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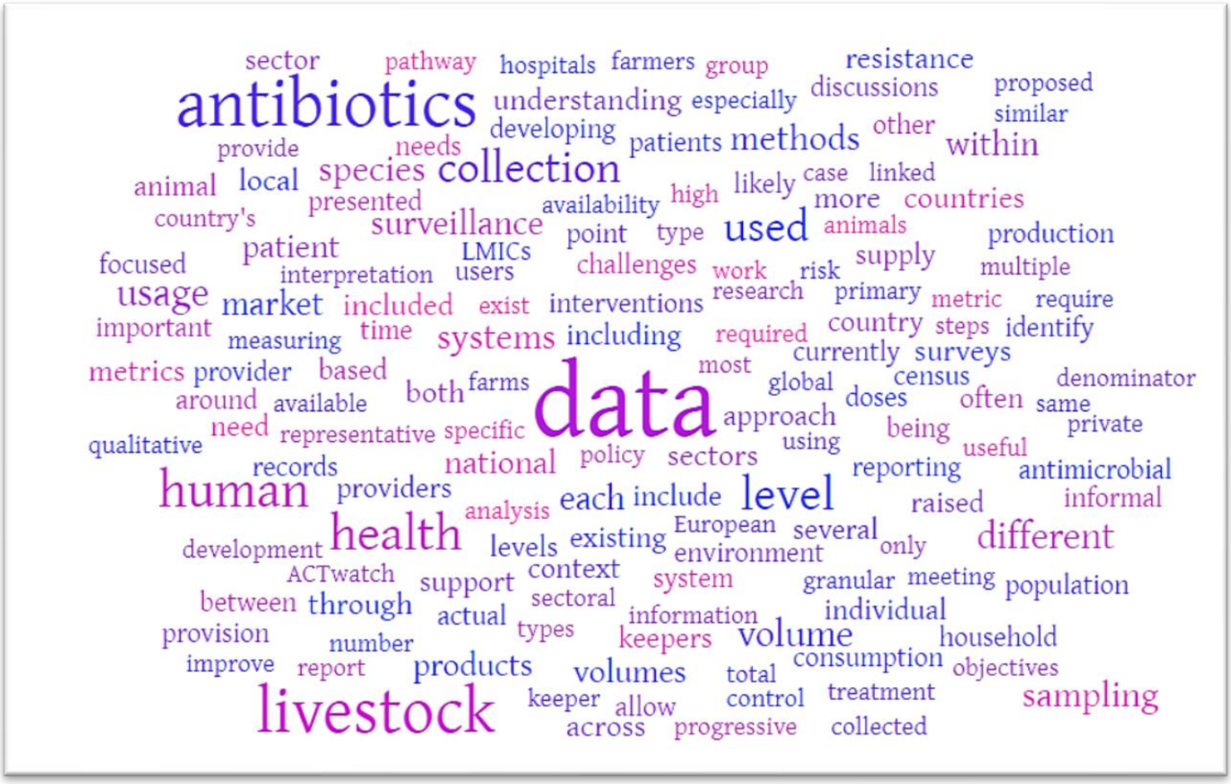
Meeting report:
Metrics and methods for assessing antibiotic use at the granular level in humans and livestock in LMICs

21st & 22nd November 2017
London

Kevin Queenan, Clare Chandler and Catherine Goodman



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Acknowledgements

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Special thanks goes to all those who took part in the meeting (Appendix 1), for their willing and active participation and valued contributions, which we have endeavoured to include in this report.

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Executive summary

The causes of antimicrobial resistance (AMR) are complex. The overuse of antibiotics is widely recognised as a contributing factor, and usage data collection is central to the global surveillance plans of the World Health Organisation (WHO) and the World Organisation for Animal Health (OIE). Interventions relating to antibiotic use in both the human and livestock health sectors typically focus on the lower level i.e. prescriber, dispenser or end user. However, since data at this level is challenging and costly to collect, it is typically scant, especially in low and middle income countries (LMICs). A rapid review of existing methods to collect such granular usage data in LMICs revealed a number of important gaps in this literature, and in particular very few protocols designed to generate volume metrics. Following-on from the review, this workshop sought to bring together a unique combination of researchers, policy makers and funders from both the human and livestock health sectors, with expertise in AMR and antibiotic use. It aimed to facilitate inter-sectoral, interdisciplinary and One Health discussions around the needs for usage data and suitable collection methods.

Global strategies were presented by the WHO, OIE and Fleming Fund. As part of WHO's aim to facilitate more disaggregated national reporting of antimicrobial use (AMU), it will soon publish methods at the hospital level, and in 2018 will begin developing methods at the community level. In 2015, the OIE began building a global database of antimicrobial use in animals, which includes three levels of increasing disaggregation of data, by which countries can report. However, to date, of the seven countries reporting usage at the farm level, only one is a LMIC. The Fleming Fund aims to support the development of in-country capacity building for their National Acton Plans for AMR surveillance, and sees antimicrobial usage surveillance and the One Health approach as key elements.

From the presentations and discussions several key themes emerged for considering metrics and measurement of antibiotic use at a granular level. (i) Objectives for collecting usage data are multiple and will shape selection of metrics and measurement approaches. Granular level data, that disaggregate the volume of antibiotics in use by different provider types, different patient / animal cases, and across different sectors and locations, were proposed to be useful for intervention targeting and evaluation as well as for understanding drivers of antibiotic resistance. It was agreed that ideally such data should be collected to represent a full One Health approach in order to inform cross-sectoral action. (ii) Heterogeneity of antibiotic provision systems and products is pronounced and needs to be accounted for in data collection planning. For example, supply systems are diverse between countries and sectors, and they sometimes overlap between animal and human health; there is a diversity of antibiotic products and they are not always easily recognised by respondents and antibiotics are used for different purposes and at different dosages. (iii) Quantitative metrics alone were considered inadequate to capture antibiotic use, and a mix of data collection approaches may be required to inform data collection and interpretation. Involvement of policy, implementation and research expertise is valuable in the planning as well as data collection processes. Capacity, resources and existing access to data may mean a staged framework for data collection could be useful. (iv) Different sampling strategies may be required at different stages of investigation and for different objectives. The optimal sampling approach will vary by level and stratum of the supply system, and a One Health approach will likely require more than one sampling approach. (v) Volume metrics, especially relative volumes by different sectors, areas, providers and case mix, were seen as valuable. To be useful for AMR, volume data must be presented using a metric based on the total population at risk. The most promising metric for use across human and livestock populations was suggested to be mg of antibiotic per weight, taking into account the 70 kg adult human and the population correction unit for livestock biomass. (vi) Volume data collection tools require further development. As well as needing to be relevant for given contexts – case mix, species mix, supply systems – data collection needs to cater for reliability of data sources where different incentives, regulations and levels of black market activity are prevalent. Volume data should be interpreted alongside actual use at the patient and farmer level. Lessons can be transferred across from other attempts to establish a total market approach, such as with antimalarials. A key advantage of such total market approaches is that relative market shares can be calculated across provider types, sectors and antibiotic classes.

Suggested priorities as next steps included the following: (1) create a sharing platform and a community of practice, (2) establish a working group to develop a progressive pathway for antibiotic use surveillance for countries to position themselves within, (3) increase dialogue between AMR modellers and AMU experts to improve the applicability of use data for analysing the drivers of resistance, and (4) develop small pilot case studies across several different country and regional sites.

