Evidence for action on antimicrobial resistance

Supplementary information – review of the policy options and summit discussion

Contents

1. Infection prevention and control in agriculture

Consistent with the One Health principle, it was seen as imperative that AMR control encompasses antibiotic use in agriculture. Antibiotics are used in agriculture as growth promoters and prophylactically to control infection. These practices were seen as posing unacceptably high risks to human health over the long term, and ones that could to a large degree be replaced by improved husbandry practices.

It was recognised that reducing antibiotic use in agriculture faced a number of challenges: global populations are rising and demand for meat products is increasing, particularly in emerging economies. This demand can only feasibly be met by intensive farming practices. In addition, animal food production is typically a low-margin industry, so measures that affect yield can have a major impact. Nevertheless, it was felt that there should be a strong drive to develop alternative antibiotic-sparing systems and to promote their use globally.

The desire to maximise productivity can lead to high animal densities and poor living conditions, conditions that promote the spread of infection. Stressed animals are also likely to be more susceptible to infection. One use of antibiotics is as a form of infection control. Improved living conditions and better farm security to prevent the introduction of infections were identified as alternatives to prophylactic antibiotic use. Transport of livestock was also identified as a potentially important target for infection control.

It was suggested that opportunities exist to reduce public exposure to bacterial contamination (and by extension antibiotic-resistant bacteria and antibiotic resistance genes) in foodstuffs through 'farm to fork' food production systems. There is already a public health imperative to prevent transmission of microorganisms to consumers, but many cases still occur and additional steps could be taken to ensure consumer safety. Surface cleansing methods, for example with lactic acid, are not employed in all countries but would help to reduce transmission of bacteria such as *Campylobacter*. However, it was acknowledged that countries differ in their capacity to regulate food production systems.

Vaccines were considered to have some potential role to play in infection control in agriculture. However, a range of technical, economic and practical obstacles were identified to their wider use.

Waste from farms was considered to be a potentially important source of environmental contamination with AMR organisms and antibiotics. However, there is currently very little known about the degree to which this contamination contributes to the overall AMR picture, making it difficult to judge whether countermeasures – which are likely to be complex and large scale – are likely to be cost-effective.

Key evidence gaps/research needs

- A better understanding of the emergence and spread of AMR in agriculture and through the environment, to support prioritisation and more targeted countermeasures.
- More research on the economic impact of antibiotic-sparing husbandry practices and ways they can be implemented globally.
- New and improved vaccines for key agricultural pathogens.

1. Increase vaccination of food animals

- Policy intervention under objective 1

- Vaccines exist for some animal diseases, with a wide range of delivery options
- In pigs and ruminants, vaccines do not exist for many of the key organisms that cause infection
- Vaccine coverage and effectiveness can limit need for antibiotics (both prophylactic and therapeutic)
- Vaccines do not select for resistance

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Danish mass swine immunization led to significant decreases in antibiotic use.
- In Norway, vaccination of farmed fish significantly reduce antibiotics use
- Specific evidence base will vary with context

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Prevent infection in farm animals
- Prevent the spread of infection within herds
- In some species, ABx consumption decrease 50% with broad-based vaccination

Other considerations

Medium	*Generalizability?*
Yes	*Apply precautionary approach?*
Medium	*Direct implementation cost?*

- Some evidence that vaccination increases yield (economic benefit)
- R&D effort needed - lack of availability of effective vaccines is a major impediment

Likely intervention mechanism

- ■ *Education / information*
- ■ *Professional standards*
- □ *Regulation*
- ■ *Technical assistance*
- ■ *Economic incentives*
- ■ *Funding / aid*

- High prices seen as the key impediment to mass vaccination
- Education campaigns could highlight benefit to farmer (e.g., better yield)

Basis of assessment	Study
Newly introduced vaccines and well-equipped facilities help alleviate the need for antibiotics. In Norwegian salmon and rainbow trout aquaculture there has been a 99% reduction in the use of antimicrobial agents despite a massive increase in fish production	5, 18, 19
Studies suggest antibiotic consumption could be halved if farm animals were properly vaccinated, with better vaccines leading to an even greater reduction	7
Mass immunization of animal herds leads to significant decreases in antibiotic use in Danish pig farms	8, 9

Points raised in discussion

- There is some evidence (mainly from high-income countries) that vaccination can reduce antibiotic usage in agriculture.
- However, there a number of obstacles to the wider use of vaccines in agriculture:
- Economic impact in a typically low-margin industry
- A lack of effective vaccines for several important diseases
- Globally, an incomplete understanding of animal disease burden
- The relatively short lifespans of many food animals
- Often unsupportive attitudes of farmers
- Lack of necessary veterinary health infrastructure in many LMICs.

Evidence gaps/research needs

- Global disease burden in food production animals
- Improved/new vaccines for most-common infections
- Most effective interventions for reducing antibiotic usage
- Cost-effectiveness data for specific vaccine interventions
- Requirements for effective implementation and evaluation of vaccine interventions.

2. Improve farm housing including mix and concentration of animals

- Policy intervention under objective 1

- The crowding and density of animals in industrial farming increases the susceptibility of animals to infection, and creates the conditions for the rapid spread of infection throughout the herd
- Reducing density and related stress would reduce the need for prophylactic and therapeutic use of antibiotics
- Also includes housing of different animal groups, pen / hutch use, feed storage, facility maintenance, and limiting mix of animals within and across farms

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Evidence suggests stress from crowding and lack of hygiene increases infection risk
- Link between infection risk and increased prophylactic / therapeutic use of antibiotics (industrial farming increases ABx load)

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Prevent infection in farm animals
- Prevent the spread of infection within herds

Other considerations

Medium *Generalizability?*
No *Apply precautionary approach?*
High *Direct implementation cost?*

- Must address perceived lower cost of production from industrial farming
- Likely more feasible to limit emergence of high-density agriculture than to shift practice

Likely intervention mechanism

- ■ *Education / information*
- ☐ *Professional standards*
- ■ *Regulation*
- ■ *Technical assistance*
- ☐ *Economic incentives*
- ☐ *Funding / aid*

- Challenging to roll-back industrial farming practices once embedded in food production system

Basis of assessment	Study
Antibiotic sales in Dutch livestock farms decreased over 50 percent as farmers shifted from antibiotic use to optimizing the living conditions of livestock.	6, 26
By 2030, consumption of antibiotics in agriculture projected to rise by two-thirds. One-third of increase due to shift from to intensive farming	12
Episodes of crowding-related stress in farm animals have been found to increase susceptibility to infection while creating the conditions for the rapid spread of infections	20, 21, 22
Infection during the final, 'finishing' (pre-slaughter) phase of pigs' lifecycle suggested to be the major source of *Salmonella* in hogs	27

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Points raised in discussion

- A growing population and changing food preferences in emerging economies are increasing demand for animal protein globally; this demand is only likely to be met through high-productivity intensive farming.
- However, highly intensive practices increase the risk of infection, by stressing animals and making them more susceptible to infection and creating conditions that favour the spread of infectious organisms. Poor biosecurity practices can also lead to more frequent introduction of infections from external sources. Antibiotics are often used prophylactically as a substitute for effective infection control.
- In developed countries, improved husbandry practices have lowered the increases in yield that can be achieved through use of antibiotics as growth promoters; in LMICs, however, use of antibiotics as growth promoters has a bigger impact on yields.
- The food production sector is strongly driven by cost considerations; relatively little consideration is given to other issues, such as animal welfare, environmental impact or implications for AMR.
- In a low-margin business, food producers are likely to need protection from the economic impact of measures put in place to reduce antibiotic use.
- Some food production systems have antibiotic use locked in, including ones being exported to LMICs to increase food production. High-income countries could consider targeting the manufacturers/exporters of such food production systems to limit their export.
- Viable alternatives to antibiotics are needed to mitigate the economic impact of reduced antibiotic usage. As well as improved husbandry practices, animal breeding may also be able to generate strains that are more resistant to infection. Modifying the gut microbiome could also be a way to influence susceptibility to infection and/or yield.
- As well as farm biosecurity, movement of livestock also needs to be considered, as this an important mechanism by which infections can be spread.

- Solutions based on greater regulation of the food production sector would be problematic in many LMICs that lack the infrastructure to enforce regulation.
- Consumer behaviour can also drive change, for example by increasing demand for antibiotic-free meat products. However, there may be consumer confusion about two distinct issues – the presence of antibiotic residues in food and use of antibiotics as growth promoters in food production.
- Although there are clear examples where antibiotic-resistant organisms have been transmitted from animals to humans, the full impact of AMR transfer from livestock animals to humans is unclear; nevertheless, the scale of potential transfer and potentially devastating consequences warrant a precautionary approach. Genomic studies provide a particularly fruitful mechanism for tracking the flow of AMR genes through agriculture and the wider environment to humans.

Evidence gaps/research needs

- Up-to-date data on antibiotic usage in agriculture
- Economic impact of low-antibiotic husbandry practices
- Evidence-based yield-promoting husbandry practices
- A better understanding of AMR transmission between the agricultural and medical domains, to support more effective targeting of countermeasures.

