The Boyd Orr Centre
for Population and Ecosystem Health

Using diversity to capture the spread and persistence of antimicrobial resistance

Dr Louise Matthews

www.gla.ac.uk/boydorr

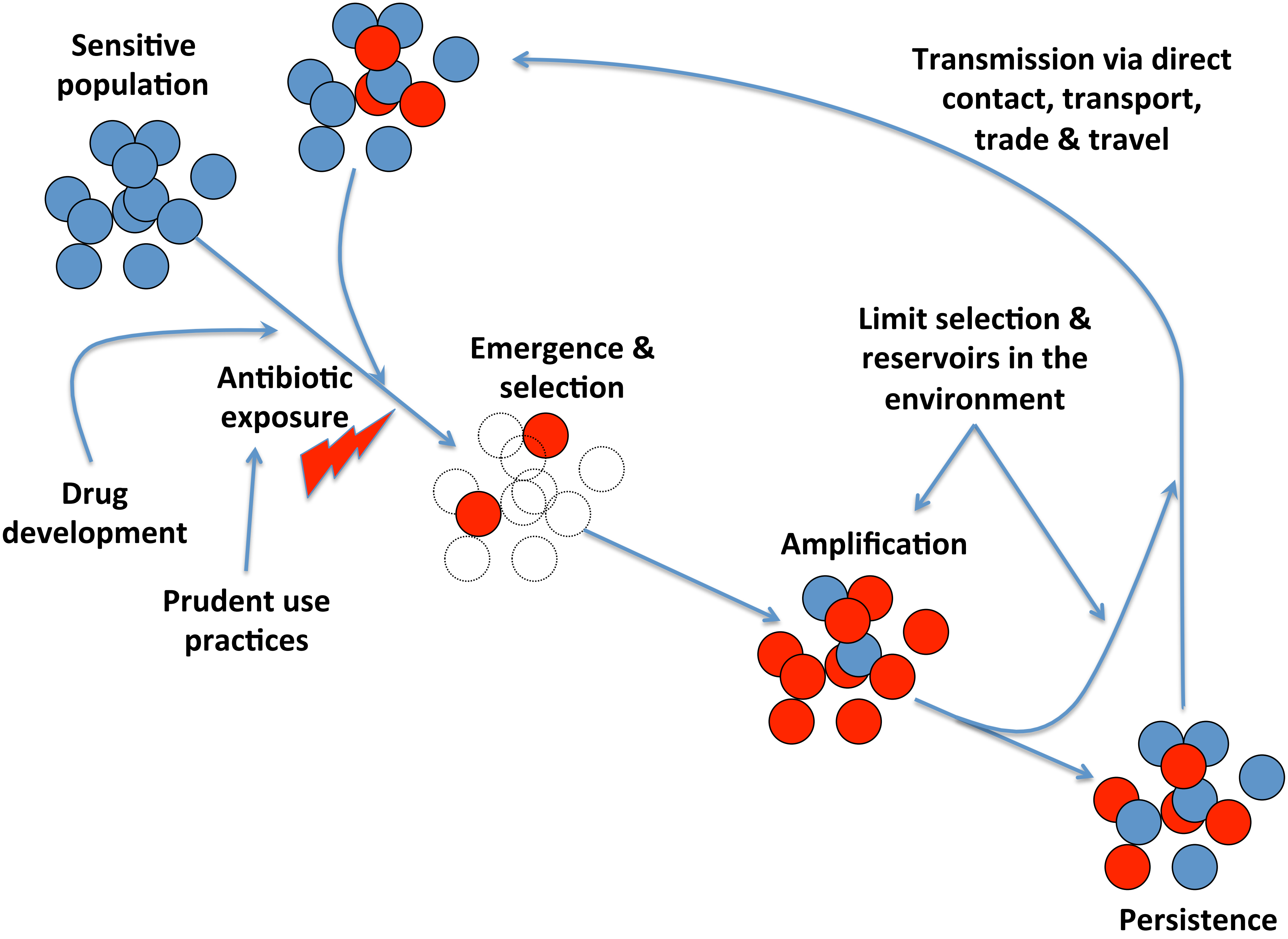
The Queen's
Anniversary Prizes
For Higher and Further Education
2013

Got an idea?

Register your interest and we'll let you know when submissions open.

THE WINNING CHALLENGE IS ANTIBIOTICS

Longitude Prize 2014 is a challenge with a £10 million prize fund to help solve one of the greatest issues of our time. It is being run and developed by Nesta, with the Technology Strategy Board as launch funding partner.


Sensitive population
Transmission via direct contact, transport, trade & travel
Antibiotic exposure
Drug development
Prudent use practices
Emergence & selection
Limit selection & reservoirs in the environment
Amplification
Persistence

Developing countries

- **Commonly lack effective regulatory framework**
  - **Quality, distribution, sales, access**

- **Nigerian case study**
  - **85% human *E. coli*, 53% animal *E. coli* resistant**
  - **In-feed use of antibiotics in poultry – oxytetracycline, gentamicin, ciprofloxacin, enrofloxacin, chloramphenicol**
  - **No attention to withholding periods**

(Nsofor et al. 2013, African J Microbiol Res 7:4646

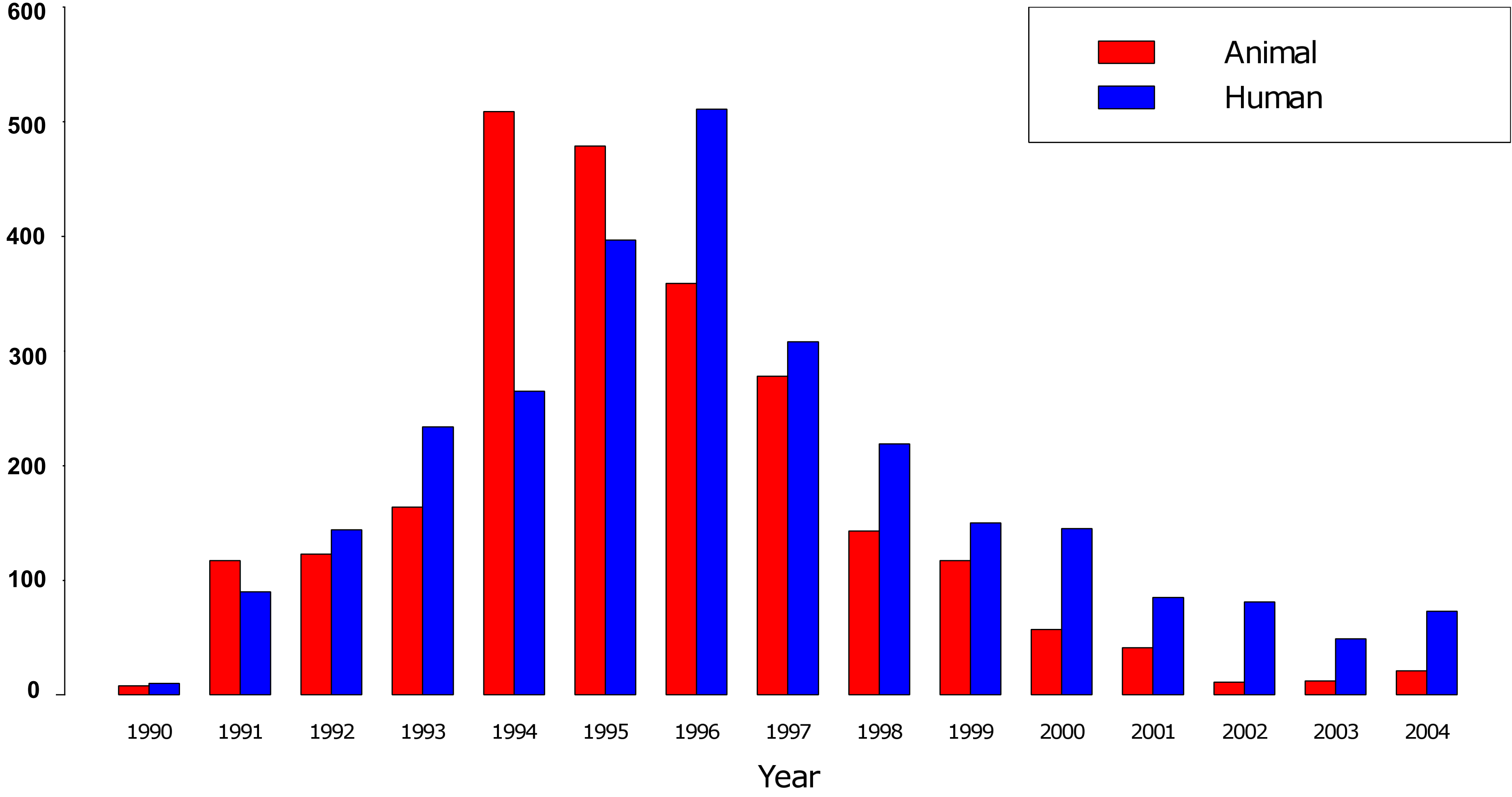
Ecological and Socio-Economic Factors Impacting Maintenance and Dissemination of Antibiotic Resistance in the Greater Serengeti Ecosystem

- Need to understand drivers of resistance in developing world
  - Unregulated availability of antibiotics
  - Often poor educational and literacy levels
  - Rapidly urbanising communities