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Abbreviations

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	Antimicrobial resistance
AMU	Antimicrobial usage
ATC	Anatomical Therapeutic Chemical
CGIAR	Consultative Group on International Agricultural Research
DDD	Defined Daily Dose
EPN	Ecumenical Pharmaceutical Network
FAO	Food and Agriculture Organisation
GAP	Global Action Plan
GLASS	Global Antimicrobial Resistance Surveillance System
GPS	Global Positioning System
HICs	High-income countries
IHH	Improving Human Health
INRUD	International Network for Rational Use of Drugs
ITM	Institute of Tropical Medicine (Antwerp)
LMICs	Low and Middle-income countries
LSHTM	London School of Hygiene and Tropical Medicine
OIE	World Organisation for Animal Health
PCU	Population correction unit
PPS	Point prevalence survey
ReACT	Action on Antimicrobial Resistance
USD	United States Dollar
WHO	World Health Organisation

Introduction

The causes of the global threat of antimicrobial resistance (AMR) are complex but the overuse of antibiotics in both the human and livestock health sectors is widely recognised as a contributing factor, and data collection on antibiotic consumption is central to the global surveillance plans of the World Health Organisation (WHO) and the World Organisation for Animal Health (OIE). Antibiotic surveillance typically begins with collation of national / aggregate sales figures, although this is often incomplete, especially in low-income and middle-income countries (LMICs). There is even less data available on antibiotic use at the *granular* level i.e. on provision by individual provider type and use by individual patients or livestock keepers. Interventions aimed at reducing risk are often aimed at this level, so maximising their effectiveness will require addressing this gap in rigorous and representative granular data in both the human and livestock health sectors, ideally within a unified One Health framework.

Collection of data at this granular level is resource intensive and challenging given the complexity of the human and livestock health systems. In human health, the provision of antibiotics in LMICs is often through complex, pluralistic health systems and private providers often have a major role, including those with very limited qualifications. We need to know how the antibiotics consumed by humans are distributed across these provider types, across different disease syndromes, and across different socio-economic groups, and how this varies by antibiotic class. In the livestock sector the private sector is usually the dominant provider. Antibiotics are used in livestock at varying doses in different species and for reasons beyond just therapeutic (e.g. prophylaxis, growth promotion). In the agricultural domain, we need to know how antibiotic use is distributed across supplier type, farm type, animal species and purpose, again by antibiotic class.

In preparation for this meeting, a rapid scoping review of the literature was conducted to identify the range of methods available for collection of antibiotic use data at the granular level in LMICs for both human and livestock health. The aim was not to conduct a systematic review of all publications involving measurement of antibiotic use, but rather to provide an overview of the types of guidance and studies currently available, and the characteristics of their data collection procedures. It included both standard survey tools and protocols (e.g. from WHO and OIE publications) and methods from published research studies (48 human and 30 livestock papers). In summary, the review showed that, whilst considerable experience, expertise and a number of valuable resources exist for collecting antibiotic use data, there are also a number of gaps. The majority of the standard tools from human health produce indicators to assess rational use of medicines, availability and affordability of medicines, or provide a rapid assessment of problem areas in prescribing behaviours and usage either within hospitals, licenced retailers or community members. However, they are not designed to generate outputs associated with usage of antibiotics by volume. Within the livestock sector, the standardised tools were limited to the OIE's global database at the national level, with none found at the granular level. No standardised tools were identified from a One Health perspective. Within the published research studies, geographical coverage was very patchy both across and within countries, with only a few hospital studies having nationwide representation, and rural areas were generally underrepresented. Most human health and livestock papers had relatively small sample sizes and, apart from studies on registered health facilities and pharmacies, it was often unclear whether the sample was drawn from a complete sampling frame. Only a minority of human health and livestock papers produced Defined Daily Dose (DDD)[1] related metrics, and only one study (livestock) was identified, which compared different data collection methods for measuring antibiotic volumes.

[1] DDD is the assumed average maintenance dose for a drug for a 70 kg adult for its main indication

Research papers tended to focus on one, or at most two provider or livestock keeper types. Most standard protocols and papers for human health focused on registered health care facilities and drug outlets, with relatively few including informal providers, and none including itinerant drug sellers and market stalls. Coverage of livestock keeper types was also patchy, with many papers giving insufficient information about livestock keeper type. Livestock papers were typically species specific, with poultry and aquatic species predominating, and no studies including all livestock. Finally, no resources or papers, which we identified, adopted a total market approach i.e. none included all providers of antibiotics within a given geographical area. The review concluded that considering a total market approach (whilst being demanding in terms of logistics and creation of comparable tools across providers), would be very valuable to assess the relative market shares of antibiotic use across different provider types.

Following-on from the review, this workshop was organised by the London School of Hygiene and Tropical Medicine (LSHTM) and supported by the Improving Human Health flagship project of the CGIAR research program on Agriculture for Nutrition and Health (A4NH). It aimed to facilitate inter-sectoral and interdisciplinary discussions by bringing together a unique combination of researchers, policy makers and funders from both the human and livestock health sectors, with interest and expertise in antibiotic resistance and the linkages with antibiotic use (Appendix 1: List of participants).

The workshop objectives were to:

i. Review the methods and metrics for collecting granular data on antibiotic use in LMICs
ii. Identify key data needs for policy making
iii. Identify challenges involved in collecting robust and comparable data both within and across the human and livestock domains, and
iv. Discuss the next steps in developing methods and metrics for widespread, One Health use in LMIC.

The workshop was held over two days and details of the agenda are in Appendix 2. It began with an introduction by Jeff Waage and Clare Chandler (LSHTM), followed by an overview of the global strategies on antimicrobial resistance and use, with presentations by Wenjing Tao from WHO, Delfy Gochez from OIE, and Toby Leslie from Mott MacDonald/ Fleming Fund. This was followed by a presentation by Catherine Goodman (LSHTM) on framing the types and purposes of antibiotic use data. The findings of the pre-workshop review were presented followed by several presentations by individual researchers on methods they have used in the field in both the human and livestock health sectors. Question and answer, and discussion sessions were conducted throughout. Day 2 included a presentation by Catherine Goodman on ACTwatch, as an example of a total market approach to gathering granular data on antimalarial drugs. To kick-start the discussion session, Koen Peeters (ITM), Mirfin Mpundu (ReACT/EPN) and Suzanne Eckford (FAO) were asked for their reflections on the meeting so far. This was followed by a small group breakout session to discuss three of the main areas of interest which had arisen from the meeting so far, namely i) metrics for measuring relative volumes, ii) sampling strategies, and iii) mixed methods approaches for data collection. The key points from the small groups were presented followed by an overall discussion on next steps and a wrap up by Jeff Waage.

This report begins with an overview of the key points from the WHO, OIE and Fleming Fund in order to situate the discussions within these global strategies. We then present a synthesis of the main themes and key points raised by participants during the workshop discussion sessions and the feedback sessions from the small groups. The report concludes with suggested next steps.

Global strategies

The WHO, in their global surveillance program for antibiotic consumption[2], uses the term *consumption* when estimates are based on aggregated data sources, such as import or wholesaler data, whereas *usage* is defined as estimates derived from patient level data. The WHO's strategy in collecting antimicrobial use (AMU) data is to gather data at the higher *consumption* level as a starting point and where available, to work towards data gathering at the lower levels including patient *usage* data. National consumption level data should be reported according to the Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) used per population at risk per unit of time (i.e. DDD/population unit/time). Wenjing Tao presented the progress being made by WHO in developing methodologies for surveillance at the patient level in LMIC, firstly in hospitals and secondly at the community level. The hospital methodology is currently being finalised, using a point prevalence survey (PPS) methodology, and will be published by the end of 2017. This methodology is adapted for use in LMICs from the European Centre for Disease Prevention and Control protocol for PPS of Healthcare Associated Infections and Antimicrobial Use in European Acute Care Hospitals and from the Global PPS. Details on sampling and data collection are included in the pre-read scoping review. Data are collected at three levels: facility, hospital ward and individual patient level. Patient data are retrieved from records, avoiding direct patient contact. Based on European data, over 90% of antibiotic use is within the community, although the proportions in LMICs are less well known. The WHO is therefore developing a methodology in 2018 for use in communities (at primary care, pharmacy and household levels). It will build on existing protocols, draw on experiences from research projects and expert and stakeholder involvement, including outputs from this workshop.

The OIE's strategy on AMR and prudent use of antimicrobials was presented by Delfy Gochez. It has four main objectives: to improve awareness and understanding, to strengthen knowledge through surveillance, to support good governance and capacity building and to encourage implementation of international standards. In 2015, the OIE began building a global database on antimicrobial agents intended for use in animals and published their first report in 2016. The disaggregation of data is dependent on its availability within each participating member country. Three reporting options exist as presented in Figure 1 below, with varying levels of disaggregation. Of the 130 participating countries, the number reporting farm level usage was seven, only one of which is classified as a LMIC (Figure 2). Usage levels are currently reported in kg of active ingredient. Progress is being made to express this with a denominator of kg of animal biomass. Currently, reporting is on a voluntary, self-reporting basis and individual countries can choose not to have their data made public.

