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SCHOOL OF PUBLIC HEALTH

Human Health Risk Assessment QMRA within holistic AMR management

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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



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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 titles¹
 - 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?

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

²Noyes *et al.* (2016) *eLife* 5, e1319; Weinroth *et al.* (2018) *Appl Env Microbiol* 84 e00610-18 ⁴

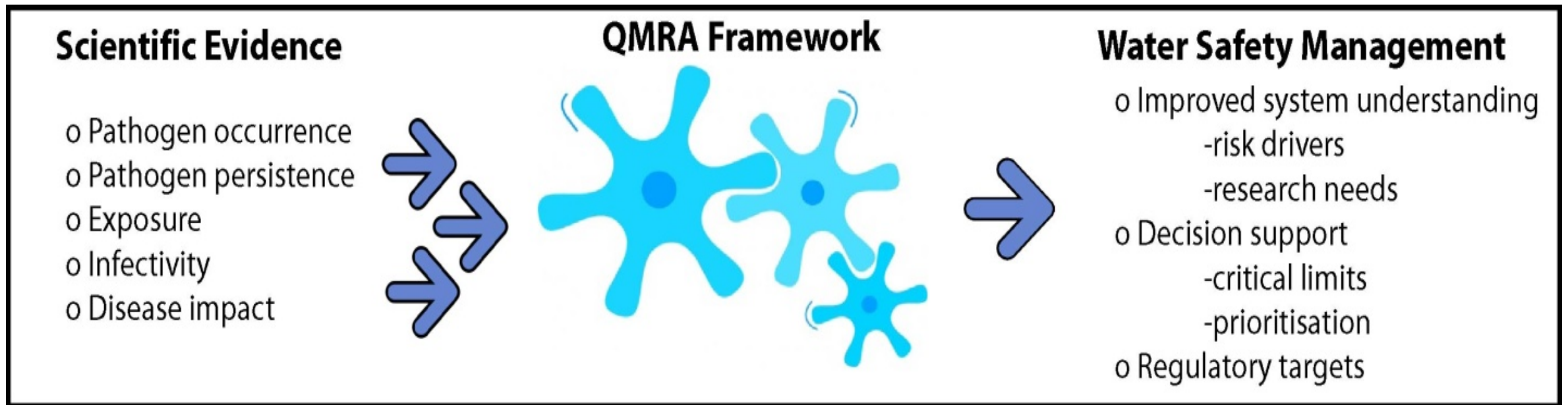
Environmental resistome is vast, ancient, mobilizable¹

