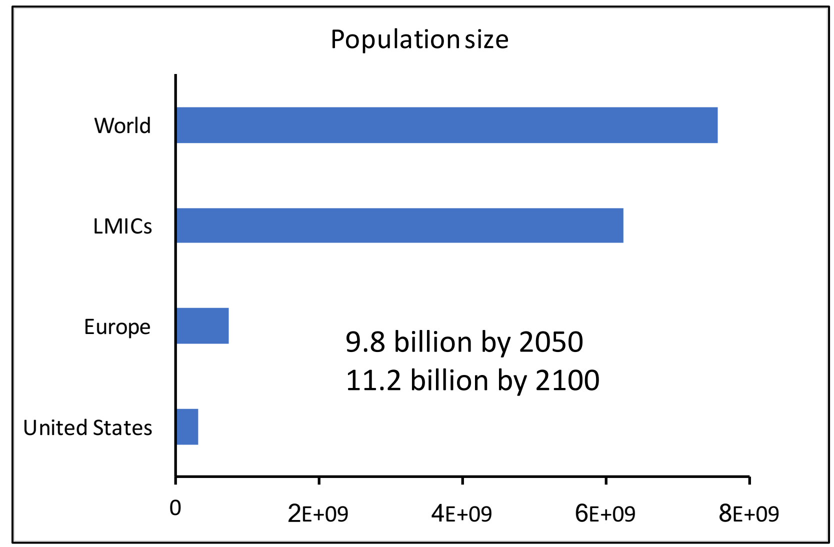
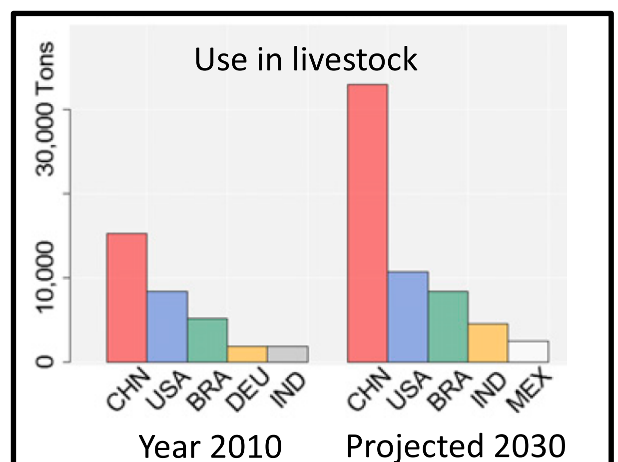
Framing the problem