Background

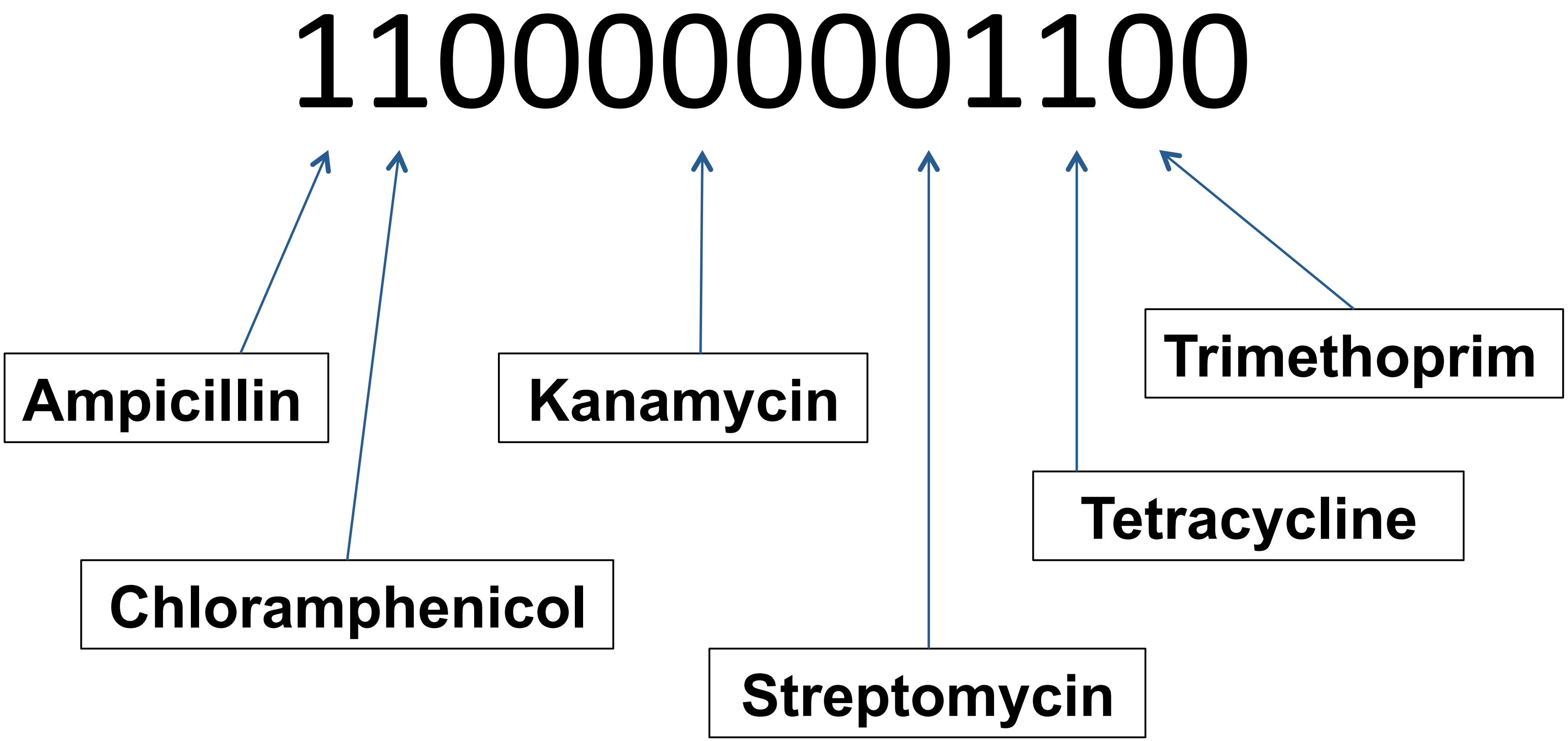
- Previous studies investigated AMR in Salmonella from Scottish human and livestock data
- Used suite of analytical approaches to investigate the flow of resistance between populations

Reported number of isolates of *S.* Typhimurium DT104



Mather et al, Proc R Soc B, 2011

Resistance profiles



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Ampicillin

Chloramphenicol

Kanamycin

Streptomycin

Tetracycline

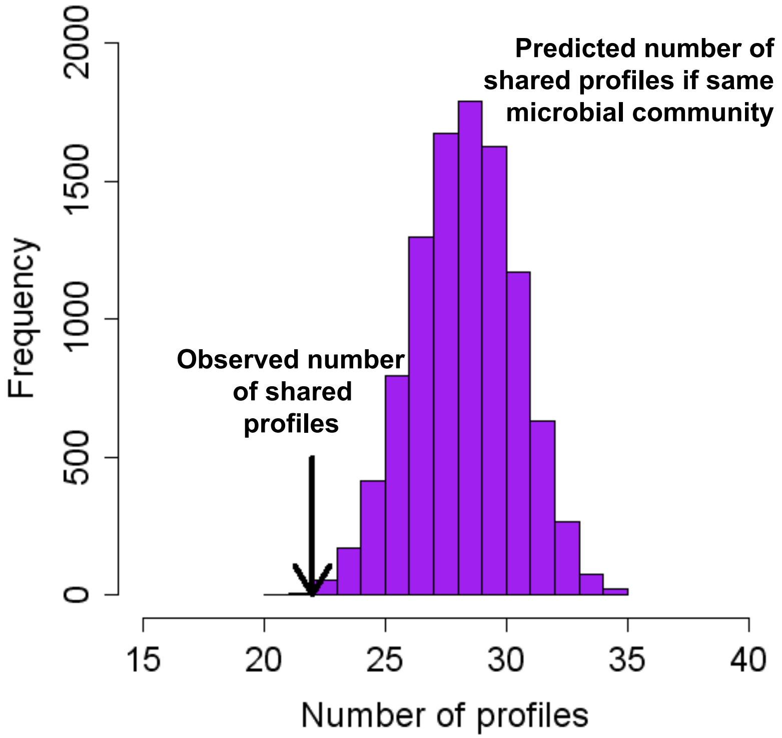
Trimethoprim

0 = susceptible
1 = resistant

Comparing human and animal profiles

Observations

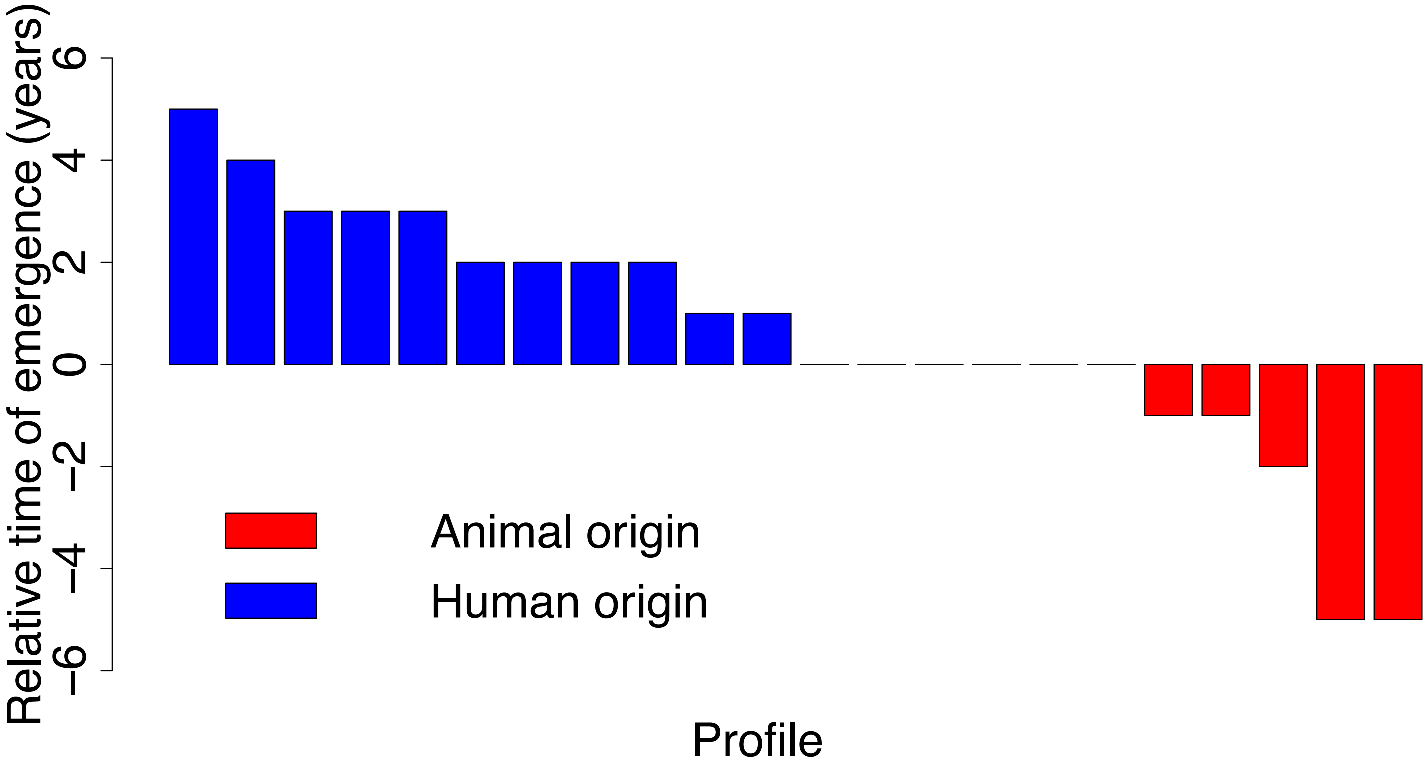
- Observed 65 unique profiles*
  - 52 in humans (30 unique)
  - 35 in animals (13 unique)
  - 22 shared



- Common microbial community?
  - No
    - Fewer profiles shared by both populations than expected

*2^{13} = 8,192 theoretically possible, but also know there are genetically linked resistances

