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Title

A One Health approach to antimicrobial resistance surveillance: Is there a business case for it?

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Abstract

Antimicrobial resistance is a global problem of complex epidemiology, suited to a broad, integrated One Health approach. Resistant organisms exist in humans, animals, food and the environment and the main driver of this resistance is antimicrobial usage. A One Health conceptual framework for surveillance is presented to include all of these aspects. Global and European (regional and national) surveillance systems are described, highlighting shortcomings compared to the framework. Policy decisions rely on economic and scientific evidence so the business case for a fully integrated system is presented. The costs of integrated surveillance are offset by the costs of unchecked resistance and the benefits arising from interventions and outcomes. Current estimates focus on costs and benefits of human health outcomes. A One Health assessment includes wider societal costs of lost labour, changes of health seeking behaviour, impacts on animal health and welfare, higher costs of animal-origin food production and reduced consumer confidence in safety and international trade of such food. Benefits of surveillance may take years to realise and are dependent on effective and accepted interventions. Benefits, including the less tangible, such as improved synergies and efficiencies in service delivery and more timely and accurate risk identification should also be recognised. By including these less tangible benefits to society, animal welfare, ecosystem health and resilience, together with the savings and efficiencies through shared resources and social capital building, a stronger business case for a One Health approach to surveillance can be made.

Keywords: Antimicrobial resistance; AMR; surveillance; One Health; business case; economics

Introduction and background

In 2001, the World Health Organisation (WHO) described antimicrobial resistance (AMR)[1] as a global problem requiring a global response [1] but until recently it has failed to gain the urgent attention it deserves. Economic evidence is used as a tool to prioritise policy decisions and it has been argued that previous estimates of the health cost of AMR have been too negligible [2] and they have failed to consider the wider impacts on health care [3]. However, recently more alarming estimates of AMR have appeared in the literature. The European Commission claimed that costs attributed to resistant bacterial infections amounted to 1.5 billion EUR annually [4]. Healthcare systems in the USA estimate the additional cost of AMR infections to be 20 billion USD a year and productivity losses 35 billion USD a year [5]. The UK government commissioned "Review of AMR", estimated that drug resistant infections could cause 10 million human deaths annually by 2050, with total costs by this date of 100 trillion USD in lost output [6].

Disease surveillance provides evidence for informed decisions on interventions and AMR surveillance is no exception [7, 8]. Surveillance of AMR is critical for impact evaluation of, for example, interventions that change guidelines of antimicrobial usage or infection control [9]. Moreover, it provides information on AMR emergence and occurrence relevant for the public, patients, health care providers, governmental agencies and researchers [7].

Despite the WHO calling for local, national and global AMR surveillance systems to be established [8], gaps in surveillance remain, primarily through lack of capacity and integration [10]. The United States' (US) National Action Plan, proposed the strengthening of a "One Health" national surveillance system (for humans, animals and environment) with improved international collaboration and capacity [11]. One Health however, also refers a broad, systems-based approach to complex problems [12]. It is therefore suited to AMR surveillance because it considers the underlying structural factors that influencing AMR, including the socio-political, material, biological and economic factors [13]. A One Health approach also includes an analysis of the context and institutional environment in which decisions are made across all levels of society [14].

In recognition of the above, this paper proposes a framework to promote a One Health surveillance system for AMR. Resistance is a global concern, with no regard of national borders, degree of healthcare sophistication or national GDP [15]. Despite this, not all regions of the world have promoted integrated AMR surveillance systems. To assess the level of integration, strengths, challenges and weakness, literature on the current global, regional (European) and selected European national surveillance systems is reviewed and positioned against the proposed framework. Whilst the economic benefits for a One Health approach to zoonotic infectious disease surveillance have been published elsewhere [16-19], this paper builds a business case for a One Health approach to AMR surveillance.

Why a One Health approach and fully integrated surveillance system?

The discussion of AMR is often focussed on human health outcomes. However, a broader consideration of the impacts on animal and environmental health is essential. Prescott (2014) [20], discussed the complex epidemiology of AMR and stated that "resistance anywhere is resistance everywhere". AMR is described as an ecological problem by Radhouani et al. (2014) [21], and as "a

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[1] AMR, although by definition refers to resistance of all microbes including bacteria, viruses, parasites and fungi, this paper and the majority of the literature uses the term with a bias towards bacterial resistance.

highly multifaceted topic at the interface of human, animal and plant health, food hygiene and environmental science" by Butaye et al. (2014) [22].