- 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?**

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

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

Using scientific evidence to prioritize risk management

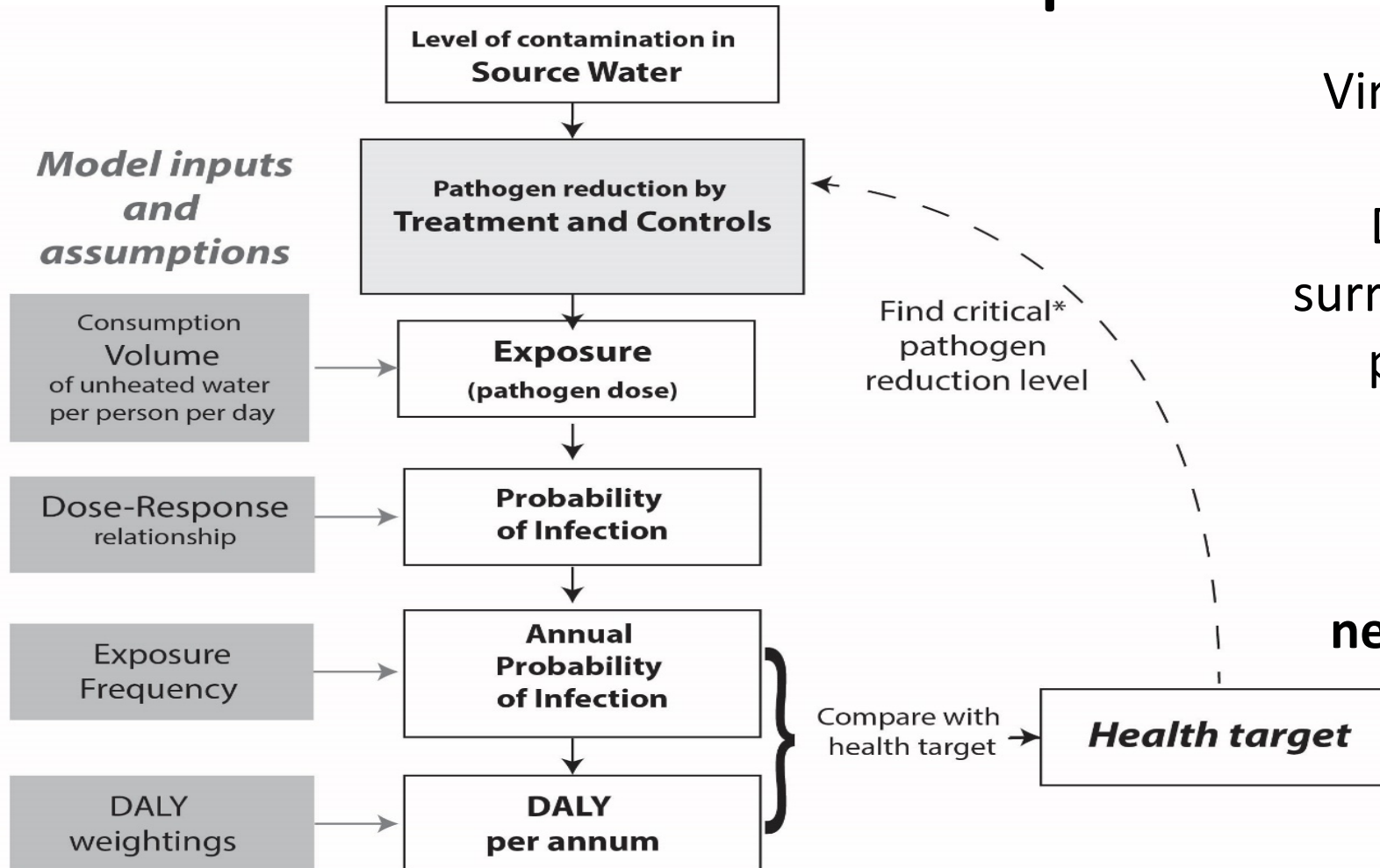


EPA (2014). *Microbiological Risk Assessment (MRA) Tools, Methods, and Approaches for Water Media*

WHO (2016). *Quantitative Microbial Risk Assessment: Application for Water Safety Management*

World Health Organization: Geneva [www.who.int/water sanitation health/publications/qmra/en/](http://www.who.int/water_sanitation_health/publications/qmra/en/)

