The One Health Approach to Antimicrobial Resistance

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Outline:
1. The problem with AMR
2. Introduction of One Health
3. One Health and efforts to tackle complex AMR issue
4. The way forward
The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. - Alexander Fleming
• Vancomycin-Resistant Enterococci (VRE)
• Methicillin-Resistant Staphylococcus aureus (MRSA)
• Extended-spectrum β-lactamase (ESBLs) producing Gram-negative bacteria
• Klebsiella pneumoniae carbapenemase (KPC) producing Gram-negatives
• MultiDrug-Resistant Gram negative rods (MDR GNR) MDRGN
Lord Jim O’Neill “... a campaign is needed to stop people treating antibiotics like sweets”.

In 2010, WHO-FAO-OIE signed a tripartite collaboration on AMR

AMR is listed as a global Grand Challenge

The aim is to:

- Ensure that antimicrobial agents continue to be effective and useful to cure diseases in humans and animals
- Promote prudent and responsible use of antimicrobial agents
- Ensure global access to medicines of good quality.
Speak with one voice and take collective action to minimize the emergence and spread of AMR using One Health approach.
So what is One Health??
One Health is the integrative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment.
One Health

• One Health is about managing health threats at the interface between ecosystem health, animal health and human health.

• It recognizes that the health of people, animals and the ecosystem of which we are a part, are interconnected.
One Health

• Not a new concept

• Since the 1800s, scientists noted similarity in disease processes among animals and humans

• Human and animal medicine were not practiced separately until the 20th century.

• In recent years, through the support of key individuals and vital events, the One Health concept has gained more recognition in the public health and animal health communities.
19th century and the early 20th century there was continued interest in linking human and veterinary medicine based on the discoveries that there were similar disease processes in both animals and humans.

Rudolph Virchow
(1821–1902)

Between animal and human medicine there is no dividing line – nor should there be.”
The term "one medicine" (forerunner of the more current term, One Health) was used by Dr. Schwabe in his 1984 book, *Veterinary Medicine and Human Health*, to bring a renewed interest to the synergy that can emerge when health practitioners and scientists collaborate. His insightful words,

"The critical needs of man include the combating of diseases, ensuring enough food, adequate environmental quality, and a society in which humane values prevail," are even more compelling today.
Challenge of One Health – “Complex Problems”...

- One Health problems tend to be complex (influenza viruses, ebola, antimicrobial resistance, tuberculosis, and now ..AMR)
- So complex that no one individual, group or discipline can completely understand
- No single solution
Complex “Wicked” Problems

• So compelling that demand action
• Most groups/agencies/researchers tend to work in silos (reductionist) – not a good strategy for complex problems
• Solutions to these issues require systems thinking - a comprehensive and interdisciplinary strategy
What is a Wicked Problem??

Social Messes
Representing Wicked, Ill-Structured Problems

- No unique "correct" view of the problem
- Ideological constraints
- Many possible intervention points
- Political constraints
- Often a-logical or illogical or multi-valued
- Great Resistance to change

Copyright 2007 Robert E. Herr
AMR is a ‘One Health’ (people-animals-environment) issue

It is difficult to imagine an issue that epitomises the principles of One Health more than AMR does.
—Tim Robinson
One Health

- the rising threat of AMR requires a holistic and multisectoral One Health’ approach

Resistant bacteria arising either in humans, animals or the environment may spread from one to the other, and from one country to another.

AMR does not recognize geographic or human/animal borders.
Human health:

Multidrug-resistance genes highly prevalent in many important and common pathogens - *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*.
Inappropriate or over prescribing, excessive and improper usage is a biggest driver for AMR in humans (Prior 2005, Livermore 2005). Contaminates the environment, from there to plants and animals.

**Antibiotic Rx for Hospitals**

*Proceed with Caution*

**If** prescriptions of high-risk antibiotics in hospitals are reduced by 30%

**Then** it could lead to 26% fewer cases of deadly diarrhea infections

Animal health:

Published estimates of the proportion of antibiotics consumed in animal agriculture—84% (for 36 antibiotics) in China and 70% in USA—suggest significant global agricultural consumption of antibiotics.
Yun Liu and colleagues published a paper in *The Lancet Infectious Diseases* journal revealing they found the MCR-1 gene in 166 out of 804 pigs at slaughter that they tested, 78 of 523 samples of chicken and pork being retailed, and in 16 of 1,322 hospital patients.

The study indicates there is a chain in the spread of resistance from the use of colistin in livestock feed, to colistin resistance in slaughtered animals, in food and human beings.