The Fleming Fund's aims were presented by Toby Leslie. They included assisting in-country capacity building to support implementation of National Action Plans within the Global AMR surveillance System (GLASS). Key principles behind their support include country ownership, alignment, sustainability and a One Health approach. The funding scope includes building capacity in laboratory infrastructure and human resources, strengthening AMR surveillance systems (including AMU) and initiatives for promoting rational use of antimicrobials. Toby proposed that both high level (consumption) and low level (use) data are needed and should be integrated within AMR surveillance systems.

[2] WHO Methodology for a global programme on surveillance of antimicrobial consumption

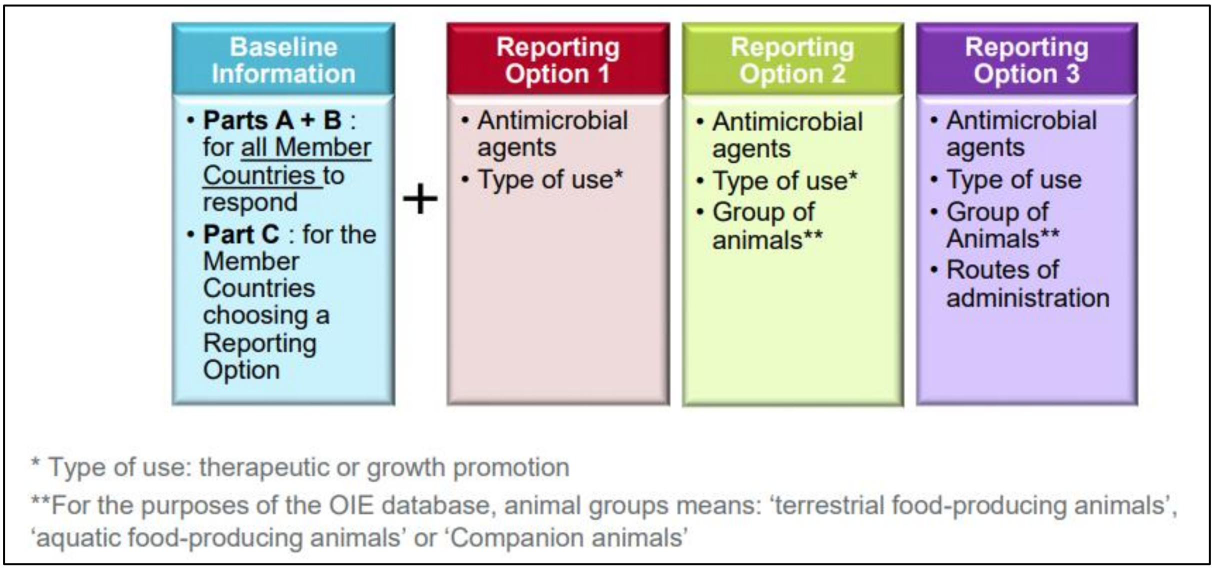

Figure 1: Reporting options for OIE global database on antimicrobial agents intended for use in animals (Source: D. Gochez, OIE)

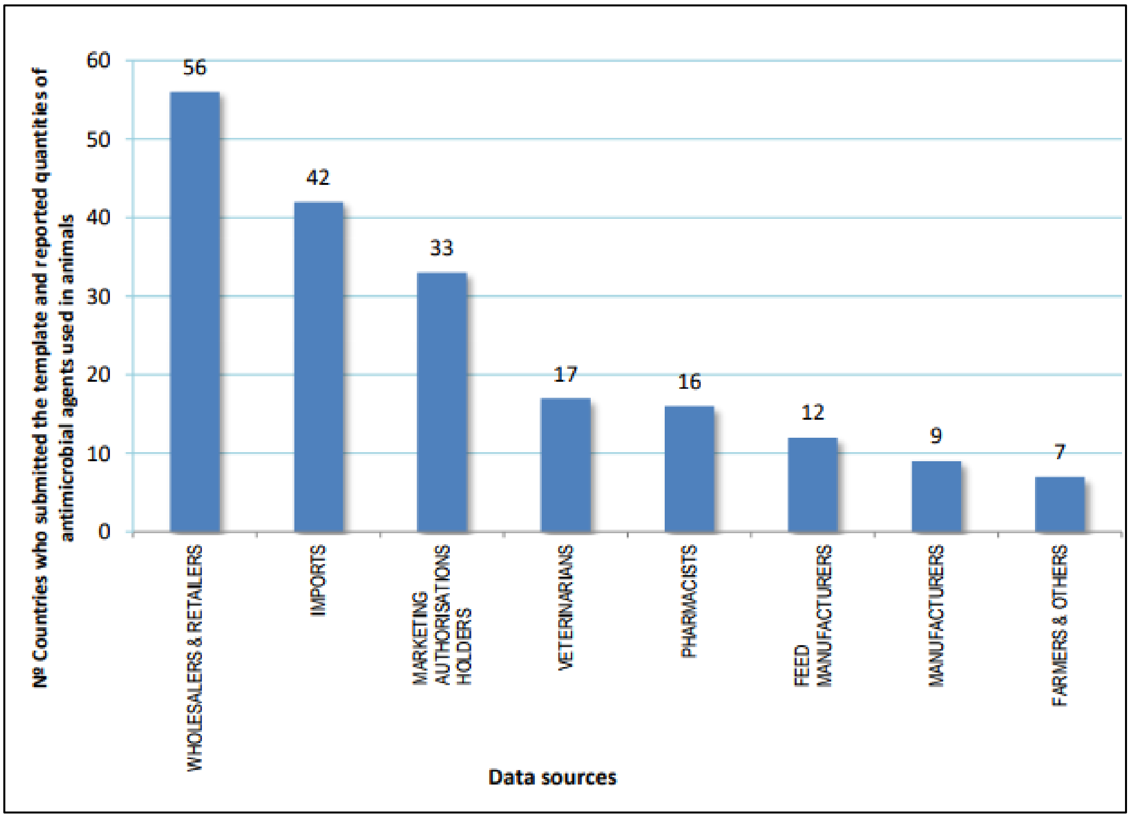

Figure 2: Number of countries reporting data to OIE global database on antimicrobial agents intended for use in animals, by source (Source: D. Gochez, OIE)

Emerging themes and key points raised

Objectives of usage data collection

Why do we want to know about antibiotic use? A crucial first step in designing AMU data collection is to specify the objectives to be addressed, acknowledging that these may be multiple (Figure 3). The objectives will determine the level of data collection, e.g. appropriate use studies may require data at patient and farm level, studies on regulation or policy compliance may need to focus on data at outlet level, whilst those focusing on drug resistant infections may need hospital in-patient data. The objectives will also influence the scope of data collection, the sampling strategies employed (see section on Sampling below), and the choice of AMU indicators. In addition, it could be beneficial if data were collected in such a way that presentation using several metrics was possible, to facilitate use for more than one purpose. The objectives will also influence the degree of rigour required in data collection. For example, where data are to be used to monitor disaggregated trends over time or to evaluate interventions and policies it will be important to ensure the data are representative and collected in a rigorous manner. However, Kathy Holloway (WHO/ IDS) proposed that, from her experience within the WHO's country situational analyses, if the aim of collecting usage data is to change behaviour or policy maker attitudes on use, then complete data may not be necessary, and the highlighting of certain particularly inappropriate behaviours may be sufficient to initiate change.