3. Improve nutrition and water quality

- Policy intervention under objective 1

- Improve quality of feedstock and water to suppress infection risk
- This intervention has been bundled with good animal husbandry practices, making it challenging to evaluate discretely

Evidence base

Expert opinion | *Association with risk of confounding* | *Longitudinal data, probability relationship is causal* | *Intervention studies / systematic review*

- No evidence found that suggests higher-quality food stock decreases infection risk

Potential impact of policy intervention

Limited or none | *Difficult to determine* | *Supportive* | *Important* | *Essential*

- Prevent infection in farm animals
- Prevent the spread of infection within herds

Other considerations

No	*Generalizability?*
No	*Apply precautionary approach?*
High	*Direct implementation cost?*

- Common feeding practice are often highly influenced by local climate, feedstock availability, and traditions

Likely intervention mechanism

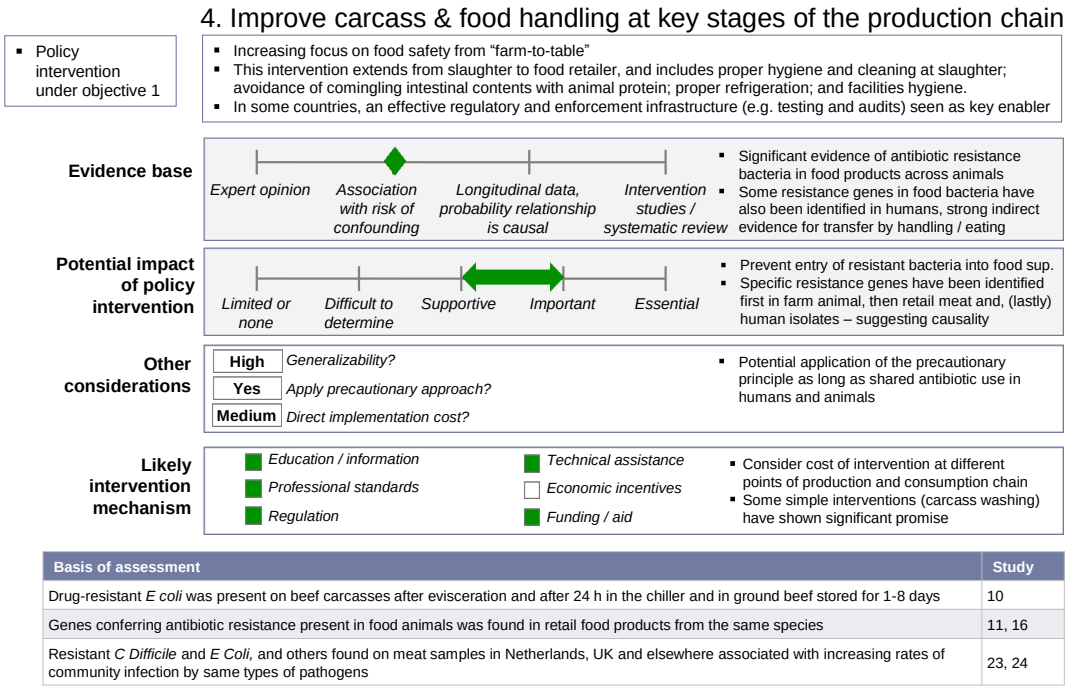
■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	□ *Economic incentives*
□ *Regulation*	■ *Funding / aid*

- In some contexts, clear long-term economic benefit from upfront investment in improve nutrition and water

Basis of assessment	Study
Improving the conditions for animal husbandry can reduce antibiotic use. When calves were provided a high level of nutrition, sub-therapeutic antibiotics provided no additional health benefits.	1

Points raised in discussion

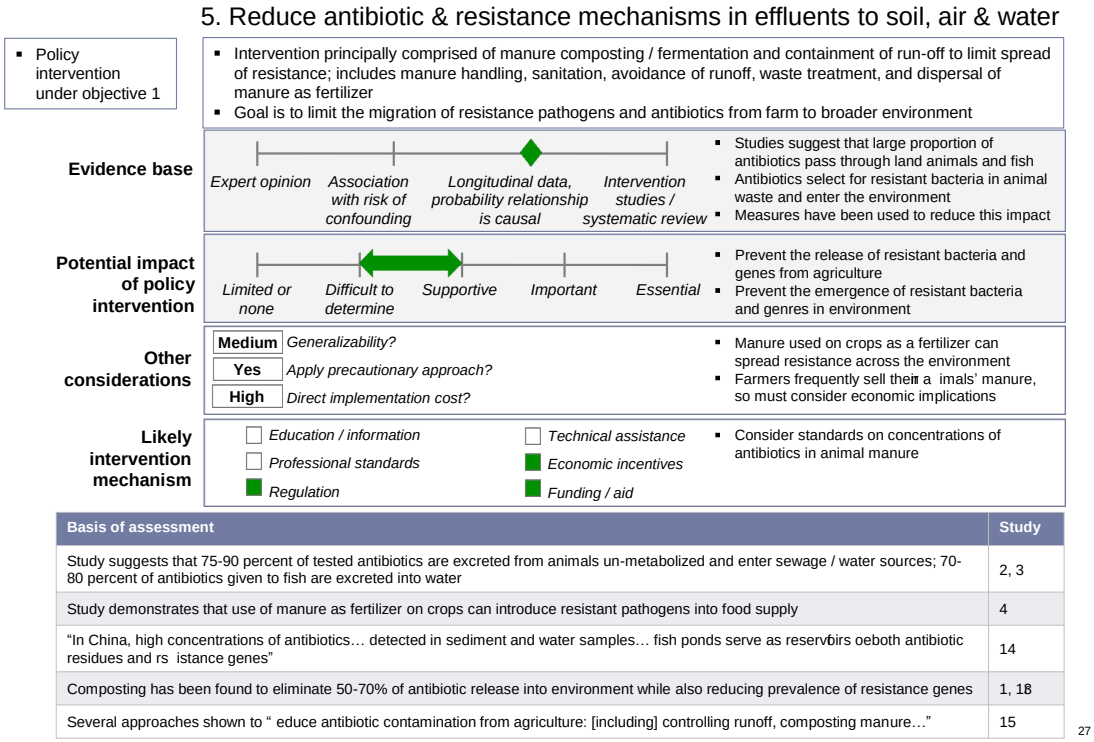
- These issues were covered through discussions on husbandry processes.



Basis of assessment	Study
Drug-resistant *E coli* was present on beef carcasses after evisceration and after 24 h in the chiller and in ground beef stored for 1-8 days	10
Genes conferring antibiotic resistance present in food animals was found in retail food products from the same species	11, 16
Resistant *C Difficile* and *E Coli,* and others found on meat samples in Netherlands, UK and elsewhere associated with increasing rates of community infection by same types of pathogens	23, 24

Points raised in discussion

- There is already a public health imperative to prevent transmission of infections from agriculture to consumers; even so, there is scope to examine the entire food chain to identify opportunities to reduce transmission still further.
- Some measures known to reduce microbial contamination, for example use of lactic acid for surface cleansing to reduce *Campylobacter* contamination, are not universally applied even in high-income countries.
- There may also be a role for consumer education, to improve hygiene and food preparation practices; however, consumers cannot be expected to shoulder the major burden of managing microbial food contamination.
- Food safety is a huge challenge in many LMICs, which may lack the infrastructure to regulate the food supply chain effectively.



Basis of assessment	Study
Study suggests that 75-90 percent of tested antibiotics are excreted from animals un-metabolized and enter sewage / water sources; 70-80 percent of antibiotics given to fish are excreted into water	2, 3
Study demonstrates that use of manure as fertilizer on crops can introduce resistant pathogens into food supply	4
"In China, high concentrations of antibiotics… detected in sediment and water samples… fish ponds serve as reservoirs of both antibiotic residues and resistance genes"	14
Composting has been found to eliminate 50-70% of antibiotic release into environment while also reducing prevalence of resistance genes	1, 18
Several approaches shown to " reduce antibiotic contamination from agriculture: [including] controlling runoff, composting manure…"	15

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Points raised in discussion

- 'Runoff' from farms may be a potentially important contributor to environmental contamination with antibiotics. However, very little is known about farm sources of environmental contamination or the contribution they make to AMR.
- The issue is part of a broader question of environmental contamination with antibiotics, for example from industrial or hospital wastewater sources, or their concentration around water treatment plants.
- Chemical treatment of animal waste products is costly and there would be large quantities of material to manage.
- Risk management would also be difficult given the scale of agriculture and the potential need for sophisticated tools to identify AMR genes.
- Technological tools exist to remove antibiotics or other chemicals from waste products but it is unclear whose responsibility it would be to finance their use.

Evidence gaps/research needs

- A deeper understanding of sources of environmental antibiotic contamination and of their contribution to the emergence of resistant organisms.
- The feasibility and cost-effectiveness of technologies for preventing antibiotic contamination of the environment and removing antibiotics from environmental reservoirs.

2. Infection prevention and control in human health

Infection prevention and control measures in human medicine do not in general have AMR prevention as their primary goal. Nevertheless, by preventing infection and the need for antibiotics, they reduce selective pressures and help to protect antibiotic resources. Although it would be difficult to argue for some measures simply to achieve better AMR control, prevention of AMR can be seen as an important additional benefit arising from initiatives promoting public health.

Improved access to clean water and sanitation were seen as potentially important contributors to AMR control. Their importance emphasised the need to consider AMR as part of a wider international development agenda. AMR needs to be integrated into the core activities of international assistance organisations, which should consider how their activities can contribute to AMR control.

Improved hand hygiene measures could contribute to enhanced infection prevention and control, and there is scope for their wider use across all countries. Although there is good evidence that such measures can reduce infections, the most effective methods for driving behaviour change are less well established, and may vary with local context. Although there may be a role for other infection prevention and control measures, such as patient screening and isolation, countries vary widely in the extent to which they can implement such measures.

Greater use of vaccination could reduce infection levels and lower antibiotic use (even vaccination against viruses could deliver AMR benefits, by reducing secondary bacterial infections and inappropriate antibiotic use in viral infections). Although new and improved vaccines are needed (for example for *Staphylococcus* and Gram-negative organisms), currently available tools are not being fully deployed, mainly because of resourcing issues in LMICs.

It is increasingly recognised that there is a complex relationship between nutrition, infection, vaccine responses and the gut microbiome. A better understanding of these interactions could suggest nutritional, microbiomic or other interventions that influence susceptibility to infection or response to vaccination and hence the need for antibiotics.

For many infection and control measures, there is good evidence of an impact on infection rates (and in some cases also on AMR). However, there is less strong evidence at a local level on cost-effectiveness and the practicalities of implementation. There may be a need for more qualitative studies and input from social scientists to better understand the obstacles and enablers to effective implementation.

Evidence gaps/research needs

- The impact of vaccination against particular pathogens on AMR
- New vaccines for a range of important pathogens
- A better understanding of the links between undernutrition, infection, the host microbiome and vaccine responses
- More information on implementation of effective public health measures and hygiene interventions at a local level.

