A review of methods and metrics for studying human and livestock antibiotic use at the granular level

A Pre-read for Roundtable discussion in London, 21&22nd November 2017

Kevin Queenan, Clare Chandler, Catherine Goodman

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Executive summary

The causes of the current 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. Data collection on antibiotic use is central to the global surveillance plans of the World Health Organisation (WHO) and the World Organisation for Animal Health (OIE). Typically, antibiotic surveillance aims to collate national sales figures expressed per human or livestock population as a starting point, although this is currently highly incomplete, especially in most low-income and middle-income countries (LMICs). However, 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; maximising effectiveness will require addressing this gap in rigorous and representative granular data.

This rapid scoping review aimed 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. It was conducted as a background document for a roundtable discussion on methods and metrics for studying human and livestock antibiotic use at the granular level in London in November 2017. We did not aim 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. Although the focus was specifically on antibiotics, we also included publications with a more general focus on all medicines, all antimicrobials or all “chemicals” (in aquaculture), if they included antibiotics. Whilst the focus of the review was on methods producing actual volume usage data at the granular level, publications containing such metrics were quite limited. We therefore also included those with other metrics relating to antibiotic use (e.g. proportion of patients receiving an antibiotic), where the methods could potentially be adapted to measure actual volumes. The publications were organised into two groups: i) standard survey tool guidelines and protocols and ii) published studies with examples of methods used in the field.

Standard survey tools and protocols within human health, published by the WHO through various channels and collaborations, include the International Network for Rational Use of Drugs (INRUD), Health Action International’s Affordability and Availability of Medicines, Country Pharmaceutical Situation Assessments, Health Care Delivery Situational Analysis and the Use of medicines by Consumers. Others are published within the Service Provision Assessment in Demographic and Health Surveys and the Hospital Antimicrobial Use investigation by Strengthening Pharmaceutical Systems. The majority of these tools 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, but 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.

Research papers were reviewed to identify the range of methods and metrics used, until saturation in methods was reached. A sample of 48 human health and 30 livestock health research papers based in LMICs were selected for a more detailed review, representing a range of methods and metrics for quantifying antibiotic use. Papers were reviewed to extract data collection points, data collection methods, metrics, sampling strategies, geographical scope and disease focus (human) or species focus (livestock).

Data collection points within the human health papers included public hospitals and primary health care facilities (e.g. dispensaries, small private hospitals and private GPs), drug retailers (e.g.

pharmacies and drug shops) and households. Within human health papers, patient exit interviews (on exiting a healthcare facility) and inpatient record analysis were the most common methods used in hospitals and primary health care facilities (referred to as *health facilities* hereafter). Exit interviews with clients were again the most common method in drug retailers whilst household questionnaires were most common at the population level. Data collection points within the livestock papers were limited to livestock keepers (who predominated), drug retailers, pharmaceutical reps, veterinarians and feed retailers. Questionnaires were the most commonly used method for livestock health across all data sources (livestock keepers, drug retailers, vets and feed retailers), whilst other methods used for livestock keepers were treatment logs and used packaging.

Most human health papers collecting data from health facilities and from drug retailers used an existing list of facilities for a sampling frame and had a relatively small sample size of either <100 facilities or <1000 patients. Household surveys typically did not state their sampling frame source and included sample sizes of mostly >100 if based on households or <1000 if based on individuals. Within livestock papers, the majority did not state their sampling frames and most had sample sizes of <500 facilities.

The vast majority of human health papers produced outputs relating to INRUD methods, which focus on % of patients prescribed or receiving antibiotics, types of antibiotics, % antibiotics supplied with or without prescription, or the % of antibiotics prescribed per disease or symptom. Only 12 of the 48 papers produced Defined Daily Dose (DDD)[1] related metrics, with most of these collected from health care facilities. Similarly only four of the 30 livestock papers used DDD associated metrics, with most producing metrics on % of respondents using antibiotics, which antibiotic type and their reasons for using.

Of the human health papers, collecting data from either health facilities or drug retailers, most were from South Asia and Sub-Saharan Africa and were predominantly from urban settings. Four papers were located in more than one country and more than one region. Livestock papers were predominantly from work in Sub-Saharan Africa and East Asia and the Pacific.

Human health papers mostly covered any or all conditions while a minority had a specific disease or symptom focus. Of the latter, most focused on antibiotic use in diarrhoea, respiratory symptoms or acute fever. Livestock papers tended not to focus on a specific disease or symptom but were more species specific. Poultry and aquatic species predominated.

Key current developments in measurement of antibiotic volumes include work by WHO to develop a protocol for measuring use in hospitals in LMICs on the basis of prescribed daily doses of inpatients. A current research project, Antibiotic Access and Use (ABACUS) is collecting data in Health and Demographic Surveillance System sites in six LMIC via patient exit interviews from providers including hospitals, smaller healthcare facilities and drug retailers (including informal). They aim to produce metrics of “antibiotic exposure” (i.e. % of customers leaving with antibiotics) and the “antibiotic burden” (i.e. the DDD supplied per 100 antibiotic encounters per antibiotic type).

In summary, while the review indicated that considerable experience and expertise exists on antibiotic use data collection, and a number of valuable resources are available, a number of gaps were identified. Geographical coverage of existing studies is very patchy both across and within countries, with only a few hospital studies having nationwide representation, and rural areas generally less likely to be studied. 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

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

was drawn from a complete sampling frame. Only a minority of human health and livestock papers produced Defined Daily Dose (DDD)[2] related metrics, and only one study (livestock) was identified which compared different data collection methods for measuring antibiotic volumes. Papers tended to focus on one or at most two providers 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. Only one paper attempted to cover both human and livestock antibiotic use. 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, though this is the aim of ABACUS. Using a total market approach is demanding in terms of logistics and creation of comparable tools across providers, but would be very valuable to assess the relatively market shares of different provider types.

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

Contents

Abbreviations

AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
DHS	Demographic and Health Surveys
EML	Essential Medicines List
FAO	Food and Agriculture Organisation
GAP	Global Action Plan
GARP	Global Antibiotic Resistance Partnership
HAI	Health Action International
HDSS	Health and Demographic Surveillance System
HICs	High-income countries
INRUD	International Network for Rational Use of Drugs
LMICs	Low and Middle-income countries
OIE	World Organisation for Animal Health
PPS	Point prevalence surveys
SPA	Service Provision Assessments
SPS	Strengthening Pharmaceutical Systems
WHO	World Health Organisation

Introduction

Antibiotics are one of the foundations of both human and veterinary medicine and surgery today, with many of the same antibiotics used across several species. The selective pressure on bacterial populations exerted through the use of antibiotics has been well documented as a driver of antimicrobial resistance (AMR). Usage data should therefore form an essential part of the surveillance system, and a key input in the development of strategies to contain AMR. Given that the terrestrial and aquatic livestock, which form our food system, are often exposed to antibiotics during their lifetime, a One Health approach to antibiotic usage surveillance is recommended.

Interventions to address resistance should be built on evidence from rigorous and representative data on the provision and use of antibiotics within different settings and across different sectors. Whilst such data are becoming increasingly available in high-income countries (HICs), they are far more limited in low and middle income countries (LMICs). Within the human health sector, the pluralistic nature of health systems makes data collection particularly challenging, with antibiotics accessed through a wide mix of public, not for-profit and both formal and informal for-profit organisations. Private for-profit providers are particularly diverse, encompassing international-standard corporate hospitals, small scale hospitals and clinics, pharmacies, drug shops, and in some settings general retailers and itinerant vendors, with smaller less qualified providers often major medicine suppliers, and on-line provision growing rapidly. Antibiotic provision in LMICs within the livestock sector is equally diverse, but with a greater proportion of suppliers in the private for-profit sector. Antibiotics in livestock are used not only for therapeutic purposes but also for growth promotion, prophylactic and metaphylactic use. Various supply chains exist depending on the scale of livestock keeping establishments, and the quantities used can be hard to interpret as they are often administered via feed and water. Furthermore, the human and livestock sectors may not be entirely distinct at the local level, with antibiotics being sold through the human health supply chain for use in livestock.

Attempts to further the agenda around collection of antibiotic use data should ideally take place within the frameworks developed at a multinational level for antibiotic consumption in both humans and livestock. Collection of data on antibiotic use is central to the World Health Organisation's (WHO) Global Action Plan (GAP) on AMR and is an expected core component of member states' National Action Plans. The WHO's Methodology for a global surveillance program of antimicrobial consumption aims to provide a common methodology for the measure of antimicrobial consumption to allow monitoring at a national, regional and global level. The manual includes suggestions on setting up a national surveillance plan, with a focus on "consumption" data (which it defines as estimates from aggregated data sources). Measuring consumption data is seen as a significant starting point for many countries with limited resources. Whilst it recommends Anatomical Therapeutic Chemical (ATC)/Defined daily Dose (DDD) metrics (i.e. DDD/population unit/time), the degree of granularity of the "usage" data (which it defines as patient level data) is left open to the individual countries to choose, based on availability of the data and their resources. The methodology does not attempt to provide advice on detailed sampling and protocols for assessing use at the granular level (i.e. by provider or patient type) for individual countries.

The World Organisation for Animal Health (OIE) has been tasked, with the support of the Food and Animal Organisation (FAO), to contribute to the Global Action Plan and is building a global database on antimicrobial agents intended for use in animals. This aims to monitor the type and use of antimicrobial products, usage trends over time, trace global circulation and usage patterns and evaluate the quality and authenticity of antimicrobials in use. This data collection process is in the early phases having been launched in the latter half of 2015. It is currently at the macro or "consumption" level, relying on member countries to report total national sales data in kilograms of

antimicrobial agent for antimicrobials "destined for use in animals" and those agents on the OIE's list of "antimicrobial agents of veterinary importance". The reporting of disaggregated data is dependent on its availability within each member country. Three reporting options exist: Option 1 requires distinction of antimicrobial agents by use (therapeutic or growth promotion); Option 2 by type of use and animal groups (all food producing, terrestrial-food producing, aquatic-food producing and companion animals) and species; and Option 3 by type of use, animal groups and species and routes of administration. The OIE reporting template lists details of possible data sources (including manufacturers, wholesalers, retailers, import, marketing authorities, veterinarians, pharmacists and agricultural stores and feed manufacturers and farmers) for use as a reference. However, as with the WHO methodology, there is a lack of detail on methods for data collection for individual countries at the granular level.

Whilst high-level macro or consumption data is a useful starting point for documenting comparisons of regions or countries and for monitoring trends over time, the design of interventions is often focussed at the lower level i.e. prescriber, dispenser and end user. To anticipate where to maximise intervention leverage, disaggregated, granular data are required. We need to know how the antibiotics consumed by humans are distributed across provider types (hospitals, pharmacies, other retailers etc.), across different disease syndromes, and across different socio-economic groups, and how this varies by antibiotic class. In the agricultural domain, we need to know how antibiotic use is distributed across supplier type, farm type, animal species and purpose (growth promotion, treatment, prophylaxis), and again by antibiotic class. For these data to be useful it is essential to use rigorous and representative methods for documenting which antibiotics are used, where and when and in what quantities within human and livestock health, taking into account the complexities of these markets outlined above.

A number of standard methods have been developed by WHO to investigate rational use of medicines in hospitals and communities, and numerous individual research studies have been conducted collecting granular data on antibiotic use within the human and livestock health sectors. The **aim of this review** is to collate these methodologies from across both sectors to help identify best practices, and to provide a foundation for developing or fine-tuning methods and metrics, with a view to designing future data collection systems and studies that can provide robust data at the granular level to inform future policy and interventions.

Review methods

We conducted a rapid scoping review of published literature to identify the range of methods available and in use for collection of antibiotic use data at the granular level in LMICs. We did not aim 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. The review included both human and livestock health (including both terrestrial and aquatic livestock). Although the focus was specifically on methods to measure use of antibiotics, we also included publications with a more general focus on all medicines, all antimicrobials or all "chemicals" (in aquaculture), if they included antibiotics. Data collection points within human studies included all those interacting directly with patients including hospitals, health centres and drug retailers, together with households. Within livestock, studies collecting data from livestock keepers, drug retailers, veterinarians, pharmaceutical reps and feed retailers were included. Literature relating to high-level "consumption" data was excluded. Whilst the focus of the review was on methods producing actual volume usage data at the granular level, publications containing such metrics were quite limited. We therefore also included those with other metrics relating to antibiotic use (e.g.

proportion of patients receiving an antibiotic), where the methods could potentially be adapted to measure actual volumes. Studies using simulated patients or hypothetical cases were excluded as these do not provide actual antibiotic use data (though they can of course be extremely useful for other purposes).

Literature searches were limited to publications in the English language and were conducted through PubMed and Science Direct to identify primary papers. Further snowball searching from the reference lists of individual primary papers was conducted. Grey literature and websites from the World Bank, WHO, OIE, Health Action International (HAI), Demographic and Health Surveys' (DHS) Service Provision Assessments (SPA), Strengthening Pharmaceutical Systems (SPS) Program, Global Antibiotic Resistance Partnership (GARP) and ReACT were also searched.

Professional networks and selected publications from the literature review were used to create an initial list of key informants to interview. These individuals were asked to identify additional resources and publications, to share knowledge of current or recent developments, and to recommend further key informants to interview, as well as workshop invitees. Where applicable, they also commented on their experience using different methods in their fieldwork. Interviews were conducted in English, primarily via Skype and a full alphabetical list of interviewees is attached as Annex 1.

The publications were organised into two groups: i) standard survey tool guidelines and protocols, and ii) published studies with examples of methods used in the field. Selected information from all included publications was abstracted using standard reporting matrices for these two groups.

Review results

The review results are presented in three sections. Firstly, the standard survey tools and protocols from the human and livestock health sectors are described. The second section covers research publications, where across a spectrum of data collection sources, we provide details of publications by their methods, sampling strategies, outputs and geographic location and scope, and disease focus and species focus (livestock). The final section highlights some current developments in standard methodologies and research projects.

