UNIVERSITY OF ALBERTA
SCHOOL OF PUBLIC HEALTH

Human Health Risk Assessment
QMRA within holistic AMR management

Nicholas ASHBOLT
Professor and Alberta Innovates Translational Research Chair in
Waterborne Disease Prevention – Ashbolt@Ualberta.ca

PACCARB, PANEL SESSION 3: Public Health Risk, Impact, and Global Implications
Sheraton Columbus Hotel at Capitol Square, September 26th, 2018

UNIVERSITY OF ALBERTA
SCHOOL OF PUBLIC HEALTH

- University of Alberta - Founded in 1908
  38,000 students from 140 countries, with 400 undergraduate and 500 graduate programs across 18 faculties
  - Ranked 90th in the 2018 QA World University Rankings
  - One of the top 5 research intensive universities in Canada
- School of Public Health, split from Medicine in 2006, first US accredited SPH in Canada
- Three existing academic units provide the core components:
  - Department of Public Health Sciences
  - Alberta Centre for Injury Control
  - Centre for Health Promotion Studies

Students

- Some 300 graduate students (14 % distance & 15 % international)
- 3 degree programs: MPH, MSc, PhD

Staff

- 37 Core faculty members , 244 Research and support staff
- 57 Jointly appointed or cross-appointed faculty members and 13 Postdoctoral fellows

Annually

- leverage over $16 million in research funding
- lead or participates in more than 150 research projects
- 175 peer-reviewed articles in academic journals
- engage in > 200 knowledge exchange activities

Quantifying drivers of Environ AMR

- Mitigating the risks of antibiotic resistance requires linking various data reported on drivers of antibiotic resistance in humans arising from human, animal & environmental reservoirs
- Needs a **One Health** approach, plus re-framing to manage risk
  - Cochrane systematic review: selected 565 studies out of 2819 titles[1]
  - Odds ratios of AMR 2-4x from antibiotic exposure, underlying disease & invasive procedures, from 88 risk factors studied; yet [1]
    - **Food/water-related transmissions frequent [1]**
- **Feedlot beef study suggests environ more than meat[2]**
- Hence, environ important but how to link information together?

[1]Chatterjee *et al.* (2018) Lancet Infect Dis doi.org/10.1016/S1473-3099(18)30296-2

[2]Noyes *et al.* (2016) *eLife 5*, e1319; Weinroth *et al.* (2018) Appl Env Microbiol 84 e00610-18

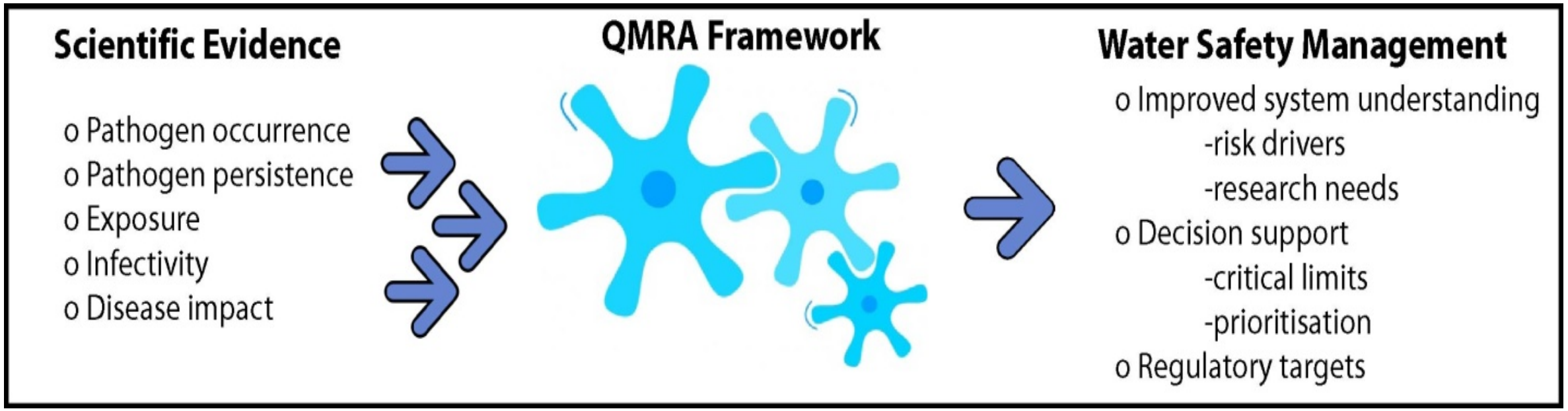
Environmental resistome is vast, ancient, mobilizable[1]