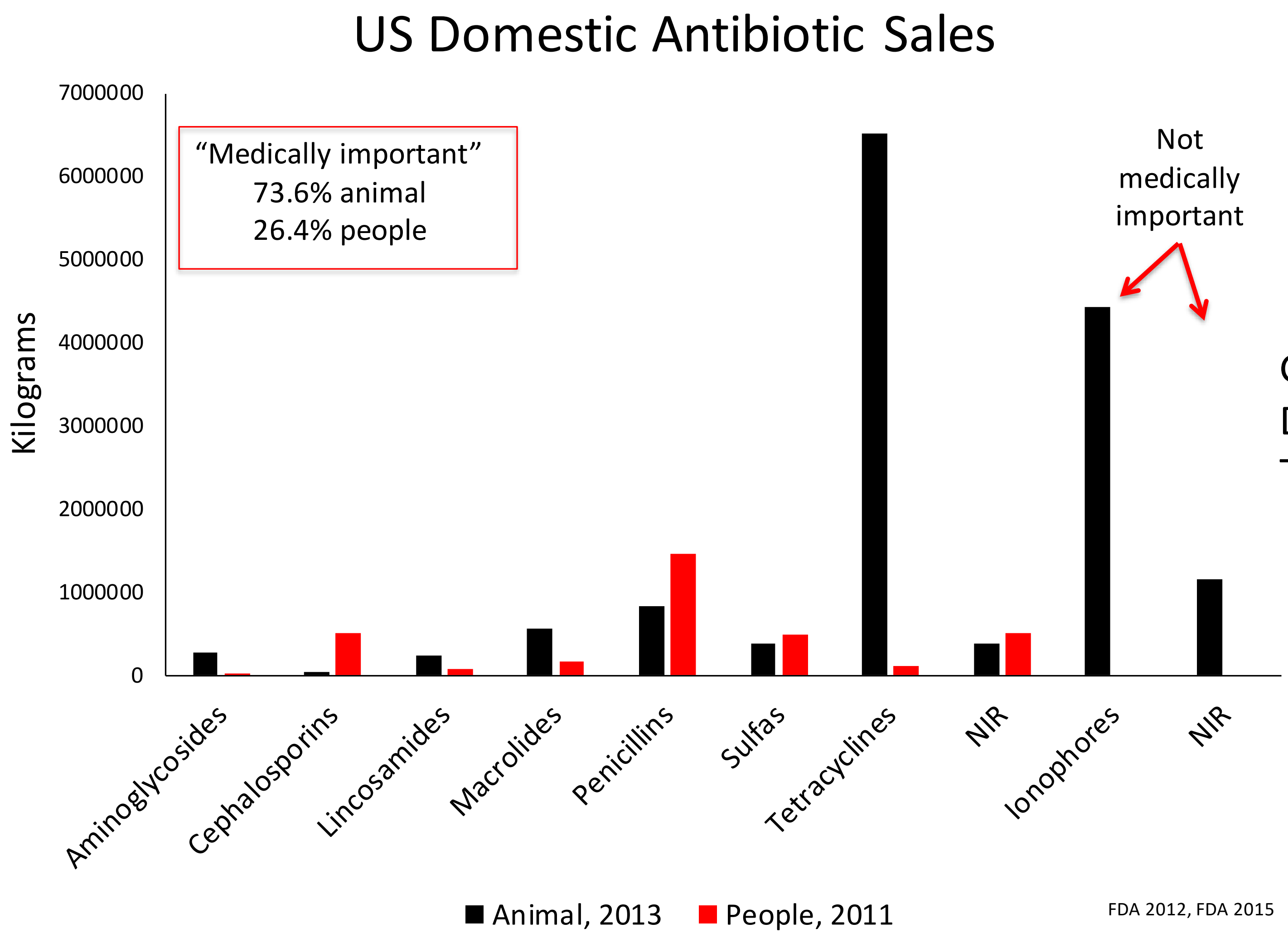
Klein et al. 2018. PNAS





Van Boeckel et al. 2015. PNAS

Framing the problem – 2015 perspective



Growth promotion
Disease prevention
Therapeutic treatment

FDA 2012, FDA 2015

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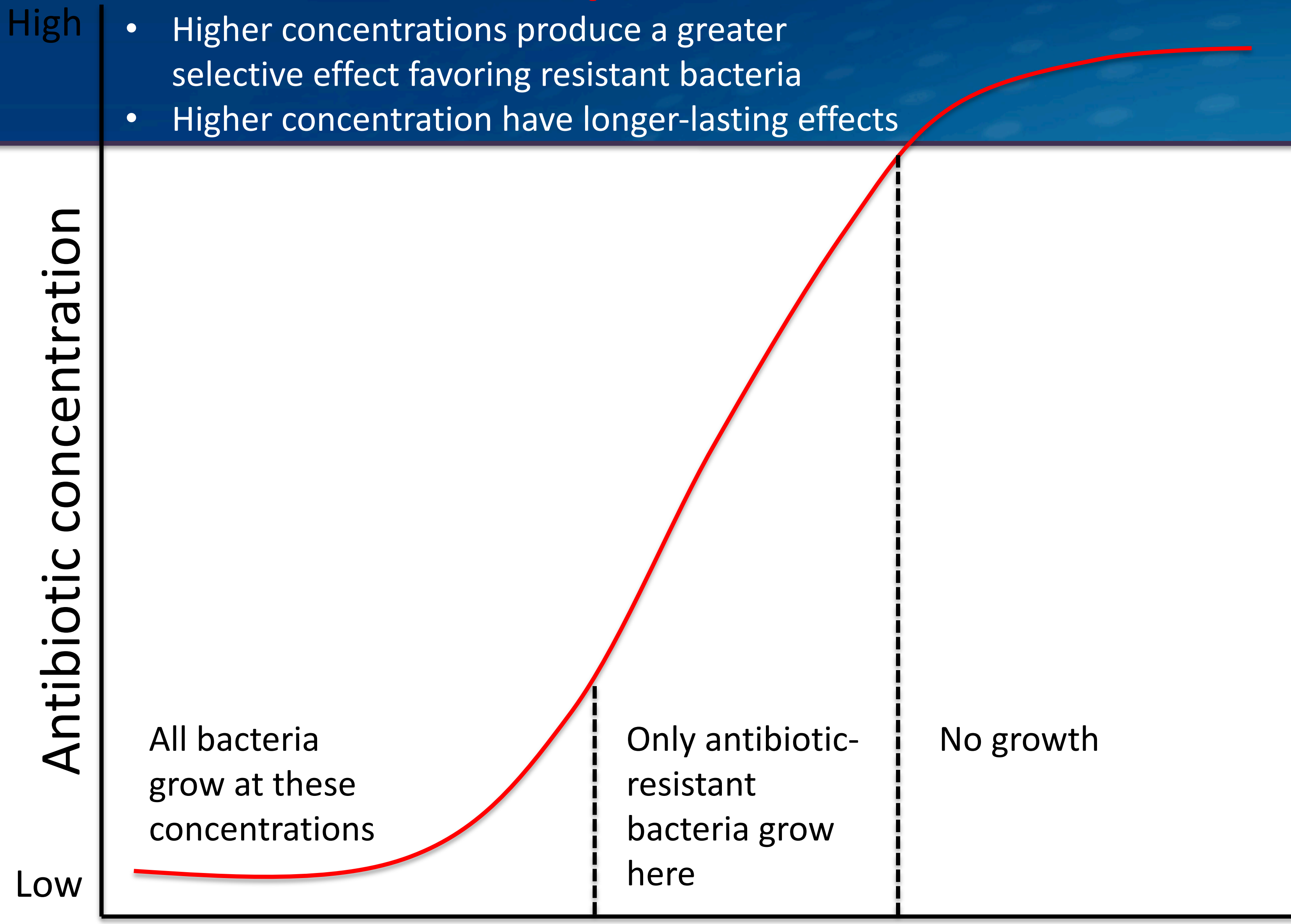
What are the major contributors to antimicrobial resistance?