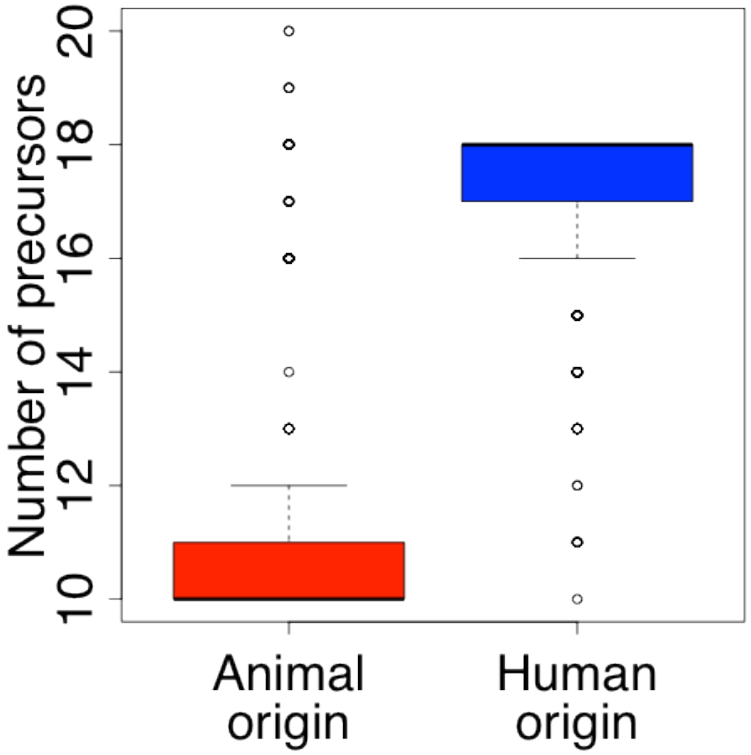
1.Relative emergence time of shared profiles



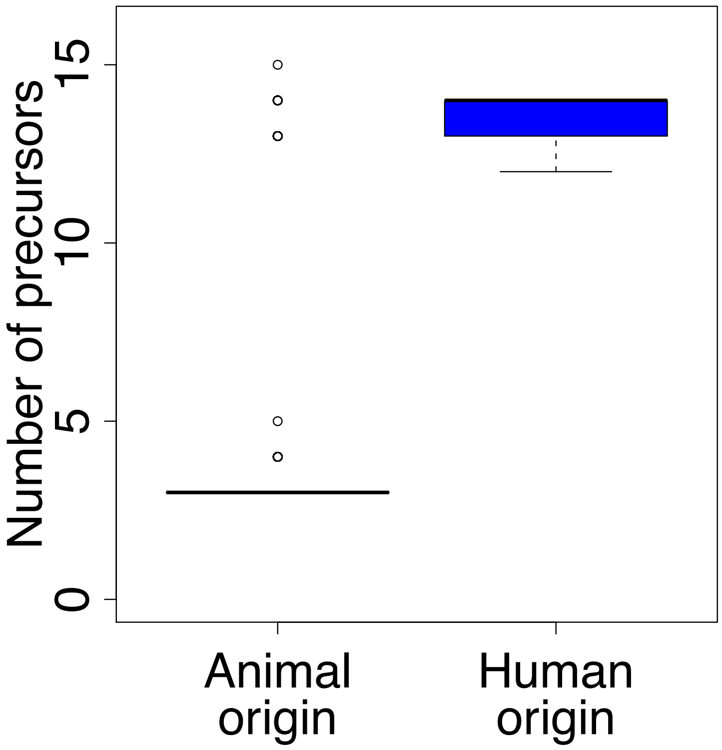
Mather et al, Proc R Soc B, 2011

2.Source of precursors of resistant profiles

Human profiles



Animal profiles



(seeding rather than transmission)

3.Quantifying Diversity

- Many ways of looking at diversity
  - Species richness
  - Relative abundance of most common species

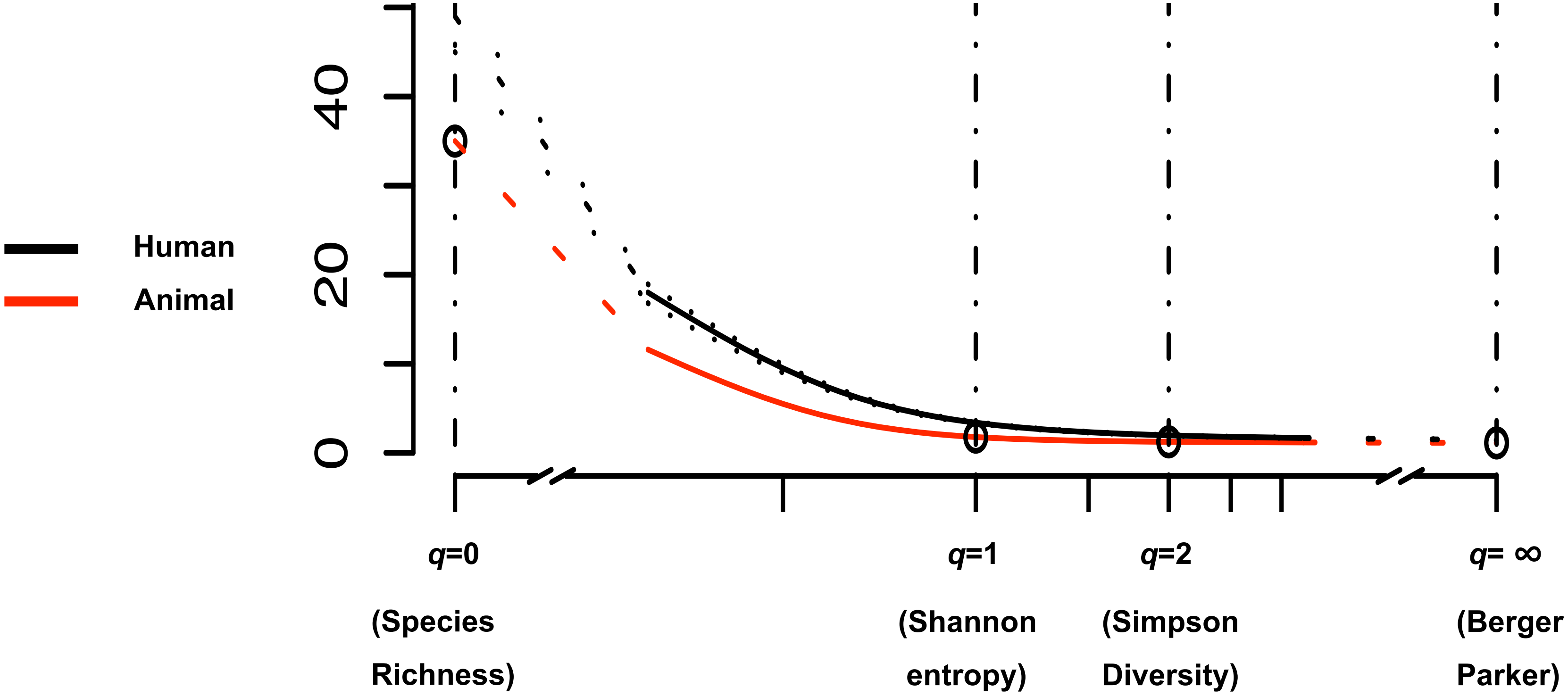
- Different measures of diversity weigh richness and abundance differently

- Family of diversity measures (related by parameter, *q*)
  - Species richness (*q*=0)
    - Rare profiles carry same weight as common profiles
  - Shannon entropy (*q*=1)
  - Simpson diversity (*q*=2)
  - Berger-Parker (*q*=∞)
    - Frequency of most common profile dominates
    - Rare profiles carry no weight

$$D_q(p_1 \cdots p_S) = \begin{cases} \left[\sum_{i=1}^{S} p_i^q \right]^{\frac{1}{1-q}} & q \neq 1 \\ \prod_{i=1}^{S} p_i^{-p_i} & q = 1 \end{cases}$$

Diversity 'fingerprint'

- Greater diversity in human samples



Findings

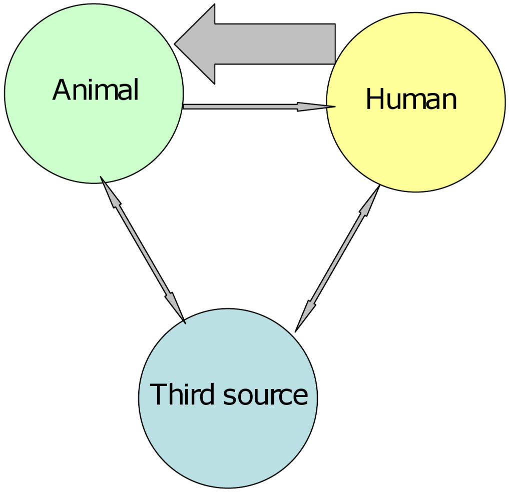
- Human population
  - More likely source for first emergence
  - More frequent source of precursors
  - Greater diversity

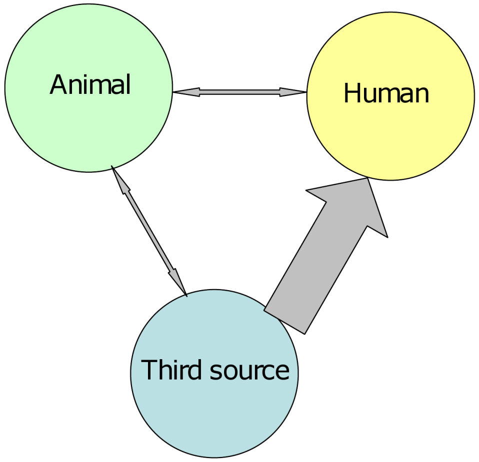
- Sympatric animal population unlikely to be major source of resistance in humans
  - Three possible scenarios