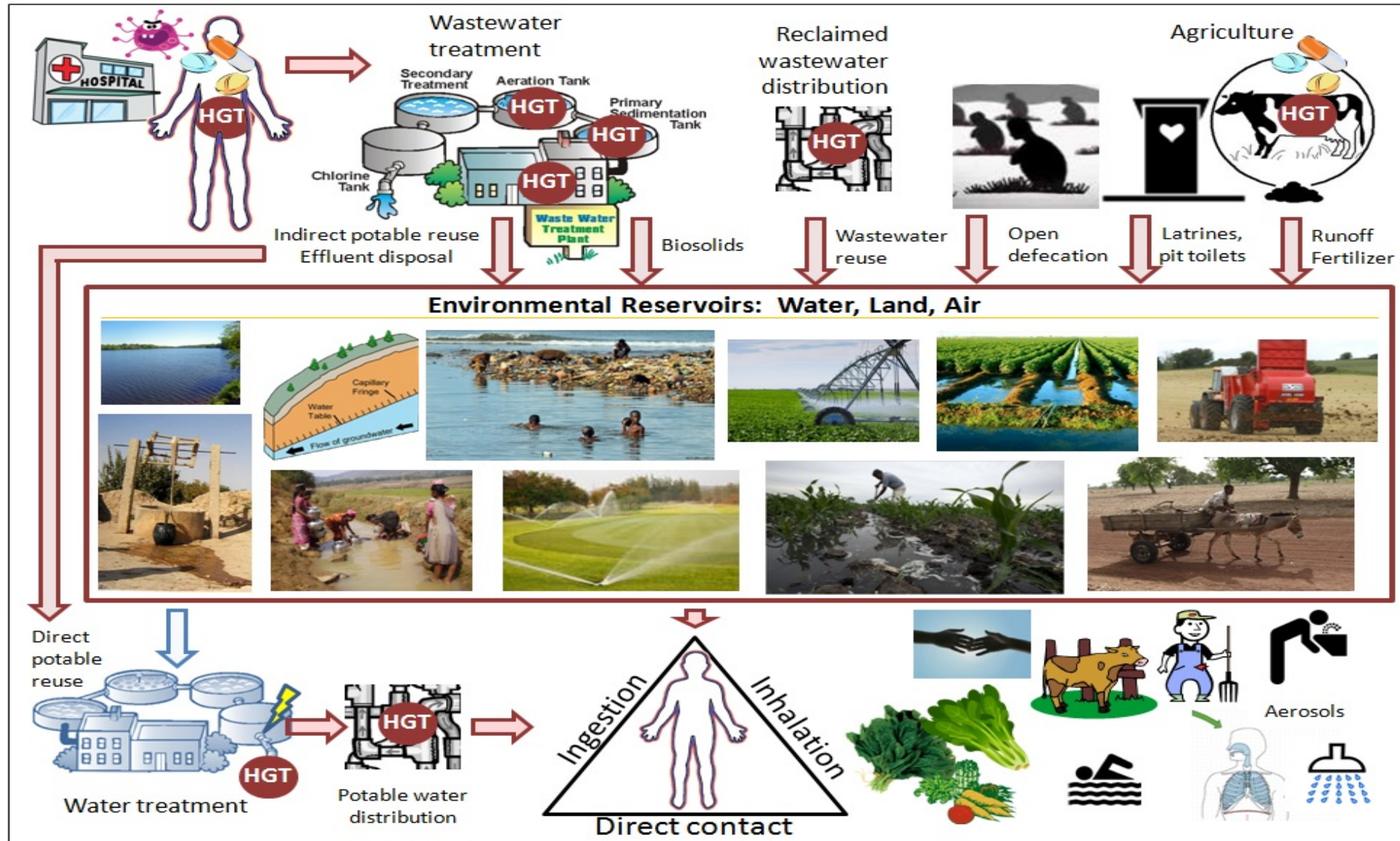
QMRA - defined treatment requirements



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**

*The critical pathogen reduction level is the Log₁₀ reduction that yields a measure of risk equal to the health target

Environmental pathways of AMR



Key questions when undertaking QMRA for AMR¹

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’?

¹Ashbolt *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 processes¹
- Nonetheless, many limitations with stakeholder participation¹
 - **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)

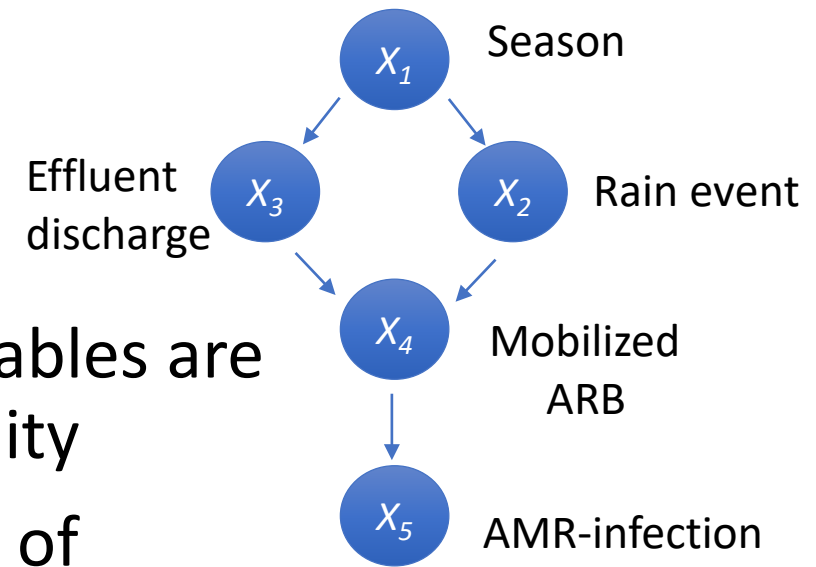
¹Reed (2008) *Biological Conservation*, 141, 2417-2431