Antimicrobial usage (more specifically antibiotics)[2] and the resultant selective pressure has been recognised as the main driver for AMR [23, 24]. It is therefore essential to link antimicrobial usage data with AMR surveillance data when considering methods for AMR containment. The combined surveillance would also facilitate monitoring of the impact of interventions aimed to improve antibiotic stewardship and reduce consumption [9]. The widespread use of biocidal soaps and gels versus simple soap hand washing and the benefits of potentially reducing the spread institutional infections versus contributing to AMR is another area for consideration [25].

Rushton (2015) [14] stated that antimicrobials should be seen as a common good. In light of this, human behaviour and attitudes around antibiotic prescribing and use should be considered in both human and veterinary medicine. Decisions around antimicrobial usage in in livestock should consider the trade offs that occur between restoring animal health and productivity, provision of animal welfare and impacts on livelihoods, hunger and poverty alleviation, versus the risk of driving resistance [14]. Prescribing decisions of companion animal veterinarians are also influenced by affordability, ease of administration and perceived compliance [26]. The environmental impact of the management of human effluent, waste from livestock and aquaculture facilities and from manufacturers of pharmaceuticals is recognised as a potential hotspot for AMR [27].

These aspects are yet more evidence that a broad, contextual or institutional analysis is required when considering the use or misuse of antimicrobials [14]. A systems based approach to surveillance will better identify critical control points thereby improving effectiveness and economic efficiency.

One Health Framework for AMR Surveillance

A conceptual framework for a One Health approach to AMR surveillance is proposed here and illustrated in Figure 1. It centralises and integrates surveillance of both antibiotic usage or consumption for humans and animals, with AMR data from humans, animals, food and the environment.

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[2] In the context of usage, the literature's focus has been on antibiotics and impact on resistance in bacteria.
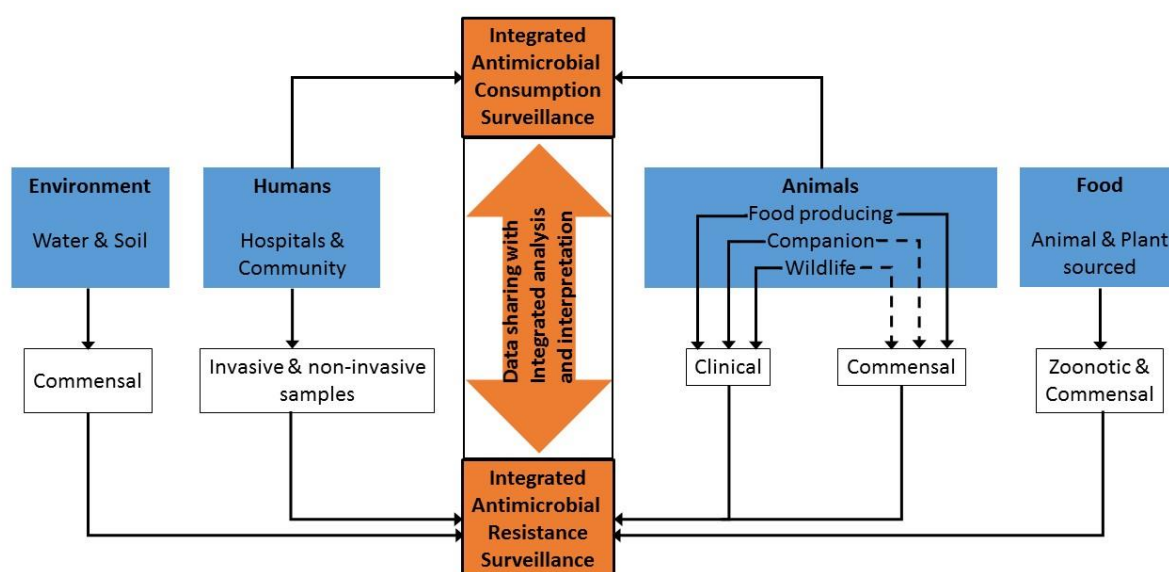
Figure 1: An interconnected and integrated One Health surveillance framework that puts at its centre antimicrobial resistance and antimicrobial consumption