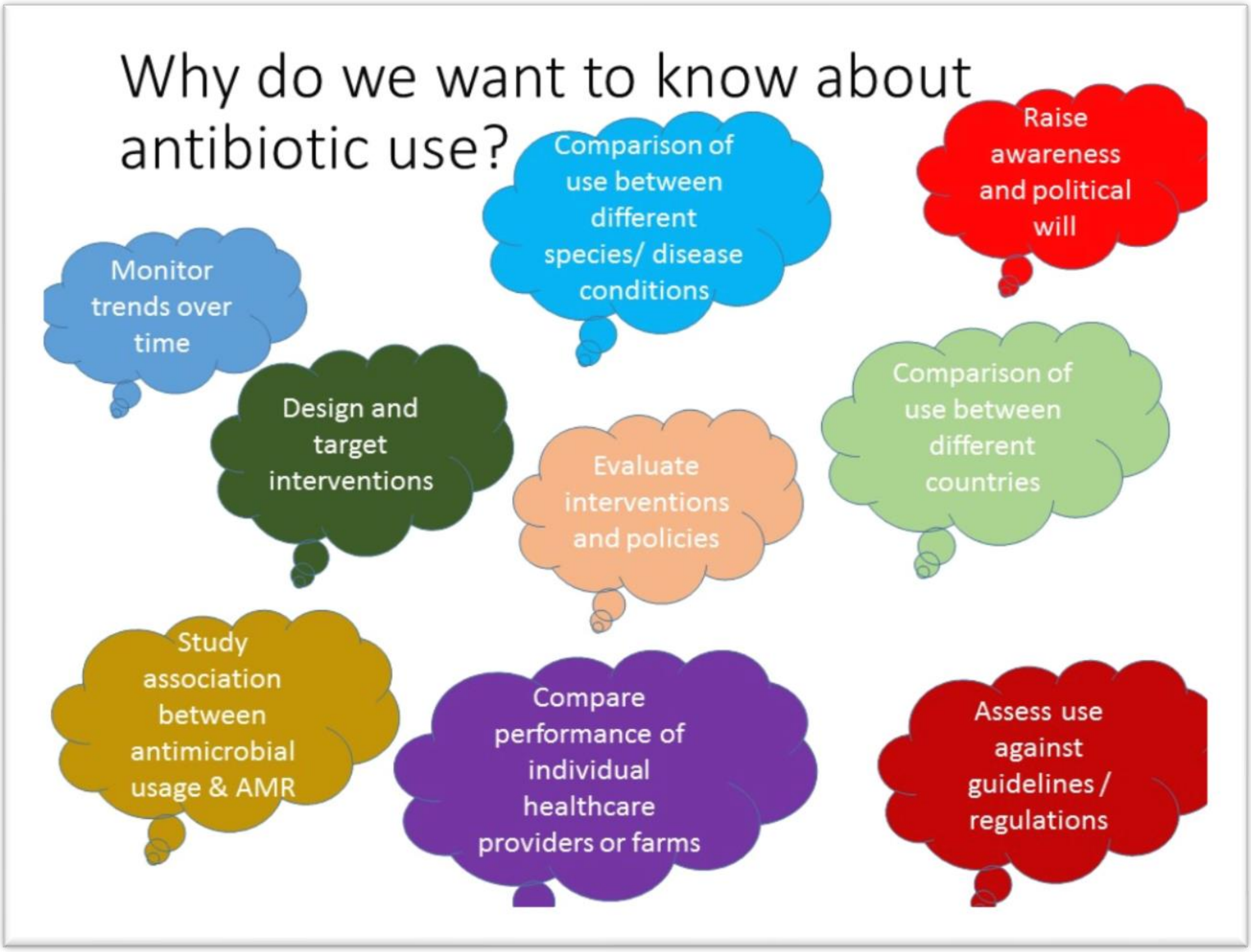

Figure 3: Multiple potential objectives of collecting antibiotic use data (Source: C Goodman LSHTM)

What is granular data and what purpose does it serve? As indicated above, consumption data refer to aggregated antibiotic volume data, generally at the national or state level. Within both human and livestock health sectors consumption data are useful for comparisons between countries or regions, for monitoring use over time and for assessing impact of high-level policy. However, such high-level data cannot be used to assess how antibiotics are actually used, or where to target interventions. Moreover, such data may be vulnerable to both gaps (particularly failing to fully cover the informal sector), or overlaps (where data for example from importers and wholesalers can end up double-counting some medicines). Usage data are defined as estimates derived from patient level data and may include disaggregation to the level of specific patient characteristics (age, gender, livestock species or diagnosis). Granular data were defined as encompassing patient level use but also including usage measured as volumes moving through the final level providers (e.g. hospitals, retail shops, vets etc). Granular data can provide information on volume and type of antibiotics distributed across provider types, and across end user types (livestock keepers, households). AMU data at the granular level can be used for surveillance, for target setting, for monitoring interventions or for behaviour change and communication of risks.

Reporting usage data could reflect the ranking of critical and important antibiotics. Antibiotics have been ranked according to their relative clinical importance in both human and veterinary medicine, and it was suggested that disaggregating these when reporting usage data would be useful. Antibiotics could also be reported according to the Access, Watch and Reserve categories of WHO Essential Medicines List.

Antibiotic use data needs to be relatable to resistance data for interpretation. From the meeting's discussions and presentations including those from the WHO, OIE and the Fleming Fund, it was clear that it would be optimal for national AMR surveillance systems to include both AMR and AMU. In addition, several participants made the point that we should consider carefully the type of AMU data required in order to enhance our understanding of the *relationship* between AMR and AMU. It was noted that for malaria, resistance is only driven through use and misuse in patients who have malaria parasites. Antibiotics however, have the potential to drive resistance in the microbiome of every human or animal receiving them, and equally in the environment if not correctly disposed of. Therefore, the way volume and usage data are interpreted in relation to resistance data will be more complex and may not be linear.

A full One Health approach would include humans, animals, plants and the natural environment. It was acknowledged that it would be a major step forward to integrate data collection on AMU in humans and livestock only, and that this may be likely to capture the bulk of usage volumes. However, it was also noted that this does not cover the full scope of One Health. The amount of antibiotics used in crop agriculture and horticulture is largely unknown, and use in other animal species, especially companion animals who often live closely with their human owners, would also need to be included. It was also proposed by Tim Robinson (FAO) that a focus on "usage" implies ignoring the issue of antibiotic waste and disposal (at the level of manufacture, facilities and end users) and the impact of this on the environment and resistance. In other words, the environment while not a "user" does bear the burden of waste and needs to be considered in metrics and measurement. Measuring "use" should therefore consider the eventual fate of all antibiotics, including those not used but discarded, and a full One Health approach should consider the collective impact of use on resistance in humans, animals, plants and the environment.

Managing objectives within individual country contexts and surveillance capabilities: Participants recognised that data collection on consumption and usage should be tailored to the individual country's systems of antibiotic provision, for example reflecting the importance of more formal /

informal channels in given settings. Kathy Holloway's presentation of country situational analysis raised the importance of understanding and mapping out the individual country's pharmaceutical situation as a precursor to such tailored volume data collection. AMU surveillance strategies will also need to reflect country data collection capabilities and financial capacity. It was proposed that a coordinated but tiered approach to AMU data collection could be helpful, with countries with varying capacities adopting different intensities of AMU surveillance strategies (see below).

Heterogeneity of provision systems and products

A high level of heterogeneity was recognised within both the human and livestock sectors, across antibiotic providers and end users, and within the antibiotic classes and products themselves. Much discussion was dedicated to consideration of this heterogeneity in the design of data collection.

The antibiotic supply systems in both human and livestock health are complex and diverse. Supply systems for antimalarials and antibiotics in human health are equally pluralistic, with a wide mix of public, not-for-profit and formal and informal for-profit organisations. Private and for-profit providers are especially diverse across all levels including corporate hospitals, small private hospitals and clinics, pharmacies and the various drug retailers and vendors. Within the livestock antibiotic supply system, although the range of providers may be smaller than in the human health sector, there is still a wide range of suppliers including corporate suppliers and pharmaceutical reps, local veterinarians, agri-stores, formal and informal drug retailers and feed retailers. These different suppliers are often linked to different production systems, and may vary in their importance across different classes of antibiotics.

There is a great diversity of antibiotic products in both the human and livestock sectors. There is a very high number of antibiotic brands and generic products available, in a range of formulations, across the spectrum of different antibiotic classes, far greater in number than, for example, antimalarials. Just the task of building a list of locally available products to assist in training fieldworkers can require considerable work, as discussed in Elizabeth Rogawski's presentation on conducting household surveys. Photocards of individual products have been useful to jog memories of respondents during surveys when many similar products are available.