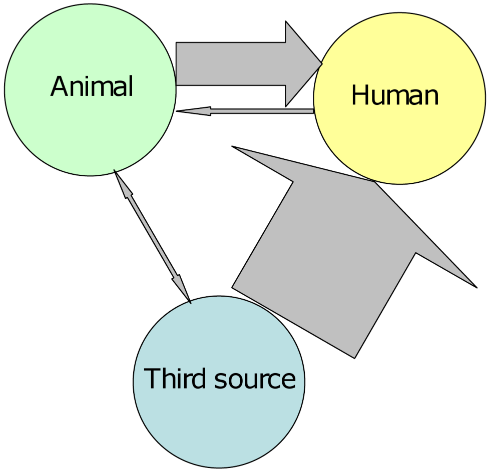
Mather et al., *Proc. Biol. Sci.* 2012. 279, 1630–1639

Mather et al. 2013. *Science* 341:1514-1517)

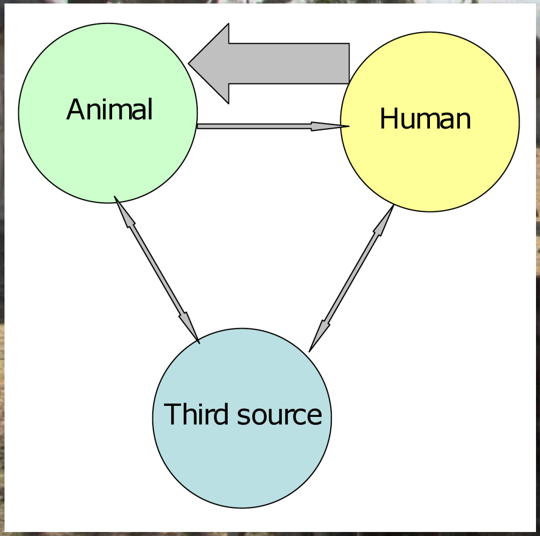
Three possible scenarios







Ecological and Socio-Economic Factors Impacting Maintenance and Dissemination of Antibiotic Resistance in the Greater Serengeti Ecosystem



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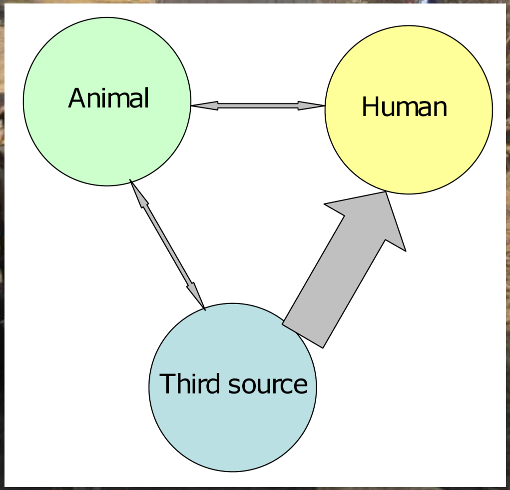

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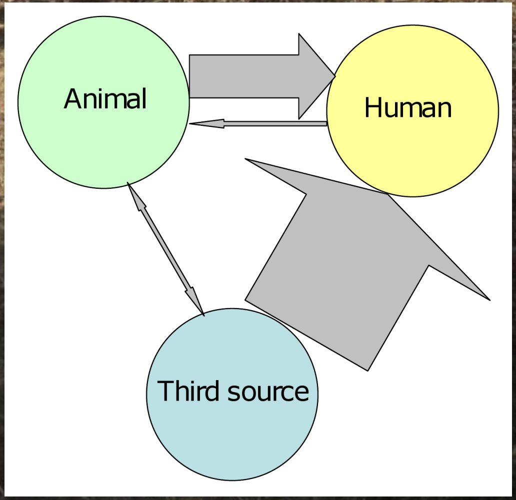

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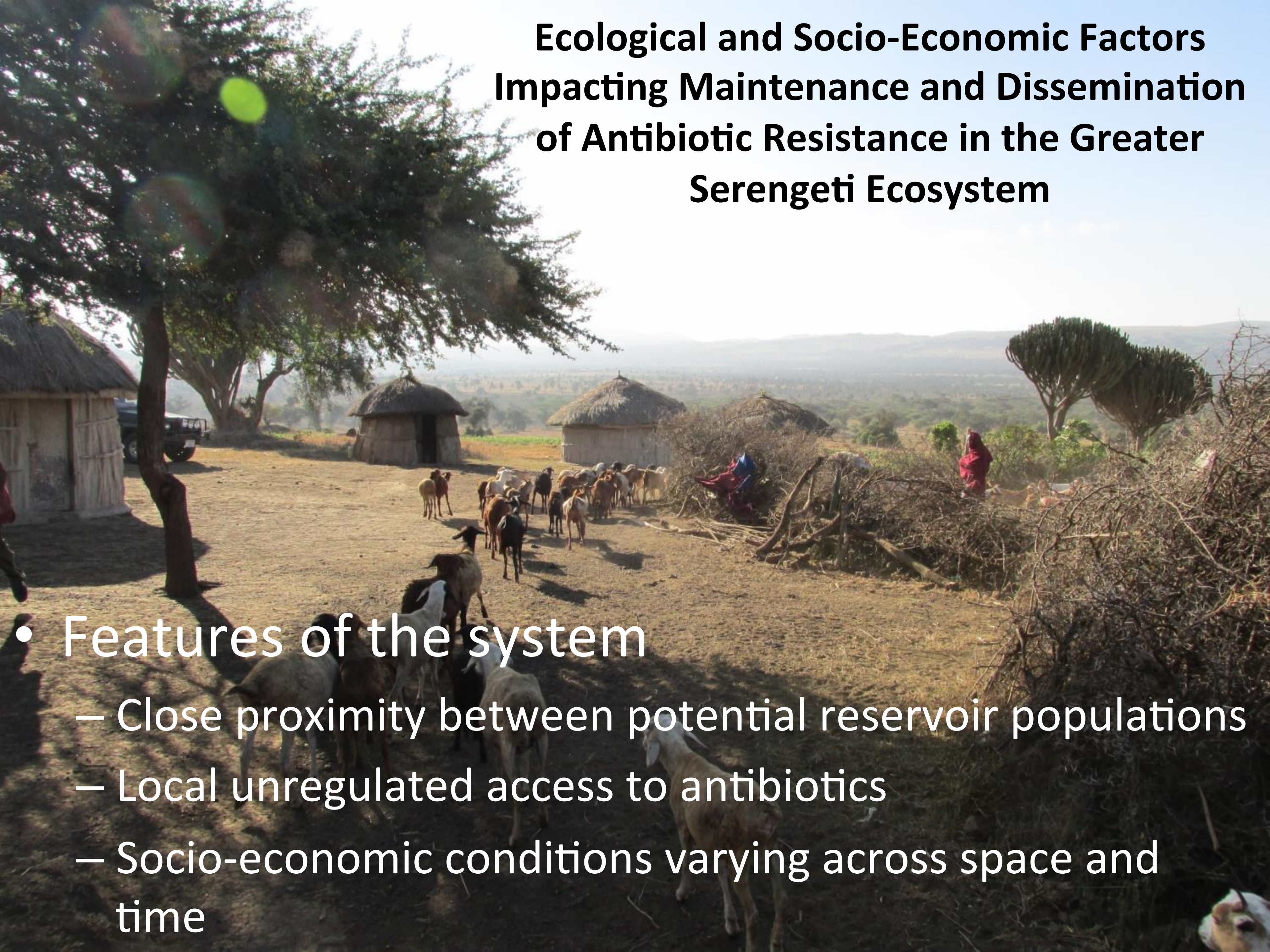
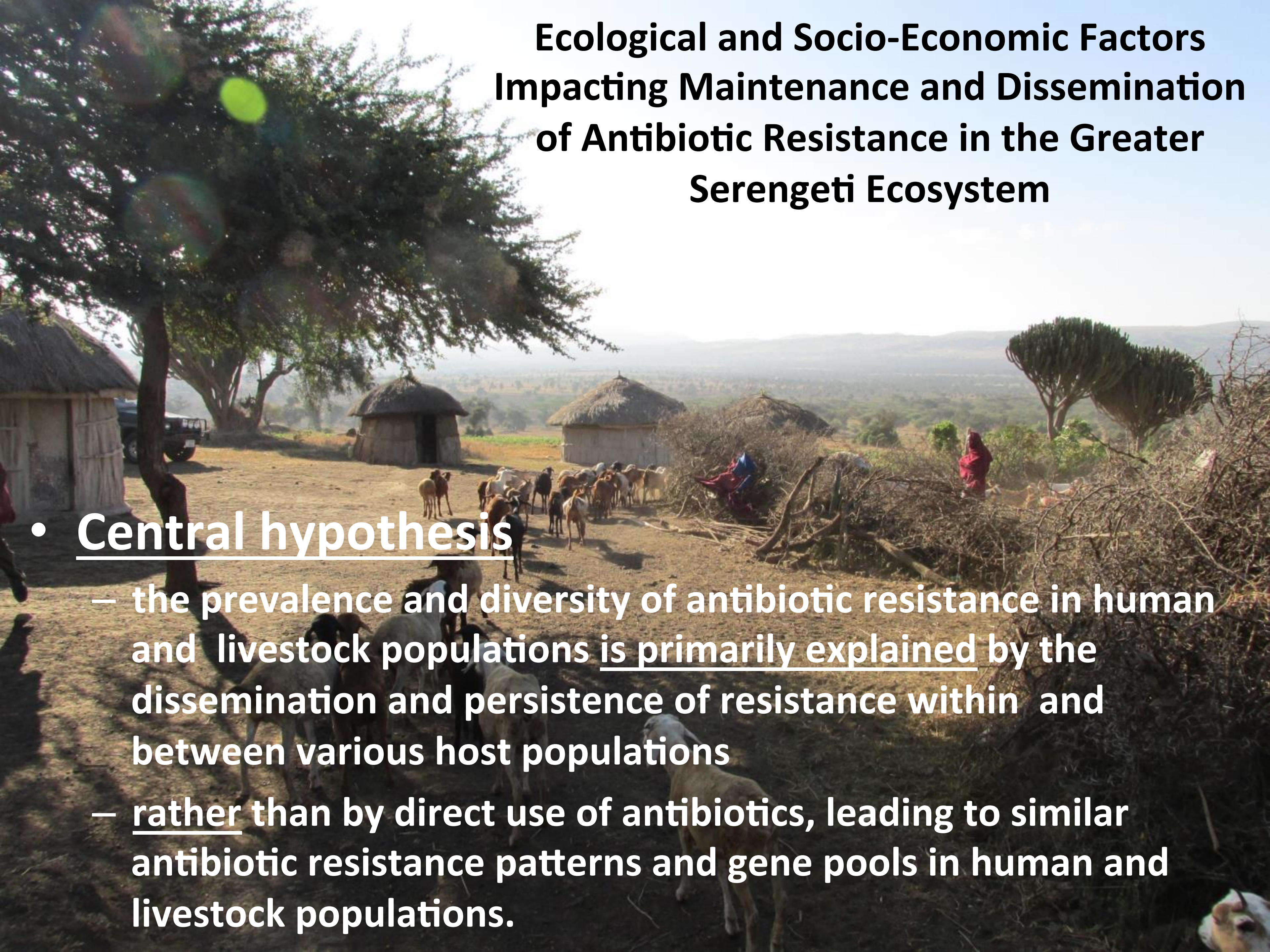