Standard survey tools and protocols

Published manuals of standard survey tools and protocols associated with usage data collection at the level of human healthcare facilities and patients/consumers were assessed for relevance to antibiotic use at the granular level in LMICs. The results are summarised below and presented in Table 1.[3]

These tools and indicators are mostly aimed at healthcare facilities and mainly derived from the drug use indicators set out by the WHO's International Network for Rational use of Drugs (INRUD). Some focus on assessing drug use behaviour in all health facilities [How to investigate drug use in health facilities (WHO, 1993) and the Drugs and Therapeutics Committees – A Practical Guide WHO 2004], whilst others focus specifically on antimicrobial use in hospitals [How to Investigate Antimicrobial Use in Hospitals: Selected Indicators. Strengthening Pharmaceutical Systems (USAID/SPS) 2012]. Indicators relevant to antibiotic use include i) *the average number of drugs (including antibiotics) per encounter*, ii) *the percentage of encounters with a prescribed antibiotic*, iii) *percentage of drug costs spent on antibiotics, iv) percentage of prescriptions in accordance with treatment guidelines, v) percentage of hospitalisations with antimicrobials prescribed, vi) average number of antimicrobials (some cases specifying antibiotics) per inpatient day, vii) average duration of treatment, viii) average cost per*

[3] Many of these tools and others related to high income county settings are collated in the ReACT Toolbox

hospitalisation, and ix) percentage of patients receiving antimicrobials for caesarean section or for pneumonia respectively.[4]

At a country level, there are assessment tools for the analysis of the pharmaceutical situation [WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations] and the management of medicines in health care [The workbook tool for Country Situational Analyses of Medicines Management in Health Care Delivery, presented by the WHO South East Asia Regional Office]. Their outputs include *percentage of patients prescribed antibiotics (including those relating to a specific symptom e.g. upper respiratory tract), percentage of prescription medicines bought without a prescription,* and *percentage of upper respiratory tract infection patients prescribed antibiotics*. Once again, these are not aimed at quantifying use but are rather a rapid assessment to identify problem areas and prioritise solutions related to prescribing behaviours and rational use.

Other tools capture data on the affordability and/ or availability of medicines, but do not capture data on use / volumes. The WHO/ Health Action International (HAI) produce outcomes including, *availability by dosage form and strength* and *price* of drugs available at a range of provider types, while health facilities may be subject to a DHS Service Provision Assessment, which includes an inventory survey of antibiotics which are currently in stock, but does not quantify them.

At the consumer level, the WHO's How to investigate the use of medicines by consumers aims to understand drug use practices and identify usage problems at the patient level. It includes a variety of methods which can be used at the consumer level, but does not specifically generate outputs associated with measuring usage by volume.

Within the Veterinary and Livestock sector, standardised tools were limited to the OIE's global system for measuring antibiotic or antimicrobial use at the higher, national level, with none found at the granular level, nor were any identified from a One Health perspective.

[4] A systematic review of studies using these indicators was published in 2009, covering published studies from 96 countries. See Medicines use in primary care in developing and transitional countries: Fact Book summarizing results from studies reported between 1990 and 2006.

Table 1: Standard survey tools and protocols for human antibiotic use, applicable at granular level

Resource	Data Collection point	Data collection methods relevant for *granular* AB use	Sampling frame	Suggested sample size	Scope of drugs covered	Output metrics relevant to AB use	Number of countries implemented
How to investigate drug use in health facilities (WHO, 1993)	Variety of public or private health facilities (health centres, dispensaries, hospital outpatients)	- Out-patient records (retrospective over 12 m) - Out-patient encounters observation (prospective) - Drug Inventory survey	Specified health facilities depending on study objectives (either from official lists or from data gathered/ census)	600 patient encounters (either from records or observation) i.e. 30 patients in 20 facilities or 100 patients per facility or prescriber or condition for inter-facility or prescriber comparisons	Specified range of available drugs, Essential Medicines List (EML) or specific lists dependent on study objectives	- average no. of drugs per encounter - % of encounters with a prescribed antibiotic - % of drug costs spent on antibiotics	n/s
How to investigate the use of medicines by consumers (WHO, 2004)	- Households - Community drug outlets (e.g. pharmacies and drug stores) - Health facilities, public and private (health centres, hospitals)	- Documents (sales, prescriptions) - Questionnaires (from all data collection points) -Simulated clients, inventories of drugs stocked	Specified health facilities depending on study objectives (either from official lists or from data gathered/ census)	If a sampling frame exists or can be created, probability sampling should be used. Sample size will depend on the variation in the data. Aim for at least 30 individuals in each group of interest (or data collection point). Consult statistician for more complex quantitative study designs	Specified range of available drugs, EML or specific dependent on study objectives	Outcomes are dependent on study objectives but aim to understand drug use practices and are not specifically volume related	n/s

Resource	Data Collection point	Data collection methods relevant for *granular* AB use	Sampling frame	Suggested sample size	Scope of drugs covered	Output metrics relevant to AB use	Number of countries implemented
How to Investigate Antimicrobial Use in Hospitals: Selected Indicators. Strengthening Pharmaceutical Systems (SPS) 2012	Hospitals (private and public)	- Hospital pharmacy inventory of drug stocks - In-patient records (retrospective or prospective)	Listed hospitals or purposively selected	100 prescribing encounters per facility	Specified range of available antimicrobials and EML, but generally exclude anti-tuberculosis drugs and anti-retroviral drugs for HIV	- % of hospitalisations with antimicrobials prescribed - average no. of antimicrobials per inpatient day - average duration of treatment - % of patients receiving antimicrobials for C-section or pneumonia	n/s
WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations (WHO, 2007)	- Public health facilities - Public and private pharmacies - Public drug supply warehouses	- Patient/ prescription records (retrospective over 12 m) - Patient exit interviews (30 patients)	Listed facilities or census for smaller/ private outlets	30 patients at 30 health facilities of each type and 5 warehouses	Specified range of available drugs, EML	- % of patients prescribed antibiotics - % of prescription medicines bought without a prescription	>40

Resource	Data Collection point	Data collection methods relevant for *granular* AB use	Sampling frame	Suggested sample size	Scope of drugs covered	Output metrics relevant to AB use	Number of countries implemented
The WHO/ Health Action International (HAI) 2008	- Public sector (hospitals, clinics, health centres) - Private sector (licensed pharmacies, drug stores) - Other (eg unlicensed drug outlets and vendors, private hospitals and GPs, NGO and religious facilities)	Questionnaire with inventory check for price	Dependent on sector: - Public and private (licenced) listed facilities - Other listed or created by census	Six regions each with 5 public (1 hospital + 4 outlets) and 5 private outlets a) and 5 "other" outlets	Specified range of up to 50 drugs made up of global core medicines list, regional core list and supplementary list based on individual country significance	- None (only collects data on availability and price)	36
The workbook tool for Country Situational Analysis of Medicines Management in Health Care Delivery, presented by the WHO South East Asia Regional Office (WHO, 2013)	Selection of public and private to represent the facility types present (university hospitals, district level public hospitals, primary health care centres, dispensaries, private and non-hospital public pharmacies)	- Patient records - Prescription records - Exit interviews - Inventory of drugs stocked	Listed and licensed facilities	2 regions each with 1-2 facilities of each type to give 16-24 facilities in total; 30-60 patient or prescribing encounters at each facility	Specified range of drugs from EML or others depending on country	- % of patients prescribed antibiotics - % of upper respiratory tract infection patients prescribed antibiotics	11 (in South East Asia Region)

Resource	Data Collection point	Data collection methods relevant for *granular* AB use	Sampling frame	Suggested sample size	Scope of drugs covered	Output metrics relevant to AB use	Number of countries implemented
The Demographic and Health Surveys' Service Provision Assessment survey and Inventory survey	Formal public and private facilities (excludes pharmacies and individual doctors)	Questionnaire with inventory check for availability of antibiotics. Backed up with observations (patient encounters) and patient exit interviews	Listed health facilities by sector (public and private) and facility type	400-700 facilities	List of 22 antibiotics including oral, injectable and ointments	- None (only data on antibiotic availability i.e. at least one of specified antibiotic is present)	15

Research publications

Research publications reporting granular data on antibiotic use are numerous, therefore we reviewed a selection of papers, to identify examples of methods and metrics used for a range of data collection points, until saturation of methods was reached. A sample of 48 papers from the human health sector (Annex 2) and 30 papers from the livestock health sector (Annex 3) were analysed. Only one paper was identified covering both human and livestock antibiotic use (Roess et al., 2015). It supplemented an existing neonate and maternal health project in Bangladesh and is included in the livestock data analysis below.

Information was extracted from each paper on key elements of the study design and methods, including data collection points, geographical scope, disease focus (human) or species focus (livestock), sampling approach, and outcomes or metrics used. The results are presented in Tables 2-7 and Figures 1-6 below.

1. Data collection methods

We categorised **human health** papers by type of data collection point, namely hospitals and primary health care facilities, drug retailers (both with a number of sub-categories), and also households (Table 2a). Several papers accessed data from more than one data collection point. The majority of the papers (21/48) involved data collection from public hospitals and primary health care facilities such as dispensaries, small private hospitals and private GPs (hereafter we refer to all these facility types as "health facilities"). Of these papers, around three quarters used public hospitals as their data collection point, with an almost even split of papers across the remaining sub-categories. Just under a third of papers (15/48) collected data from drug retailers, which included licensed and unlicensed pharmacies and drug shops, with pharmacies being the predominant sub-category, whilst 19 papers obtained data from households. We did not identify any studies of itinerant vendors or market stalls though these are significant medicine providers in some contexts.

The data collection methods used in these human health studies were categorised into the following eight types (Table 2a shows methods used across the full spectrum of data collection points whilst Figure 1 shows them across three main categories):

1. **Exit interviews:** patients exiting health care facilities or clients exiting retailers are selected to take part in an interview regarding their antibiotic purchase
2. **Encounter observation:** the encounter of the patient with the prescriber, dispenser or supplier of antibiotics is observed by the researcher and details recorded.
3. **Inpatient records:** these draw on routine provider records, and can be retrospective studies, looking at patient usage over a period of time, or prospective, involving a number of current patients over usually a shorter period.
4. **Prescribing or dispensing records:** similar to patient records but based on outpatient records and outlet dispensing records
5. **Bulk purchase and/or sales records:** from individual outlets over a period of time
6. **Provider questionnaire:** structured or semi-structured, usually conducted via face-to-face interviews with drug provider
7. **Household questionnaire:** as above but at the household level.
8. **Inventory of drugs stocked:** checking antibiotics stocks on shelves of outlets or those kept in patients' households
9. **A combination of the above:** either a combination of different methods or a blend e.g. patient exit interviews, which included observation of medications dispensed or details of written prescription received

Typically, patient exit interviews were conducted by trained individuals including pharmacists or medical or pharmacy students, often working in pairs, one to identify the patients receiving antibiotics and the other to conduct the interview (Kotwani et al., 2009). Patients may be interviewed within the facilities or on the street outside (Kotwani and Holloway, 2011).

Encounter observations were conducted by investigators who observed and recorded all information on a form; details relating to the individual patient and the drugs which were prescribed or dispensed, including compliance with prescribing the actual drug on the prescription. Typically, investigators were masters students or newly qualified pharmacists. The facility under observation was often told that the study was interested in all drugs, not antibiotics specifically to reduce potential bias (Nga et al., 2014).

Retrospective data were commonly extracted manually from inpatient records or from outpatient registers at health centre facilities (Guyon et al., 1994). Bulk purchase data were extracted from purchase receipts using a detailed form with names and strengths of drugs of interest. Data were usually collected in pairs using data collectors with pharmacy backgrounds, who would visit every 15 days to collect and analyse receipts (Kotwani et al., 2009).

Questionnaires conducted at the household level usually requested recall of antibiotic use over the past week or up to a month. They were typically a combination of structured and semi-structured questionnaires (Larsson et al., 2000). Photo-cards may be used to help identify drugs by name and determine whether they were indeed antibiotics. In Kerala State, South India patients were found to commonly retain their prescription slips at home together with packaging and wrappers, which assisted researchers in confirming medication received (Saradamma et al., 2000).

While provider questionnaires were commonly used to obtain antibiotic use data from drug retailers and household questionnaires from individuals, this method was not used at health facilities. Within the 21 health facility papers, an equal number (nine) used patient exit interviews and inpatient records, whilst six used prescription or dispensing records.

Of the 15 papers which focused on drug retailers, nine used exit interviews followed by six using provider questionnaires, while four used encounter observations and four dispensing records. Out of the 19 papers using household data, all used questionnaires, whilst six included an inventory check of drugs kept in the house. One household study (Rogawski et al., 2017) additionally randomly selected medical care reports from health care workers to validate questionnaire results.