A food-animal perspective

Concentration is important

- Higher concentrations produce a greater selective effect favoring resistant bacteria
- Higher concentration have longer-lasting effects



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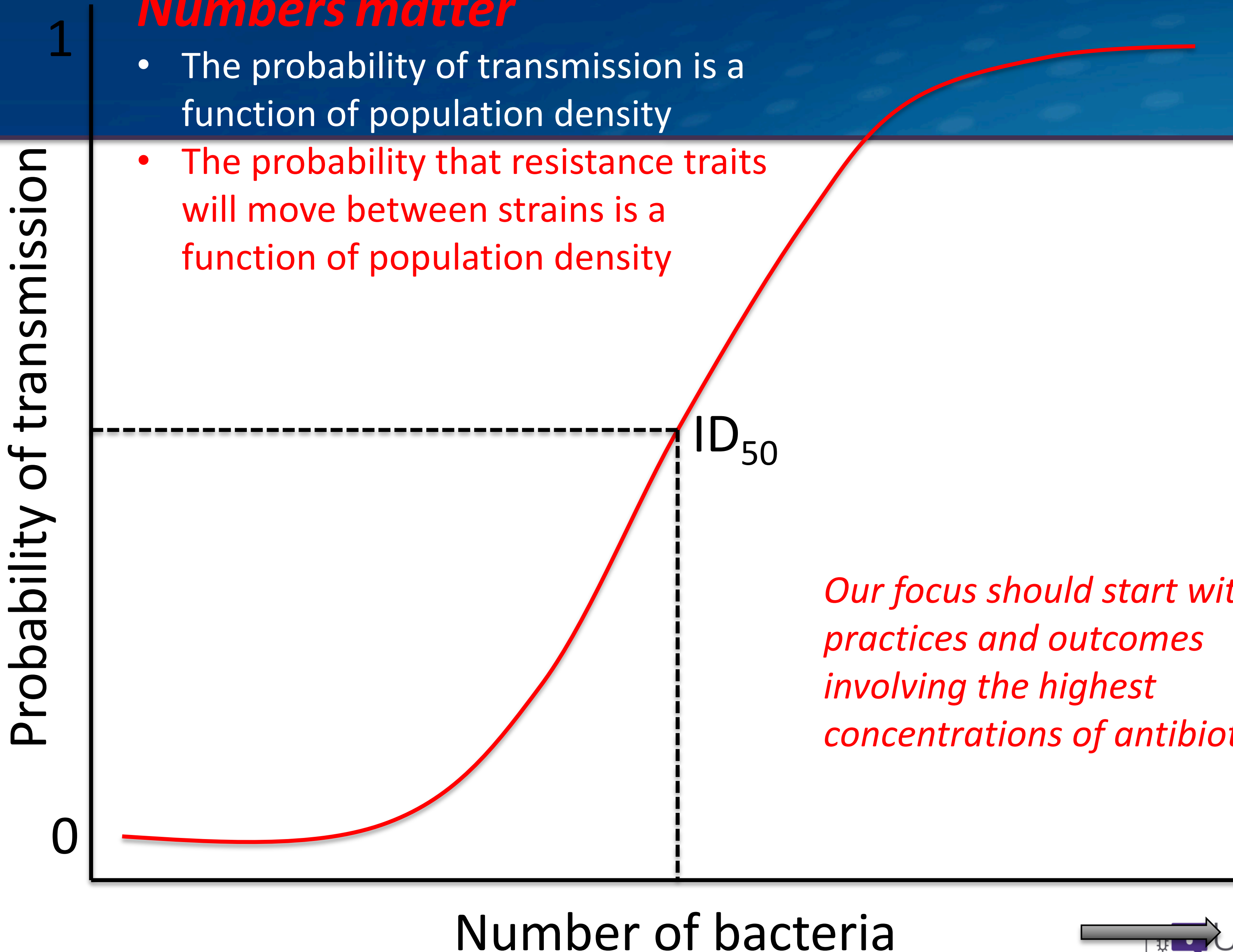
Numbers matter

- The probability of transmission is a function of population density
- The probability that resistance traits will move between strains is a function of population density



Our focus should start with practices and outcomes involving the highest concentrations of antibiotics

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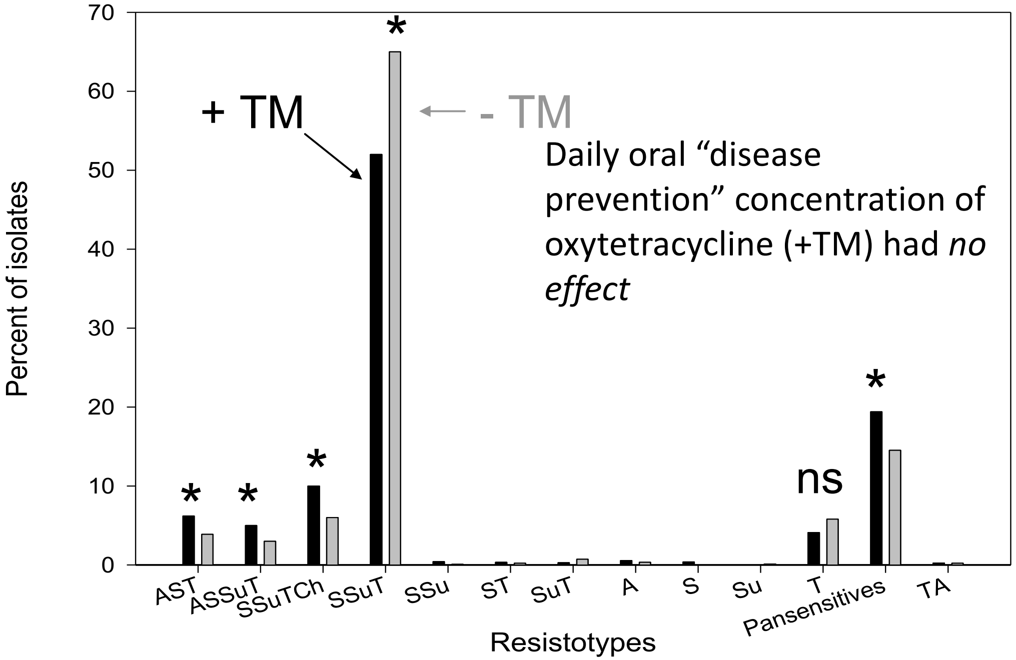
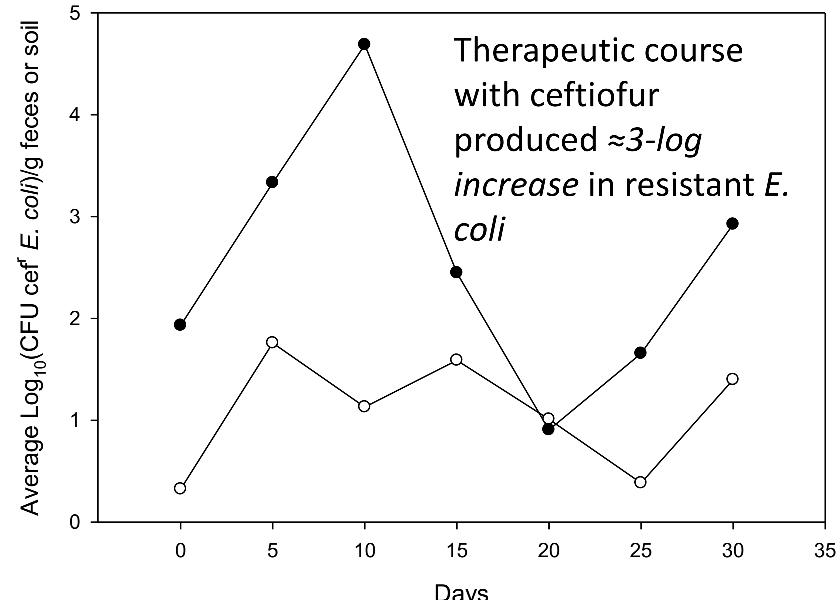
Therapeutic applications have a far greater selective impact compared to lower doses





