Chapter: Antimicrobial Resistance, Risk Assessment and Management, and Potable Water reclamation and recycling

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Summary

This chapter presents the authors' findings from reviewing literature pertaining to Antimicrobial Resistance (AMR) to determine the significance of the AMR issue for potable reuse and whether risk assessment of AMR microorganisms might be undertaken.

The issue may be a 'game changer' for water quality risk assessment and management and compromise our drawing conclusions about recycled water safety based primarily on established QMRA and QCRA modelling of conventional pathogens and chemicals.

Conclusions include the following:

1. AMR has emerged as a major water and sanitation risk which potable water recycling must include in its system design and management.
2. This process must integrate work in the water sector with public information provision and risk management by the healthcare and food production sectors.
3. A range of new information is needed on AMR hot-spots, fate and transport even before the risks posed by potable and non-potable recycling can be credibly assessed. Extensive research is needed probably including much primary environmental monitoring.
4. Development of conceptual and mathematical models is needed to integrate primary data, help identify gaps, prioritize critical control points for management and assess the impact and cost effectiveness of proposed controls.
5. Potable recycling of reclaimed water needs to consider not only AMR removal from the primary waste stream but also AMR from secondary streams – e.g. biosolids, brine, overflows, exfiltration and how pre-treatment releases are to be avoided.
6. There is already a substantial body of knowledge on environmental fate and transport of AMR. This needs to be integrated along the lines of the tables in Ashbolt et al. (2018).
7. The current risk assessment HHRA framework appears suited to ensuring potable water and returns to the environment are safe.

Because of the complexity of the AMR issue we have explored the wider issue of AMR and the water sector to provide a basis for developing this chapter. The findings of this exploration as contained in a separate supplementary literature review. This review looks at the relevance of AMR to the water sector's water and sanitation mission generally. Its implications for potable recycling have then been distilled into this current chapter. Development of a supplementary review was seen as essential because a claim as dramatic as 'AMR being a game changer', needed to be based on a larger overview which was not available in the literature though there were many useful reviews of aspect of AMR related to the water cycle.

Background

O'Neill (2014) explains the general Antimicrobial resistance[1] (AMR) problem in plain English as follows:

> *"In 1928 a piece of mould fortuitously contaminated a petri dish in Alexander Fleming's Laboratory at St Mary's Hospital London, and he discovered that it produced a substance (penicillin) that killed the bacteria he was examining. Within 12 years Fleming and others,[2,3] had turned this finding into a wonder drug of its time, which could cure patients with bacterial infections. Further antibiotics were discovered and went on to revolutionise healthcare, becoming the bedrock of many of the greatest medical advances of the 20th century. Common yet frequently deadly illnesses such as pneumonia and tuberculosis (TB) could be treated effectively. A small cut no longer had the potential to be fatal if it became infected, and the dangers of routine surgery and childbirth were vastly reduced. More recently, advances in antiviral developments over the past 20 years have transformed HIV from a probable death sentence into a largely manageable lifelong condition.*
>
> *But bacteria and other pathogens have always evolved so that they can resist the new drugs that medicine has used to combat them. Resistance has increasingly become a problem in recent years because the pace at which we are discovering novel antibiotics has slowed drastically, while antibiotic use is rising. And it is not just a problem confined to bacteria, but all microbes that have the potential to mutate and render our drugs ineffective. The great strides forward made over the past few decades to manage malaria and HIV could be reversed, with these diseases once again spiralling out of control."*

When we proposed AMR as a chapter in this review of risk assessment and management for water recycling, we expected it would be a secondary 5-10 page chapter, briefly updating the state of the research since the early 2010s and indicating that no urgent action modification would be needed in respect to water and sewage policies including those related to water recycling. For further information we expected to refer the reader to existing and new reviews along the lines of Jury et al. (2011) and Kümmerer (2009b, 2009a) and water management guidelines (NH&MRC, 2013). In the process we hoped to assess a. when concerns about AMR in relation to the water supply and wastewater management industries might be resolved and b. when it might be possible to incorporated AMR issues into the established QMRA framework. In short we accepted AMR as a health concern but did not see it as an operational concern for the water industry or recycling as yet.

The literature which emerged, however, indicated Antimicrobial Resistance (AMR) is now very widely viewed as an extreme/existential challenge for the water industry and public health based sanitation generally, including by implication water recycling. It also appeared that AMR management needs to be incorporated into broader infrastructure policy as soon as possible

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[1] Possibly more familiar as 'antibiotic resistance'. The term has been modified to a generic 'antimicrobial' So as to include resistance to antiviral, antifungal and antiprotozoal drug resistance.
[2] Especially Australian Howard Florey, and Ernst Chain and Edward Abraham who together (except EA) received the 1945 Nobel Prize in Medicine for their work.
[3] In fact antimicrobials preceeded this, notably Salvarsan and the Sulphonamides which established the basic search approach though these drugs were not as broad spectrum as the Penicillin.

especially the water, food production and healthcare sectors. The fact that this had been unanticipated appears due to a 'paradigm shift' having occurred very recently and rapidly. This reflects the following developments in particular over the past 3 to 4 years:

1. Recognition that if the current trajectory of AMR spread is maintained, by 2050 there will be a return to the 'pre-antibiotic era' with ascribable deaths reaching catastrophic proportions (at a minimum, exceeding those for all cancers today combined).
2. Current and past healthcare and food animal production based management approaches have not contained AMR despite 50 years of efforts.
3. The application of very large scale gene sequencing technologies to a variety of samples from waste streams and the natural environment has demonstrated in increasing detail the scale, locations, evolution and exchange of both AMR carrying microorganisms and Mobile Genetic Elements (MGEs) occurring along water cycle pathways. The foremost critical control points on concern include wastewater, treatment plants, drinking water and biosolids.
4. Water supply and wastewater management are now seen as the 'new battlefront' (Bürgmann et al., 2018) in the control of AMR. And efforts in these areas must be integrated with other fields (mainly healthcare and animal production) if return to the pre-antibiotic era is to be achieved before the benefits of antimicrobials are lost entirely. The inclusion of the water cycle also reflects the WHO's evolving 'One Health' concept.