Antibiotics are used for a range of different purposes and at different doses. Antibiotics are used for a wide range of symptoms and diagnoses and sometimes at different doses for each. Beyond therapeutic use, antibiotics are also used in livestock for prophylactic, metaphylactic and growth promotion purposes. The point was also raised that the doses (mg/kg liveweight) used in livestock differ according to the indication for use, but may also differ between different species for the same condition, and actual doses administered are often the decision of the livestock keeper.

Supply chains for human and livestock antibiotics sometimes overlap. Antibiotics from the human supply chain are sometime sold for use in livestock and vice versa, especially in situations where antibiotics are freely available over the counter. The degree to which this happens may be context specific and often relates to the lack of availability in one sector versus the other. This is more likely to occur at the lower and informal provider levels and households, and qualitative methods may be useful to assess this.

Appropriate mix and staging of data collection approaches

An appropriate and context specific mix of data collection approaches is advised, incorporating a strong element of qualitative research to complement quantitative volume data collection. While the importance of collecting quantitative data, including on volumes, was well recognised, the group also emphasised the importance of informing such data collection through use of a wider range of methods, both in preparation for collecting quantitative data (formative research), and to assist with the interpretation of the quantitative results. This is summarised in Figure 4, with the different phases of data collection elaborated further below.

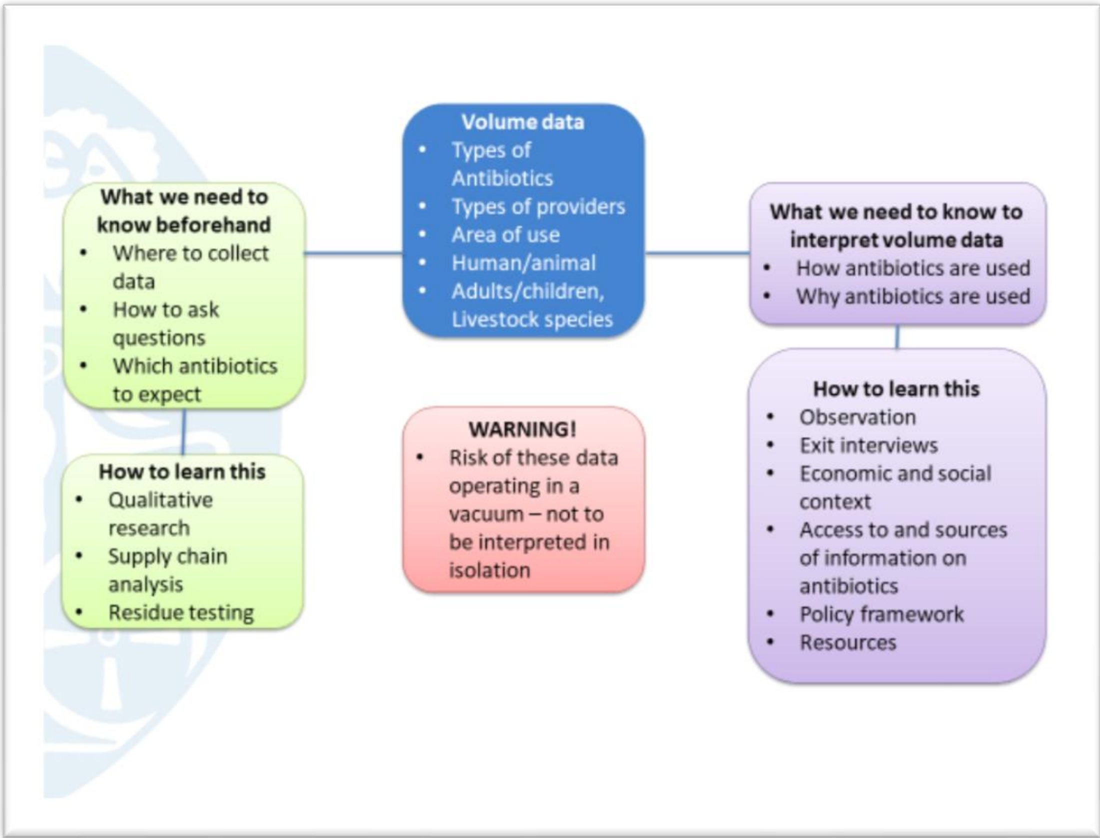

Figure 4: Mix of data collection approaches to both improve validity of data collection on volumes and its interpretation and policy relevance

Before volume data are collected, details are needed in each country of the structure of the supply chain, potential sources of reliable data, how questions should be formulated and which antibiotics are likely to be of importance. This information could be found through a mixture of methods including qualitative research, testing for residues for example in meat or sewerage systems, and a supply chain analysis including the informal and black market. Qualitative methods could include ethnographic approaches and participatory tools e.g. photovoice. The specific example of the roles of informal providers of advice and veterinary services in Myanmar, as presented by Hayley MacGregor (IDS), was used to illustrate the idiosyncrasies of suppliers and expertise in different contexts. Without preliminary qualitative research to highlight the roles of informal providers of antibiotics they might be missed in larger scale quantitative data collection. In order to develop reliable data collection tools an understanding is also needed of which products are recognised by patients and farmers as antibiotics, with indications that this varies across counties and contexts.

The interpretation of volume data requires the use of a mix of data collection methods to understand how and why antibiotics are used. The participants raised the risk of interpretation of volumes data that are disconnected from the local context. Interpretation needs to be based on field data or eye witness accounts. Examples of methods that can deepen an understanding of quantitative findings include in-depth interviews, observations, exit interviews, a study of the economic and social context and antibiotic regulations and policy framework.

There is value to both data collection by research specialists / experts, and to data collection involving policy makers themselves. As mentioned above, the disconnect between data and their context that can occur when interpreting quantitative data may lead to misinterpretation of the data and therefore mis-judged actions to address what is understood to be the problem. Additional qualitative data collected by research experts can be helpful to contextualise quantitative findings. Value was also placed on the facilitation of eye witness experiences for policy makers to understand the context and situation behind the numbers, to stimulate appropriate interventions. This is captured in Figure 5 which highlights the importance for data collection to be embedded in relation not only to research, or implementation but also to policy. It was proposed that to do this well, research experts were required for rigorous data collection at scale but also policy participation in data collection would have value.

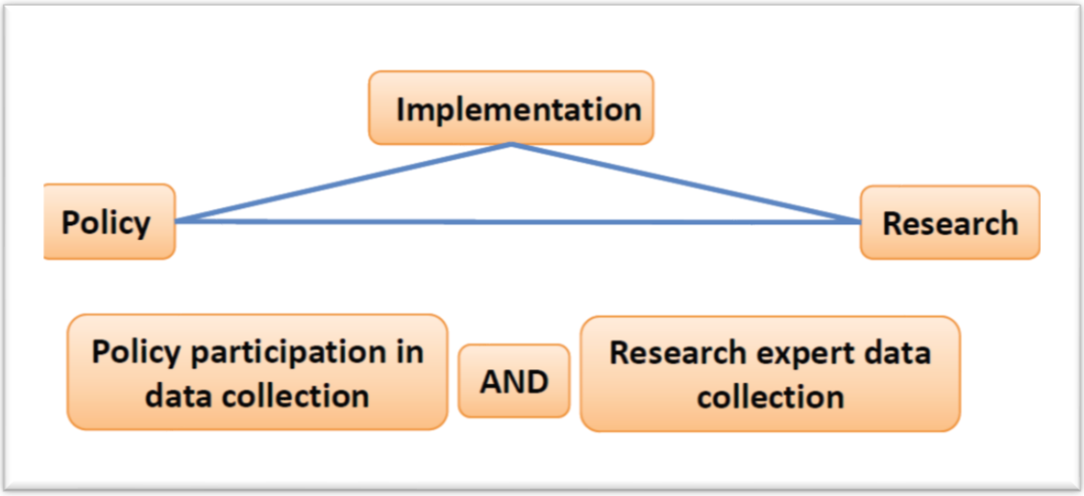

Figure 5: Data collection should be co-produced in relation to research, implementation and policy, for example with policy professionals carrying out some of the data collection and gaining eye witness accounts.