Khachatryan et al. 2004 Appl Environ Microbiol; Subbiah et al. 2015 JEQ, Liu et al. 2016 Environ Microbiol

Dose matters…

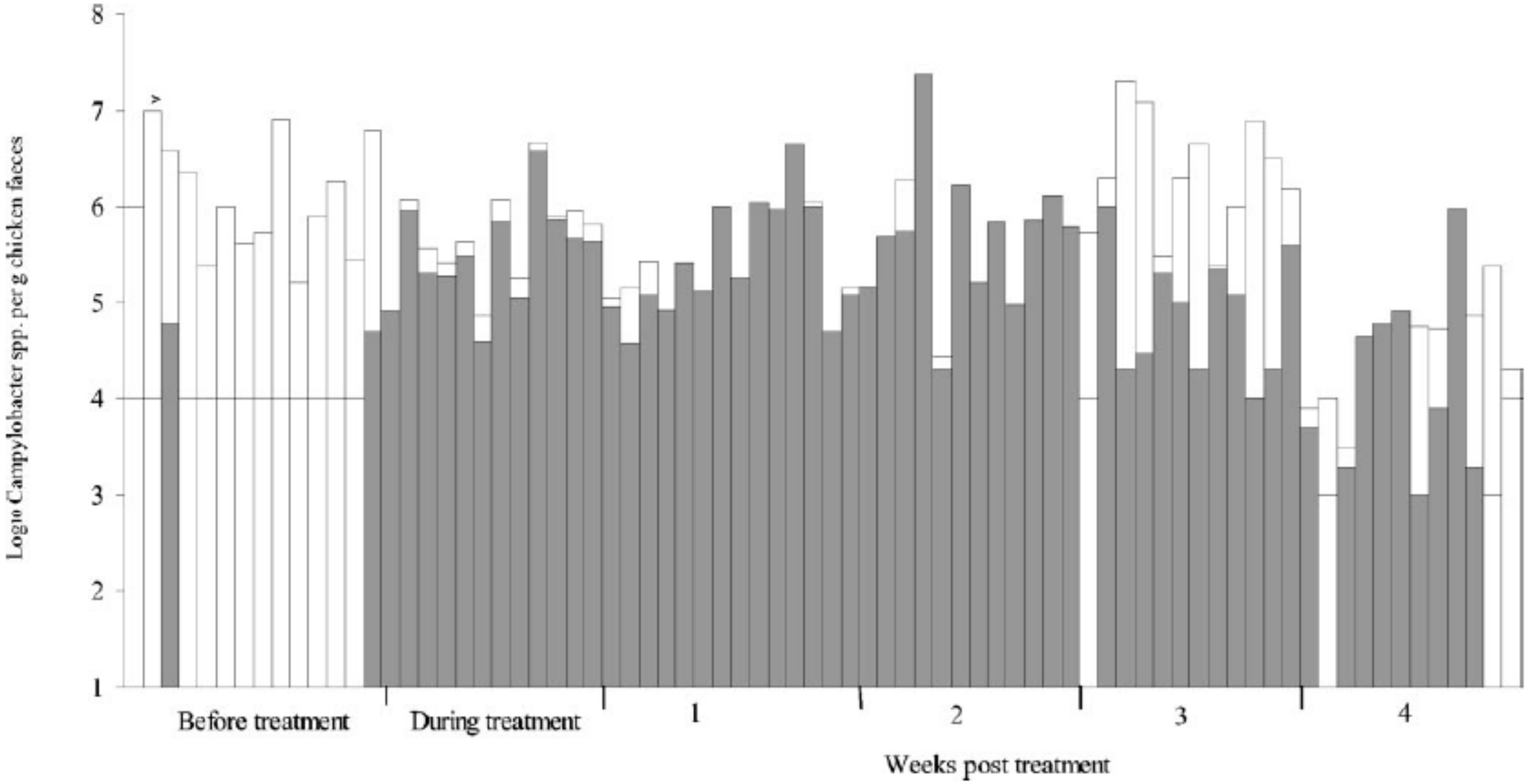
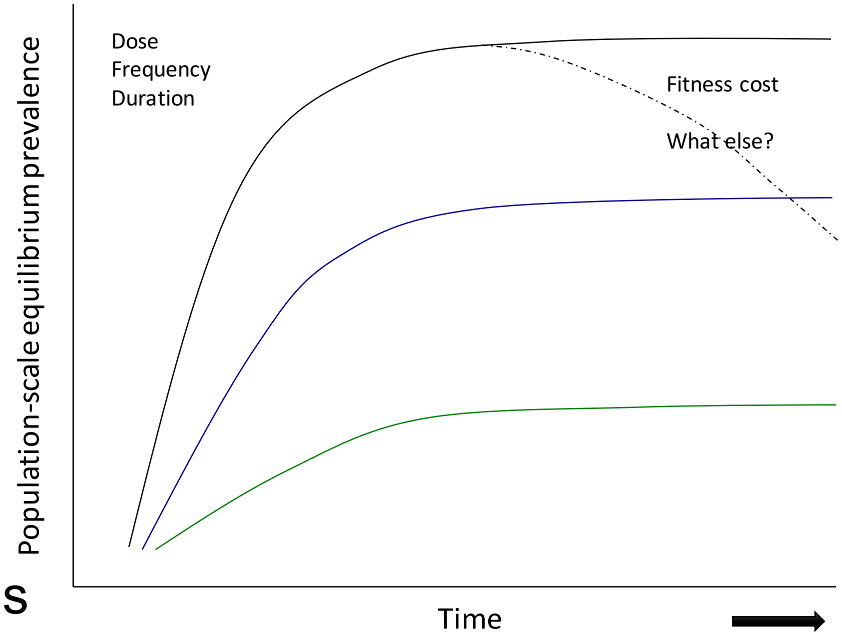