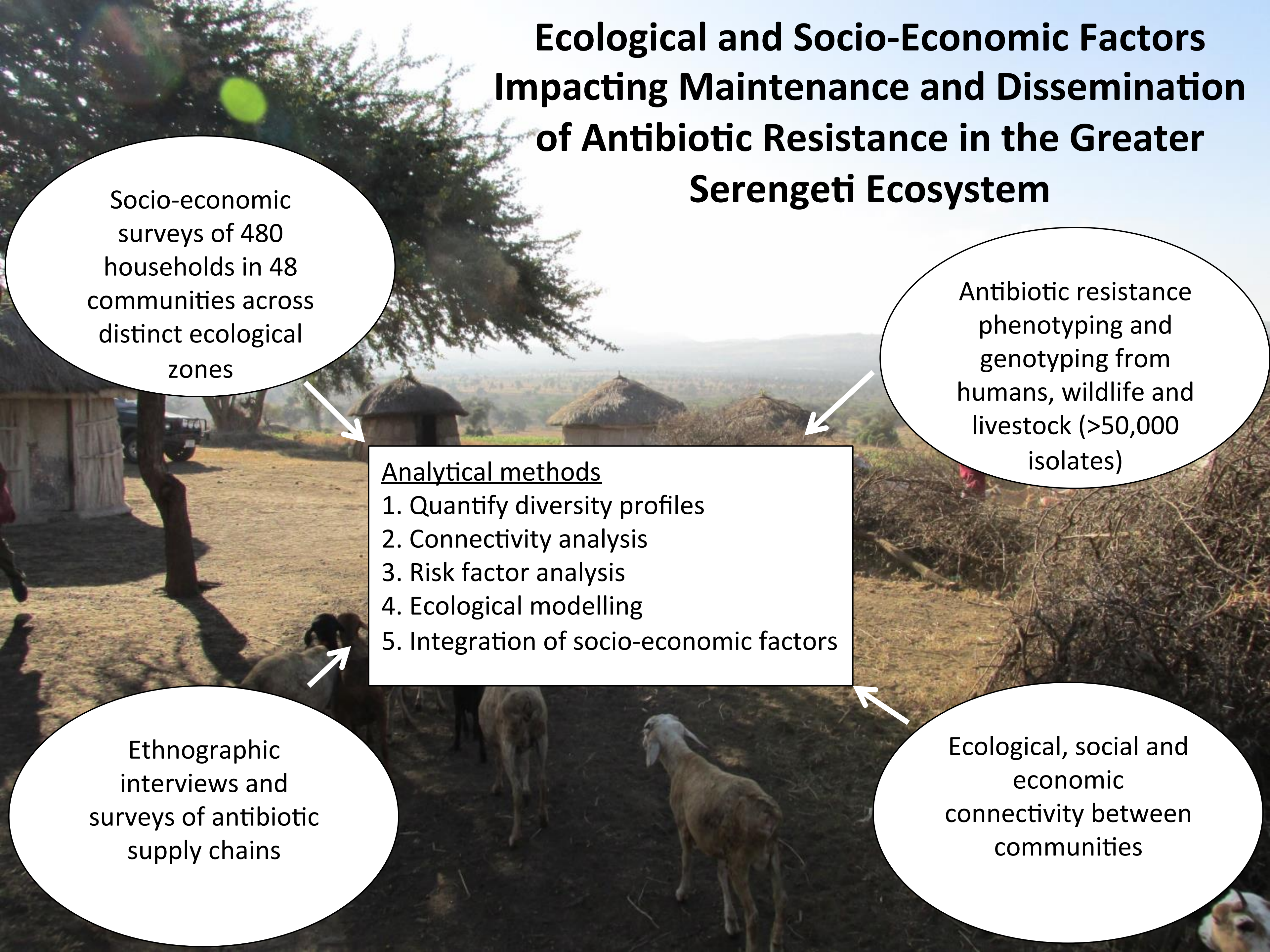
- Features of the system
  - Close proximity between potential reservoir populations
  - Local unregulated access to antibiotics
  - Socio-economic conditions varying across space and time



Ecological and Socio-Economic Factors Impacting Maintenance and Dissemination of Antibiotic Resistance in the Greater Serengeti Ecosystem

- Central hypothesis
  - the prevalence and diversity of antibiotic resistance in human and livestock populations is primarily explained by the dissemination and persistence of resistance within and between various host populations
  - rather than by direct use of antibiotics, leading to similar antibiotic resistance patterns and gene pools in human and livestock populations.

Ecological and Socio-Economic Factors Impacting Maintenance and Dissemination of Antibiotic Resistance in the Greater Serengeti Ecosystem



Socio-economic surveys of 480 households in 48 communities across distinct ecological zones

Antibiotic resistance phenotyping and genotyping from humans, wildlife and livestock (>50,000 isolates)

Analytical methods

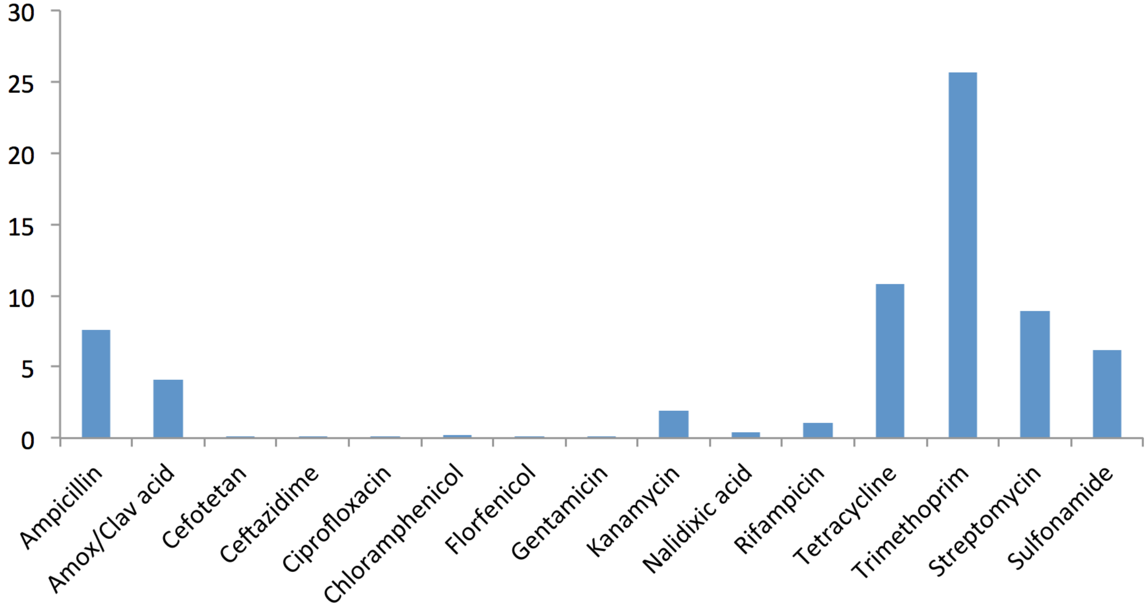
1. Quantify diversity profiles
2. Connectivity analysis
3. Risk factor analysis
4. Ecological modelling
5. Integration of socio-economic factors