There are many documents which confirm this paradigm shift is real an exaggeration created by researchers in order to obtain new funding. Some particularly stood out in the literature reviewed. They provide primers for SWC strategic and operations managers to understand the overall problem as a precursor for developing water sector AMR management policies. They are also sufficiently strategic, concise and lacking in jargon for consideration by senior management. Most are freely available, offer precursor reading for evaluating the implications of AMR for SWC's core activities of clean water supply and safe (environmental and public health wise) return, as well as the reclamation of wastewater be it for potable or non-potable uses:

1. The work overseen by the O'Neill committee (2016, 2014) for the UK government;
2. The emerging international position/policy on AMR notably:
    a. The United Nations Environment Program placing Antimicrobial Resistance (AMR) in its top 5 priorities for the 2100s alongside the more familiar problems/priorities of climate change mitigation and biodiversity preservation (United Nations Environment Program, 2017) and strongly water related areas of clean production; and
    b. WHO's recent update of its 'One Health' and Sustainable Development goals report (IACG, 2019) "No time to wait: Securing the future from drug-resistant infections" which liberally identifies the centrality of water and sanitation in the control of AMR;
3. Prescott's (2017) history of Antimicrobial Drugs and their use in veterinary medicine;
4. Bürgmann et al.'s (2018) and Singer et al.'s (2016) reviews of "Water and sanitation: an essential battlefront in the war on antimicrobial resistance." and "Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators.";

5. The increasing appearance of the AMR issue in the quality press (Harvey, 2019, Jacobs and Richtel, 2019).

The global risk problem is captured in Figure 1, i.e. the human health risk in event of a loss of antibiotic availability. In fact this graph and the 10 million deaths per annum figure likely provide a lower global risk estimate for the impact of failure to control AMR (O'Neill, 2016):

> *"As with all forecasts of this sort, it is of course possible that our estimates may turn out to be too large, but we believe it is even more likely that they could be too small. This is because we did not even consider the secondary effects of antibiotics losing their effectiveness, such as the risks in carrying out caesarean sections, hip replacements, or gut surgery."*

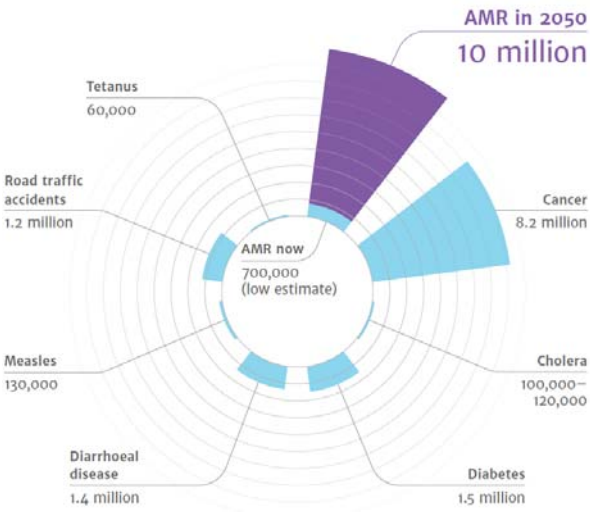

Figure 1. Deaths attributable to AMR every year (reproduced from O'Neill, 2016)

The UNEP (2017) report confirms the emerging international consensus that the control of AMR is a primary global environmental health challenge on par with climate change and biodiversity protection. It shows that:

1. AMR management needs to move beyond the historical foci of healthcare settings and the use of antimicrobials in animal production and consider AMR fate and transport in the environment generally; and
2. Qualitative and Quantitative Microbial Risk Assessment need to be expanded to include risks arising from antimicrobial resistance.

As the water cycle is a key conduit controlling the transport and fate of pathogens in the environment it follows that AMR control needs to consider this. WHO (IACG, 2019) explains the need for an holistic approach that integrates all critical control points (CCPs) in the AMR cycle. Compared with slightly older references it highlights the central place of water and sanitation management. Prescott (2017) provides a concise detailed history of the evolution of, and failure to control AMR in general, and in relation to animal food production. It is notable that the problem is still growing despite 50 years of efforts since for example the seminal Swann et al. (1969) report on the use of antimicrobials in the production of food animals. Bürgmann et al. (2018) and Singer et al. (2016) review the operational risks and management options for water and sanitation and the environment respectively and are of most practical interest for water management policy developers. The newspaper articles illustrate the rising public profile of the AMR issue and its impact on both the advanced economies and developing world countries

What has AMR has got to do with potable water recycling?

Figure 2 shows the one health perspective and the historical focus of AMR research and management in red. The 'One Health' approach implies much more research is needed for starters to understand the environmental water cycle and AMR fate and transport. Deliberate and unintentional water recycling are self-evidently parts of that cycle.

Figure 3 illustrates some of the water transfer links between compartments in the urban water cycle, especially in advanced economies, and by inference likely AMR fate and transport barriers/CCPs and pathways of interest to WSP (HACCP) developers. Though detailed, even Figure 3 is incomplete. Notable omissions are raw sewerage exfiltration, overflows and discharges from breakdowns, groundwater interactions, mixing with stormwater, Biosolids application to land, membrane brine streams, and other wastes arising in treatment processes. Nor does it touch on existing recycled water subsystems or 'hot-spots', that is environments where AMR gene generation and horizontal exchanges are promoted disproportionately and are potentially major sources of antimicrobials and AMR.

Figures 2 and 3 below and policy development needs outlined above indicate that urban water utilities should now also incorporate the risks posed by AMR into their existing risk assessment and management activities. Potable recycling involves the direct or near direct return of AMR contaminated water to human consumers in the event of barriers being insufficient and so raises a range of questions such as:

- How effective are the planned, proposed and existing water recycling barriers to AMR?
- How effective are the existing water recycling schemes and sewage disposal arrangements? Do they need upgrading?
- How should AMR risk be assessed? How useful is qualitative assessment? What does quantitative AMR risk assessment look like? How does the risk arising from exposure to conventional water borne pathogens compare with that from AMR exposure.
- What treatment targets and end product benchmarks are applicable or appropriate?