FIG. 2. Numbers of *Campylobacter* spp. in chicken feces collected before, during, and after fluoroquinolone treatment on a free-range commercial chicken farm (flock 5). Each bar represents an individual freshly voided fecal sample. Shading indicates the numbers of ciprofloxacin-resistant *Campylobacter* 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.

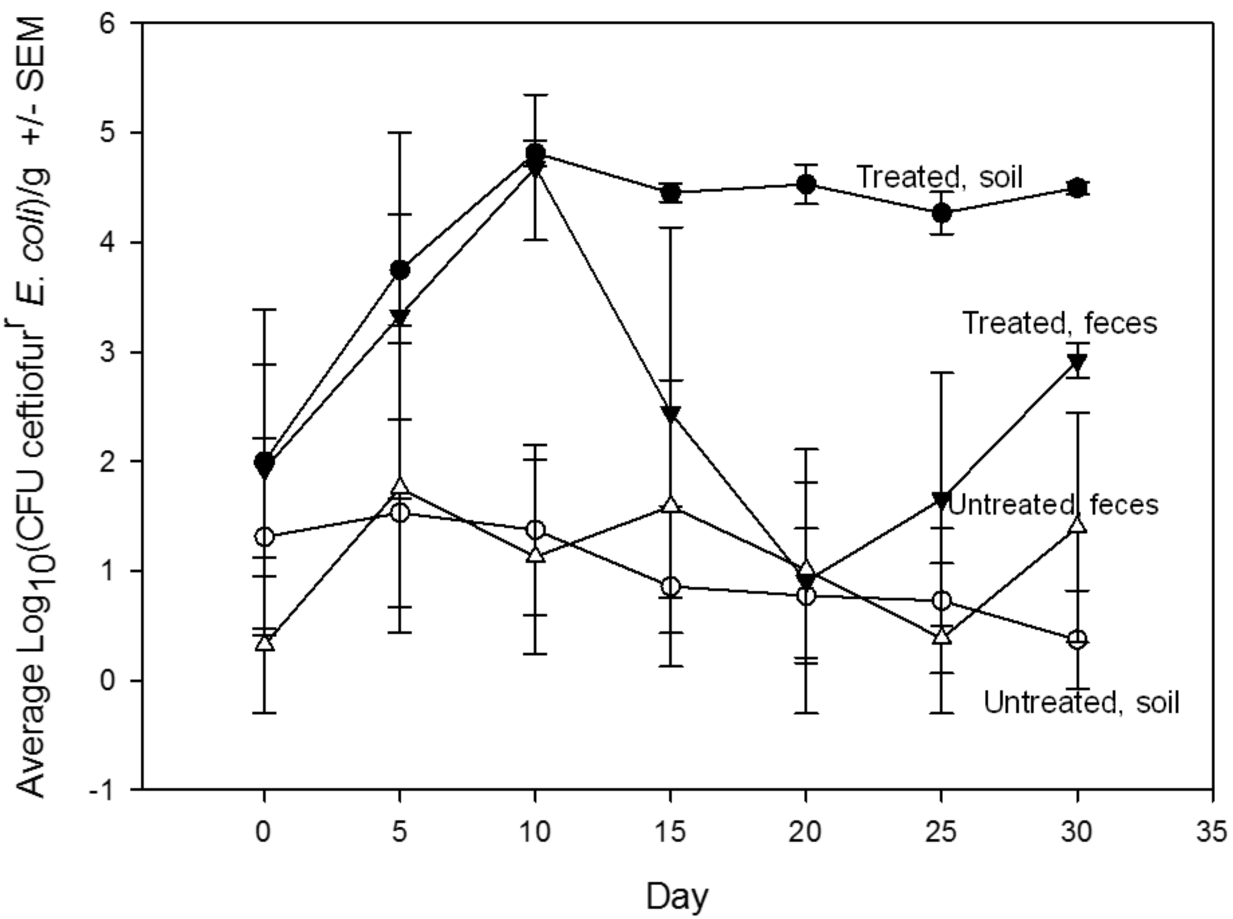
Humphrey et al. 2005 AAC

How do we effectively combat AMR? Reducing therapeutic demand is critical

- Husbandry
- Biosecurity
- Probiotics
- Waste management
- Vaccines
- Alternative antibiotics
  - Bacteriocins
  - Phage lysins
  - Antibody prophylactic
  - Antimicrobial peptides
  - Electrochemical techniques