- Ample evidence that resistance elements currently circulating in pathogens belong to gene families with origins in the environment
- **Hypothesis**: use of antibiotics in bulk provides a strong selection for stochastic capture of environmental resistance genes, e.g.
  - mobile genetic elements (MGE) eventually acquired by pathogens
  - Frequency of these capture events correlates with gene diversity & environ burden
- **Goal: manage hot-spots where mixing of pathogens, mobile elements, and resistance genes is higher (manure, wastewater treatment, sediments etc.) – but what level?**

[1]Surette & Wright (2017) *Annu Rev Microbiol 71*, 309-330

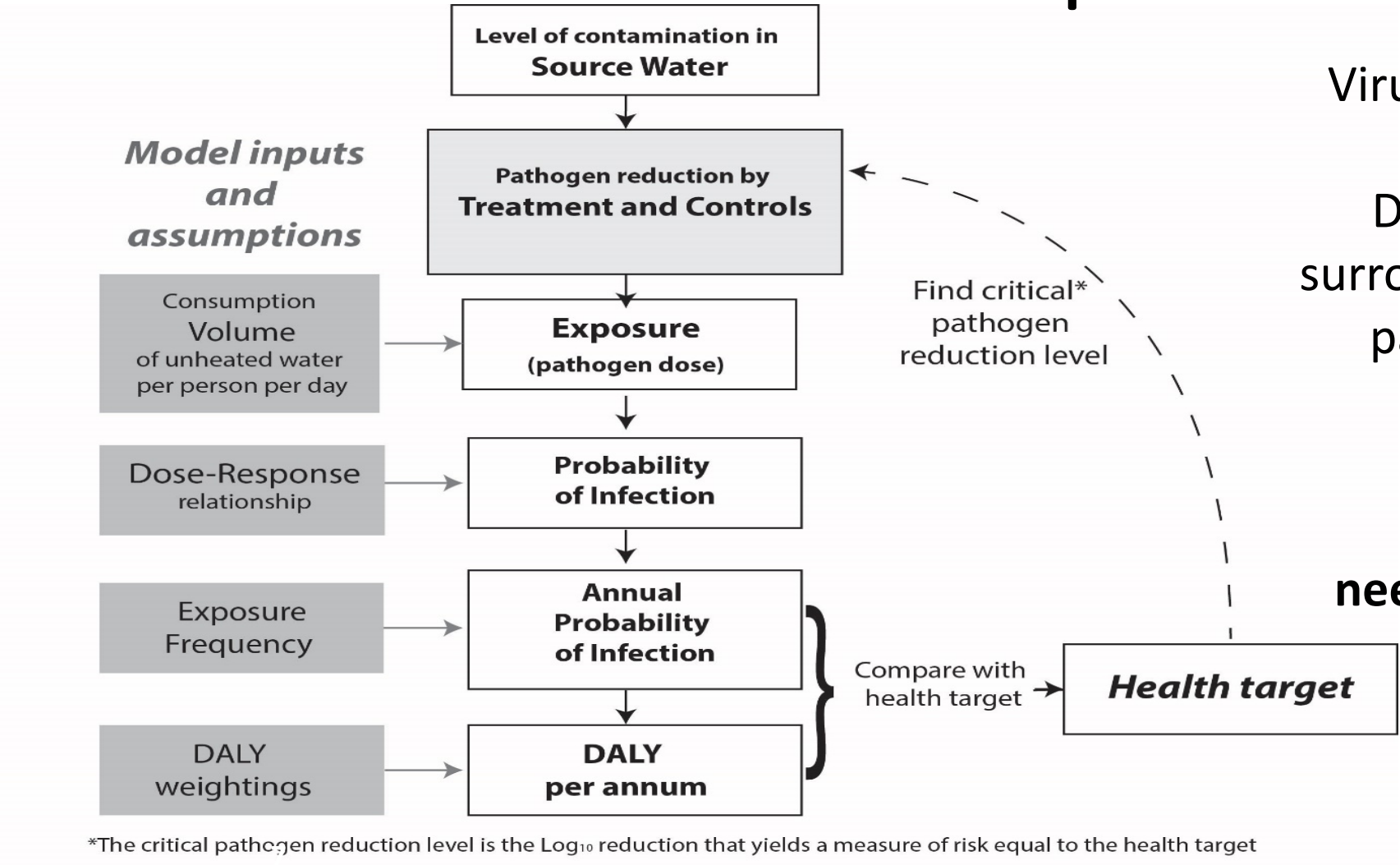
QMRA process (U.S. EPA 2014; WHO 2016)