The answers to these questions are unclear beyond the fact that AMR needs to be urgently addressed for potable recycling to be accepted if only because the future promises concurrent widespread public campaigns for the to minimize AMR hazards (a current example is the wide promotion of disinfectant use in toilets). When this happens the development of questions in the public's mind to the consumption of water from the most concentrated AMR waste-stream seems likely.

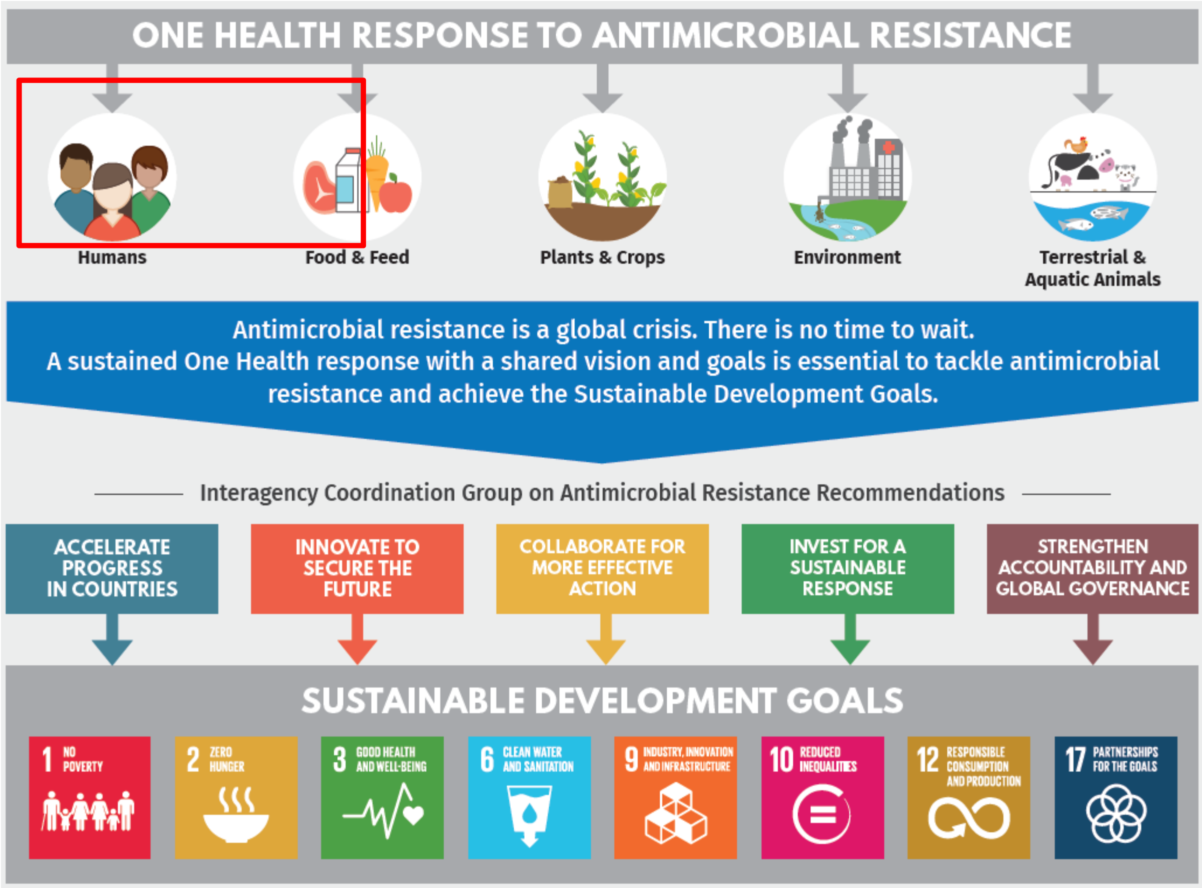

Figure 2. One Health, IACG recommendations and the Sustainable Development Goals (reproduced from IACG, 2019)

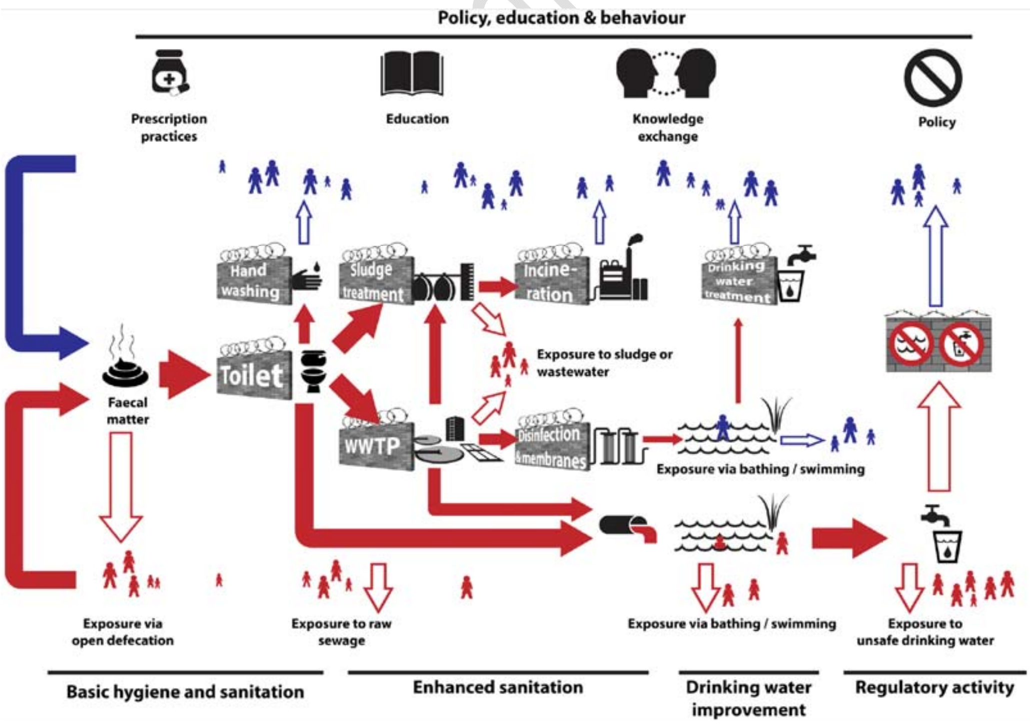

Figure 3. Promising barriers to environmental dissemination of antimicrobial resistance along the water and sanitation continuum and ultimately to human exposure (reproduced from Bürgmann et al., 2018).