On farm -- where is selection occurring & can we do more to limit the effects? Ceftiofur example



Liu et al. 2016. Environ Microbiol

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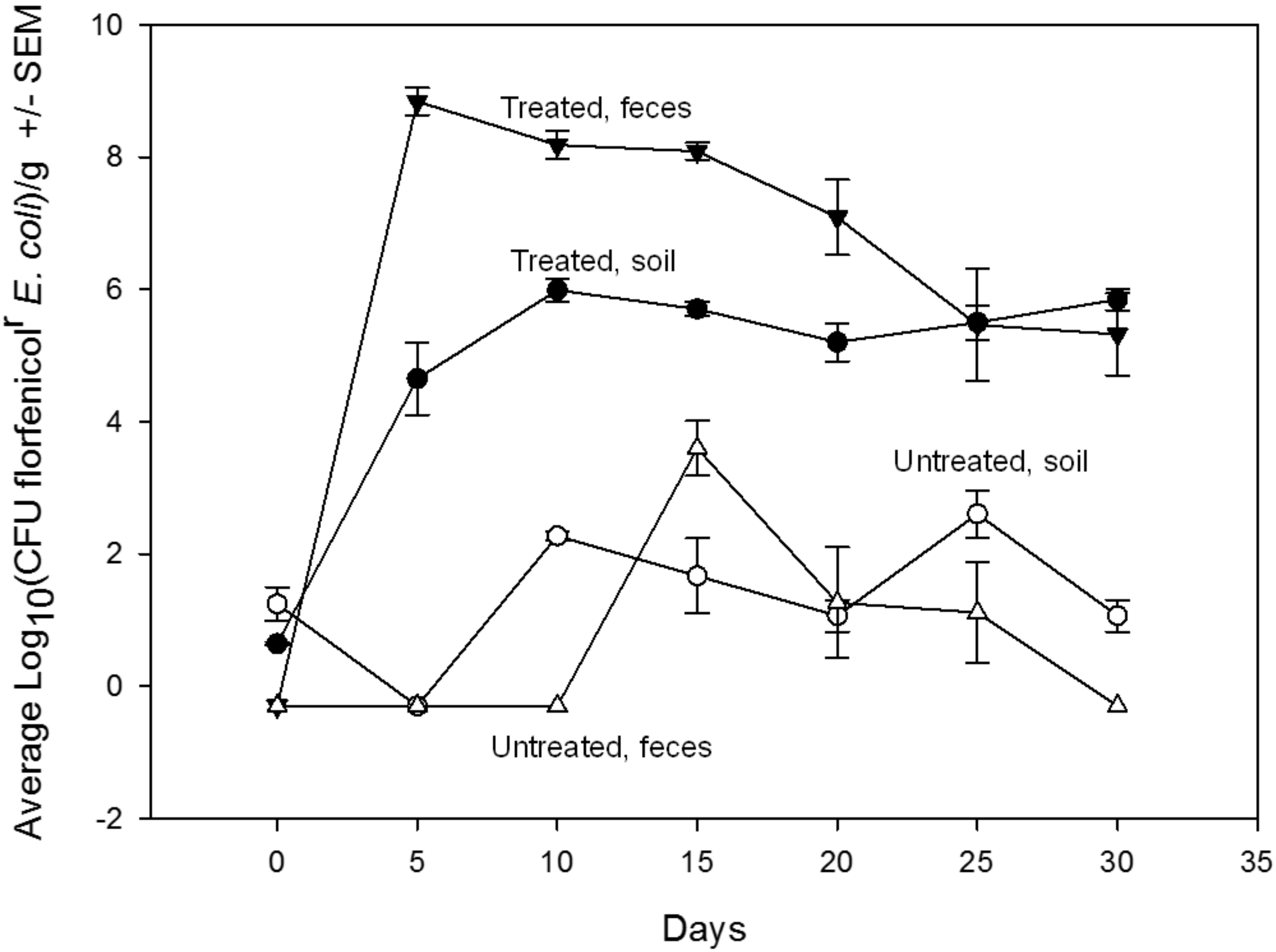
Florfenicol example