One of the authors, Prof. Jian-Hua Liu from South China Agricultural University, was quoted by the *Guardian* as saying these are extremely worrying results, which countries is “deeply concerning”, said the authors.

After the paper was published, new papers and information have shown that the MCR-1 gene has been found in bacterial samples in many other countries, including Thailand, Laos, Brazil, Egypt, Italy, Spain, England and Wales, the Netherlands, Algeria, Portugal and Canada.

The most frightening thing about MCR-1 is the ease with which it can spread resistance to other species of bacteria through a process known as horizontal gene transfer.

A few years ago, there was a similar scare about NDM-1, a gene with the ability to jump from one bacteria to other species, making them highly resistant to all known drugs. except two, including colistin.
Major usage are for therapy but.....

and controversial use as animal growth promotant (AGP) and additives in feed
Growth promoters

- Use not for managing a specific disease (present or at risk)
- Sub-therapeutic doses
- Used for ~60 years... still unclear on its mechanism of action
  - Reduction of microbial use of nutrients and growth-depressing metabolites
  - Thinner intestinal wall leading to enhanced nutrient uptake and use
  - (subclinical) disease prevention
Growth promoters

- Use harder to justify
- Decreased beneficial effect? (finishing)
- Better production conditions (hygiene, nutrition...)
- Better baseline weight gain
- Increased AMR?

- On the spot!
  Europe: discontinued (1986-2006)
  USA: discontinued (2017)

Laxminarayan et al., 2015
Antimicrobials and animals?

- Use of AM in livestock production followed human use (1940’s → increase in poultry production)
- Beneficial effect in production (swine, poultry)
- Potential threat? Debate started >40 years ago

“It is clear that there has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics. Further, these resistant strains are able to transmit this resistance to other bacteria. This resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock”

Swann report, 1969

Laxminarayan et al., 2015
AMU leads to AMR, AMR is one of the biggest threats to mankind, and AMU is primarily driven by animal production, hence AMU in animals is a major concern.

Risk posed by AMU in animal production is small compared with human AMU, there is no proof of treatment failure in people due to AMU in animals.

So what… heaven or hell?

Where do you Stand on the Antibiotics Debate?
Is AMU/AMR in animals linked to AMR in humans?

• Probably... to some extent → direct link: foodborne pathogens
  ➢ Outbreak investigations/case reports (Angulo et al., 2004)
  ➢ Ecological studies: Fluoroquinolone-R Campylobacter
  ➢ Molecular typing (WGS)

• However, hard to quantify actual risk (Phillips et al., 2004) → precautionary principle cannot be the only answer, need (proper) data!

Specifically, this review addressed the question: "Is there evidence from the literature that antimicrobial use in food animals is directly or indirectly involved in the emergence and spread of foodborne antibiotic-resistant Salmonella?" This systematic literature review was conducted to determine what is and is not known about the relationship between food animal production practices and the emergence and spread of antibiotic resistance.

Helke et al., 2017

• Lack of information also for Campylobacter spp. (McCrackin et al., 2015)
Not always a simple relationship!

- MDR *Salmonella* Typhimurium DT104 emergence in 1990’s in animals and humans → reservoir of infection? The Scottish example
  - AMR profiles in 5,200 human and animal isolates (Mather et al., 2012)
  - WGS + Bayesian phylogenetic modeling in 248 isolates (Mather et al., 2013):

  conclude that, while ecologically connected, animals and humans have distinguishable DT104 communities, differing in prevalence, linkage and diversity. Furthermore, we infer that the sympatric animal population is unlikely to be the major source of resistance diversity for humans. This suggests that current policy emphasis on restricting antimicrobial use in domestic animals may be overly simplistic. While these conclusions pertain to DT104 in Scotland, this approach could be applied to AMR in other bacteria–host ecosystems.

  genes through the course of an epidemic. Contrary to current tenets supporting a single homogeneous epidemic, we demonstrate that the bacterium and its resistance genes were largely maintained within animal and human populations separately and that there was limited transmission, in either direction. We also show considerable variation in the resistance profiles, in contrast to the largely
Do changes in AMU impact AMR in animals?

- Sure... to some extent: the European example
  - 1996-2008: Avoparcin ban and decrease in prevalence of VRE in broilers and pigs
  - 2009-2011: cephalosporin ban and decrease in prevalence of extended spectrum cephalosporinase- 
    *E. coli* in swine in Denmark

- But not all follows the easy pattern!
  - VRE in Denmark (Bortolaia et al., 2015): 47% flocks VREF+ (low proportion) 15 years after avoparcin ban
  - Farm-level: use of chlortetracycline following ceftiofur in cattle increases probability of persistence of 
    ceftiofur *E. coli* isolates (Kanwar et al., 2013, 2014)
The contribution of animal production, both terrestrial livestock and aquaculture, to the global AMR crises is questioned. We don't see so many animal-associated infections in humans.