Supplementary report on water and the environment and AMR

None of the reviews examined provided a comprehensive picture of AMR sufficient to inform the water industry on risk management for its existing systems, let alone new ones supporting potable recycling. One reason is that AMR related issues are enormously diverse and data on environmental AMR fate and transport has yet to be integrated beyond the conceptual. For example Bürgmann et al. (2018) outline a number of management options but do not explain the AMR history above, consider the existing risk management frameworks in place for water and wastewater management, the monitoring challenges or the biology of mobile genetic elements. To address these gaps a supplementary report has been prepared on "Antimicrobial Resistance, Risk Assessment and Management and the Water Cycle" more generally.

Relationship to this chapter

Preparation of this supplementary report was used by the authors to obtain an initial understanding of the larger AMR context and assess in a preliminary way how significant the issue was before preparing this current chapter. In particular we wished to know whether the assertions of Bürgmann et al. (2018) and Singer et al. (2016) made for sound policy directions and reflected a wider scientific literature consensus. This supplementary report's major headings are as follows:

- An introduction explaining the basic AMR concept and associated risk, terminology and why antibiotics are central to the health systems of modern advanced economies and society;
- AMR ecology and the environment - covering how bacterial resistance develops and the new developments in microbial ecology relevant to understanding water borne AMR;
- AMR and the water sector - covering its natural occurrence, drivers of its spread, water related 'hot-spots' and a history of literature on AMR and the water cycle;
- AMR modelling - covering different styles of 'model' which will be needed for integrating the diverse knowledge base on AMR and predicting the likely impacts of management options;
- Current AMR risk assessment and management options and ideas - covering the current level of risk assessed, management proposals, modelling and management, and uncertainties;
- Summary and conclusion - covering how far the supplementary report's specific aims were addressed and providing preliminary conclusions and recommendations from a water risk management point of view.

The assertions made in this chapter and the literature cited in respect to AMR and potable recycling reflect the material in this Supplementary Review.

What may be at stake – the partial loss of the gains from clean water and sanitation

Water and sanitation advances in general are sometimes identified as the primary reason for the great advance in human health in advanced economies during the 20th century. It is true that for example between 1900 and 1997 average life expectancy in the United States increased by more than 60% to 76 years and the predominant causes of death has shifted from infectious to chronic diseases (Cohen, 2000 Figure 1) and water and sanitation was crucial to this shift (Figure 4). However, the current consensus is that the change occurred not from clean water and sanitation alone but because of a combination of this together with vaccination, antibiotics and most recently, better control of food pathogens and ongoing poverty alleviation (Cohen, 2000). This 'multi-barrier' based protection is arguably analogous to the water supply catchment to consumer barrier concept familiar to water managers. Its loss presumably would lead to a return to infectious disease related mortality patterns and marked reduction in life expectancy.

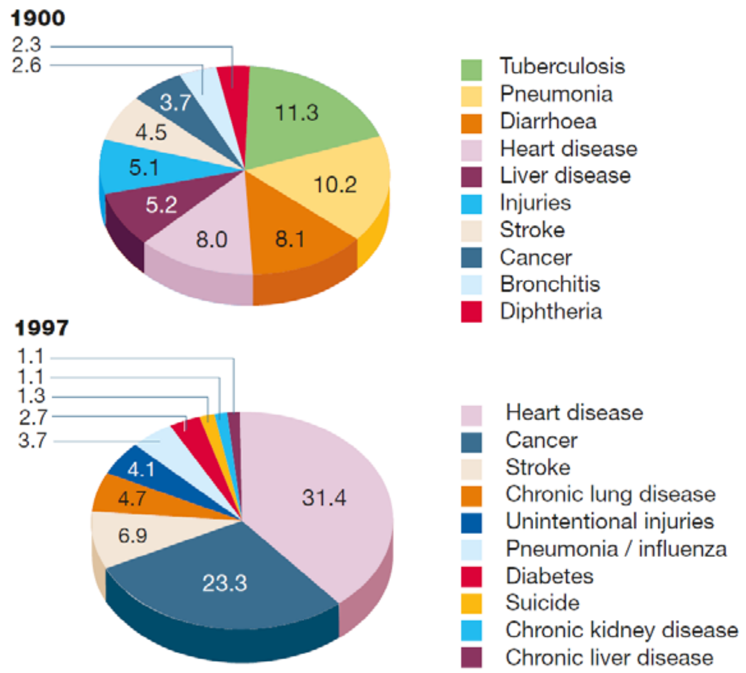

Figure 4. The ten leading causes of death in the United States in 1900 and 1997. (Infectious diseases that were the most important causes of death at the beginning of the twentieth century have been replaced by chronic diseases.(reproduced from Cohen, 2000)

Unfortunately the rise in AMR compromises four of these five barriers: a. AMR negates antibiotics by definition, b. clean water and c. food and sanitation are compromised if they can no longer control the spread of disease; and d. poverty alleviation is compromised by the inability of the sick to work. Beyond these is the potential for public disillusionment with pillars of modern health and medicine, arising from reduce safety of invasive operations and increased vulnerability of the aged and infirm, on top of scepticism about vaccination.

What is at stake, and the striking differences between now and society in the pre-antibiotic era, is illustrated by consideration of tuberculosis. Prior to its control western countries were rife with sanatoria, that is communal living establishments where large numbers of diseased individuals were quarantined to notionally rest and try and recoup, but who often in reality went into decline over a period of many months. The rise of AMR is such that their return is now being proposed as a serious management option (Dheda and Migliori, 2012). The history of tuberculosis also appears to illustrate the combined impact of sanitation and antibiotics and the multi-barrier effect. Prior to 1950 significant success had been achieved in controlling TB via improved sanitation and hygiene measures (e.g. milk pasteurization) corresponding to a risk decline of *ca* 90%. This decline was impressive but the residual infection rate was still high by current standards in advanced economies. Apparently concurrent with the advent of antibiotics effective against this pathogen, however, infection dropped by a further 99% (Lienhardt et al., 2012)(Figure 5)[4]. The accompanying supplementary report provides further background on the larger picture by way of leading into water and sanitation aspects.