Consumption data in humans is gathered in hospital and community settings, whilst in animals it is gathered at the species level i.e. food producing animals (including fish), companion animals and wildlife. AMR surveillance in humans includes invasive sampling of clinical cases from hospital and community care settings as well as non-invasive sampling of commensals. In food producing animals, isolates are accessed from clinical cases and commensals from healthy animals (available at slaughter). Similarly, samples of clinical cases in companion animals and wildlife are easily accessed through veterinarians, although commensals from both groups, especially wildlife may be less feasible. Surveillance of AMR in organisms isolated from food, includes food originating from animals and plants (zoonotic pathogen surveillance from the former and commensals from both). Environmental surveillance includes samples from water sources and soil.

Data collected within the various categories requires an integrated analysis, facilitated by teams with experience across the sectors. Similarly, interpretation of the analysis requires teams of sectoral experts who also possess inter-sectoral knowledge and understanding and the collaborative skills to work with those from other sectors, including social scientists and behaviour change experts. This is to ensure a One Health approach to developing the subsequent recommendations.

A centralised programme is required to set standards for data collection, which is critical at all levels for ease of analysis and interpretation. This will also improve communication and networking between disciplines and sectors through shared meetings, discussions and report editing. Centralised leadership and budgeting will be responsible for supporting and enabling peripheral capacity and compliance. However, this ideal, multi-dimensional, integrated surveillance may be difficult to achieve across all categories given the high level of capacity and logistics required and the commonly found barriers between siloed institutions. A tiered approach to integration may assist in building capacity. Within each tier, globally recognised techniques and standards must be adopted and adhered to. The initial tier would involve relatively standard collection, sharing and analysis of

data and therefore involve less integrated interpretation. The progression into the higher tiers would involve broadening data collection sources (from Figure 1). This would require a shift in institutional mind-sets to support the increasing degrees of co-operation and integration required to facilitate the analysis and interpretation of results and evolution of joint recommendations.

A review of current surveillance systems, from global to local

A review of the current global and European (regional and national) surveillance systems was conducted to identify degrees of integration, with attention to AMR and usage data, sectoral integration, which species and which food types and environmental elements were included in sampling.

1. Global Systems

The 2008 WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), has 31 internationally renowned expert advisors including representatives from the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation (FAO). Their aims include developing standardised sampling techniques and methodology, providing expert advice, promoting information sharing and supporting capacity building for AMR surveillance and antimicrobial usage in member states.

The Global Foodborne Infections Network (GFN) has public health, veterinary and food-sector professionals, all working towards a global integrated AMR surveillance system.

Codex Alimentarius (commissioned by WHO and FAO) includes a task force to integrate AMR surveillance in humans with that in food producing animals, crops and food.

WHONET is a WHO initiative to support harmonisation of global surveillance data by providing free software and training to laboratories in over 100 countries within all six WHO regions. The software facilitates standardised data collection and analysis and also informal sharing and networking.

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established in 2009 as a collaboration between the US and the EU. It aims to promote appropriate use of antimicrobials in human and veterinary medicine, prevent resistant infections in hospital and communities and improve development of new antimicrobials.

The Joint Programming Initiative on AMR (JPIAMR) is a research group which co-ordinates global research in AMR. Their One Health research agenda includes AMR in humans, animals and the environment.

2. Regional (European) Systems

The European Centre for Disease Control (ECDC) conducts surveillance for AMR and antibiotic consumption in human health through several networks.

- The European Antimicrobial Resistance Surveillance Network (EARS-Net) provides guidance to members on data collection, management, analysis and validation. It collates data from over 900 public health laboratories, which process samples from clinical cases in over 1,400 hospitals in 30 EU/EEA countries.