Table 2a: Data collection methods used by type of data collection point in human health sector

Human health papers n=48		Method						
Data collection points	**No. of papers**	**Exit interviews**	**Encounter observation**	**Inpatient records**	**Prescription/ dispensing records**	**Bulk purchase/ sales records**	**Questionnaire Provider/ Household**	**Inventory of drugs stocked/ kept**
All data collection points	**48**	**14**	**7**	**9**	**9**	**3**	**21**	**6**
Hospitals and primary health care facilities	**21**	**9**	**3**	**9**	**6**	**2**	**0**	**0**
Public hospital	20	7	2	8	7	1		
Primary Health care facilities	5	5	1	1	1			
Private hospital	5	4	1	1	2	1		
Private GP	6	6	1		1			
Drug retailers	**15**	**9**	**4**	**0**	**4**	**2**	**6**	**0**
Pharmacy	13	8	3	0	4	2	4	
Drug shop	4	3	1	0	1	1	2	
Households	**19**	**0**	**0**	**0**	**1**	**0**	**19**	**6**

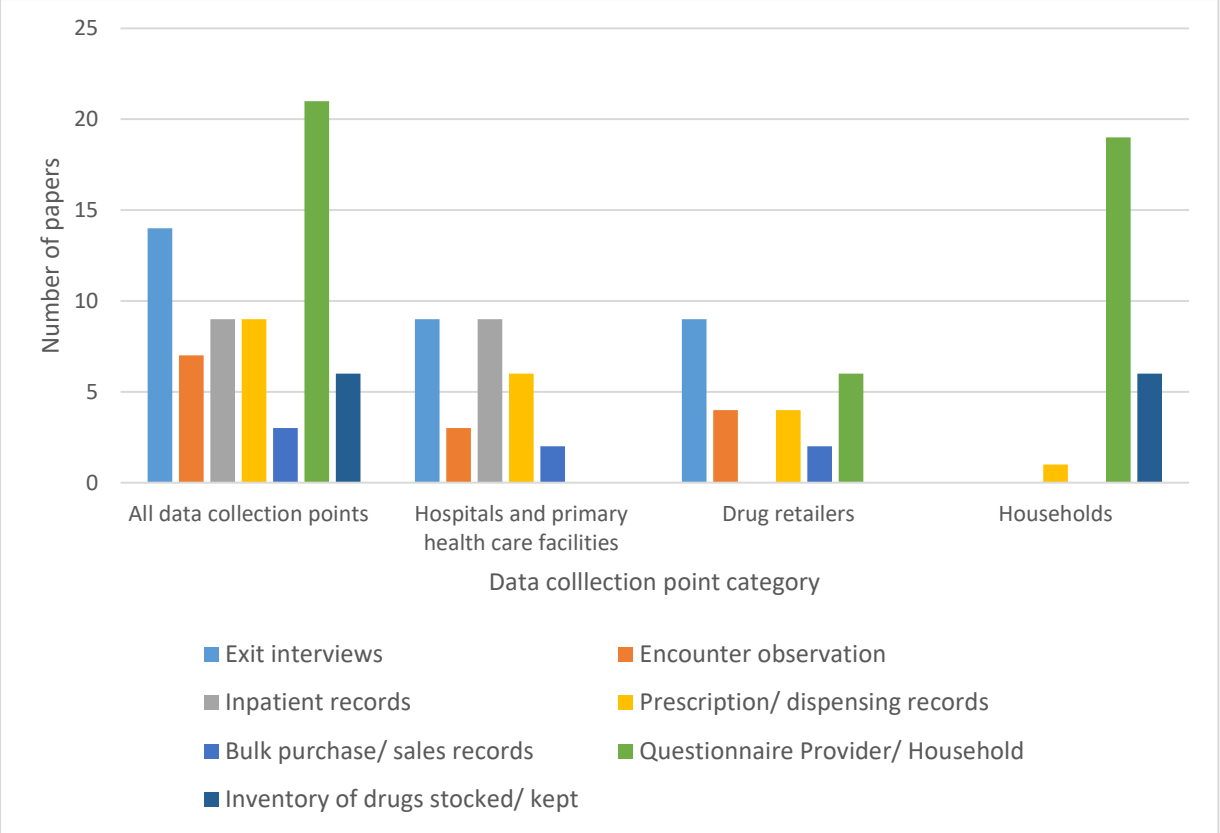

Figure 1: Data collection methods by type of data collection point category (Human Health)

We categorised **livestock health** papers according to data collections points, included antibiotic suppliers and those who administer them, resulting in five categories: livestock keepers, drug retailers, pharmaceutical representatives (suppliers of drugs direct to livestock keepers in some settings e.g. Bangladesh aquaculture), veterinarians and feed retailers (Table 2b). Papers often did not give specific details of type of livestock keepers including scale of their enterprise e.g. commercial farmers or small holders or households with livestock or pastoralists and similarly with fish farmers. In addition, drug retailers were often not described or broken down into categories of registered or informal, veterinary drug stores or agri-stores etc. As with human health studies, several papers covered more than one data collection point. All of the 30 papers reviewed included livestock keepers, and 13 used an additional source of data, which included six papers using drug retailers, four using pharmaceutical reps, two using veterinarians and one using a feed retailer.

The methods used in these livestock health studies were fewer than those in the human studies, with only three types (Table 2b):

1. **Questionnaire:** structured and semi-structured usually conducted face-to-face with livestock keepers, drug retailers, veterinarians etc.
2. **Treatment log:** the treatment records kept by livestock keepers for individual animals or groups (flocks, herds or ponds)
3. **Used packaging bins**: the packaging of all antibiotics used during a specified time period are collected in bins and analysed. This method can be used on its own or to validate questionnaires recalling usage over the same period.
4. **A combination of the above**: typically this was a questionnaire together with treatment log or used packaging bins

A questionnaire was the most common method, used in almost all of the studies (28/30) that included livestock keepers as a source and these often included recall questions on medications used in the production cycle, the past month or up to 6 months prior. Data from livestock keepers was also captured using treatment logs in three papers. In one of these, treatment logs were available as the farm was a national research farm (Manimaran et al., 2014) whilst in another, logs were being kept prospectively as part of the research project (Roderick et al., 2000). Similarly, in the third paper, records were being kept prospectively as part of farmers' participation in a project on antimicrobial usage, which included an intervention of free advice on husbandry and disease diagnostics and management as an incentive (Carrique-Mas and Rushton, 2017). This same project also asked farmers to keep all packaging of medications, which were later used to validate records. The researchers commented that previous attempts to collect data on antimicrobial usage on farms through unannounced visits had been full of challenges; famers recall was poor due to lack of record keeping and there was an element of mistrust. A second paper, which used packaging bins, compared contents with recall over a one month and a six-month period (Redding et al., 2014)[5]. Data collection from all other types involved the use of face-to-face questionnaires only.

Table 2b: Data collection methods used by type of data collection point in livestock health sector

Livestock Papers n=30		Methods		
Data collection points	**No. of papers**	**Questionnaire**	**Treatment Log**	**Used packaging bin**
All data collection points	30	28	3	2
Livestock keepers	30	28	3	2
Drug retailers	6	6		
Pharmaceutical reps	4	4		
Veterinarians	2	2		
Feed retailers	1	1		

2. Sampling strategies

Table 3a presents the sampling strategies used by the **human health** papers, highlighting the type of sampling frame used from which to select the sample, and sample sizes. Figure 2 presents the analysis of sampling frame sources only, over the three main categories of data collection points. Of the 21 papers analysed within the health care facilities group, 17 relied on existing lists of health facilities and/ or patient lists within these facilities as a sampling frame, while four papers did not state their source. None of the papers in this group conducted their own census. Sample sizes in papers on health care facilities were mostly small (up to 100 facilities) with only two papers including >100 facilities. The highest (Guyon et al., 1994), included 635 facilities (177 health centres and 461 sub-centres) in Bangladesh. Sample sizes at the patient level within the health care facility group were mostly less than 1,000 patients, with three papers between 1,001 and 10,000, three between 10,001-100,000 and

[5] Method comparison gave mixed results: *"Agreement between the bins and self-report was relatively poor for both the quantity and types of antibiotics used. The bins appeared to perform better than self-report when bottles and mls of antibiotics were measured, while self-report appeared to perform better for intra-mammary infusions. The bins also appeared to perform better when data pertaining to an extended time period (six months) were collected." (Redding et al., 2014)*

two studies over 100,000. These two papers with the largest sample sizes involved longitudinal studies for a year or more. They may be hospital based and would include inpatient as well as outpatients records (Alvarez-Uria et al., 2014). Alternatively, they may cover a range of provider types with exit interviews e.g. 10 hospitals, 10 private clinics and 10 pharmacies with 30 “antibiotic encounters” (i.e. administered, prescribed or dispensed) in each, i.e. 900 each month for 24 months (Chandy et al., 2013).

Of the 15 papers using drug retailers, eight used existing lists of formal outlets for their sampling frame, either from lists of government registered / licenced outlets or pharmacy association lists. The remainder reported no sampling frame details. None of the papers in the drug retailer group conducted their own census. Sample sizes were mostly between 21-100 retailers, with patient numbers of up to 10,000 (e.g. 7,200 “antibiotic encounters” via exit interviews from 30 pharmacies over 24 months (Chandy et al., 2013) or similarly 30 pharmacies for 12 months (Kotwani et al., 2009) both from India).

Eight of the 19 papers using households used existing lists (from government census, local health centre patient lists, or households already part of an existing study) for a sampling frame, whilst the remainder used none. None of these papers conducted their own census. Sample sizes were almost all over 100 households, with seven papers involving up to 1,000 individuals and four up to 10,000 individuals which were regionally widespread (Jordan: 1943 families, 9282 individuals, Mexico: 1751 families, Nigeria: 1080 households, Ethiopia: 1034 households).

Table 3a: Sampling frame sources and sample size of human health papers by type of data collection point

Human health papers n=48		Sampling Frame			Sample size facilities/households			Sample size patients/ encounters/ prescriptions			
Data collection points	**No. of papers**	**Existing list**	**Conducted census**	**Not stated**	**<=20**	**21-100**	**>100**	**<=1,000**	**1,001-10,000**	**10,001-100,000**	**>100,000**
All data collection points	**48**	**29**	**0**	**18**	**3**	**8**	**13**	**16**	**8**	**4**	**2**
Hospitals and primary health care facilities	**21**	**17**	**0**	**4**	**3**	**3**	**2**	**5**	**3**	**3**	**2**
Public hospital	20	17		3	7	4		7	6	2	2
Primary health care facility	5	4		2	1		2	2	2		
Private hospital	5	5		1	2	2		1	2	1	
Private GP	6	3		3	2	1		3	2		
Drug retailers	**15**	**8**	**0**	**7**	**2**	**4**	**2**	**4**	**1**	**3**	**0**
Pharmacy	13	7		5	5	3	2	5	3	3	
Drug shop	4	3		1	2	1	2	2			
Households	**19**	**8**	**0**	**11**	**0**	**1**	**9**	**7**	**4**	**0**	**0**

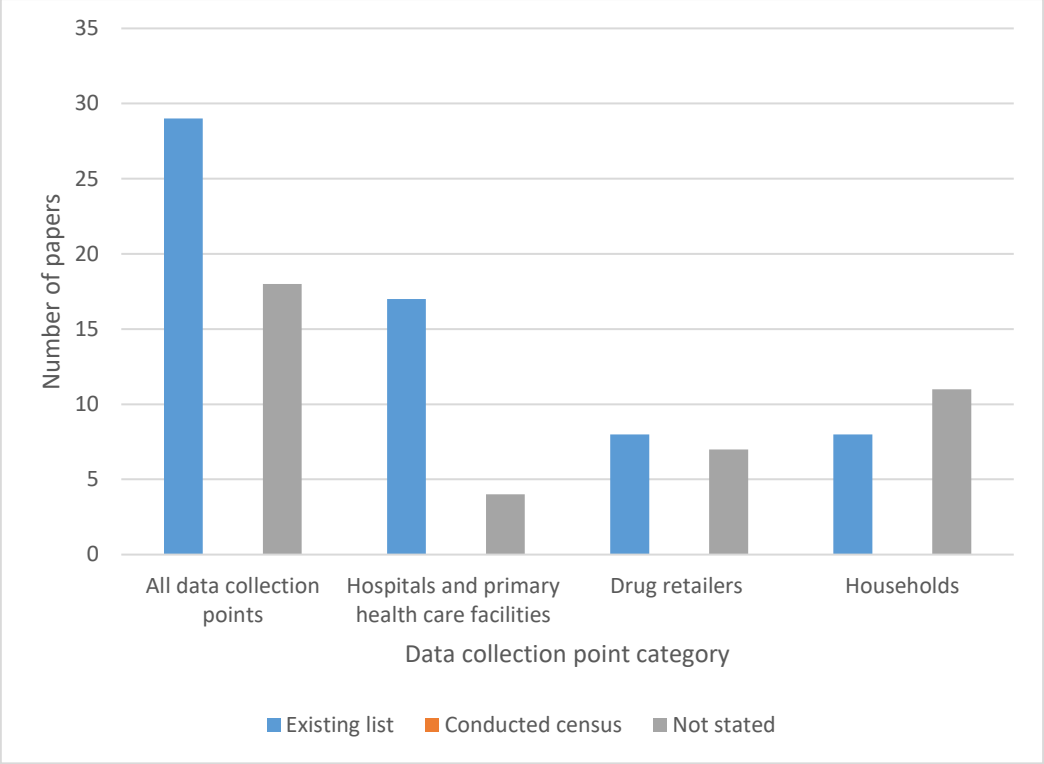

Figure 2: Sampling frame sources by data collection point category (Human Health)

The sampling strategies of the **livestock sector** papers are presented in Table 3b. Twenty-one of the 30 papers involving livestock keepers did not report using a sampling frame, whilst nine used an existing list of farms or livestock keepers (from government offices e.g. Department of Agriculture or District Livestock Production office, or from existing studies). Only one of these papers also accessed data from vets and drug retailers, again using an existing list from the District Livestock Production office. The remainder of the papers in the other categories did not report using any sampling frame. None of the livestock sector papers conducted their own census to form a sampling frame. Sample sizes were mostly between 11-500 livestock keepers, with only two over 500. Both of the latter were in Bangladesh, one with 1890 fish farmers (Ali et al., 2016), the other with 521 livestock keeping households (Roess et al., 2015). Most studies involving drug retailers and pharmaceutical reps had a sample size of 10 or less, as did both of the veterinarian studies and the feed retailer study. Sample sizes based on number of animals treated were not stated apart from in two studies, one of which was a single dairy farm in India with 119 cases of mastitis (Manimaran et al., 2014) and the other involved a total of approximately 220,000 chickens spread over 92 farms in the Cameroon (Kamini et al., 2016).