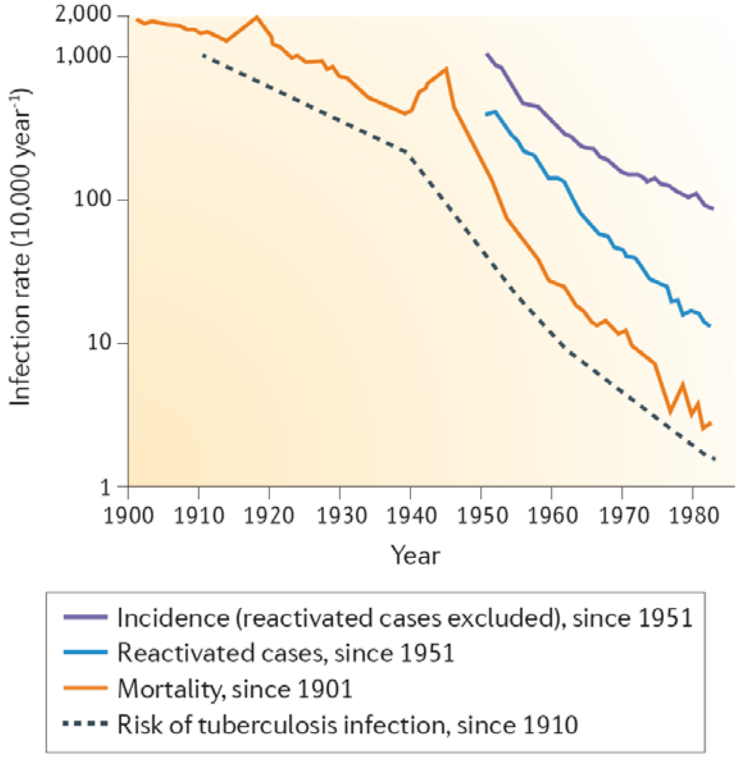

Figure 5. TB incidence, reactivation and death rates (per 100,000) and the average annual risk of TB infection (per 10,000) in the Netherlands for the period 1901–1983 (reproduced from Lienhardt et al., 2012).

[4] Despite many efforts a universally effect Tuberculosis vaccine has not been developed and so does not account for this decline, though the Manteaux test had proved useful for diagnosis.

Implications for reclamation of wastewater for potable use and its management

Significance for, and relationship to, QMRA, QCRA and qualitative risk assessment and management

Provision and management of clean water is increasing based on application of qualitative and quantitative risk assessment. Though the approach has its limitations (Australian Water Recycling Centre of Excellence, 2014) it has proved generally possible to deal with emerging pathogen and chemical contaminants within this framework and the same might be expected of AMR if knowledge of critical control points was available. To a degree this is illustrated by some early food safety work (Cox Jr, 2006) and the strategic application of HHRA/ERA to AMR has certainly been proposed (Ashbolt et al., 2013).

However, AMR has a number of distinct features which prevent adaptation to HHRA/QMRA from being as straightforward as when new water borne pathogens or chemicals are identified. These features can be divided up using the standard HHRA steps/headings : hazard identification, dose response assessment, exposure assessment and risk characterisation. Cursory consideration reveals each sub area requires major development and how much greater a challenge these will prove before there is sufficient understanding to incorporate AMR into potable recycling risk assessment.

Hazard identification

The AMR hazard includes not only classic acute water borne pathogens but also opportunistic and saprozoic pathogens, AMR genes, their various mobile genetic elements, and the interactions between these and the non-pathogenic autochthonous microorganisms inhabiting a diversity of environmental biomes. Part of the hazard story is the ability of Mobile Gene Elements (MGEs) to be transferred 'horizontally', that is between microbial species in microbially active environments such as biofilms and the flocs formed in activated sludge (Guo et al., 2017). Hazard identification also needs to consider ongoing AMR microorganism, biome and genome evolution. The natural ecology of many AMR pathogens e.g. *Staphylococcus aureus*, Vancomycin resistant enterococci, pneumococci (Kramer et al., 2006); is not well characterised in respect to water or environmental transfer, even in healthcare settings. Their impacts are felt not only in the human gut but also other human biome compartments notably the skin, respiratory tract and urogenital system.

Dose response assessment

The ingestion related dose response algorithms of AMR pathogens are poorly developed. *S. aureus* and enterococci are also part of the normal commensal microflora whose concurrent removal is undesirable. For example disruption of the gut microflora can lead to blooms of other pathogens notably *Clostridium difficile* (Mitchell, 2015, Frieri et al., 2017). Dose response theory has not yet been developed for mobile genetic elements or harmless/commensal AMR carrying bacteria either. The impact of resistance in classic pathogens such as TB is possible to assess but the current microDALY conversion factors will probably need modifying. AMR is of much more concern with increasing numerous vulnerable populations notably the very old, very young and the immunocompromised as their members tend to have lower natural resistance to pathogens which occur in environments that potentially promote AMR infection and selection (Nicolle et al., 1996). Classical dose response relationships have been developed with the overall healthy population in mind. The human microbiome is viewed as interacting with AMR colonisation. Full dose response analysis probably needs to be extended beyond primary exposure as proposed by the Key Events Dose Response Framework (KEDRF) proponents (Buchanan et al., 2009, Julien et al., 2009).