Ethnographic interviews and surveys of antibiotic supply chains

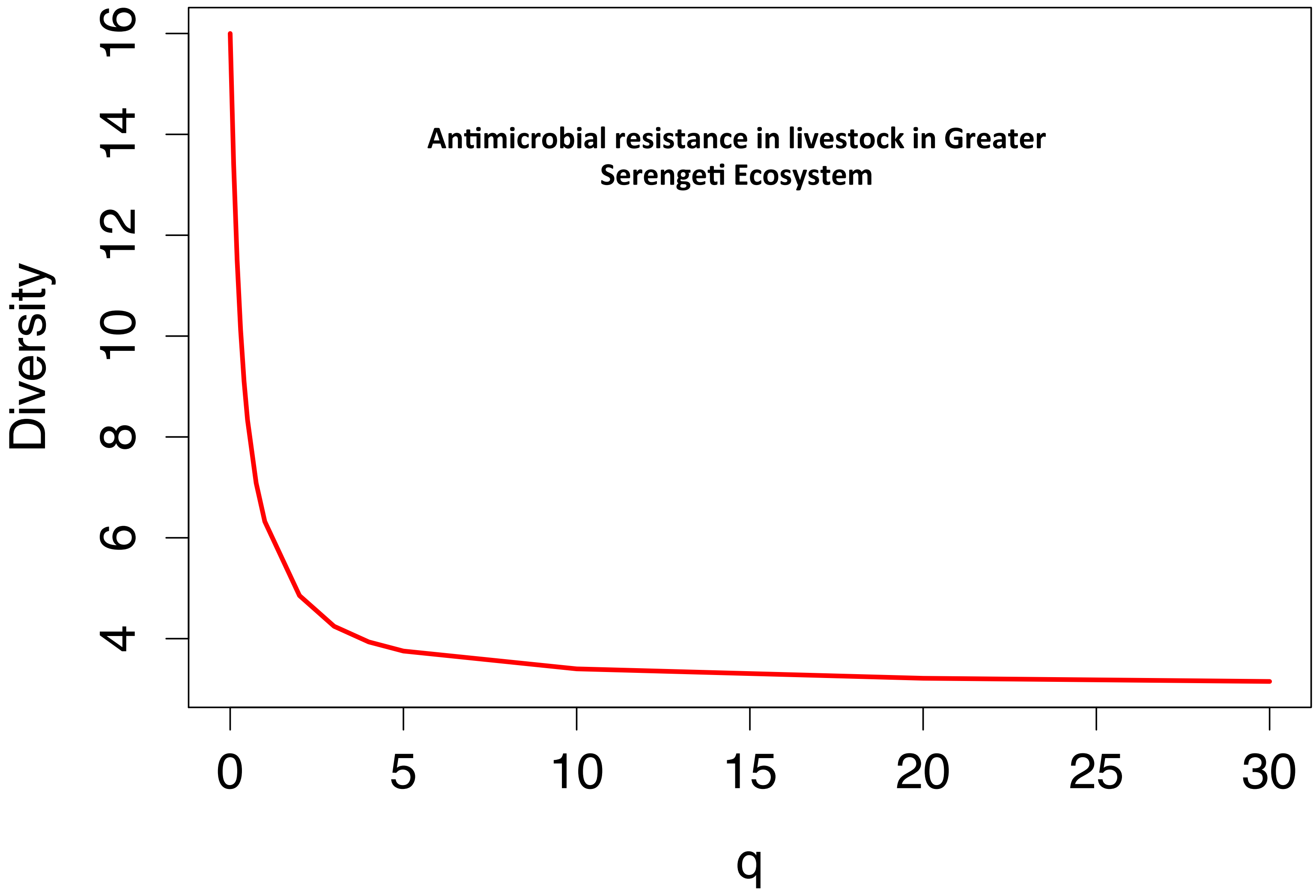
Ecological, social and economic connectivity between communities

Data: hot off the press

Antibiotic	%	Number
Ampicillin	7.6	8
Amox/Clav acid	4.09	4
Cefotetan	0.05	0
Ceftazidime	0.04	0
Ciprofloxacin	0.04	0
Chloramphenicol	0.18	0
Florfenicol	0.05	0
Gentamicin	0.05	0
Kanamycin	1.91	2
Nalidixic acid	0.41	0
Rifampicin	1.03	1
Tetracycline	10.8	11
Trimethoprim	25.68	26
Streptomycin	8.91	9
Sulfonamide	6.19	6
Susceptible	32.97	5487
Total	100	5554



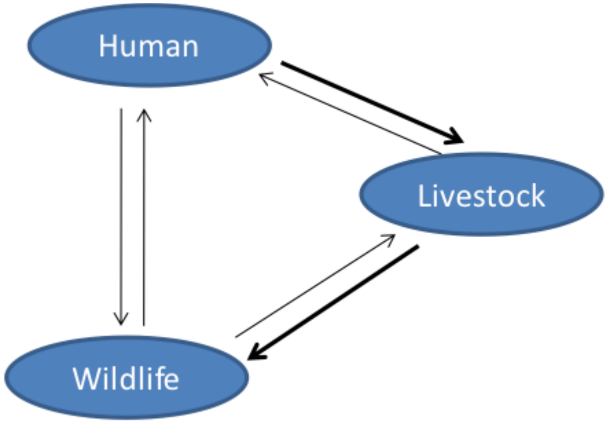
First diversity profile



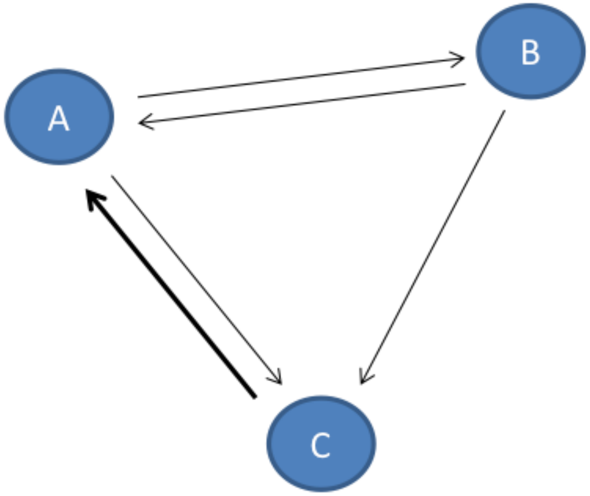
US-UK Collab: Ecological and Socio-Economic Factors Impacting Maintenance and Dissemination of Antibiotic Resistance in the Greater Serengeti Ecosystem

- Quantifying the diversity of resistance
  - diversity "fingerprint"
  - compare diversity between host types and communities

- Advances on previous analyses…



Within-community transmission of AMR

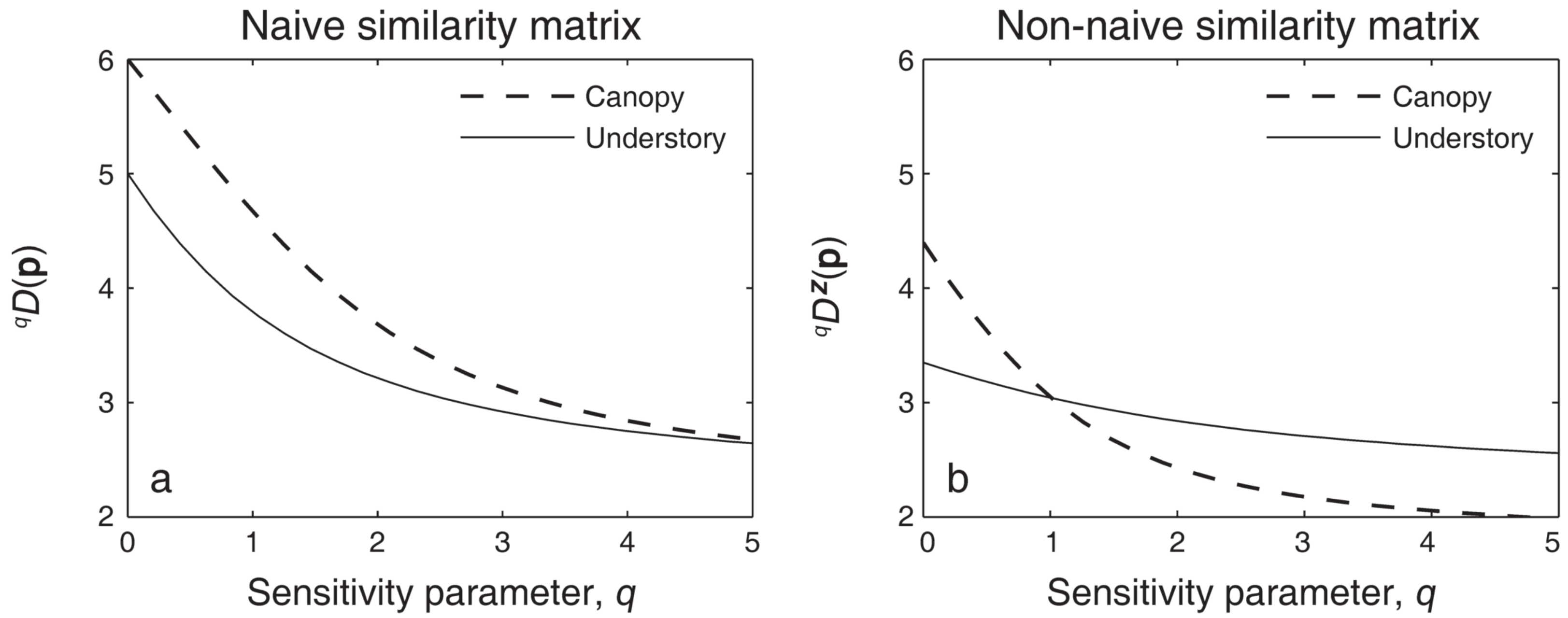


Between-community transmission of AMR

1. Inclusion of similarity

- Delivers more accurate representation of diversity

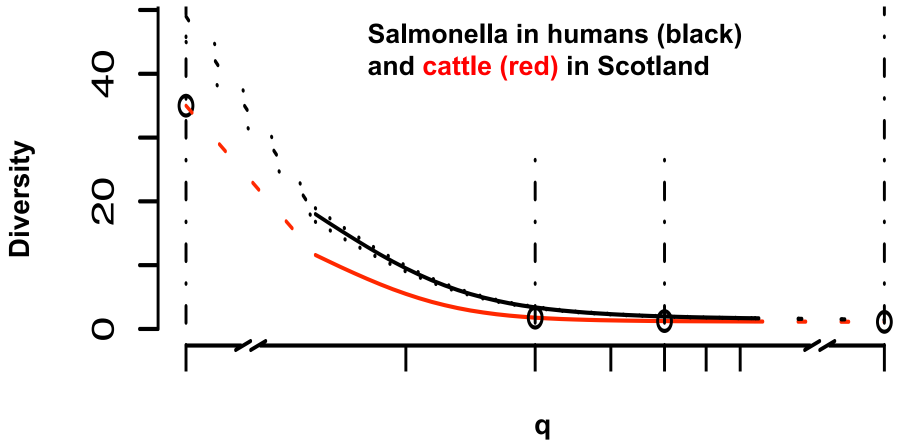
$$ {}^{q}D^{Z}(\boldsymbol{p}) = \left(\sum_{i=1}^{S} p_i (\boldsymbol{Zp})_i^{q-1} \right)^{1/(1-q)} $$