6. Improve vaccination coverage

- Policy intervention under objective 2

- Includes improving coverage for existing vaccines (e.g. pneumococcal pneumonia and rotavirus) and adding vaccines to existing immunization programs
- Both vaccine for bacterial and viral diseases reduce antibiotic use (e.g., many viral infections are mistakenly treated with antibiotics)

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Multiple studies of vaccine introductions found clear evidence of lower infection rates
- Lower rates of infection leads to lower rates of antibiotic use
- Lower antibiotic use lowers selective resistance

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Prevent infection in community & healthcare settings
- Prevent the spread of drug-resistant infections
- Improve health outcomes and reduce later cost

Other considerations

High	*Generalizability?*
Yes	*Apply precautionary approach?*
Medium	*Direct implementation cost?*

- Well established immunization networks cover much of the world (e.g. UNICEF)
- Can be cost-effective in light of infrastructure already in place

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	□ *Economic incentives*
□ *Regulation*	■ *Funding / aid*

- Historic success establishing transfer payments or subsidies for vaccine payments in lower income countries (e.g. GAVI)

Basis of assessment	Study
Streptococcus pneumoniae vaccination of infants directly reduced the incidence of pneumococcal disease, related antibiotic use and antibiotic resistance	6
In 200, US introduction of the pneumococcal vaccine reduced pneumonia in children under two by ~40 percent and prevented 700,000 hospitalizations in adults 18 and older over five years due to herd immunity	7, 8
In Canada, the introduction of population-wide influenza vaccines in one province resulted in a relative decrease in antibiotic prescribing for URI by 64 percent	9
South Africa's introduction of the pneumococcal vaccine significantly reduced infections with serotypes included in the vaccine	10, 28
In France, 2002 introduction of a 7-valent protein-conjugate pneumococcal vaccine contributed to decrease in antibiotic consumption and reversing trends in penicillin resistance in S. pneumoniae.	13

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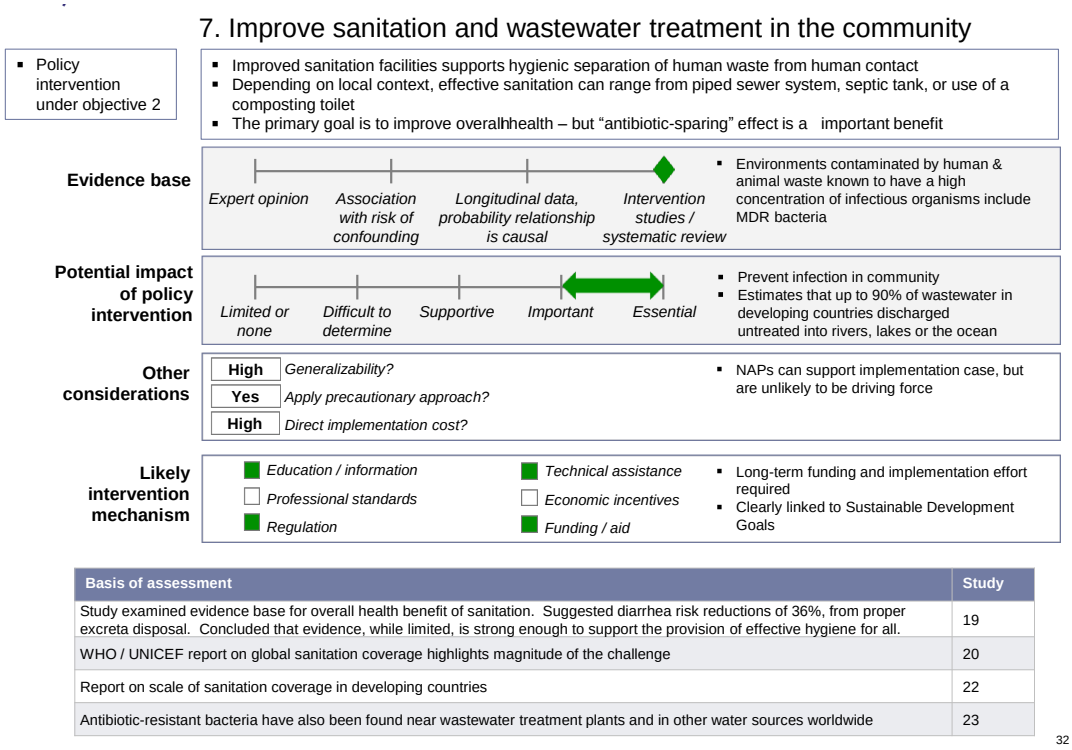
Points raised in discussion

- There is good evidence that vaccination prevents infection, and reduces antibiotic use and the development on antibiotic resistance; however, fewer data are available for LMICs.
- Vaccination against viral infections can also benefit AMR control, by reducing the numbers of secondary bacterial infections and inappropriate use of antibiotics.
- Vaccination is unlikely to be cost-effective if used primarily for AMR reduction; however, vaccination is usually used for other public health reasons and its impact on AMR provides an additional benefit.
- Although vaccines are lacking for some important infections (e.g. *Staphylococcus aureus*, Gram-negatives), those that are available are not being fully utilised in LMICs, mainly because of financial restraints.

Evidence gaps/research needs

- Further evidence of the impact of vaccination on AMR.
- New vaccines for important bacterial pathogens for which effective vaccines are currently unavailable.



Points raised in discussion

- This area is of fundamental importance to human health and wellbeing; AMR control adds to the global need to provide the world's population with access to clean water and effective sanitation systems.
- The links between water/sanitation and AMR emphasise the need to consider AMR as part of the international development agenda.
- Infection control also needs to consider links between infection, nutrition and the gut microbiome; infection and undernutrition have harmful reciprocal impacts on growth and immune system function, while damage to the gut interferes with oral vaccine responses.
- The impact of AMR control measures in different situations or across different countries can be difficult to compare in the absence of agreed AMR metrics.

Evidence gaps/research needs

- Evidence of the impact of improved sanitation and wastewater treatment on AMR.
- Most cost-effective approaches for delivering clean water and sanitation services at a local level.
- Development of an agreed set of AMR metrics to facilitate target setting, progress monitoring and international comparisons.
- A better understanding of the links between infection, undernutrition and the gut microbiome, to support the development of nutritional or other interventions to reduce stunting and enhance host responses to infection and vaccination.

8. Improve access to clean water to limit water-born infection risk

- Policy intervention under objective 2

- Contamination of water supply with virus or bacteria can lead to infection and (avoidable) use of antibiotics
- Ideally, water supply systems are designed, constructed and managed to minimize risk of contamination
- The primary goal of this public health measure is to improve overall health and well-being – but "antibiotic sparing" effect is a important side benefit.

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Reviews demonstrate clear link between fecal contamination and infection risk

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Prevent infection in community and healthcare settings
- ~750 million people lack access to safe drinking water (2012), many in rural LMICs

Other considerations

High	*Generalizability?*
Yes	*Apply precautionary approach?*
High	*Direct implementation cost?*

- NAPs can support implementation case, but unlikely to be driving force

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	□ *Economic incentives*
■ *Regulation*	■ *Funding / aid*

- Long-term capital investments required
- Active monitoring of water safety (quality testing and risk management measures) key to this intervention

Basis of assessment	Study
Study examined evidence base for overall health benefit of clean water. Suggested diarrhea risk reductions of 17% from access to clean water. Conclude that evidence, while limited, is strong enough to support the provision of clean water	19
WHO / UNICEF report on global sanitation coverage highlights magnitude of the challenge	20
A systematic review of 345 studies on drinking water quality data estimated global exposure to fecal contamination (*E.Coli* used as signal pathogen) in drinking water estimated 1.8 billion people globally use a source of drinking water with fecal contamination	21
Antibiotic-resistant bacteria have also been found near wastewater treatment plants and in other water sources worldwide	23

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Points raised in discussion

- These issues were covered in discussions on sanitation.

9. Implement health worker and patient hygiene programs to prevent infection

- Policy intervention under objective 2

- Cluster of related behavioral interventions that prevent spread of healthcare-associated infections through good hygiene
- Infections commonly spread through the hands of healthcare workers, by medical equipment (especially intravenous and urinary catheters and ventilators), and wound contamination during surgery
- Examples of specific interventions including effective hand hygiene training and compliance programs

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Multiple studies support ability of hand hygiene and other measures to reduce infection
- Interventions d n't have common definitions and include blend of behavioral, environmental, and institutional components

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Prevent infection in healthcare settings
- Avoiding infections has direct benefits to patients, hospitals and healthcare systems
- Rate of device-related infections and surgical site infections much higher in LMICs

Other considerations

High *Generalizability?*
Yes *Apply precautionary approach?*
Low *Direct implementation cost?*

- Hand and other hygiene measure widely considered to be simple and cost-effective
- Must adapt for range of care environments (e.g. lack of water, soap, lack of access to PPE)

Likely intervention mechanism

- ■ *Education / information*
- ■ *Professional standards*
- □ *Regulation*
- ■ *Technical assistance*
- □ *Economic incentives*
- □ *Funding / aid*

- Barriers to hand hygiene include time, understaffing, and access to water / soap
- Intervention considered cost-saving due to avoided infections and associated cost

Basis of assessment	Study
ESCMID offers strong recommendations for hand hygiene education programmes in both endemic and epidemic settings, though strength of evidence varies for different pathogens	4
Hand hygiene measures associated with 47% decrease in Vancomycin-resistant enterococci acquisition rate in US, UK and Canada	3
English evidence review supports following interventions: hospital environmental hygiene, hand hygiene, use of personal protective equipment and the safe use and disposal of sharps; preventing infections associated with catheters; preventing infections associated with the use of central venous access devices	2
While insufficient evidence of the epidemiology of healthcare-associated infections in African countries, some papers suggest surgical site infection and HAI following surgical procedures was markedly higher in African countries than high-income countries	1
Infection control programs reduced non-prophylactic antibiotic use for heart surgery patients by >40 percent	11
Infection control programs reduced urinary tract infections (as measured by reduction of 2 defined daily doses per patient / day)	12
WHO guidelines developed through literature review and expert opinion "consistently recommend hand hygiene as an essential method of controlling the spread of infections including those with AMR."	14
From 1995 to 2000 at the University of Geneva Hospitals in Switzerland, an intervention promoting good hand hygiene led to a decrease of almost 50% in health care-associated infections in parallel with a sustained improvement in hand hygiene compliance	15
The Australian state of Victoria introduced a centrally coordinated hand hygiene education and change programme over a two year period across 6 healthcare institutions. Rate of hand hygiene compliance improved significantly. In parallel, patients with MRSA and MRSA clinical isolates were significantly reduced.	16
In Karachi, Pakistan 300 households with an aggressive hand-washing intervention had a 50% lower incidence of pneumonia than control households and a 53% lower incidence of diarrhea	29

Points raised in discussion

- Hygiene-promoting programmes are seen as highly cost-effective, reducing costs linked to HAI management.
- However, compliance is often low, and there is a lack of understanding of how to drive effective behaviour change.
- There is scope to improve hand hygiene practices in high-income countries as well as LMICs.
- Principles are well understood – key challenge is local implementation, where data are often lacking; local context is likely to be important in design of programmes promoting hand hygiene.