Exposure assessment

Current water-borne pathogen QMRA stops at the point of ingestion. However, AMR pathogen fate and transport needs to be extended beyond this point. This is illustrated in the controversial food AMR modelling study of Smith et al. (2002). AMR impacts from opportunistic pathogens likely arise not only from primary exposure but also from subsequent colonization and amplification within vulnerable populations. AMR is much slower to develop than acute infection and probably arises from sporadic colonisation occurring over an extended period of time, most likely years. But once established, AMR may also persist for years in a sensitive subpopulation. So AMR levels are conceived as the product of processes which shift exposure likelihood from very low/negligible to very high in the manner of disease outbreaks. In these instances an endemic pathogen's numbers cross a threshold where their survival is sufficiently promoted for an epidemic to be generated (cf. the periodic influenza Ebola outbreaks). The epidemic phenomenon is captured by what is known as the Reproduction Number R (Deijfen, 2011). If R is less than 1, the epidemic subsides, if it is > 1 the number of cases multiplies exponentially. The rise of AMR pathogens appears to be a slow moving epidemic where R is above 1 but colonization and decolonization rates are very low. Depending on population susceptibility, exposure and colonization probabilities may be much lower than 1 per day and still be of concern because of the slow change dynamic change. Conventional waterborne pathogens QMRA risk estimation can usually ignore feedback cycles. However, with AMR it is not possible to ignore these because of the potential for small environmental inputs to trigger exponential (epidemic) increases in infection in vulnerable populations. Feedback is most important in the form of person to person transfer in healthcare settings once the numbers of AMR microorganisms is relatively high. But AMR outbreaks can be triggered by relatively low levels of environmental inputs that may be a concern in environmental settings. In short the barriers provided historically by control of water supply and wastewater disposal may not be sufficient to halt dangerous AMR transfer over the long term.

Risk characterisation

Risk characterisation conventionally involves integration of hazard assessment and exposure assessment. But the complications above make classic risk characterisation in terms of microDALYs or even infection or illness risk largely impossible at present, apart from special situations such as Cox's *Campylobacter* risk assessment (Cox Jr, 2006).

Beyond this is the need to integrate water industry QMRA with analogous activities in the healthcare and food sectors. HHRA/QMRA still seems to provide a reasonable framework for AMR risk characterization. However, there is an interesting feature of healthcare sector which water QMRA needs to be harmonised with. This is diverse set of activities which might also be described as "qualitative and quantitative microbial risk assessment". Despite having the same primary aim of risk definition, management etc. healthcare management methods and modelling are quite different to the qualitative risk assessment, and the QMRA familiar to the water industry, are much more extensive, and historically are much older (Kermack William et al., 1927, Abbey, 1952).

What constitutes 'tolerable risk' when it comes to AMR genetic elements, especially with AMR, carrying non-pathogens remains to be determined. How to adapt traditional benchmarks (Hunter and Fewtrell, 2001) is unclear.

Uncertainties

It is clear that, other than the consensus that AMR poses and existential risk to human health, there is a litany of uncertainties about how to characterise water related risk based on the classic HHRA scheme.

The popular risk matrix approach is as yet of little use for two reasons. Firstly there are a range of theoretical problems associated with its application to complex networks (Cox, 2008, Cox Jr, 2008, Fenton and Neil, 2012). Secondly at present the empirical expertise that experts need to apply this tool is largely unavailable within the water industry. When the risk matrix approach was implemented around 2000 there existed within the water engineering and public health sectors a 100+ years empirical body of knowledge on what would and wouldn't control conventional pathogens such as *Shigella*. This was being supplemented at the time by new basic knowledge on the microbial ecology of water born pathogens which allowed catchment to consumer barriers to be put in place even before their limits and effectiveness were fully quantified. This information does not exist as yet for AMR.

Ashbolt et al. (2013) proposed a possible way forward involving the use of either MCDA or Bayes Nets combined with expert opinion so as to prioritize research areas. However, the information needed to underpin this approach is still sparse as is understanding of the fate and transport and interactions of AMR microorganisms and mobile genetic elements in the water infrastructure and wider environments.

Resolving these uncertainties is unlikely to be rapid or straightforward.

Implications for potable recycling QMRA

In the past, uncertainties about QMRA and QCRA have not prevented credible order of magnitude risk being estimated arising for water and wastewater treatment. AMR is clearly an emergent microbial risk of such magnitude that it must now also be incorporated. Also it must be questioned how reliable past assessments of recycled water schemes were?

This has several important implications for QMRA of potable and non-potable water reclamation and recycling:

1. We are not at a point where we can undertake full system wide QMRA on AMR though there are some in principles precedents (food) and equivalents in the health sector which suggest the QMRA principles are sound and it may be possible to start 'moving forward'. Smith et al. (2002) provide an excellent mathematical 'exposure assessment' model in principle in all but name.
2. How should this current potable recycling project's quantitative risk assessment outputs be viewed? Do they provide sufficient decision support for designing potable water recycling schemes or is this premature? (The answer to this has significant cost and planning implications for water utilities).

3. Will potable recycling schemes actually provide more control over the water cycle and hence allow greater control of AMR risk than currently? (This seems plausible and is discussed further below.)
4. How should risk assessments of past potable and non-potable schemes be viewed? Do they need to be revisited and amended? (The answers to this seem 'yes' and 'urgently' if it is accepted that AMR is the problem highlighted in the introduction.)
5. Separately bearing in mind the Precautionary Principle (Salgot, 2008) it is unclear whether existing potable (and non-potable) recycling schemes themselves sufficiently account for AMR. Of particular concern would be second pipe systems involving irrigation of lawns where close human contact is possible and irrigation of crops destined from human consumption where the farming was seen as providing one of the major barriers based on field measurements of pathogen loading and inactivation rates. What should be done?

Historically, screening level risk assessment based on the risk matrix approach did incorporate possibilities up to and including 'catastrophic risk' ("major impact for large population, complete failure of systems") (Nadebaum et al., 2004) and varying degrees of likelihood. At this time AMR did not rate a mention and so was not considered at all, including by the authors of this report themselves during the 2006 replacement flows project (Khan et al., 2007, Roser et al., 2006). The past 5 years' developments suggest AMR is a catastrophic risk and depending on the situation its transfer likelihood appears to range from 'almost certain' to 'possible'. Together guideline's risk criteria suggest a risk rating of 'very high' and hence the need for timely response.

In considering these implications it will nevertheless be essential to not over-react. It is still unclear whether AMR increases are primarily a healthcare sector problem and resolving this question is where research and management efforts seem desirable. Also AMR is not yet at the projected 2050 level though as O'Neill (2016) points out it is already at very concerning levels.