Leinster and Cobbold (2012)

1. Inclusion of similarity

- Previous study compared naïve diversities
- New analyses will account for
  - genetic and phenotypic similarity
  - overlap between communities



2. Formally partition diversity

- Similarity sensitive measure

$${}^{q}D^{Z}(\boldsymbol{p}) = \left(\sum_{i=1}^{S} p_i (\boldsymbol{Zp})_i^{q-1}\right)^{1/(1-q)}$$

- Alpha diversity
  - <u>**A**verage</u> diversity of communities
- Gamma diversity
  - <u>**G**lobal</u> diversity across all communities

$${}^{q}_{\gamma}D^{Z}(\boldsymbol{p}) = \left(\sum_{i=1}^{S} p_i (1/\gamma_i)^{q-1}\right)^{1/(1-q)}$$

- Beta diversity
  - <u>**B**etween community</u> diversity
  - Long and varied history!

$${}^{q}_{\beta}D^{Z}(\boldsymbol{p}) = \left(\sum_{i=1}^{S} p_i (1/\beta_i)^{q-1}\right)^{1/(1-q)}$$

Individual community contribution

Individial community distinctiveness

- Both ecosystems have same gamma diversity
  - ecosystem gamma diversity=5
    - (5 equally present species)
- Ecosystem A
  - α_i=1, β_i=5, γ_i=5
  - ecosystem alpha diversity=1
  - ecosystem beta diversity=5
- Ecosystem B
  - α_i=4, β_i=1.25, γ_i=5
  - ecosystem alpha diversity=4
  - ecosystem beta diversity=1.25

$$\begin{array}{cccccl} \text{Community 1} & \text{Community 2} & & & \text{Community 5} & \\ 100 & 0 & 0 & 0 & 0 & \text{Species 1} \\ 0 & 100 & 0 & 0 & 0 & \text{Species 2} \\ 0 & 0 & 100 & 0 & 0 & \ldots \\ 0 & 0 & 0 & 100 & 0 & \\ 0 & 0 & 0 & 0 & 100 & \text{Species 5} \end{array}$$

Ecosytem A

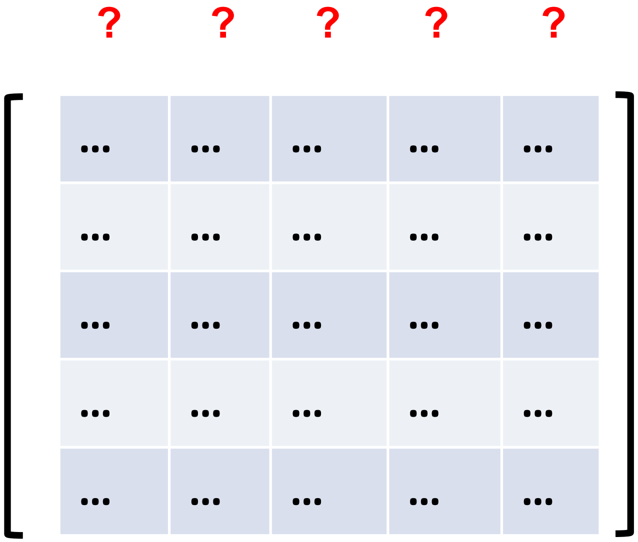
$$\begin{bmatrix} 25 & 25 & 25 & 25 & 0 \\ 25 & 25 & 25 & 0 & 25 \\ 25 & 25 & 0 & 25 & 25 \\ 25 & 0 & 25 & 25 & 25 \\ 0 & 25 & 25 & 25 & 25 \end{bmatrix}$$

Ecosytem B

Exposing community structure

- Which communities have distinct ecologies/dynamics?

- Which partitioning of the data maximises beta diversity?



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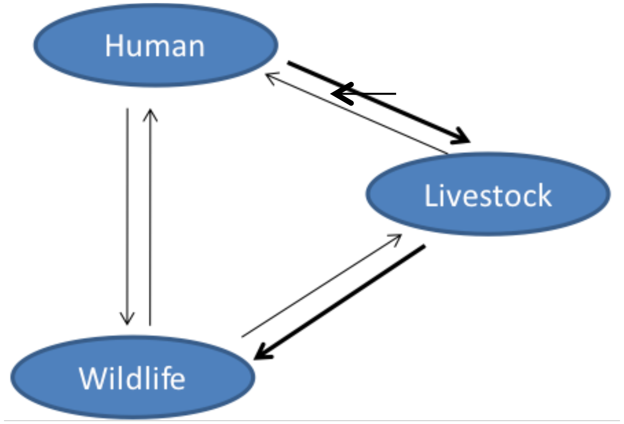
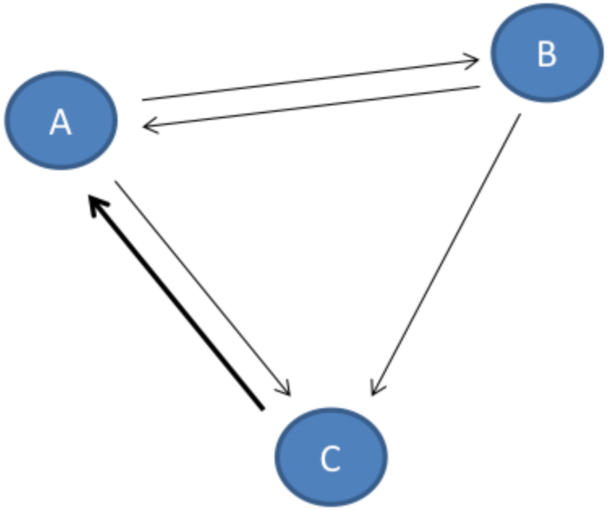


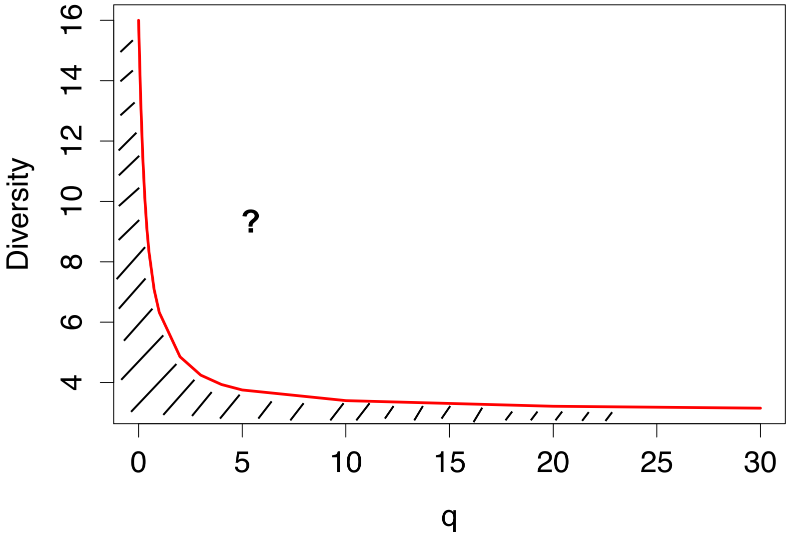
Within-community transmission of AMR



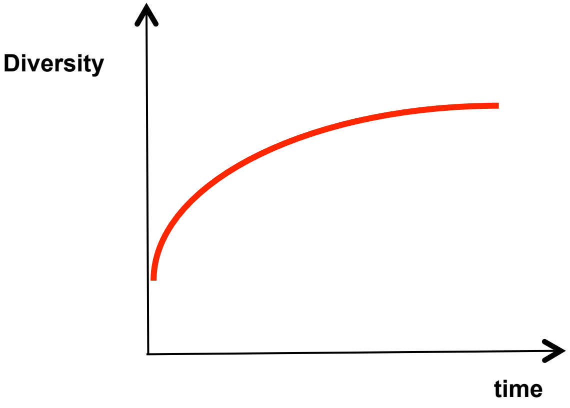
Between-community transmission of AMR

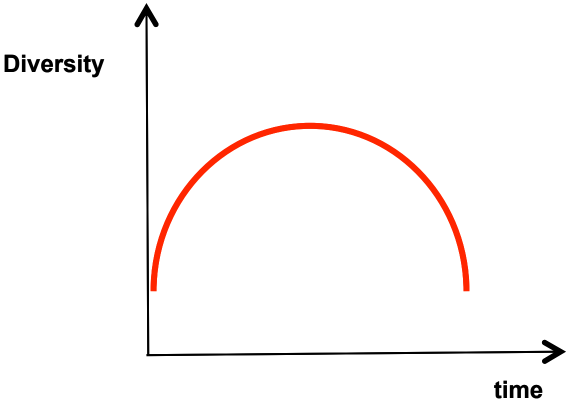
3. Statistics and diversity

- Risk factor analysis
  - use ‘diversity’ as an outcome in statistical models
  - find risk factors based on community types, classified by
    - rural, peri-urban
    - connectivity (trading, animal movements)
    - educational status
    - availability of antibiotics
  - appropriate outcome variables?
    - diversity (which value of q?)