Evidence gaps/research needs

- Information on effective implementation of hand hygiene measures at a local level.

10. Improve patient screening, isolation, and health facility management

- Policy intervention under objective 2

- Includes screening and potentially isolating patients for MDR pathogens upon admission
- Screening and optimizing patient placement in healthcare facility limits spread of resistant bacteria across wards
- Additionally, optimizing healthcare facility infrastructure, facility cleaning, management, and staffing part of this intervention

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Screening patients for resistant bacteria on admission has produced conflicting results on efficacy and cost-effectiveness
- Studies demonstrate that shared clinical equipment becomes contaminated

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Prevent the spread of drug-resistant infections
- In low and middle-income countries, >10% of all hospital-admitted patients will develop an HAI infection.

Other considerations

Medium *Generalizability?*
No *Apply precautionary approach?*
High *Direct implementation cost?*

- Isolation of infected patients in single rooms not always practical – alternative of grouping similarly affected patients in part of the ward

Likely intervention mechanism

- *Education / information*
- *Professional standards*
- *Regulation*
- *Technical assistance*
- *Economic incentives*
- *Funding / aid*

- Gaps to optimal healthcare facility infection control include administrative commitment, funding, staffing levels, and country-specific historical and cultural factors

Basis of assessment	Study
Report strongly recommended specific cohort staff to reduce the risk of acquisition of MDR pathogens, and ensuring consistent environmental cleaning of infection wards.	24
A body of clinical evidence derived from case reports and outbreak investigations suggests an association between poor environmental hygiene and the transmission of microorganisms causing healthcare-associated infections in hospital	2
Isolation and screening for MRSA lead to a reduction of MRSA colonization and infection in hospital inpatients	17
Report strongly recommends i) Implementing a programme of active screening culture at hospital admission and ii) isolating colonized and infected patients in a single room to reduce the risk of acquisition of MDR-pathogens	24

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Points raised in discussion

- Patient isolation has great potential in infection control, but is not feasible in many LMICs, which lack the capacity to characterise infections and the healthcare infrastructure to isolate patients.

3. Optimal use of antibiotics in agriculture

Antibiotics are used in agriculture for three reasons: growth promotion, prevention of infection, and treatment of infection. It was strongly felt that antibiotic use for growth promotion should be phased out as rapidly as possible, as has already been achieved in a number of countries. As a ban on use of antibiotics for growth promotion could lead to increased use for prophylaxis, antibiotic use for prevention of infection was also seen as inappropriate.

Phasing out was felt to be more appropriate than an immediate ban, to give food producers time to adapt. Innovative insurance schemes could be envisaged to mitigate the risk of potential reductions in yields and hence income during the transition to low-antibiotic production systems. Nevertheless, it was recognised that many countries currently lack the infrastructure necessary to implement regulations on antibiotic use in agriculture.

Education was felt to have an important role to play in communicating the rationale for antibiotic withdrawal, encouraging adherence and promoting the use of alternatives. As well as veterinary education, agriculture courses could also be targeted to encourage good practice among food producers.

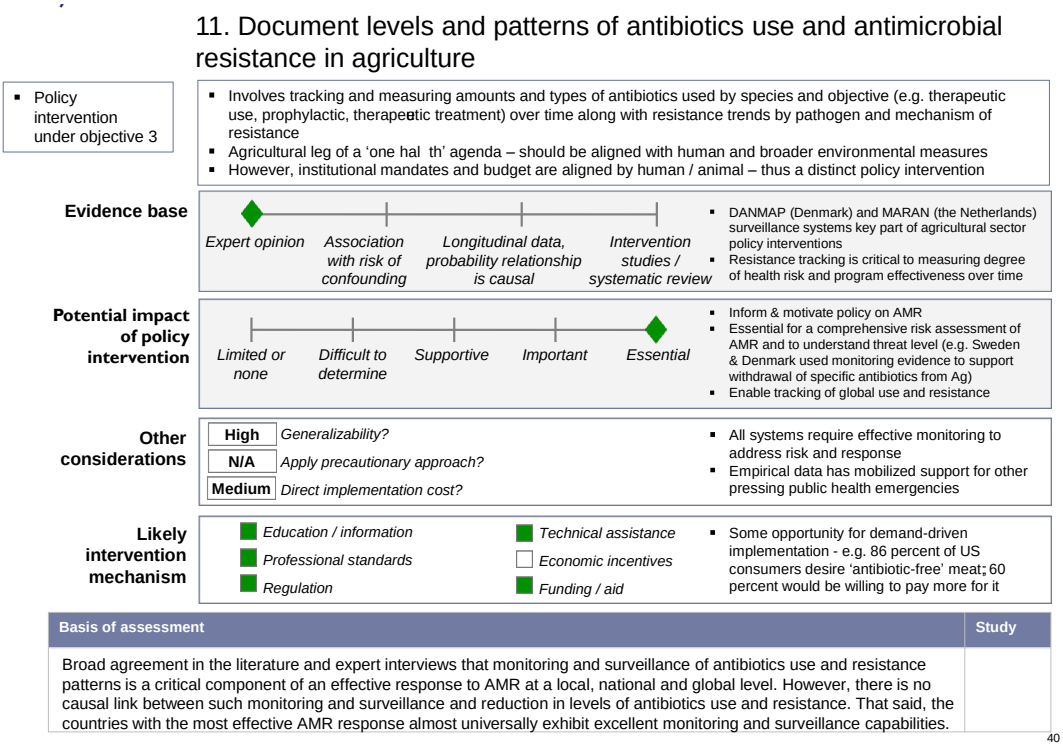
Consumers may also be able to pressure food companies into reducing their use of antibiotics, or encourage governments to introduce new regulations.

Better data on antibiotic usage and on AMR in agriculture were felt to be essential, with up-to-date data on usage often hard to come by even in high-income countries. International standards were considered to be important to ensure data reliability and consistency; the IOE is developing one such set of standards. Consistent high-quality data would also support target setting for reductions in antibiotic use. Targets would also need to reflect wide variation in the numbers and types of animals used in different countries for food production.

Restricting antibiotics to either medical or veterinary use was considered to be problematic – in most antibiotic classes, drugs are currently used in both sectors. In some cases, most notably with colistin, relatively toxic antibiotics have been used only in veterinary medicine, but have subsequently turned out to be required in human medicine; it is now challenging to withdraw colistin from veterinary use. Nevertheless, there is a strong case for restricting use of second- and third-line drugs to human medicine.

Key evidence gaps/research needs

- Improved husbandry methods or other innovative approaches (such as modification of the gut microbiome) to increase yield without use of antibiotics.
- The economic impact of low-antibiotic food production systems, and of husbandry practices or other approaches used to improve yields without the need for antibiotics.
- Better antibiotic use and AMR surveillance mechanisms in agriculture.
- Effective approaches for local implementation of low-antibiotic food production systems.
- Over the long term, effective alternatives to antibiotics for use in veterinary medicine.



Points raised in discussion

- The One Health, cross-sectoral approach was seen as critical to AMR control, requiring a strong focus on the agricultural sector as well as medicine.
- Documenting antibiotic use in the agricultural sector is a prerequisite for ensuring appropriate use. Nevertheless, antibiotic usage data can be hard to obtain, even in high-income countries. Many LMICs have almost no infrastructure to collect data on antibiotic usage or resistance levels in agriculture.
- For international comparisons, there is an important role for standards such as those developed by the IOE.
- Reliable antibiotic usage data would support target setting for usage reduction.
- Variation in agricultural use of antibiotics between countries is far greater than medical use, suggesting considerable scope for reductions.
- It would be important to consider appropriate measures of antibiotic use, to take account of national differences in the size of the livestock sector and types of animals used in food production; mg of antibiotic per kg of animal protein produced is one possible measure.
- Development assistance funding could include agriculture antibiotic use as an outcome to be monitored.
- It is important to recognise the diversity of agriculture, including the importance in many countries of aquaculture, where excessive antimicrobial use and AMR is also a major issue.
- Antimicrobial agents are also used in crop pest control, and pressures to reduce pesticide use may lead to increases in antimicrobial use.

Evidence gaps/research needs

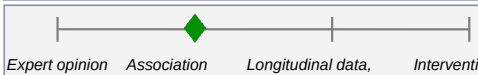
- Effective surveillance systems to monitor antibiotic usage and AMR levels in agriculture.

12. Develop and enforce optimal use guidelines for antibiotics in animals

- Policy intervention under objective 3

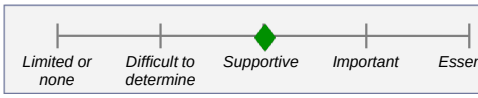
- A variety of governments, supra-national authorities, and multi-lateral agencies have developed guidelines for the appropriate use of antibiotics in animals
- Example interventions via guideline include limiting prophylactic use, requiring veterinary prescription, eliminating access to antibiotics of highest value to human health, and supporting optimal use and dosing
- Each of these acts limits emergence of resistance and support good therapeutic outcomes for animal and herd

Evidence base



- Guidelines reflect expert opinion and stakeholder consultations, and represent broad consensus within existing legal frameworks (e.g., ban on growth promotion in Europe)
- There is limited evidence evaluating the direct impact of such standards on ABx use and AMR

Potential impact of policy intervention



- Reduce the volume of antibiotics used
- Reduce the use of antibiotics critical to human health
- Support the selection of the right antibiotic

Other considerations

High	*Generalizability?*
Yes	*Apply precautionary approach?*
Medium	*Direct implementation cost?*

- Need for national authorities to implement and enforce the guidelines, as well as their impact
- Cost is related to enforcing guidelines, and evolving therapeutic approach

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
■ *Professional standards*	□ *Economic incentives*
■ *Regulation*	■ *Funding / aid*

- In Sweden, implementation of comprehensive guidelines has been supported by technical assistance to farmers
- Regulatory requirements for compliance are likely to increase impact

Basis of assessment	Study
The European Commission, The World Organization for Animal Health (OIE), and The Codex Alimentarius are among several bodies that have developed guidelines for veterinary use of antimicrobials in order to limit AMR	10, 11, 12, 13
Sweden developed comprehensive guidelines on animal husbandry to facilitate the earliest ban on ABx for growth promotion, including on medication. Agricultural use of antibiotics dropped substantially, but infections rose temporarily in the transition	2

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Points raised in discussion

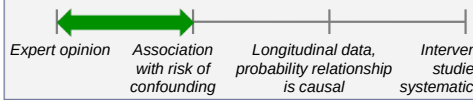
- Antibiotic use policies are an important component of the AMR response, but need to be accompanied by other measures (e.g. education, enforcement, target setting).
- Regulation (or anticipation of regulation) can be an important driver of innovation.
- Some countries may lack the infrastructure to implement or enforce guidelines.