- The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) collates data on systemic use of antibiotics, antifungals and antivirals in hospital and community sectors from 32 EU/EEA countries.
- The European Food and Waterborne Diseases and Zoonoses Network (FWD-Net) is responsible for surveillance of human pathogens from water, food or animal contact. The data contributes to the European Food Safety Agency (EFSA) and ECDC annual summary report.
- The Healthcare Associated Infection Network (HAI-Net) coordinates AMR surveillance and antimicrobial use in acute (intensive care) and long term care facilities and the surveillance of surgical site infections

Surveillance of AMR in food producing animals and food products and veterinary antibiotic consumption are covered by the following:

- The European Centre for the study of Animal Health (CEESA) collects standardised AMR data for a central laboratory, from healthy animals at slaughter and clinically ill food producing and companion animals.
- The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) aims to collect harmonised data on the sales of veterinary antimicrobials (from wholesalers, veterinarians and pharmacies) so as to enable comparison with human consumption data. Its 4th annual report [28] included data from approximately 95% of food producing animals in 26 EU/EEA countries.
- The European Food Safety Authority (EFSA) collates AMR data within its surveillance of zoonoses and disease outbreaks from food and food producing animals. It supports EU members, providing guidelines on standardising sampling and processing, so as to harmonise data for analysis. It produces an annual summary report in conjunction with the ECDC.

In addition, the ECDC facilitates collaboration of surveillance groups with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). ESCMID has been active for over 25 years, with a wide range of study groups, some concerned with specific disease agents and others covering antimicrobial policy (ESGAP), antimicrobial resistance surveillance (ESGARS) and veterinary microbiology (ESGVM).

In 2012, building on the success of the ECDC programs, EARS-Net was expanded and the Central Asia and European Surveillance of Antimicrobial Resistance Network (CAESAR) was established.

3. National systems

The WHO's Global Report on Surveillance of AMR [10], is based on data from the 129 contributing member states. The report highlighted individual national systems which attempt to integrate surveillance in humans, food producing animals and food. (Table 1).

Table 1: Antimicrobial resistance surveillance systems [10]

	Surveillance of resistant bacteria from					Bacterial species included				
	Healthy animals	Diseased animals	Food	Healthy humans	Diseased humans	Salmonella	Campylobacter	Escherichia coli	Enterococci	Animal pathogens
CIPARS Canada	X	X			X	X	X	X	X	X
DANMAP Denmark	X	X	X	X	X	X	X	X	X	X
FINRES-VET Finland	X	X	X		X	X	X	X	X	X
GERM-VET Germany		X				X		X	X	X
ITAVARM Italy	X	X	X		X	X		X	X	X
JVARM Japan			X			X	X	X	X	
NARMS United States	X		X		X	X	X	X	X	X
NETHMAP/MARAN Netherlands	X	X			X	X	X	X	X	X
NORM/NORMVET Norway	X	X	X		X	X	X	X	X	X
ONERBA France	X	X	X		X	X	X	X	X	X
SWEDRES/SVARM Sweden	X	X	X		X	X	X	X	X	X

Several national systems within EU states have been guided towards integration through the direction of the European regional systems as mentioned in the previous section. Longstanding examples include the following:

i.   The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) was established in 1995 as a collaborative programme between the Ministry of Health and the Ministry of Food, Agriculture and Fisheries. DANMAP has implemented a "farm to fork to sickbed" approach to surveillance [29] to include the whole supply chain. Sampling includes human and animal clinical cases, healthy animals (randomly at slaughter) and locally produced and imported meat products at wholesale and retail outlets. Consumption data is collected from hospitals, primary health care centres and from pharmacies. Veterinary medicine usage is registered at a species level (food producing animals (including fish), and companion animals) by veterinarians, pharmacies and feed mills.

ii. The Swedish Strategic Programme Against Antibiotic Resistance (STRAMA), founded in 1995, aims to preserve antimicrobial agent effectiveness in public health. The Swedish Veterinary Antimicrobial Resistance Monitoring Programme (SVARM) was established in 2000. STRAMA has produced an annual report (SWEDRES) on antibiotic use and resistance in humans since 2001, whilst SVARM's annual report covered AMR surveillance in zoonotic bacteria, specific animal pathogens, commensal enteric bacteria and bacteria from food of animal origin.

Since 2011, a combined, integrated SWEDRES/SVARM annual report has been published, demonstrating inter-sectorial collaboration.

iii. The Netherlands has, since 2003 produced NethMap, an annual report on AMR and antibiotic consumption trends in humans. MARAN, the veterinary surveillance system, has done the same for food producing animals and also includes isolates from vegetables, fruits and herbs. Since 2012 a single, combined (NethMap-MARAN) report has been published.

