Presentation to Intersectoral Committee on Antimicrobial Resistance.

Antimicrobial Resistance and EnvirONEment. (April 13 2016)

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Suggested things to do in relation to antimicrobial resistance and environment

1. Reduce /eliminate discard of unused antimicrobials (and other drugs) and biocides into toilet and landfill.
2. Identify, monitor and manage intense point source environmental discharges of antimicrobial agents.
3. Overall better management of sewage (at least secondary treatment) and animal waste to reduce dissemination of antimicrobial resistant bacteria.
4. Identify, monitor and manage likely intense point source environmental discharges of novel high-risk antimicrobial resistant bacteria (hospitals).
5. Assess antimicrobial classes for risk of environmental persistence and impact and target use reduction on those greatest risk.
6. Overall reduction in volume of production and use.

Introduction.

The "One Health" concept is widely accepted as central to dealing effectively with the challenge of acquired antimicrobial resistance. "One Health" links humans and animal health and wellbeing through a shared environment.

While Ireland can achieve useful progress within our borders it is essential in the context of antimicrobial resistance also to engage with partners from the perspective of one global environment. Trade and travel means that any antimicrobial resistance problem is likely to disseminate rapidly and often silently from the country where it emerges. This is illustrated most recently by the report of transferrable colistin resistance. New resistance phenomena are probably often globally disseminated before we know of their existence. Weak on non existent management of sewage and animal waste in many parts of the world is likely to play a significant part in dissemination in low income countries only a few hours by plane from Ireland.

Bacteria and Antimicrobial Resistant Bacteria in the Environment.

The global environment is home to a microbiome. We can think of this as a vast, diverse and dynamic cloud of genetic information much of which we barely understand. Data transfer within this cloud occurs between water, soil and air. Of particular interest are microorganisms that we think of as primarily animal and human gut residents but which are also resilient in the environment which is often the conduit that takes them from one anus to a mouth in the same house, in the same hospital ward, down the road, perhaps many miles away if carried in water or a continent away if carried by a traded food product. The efficiency of population wide water borne dispersal of gut bacteria systems is well illustrated by the classical waterborne diseases. We have performed studies showing that antimicrobial resistant bacteria are very widely disseminated in Ireland not just in sewers but also in rivers and lakes and in rural drinking water sources. As a specific example we have recovered extended spectrum beta-lactamase (ESBL) *E. coli* is extensively in the environment. This is a biological entity that essentially did not exist 50 years ago.

Gut organisms such as *E. coli* in transit between anus and mouth are not inert. They interact with and compete with the environmental microbiome. We have examples of genes that code for inactivation of antimicrobial agents that are now well established in *E. coli* and other *Enterobacteriaceae* in the gut that originated from bacterial species normally resident in the environment. We do not know if the gene transfer occurred when the gut bacteria were transiting through the environment or when environmental bacteria were transiting through the gut.

Antimicrobial Agents in the Environment.

We, and many others have performed studies documenting the presence of antimicrobial substances in the environment. There is evidence that the composition of the environmental gene cloud (microbial biodiversity) that I referred to earlier is altered by anthropogenic antimicrobial discharges. Antimicrobial resistance genes are generally increased in aquatic environments impacted by urban discharge. This is not just antibiotics but the detritus of all the disinfectants, biocides and heavy metals that are used. The contamination of the environment with substances with antimicrobial activity is also likely to impact on the preferential survival of antimicrobial resistant gut bacteria and to impact on which genetic interchange with environmental bacteria are most favoured.

Antimicrobial agents enter the environment in two principal ways. One is that people throw taken medication into the toilet or into the bin for landfill. We have show that this is a common practice in Ireland. My understanding is that the Animal Remedies Regulations, S.I. No. 734 of 2005 requires veterinarians and pharmacist to have in place a system for accepting returns and to make farmers aware of this. I understand that the Regulation of Retail Pharmacy Businesses Regulations, S.I. No. 488 of 2008 indicates only that a pharmacy "may" accept returns. It makes no scientific sense that I can see for that obligation to apply to animal remedies but not to human medicines. Some initiatives to collect unused medicines in both human and animal domains have yielded substantial hauls (in some cases tonnes of material) suggesting that we could do better across the board in this area. A number of EU member states have well-structured systems for safe collection and disposal of unused pharmaceutical agents.

The other route is that antimicrobial agents administered to humans or animals are excreted in faeces and urine. The extent to which this happens is variable but in some cases 90% or more of the active compound is excreted unaltered in urine or faeces. We estimate for example that a major hospital may discharges of the order of 0.5kg per day of ciprofloxacin in sewage. In addition to therapeutic antimicrobials agents such as ciprofloxacin there are many other pharmaceutical agents discharged in human waste from hospitals. The World Health Organization has recommended monitoring and control of such discharges from hospitals for more than 20 years but until recently this has been almost universally ignored. However this is now changing with implementation of management processes in many hospitals in Europe. Nursing homes and centres of intensive animal production are also likely to be intense point sources of antimicrobial discharge but to my knowledge we know every little about them. It is increasingly feasible to control these point source discharges at source. I am very confident that no one would permit a pharmaceutical company to discharge kilograms of active product in the effluent from their plant. For example some pharmaceutical plants in Ireland are required to treat effluent with ozone in addition to general waste-water treatment to prevent discharge of active compounds. There is no reason to suppose that the environmental impact of unaltered pharmaceutical is different because it is has passed through a human or animal body.

Risk Assessment, Pandora's Box and the Tragedy of the Commons

Like others we have tried to estimate the risk to individuals related to certain discharges of antimicrobial resistant bacteria and antimicrobial agents. Our estimate is that the risk to the individual as a result of exposure to discharges of antimicrobial resistant bacteria and antimicrobial agents is very low at least in the context of secondary sewage treatment and dilution. However it seems to me now that the paradigm of assessment of risk of individual exposure is not really valid in this context. The issue is population exposure. I refer again to the *mcr*-1 colistin resistance gene reported last year. This illustrates how a very rare event (the emergence of a transferrable *mcr*-1 gene) that generates or transfers a highly advantageous resistance gene to the global human-animal gut microbiome is essentially an irreversible event of permanent consequence with unquantifiable costs.

Conclusion.

Assessing the different risks that a government has to manage is difficult. I understand also that it is difficult to communicate the assessment of those risks and to win public support for measures to manage a risk that may seems somewhat technical and remote. Reducing antimicrobial use and improving infection prevention and control within human and animal health care are clearly critical to control of antimicrobial resistance. This is a challenging task with significant resource requirements and there are many conflicting interests. The environment that sustains us all and connects the microbiome of the individual person, animal, hospital, farm, nursing homes and households must also be addressed. I have tried to identify some things that we could do in this domain that are of value, that are likely to conflict with fewer stakeholders that certain other measures and may help build some momentum for change. The lowest hanging fruit here is surely to stop the dumping of unused antimicrobial and microbicides into the environment. We have put in place a pretty effective system for batteries why can we not do something similar for antimicrobial agents and other pharmaceutical agents.