13. Incorporate optimal use guidelines into professional training & accreditation

- Policy intervention under objective 3

- Veterinarians undergo rigorous professional training, and with varying continuing education requirements
- Guidelines could reflect latest evidence on dosing, sequencing, treatment duration, etc.
- Guidelines could evolve to reflect urgency of public health threats and local resistance patterns

Evidence base



- Training on guidelines have been demonstrated to be one of the most effective interventions when evaluating optimal prescribing in human health

Potential impact of policy intervention

- Reduce the volume of antibiotics used
- Reduce the use of antibiotics critical to humans
- Support the selection of the right antibiotic

Other considerations

Medium	*Generalizability?*
No	*Apply precautionary approach?*
Medium	*Direct implementation cost?*

- Optimal use will be informed in part by local resistance patterns
- Developing voluntary guidelines relatively straight-forward, but enforcement more costly

Likely intervention mechanism

■ *Education / information*	□ *Technical assistance*
■ *Professional standards*	■ *Economic incentives*
■ *Regulation*	□ *Funding / aid*

- Potential for professional societies to play leading role in development, roll-out, and compliance

Basis of assessment	Study
Several types of resources have been developed in the US, Europe and elsewhere to provide training to veterinarians on optimal use of antibiotics in light of AMR (e.g., in the United States, booklets, videos and web-based learning tool)	19, 20
The EU Guidelines for prudent use of antimicrobials in veterinary medicine call on veterinary colleges and professional associations to provide training on optimal use	12
In the human health context, a study concluded that undergraduate training of doctors and nurses in antibiotics treatment guidelines had one of the highest associations with high quality use of medicines (QUM) indicators among 36 policy tools.	21

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Points raised in discussion

- Optimal use should be an essential part of veterinarian training and professional development.
- Optimal use could also be incorporated into animal production teaching/training programmes.

14. Limit antibiotics as growth promoter

- Policy intervention under objective 3

- Majority of global antibiotics use by tonnage is in animals, especially pigs, chicken and fish
- EU has outright ban, though prophylactic use often replaces growth-promotion in total tonnage post-ban
- Limitation can be tailored to restrict most critical antibiotics classes for human use
- Multiple examples illustrate that resistance increases with growth-promotion and decreases following phase-out

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Significant correlation between non-therapeutic use and selection & release of resistant pathogens from farms
- Suggestive evidence of human disease impact
- Economic impact of ban has been manageable

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Reduce the volume of antibiotics used
- Prevent the emergence of resistant bacteria
- Prevent human infection in community

Other considerations

High *Generalizability?*
Yes *Apply precautionary approach?*
Medium *Direct implementation cost?*

- Significant evidence that using antibiotics as a growth promoter has a limited impact on yield
- Some evidence that benefit of phase-out is highest when resistance remains rare

Likely intervention mechanism

- ■ *Education / information*
- □ *Professional standards*
- ■ *Regulation*
- □ *Technical assistance*
- ■ *Economic incentives*
- □ *Funding / aid*

- Regulation common implementation vehicle
- Some industry groups active (e.g., NL)
- Need to guard against sustained use under different label (e.g., prophylactic) following ban

Basis of assessment – evidence opposing a phase-out	Study
The scientific consensus is that human use of ABx is a more significant driver of AMR than use in animals	26
Some studies question the direct transfer of resistant bacteria from animals to humans	24, 25
Some studies (e.g., in Western Europe and the USA) suggest that food-borne pathogens are a limited contributor to multi-resistant bacteria in human found in the healthcare sector	24, 27

In light of the controversial nature of this intervention, a more thorough evidence review was conducted to look at evidence favoring a phase-out. This is summarized on the next page.

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Basis of assessment – favoring a phase-out	Study
Phase-outs have reduced volume of use – In most, but not all, markets, ban on use for growth promotion has led to substantial declines in total tonnage (e.g. Sweden after ban, sales of antibiotics for ag fell from ~45 tons of actives substances to ~15 tons by 2009).	2
Selects for resistant bacteria – In Europe, the United States and China, antibiotics used for growth promotion have been associated with the emergence and spread of MDR bacteria from the animals that are resistant to ABx beyond those used on them (e.g., avoparcin use led to vancomycin resistance); and resistance has spread to multiple bacteria. However, *some* resistance has been found in antibiotic-free animals as well	4, 6, 7, 14
May migrate to humans – Multiple studies have shown associations with antibiotic use in animals and resistant bacteria found in humans, with agricultural workers and their families being most at risk.	4
Moves into food supply – Resistant bacteria of animal origin have been found to propagate to people through consumer meat and fish products	4, 14, 15
Resistant infections in humans traced to animals fed antibiotics – While evidence is suggestive that resistant pathogens that originate in antibiotic-fed animals have caused resistant infections in humans, the link has been less firmly established (e.g., multi-drug resistant *salmonella* infections in the US traced to raw milk; *Salmonella* resistance pattern in Danish human outbreak nearly identical to that in pork farm-to-fork chain; urinary tract infections in China virtually identical to resistant isolates from chickens; etc.)	4, 15, 17
Infections in humans correlated with animal use – In the USA, Spain, and the Netherlands, a close temporal relationship was document between the introduction of fluoroquinalone therapy in poultry and the emergency of flouroquinalone-resistant *Campylobacter* in human infections. For example, in Spain, where fluoroquinalones were introduced were introduced into poultry production in 1993, resistance to the drug in human isolates quickly rose to over 80%.	4, 14, 17
Phase-outs reduced prevalence of resistance – In multiple countries, the 1995 ban on the growth promoter avoparcin led to a significant decline in resistant bacteria in farm animals (Denmark, Italy, Germany, and Taiwan [2000 ban], and to a similar decline in human carriage of related resistant bacteria (VRE) (Hungary, Germany, Belgium). In Denmark, use of avilamycin, erthromycin, vancomycin and virginiamycin caused an increase in resistance, which declined after use of these drugs was banned..	4, 14, 18
Phase-outs reduced MDR bacteria in humans – Several studies have found that the human carriage of MDR bacteria declined after phase-out of ABx phased out as growth promoters in Denmark after link between *avoparcin* use in boiler chickens and vancomycin-resistant *enterococcocal* infections in humans. Phase-out led to marked reductions of antibiotic resistance among fecal enterococci and human isolates. In Canada, resistant strains of *Salmonella* and *E Coli* in chickens and humans rose with the use of the 3rd. gen. cephalosporin ceftiofur, declined when use was stopped temporarily, and rose again when use resumed.	3, 15, 16
Limitations on risk assessment – The absence of robust surveillance data in most parts of the world makes a comprehensive risk assessment called for by opponents of a phase-out difficult, if not impossible	4
Economic impact of ban is manageable – These bans did require modifications to animal husbandry practices to mitigate impact, but both US and European experience, as well as modeling, suggest that antibiotics use in animals can be limited with small to "minimal" effects on production.	4, 15

Points raised in discussion

- There was strong support for the elimination of antibiotics as growth promoters.
- Phasing out rather than an immediate ban was felt to be necessary, to give food producers opportunity to introduce alternative approaches.
- Bans on antibiotic use for growth promotion could lead to increased prophylactic use; one approach is to restrict antibiotic use to situations in which infection or a pathogenic organism has been identified.
- Improved husbandry practices can substantially reduce the enhanced yield obtained by use of antibiotics as growth promoters.

- Innovative insurance schemes may be needed to mitigate the risk for food producers transitioning to antibiotic-sparing practices.
- In many LMICs, regulatory systems are ill-equipped to develop and implement such policies and practices.
- Ideally, policies need to be implemented at a regional level, to avoid producers adhering to good practice in one country being outcompeted by antibiotic-using producers in nearby countries.
- Consumers may be able to exert pressure on companies and politicians to drive changes in food production practices.

Evidence gaps/research needs

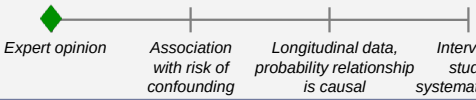
- More data on the economic impact of transitions to antibiotic-sparing husbandry practices.
- Continuing research on husbandry practices that enhance yield without the need for antibiotics.
- Research into innovative alternatives to enhance yield (e.g. manipulation of the animal gut microbiome).

15. Develop and disseminate alternative treatments to antibiotics

- Policy intervention under objective 3

- This category includes phages and other potential or existing alternative therapies
- We consider vaccines as a separate policy intervention (*see above*)
- Metals such as copper, zinc, and arsenic are used therapeutically, but can accumulate in the soil and food chain
- Includes classes of antibiotics such as ionophores that have no current human therapeutic use

Evidence base



- No viable alternative of general applicability has been identified

Potential impact of policy intervention

- Opportunity currently limited - requires R&D to develop viable alternative to treatments
- Reduce use of antibiotics critical to human health

Other considerations

- **High** *Generalizability?*
- **No** *Apply precautionary approach?*
- **Medium** *Direct implementation cost?*

- Effective treatments should be generalizable across a range of agricultural environments