Table 3b: Sampling frame sources and sample size of livestock health papers by type of data collection point

Livestock papers n=30		Sampling frame			Sample size* facilities/ veterinarians/ farms & livestock keepers		
Data Collection points	**No. of papers**	**Existing List**	**Conduct census**	**Not stated**	**<=10**	**11-500**	**>500**
All data collection points	**30**	**9**	**0**	**21**	**4**	**24**	**2**
Livestock keepers	30	9		21	6	25	2
Drug retailers	6	1		5	4	1	
Pharmaceutical reps	4			4	2	1	
Veterinarians	2	1		1	2		
Feed retailers	1			1	1		
*** Does not include patient numbers (only two studies included number of animals as flock/herd sizes)**							

3. Metrics and outcomes

The antibiotic use metrics/ outcomes from the **human health** papers across the full spectrum of data collection points are presented in Table 4a, whilst Figure 3 shows them across the three main categories. Antibiotic use can be described as the exposure of a given individual or population over a given time period to a technical unit of antibiotic, i.e. quantification of antibiotics e.g. number of mg or packages (Collineau et al., 2017). For human use, the Defined Daily Dose (DDD) 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 70 kg adult for its main indication. Only 12 papers included a DDD associated metric and they were all in papers using providers, not households, as data collection points. Of the 21 papers collecting data from health care facilities, nine used a DDD associated metric whilst only five of the 15 papers from drug retailers did the same. The vast majority of papers collecting data from health care facilities produced metrics based on the WHO INRUD methods i.e. *% of patients prescribed, dispensed or using antimicrobials or antibiotics*, and *% of antibiotics prescribed, dispensed or used by antibiotic type*. In 15 papers collecting data from drug retailers, again INRUD metrics predominated but with a wider range of indicators i.e. *% of patients prescribed, dispensed or using antimicrobials or antibiotics, % of antibiotics prescribed, % of antibiotics dispensed with or without a prescription, % dispensed or used by antibiotic type*, and *% of antibiotics prescribed, dispensed or used by symptom or diagnosis*. Household studies reported a similar range of metrics to the drug retailer papers, with all 19 of them collecting data *on % of patients using antimicrobials or antibiotics*.

Table 4a: Main antibiotic use metrics or outcomes for human health papers by type of data collection point

Human health papers n=48		Main Metrics/ Outcomes						
Data collection points	**No. of papers**	**DDD associated metric**	**% patients P/D/U AMs or ABs**	**% of antibiotics P/D/U by AB type**	**% of AMs or ABs dispensed with or without Rx**	**% of antibiotic P/D/U by symptom or diagnosis**	**Course duration**	**Inappropriate use or non-compliant dispensing**
All data collection points	**48**	**12**	**39**	**20**	**18**	**19**	**9**	**8**
Hospitals and primary health care facilities	**21**	**9**	**18**	**9**	**0**	**3**	**4**	**3**
Public hospital	20	9	16	12		4	4	4
Primary Health care facilities	5	4	5	4		1		
Private Hospital	5	3	5	3				
Private GP	6	4	6	3		1		
Drug Retailers	**15**	**5**	**10**	**4**	**8**	**5**	**1**	**1**
Pharmacy	13	5	9	3	8	5		1
Drug Shop	4		4	3	2	3	1	
Households	**19**	**0**	**19**	**11**	**12**	**11**	**5**	**1**
Table Key: AMs = Antimicrobials, ABs = Antibiotics, P = Prescribed, D = Dispensed, U = Used, Rx = Prescription								

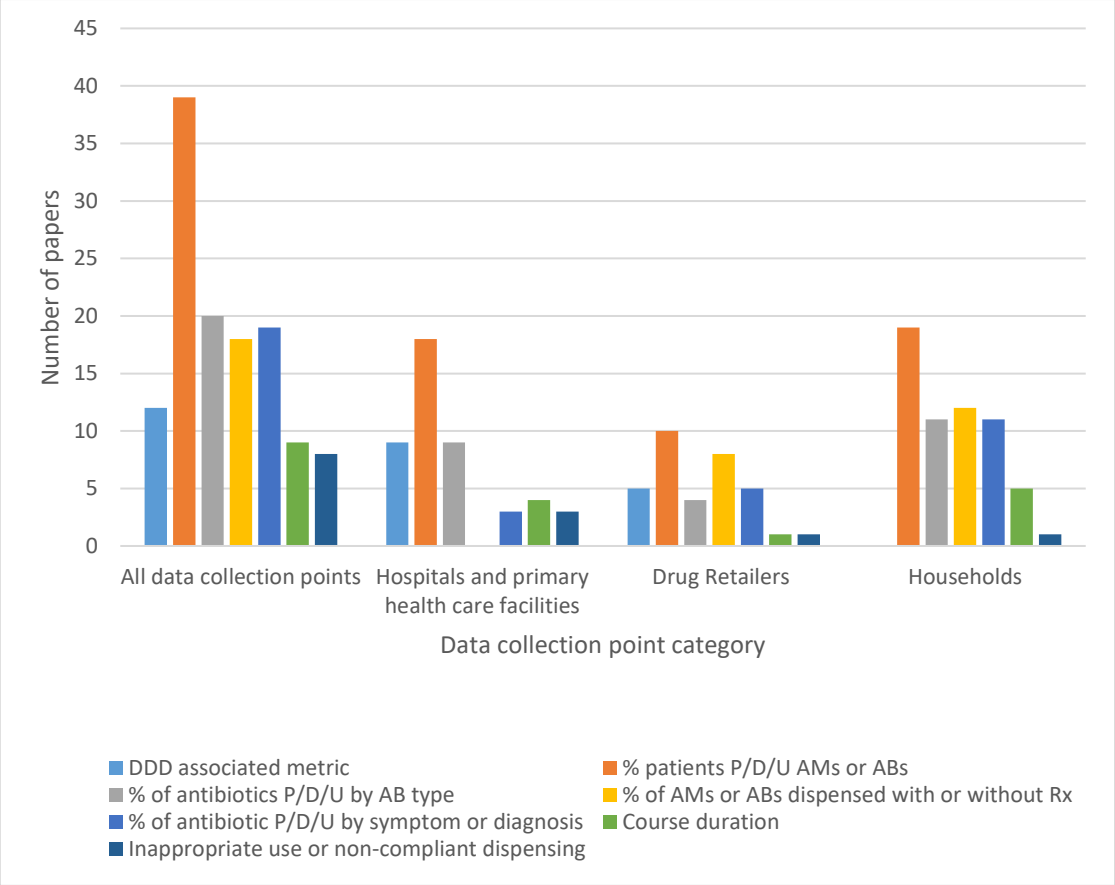

Figure 3: Main metric or outcome by type of data collection point category (Human Health)

[Key: AMs = Antimicrobials, ABs = Antibiotics, P = Prescribed, D = Dispensed, U = Used, Rx = Prescription]

Antibiotic use metrics/ outcomes used in **livestock sector** papers are presented across the range of data collection points in Table 4b, and shown specifically for livestock keepers in Figure 4. Several metrics exist in the livestock sector which attempt to match the human DDD metric such as DDDvet, mg used per kg of meat produced or per population correction unit (PCU) and Defined Course Dose (DCDvet) (Collineau et al., 2017). Only four of the 30 papers involving livestock keepers presented DDD associated metrics. The most common outcomes from the papers collecting data from livestock keepers were *reasons for using antibiotics* (21/30 papers), followed by *% of respondents using antibiotics* (20) and *most common antibiotic used by type* (17). The "Reason for use" outcome included data based on symptoms or conditions and whether antibiotics were used for diseased animals (therapeutic), to prevent spread of disease within an exposed population (prophylactic) or within an unexposed but at risk group (metaphylactic). Livestock keepers were also asked whether they used the antibiotics appropriately (primarily observation of withdrawal periods) and the dose, course duration and administration route. The only paper identified covering both human and livestock antibiotic use Roess et al. (2013), involved asking individuals within a human health study whether they kept any livestock. If so, they were asked to recall if any "treatments" (which included antibiotics, anti-parasitics or herbal) had been given in the past six months and their reasons for use. The studies using retailers, pharmaceutical reps, vets and feed retailers focussed almost exclusively on the most common antibiotics prescribed, dispensed or used or on the reasons for use (as above).

Table 4b: Main antibiotic use metrics or outcomes for livestock health papers by type of data collection point

Livestock papers n=30		Main Metrics/ Outcomes								
Data collection points	**No. of papers**	**DDD associated or similar metric**	**% respondentsP/D/U AMs or ABs**	**Most common antibiotics P/D/U by type**	**% of AMs or ABs dispensed with or without Rx**	**Reasons for use by symptom, diagnosis or Th/Pr/Me**	**Route**	**Dose**	**Course duration**	**Inappropriate use / observation of withdrawal time**
All data collection points	**30**	**4**	**20**	**21**	**1**	**21**	**6**	**5**	**5**	**7**
Livestock Keepers	30	4	20	17	1	21	6	5	5	7
Drug Retailers	6			5		4	1	1	1	
Pharmaceutical reps	4			3		4	1	1	1	
Veterinarians	2			2		2				
Feed retailers	1			1		1				
Table Key: DDD = Defined Daily Dose, AMs = Antimicrobials, ABs = Antibiotics, P = Prescribed, D = Dispensed, U = Used, Rx = Prescription, Th = Therapeutic, Pr = Prophylactic, Me = Metaphylactic										

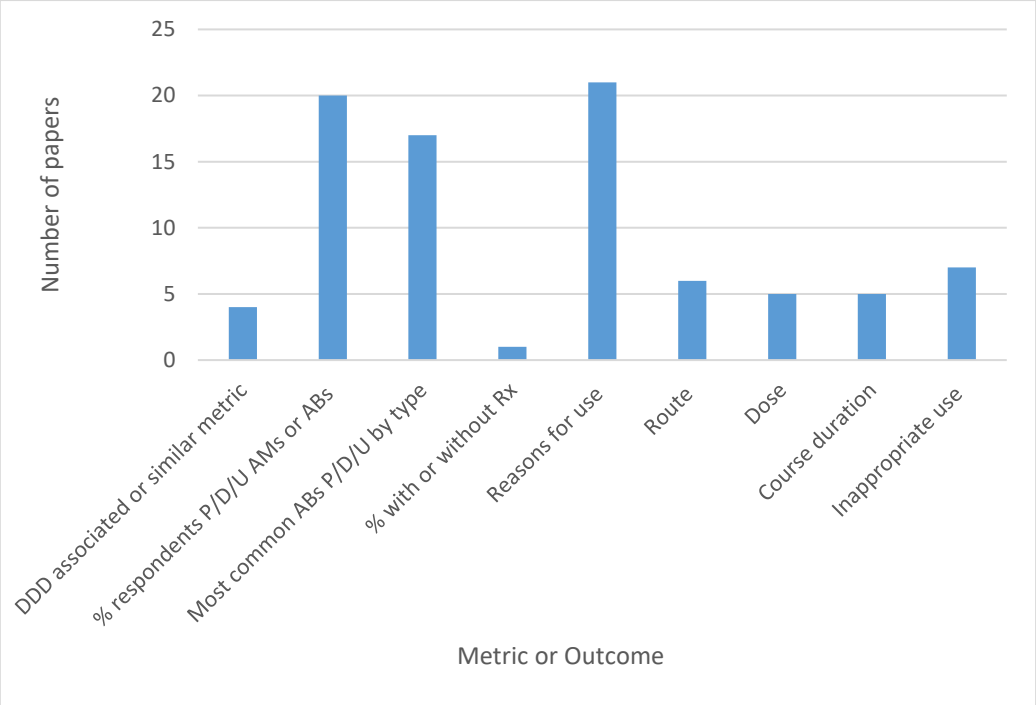

Figure 4: Main metric or outcome from livestock keepers as data collection point

[Key: DDD = Defined Daily Dose, AMs = Antimicrobials, ABs = Antibiotics, P = Prescribed, D = Dispensed, U = Used, Rx = Prescription, Th = Therapeutic, Pr = Prophylactic, Me = Metaphylactic]

4. Geographical location and scope

Table 5a shows the location, including the global region (also Figure 5), urban or rural location, and geographical scope of the **human health** papers. Four of the 48 papers were located in multiple countries and from more than one region: eight countries were included from across South Asia, Sub-Saharan Africa and Latin America by Rogawski et al. (2017), six countries from Sub-Saharan Africa and South Asia by Hopkins et al. (2017), three countries from the Middle East and North Africa and Central Asia by Belkina et al. (2014) and both India and South Africa by Holloway et al. (2011).

Fifteen of the 21 papers involving health care facilities took place in South Asia and six in sub-Saharan Africa, with public hospitals being the main source of data. Similarly, papers including drug retailers were also in sub-Saharan Africa (10/15) and S Asia (7/15) with pharmacies being the main data collection points. Household survey studies were more evenly spread across S Asia, sub-Saharan Africa, the Middle East and North Africa, and East Asia and Pacific. The urban setting predominated in the papers using data collection points from all three categories, with roughly twice as many of the reviewed papers being in urban as opposed to rural areas. Only a few studies had nationwide representation, all of which used public hospitals or private hospitals as a data collection point. Of the remainder, the majority of papers using health care facilities covered several major administrative areas, whilst drug retailer papers were mostly from smaller areas, either i) a single city (Cairo: Sabry et al. (2014)), ii) a group of wards within a city (New Delhi: Kotwani and Holloway (2011)), or a single district (Vellore, India: Chandy et al. (2013)). Similar results were found in papers using household data collection.