A progressive pathway of data collection and surveillance would be appropriate. Reflecting the varying availability of reliable and accessible data within different countries, and varying capacities to capture such data and fund data collection, a progressive, tiered approach was proposed. This would set out a range of data collection options in terms of level of aggregation / intensity / scope / rigour. Countries could then select which would be most relevant and feasible at a given point in time. Suzanne Eckford (FAO) mentioned that the FAO is currently working on a similar progressive management pathway to control AMR in poultry.

Sampling

Sampling strategies will depend on the purpose of data collection. The importance of representative sampling was recognised, particularly for objectives that required robust estimation of volumes and other parameters across groups and over time. Different sampling methods may be required at different stages of investigation, and for different objectives. For example, for estimates of total market share a nationally representative sampling approach might be required, while for other purposes it might be more appropriate to sample around hotspots of resistance e.g. geographical locations, health facilities where resistant organisms were common, or productions systems where resistant zoonotic food borne infections were common. Similarly some objectives may require collection of data on all antibiotics while in other settings it might be appropriate to focus on those antibiotics with high or increasing rates of resistance.

The optimal sampling approach will vary by level and stratum of the supply system. Human samples might be stratified by provider type, and livestock samples by farm size, production system type, species and age group of animals reared, with the sampling approach varying according to availability of existing sampling frames for each of these strata. For example, existing lists of registered pharmacies, hospitals, GPs or veterinarians may provide fairly accurate sampling frames. However, informal providers are by nature not registered or listed, and will require the creation of a sampling frame by conducting a primary census. Likewise, sampling from households or farms may be possible from national census data and lists of commercial or registered farms or from lists of farmers' association members, however informal settlements and small holder and backyard livestock keepers will require a primary census to identify them.

A One Health approach may still require more than one sampling approach. While a One Health approach, incorporating human health, livestock, crops and the environment may be recommended, it may be appropriate to vary the sampling approach across these spheres, reflecting both variations in the nature of providers/users, their geographical concentration, and variation in location of human and livestock resistance hotspots. There is also potential to consider a targeted One Health approach, for example prioritising species and production groups of food producing animals receiving the most antibiotics and those known to carry bacteria of significance to human health (WHO/AGISAR report).

The 80:20 rule was raised i.e. that 20% of users/providers may account for 80% of the antibiotics. In such situations targeted sampling could be used to focus on the 20%, but the challenge of identifying the 20% group without first conducting more comprehensive sampling and data collection was recognised.

Opportunistic sampling approaches may have merit in some situations. While certain objectives may require primary data collection based on large scale representative sampling, in some contexts one should consider other possible approaches, including i) using existing data collection systems e.g. microbiological AMR surveillance systems as a source of AMU data; ii) adding a limited set of key questions on antibiotic volumes to existing reporting systems e.g. Health Management Information Systems (HMIS); and iii) using legislation to mandate reporting by larger farms, manufacturers, importers or distributers.

Volume metrics

Volume data alone will not relate to AMR unless it is linked to the population at risk. The denominator should not just include those patients or livestock receiving antibiotics but also the population at risk. This denominator is typically hard to define even at the national level, especially in livestock in LMICs, where census data are often very inaccurate. At the more granular level, challenges exist in determining the denominator especially in rural areas, where individuals may travel long distances to access human and livestock health services and products in better serviced locations. At a local level, the patient registration records in human health clinics may be incomplete or absent. Local livestock estimates often rely on self-reporting and may also be inaccurate, with some livestock keepers overstating numbers to imply wealth and other understating to avoid taxes. Francis Murray (Stirling University) mentioned that in non-intensive aquaculture systems typical of many small-holders, accurate estimation of stock numbers is highly challenging, and further complicated by the common practice of culturing a mixture of species (polyculture) in the same pond, cage or enclosure.

The most promising metric for use across human and livestock populations was suggested to be mg of antibiotic per weight (i.e. using the DDD human patient weight of 70kg or biomass of treated animal). For human antibiotic use, the Defined Daily Dose (DDD) metric is commonly proposed and recommended by WHO as the assumed measure of use, calculated as the assumed average maintenance dose for a drug for a 70kg adult for its main indication. In livestock, the population correction unit (PCU) was developed by the European Medicines Agency for use in Europe. It takes into account not only the animal population but also the estimated body weight of each species at the time of likely treatment with antibiotics. The PCU is calculated by multiplying the population census for each livestock species by the estimated weight at time of treatment; the sum of PCUs for each species group giving the total. Antibiotic usage can then be expressed as mg/PCU/unit of time. This could be compared with a similar figure for human use based on the average 70kg weight used in the DDD metrics for humans.

Different doses and purposes of antibiotic use complicates volume metrics. As described above, the range of uses of antibiotics for different cases in both humans and animals means that metrics based on recommended dosages would require further information about the purpose of use in order to interpret whether the amount per case is more or less than expected. This makes summarising antibiotic volumes per case more complicated for antibiotics than for say antimalarials, and also more complex in livestock than in human health.

DDDvet could be used for comparison with human DDD metric. Attempts have been made to adapt the DDD metric in veterinary medicine to produce a DDD for each antibiotic in livestock (DDDvet), which could be used for comparison with human DDDs. It is however complicated by the different doses recommended in different species, which results in a different DDDvet figures for each species.

Volume data collection tools

Data collection tools would need to fit the situation and context. It was raised several times that understanding the system of provision and health seeking behaviour of patients and livestock keepers was important to inform the choice of data collection tools for volumes. Beyond the system of provision, the livestock sector also requires an understanding of the predominant species and production systems.

Accessibility and reliability of data was raised as an issue in certain situations. Where the public sector dominates provision of antibiotics in human health, records were more likely to be relatively well-kept and accessible. However, the private sector often plays an important role in provision of antibiotics in LMICs for human health and a dominant role for livestock health, potentially accounting for a large share of the total antibiotic market. Collecting data from both human and livestock private actors could be difficult with concerns that this may implicate providers in regulatory infringement or increase their tax liabilities, or claims that data are commercially sensitive and company owned. The latter is particularly the case for large commercial farms who may be large volume users. Suspicion among these respondents is usually higher with a one-off cross-sectional survey style data collection, but this can be eased by establishing relationships of trust over time. For example, the ViParc project, which monitors antibiotic use in poultry in Vietnam, incentivises participation of farmers by providing free veterinary health advice and economic analysis of their production system.

In countries where there is a lack of capacity to enforce regulations to control antibiotic prescribing and dispensing, illegal activities can form a significant portion of the market. These data will not be included if only data from official providers are included. It was suggested that identifying these informal and illegal providers might require qualitative methods and/or household or livestock keeper surveys, and that time may be needed to establish a relationship of trust with informal providers to ensure that data are shared freely without fear of incrimination. However, in some settings such regulatory infringements are so commonplace that the "illegal" providers may be operating very openly. Records from these providers are usually non-existent and volume data collection would need to rely on provider recall, exit interviews, or household or livestock keeper surveys.

A total market approach to volume data collection has both merits and challenges. Volume data collection can be focused on one provider type such as the WHO's hospital protocol, or a couple of provider types. Alternatively, a total market approach can be taken, which includes all providers or users in the market. A key advantage of a total market approach is that relative market shares can be calculated across provider types, sectors, antibiotic classes etc.

Catherine Goodman presented ACTwatch, as an example of a total market approach to data collection. ACTwatch aimed to provide timely, relevant and high quality evidence to inform and monitor policies and strategies for malaria control and elimination. This including providing analyses of the total antimalarial market, though a mix of supply chain studies, household surveys and outlet surveys. The latter were cluster-based and covered all sources of antimalarials for patients. Nationally representative data were obtained on the total antimalarial market, which could be presented by sector, by outlet type (Figure 6) or by relative distribution by antimalarial types (Figure 7).