Using scientific evidence to prioritize risk management



EPA (2014). *Microbiological Risk Assessment (MRA) Tools, Methods, and Approaches for Water Media*
WHO (2016). *Quantitative Microbial Risk Assessment: Application for Water Safety Management* World Health Organization: Geneva www.who.int/water_sanitation_health/publications/qmra/en/

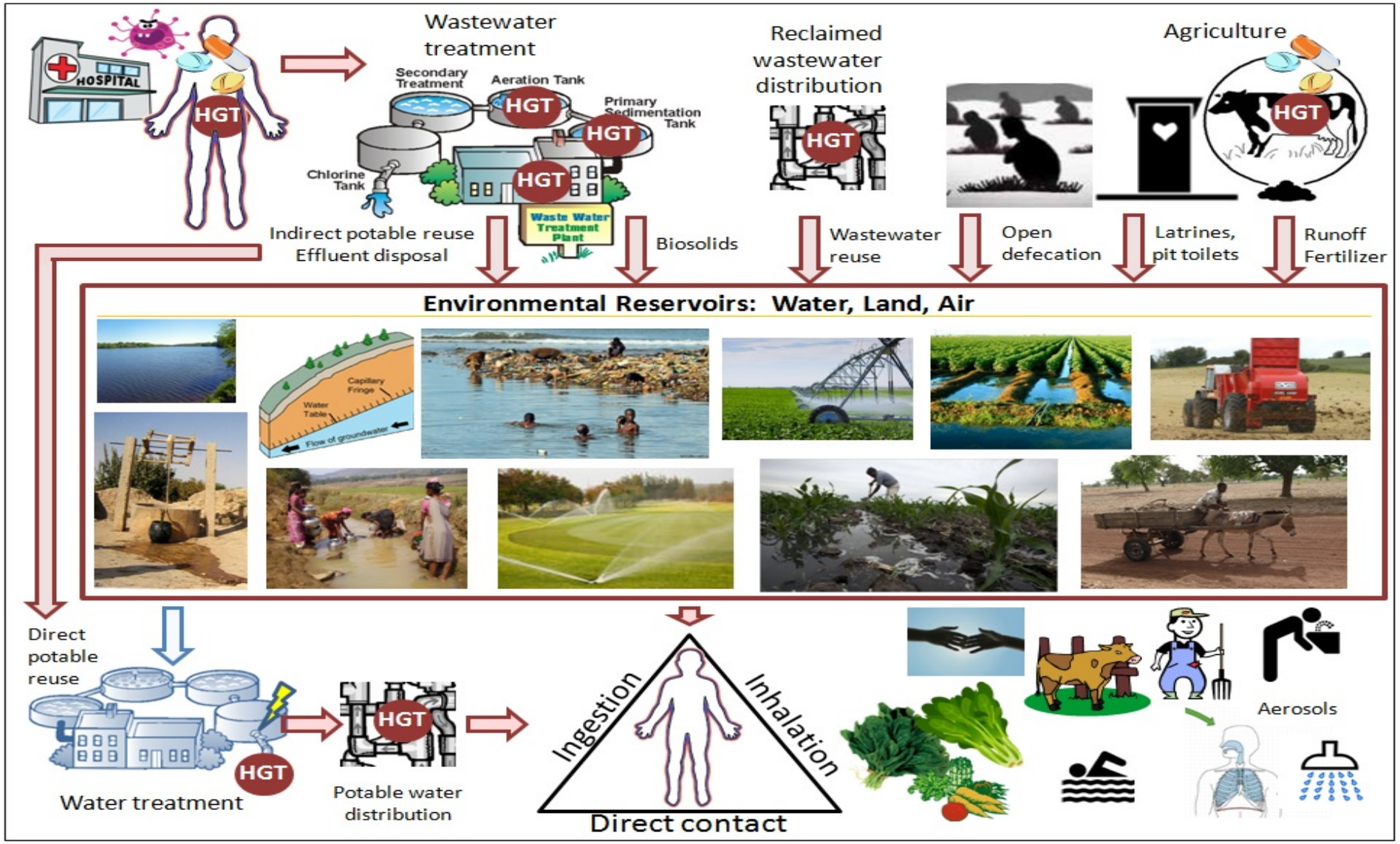
QMRA - defined treatment requirements



Virus, bacteria & parasite levels for safe uses.
Drives regulations then surrogates to demonstrate pathogen reductions at control points -
However AMR, as for saprozoic pathogens, need additional controls

Petterson & Ashbolt (2016) J Wat Health 4(4), 571-589
WHO (2016) *Quantitative Microbial Risk Assessment, Geneva*

Environmental pathways of AMR



Ashbolt *et al.* (2018) Antimicrobial Resistance…Global Water Pathogens Project; waterpathogens.org

Key questions when undertaking QMRA for AMR[1]

1. Which reference pathogens, ARGs or resistome: (WHO 2017) *priority list* ?
2. Environmental pathways of exposure or just deal with hot-spots?
   - AMR is a One Health problem, but has local, national & international aspects
3. Dose-response?
   - Does AMR change the probability of infection or just illness/treatment time and therefore health burden (need DALY/QALY estimates)?
     - Some quantitative evidence for increased health burden
   - How much HGT occurs on/within human host from environmental bacteria?
4. Benchmark risk – annual 10^{-4} infection, 10^{-6} DALY or Utility function?
   - Would log-removal targets work at treatment given episodic & environ pathways?
   - How to address (what level is OK) given post treatment 'hot-spots'?

[1]Ashbolt *et al.* (2013) *Environ Health Perspect 121*(9), 993-1001

How to capture missing data & management links?

- Traditionally from groups of experts & published literature
- Which has evolved into broader stakeholder groups to provide local, scientific and a more comprehensive understanding of complex and dynamic socio-ecological systems and processes[1]
- Nonetheless, many limitations with stakeholder participation[1]
  - **To reduce limitations, the process must be institutionalised, creating organisational cultures spanning one-health to facilitate processes where goals are negotiated & outcomes are necessarily uncertain**
- In part, models aid in aggregating the collection of missing data
  - Specific use of Conceptual Models & Bayesian Networks (Bayes Nets)