Table 5a: Geographical location and scope of human health papers

Human health papers n=48		Geographical location by World Bank region						Urban (U) or Rural (R)			Geographical scope		
Data collection points	**No. of papers**	**East Asia & Pacific**	**Europe & Central Asia**	**Latin America & the Caribbean**	**Middle East & North Africa**	**South Asia**	**Sub-Saharan Africa**	**U**	**R**	**Not stated**	**Nationwide**	**Several major administrative areas**	**Small selected area, single city or district**
All data collection points	**48**	**9**	**2**	**3**	**7**	**23**	**17**	**30**	**13**	**15**	**3**	**15**	**33**
Hospitals and primary health care facilities	**21**	**3**	**0**	**0**	**0**	**15**	**6**	**12**	**7**	**7**	**3**	**7**	**14**
Public hospital	20	3				12	10	11	5	8	3	8	9
Primary Health care facilities	5					5		10	2			3	2
Private Hospital	5					4	2	4	5	1	1	4	1
Private GP	6					7		6	4			5	2
Drug Retailers	**15**	**1**	**0**	**1**	**1**	**7**	**10**	**13**	**5**	**2**	**0**	**5**	**12**
Pharmacy	13	1			1	7	10	12	5	1		5	8
Drug Shop	4			1		1	7	4	3	1		2	4
Households	**19**	**5**	**2**	**2**	**6**	**6**	**7**	**9**	**4**	**7**	**0**	**8**	**11**

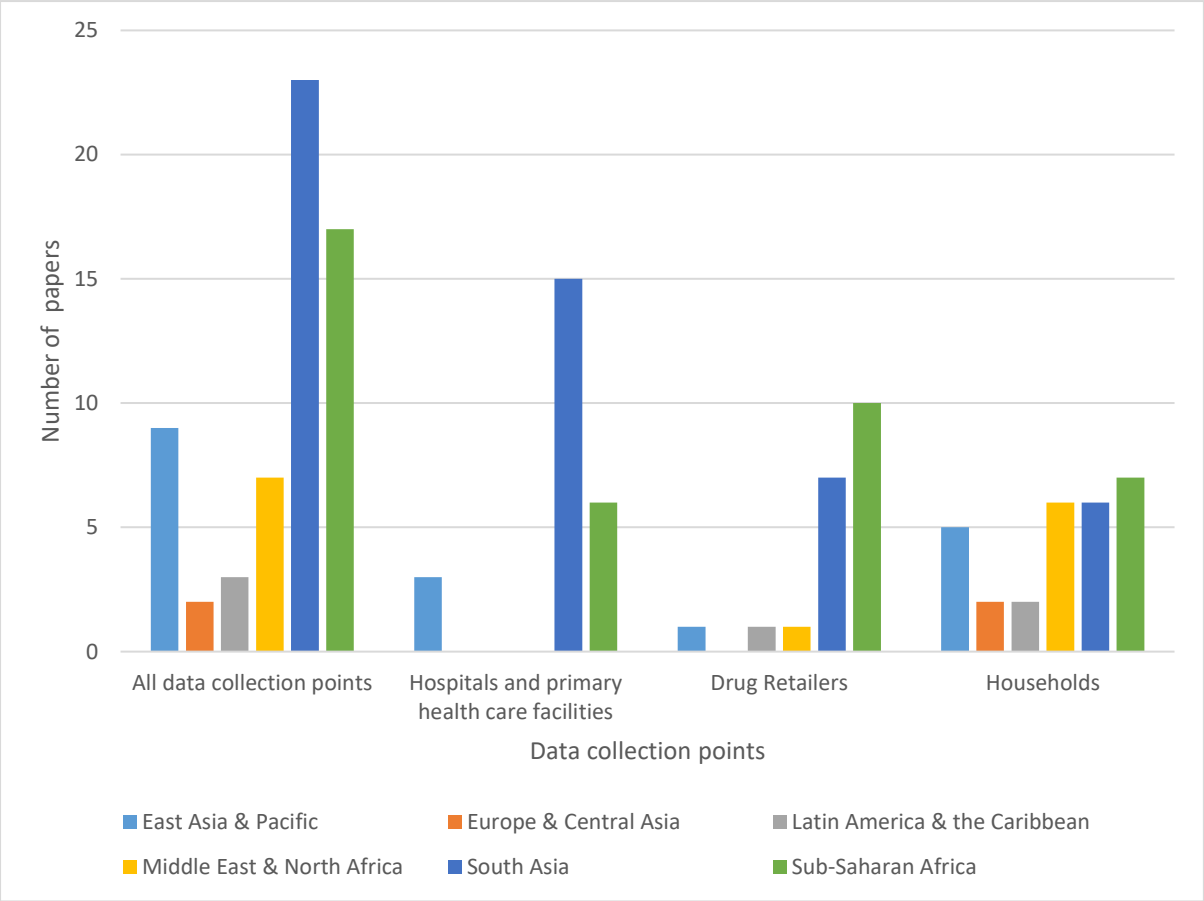

Figure 5: Location by World Bank region by data collection point category

Table 5b presents the geographical location (also Figure 6) and scope of **livestock sector** papers. Sub-Saharan Africa and East Asia and the Pacific were the predominant areas covered followed by S Asia and one study from Latin America. No papers in the review were from the regions of the Middle East and North Africa or Europe and Central Asia. Most studies did not specify if they were rural or urban, but of the 10 that did, most were urban or likely peri-urban and covered a range of animals including poultry, pigs, dairy cows and fish. No studies had nationwide coverage, only a handful (5/30) covered several administrative areas, with the rest focusing on a small selected area (often selected purposively for its density of livestock).

Table 5b: Geographical location and scope of livestock papers

Livestock papers n=30	Geographical location by World Bank region					Urban (U) or Rural (R)			Geographical scope		
Data collection points	**No. of papers**	**East Asia & Pacific**	**Latin America & the Caribbean**	**South Asia**	**Sub-Saharan Africa**	**U**	**R**	**Not Specified**	**Nationwide**	**Several major administrative areas**	**Small selected area, single city or district[1]**
All data collection points	**30**	**10**	**1**	**8**	**11**	**6**	**4**	**20**	**0**	**5**	**25**
Livestock Keepers	30	10	1	8	11	6	4	20		5	25
Drug Retailers	6			3	3	1	1	4			6
Pharmaceutical reps	4			4				4			4
Veterinarians	2	1			1	1		1			2
Feed retailers	1	1				1					1

[1]Some of these were purposively selected for density of livestock keeping establishments

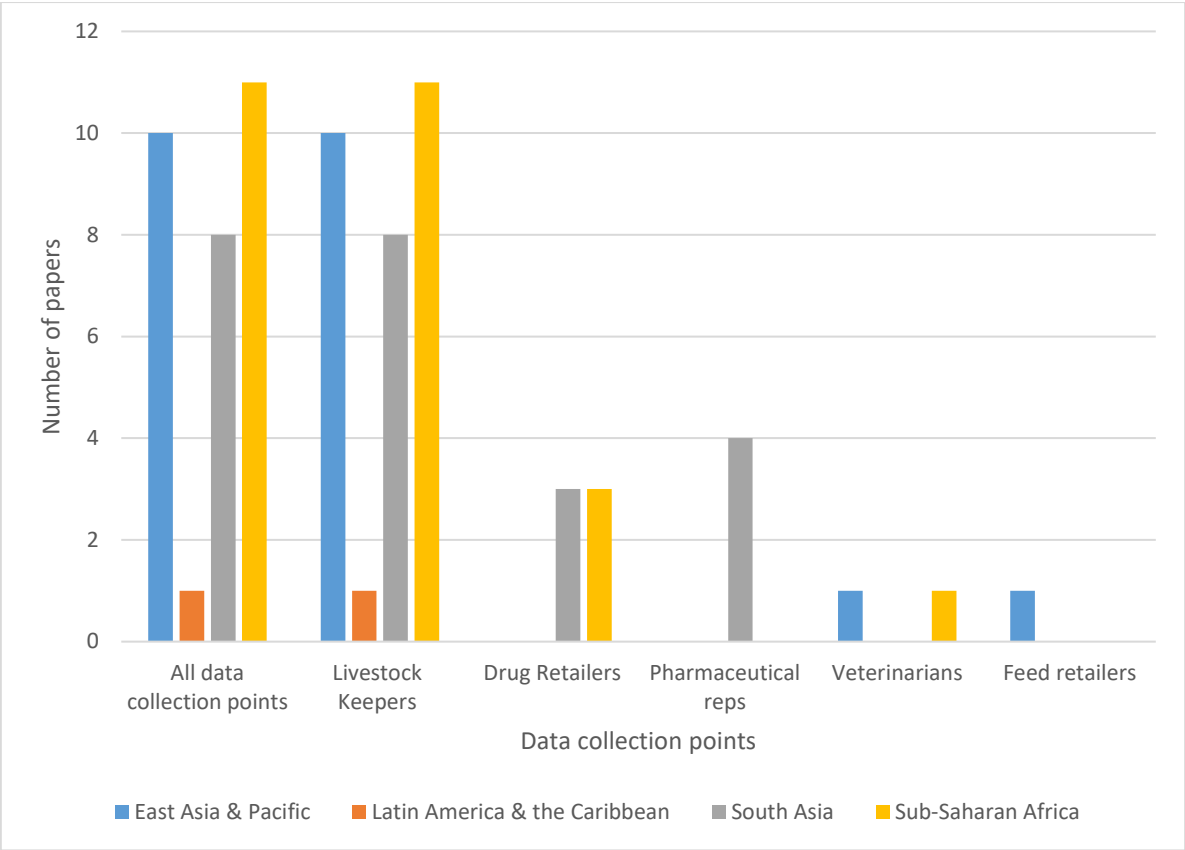

Figure 6: Location by World Bank regions by data collection point (Livestock Health)

5. Symptoms or diagnosis in human health papers[6]

Table 6 shows the scope of the **human health** papers with respect to symptoms or diagnoses covered. Overall, most studies, including those with households, did not have a specific disease focus and covered antibiotic use for all or any conditions. Of those with a symptom/disease focus, most covered more than one or used broad symptoms such as diarrhoea, respiratory symptoms or acute fever. Three studies related to antibiotic use for suspected or confirmed cases of malaria from a variety of health care facilities or drug retailer outlets.

[6] Livestock studies did not focus on specific diseases apart from one study on mastitis in dairy cows

Table 6: Scope of human health papers by symptom or diagnosis

Human health papers n= 48		Symptom or Diagnosis						
Data collection point	**No. of papers**	**Acute respiratory infection**	**Acute fever**	**Diarrhoea**	**Malaria**	**Orthopaedic**	**Pneumonia**	**Any condition**
All data collection points	**48**	**9**	**4**	**8**	**3**	**1**	**2**	**32**
Hospitals and primary health care facilities	**21**	**3**	**3**	**4**	**3**	**1**	**1**	**11**
Public hospital	20	3	3	3	3	1		12
Primary Health care facilities	5	2	1	3			1	1
Private Hospital	5	1	1	2	1			3
Private GP	6	2	1	3				3
Drug Retailers	**15**	**1**	**2**	**4**	**1**	**0**	**0**	**13**
Pharmacy	13		1		1			11
Drug Shop	4	1	1	1	1		1	2
Households	**19**	**5**	**2**	**4**	**0**	**0**	**0**	**13**

6. Species included in livestock papers

The livestock papers reviewed did not have a specific disease focus apart from one study, which related to mastitis in dairy cows. As an alternative, Table 7 presents the analysis of **livestock papers** based on the species included. The majority of papers (24/30) focussed on a single species, the most common being poultry followed by aquatic species, cattle and pigs and in a couple of studies, sheep and goats. All studies using pharmaceutical reps involved aquaculture. The single study involving feed retailers involved pigs and poultry (Om and McLaws, 2016).

Table 7: Scope of Livestock studies by species

Livestock papers n=30		Species included				
Data collection point	**No. of papers**	**Aquatic**	**Bovine**	**Porcine**	**Poultry**	**Sheep & Goats**
All data collection points	**30**	**11**	**7**	**6**	**14**	**2**
Livestock Keepers	30	11	7	6	14	2
Drug Retailers	6	3	1		2	
Pharmaceutical reps	4	4				
Veterinarians	2			1	2	
Feed retailers	1			1	1	

Current developments

Based on our key informant interviews we have included a couple of key current developments in this area of granular data collection in LMICs, in terms of both standard methodologies and research projects.

Standard methodologies

In the near future, the WHO is due to publish an updated methodology on measuring antibiotic use in hospitals using point prevalence surveys (PPS) (WHO, 2017b). The 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 (ECDC, 2016) and from the Global PPS, Antwerp, Belgium. The methodology aims to provide a standard to collect data on prescribing of antibiotics for inpatients by substance name, indication and by facility. Details of sampling are provided. At a hospital level, either all hospitals should be included or a representative sample is made using the ECDC's systematic sampling design. The latter includes using a list of hospitals, which are ranked based on bed numbers. The number of hospitals is calculated from estimated prevalence of antibiotic use and desired confidence level. A sampling interval is then calculated for systematic sampling of the hospitals. At a patient level, all inpatients are to be included in hospitals with <700 beds. For larger hospitals, every second or third patient is included. Epidemiological and risk factor data are also to be collected for all inpatients, with or without antibiotic use. Data collection on antibiotic treatments must be based on international non-proprietary names and include the single dose unit and the daily frequency to enable calculation of the prescribed daily dose. Information on indication and diagnosis are also to be collected. In addition, outward antibiotic stock movements and availability are to be recorded at the hospital level and patient level. Similarly, the WHO has plans for developing a methodology for surveying use at the community level in LMICs at the level of the prescriber, dispenser and individual, though work on this is currently in the very early stages.

Research projects

A current research project is investigating community level Antibiotic Access and Use (ABACUS) in LMICs (Wertheim et al., 2017), within the INDEPTH-Network Health and Demographic Surveillance System (HDSS) sites. It is a multicentre study using interviews among drug suppliers and community members across Bangladesh, Mozambique, Vietnam, Ghana, Thailand and South Africa over a 2.5-year period and will be completed by the end of 2018. Antibiotic suppliers are mapped using official local authority lists and local community knowledge through household surveys so as to include informal suppliers such as street vendors. As per the INRUD/WHO methodology, twenty suppliers will be selected for customer exit interviews based on exploratory studies of number of antibiotic encounters per day. At each, up to 30 antibiotic encounters will be observed for a single day for four separate days, spread over a year to account for seasonal variations. This will total 2,400 antibiotic encounters at each study site. Outcomes will focus on i) antibiotic exposure: the proportion of customers leaving a supplier with antibiotics and ii) the antibiotic burden: the DDD supplied per 100 customer encounters for each type of antibiotic. To enable the latter to be calculated, the antibiotic name, strength, units and dose will be recorded at the exit interview. A copy of the exit interview questionnaire is available as open access and is included as Annex 4.