Challenges and shortcomings, recent developments and future improvements

The review demonstrates evidence of broader sampling, integration and shared analysis, however, thus far no fully integrated and standardised surveillance system for AMR and antimicrobial usage, which functions both locally and globally, exists. A lack of data quantity and quality persists, the latter affected by a lack of standardisation [30]. There is still insufficient comparable data of AMR in humans and livestock to develop global mapping of resistance and allow accurate comparisons between humans, various livestock species, industries, countries or regions [31].

In 2012 the WHO published results of a survey of existing surveillance networks [32]. Five international and 22 national networks responded. Only 30% had a nationally coordinated body, whilst less than 40% had formal quality assurance requirements whilst antimicrobial usage data was generally absent. In the WHO's Global Report on Surveillance of AMR [10], there was no formal consensus on methodology and data collection among the 129 contributing member states. At the European level, although EARS-Net advises and encourages standardisation using EUCAST guidelines, only 64% of the participating laboratories do so [23]. Global systems are reliant on data collected nationally. Therefore, standards within data collection need to be applied at source to allow meaningful interpretation at all levels, which will require significant investment in developing capacity. Therefore, in the next section we discuss a business case for a One Health approach to AMR surveillance.

The business case for a One Health approach to AMR surveillance

Whilst Babo Martins et al. (2015) [19] provided a framework for a broad economic assessment of integrated zoonotic disease surveillance in a One Health context, publications showing direct measureable impacts of AMR surveillance and interventions from a One Health perspective were not found. Similarities exist between the business case for AMR surveillance and of emerging zoonotic infectious diseases. In both cases their unpredictable nature makes economic evaluation dependant on assumptions and/or predictive modelling, which are often subject to considerable uncertainty. Appreciating the broad complexity and interconnectivity of human, animal and environmental outcomes, a One Health, systems-thinking approach is needed to measure the benefits of investment in integrated surveillance. Evaluation of economic and empirical scientific aspects must be blended with an appreciation of the social, cultural and ecological aspects [33]; the less tangible and non-monetary outcomes should be considered in addition to the monetary. These less tangible benefits include knowledge creation, social and intellectual capital, reduced anxiety, political reassurance and technical capacity building. Whilst these not always easily quantifiable, they should be considered nonetheless [19].

Table 2 summarises the costs and benefits envisaged from integrating surveillance of AMR to a One Health level and also the costs and benefits of the integrated interventions arising from the One Health surveillance.

Table 2: Summary of costs and benefits of One Health AMR surveillance and resultant interventions

Integrating AMR Surveillance to a One Health level	
Costs	**Benefits**
1. Costs of design and setup including time to agree on common goals, new roles and duties, dispersal of funding and resolving issues of conflict. 2. Costs of training staff in interdisciplinary work. 3. Costs of additional staff, expert consultants, joint consultations and meetings. 4. Costs of collating additional data and joint analysis and communication of results. 5. Additional costs for extending the breadth and depth of coverage of surveillance.	1. Improved service delivery 2. Improved efficiency by sharing scarce resources or better use of underutilised resources. 3. Social capital gains through sharing skillsets and networking. 4. Improved synergies between empirical, social, environmental and ecological sciences. 5. Enriched and more efficient research outcomes. 6. More timely and accurate identification of risks through broader surveillance and integration. 7. Improved, more timely and efficient interventions based on improved risk assessments.
Integrated interventions arising from One Health Surveillance	
Costs	**Benefits**
1. Increased costs of wider interventions across human and animal health and the environmental sectors. 2. Potential increased costs of livestock production through use of improved biosecurity in contrast to prophylactic use of antibiotics.	1. Broader benefits across sectors arising from a systems approach vs. narrow reactionary solutions. 2. Improved and broader valuation of benefits by including intangible societal and environmental benefits. 3. Reduced health care costs (prevention of longer hospitalisation, more expensive drugs, intensive infection control measures etc.) 4. Decreased morbidity and mortality. 5. Prevention of reduced workforce productivity due to prolonged recovery or caring for relatives. 6. Prevention of costs of litigation against hospital and staff. 7. Prevention of lost income through reduced cross border travel and tourist income, and from reduced trade in live animals and food of animal origin. 8. Reduced cost of animal health care and infection control in food producing animal systems. 9. Prevention of increased cost in foodstuffs from animal origin. 10. Improved consumer confidence in food safety. 11. Improved ecosystem resilience.