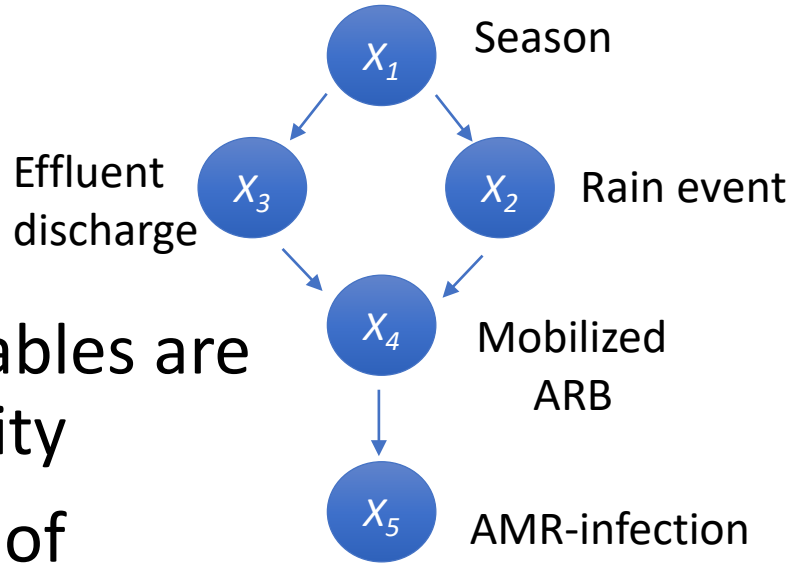
[1]Reed (2008) *Biological Conservation,* 141**,** 2417-2431

Bayes Nets vs Multi-Criteria Decision Aiding (MCDA)[1]

- "Weighing available evidence in the process of decision-making is unavoidable, yet it is one step that routinely raises suspicions:
  - **what evidence, its weigh, and whose thumb may be tipping the scales?**
- U.S. National Res Council critiqued 'weight of evidence' (WoE) as too vague and detractive for chemical risk assessment, so for AMR?
- How to move from qualitative, vague & controversial methods?
  - **Bayesian WoE or MCDA?**
- Inexact science of converting existing health/infection knowledge into risk management decisions and policies
  - **Noting 'colloquial WoE use' is the problem [1]**

[1]Linkov *et al.* (2015) *ALTEX 32* (1), 3-8

Bayes net (BN)[1]



- Form of directed acyclic graph (DAG), where variables are represented by nodes & linking arrows for causality
- The DAG provides an initial visual representation of relationships of influence among the variables (from Conceptual diagram)
- Each node or variable has a number of user-defined states that can be qualitative, discrete or continuous
  - e.g., 'high/low', 'true/false', '$\leq 10^4$ / $> 10^4$ gene copies ▪ $gram^{-1}$'
- Each of the variable states is assigned a conditional probability, derived from published empirical data, models, simulations, or expert opinion
  - Use of **Noisy-based logic** functions (multivaled deterministic logic schemes)

[1]Judea Pearl (2009) Causal inference in statistics: An overview. Statistics Surveys 3, 96-146
Pearl & Russell (2001) Bayesian Networks, http://ftp.cs.ucla.edu/pub/stat_ser/R277.pdf