A final important caveat to recognise in regarding to deficiencies in the current risk assessment situation is this. Without conventional qualitative risk assessment, QMRA and QCRA, the water sector would not even be at a point where it could systematically consider how to deal with this emergent environmental and water AMR dimension. Reflecting this, the existing framework does appear to provide a range of starting points for AMR assessment and management.

Water and sanitation barriers to AMR

Despite the information gaps outlined above, our supplementary review showed there are also bright points in this story.

Treatment infrastructure

The technology to treat and remove relatively labile DNA has been long under development albeit with the aim of removing persistent organic pollutants. Though normal UV and chemical disinfection are largely insufficient to remove nucleic acid, their inactivation of primary pathogens (LeChevallier and Au, 2004) is still valuable. Further, reverse osmosis and probably nanofiltration can physically remove large MGE molecules as the latter necessarily are thousands of Daltons reflecting the proteins which they must codes for. Emerging high intensity UV radiation and advanced oxidation processes, are sufficient to completely oxidise a range of recalcitrant chemicals so they are probably even more effective with DNA. Finally many 'conventional treatment' physical treatments have been shown to reduce genetic material as well as or along with the carrier microorganisms (Ashbolt et al., 2018, U.S. Environmental Protection Agency, 2012 Table 6-5). In short removal of AMR microorganisms and MGEs would incur additional significant costs for the water sector. But the technology fortunately already exist in relatively mature forms and are already being seen as part of potable recycled water advanced treatment systems.

Ecological principles and decolonization

As with convention pathogen driven epidemics, AMR exposure, colonization and 'amplification' (e.g. serious infection) are believed to be dynamic processes, and their converse - 'decolonization' and deamplification and reduced exposure - also exist (Smith et al. 2002). And the relative rates of these processes can in theory be quantified and modelled to provide input to management policies. That is AMR occurrence in human populations and the wider environment may be reversed or prevented by adjusting water treatment, environmental and ecological conditions. In hospitals and nursing homes an example here is the cohorting of patients and care staff so as to reduce transfer probability (Milazzo et al., 2011, Pelat et al., 2015). One possible reason for this is that carrying AMR genes incurs an ecological cost for those microorganisms that possess these genes. This may also account for why, despite the very widespread occurrence of 'natural' antibiotic resistance now recognised, most pathogens in the past did not tend to carry such resistance.

The AMR shedding process may be slow but could offer much promise (and benchmarks?) for long term management. A difficulty will be how to measure improvements given many monitoring and research programs last only a few years at best. Historically sanitation, hygiene and epidemic control e.g. avoidance of contaminated materials and situations, washing; in fact operated by reducing the opportunities for disease spread and reproduction rather than via direct inactivation. Many of these principles apply to AMR and this is in fact the basis for what are known as healthcare Antimicrobial Stewardship Programs (Smith et al., 2008). It follows that the accumulating knowledge of AMR organism and MGE ecology should also help identify strategies for reducing exposure to environmental/water AMR etc. A different form of environmental modification is already being proposed in the healthcare fields in the form of 'probiotics' (Daliri and Lee, 2015). There is no reason why the same principle could not be developed in the water sector, along the lines of research on pathogen fate and transport e.g. control of sources of *Cryptosporidium*, quantification of solar radiation disinfection (Nelson et al., 2018).

Management initiatives and proposals

The supplementary review revealed a range of management recommendations albeit mainly at the strategic and still conceptual level and involving data gap identification. Many are in part a restatement of the need to understand AMR ecology better. For example Singer et al. (2016) and Topp et al. (2018) offer two lists, in effect of recommended next steps, applicable to managing water AMR. These in summary are:

1. *"Determine the direct or indirect implications to the health, reproduction or ecosystem services of organisms or populations resulting from chronic exposure to elevated AMR drivers.*
2. *Determine the relative contributions of the different AMR pathways, for establishing, maintaining and disseminating ARGs*[5] *in the environment?*

[5] Antimicrobial Resistance Genes

3. *Determine the relative contributions of the different AMR drivers, for establishing, maintaining and disseminating ARGs in the environment?*
4. *Determine what concentrations of AMR drivers are relevant for assessing the risk of AMR selection and co-selection?*
5. *Determine the direct or indirect implications from the trophic transfer of antibiotics, biocides, metals, or ARGs found within microorganisms, animals (aquaculture), or plants?*
6. *Recycling wastewater for crop irrigation is commonly practiced. Therefore the risks of soil, water and crop contamination, and how these vary with production practice, remain to be adequately characterised noting that wastewater reuse and fertilization with sewage sludge have the potential to entrain antibiotic-resistant bacteria generate in humans, into agroecosystems, underscoring the complexity of the issue.*
7. *Assess the risks associated with aquaculture and antibiotics and how these affect the present of AMR upstream, post-treatment or downstream.*
8. *Assess the impact of AMR "tradewaste" discharges from manufacturing and healthcare"*

Further suggested technical risk assessment and management related reviews whose titles indicate their relevance include:

- Ashbolt et al. (2013) *Human Health Risk Assessment (HHRA) for Environmental Development and Transfer of Antibiotic Resistance*.;
- Pruden et al. (2013) *Management Options for Reducing the Release of Antibiotics and Antibiotic Resistance Genes to the Environment.;*
- Cantas et al. (2013) *A brief multi-disciplinary review on antimicrobial resistance in medicine and its linkage to the global environmental microbiota.*;
- Berendonk et al. (2015) *Tackling antibiotic resistance: the environmental framework*.;
- Singer et al. (2016) *Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators*.;
- Ashbolt et al. (2018) *Antimicrobial Resistance: Faecal Sanitation Strategies for Combatting a Global Public Health Threat*.;
- Bürgmann et al. (2018) *Water and sanitation: an essential battlefront in the war on antimicrobial resistance*.
- Ben et al. (2019) *Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A review.*

Would upgrading water and sanitation actually be cost effective in advanced economies?

An interesting question to address is whether resources most need to be directed toward environmental AMR or healthcare AMR control.