Likely intervention mechanism

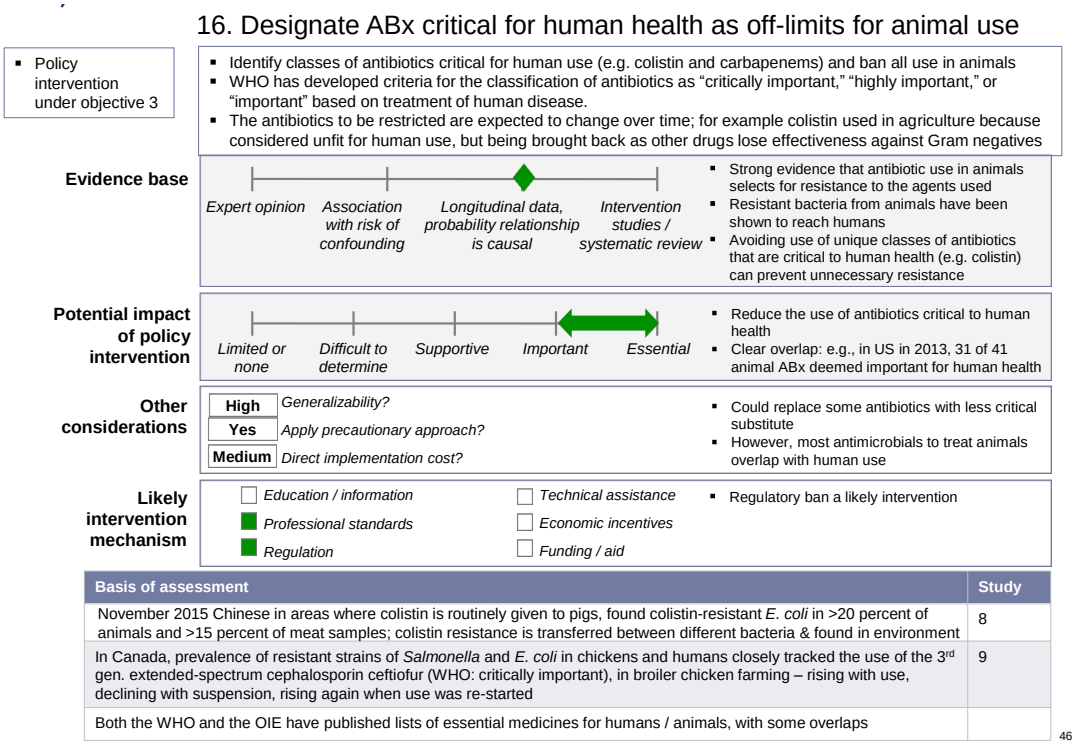
- ☐ *Education / information*
- ☐ *Professional standards*
- ☐ *Regulation*
- ☐ *Technical assistance*
- ☐ *Economic incentives*
- ☐ *Funding / aid*

- The development and validation of new therapies is an expensive and time-consuming enterprise
- Once developed, guidance or regulation could be used to motivate substitution for ABx

Basis of assessment	Study
Multiple commentators have called for the development of new, alternative treatments and / or the re-purposing of antibiotics not fit for human use for use in agriculture	Summar -ized in 3

Points raised in discussion

- Alternative treatments (or animal-specific antibiotics) are likely to be expensive and time-consuming to develop, arguing for the importance of more immediate infection control measures and preservation of existing stocks of antibiotics.



Points raised in discussion

- Some antibiotics (notably colistin) initially considered too toxic for human use have been widely used in agriculture, but have subsequently turned out to be needed for human medicine. This has led to the likely emergence of colistin resistance in agriculture, arguing for its withdrawal from veterinary use (or more restricted use).
- Although particular antibiotics could be restricted to either the medical or veterinary sector, in practice there is significant overlap in the classes of antibiotic used in the two sectors.
- There is a strong argument to restrict antibiotics of last resort to human medicine.

4. Optimal use of antibiotics in human health

A range of measures were seen as critical to optimal use of antibiotics in medicine. Data from surveillance of antibiotic usage and of AMR levels were considered to be of fundamental importance for a multitude of reasons – to provide a clear picture of local situations, to influence local decision makers, to support target setting, to provide a mechanism for evaluating the impact of policy interventions, and to ensure accountability.

Target setting was seen as a potentially powerful motivator of action; policies, guidelines, checklists and measurement systems may not be sufficient to change prescribing behaviour. However, it can be challenging to identify appropriate targets and the risks of unintended consequences need to be considered; drives to improve access could also complicate antibiotic-usage target setting in LMICs. Target setting and international comparisons require the adoption of common standards and would benefit from agreement on suitable AMR metrics. To be effective, targets should be realistic and underpinned by reliable data and monitoring practices; accountability and transparency are also important.

Improved laboratory facilities could support surveillance, but it was recognised that many countries lack the technical capacity and human resources and expertise in this area. Individual countries may not need to develop their own technical infrastructure, relying instead on regional centres.

Education of healthcare professionals was also seen as crucial, alongside implementation of antibiotic stewardship programmes. Public education was viewed as important, although it is unclear what form this should take; a better understanding is needed of public knowledge, perceptions and expectations and how these affect physicians' antibiotic-prescribing behaviour (factors likely to be highly context specific).

Reducing over-the-counter sales of antibiotics, by 'gating' access through appropriately trained healthcare professionals, was also seen as essential, although it was recognised that this had the potential to reduce some populations' access to antibiotics. It was also acknowledged that countries differed in the degree to which they could implement such measures. Initial steps could include removal of second-line or third-line antibiotics from general sale.

It was suggested that the most appropriate antibiotic treatment regimes were still unclear, even for some common infections, requiring new randomised controlled trials. Whether strategies such as antibiotic rotation – varying the antibiotic given to patients to delay the development of resistance – have any impact on AMR is also not clear.

It was widely felt that economic models linking revenues to volumes of antibiotic sales need to be revised. Alternative models are needed that delink rewards and sales but compensate antibiotic producers and suppliers appropriately.

Labelling was felt to have several important roles in the battle against AMR. Distinctive labelling (such as the 'red line' labelling adopted in India) could help to communicate the special status of antibiotics. Labelling can also support effective supply chain management, providing a source of data on usage. More sophisticated

packaging and labelling may also be a tool to combat the distribution of potentially substandard counterfeit drugs.

Rapid point-of-care diagnostics are likely to play an important role in tackling AMR in the future, but few have yet entered routine care. There are also important question marks about their integration into health systems (particularly their implications for reimbursement mechanisms) and their capacity to change physicians' behaviour.

A lack of evidence at a local level was seen as in important barrier to implementation. As AMR policies and programmes are implemented and evaluated, there are opportunities to capture and share information on local implementation. A new online platform could be established to support global dissemination of this information.

Key evidence gaps/research needs

- Surveillance systems and laboratory facilities in many LMICs.
- Internationally agreed AMR metrics.
- The most appropriate data to collect on antibiotic usage and AMR, and the best approaches for data collection.
- Most appropriate antibiotic regimes for many common infections, and value of strategies such as antibiotic rotation.
- Public knowledge of AMR, perceptions and expectations and how these affect physicians' antibiotic-prescribing behaviour, as well as the most effective methods of communication/education to influence public attitudes.
- The impact and effectiveness of new reward models for antibiotic production and distribution.
- As well as new rapid point-of-care diagnostics, research is needed on their effective implementation into healthcare systems and their impact on physicians' antibiotic prescribing.
- Information is needed on local implementation of AMR policies and programmes, and new platforms may be needed to support sharing of this information.

17. Deliver educational and training programs for healthcare workers on appropriate use

- Policy intervention under objective 4

- Clinical education programs focusing on evidence-based medicine
- Some interventions focus on communication skills, educational outreach visit, and clearer guidelines
- Format for programs can range from interactive continuing education seminars to mailing campaigns
- This intervention could include task sharing / shifting based on composition of healthcare workforce

Evidence base

- Most campaigns show a mixed reduction in antibiotic prescribing, with some questioning the long-term impact
- Parallel education of patients increases probability of success

Potential impact of policy intervention

- Reduce the volume of antibiotics used
- Prevent the emergence of resistant bacteria
- ABx routinely prescribed for infections not caused by bacteria

Other considerations

Low	*Generalizability?*
No	*Apply precautionary approach?*
Low	*Direct implementation cost?*

- Stewardship often a part of broader set of interventions (e.g. infection control)
- Many healthcare workers in LMICs have more limited access to continued education

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	□ *Economic incentives*
■ *Regulation*	□ *Funding / aid*

- Could be implemented through continuing education / professional societies

Basis of assessment	Study
Systematic review of educational programs for antibiotics prescribers showed a reduction in antibiotic prescribing was achieved through interventions focused on clinical education programs (intervention group 41% lower inappropriate prescribing).	1
Literature review demonstrates that physician education is effective in decreasing antibiotic use for respiratory tract infections.	2
Reviews from Finland, Norway, US found meetings to educate physicians improved their prescribing.	3
17 studies systematically reviewed showed the most effective interventions target both patient and clinicians during consultation	4, 25

Points raised in discussion

- Appropriate use of antibiotics was seen as a fundamental aspect of the training and professional development of healthcare professionals.
- Antibiotic use should form part of the earliest stages of medical training.
- It is important for ministries of health to play a leadership role in promoting the importance of appropriate antibiotic use.

18. Deliver educational programs for general public on appropriate antibiotic use

- Policy intervention under objective 4

- Public campaign can range from targeted Internet education campaigns to broader mass-media campaigns
- Some campaigns have targeted eliminating community use of antibiotics use for respiratory infections
- Estimated 20-50% of antibiotic use is "inappropriate"r including use when no health benefit is possible o suboptimal use including poor patient adherence

Evidence base

Expert opinion | *Association with risk of confounding* | *Longitudinal data, probability relationship is causal* | *Intervention studies / systematic review*

- A relatively well-studied discrete intervention with results back from multiple countries over significant time periods
- Success depends on social, cultural, and geographic factors

Potential impact of policy intervention

Limited or none | *Difficult to determine* | *Supportive* | *Important* | *Essential*

- Reduce the volume of antibiotics used
- Prevent the emergence of resistant bacteria (though impact on AMR less well-understood)
- Impact might be smaller in hospital settings

Other considerations

High *Generalizability?*
Yes *Apply precautionary approach?*
Low *Direct implementation cost?*

- Multifaceted interventions (physicians and public/patients) seen as most effective
- Positive indirect impacts – e.g. broadening political support for other AMR policies

Likely intervention mechanism

- ■ *Education / information*
- ☐ *Professional standards*
- ☐ *Regulation*
- ☐ *Technical assistance*
- ☐ *Economic incentives*
- ■ *Funding / aid*

- Regulating direct-to-consumer advertising of medicines one potential tool

Basis of assessment	Study
Public campaigns aimed at improving antibiotic use in the general population have led to substantial reduction in prescribing in Australia, the United States, and Europe.	1
17 studies systematically reviewed showed the most effective interventions target both parents and clinicians during consultation	4
Review of 22 public education campaigns to promote a more prudent use of antibiotics at national or regional levels in high-income countries between 1990 and 2007 across Europe (16), North America (3), Oceania (2), and Israel (1). Most campaigns that were evaluated decreased antibiotic use, though causality difficult to establish and long-term impact on resistance not determined,	5
Awareness campaign in France reduced antibiotic prescribing by 27 percent over five years	6
Belgian national media campaign in reduced antibiotic prescribing by 36 percent over seven years	7
Several US studies found that patient-doctor contacts where patients are expecting an antibiotic to be prescribed more likely to result in the prescription of an antibiotic	21
Campaign success depends on social, cultural, and geographic factors as well as existing barriers to prescribing	25

Points raised in discussion

- Patient expectations were widely felt to be a driver of antibiotic prescribing in primary practice.
- However, it was suggested there might be a mismatch between physicians' assumptions about patient expectations and their actual expectations.
- Consumer attitudes and physician practices are often considered in isolation; it may be preferable to take a more holistic look at 'prescribing culture', which is likely to vary significantly between countries.
- There is limited evidence that public education campaigns have changed attitudes and influenced antibiotic-prescribing practices, although there are questions about how impact can be assessed and which outcome measures are most appropriate.
- Evaluations of communication/education programmes are not always widely available – platforms could be established to support wider sharing of results and experience.
- The general public may have a limited understanding of AMR and common misperceptions; a better understanding of public knowledge and attitudes might be needed to support more effective and targeted communication/education campaigns.
- Use of antibiotics and AMR could also be integrated into young people's education.
- It would be useful to know whether giving patients alternatives reduces demand for antibiotics; one possibility is that a diagnostic test result (e.g. confirming a viral infection) would meet patients' expectations.