Liu et al. 2016. Environ Microbiol

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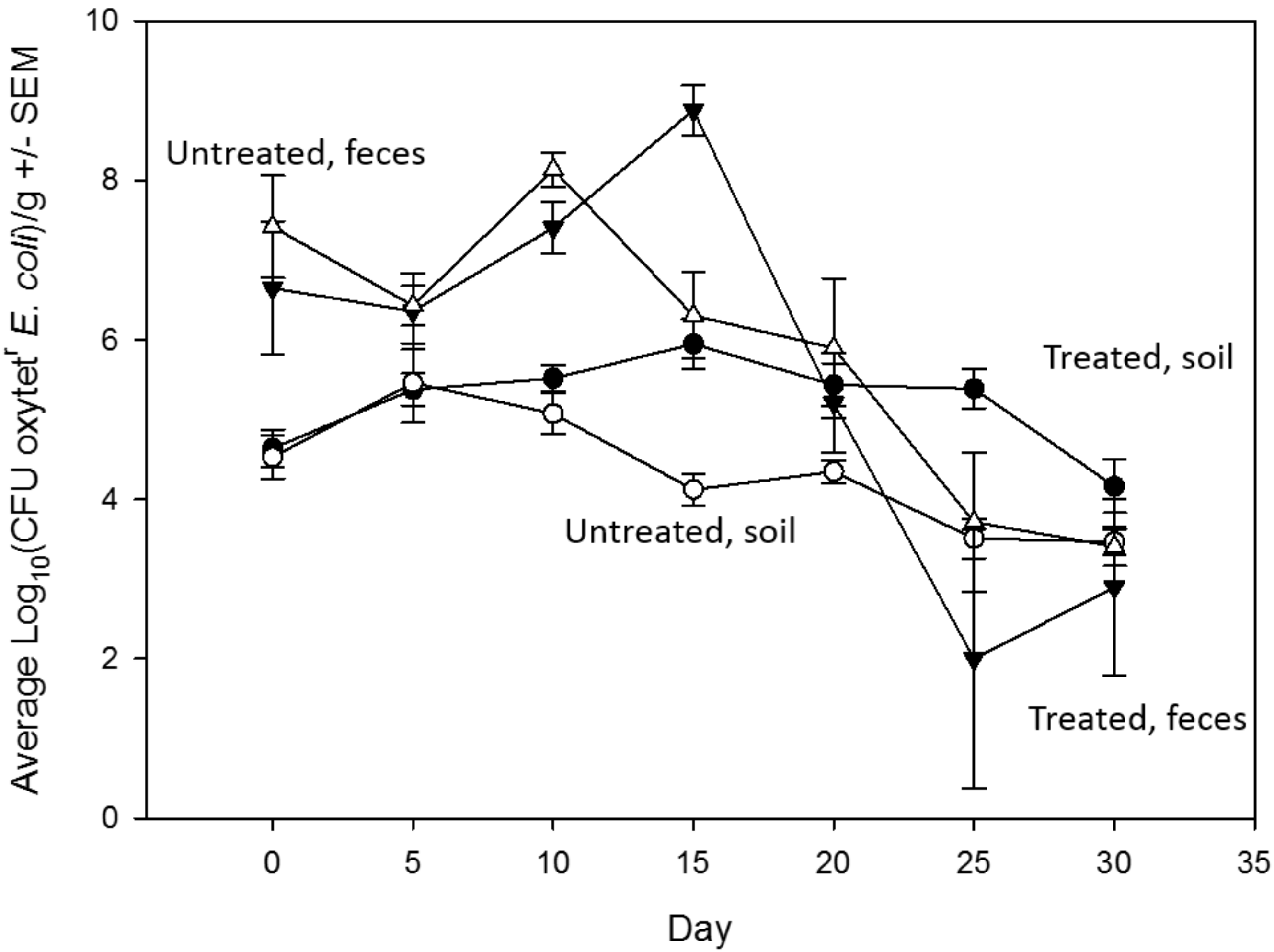
Oxytetracycline example



Liu et al. 2016. Environ Microbiol

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A counter-intuitive example for avoiding unintended consequences

- 300 calves arrived 9 Feb 2015; on 14 Feb, 150 calves received 5-day in-feed CTC prophylaxis treatment; 150 untreated control calves.
- 25% of control calves developed illness requiring treatment with a macrolide, third-generation cephalosporin, or phenicol.
- Only 2 animals in CTC group required treatment
- No difference in AMR after 27 days.
- Highest AMR shedding rate for both groups was 75 and 117 days post treatment.