Reflecting the historical catchment to consumer philosophy familiar to water managers it seems likely that both environmental and healthcare barriers are needed to control AMR and their effects would tend to be multiplicative. So as with the tuberculosis example listed above, log reductions in AMR may be achievable by a whole health approach as proposed by WHO. And the question of which sector is more to blame for the current dilemma becomes secondary/irrelevant to AMR control.

Conceptual benefits of planned direct potable recycling - How potable recycling could address the AMR challenge?

An intriguing implication arising from considering the impact of potable reclamation on AMR on the cycle described in Figure 3 is that taking full control of the urban water cycle via direct potable recycling could cut out or neutralize most human AMR sourced from sewage and break this critical transport pathway or at least bring it under much better management.

There would also be major secondary benefits from doing this such as providing support for two other UNEP (2017) environmental health priorities:

- *"I…environmentally sound management of chemicals and all wastes throughout their life cycle;*
- *V… sustainable consumption and production, resource efficiency, life cycle approaches,"*

That said there are also provisos for the success of this strategy:

1. The recycling system would have to have redundancies and controls well beyond those which currently in place. Cost benefit analysis based on the short term while discounting the future might prove insufficient or inappropriate for providing system reliability criteria.
2. The public would have to be fully included in the process and convinced of its safety, no small task at a time of increasing distrust in government and large corporations. A credible answer would be needed for the question

   > "How did public health and water let it come to this when there have been warnings about AMR for decades?"
3. All the secondary waste streams arising from sewage and reclaimed water treatment would have to be managed more tightly and effectively to prevent the release of AMR microorganisms, genes and antimicrobials. Biosolids application to agricultural land in particular might need to be revisited.
4. Much sewage is lost before it reaches sewage treatment plants (STPs) due to exfiltration and overflows. The quantity of raw sewage lost by these two related paths varies markely from place to place, system to system, and it is very difficult to get exact general estimates as a result. However in the case of CSOs one USEPA estimate places the figure appears to be of the order of 20-25% (USEPA, 2004 page 4-17). For exfiltration figures up to 20% of total dry weather flow load are also reported periodically (Rutsch et al., 2006 Table 3). This suggests that subsequent removal at STPs of more than 1 LRV of ARGs, MGEs and antibiotics by treatment plants have little effect as judged on a crude loading comparison basis. The implication here is that the integrity of sewers needs to be tightened up greatly. A clear concern here is the impact of AMR releases on natural bathing where relatively high numbers of indicator bacteria are current tolerated compared to drinking water levels.
5. The O'Neill (2016) report suggests that changes whether they involve potable recycling or not need to be in place within 10 to 15 years to avoid the 2050 scenario. Such a rapid change in the water management system would be without precedent.

All of these issues have been looked at in the recent past by SWC. But the risks need to be revisited now if the Precautionary Principle is to be addressed.

Healthcare discharges as tradewaste?

An intriguing question related to 'who pays?' for AMR control is whether facilities discharging disproportionate levels of antimicrobial and AMR contaminated sewage should be treated in the manner of trade waste dischargers including the promotion of pre-treatment or equivalent to remove AMR contaminants at source. It is as yet unclear whether placing treatment facilities on healthcare facility discharge pipes would be practical though assurance of agreed management arrangements might be possible.

As discussed. healthcare facilities are actively trying to better management antibiotic use via Antimicrobial Stewardship Programs. However, the benefits of such an approach would likely be marginal as 10-80% of antibiotics consumed by patients and most of the faecal, urine based, skin and nasal microorganisms and MGEs are still excreted and exported in sewage in any case. This raises the question of whether healthcare facilities should be charged for the cost of treating these pollutants specifically.

Further challenges

There are further challenges for the water sector including the following:

1. Regulation, policy development coordination and research which are integrated with those in the health care sector. One issue requiring addressing is the role of EPA in regulating AMR in the natural environment.[6]
2. Despite the revolution in genomics technologies a full understanding and descriptions of the human and environmental microbiomes is still some way off. Current technologies are still evolving and expensive begging the question of monitoring and monitoring benchmarks.
3. Small drinking supplies and wastewater treatment systems e.g. septic tanks and on site disposal; are numerous and not yet suited to controlling AMR except in respect to conventional disinfection. These system provide organic matter rich environments where AMR could evolve and prior to environmental release.
4. Overseas, AMR is already at catastrophic levels and international travel provides as rapid conduit for introduction. How to integrate its control is unclear.

[6] Links between environmental regulators and public health authorities exist but not so much with the operational healthcare sectors. Also in NSW expertise in microbiology has been historically very limited in EPA whereas public health experts do not tend to have internal expertise relating to the natural environment. A related issue is the development of laws and regulations relating to the what level of undesirable genetic material in wastes is tolerable (complete elimination is not practical and ignores the reality of naturally occurring AMR).

Conclusions and recommendations

1. AMR has emerged as a major water and sanitation risk which potable water recycling must include in its system design and management.
2. This process must integrate work in the water sector with public information provision and risk management by the healthcare and food production sectors.
3. A range of additional information is needed on AMR hot-spots, fate and transport even before the risks posed by potable and non-potable recycling can be credibly assessed. Extensive research is needed probably including much primary environmental monitoring.
4. Development of conceptual and mathematical models is needed to integrate primary data, help identify gaps, prioritize critical control points for management and assess the impact and cost effectiveness of proposed controls.
5. Potable recycling of reclaimed water needs to consider not only AMR removal from the primary waste stream but also AMR from secondary streams – e.g. biosolids, brine, overflows, exfiltration and how pre-treatment releases are to be avoided.
6. There is already a substantial body of knowledge on environmental fate and transport of AMR. This needs to be integrated along the lines of the tables in Ashbolt et al. (2018).
7. The current risk assessment HHRA framework appears suited to ensuring potable water and returns to the environment are safe. This provides a range of heads of consideration for understanding the potable reuse risks and challenges. The larger ISO 31010 and related risk tool guidelines provide additional perspectives e.g. Bow Tie/Cause => Consequence analysis for assessing recycled water risks.
8. Costing of lives at risk v. financial costs for infrastructure needs balancing.

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