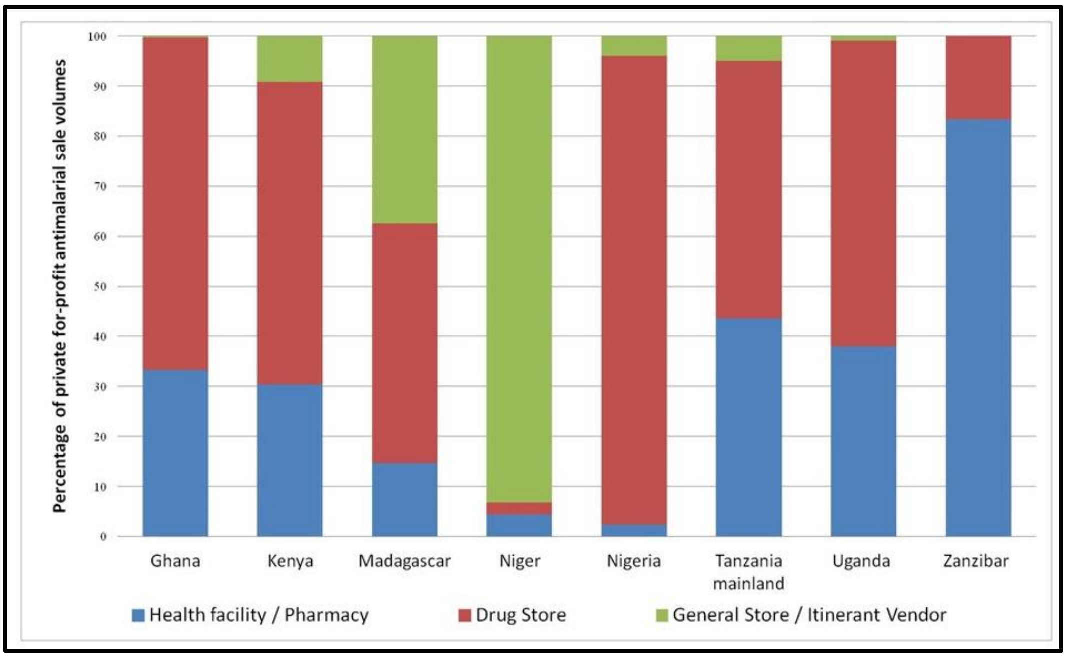

Figure 6: ACTwatch data on market share of antimalarials delivered through the private for profit sector by outlet type

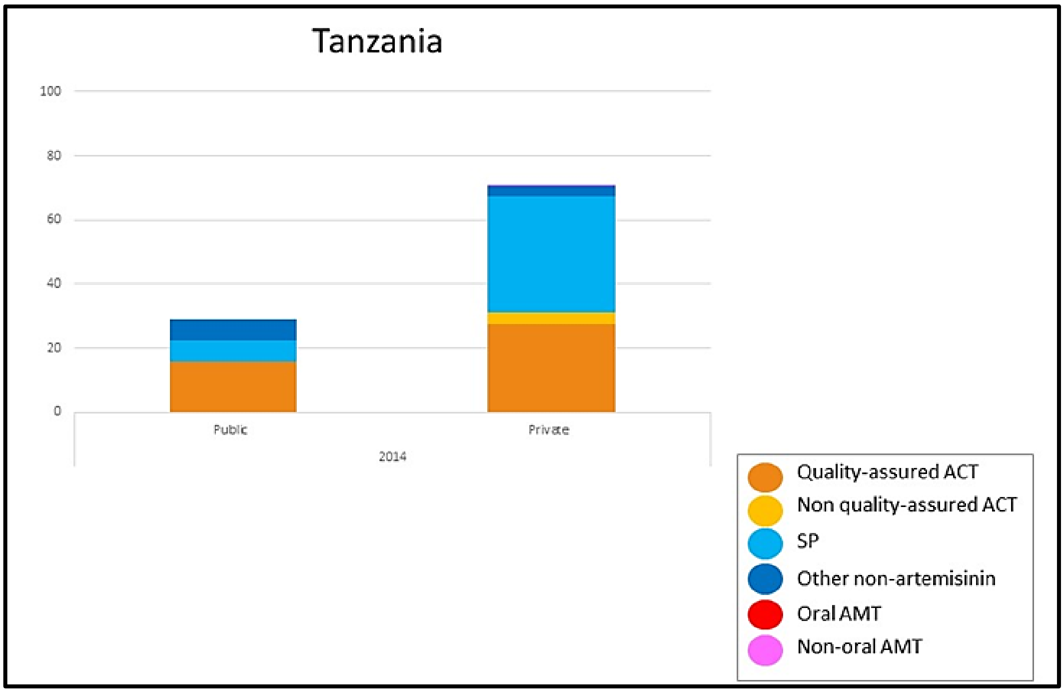

Figure 7: ACTwatch data on market share of antimalarials distributed by sector and antimalarial type

Carrying out the ACTwatch programme was not without challenges, which included the time taken to conduct a census of all outlets in selected clusters, the intensive training required for interviewers and overall costs per survey (approximately 100,000-200,000 USD/ country in Asia and 200,000 to 400,000 USD in Africa). This meant that data could only be collected at one point in the year, meaning that it was not possible to assess seasonal variation. Given that many providers did not keep good records, volumes were based on provider recall, which may have led to recall or deliberate bias in reporting data that are perceived to be sensitive.

Additional challenges of creating a similar system for the antibiotic market were considered. Most issues focused around the diversity of antibiotic products available across the different classes and the overlap of human and livestock use of the same products. Some participants raised concerns about the costs of such a system. Others thought that the increasing willingness to invest in AMR surveillance could accommodate such a system, if it is allows us to better understand the antibiotic market and usage data at the granular level and is linked to resistance. Francis Murray (Stirling University) shared that a similar approach was being taken to measuring drug use in aquaculture in Asia (**seatglobal**.eu, www.stir.ac.uk/**imaqulate)**. Outlets serving farming clusters were mapped using GPS, mobile phones and Google Map pictures, and farmers who sell drugs to others were also identified and included.

Volume data from providers should be interpreted together with data on how antibiotics are used at the patient and farmer level. Collecting data on appropriate prescribing, dispensing and most importantly the appropriate and actual use by end users, be it human patients or livestock keepers, should be included and used in conjunction with volume usage data to allow for meaningful interpretation. Household surveys (including household inventory stock checks) can assist in measuring actual usage by individual human patients. Likewise, livestock keeper surveys can be used to measure usage at the level of different animal species. The livestock sector however, presented unique challenges in measuring use at the patient level. Several antibiotic products are licensed for use in multiple species and at different doses/ kg of bodyweight, whilst off-label use of products in other species (commonly aquatic species) occurs where there is a shortage of licenced products. Recall can be used in surveys but with livestock keepers who have large numbers of different species, this may be unreliable. Treatment records can provide more detailed data but they are often unavailable, in which case prospective record keeping can be instituted, but may be subject to bias and require incentives for commitment in longitudinal studies. The collection of used packaging can be used to support recall and verify treatment records. However, packaging bins can also be difficult to interpret on mixed species farms and when antibiotics are packaged with multiple doses or courses in one container (i.e. a course may be given but the container is not emptied or discarded so the amount given is not accounted for).

Consider methods from HICs which may be adaptable for use in LMICs. Innovative smart phone technology and barcode reading smart phone apps are being developed and used in Europe (AHEAD), to capture real time data at the point of treatment of the animal. This has been adapted from an app for recording medication taken by human patients and may have potential to be adapted to improve record keeping for livestock keepers in LMICs.

In addition, the network AACTING (**A**ntimicrobial usage at herd level and **A**nalysis, **C**ommunica**T**ion and benchmark**ING** to improve responsible usage) was mentioned. It is currently a European and Canadian initiative, which aims to develop best practices to establish AMU surveillance systems at the farm level. They aim to review and analyse the strengths and weaknesses of existing systems in the participating countries. They plan to use their website to disseminate their findings and will also hold an open conference in Feb 2018. It was suggested that this project may provide lessons which could be adapted for LMICs.