In addition, Meenakshi Gautham and colleagues are conducting an exploratory study of antibiotic use by informal providers without medical qualifications in rural West Bengal India, using a mix of quantitative and qualitative methods (Gautham et al., 2014).

Summary and reflections on the literature

This review has identified and collated current standard procedures and protocols, and the range of methods used by research projects, as well as identifying some recent developments in antibiotic usage data collection at the granular level in LMICs. The review indicated that considerable experience and expertise exists on antibiotic use data collection, and a number of valuable resources are available. Several standard tools for assessing medicine use at the granular level exist in human health for a variety of data collection points, mainly linked to WHO and/or INRUD, and focused on measuring rational drug use (rather than volumes per se). However, none were found in livestock health at the granular level, and therefore none from a One Health perspective. Numerous research papers have been published in this area, particularly in human health and to a somewhat lesser extent for livestock (only one attempting to cover both). A wide range of methods have been used to study antibiotic use in human health and a more limited range in livestock health. Within human health, the most common are patient exit interviews, record extraction and household questionnaires, with questionnaires also very common in the livestock field, though other approaches include observation, bulk purchase /sales records and inventories for human health, and treatment logs and used-packaging bins for livestock. The vast majority of human health papers produced outputs relating to INRUD methods, e.g. % of patients prescribed or receiving antibiotics, with most livestock papers using similar metrics e.g. % of livestock keepers using antibiotics. Only a minority of human health and livestock papers produced Defined Daily Dose (DDD)[7] related metrics. Only one study (livestock) was identified which compared different data collection methods for measuring antibiotic volumes.

A number of additional gaps are notable in the existing tools and literature as a basis for studying antibiotic volumes and use. Firstly, geographical coverage of existing studies is very patchy both across and within countries, with only a few hospital studies having nationwide representation, and rural areas generally less likely to be studied. 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. 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, though this is the aim of ABACUS. Using a total market approach is demanding in terms of logistics and creation of comparable tools across providers, but would be very valuable to assess the relatively market shares of different provider types.

Next steps

A roundtable workshop and discussion will be held in London on 21 and 22 November 2017. On Day One we will hear updates from the WHO, OIE and Fleming Fund on current plans for capturing antibiotic use data and the results of this review will be presented along with presentations from a number of researchers from both human and livestock health sectors, focusing on their methods and their experiences and challenges from the field. Day Two will consist of open discussions on the methodological issues and challenges from Day One's presentations and from fellow participants and a final session to discuss how to move forward.

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

References

AL-AZZAM, S. I., AL-HUSEIN, B. A., ALZOUBI, F., MASADEH, M. M. & AL-HORANI, M. A. 2007. Self-medication with antibiotics in Jordanian population. *Int J Occup Med Environ Health,* 20**,** 373-80.

ALAM, M. A. & RASHID, M. M. 2014. Use of Aqua-Medicines and Chemicals in Aquaculture in Shatkhira District, Bangladesh. *IOSR Journal of Pharmacy and Biological Sciences,* 9**,** 05-09.

ALI, H., RICO, A., MURSHED-E-JAHAN, K. & BELTON, B. 2016. An assessment of chemical and biological product use in aquaculture in Bangladesh. *Aquaculture,* 454**,** 199-209.

ALI, S. R., AHMED, S. & LOHANA, H. 2013. Trends of empiric antibiotic usage in a secondary care hospital, karachi, pakistan. *Int J Pediatr,* 2013**,** 832857.

ALVAREZ-URIA, G., ZACHARIAH, S. & THOMAS, D. 2014. High prescription of antimicrobials in a rural district hospital in India. *Pharmacy Practice,* 12**,** 384.

AWAD, A., ELTAYEB, I., MATOWE, L. & THALIB, L. 2005. Self-medication with antibiotics and antimalarials in the community of Khartoum State, Sudan. *J Pharm Pharm Sci,* 8**,** 326-31.

BARAH, F., MORRIS, J. & GONCALVES, V. 2009. Irrational use and poor public beliefs regarding antibiotics in developing countries: a pessimistic example of Syria. *Int J Clin Pract,* 63**,** 1263-4.

BASAK, S. C. & SATHYANARAYANA, D. 2010. Evaluating medicines dispensing patterns at private community pharmacies in Tamilnadu, India. *Southern Med Review,* 3.

BASHAHUN, D. & ODOCH, T. 2015. Assessment of antibiotic usage in intensive poultry farms in Wakiso District, Uganda *Livestock Research for Rural Development.,* 27.

BELKINA, T., AL WARAFI, A., HUSSEIN ELTOM, E., TADJIEVA, N., KUBENA, A. & VLCEK, J. 2014. Antibiotic use and knowledge in the community of Yemen, Saudi Arabia, and Uzbekistan. *J Infect Dev Ctries,* 8**,** 424-9.

BHARATHIRAJA, R., SRIDHARAN, S., CHELLIAH, L. R., SURESH, S. & SENGUTTUVAN, M. 2005. Factors affecting antibiotic prescribing pattern in pediatric practice. *Indian J Pediatr,* 72**,** 877-9.

CALVA, J. 1996. Antibiotic use in a Peruvian community in Mexico: a household and drugstore survey *Soc Sci Med,* 42**,** 1121-1128.

CARRIQUE-MAS, J. J. & RUSHTON, J. 2017. Integrated Interventions to Tackle Antimicrobial Usage in Animal Production Systems: The ViParc Project in Vietnam. *Front Microbiol,* 8**,** 1062.

CARRIQUE-MAS, J. J., TRUNG, N. V., HOA, N. T., MAI, H. H., THANH, T. H., CAMPBELL, J. I., WAGENAAR, J. A., HARDON, A., HIEU, T. Q. & SCHULTSZ, C. 2015. Antimicrobial usage in chicken production in the Mekong Delta of Vietnam. *Zoonoses Public Health,* 62 Suppl 1**,** 70-8.

CHANDY, S. J., THOMAS, K., MATHAI, E., ANTONISAMY, B., HOLLOWAY, K. A. & STALSBY LUNDBORG, C. 2013. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore, South India. *J Antimicrob Chemother,* 68**,** 229-36.

COLLINEAU, L., BELLOC, C., STARK, K. D., HEMONIC, A., POSTMA, M., DEWULF, J. & CHAUVIN, C. 2017. Guidance on the Selection of Appropriate Indicators for Quantification of Antimicrobial Usage in Humans and Animals. *Zoonoses Public Health*.

DANG PHAM KIM, CLAUDE SAEGERMAN, CAROLINE DOUNY, TON VU DINH, BO HA XUAN, BINH DANG VU, NGAN PHAM HONG & SCIPPO, M.-L. 2013. First Survey on the Use of Antibiotics in Pig and Poultry Production in the Red River Delta Region of Vietnam. *Food and Public Health,* 3**,** 247-256.

DHS. 2017. *Service Provision Assessments* [Online]. Available: https://dhsprogram.com/What-We-Do/Survey-Types/SPA.cfm [Accessed 20/09/2017].

DONKOR, E. S., NEWMAN, M. J. & YEBOAH-MANU, D. 2012. Epidemiological aspects of non-human antibiotic usage and resistance: implications for the control of antibiotic resistance in Ghana. *Trop Med Int Health,* 17**,** 462-8.

ECDC 2016. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals – protocol version 5.3. Stockholm: ECDC.

ESIMONE, C. O., NWORU, C. S. & ODEOGARANYA, O. P. 2007. Utilization of antimicrobial agents with and without prescription by out-patients in selected pharmacies in South-eastern Nigeria. *Pharm World Sci* 29**,** 655-670.

FEDERAL MINISTRY OF HEALTH, N. 2010. Access to and rational use of Medicines at the household level. Abuja, Nigeria: Federal Ministry of Health, Nigeria.

GARP 2010. First report on antibiotic use and resistance in Vietnam hospitals in 2008-2009. Ministry of Health of the Socialist Republic of Vietnam and the Global Antibiotic Resistance Partnership and Oxford University Clinical Research Unit.

GAUTHAM, M., SHYAMPRASAD, K. M., SINGH, R., ZACHARIAH, A., SINGH, R. & BLOOM, G. 2014. Informal rural healthcare providers in North and South India. *Health Policy Plan,* 29 Suppl 1**,** i20-9.

GEBREKIRSTOS, N. H., WORKNEH, B. D., GEBREGIORGIS, Y. S., MISGINA, K. H., WELDEHAWERIA, N. B., WELDU, M. G. & BELAY, H. S. 2017. Non-prescribed antimicrobial use and associated factors among customers in drug retail outlet in Central Zone of Tigray, northern Ethiopia: a cross-sectional study. *Antimicrob Resist Infect Control,* 6**,** 70.

GEIDAM, Y. A., IBRAHIM, U. I., GREMA, H. A., SANDA, K. A., SULEIMAN, A. & MOHZO, D. L. 2012. Patterns of Antibiotic Sales by Drug Stores and Usage in Poultry Farms: A Questionnaire-Based Survey in Maiduguri, Northeastern Nigeria. *Journal of Animal and Veterinary Advances,* 11**,** 2852-2855.

GUYON, A. B., BARMAN, A., AHMED, J. U., AHMED, A. U. & ALAM, M. S. 1994. A baseline survey on use of drugs at the primary health care level in Bangladesh. *Bull World Health Organ,* 72**,** 265-71.

HADI, U., KEUTER, M., VAN ASTEN, H., VAN DEN BROEK, P., STUDY GROUP 'ANTIMICROBIAL RESISTANCE IN INDONESIA, P. & PREVENTION 2008. Optimizing antibiotic usage in adults admitted with fever by a multifaceted intervention in an Indonesian governmental hospital. *Trop Med Int Health,* 13**,** 888-99.

HAI 2008. Measuring medicine prices, availability, affordability and price components. World Health Organisation, Health Action International.

HOLLOWAY, K., MATHAI, E., GRAY, A., COMMUNITY-BASED SURVEILLANCE OF ANTIMICROBIAL, U. & RESISTANCE IN RESOURCE-CONSTRAINED SETTINGS PROJECT, G. 2011. Surveillance of antimicrobial resistance in resource-constrained settings - experience from five pilot projects. *Trop Med Int Health,* 16**,** 368-74.

HOLMSTRÖM, K., GRÄSLUND, S., WAHLSTRÖM, A., POUNGSHOMPOO, S., BENGTSSON, B.-E. & KAUTSKY, N. 2003. Antibiotic use in shrimp farming and implications for environmental impacts and human health. *International Journal of Food Science & Technology,* 38**,** 255-266.

HOPKINS, H., BRUXVOORT, K. J., CAIRNS, M. E., CHANDLER, C. I., LEURENT, B., ANSAH, E. K., BAIDEN, F., BALTZELL, K. A., BJORKMAN, A., BURCHETT, H. E., CLARKE, S. E., DILIBERTO, D. D., ELFVING, K., GOODMAN, C., HANSEN, K. S., KACHUR, S. P., LAL, S., LALLOO, D. G., LESLIE, T., MAGNUSSEN, P., JEFFERIES, L. M., MARTENSSON, A., MAYAN, I., MBONYE, A. K., MSELLEM, M. I., ONWUJEKWE, O. E., OWUSU-AGYEI, S., REYBURN, H., ROWLAND, M. W., SHAKELY, D., VESTERGAARD, L. S., WEBSTER, J., WISEMAN, V. L., YEUNG, S., SCHELLENBERG, D., STAEDKE, S. G. & WHITTY, C. J. 2017. Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: analysis of observational and randomised studies in public and private healthcare settings. *BMJ,* 356**,** j1054.

IRUNGU, P. A pilot survey of farmers' antibiotic use in livestock in Kenya. 1st Global Forum on Bacterial Infections: Balancng treatment access and antibiotic resistance. Session 9a: Antibiotics in Agriculture: Consequences for Resistance, 2011 3–5 October 2011, New Delhi, India.

ISLAM, M. A., HASAN, M. N., MAHMUD, Y., REZA, M. S., MAHMUD, M. S., KAMAL, M. & SIDDIQUEE, S. 2014. Obtainable Drugs for Fish Hatchery Operation and Grow-out Ponds in Bangladesh. *Annual Research and Review in Biology,* 4.

JASSIM, A. M. 2010. In-home Drug Storage and Self-medication with Antimicrobial Drugs in Basrah, Iraq. *Oman Med J,* 25**,** 79-87.

KABIR, J., UMOH, V. J., AUDU-OKOH, E., UMOH, J. U. & KWAGA, J. K. P. 2004. Veterinary drug use in poultry farms and determination of antimicrobial drug residues in commercial eggs and slaughtered chicken in Kaduna State, Nigeria. *Food Control,* 15**,** 99-105.

KAGASHE, G. A., MINZI, O. & MATOWE, L. 2011. An assessment of dispensing practices in private pharmacies in Dar-es-Salaam, Tanzania. *Int J Pharm Pract,* 19**,** 30-5.

KAMINI, M., KEUTCHATANG, F., MAFO, H., KANSCI, G. & NAMA, G. 2016. Antimicrobial usage in the chicken farming in Yaoundé, Cameroon: a cross-sectional study. *International Journal of Food Contamination,* 3.

KIBUULE, D., KAGOYA, H. R. & GODMAN, B. 2016. Antibiotic use in acute respiratory infections in under-fives in Uganda: findings and implications. *Expert Rev Anti Infect Ther,* 14**,** 863-72.

KODIMALAR, K., RAJINI, R. A., EZHILVALAVAN, S. & SARATHCHANDRA, G. 2014. A survey of chlortetracycline concentration in feed and its residue in chicken egg in commercial layer farms. *Journal of Biosciences,* 39**,** 425-431.