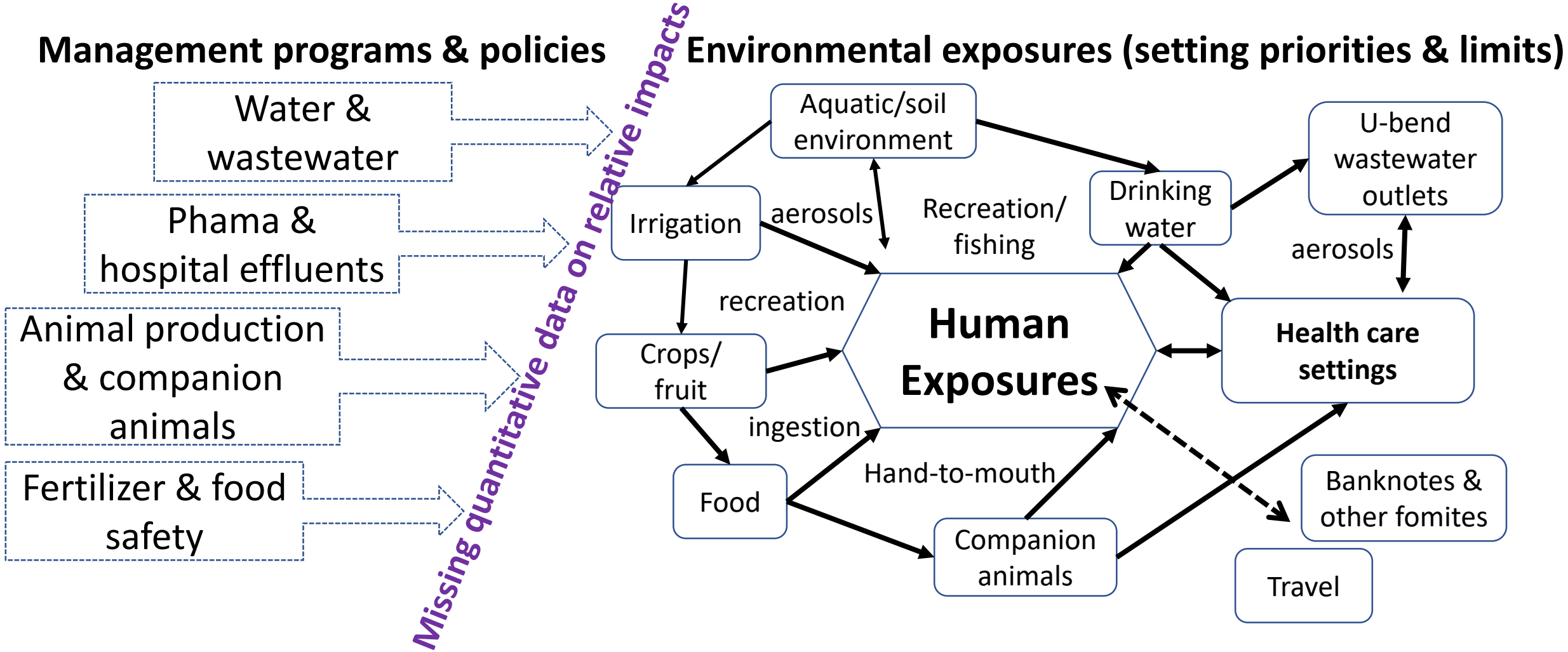
Burden of disease: Use of Disability-adjusted life year (DALY) or the Utility function in Bayesian modelling?

- DALY is a common health metric
  - Adopted by WHO and many other health agencies, for:

    1) the 'positive' exercise of measuring the burden of disease; and 2) The 'normative' exercise of resource allocation
- However, the implications of age-weighting, blindness towards equity and discounting are unacceptable to some[1]
  - Does not distinguish between measuring burden of disease and allocation of resources – as information sets are quite different between the two
  - Allocating resources by aggregate DALY-minimisation is inequitable
- Therefore suggest use of '**Utility**' function (Von Neumann Morgenthau Utility theorem)[2]
  - Utilities can be used as the quality-adjustment weights in DALYs or QALYs
  - Variation on cost-effectiveness analysis known as cost-utility analysis

[1]Anad & Hanson (1997) *J Health Econ 16* (6), 685-702
Whitehead & Ali (2010) *Br Med Bull 96*, 5-21
[2]Torrance & Ferny (1989) *Int J Technol Assess Health Care 5* (4), 559-575

Unknowns: environ exposure, growth & impacts of AMR bacteria[1] – what Bayes Nets could address



[1]Ashbolt *et al.* (2013) *Environ Health Perspect 121*(9), 993-1001

Conclusion: QMRA-driven AMR risk management should create and protect value/utility

- AMR management is all about risk minimization and health value/utility maximisation
  - As a result we are faced with the same task as economists
  - But microbiologists generally don't talk or think about economics
- Arguable we have a universal utility metric, the µDALY
  - Next logical step in QMRA – along with QMRA fitting risk tools (ISO 31010/ANSI Z690) is **introduce Utility into AMR management**
  - Bayes Nets and Bayes theory can facilitate the whole process by providing a single framework – focused on informing management