Next steps

The meeting has confirmed that although there is a keen interest in antibiotic use data, there is a lack of such data at the granular level especially in LMICs in both human and veterinary sectors, and an urgent need for the development and testing for good methods to address this. The WHO, OIE and FAO have recognised the need for more disaggregated data and were broadly supportive of the discussions in this workshop. They are open to, and have encouraged feedback of ideas and findings to them, to support their continuing plans to improve methods of disaggregated data collection and interpretation.

Suggested priorities and ideas to move forward included:

1. **Create a sharing platform and a community of practice:** to share ideas, new tools and resources and to create opportunities for collective learning and future interactions.
2. **Establish a working group to develop a progressive pathway for antibiotic use surveillance.** The approach could be modelled on the tiered approach to supporting laboratory capacity for AMR surveillance (Seale et al 2017). The pathway could include a matrix or decision tree to help prioritise data collection options, and give individual countries options of strategies tailored to their context and finances. In developing such a pathway, dialogue would be maintained with i) the WHO, around their new community level protocol, ii) the OIE, in relation to improving the reporting of more disaggregated data, and iii) the Fleming Fund, to understand how usage data can feed into their activities on AMR surveillance.
3. **Increase dialogue between AMR modellers and AMU experts.** Creating a working group of resistance modellers and antibiotic use researchers would facilitate discussions to refine methods and metrics for collecting granular AMU data which can inform analysis of the drivers of AMR, and therefore the design of strategies to tackle AMR.
4. **Develop small pilot case studies across several varied country and regional sites.** This would allow for the testing and further development of data collection methodologies. Such pilot studies could link into existing AMR surveillance work, which may have already identified resistance hotspots, where volume and usage data would be of particular relevance and value.

Appendices

Appendix 1: List of attendees

	Name	Organisation
1	Angkana Sommanustweechai	London School of Hygiene and Tropical Medicine (LSHTM)
2	Anita Kotwani	University of Delhi
3	Barbara Häsler	Royal Veterinary College (RVC)
4	Barbara Wieland	International Livestock Research Institute (ILRI)
5	Catherine Goodman	London School of Hygiene and Tropical Medicine (LSHTM)
6	Charles Penn	Department of Health, UK
7	Christie Peacock	Sidai Africa Ltd. Kenya
8	Claire Heffernan	London International Development Centre
9	Clare Chandler	London School of Hygiene and Tropical Medicine (LSHTM)
10	Delfy Gochez (Skype)	World Organisation for Animal Health (OIE)
11	Elizabeth Rogawski	University of Virginia
12	Francis Murray	Stirling University
13	Gerardo Alvarez-Uria	Rural Development Trust, Bathalapalli Hospital, India
14	Gwen Knight	London School of Hygiene and Tropical Medicine (LSHTM)
15	Gwen Rees	Bristol Vet School
16	Hayley MacGregor	Institute of Development Studies
17	Jackson Mukonzo (Skype)	Makerere University
18	Jeff Waage	London School of Hygiene and Tropical Medicine (LSHTM)
19	Jo Lines	London School of Hygiene and Tropical Medicine (LSHTM)
20	Jo Mckenzie	Massey University
21	Kathy Holloway	World Health Organisation/ Institute of Development Studies
22	Kevin Queenan	Royal Veterinary College (RVC)
23	Koen Peeters	Institute of Tropical Medicine, Antwerp, Belgium
24	Kristen Reyher	Bristol Vet School
25	Lucie Collineau	Public Health Agency of Canada
26	Lucy Brunton	Royal Veterinary College (RVC)
27	Lucy Coyne	Liverpool University
28	Meenakshi Gautham	London School of Hygiene and Tropical Medicine (LSHTM)
29	Micky Ndhlovu	Chainama College
30	Mirfin Mpundu	REACT/ Ecumenical Pharmaceuticals Network
31	Phyllis Awor (Skype)	Makerere University
32	Rezin Odede	Sidai Africa Ltd. Kenya
33	Sheila Mburu	United Kingdom Collaborative on Development Studies
34	Suzanne Eckford	Food and Agriculture Organisation
35	Tenaw Tadege (Skype)	Food and Agriculture Organisation
36	Timothy Robinson	Food and Agriculture Organisation
37	Toby Leslie	Mott McDonald/ Fleming Fund
38	Wenjing Tao (Skype)	World Health Organisation

Appendix 2: Roundtable Agenda

Roundtable on "Metrics and methods for assessing antibiotic use at the granular level in humans and livestock in LMICs"

Dates: Tues 21st and Wed 22nd November 2017

Venue: Mary Ward House (Voysey Room)

5 - 7 Tavistock Place, London

WC1H 9SN

ROUNDTABLE AIMS

1. Review the methods and metrics for collecting granular data on antibiotic use in LMICs from a One Health perspective
2. Identify key data needs for policy making
3. Identify challenges involved in collecting robust and comparable data both within and across the human and livestock domains
4. Discuss the next steps in developing methods and metrics for widespread, One Health use in LMIC

Tuesday 21st November	
Time	*Activity*
10:30 - 11:00	Registration (Tea and coffee)
	Introduction and background (Chair: Clare Chandler)
11:00 – 11:20	Introduction and Objectives of the meeting, and round the table introductions: Jeff Waage and Clare Chandler
11:20 – 11:40	WHO: Methodology for a global programme on surveillance of antimicrobial consumption: Hospitals and community level: Wenjing Tao (Via Skype)
11:40 – 12:00	OIE Strategy on AMR and Prudent use of Antimicrobials: Delfy Gochez (Via Skype)
12:00 – 12:15	Fleming Fund: Plans for work on antibiotic use: Toby Leslie
12:15 – 12:30	Framing the types and purposes of antibiotic use data: Catherine Goodman
12:30 – 13:00	Discussion

13:00 – 14:00	**Lunch break**
	Methods and metrics for studying antibiotic use – Livestock **(15 min each + 5 min Q&A)** (Chair: Suzanne Eckford)
14:00 – 14:20	Review of methods and metrics in human and livestock antibiotic use studies: Kevin Queenan
14:20 – 14:40	AMU use in livestock, CGIAR Research Program on Livestock: Barbara Wieland
14:40 – 15:00	Social Science methods for Myanmar Pig project: Hayley MacGregor
15:00 – 15:20	Aquaculture in China, Vietnam, Thailand, Bangladesh: Francis Murray
15:20 – 15:40	AMU at the granular level in livestock: could we adapt HIC approaches to LMICs? Lucie Collineau
15:40 – 16:10	**Tea/ Coffee Break**
	Methods and metrics for studying antibiotic use – Human health **(15 min each + 5 min Q&A)** (Chair: Jo Lines)
16:10 – 16:30	Antibiotic provision by informal providers in India: Meenakshi Gautham
16:30 – 16:50	Country Situational analysis of medicines in health care delivery (WHO/SEARO): Kathy Holloway
16:50 – 17:10	Household visits to assess children's antibiotic use across 8 countries: Elizabeth Rogawski
17:10 – 17:30	Antibiotic use among patients at primary health care facilities in Zambia: Micky Ndhlovu
17:30 – 17:50	Discussion
17:50 – 18:00	Wrap up of Day 1 and introduction to Day 2: Catherine Goodman

Wednesday 22st November	
09:00 – 09:10	Welcome back and introduction of Day 2: Clare Chandler
09:10 – 09:40	An example of granular data collection from malaria (ACTwatch): Catherine Goodman
09:40 – 11:00	Reflections from: Koen Peeters, Mirfin Mpundu, and Suzanne Eckford
11:00 – 11:30	**Tea/ Coffee break**
11:30 – 12:30	Discussion session: Methodological issues and challenges in measuring volumes at a granular level (Chair: Clare Chandler) Group work: 1. Metrics for relative volumes: Any common unit of measurement for humans and livestock? 2. Sampling frame for data collection points: Any common sampling approach across human and livestock? 3. Integrating approaches
12:30 – 13:30	**Lunch break**
13:30 – 14:45	Feedback from Groups Discussion of next steps: Chair Jeff Waage - What approaches would we like to take forward? - How should we continue working together? - Sources of funding and organisational support - Piloting opportunities
14:45 – 15:00	Wrap up: Catherine Goodman and Clare Chandler