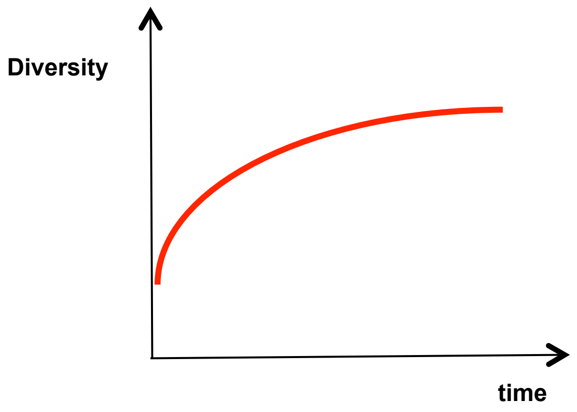
4. The dynamics of diversity

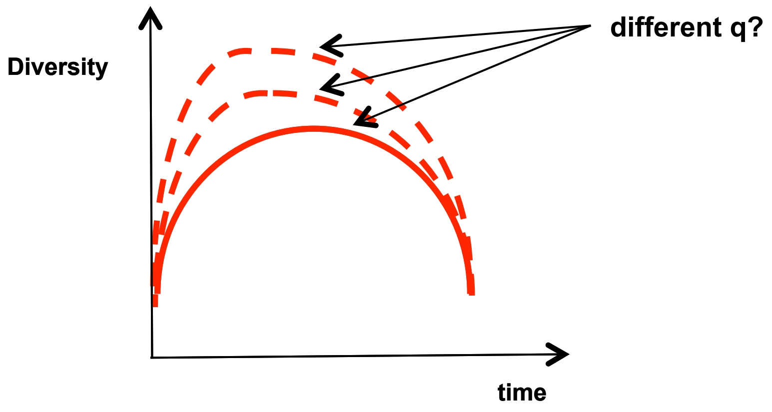




- Modelling the flow of resistance
  - allow diversity “fingerprint” to change over time

4. The dynamics of diversity





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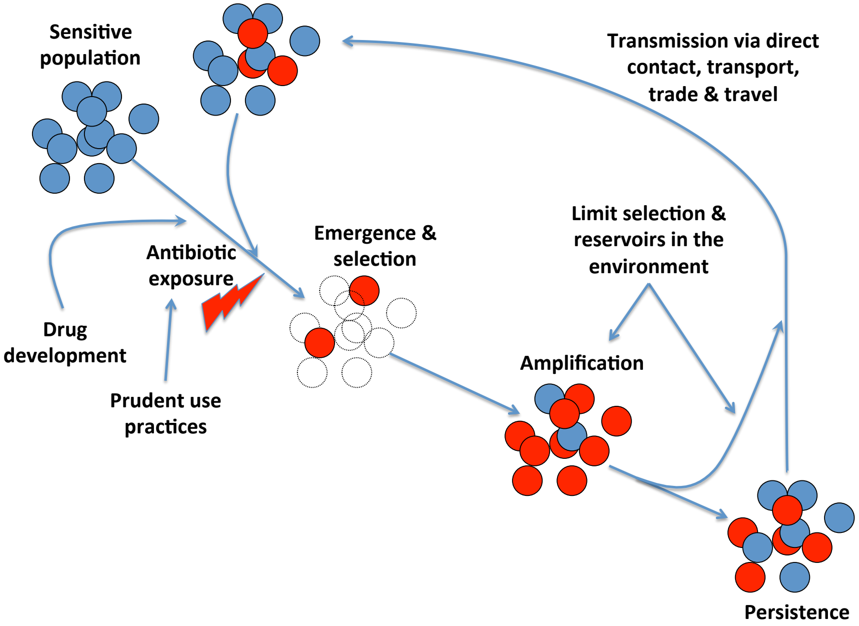

Sensitive population

Transmission via direct contact, transport, trade & travel

Antibiotic exposure

Emergence & selection

Limit selection & reservoirs in the environment

Drug development

Amplification

Prudent use practices

Persistence

- Modelling the flow of resistance
  - allow diversity “fingerprint” to change over time
  - capture generation and spread of resistance

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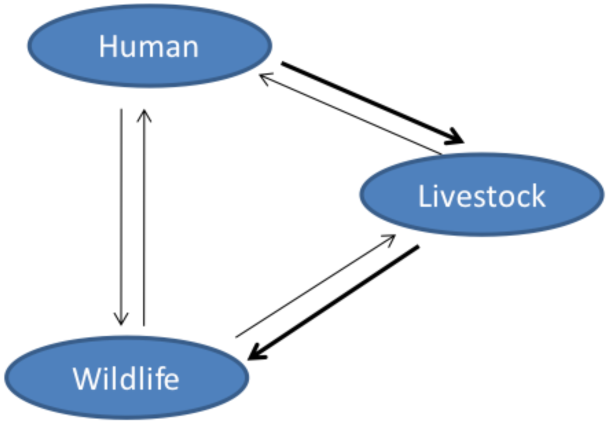
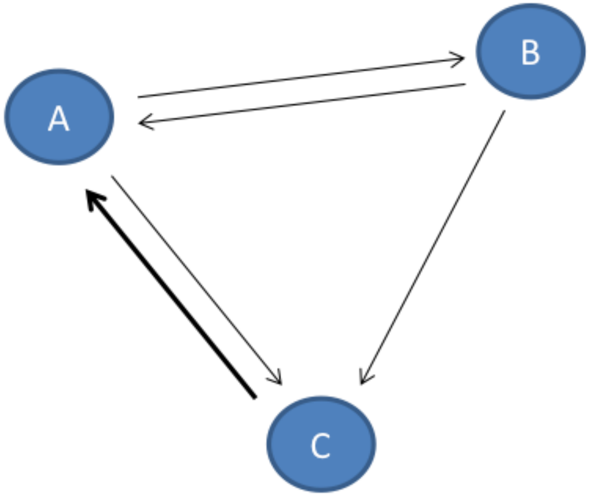


Within-community transmission of AMR



Between-community transmission of AMR

- Modelling the flow of resistance
  - allow diversity "fingerprint" to change over time
  - capture generation and spread of resistance

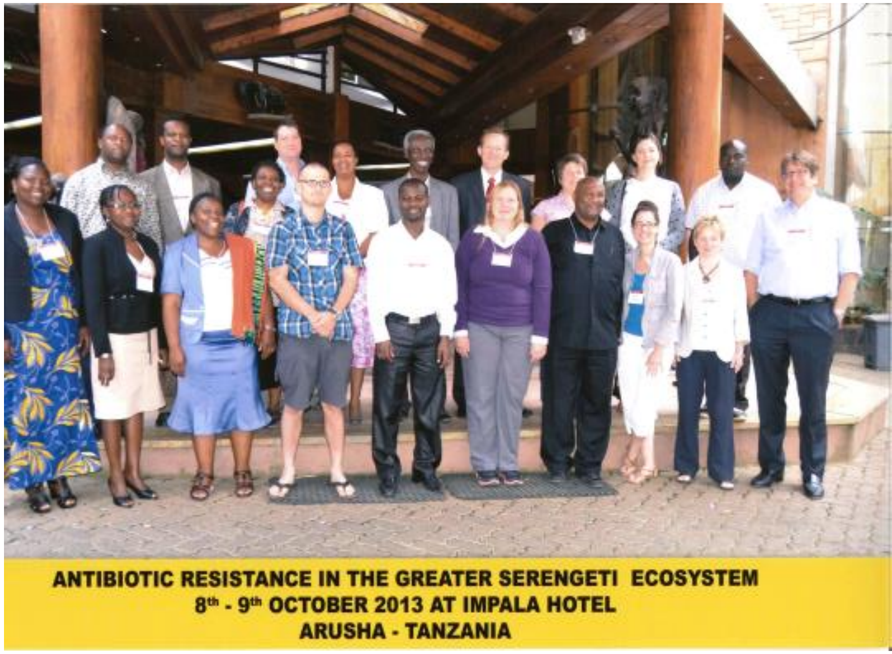
Summary

- New and powerful tools
  - Similarity-sensitive diversity
  - Partitioning of diversity

- Emerging areas of interest
  - Diversity and statistics
  - The dynamics of diversity

- Developing and deploying these tools as large amounts of AMR data come on line

- Washington State University (USA)
  - Doug Call, Margaret Davis, Terry McElwain, Guy Palmer, Rob Quinlan, Marsha Quinlan, Mark Caudell, Felix Lankester
- University of Glasgow
  - Jo Sharp, Sarah Cleaveland, Richard Reeve, Dan Haydon, Colette Mair
- Duke University (USA) & University of Otago (New Zealand)
  - John Crump
- Nelson Mandela African Institute for Science and Technology (TZ)
  - Francis Shahada, P. Gwakisa
- Tanzania Wildlife Research Institute (TZ)
  - Julius Keyyu
- Kilimanjaro Christian Medical Centre & Kilimanjaro Clinical Research Institute (TZ)
  - G. Kibiki, M. Ntabaye



ANTIBIOTIC RESISTANCE IN THE GREATER SERENGETI ECOSYSTEM
8th - 9th OCTOBER 2013 AT IMPALA HOTEL
ARUSHA - TANZANIA

- University of Dodoma (TZ)
  - D. Mwamfupi, Benta Matunga, Deman Yusuph, Eva Ombaka
- RVC (UK)
  - Jonathan Rushton, Ruth Rushton, Stuart Reid
- Directorate of Veterinary Services (TZ)
  - Emanuel Swai

BBSRC
bioscience for the future

NSF

Summary and future

- Central hypothesis
  - the prevalence and diversity of antibiotic resistance in human and livestock populations is primarily explained by the dissemination and persistence of resistance within and between various host populations
  - rather than by direct use of antibiotics, leading to similar antibiotic resistance patterns and gene pools in human and livestock populations.

- Consistent observations

1. No role of antibiotic usage!
   1. No differences between communities or host types!
   2. Better connected communities have greater diversity
2. Or, differences seen between community types, explained by differing antibiotic usage, but within communities
   - extent of shared diversity (flow of resistance) independent of antibiotic usage patterns
   - acquisition of new resistance types) more strongly related to contact patterns than usage patterns