KOTWANI, A., CHAUDHURY, R. R. & HOLLOWAY, K. 2012. Antibiotic-prescribing practices of primary care prescribers for acute diarrhea in New Delhi, India. *Value Health,* 15**,** S116-9.

KOTWANI, A. & HOLLOWAY, K. 2011. Trends in antibiotic use among outpatients in New Delhi, India. *BMC Infectious Diseases,* 11**,** 99.

KOTWANI, A. & HOLLOWAY, K. 2014. Antibiotic prescribing practice for acute, uncomplicated respiratory tract infections in primary care settings in New Delhi, India. *Trop Med Int Health,* 19**,** 761-8.

KOTWANI, A., HOLLOWAY, K. & CHAUDHURY, R. R. 2009. Methodology for surveillance of antimicrobials use among out-patients in Delhi. *Indian J Med Res,* 129**,** 555-60.

KUMARI, K. S., CHANDY, S., JEYASEELAN, L., KUMAR, R. & SURESH, S. 2008. Antimicrobial prescription patterns for common acute infections in some rural & urban health facilities of India. *Indian Journal of Medical Research,* 128**,** 165-171.

LARSSON, M., KRONVALL, G., CHUC, N. T., KARLSSON, I., LAGER, F., HANH, H. D., TOMSON, G. & FALKENBERG, T. 2000. Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community. *Trop Med Int Health,* 5**,** 711-21.

MAHARANA, S., PAUL, B., DASGUPTA, A. & GARG, S. 2017. Storage, reuse, and disposal of unused medications: A cross-sectional study among rural households of Singur, West Bengal. *International Journal of Medical Science and Public Health***,** 1.

MANIMARAN, A., LAYEK, S. S., KUMARESAN, A., PRASAD, S., SREELA, L., BOOPATHI, V., KUMAR, K. & VENKATASUBRAMANIAN, V. 2014. Estimation of antimicrobialdrug usage for treatment of c;inical mastitis cases in organised dairy farm *Ind. J. Vet & Anim. Sci. Res. ,* 43**,** 140-150.

MBONYE, A. K., BUREGYEYA, E., RUTEBEMBERWA, E., CLARKE, S. E., LAL, S., HANSEN, K. S., MAGNUSSEN, P. & LARUSSA, P. 2016. Prescription for antibiotics at drug shops and strategies to improve quality of care and patient safety: a cross-sectional survey in the private sector in Uganda. *BMJ Open,* 6**,** e010632.

MEANS, A. R., WEAVER, M. R., BURNETT, S. M., MBONYE, M. K., NAIKOBA, S. & MCCLELLAND, R. S. 2014. Correlates of inappropriate prescribing of antibiotics to patients with malaria in Uganda. *PLoS One,* 9**,** e90179.

MUKASA, D., MUGASA, C. M. & NAKAVUMA, J. L. 2012. Antibiotic misuse by farmers in Ngoma subcounty Nakaseke district, Uganda. *Africa Journal of Animal and Biomedical Sciences,* 7.

MUKONZO, J. K., NAMUWENGE, P. M., OKURE, G., MWESIGE, B., NAMUSISI, O. K. & MUKANGA, D. 2013. Over-the-counter suboptimal dispensing of antibiotics in Uganda. *J Multidiscip Healthc,* 6**,** 303-10.

NDHLOVU, M., NKHAMA, E., MILLER, J. M. & HAMER, D. H. 2015. Antibiotic prescribing practices for patients with fever in the transition from presumptive treatment of malaria to 'confirm and treat' in Zambia: a cross-sectional study. *Trop Med Int Health,* 20**,** 1696-706.

NGA, D. T. T., CHUC, N. T. K., HOA, N. P., HOA, N. Q., NGUYEN, N. T. T., LOAN, H. T., TOAN, T. K., PHUC, H. D., HORBY, P., YEN, N. V., KINH, N. V. & WERTHEIM, H. F. 2014. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. *BMC Pharmacology and Toxicology* 15.

NGUYEN DANG GIANG, C., SEBESVARI, Z., RENAUD, F., ROSENDAHL, I., HOANG MINH, Q. & AMELUNG, W. 2015. Occurrence and Dissipation of the Antibiotics Sulfamethoxazole, Sulfadiazine, Trimethoprim, and Enrofloxacin in the Mekong Delta, Vietnam. *PLoS One,* 10**,** e0131855.

NGUYEN, N. T., NGUYEN, H. M., NGUYEN, C. V., NGUYEN, T. V., NGUYEN, M. T., THAI, H. Q., HO, M. H., THWAITES, G., NGO, H. T., BAKER, S. & CARRIQUE-MAS, J. 2016. Use of Colistin and Other Critical Antimicrobials on Pig and Chicken Farms in Southern Vietnam and Its Association with Resistance in Commensal Escherichia coli Bacteria. *Appl Environ Microbiol,* 82**,** 3727-35.

NGUYEN, Q. H., NGUYEN, T. K., HO, D., LARSSON, M., ERIKSSON, B. & LUNDBORG, C. S. 2011. Unnecessary antibiotic use for mild acute respiratory infections during 28-day follow-up of 823 children under five in rural Vietnam. *Trans R Soc Trop Med Hyg,* 105**,** 628-36.

NWOLISA, C. E., ERINAUGHA, E. U. & OFOLETA, S. I. 2006. Prescribing practices of doctors attending to under fives in a children's outpatient clinic in Owerri, Nigeria. *J Trop Pediatr,* 52**,** 197-200.

OCAN, M., BBOSA, G. S., WAAKO, P., OGWAL-OKENG, J. & OBUA, C. 2014. Factors predicting home storage of medicines in Northern Uganda. *BMC Public Health,* 14**,** 650-650.

OKUMURA, J., WAKAI, S. & UMENAI, T. 2002. Drug utilisation and self-medication in rural communities in Vietnam. *Soc Sci Med,* 54**,** 1875-86.

OLATOYE, I. O. & BASIRU, A. 2013. Antibiotic Usage and Oxytetracycline Residue in African Catfish (Clarias gariepinus in Ibadan, Nigeria). *World Journal of Fish and Marine Sciences,* 5**,** 302-309.

OLUWASILE, B. B., AGBAJE, M., OJO, O. E. & DIPEOLU, M. A. 2014. Antibiotic usage pattern in selected poultry farms in Ogun state. *Sokoto Journal of Veterinary Sciences,* 12**,** 45.

OM, C. & MCLAWS, M. L. 2016. Antibiotics: practice and opinions of Cambodian commercial farmers, animal feed retailers and veterinarians. *Antimicrob Resist Infect Control,* 5**,** 42.

PAUDEL, K. R., SHARMA, M. & DAS, B. P. 2008. Prevalence of antimicrobial chemotherapy in hospitalized patients in the department of internal medicine in a tertiary care center. *Nepal Med Coll J,* 10**,** 91-5.

PHAM, D. K., CHU, J., DO, N. T., BROSE, F., DEGAND, G., DELAHAUT, P., DE PAUW, E., DOUNY, C., NGUYEN, K. V., VU, T. D., SCIPPO, M. L. & WERTHEIM, H. F. 2015. Monitoring Antibiotic Use and Residue in Freshwater Aquaculture for Domestic Use in Vietnam. *Ecohealth,* 12**,** 480-9.

REDDING, L. E., CUBAS-DELGADO, F., SAMMEL, M. D., SMITH, G., GALLIGAN, D. T., LEVY, M. Z. & HENNESSY, S. 2014. Comparison of two methods for collecting antibiotic use data on small dairy farms. *Prev Vet Med,* 114**,** 213-22.

RICO, A., OLIVEIRA, R., MCDONOUGH, S., MATSER, A., KHATIKARN, J., SATAPORNVANIT, K., NOGUEIRA, A. J., SOARES, A. M., DOMINGUES, I. & VAN DEN BRINK, P. J. 2014. Use, fate and ecological risks of antibiotics applied in tilapia cage farming in Thailand. *Environ Pollut,* 191**,** 8-16.

RICO, A., PHU, T. M., SATAPORNVANIT, K., MIN, J., SHAHABUDDIN, A. M., HENRIKSSON, P. J. G., MURRAY, F. J., LITTLE, D. C., DALSGAARD, A. & VAN DEN BRINK, P. J. 2013. Use of veterinary medicines, feed additives and probiotics in four major internationally traded aquaculture species farmed in Asia. *Aquaculture,* 412-413**,** 231-243.

RODERICK, S., STEVENSON, P., MWENDIA, C. & OKECH, G. 2000. The use of trypanocides and antibiotics by Maasai pastoralists. *Tropical Animal Health and Production,* 32**,** 361-374.

ROESS, A. A., WINCH, P. J., AKHTER, A., AFROZ, D., ALI, N. A., SHAH, R., BEGUM, N., SERAJI, H. R., EL ARIFEEN, S., DARMSTADT, G. L., BAQUI, A. H. & BANGLADESH PROJAHNMO STUDY, G. 2015.

Household Animal and Human Medicine Use and Animal Husbandry Practices in Rural Bangladesh: Risk Factors for Emerging Zoonotic Disease and Antibiotic Resistance. *Zoonoses Public Health,* 62**,** 569-78.

ROGAWSKI, E. T., PLATTS-MILLS, J. A., SEIDMAN, J. C., JOHN, S., MAHFUZ, M., ULAK, M., SHRESTHA, S. K., SOOFI, S. B., YORI, P. P., MDUMA, E., SVENSEN, E., AHMED, T., LIMA, A. A., BHUTTA, Z. A., KOSEK, M. N., LANG, D. R., GOTTLIEB, M., ZAIDI, A. K., KANG, G., BESSONG, P. O., HOUPT, E. R. & GUERRANT, R. L. 2017. Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. *Bull World Health Organ,* 95**,** 49-61.

SABRY, N. A., FARID, S. F. & DAWOUD, D. M. 2014. Antibiotic dispensing in Egyptian community pharmacies: an observational study. *Res Social Adm Pharm,* 10**,** 168-84.

SARADAMMA, R. D., HIGGINBOTHAM, N. & NICHTER, M. 2000. Social factors influencing the acquisition of antibiotics without prescription in Kerala State, south India. *Soc Sci Med,* 50**,** 891-903.

SASANYA, J. J., OGWAL OKENG, J. W., EJOBI, F. & MUGANWA, M. 2005. Use of sulfonamides in layers in Kampala district, Uganda and sulfonamide residues in commercial eggs. *African Health Sciences,* 5**,** 33-39.

SHAMSUZZAMAN, M. & BISWAS, T. 2012. Aqua chemicals in shrimp farm: A study from south-west coast of Bangladesh. *The Egyptian Journal of Aquatic Research,* 38**,** 275-285.

SHANKAR, P. R., PAI, R., DUBEY, A. K. & UPADHYAY, D. K. 2007. Prescribing patterns in the orthopaedics outpatient department in a teaching hospital in Pokhara, western Nepal. *Kathmandu Univ Med J (KUMJ),* 5**,** 16-21.

SHANKAR, P. R., UPADHYAY, D. K., SUBISH, P., DUBEY, A. K. & MISHRA, P. 2006. Prescribing patterns among paediatric inpatients in a teaching hospital in western Nepal. *Singapore Med J,* 47**,** 261-5.

SHARKER, R., SUMI, K., ALAM, J., RAHMAN, M., FERDOUS, Z., ALI, M. & CHAKLADER, R. 2014. *Drugs and chemicals used in Aquaculture activities for fish health management in the coastal region of Bangladesh*.

SPS 2012. How to investigate antimicrobial use in hospitals: selected indicators. Arlington, USA: Agency for International Development by the Strengthening Pharmaceutical Systems Program.

STRATCHOUNSKI, L. S., ANDREEVA, I. V., RATCHINA, S. A., GALKIN, D. V., PETROTCHENKOVA, N. A., DEMIN, A. A., KUZIN, V. B., KUSNETSOVA, S. T., LIKHATCHEVA, R. Y., NEDOGODA, S. V., ORTENBERG, E. A., BELIKOV, A. S. & TOROPOVA, I. A. 2003. The inventory of antibiotics in Russian home medicine cabinets. *Clin Infect Dis,* 37**,** 498-505.

THU, T. A., RAHMAN, M., COFFIN, S., HARUN-OR-RASHID, M., SAKAMOTO, J. & HUNG, N. V. 2012. Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *Am J Infect Control,* 40**,** 840-4.

TOGOOBAATAR, G., IKEDA, N., ALI, M., SONOMJAMTS, M., DASHDEMBEREL, S., MORI, R. & SHIBUYA, K. 2010. Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia. *Bull World Health Organ,* 88**,** 930-6.

WERTHEIM, H. F. L., CHUC, N. T. K., PUNPUING, S., KHAN, W. A., GYAPONG, M., ASANTE, K. P., MUNGUAMBE, K., GÓMEZ-OLIVÉ, F. X., ARIANA, P., JOHN-LANGBA, J., SIGAUQUE, B., TOAN, T. K., TOLLMAN, S., CREMERS, A. J. H., DO, N. T. T., NADJM, B., VAN DOORN, H. R., KINSMAN, J. & SANKOH, O. 2017. Community-level antibiotic access and use (ABACUS) in low- and middle-income countries: Finding targets for social interventions to improve appropriate antimicrobial use – an observational multi-centre study. *Wellcome Open Research,* 2**,** 58.

WHO 1993. How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators. World Health Organisation.

WHO 2004. How to investigate the use of medicines by consumers. *In:* HARDON, A., HODGKIN, C. & FRESLE, D. (eds.). World Health Organisation.

WHO 2007. WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations Guide for coordinators and data collectors. World Health Organisation.

WHO. 2017a. *Country Situational Analyses of Medicines Management in Health Care Delivery* [Online]. Available: http://www.searo.who.int/entity/medicines/country_situational_analysis/en/ [Accessed 12/09/2017].

WHO 2017b. WHO Methodology for Point Prevalence Survey on Antibiotic Use in Hospitals. Version 1.0 [DRAFT]. World Health Organisation.