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**

¹Linkov *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 $\cdot \text{gram}^{-1}$ '
- 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 (multivalued deterministic logic schemes)

¹Judea 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 12

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 some¹
 - 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

¹Anad & Hanson (1997) *J Health Econ* 16 (6), 685-702

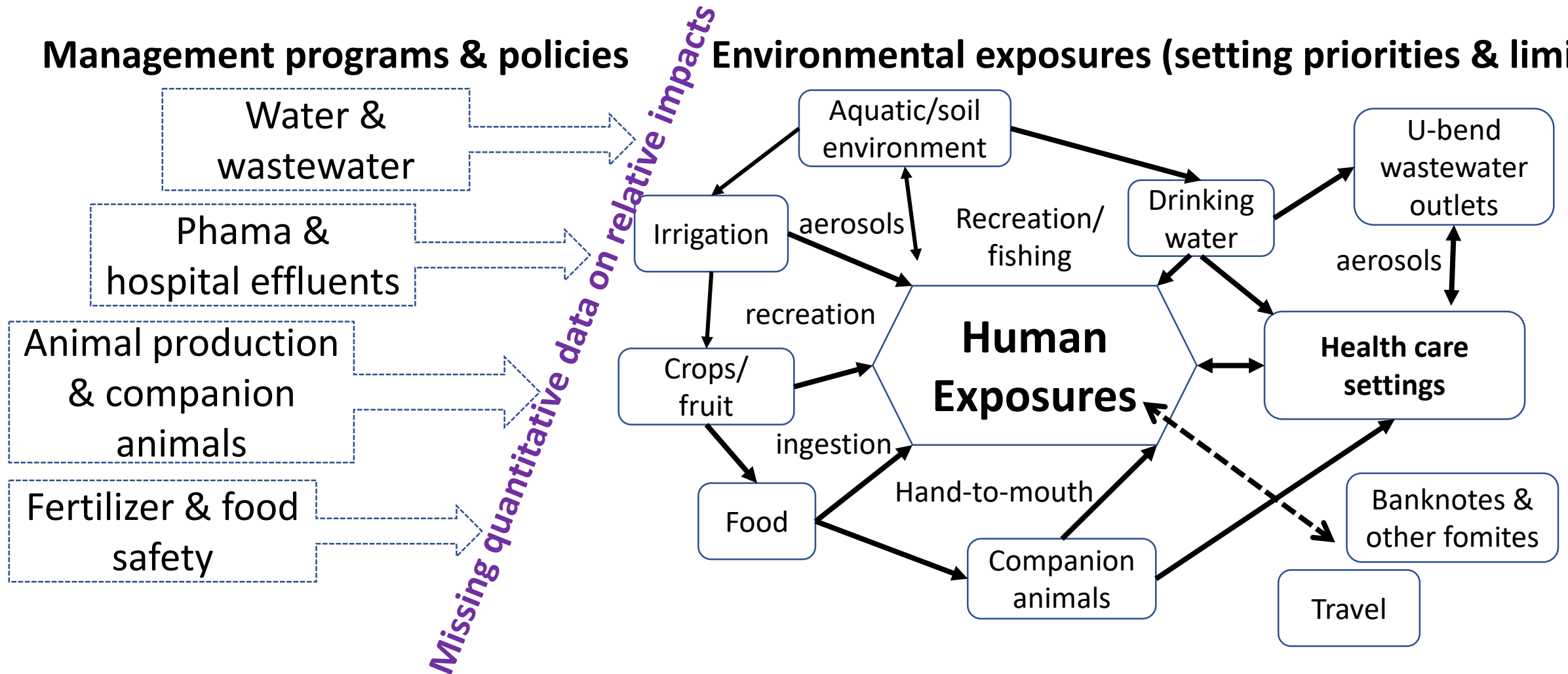
Whitehead & Ali (2010) *Br Med Bull* 96, 5-21

²Torrance & Ferny (1989) *Int J Technol Assess Health Care* 5 (4), 559-575

Unknowns: environ exposure, growth & impacts of AMR bacteria¹ – what Bayes Nets could address

Management programs & policies

Environmental exposures (setting priorities & limits)



¹Ashbolt *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 μ DALY
 - 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