Although costs are incurred in the setup of or conversion into a One Health system, savings are expected from the effects of shared and more efficient use of resources, shared running costs and improved outcomes. Using the H5N1 (HPAI) campaign as an example, the World Bank estimated cost savings of 10-30% from joint investment and 20-40% in costs of ongoing surveillance through shared staff and facilities. Further savings in training and research are estimated at 5-10% [34].

Surveillance benefits primarily relate to those arising from the interventions it spawns. Interventions are often delayed whilst sufficient data is collected and analysed. Benefits may not be immediate (e.g. the impact on public health outcomes from reduced antimicrobial use) and may also be confounded by several factors over time [35]. Global travel is an example; despite Denmark's attempts to control resistance in *Campylobacter*, 37% of campylobacteriosis cases in humans were

related to international travel, with a higher proportion of these being resistant compared to domestic cases [29].

Positive knock-on effects also need to be recognised. Denmark's integration of antimicrobial consumption data with resistance data, identified specific links, resulting in improved public awareness and government policy [36], which included a ban of the use of certain antibiotics in livestock and restrictions on veterinarians' profits from antibiotic sales [37]. In addition, a voluntary ban against using cephalosporins and fluoroquinolones in food producing animals followed. As a result, food producing animals in Denmark consume 80% less antimicrobials per kg of meat produced that those in the USA [37].

A greater understanding is required of the wider implications and costs of AMR on society. Implications include changes in health seeking behaviour e.g. avoiding invasive procedures because of the (perceived) risk of untreatable infections [2], increased hospital infection control measures, litigation and reduced international travel and trade [38]. Furthermore, reports on the costs of unchecked AMR fail to consider the impact on the food producing animal sector and the effect on livestock dependent communities and national economies. The costs of untreatable livestock diseases, increased biosecurity costs and the costs of lost consumer confidence in the safety of food of animal origin as well as animal welfare issues need to be included.

Discussion

Recent calls to improve the integration of AMR and consumption surveillance are welcomed. This complex, interconnected problem with negative externalities will require international inter-sectoral collaboration. It therefore favours the application of a One Health approach to the surveillance systems, the interventions and the evaluation of outcomes.

The European national surveillance systems reviewed in this paper all fall short of the One Health framework presented above, with none mentioning the environment or wildlife. DANMAP is the only national system to include commensals from healthy humans but lacks data from companion animals. The Netherlands has extended its surveillance in foodborne microbes to include non-animal origin foodstuffs.

The recommendations for a One Health approach at a global level by JPIAMR, the White House and WHO will hopefully influence those national systems committed to being part of the global system. The significant challenge to build capacity at local and national levels persists. Modern technology may hold some solutions to data management but using high tech systems in remote, underdeveloped regions may be difficult. Yet developing countries will potentially have the greatest influence on the future of AMR. Global investment is needed for capacity building to improve the control of hospital infections, control antimicrobial usage in food producing animals and control the sale of antibiotics without prescription and counterfeit drugs [39,40]. The inclusion of their surveillance data is therefore crucial.

The Who identified data quality as the major shortcoming of existing systems. Without standardised laboratory techniques and reconcilable data, meaningful analysis and constructive interventions will fall short of expectations. Once laboratory standards and methods of data recording are agreed on, the surveillance systems should develop and extend to incorporate as much of the One Health framework as possible, with increasing degrees of integration.

Conclusion

As the increase in antimicrobial resistance continues and fewer new drugs are being developed, calls for action to avert the impending crisis of a "post antibiotic era" are being heard. To promote effectiveness and economic efficiency, interventions need to be designed from sound evidence gained from surveillance. A broad One Health approach to the evidence gathering surveillance, data analysis, intervention design and evaluation is proposed. Given the scale of the problem and the expected socio-economic costs, the additional monetary, social and time investments are likely to be recovered by the resulting benefits, which include quantifiable financial efficiencies and improved human and animal health outcomes. In addition, if one looks broadly and includes the less tangible benefits to society (open trade and travel), animal welfare, ecosystem health and environmental resilience, then the business case for a One Health approach to AMR surveillance is strengthened.

Based on the framework presented in this paper, the development of a One Health surveillance system is called for. Its foundation must be based on standard laboratory techniques and data management, which can be integrated, compared and interpreted at all levels. This will require global and local governance to work together. Widening the scope of surveillance to include all aspects within the proposed framework can be built on this foundation over time but may require a shift in institutional mind-sets.

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