Evidence gaps/research needs

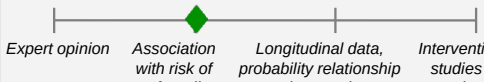
- A deeper understanding of patient/public knowledge and beliefs, and of physicians' perceptions of patient attitudes, and how such factors affect prescribing practice; these issues are likely to be highly context-specific.
- The most effective ways to influence public perceptions and behaviour; again, these issues are likely to be highly context-specific.

19. Gate antibiotics access through healthcare workers

- Policy intervention under objective 4

- Limit patient self-diagnosis and self-medication in the absence of a consultation with a healthcare worker appropriate for the health system context
- Many countries have prescription-only access laws for some antibiotics, but often poorly enforced
- Key concern is to ensure patients who need antibiotics do receive them, especially where access to healthcare infrastructure is limited

Evidence base



- Some estimates that half of community use inappropriate in many countries
- However, restrictions need to balance access where healthcare system access is limited [specifically few HCWs]

Potential impact of policy intervention

- Reduce the volume of antibiotics used
- Prevent the emergence of resistant bacteria and genes
- Ensure patient access to beneficial antibiotics

Other considerations

Low	*Generalizability?*
No	*Apply precautionary approach?*
High	*Direct implementation cost?*

- Carbapenems retail sales growing in some countries, suggesting need to address access
- Healthcare worker consultation thought to increase patient adherence

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	■ *Economic incentives*
■ *Regulation*	■ *Funding / aid*

- In LMICs, absence of qualified health workers and dispensaries suggests significant implementation difficulty

Basis of assessment	Study
Literature review from 1970 to 2009 of non-prescription antimicrobials demonstrated that over-the-counter sales Globally accounted for 19%–100% of antibiotic use outside northern Europe and North America	17
In 1999, Chile introduced regulation to restrict antibiotic sales to prescription only. This resulted in a reduction per capita consumption of the seven antibiotics monitored. However, total antibiotics sales later rebounded to pre-intervention levels.	18
Antibiotics not available over-the-counter increases appropriate use	24

Points raised in discussion

- Over-the-counter (OTC) access to medicines was seen as an important driver of inappropriate antibiotic use.
- It was recognised that reducing OTC sales had the potential to limit some populations' access to important medicines.
- Some countries have very little infrastructure to regulate OTC sales. Even when countries have regulations in place to restrict OTC antibiotic sales, these are not always rigorously enforced.
- A tiered approach could be introduced in countries with significant OTC sales, with restricted access to second-line and third-line antibiotics and continuing access to common antibiotics.
- Online antibiotic sales pose a particular challenge to national regulation.

20. Remove provider financial incentives to prescribe antibiotics

- Policy intervention under objective 4

- Incentives often affect hospitals, physicians, or other healthcare providers and pharmacists.
- Specific financial incentives vary by country and care setting, and range from direct (% of sales) to indirect
- Most commonly, pharmaceutical sales constitute a direct source of income for hospitals, clinics and individual health-care providers

Evidence base

Expert opinion | *Association with risk of confounding* | *Longitudinal data, probability relationship is causal* | *Intervention studies / systematic review*

- A handful of studies have associated financial gain from prescribing with higher prescription levels

Potential impact of policy intervention

Limited or none | *Difficult to determine* | *Supportive* | *Important* | *Essential*

- Reduce the volume of antibiotics used
- Support the selection of the right antibiotic

Other considerations

Medium *Generalizability?*
No *Apply precautionary approach?*
High *Direct implementation cost?*

- Refocusing incentives on "optimal use" could create effective change across health system
- Compensation of health workers needs to change to replace lost income

Likely intervention mechanism

☐ *Education / information*
☐ *Professional standards*
■ *Regulation*
■ *Technical assistance*
■ *Economic incentives*
☐ *Funding / aid*

- Incentives could instead focus on successful stewardship

Basis of assessment	Study
Study found decrease in antibiotic prescribing after financial incentives were eliminated in China	13, 25
Study noted decreases in antibiotic prescribing after financial incentives were eliminated in Iceland	14
In Thailand, behavior change to reduce antibiotic prescribing found the provision of therapeutic alternatives – including herbal remedies – allowed prescribers to benefit financially without prescribing antibiotics, and this accelerated physician behavior change to reduce prescribing	15

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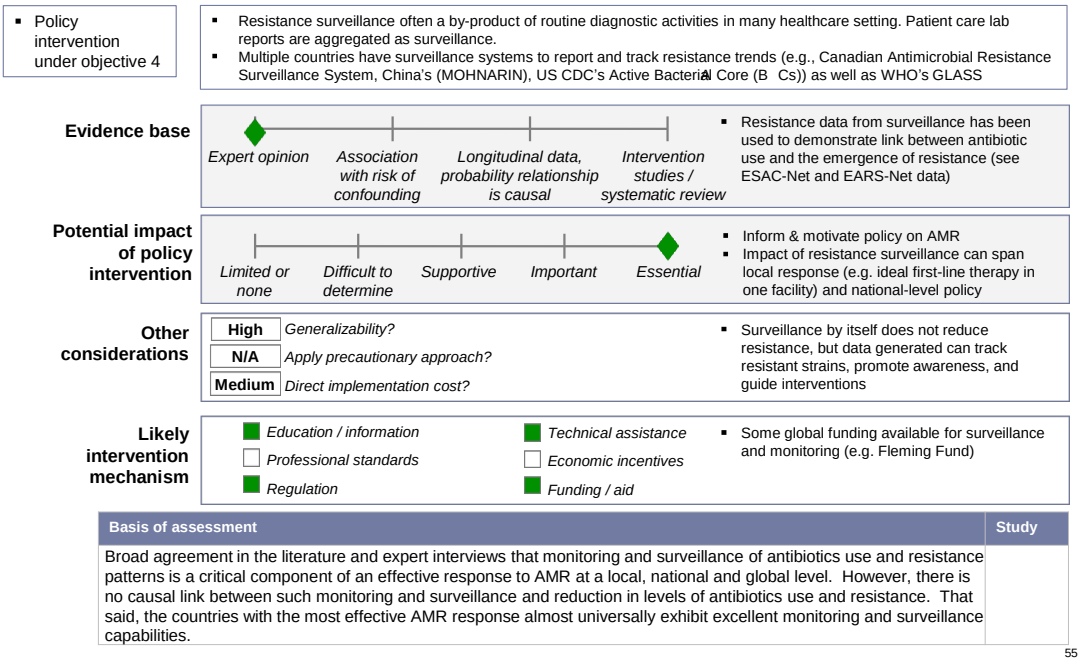
Points raised in discussion

- In conventional economic models, the income received by pharmaceutical manufacturers and antibiotic suppliers (e.g. hospitals, pharmacies) depend on sales volumes, incentivising consumption; it was widely recognised that alternative models are needed.
- Some progress has been achieved in countries such as China in de-linking sales volumes from income.
- Discussions between government and industry are underway in at least two European countries on alternative funding mechanisms for antibiotics.
- More generally, reimbursement practices are a potentially powerful mechanism for influencing antibiotic-prescribing behaviour.
- Prescribing metrics can also be integrated into performance frameworks to modify antibiotic-prescribing behaviour.

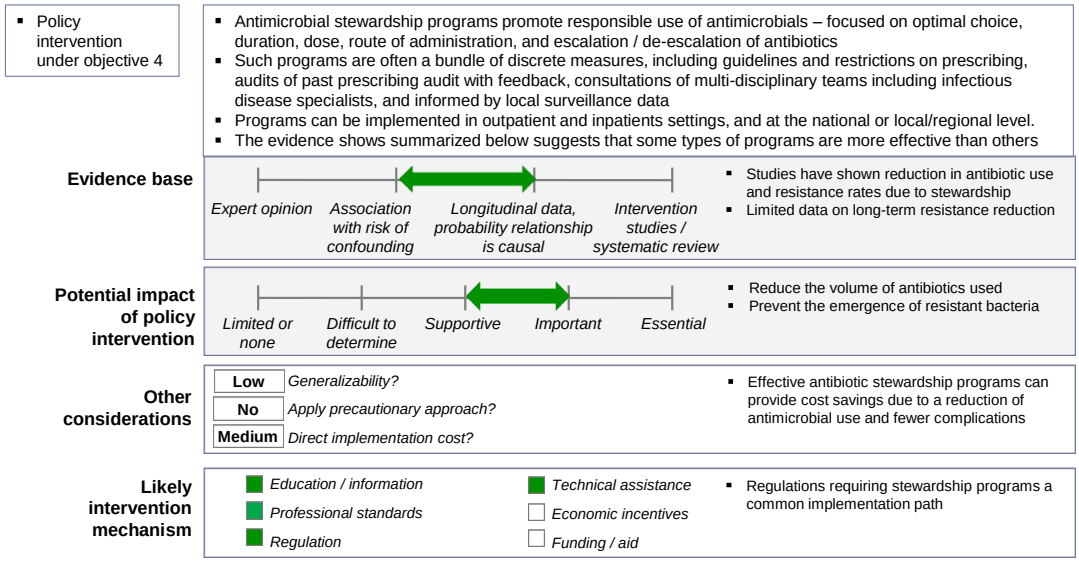
21. Document levels and patterns of antibiotics use and antimicrobial resistance in humans



Points raised in discussion

- Surveillance systems for antibiotic use and assessing AMR levels were widely seen as essential for effective AMR control.
- As well as having immediate clinical value, national data are important for convincing local decision makers of the need for action, for identifying priorities, for establishing targets, and for establishing accountability.
- Standards are essential for ensuring the reliability of data and enabling cross-country comparisons.
- Agreed AMR metrics would be useful to support international comparisons.
- Mechanisms such as the Fleming Fund, developed by the UK Department of Health, the Wellcome Trust and other partners, are providing resources to enable countries to establish cross-sector surveillance mechanisms, and to develop laboratory capacity and AMR response capabilities.
- Some countries may lack the capacity to carry out laboratory tests – regional centres may be better placed to support groups of countries lacking the appropriate technical infrastructure and/or skilled workforce.
- It is unclear whether data on antibiotic usage alone are sufficient to drive action, or whether AMR data are also required. Antibiotic usage is relatively easy to obtain, for example from point prevalence surveys. Use of a small number of sentinel sites can provide a simple source of AMR data.