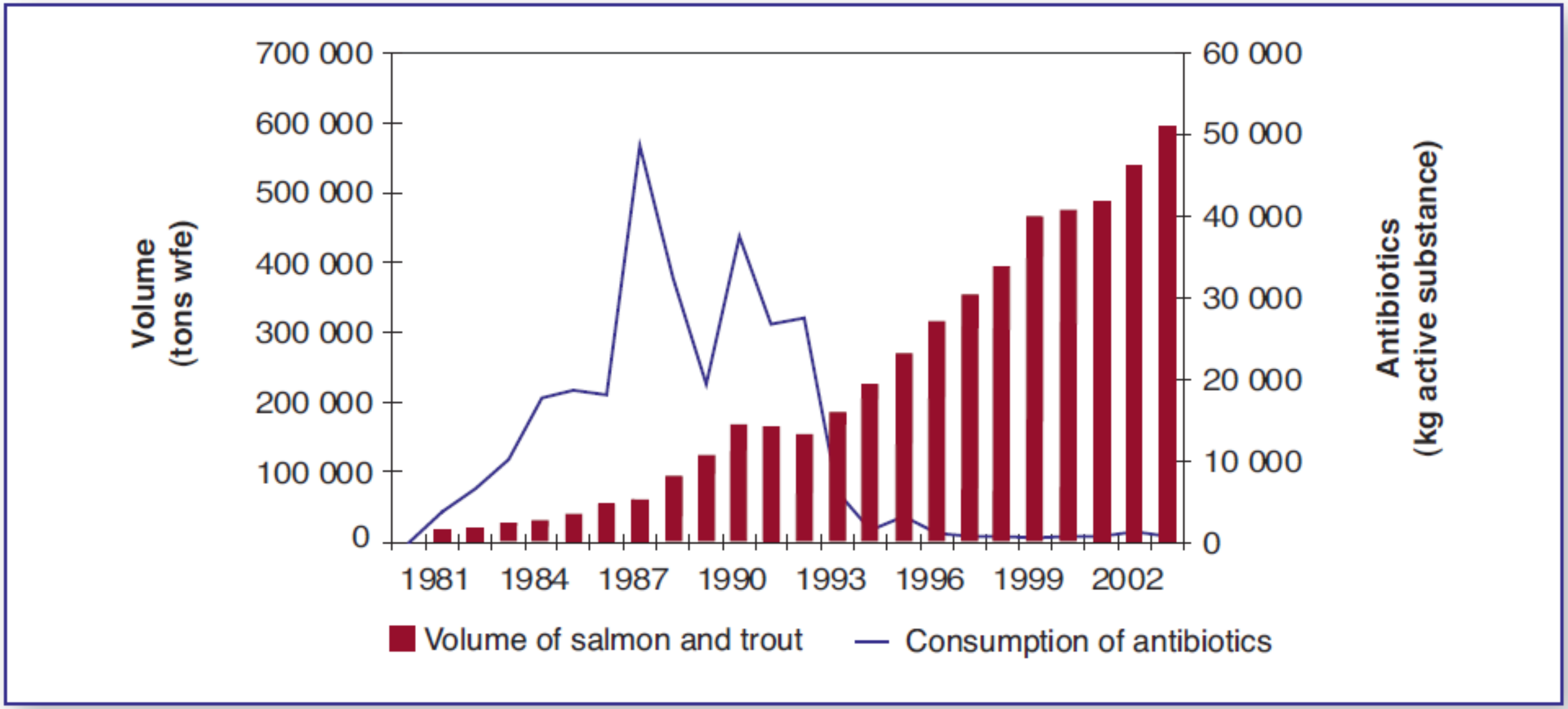
Agga et al. 2016. AEM

Conclusions

- Our best defense is to reduce the demand for antibiotics…and that means *investment* in animal health and alternative prevention and therapeutics
- When antibiotics are needed, some will have less impact than others – i.e., best practices can reduce selection (therapuetic and prophylactic)
- Environmental reservoirs of AMR may be an important part of the problem – but also an potentially important opportunity for intervention

Example of what investment can yield

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%**

  - Tools & resources – animal breeding, genetics & genomics
  - Tools & resources – veterinary immune reagents

Recent FDA responses

- 2005 – prohibited metaphylactic use of fluoroquinolones
- 2012 – prohibited use of cephalosporins for disease prevention
- 2017 – full implementation of Guidance to Industry #213

FDA Guidance to Industry #213

Principles underpinning guidance:

- The use of medically-important antimicrobial drugs in food-producing animals should be limited to uses that are considered necessary for assuring animal health
- The use of medically important antimicrobial drugs in food-producing animals should include veterinary oversight or consultation
- Voluntary and fully adopted, January 2018

FDA Guidance to Industry #213

With respect to medically-important antibiotics:

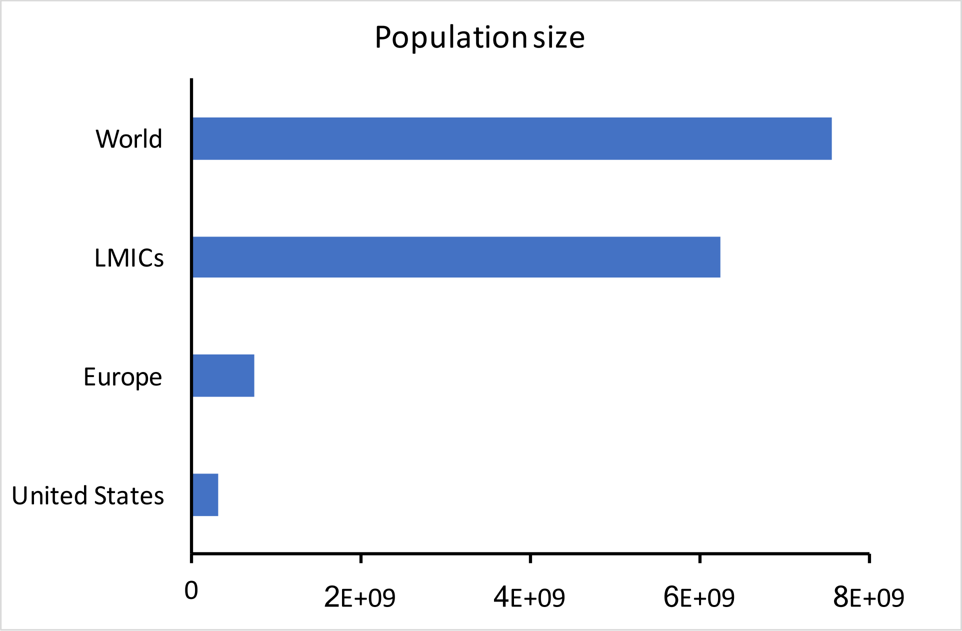
- Phase-out growth promotion indications
- Establish therapeutic treatment indications
- Change OTC to VFD regulation status for medicated feed products.
- Change from OTC to prescription (Rx) status for medicated drinking water products

We are moving in the right direction*

- Nearly 1.6 million kg reduction in antibiotic sales between 2015 and 2016
- We can expect further improvements under FDA Guidance to the Industry #213 because 69% of Abx sales are now covered under VFD

*FDA, 2016 Summary report on antimicrobials sold or distributed for use in food-producing animals. Dec 2017.

Globally, the picture is not good…



Example from swine farm, Brazil

- Weaning to 50 d, 250 ppm amoxicillin
- 50-70 d, 100 ppm florfenicol
- 70-90 d, 150 ppm tiamulin & 200 ppm doxycycline
- 22 different medically-important antibiotics were being used in this industry.

Our work in TZ and KE shows that bacterial transmission best predicts carriage of AMR bacteria – i.e., without good sanitation and hygiene, stewardship efforts will only go so far.

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