While this may be true, many antibiotics are used in animal production in sub-therapeutic doses and with long exposure periods, these production systems create ideal conditions for bacteria to fix genes that confer resistance.

These genes can subsequently be transmitted to human-adapted pathogens or to human gut microbiota via people, contaminated food or the environment.
Environmental health:

Environmental bacteria, the most prevalent organisms, serve as sources for AMR genes that can become incorporated, over time, into pathogens of people and animals.

Influx to the environment of AMR genes from human and livestock waste and by the vast quantities of antibiotic residues that enter the environment from the pharmaceutical industry, from hospitals and intensive livestock farms.
Drivers for resistance:

- Poor prescribing and application for both human and animals
- Counterfeits
- Inappropriate dosing
- Slow diagnostics
- Market disincentives
- Globalization
- Pollution
In conclusion

• AMR is ...

Not a human health issue

Not an animal or livestock issue

It is absolutely a One Health issue
• Understanding the contribution from each sector is essential to curb AMR, and potentially reverse the acceleration and spread that is putting the world at risk.

• Policy makers and scientific communities with differing perspectives and priorities (i.e. human health vs. animal health) need to come to a consensus on antibiotic use, including the risks and benefits (Bell 2001).
What we strive for...

- Political commitment, good governance, and relevant capacity across ministries and sectors to implement international standards and guidelines, and to establish appropriate national legislation across sectors.
- Human and animal health sectors working together naturally to align policies, strategies and activities, in collaboration with other stakeholders in the private and public sectors.
  - Accurate, relevant, and consistent data on antibiotic use across all sectors through increased surveillance, stewardship, and national information sharing.
- Increased research capabilities on interventions to address AMR in a safe and sustainable manner.
Efforts to tackle AMR Issue: One Health approach

- Late 2016 – Formulation of National Antimicrobial Resistance Committee (NARC)
- Interagency and interministrial cooperation to tackle AMR issues
- 4 technical working group addressing 4 objectives
- National Action Plan for AMR and AMU in human, animals and food and integrated Surveillance System.
AMR Surveillance in Food

At present performed routinely by:

- Ministry of Agriculture:
  - Department of Veterinary Services (Veterinary Public Health Lab): processing plants/abattoir, imported animal products
  - Department of Fisheries: no AMR related testing at present but test on SPS Aquaculture, National Shellfish Sanitation Program

- Ministry of health (Food Safety and Quality Division): retailed food and animal related products
Situational Analysis: AMR Surveillance in Food Producing Animals (abattoir)

- Monitoring of AMR from processing plants and imported animal related products:
  - Abattoir
    - Usually poultry, pigs, cattle, goats.
    - Bacterial monitored - E.coli, Salmonella spp., and Staphylococcus spp.
AMR AND AMU SURVEILLANCE OR MONITORING PROGRAMME IN 2017 - 2020.

1. Data collection for baseline
   • First phase of data collection was initiated in early of 2017.
     • AMR data in animal pathogens from routine clinical cases for 5 years (2011-2015) from all the DVS laboratories
     • AMR data in food of animal origin in poultry and pigs for 5 years (2011-2015) from Veterinary Public health Laboratory.
     • Data of antimicrobial usage (AMU) according to different purposes in poultry and pigs.
Ongoing Program for AMR Surveillance – FSQD MOH Malaysia

- Food sampling from local markets in all states
- Average of 3 samples per site
- Food samples are raw product
  - Fish, chicken, beef, mutton, Pork
- Tests conducted on food samples
  - Detection of *Escherichia coli*, *Salmonella*, *Staph aureus*, *Listeria monocytogenes*, *Campylobacter sp*
  - Antibiotic susceptibility testing
  - DNA fingerprinting (PFGE)
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AMR ISSUE IS NOT GOING AWAY
Interagency seminar on AMR organized by MyOHUN/MOH/DVS
3-day Workshop to develop integrated surveillance module on AMR in human, animals and food
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SALMONELLA

Farm Poultry Nationl Program
- Broiler: 51 x 12 x 600 Eggs
- Layer: 26 x 12 x 300
- others

Swine
- Piglet: 34 x 12 x 200
- others

SLAP
- Epsip Epsil SL (100) (g/g)
- Resp (animal) (g/g)
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