22. Implement stewardship and responsible use programs



Basis of assessment	Study
Stewardship programs in **hospitals and critical-care facilities** across 10+ countries (including China and South Africa) showed reduction of ABx use by 10 to 40%, shorter antibiotic therapy duration, reduction of inappropriate use, reduction in antibiotic resistance in general and in incidence of *C. difficile*	9, 10, 11, 12, 19
Hospital prescribing guidelines in particular have been found to have the most compelling evidence of effectiveness, with some 80% reduction in some key ABx prescribing	25
A survey of 660 hospitals in 67 countries found that the **main barriers** to implementing stewardship programs were perceived to be a lack of funding or personnel, a lack of information technology and prescriber opposition	28
In several countries, incl. Thailand, France, Iceland, and Belgium, appropriate use policies in **outpatient and primary care settings** have had smaller benefits than in hospitals and are harder to sustain, but can still reduce antimicrobial consumption, decrease resistance, and save money	25
WHO literature review found that **prescription audit or drug use evaluation programs**, with feedback to prescribers, were effective in changing behavior with respect to the prescription and use of antimicrobials	20
Review of 31 studies found that **presence of infectious disease specialists** in care settings was associated with a significant improvement in the appropriateness of antibiotic prescribing and decreased antibiotic consumption.	22
There is less evidence to suggest that **national guidelines** by themselves result in meaningful improvement	24
South African study suggests stewardship programs lead to a reduction in antibiotic prescribing by ~20%	34

Points raised in discussion

- There are still major gaps in understanding of optimal antibiotic regimes, particularly in LMICs; major randomised controlled trials may be needed to fill such gaps.
- There is also very little knowledge of the potential of strategies such as antibiotic rotation to preserve antibiotics.
- Although effective stewardship was seen as essential, guidelines alone may not be effective but may need to be backed up by other measures such as feedback/peer comparisons, education and training, target setting or use of incentives/penalties to drive changes in antibiotic-prescribing behaviour.
- In the future, increasing use of digital tools could support antibiotic stewardship programmes by monitoring/querying physicians' antibiotic-prescribing decision making.

Evidence gaps

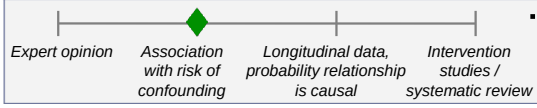
- In several clinical situations, the most appropriate antibiotic regimen.
- The potential value of antibiotic rotation to preserve antibiotic potency.
- The most effective mechanisms for implementing antibiotic stewardship at a local level.

23. Improve laboratory diagnostic capacity

- Policy intervention under objective 4

- Diagnostics can serve many roles: enabling surveillance, supporting infection control, informing healthcare prescribers of local pathogens and resistance patterns, selecting the right treatment, and avoiding unnecessary prescribing
- Enhancing laboratory capacity to deliver on these objectives is seen as crucial, especially in LMICs
- Lab services are not readily available in many LMICs, and there is often wide variation in quality of testing
- A network of reference laboratories as well as local / regional labs is a common successful approach

Evidence base



- Extensive expert opinion and some observed association between laboratory performance and optimal antibiotic use

Potential impact of policy intervention

- Inform & motivate policy on AMR
- Prevent the emergence of resistant bacteria
- Support the selection of the right antibiotic
- Critical enabler of surveillance & stewardship

Other considerations

High	*Generalizability?*
No	*Apply precautionary approach?*
Medium	*Direct implementation cost?*

- Since laboratory capacity is an enabler of other, more direct actions to address AMR, enhancing laboratory capacity needs to be part of a more comprehensive AMR response

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	□ *Economic incentives*
■ *Regulation*	■ *Funding / aid*

- Projects such as VINARES in Vietnam provide a template for improving laboratory capacity

Basis of assessment	Study
In LMICs such as Vietnam, inadequate laboratory diagnostic capacity has been identified as one of the drivers of resistance	26, 27
Appropriate laboratory capacity in LMICs allows for selective treatment tailored to the cause of symptoms, rather than treating for all possible causes of a set of symptoms	29
The WHO considers laboratory capacity to be an essential component of surveillance, the finding are key for establishing and revising national treatment guidelines and control strategies	30
Screening patients with AMR and using isolation methods for infected patients can further assist to AMR containment. Laboratory capacity supports infection prevention and control by informing the need for patient isolation and antimicrobial susceptibility	30

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Points raised in discussion

- Many countries lack laboratory diagnostic facilities and/or technical expertise; given resource constraints, regional centres may be a useful approach, although transportation of samples across national borders can be an issue.

24. Enable access to rapid point-of-care diagnostics

- Policy intervention under objective 4

- Pathogen-specific rapid diagnostic tests (e.g. malaria) can limit empirical antibiotic use
- Additionally, point-of-care C-reactive protein tests identify a biomarker of inflammation, a sign of infection. This serves as a rapid test to guide antibiotic prescribing decisions for acute cough and lower respiratory tract infections.
- Other potentially important rapid tests (e.g. dengue, typhoid, measles) show promise but barriers to access exist (e.g. cost, need for further validation, efforts to make technology appropriate for a low-resource environment, …)

Evidence base

Expert opinion — *Association with risk of confounding* — *Longitudinal data, probability relationship is causal* — *Intervention studies / systematic review*

- Studies have demonstrated impact of rapid diagnostics on lowering total antibiotic use
- Direct impact on resistance less well understood but probable, particularly for healthcare-associated infections

Potential impact of policy intervention

Limited or none — *Difficult to determine* — *Supportive* — *Important* — *Essential*

- Reduce the volume of antibiotics used
- Prevent the emergence of resistant bacteria
- Support the selection of the right antibiotic
- Improve health outcomes & reduce cost

Other considerations

High *Generalizability?*
No *Apply precautionary approach?*
Medium *Direct implementation cost?*

- Malarial rapid tests can detect malaria antigens within 15-30 minutes and are effective in locations lacking lab capacity
- Such tests do not require significant expertise

Likely intervention mechanism

- ■ *Education / information*
- ☐ *Professional standards*
- ☐ *Regulation*
- ■ *Technical assistance*
- ■ *Economic incentives*
- ■ *Funding / aid*

- Some critical diagnostic tools exist - the challenge is affordability and scalability to a range of health care settings

Basis of assessment	Study
Primary care study in Norway and Sweden found C-reactive protein test was associated with reduction in antibiotic prescribing and is likely a cost-effective diagnostic tool	31
WHO for the *World Malaria Report 2014* reported a total of 319 million RDT sales in 2013, showing broad diffusion	32
Study highlighted ability of rapid diagnostics to reduce antibiotic prescribing for adults in US ambulatory care setting	33

Points raised in discussion

- Diagnostic tools (particularly rapid point-of-care diagnostics) have been identified as an important tool in the battle against AMR. However, it was felt that their routine use was still some way off, and it was uncertain how the would be deployed in practice.
- Use of diagnostic tests might also require significant changes in reimbursement practices.
- How results were interpreted and used by physicians was also seen as an issue.

Evidence gaps/research needs

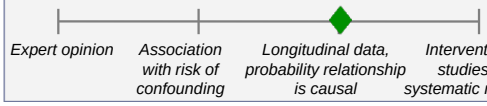
- Rapid point-of-care tests meeting specific clinical needs.
- An understanding of how diagnostic tools fit in patient management pathways and reimbursement systems.
- An understanding of how test results are received by physicians and influence antibiotic-prescribing behaviour.

25. Remove falsified and sub-standard antibiotics from circulation

- Policy intervention under objective 4

- Poor quality antibiotics can result from poor manufacturing practices, degradation over time due to climate or distribution challenges, or can reflect a deliberate decision to falsified and counterfeit drugs

Evidence base



- Falsified/counterfeit drugs more likely to drive resistance in LMICs

Potential impact of policy intervention

- Prevent the emergence of resistant bacteria
- Ensure patient access to beneficial antibiotics
- Improve human health outcomes

Other considerations

Medium	*Generalizability?*
No	*Apply precautionary approach?*
Medium	*Direct implementation cost?*

- Typically enforced through effective drug regulatory system to ensure illegal and substandard manufacturing are detected and appropriately sanctioned

Likely intervention mechanism

■ *Education / information*	■ *Technical assistance*
□ *Professional standards*	□ *Economic incentives*
■ *Regulation*	■ *Funding / aid*

- Proposed interventions range include global standards on antibiotics quality, strict punishments for counterfeiters, and drug regulatory system capacity building

Basis of assessment	Study
Counterfeit drugs are widely considered to increase rates of drug resistance, though no specific correlation studied in antibiotics	8
WHO survey of Africa and Eastern Med. highlights weak cooperation among the various key players at national, regional and global level to combat counterfeit medicines, and weak market control systems within most surveyed countries. Also concludes that sale and use of substandard and counterfeit drugs are common problems, particularly in low- and middle-income countries.	16

Points raised in discussion

- The supply of counterfeit medicines was seen as an issue that governments needed to tackle at a local or regional level.

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Objective 3: optimal use in agriculture

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Objective 4: optimal use of antibiotics in human health

Study	Authors	Journal	Title	Edition	Pages	Date
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