WONDIMU, A., MOLLA, F., DEMEKE, B., ETICHA, T., ASSEN, A., ABRHA, S. & MELKAM, W. 2015. Household Storage of Medicines and Associated Factors in Tigray Region, Northern Ethiopia. *PLoS One,* 10**,** e0135650.

YOUSIF, M. A. 2002. In-home drug storage and utilization habits: a Sudanese study. *East Mediterr Health J,* 8**,** 422-31.

Annexes

Annex 1: Alphabetical list of key informant interview participants

Name	Institution
Angkana Sommanustweechai	LSHTM
Arno Muller	WHO
Barbara Häsler	RVC
Barbara Wieland	CGIAR
Christie Peacock	SIDAI
Cristina Lussiana	PSI
Dishon Muloi	Edinburgh University
Elisabeth Erlacher-Vindel	OIE
Eric Fevre	Liverpool University
Franck Berthe	World Bank
Jonathan Rushton	Liverpool University
Kathy Holloway	IDS/WHO
Liz Tayler	WHO
Lucy Coyne	Liverpool University
Marco Haenssgen	Oxford University
Megan Littrell	PATH
Nigel French	Massey University
Paul Coleman	H2O Venture Partners
Rezin Odede	SIDAI
Stephen Poyer	PSI

Annex 2: Human health papers reviewed

	Author	Title	Country
1	Al-Azzam et al. (2007)	Self-medication with Antibiotics in Jordanian population	Jordan
2	Ali et al. (2013)	Trends of empiric antibiotic usage in a secondary care hospital, Karachi, Pakistan	Pakistan
3	Alvarez-Uria et al. (2014)	High prescription of antimicrobials in a rural district hospital in India	India
4	Awad et al. (2005)	Self-medication with Antibiotics and Antimalarials in the community of Khartoum State, Sudan	Sudan
5	Barah et al. (2009)	Irrational use and poor public beliefs regarding antibiotics in developing countries: a pessimistic example of Syria	Syria
6	Basak and Sathyanarayana (2010)	Evaluating medicines dispensing patterns at private community pharmacies in Tamilnadu, India	India
7	Belkina et al. (2014)	Antibiotic use and knowledge in the community of Yemen, Saudi Arabia, and Uzbekistan	Yemen, Saudi Araba, Uzbekistan
8	Bharathiraja et al. (2005)	Factors affecting antibiotic prescribing pattern in paediatric practice	India
9	Calva (1996)	Antibiotic use in a Periurban community in Mexico: a household and drugstore survey	Mexico
10	Chandy et al. (2013)	Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore, south India	India
11	Nga et al. (2014)	Antibiotic sales in rural and urban pharmacies in Northern Vietnam: an observational study	Vietnam
12	Esimone et al. (2007)	Utilization of antimicrobial agents with and without prescription by out-patients in selected pharmacies in South-eastern Nigeria	Nigeria
13	Federal Ministry of Health (2010)	Access to and rational use of medicines at household level	Nigeria
14	GARP (2010)	First report on antibiotic use and resistance in Vietnam hospitals in 2008-2009	Vietnam
15	Gebrekirstos et al. (2017)	Non-prescribed antimicrobial use and associated factors among customers in drug retail outlet in Central Zone of Tigray, northern Ethiopia: a cross-sectional study	Ethiopia
16	Guyon et al. (1994)	A baseline survey on use of drugs at the primary health care level in Bangladesh	Bangladesh
17	Hadi et al. (2008)	Optimizing antibiotic usage in adults admitted for fever by a multifaceted intervention in an Indonesian governmental hospital	Indonesia
18	Holloway et al. (2011)	Surveillance of community Antimicrobial Use in resource-constrained settings: experience from five pilot projects	India
19	Hopkins et al. (2017)	Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: analysis of observational and randomised studies in public and private healthcare settings	Afghanistan, Cameroon, Ghana, Nigeria, Tanzania, and Uganda
20	Jassim (2010)	In-home Drug Storage and Self-medication with Antimicrobial Drugs in Basrah, Iraq	Iraq
21	Kagashe et al. (2011)	An assessment of dispensing practices in private pharmacies in Dar-es-Salaam, Tanzania	Tanzania
22	Kibuule et al. (2016)	Antibiotic use in acute respiratory infections in under-fives in Uganda: findings and implications	Uganda
23	Kotwani et al. (2009)	Methodology for surveillance of antimicrobials use among out-patients in Delhi	India
24	Kotwani and Holloway (2011)	Trends in antibiotic use among outpatients in New Delhi, India	India
25	Kotwani et al. (2012)	Antibiotic-Prescribing Practices of Primary Care Prescribers for Acute Diarrhea in New Delhi, India	India
26	Kotwani and Holloway (2014)	Antibiotic prescribing practice for acute, uncomplicated respiratory tract infections in primary care settings in New Delhi, India	India

	Author	Title	Country
27	Kumari et al. (2008)	Antimicrobial prescription patterns for common acute infections in some rural & urban health facilities of India	India
28	Larsson et al. (2000)	Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community	Vietnam
29	Maharana et al. (2017)	Storage, reuse, and disposal of unused medications: A cross-sectional study among rural households of Singur, West Bengal	India
30	Mbonye et al. (2016)	Prescription for antibiotics at drug shops and strategies to improve quality of care and patient safety: a cross-sectional survey in the private sector in Uganda	Uganda
31	Means et al. (2014)	Correlates of Inappropriate Prescribing of Antibiotics to Patients with Malaria in Uganda	Uganda
32	Mukonzo et al. (2013)	Over-the-counter suboptimal dispensing of antibiotics in Uganda	Uganda
33	Ndhlovu et al. (2015)	Antibiotic prescribing practices for patients with fever in the transition from presumptive treatment of malaria to 'confirm and treat' in Zambia: a cross-sectional study	Zambia
34	Nguyen et al. (2011)	Unnecessary antibiotic use for mild acute respiratory infections during 28-day follow-up of 823 children under five in rural Vietnam	Vietnam
35	Nwolisa et al. (2006)	Prescribing Practices of Doctors Attending to Under Fives in a Children's Outpatient Clinic in Owerri, Nigeria	Nigeria
36	Ocan et al. (2014)	Factors predicting home storage of medicines in Northern Uganda	Uganda
37	Okumura et al. (2002)	Drug utilisation and self-medication in rural communities in Vietnam	Vietnam
38	Paudel et al. (2008)	Prevalence of antimicrobial chemotherapy in hospitalized patients in the department of internal medicine in a tertiary care center	Nepal
39	Rogawski et al. (2017)	Use of antibiotics in children younger than two years in eight countries: a prospective cohort study	Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, Tanzania
40	Sabry et al. (2014)	Antibiotic dispensing in Egyptian community pharmacies: An observational study	Egypt
41	Saradamma et al. (2000)	Social factors influencing the acquisition of antibiotics without prescription in Kerala State, south India	India
42	Shankar et al. (2006)	Prescribing Patterns among Paediatric Inpatients in a Teaching Hospital in Western Nepal	Nepal
43	Shankar et al. (2007)	Prescribing Patterns in the Orthopaedics Outpatient Department in a Teaching Hospital in Pokhara, Western Nepal	Nepal
44	Stratchounski et al. (2003)	The Inventory of antibiotics in Russian Home Medicine cabinets	Russia
45	Thu et al. (2012)	Antibiotic Use in Vietnamese hospitals: A Multicenter Point-Prevalence Study	Vietnam
46	Togoobaatar et al. (2010)	Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia	Mongolia
47	Wondimu et al. (2015)	Household Storage of Medicines and Associated Factors in Tigray Region, Northern Ethiopia	Ethiopia
48	Yousif (2002)	In-home drug storage and utilization habits: a Sudanese study	Sudan

Annex 3: Livestock health papers reviewed

	Reference	Title	Country
1	Alam and Rashid (2014)	Use of Aqua-Medicines and Chemicals in Aquaculture in Shatkhira District, Bangladesh	Bangladesh
2	Ali et al. (2016)	An assessment of chemical and biological product use in aquaculture in Bangladesh	Bangladesh
3	Bashahun and Odoch (2015)	Assessment of antibiotic usage in intensive poultry farms in Wakisa District, Uganda	Uganda
4	Carrique-Mas et al. (2015)	Antimicrobial Usage in Chicken Production in the Mekong Delta of Vietnam	Vietnam
5	Carrique-Mas and Rushton (2017)	Integrated Interventions to Tackle Antimicrobial Usage in Animal Production Systems: The ViParc Project in Vietnam	Vietnam
6	Donkor et al. (2012)	Epidemiological aspects of non-human antibiotic usage and resistance: implications for the control of antibiotic resistance in Ghana	Ghana
7	Geidam et al. (2012)	Patterns of antibiotic sales by drug stores and usage in poultry farms: a questionnaire based survey in Maiduguri, Northeastern Nigeria	Nigeria
8	Nguyen Dang Giang et al. (2015)	Occurrence and Dissipation of the Antibiotics Sulfamethoxazole, Sulfadiazine, Trimethoprim, and Enrofloxacin in the Mekong Delta, Vietnam	Vietnam
9	Holmström et al. (2003)	Antibiotic use in shrimp farming and implications for environmental impacts and human health	Thailand
10	Irungu (2011)	A pilot survey of farmers' antibiotic use in livestock in Kenya	Kenya
11	Islam et al. (2014)	Obtainable drugs for fish hatchery operation and grow-out ponds in Bangladesh	Bangladesh
12	Kabir et al. (2004)	Veterinary drug use in poultry farms and determination of antimicrobial drug residues in commercial eggs and slaughtered chicken in Kaduna State, Nigeria	Nigeria
13	Kamini et al. (2016)	Antimicrobial usage in the chicken farming in Yaoundé, Cameroon: a cross-sectional study	Cameroon
14	Dang Pham Kim et al. (2013)	First Survey on the Use of Antibiotics in Pig and Poultry Production in the Red River Delta Region of Vietnam	Vietnam
15	Kodimalar et al. (2014)	A survey of chlortetracycline concentration in feed and its residue in chicken egg in commercial layer farms	India
16	Manimaran et al. (2014)	Estimation of antimicrobial drug usage for treatment of clinical mastitis cases in organised dairy farm	India
17	Mukasa et al. (2012)	Antibiotic misuse by farmers in Ngoma subcounty Nakaseke district, Uganda	Uganda
18	Nguyen et al. (2016)	Use of Colistin and Other Critical Antimicrobials on Pig and Chicken Farms in Southern Vietnam and Its Association with Resistance in Commensal Escherichia coli Bacteria	Vietnam
19	Olatoye and Basiru (2013)	Antibiotic usage and oxytetracycline residue in African Catfish (*Clarias gariepinus)* in Ibadan, Nigeria	Nigeria
20	Oluwasile et al. (2014)	Antibiotic usage pattern in selected poultry farms in Ogun state	Nigeria
21	Om and McLaws (2016)	Antibiotics: practice and opinions of Cambodian commercial farmers, animal feed retailers and veterinarians	Cambodia
22	Pham et al. (2015)	Monitoring Antibiotic Use and Residue in Freshwater Aquaculture for Domestic Use in Vietnam	Vietnam
23	Redding et al. (2014)	Comparison of two methods for collecting antibiotic use data on small dairy farms	Peru
24	Rico et al. (2013)	Use of veterinary medicines, feed additives and probiotics in four major internationally traded aquaculture species farmed in Asia	Vietnam
25	Rico et al. (2014)	Use, fate and ecological risks of antibiotics applied in tilapia cage farming in Thailand	Thailand
26	Roderick et al. (2000)	The Use of Trypanocides and Antibiotics by Maasai Pastoralists	Kenya

	Reference	Title	Country
27	Roess et al. (2015)	Household Animal and Human Medicine Use and Animal Husbandry Practices in Rural Bangladesh: Risk Factors for Emerging Zoonotic Disease and Antibiotic Resistance	Bangladesh
28	Sasanya et al. (2005)	Use of sulphonamides in layers in Kampala district, Uganda and sulphonamide residues in commercial eggs	Uganda
29	Shamsuzzaman and Biswas (2012)	Aqua chemicals in shrimp farm: A study from the south-west coast of Bangladesh	Bangladesh
30	Sharker et al. (2014)	Drugs and chemicals used in Aquaculture activities for fish health management in the coastal region of Bangladesh	Bangladesh

Annex 4: Example of Exit Interview Questionnaire (ABACUS study)

Reproduced from open access publication (Wertheim et al., 2017)

Supplementary File 8: eCRF_ antibiotic encounter customer exit questionnaire

i. The following questions will be answered for each type of antibiotic supplied to a particular customer.

ii. Tablets, capsules, paediatric formulations, as well as intravenous and intramuscular antibiotics are to be assessed, but not other formulae like droplets or creams.

iii. The reason-for-encounter symptoms are based on the International Classification of Primary Care (ICPC-2e v5 May 2015).

iv. As a matter of courtesy, the antibiotic supplier/dispenser should be informed that exit interviews will be conducted outside their facility.

CUSTOMER EXIT INTERVIEW PARTICIPANT

……_....._.....

[study site]_[antibiotic supplier]_[customer exit interview participant]

Demographics

1) Age ……years
2) Sex male / female
3) Only if you are comfortable with it, I would like to ask for your permission to examine your antibiotic/s together with you. If you are not comfortable with this, I will respect this and complete the interview without inspection of your antibiotics.

   Permission provided? yes / no

Antibiotics

4) What is the name of the antibiotic/s you receive (Generic name, not brand name)?

   …….
5) What is the size of one tablet? ……mg / unknown
6) How many tablets are supplied?

   …….
7) For how many days is this antibiotic supplied? ……days / unknown
8) Were these antibiotics prescribed by a health professional? Yes / no
9) For who is this antibiotic?
   (tick one; Myself/ Child family member / adult family member / friend or relative / animal / unspecified / other: …../ unknown)
10) Are you comfortable with telling us about the illness for which you got this antibiotic?

    Yes / no

    If no, skip to Question 12
11) *If yes*, for what illness did you receive this antibiotic? Sore throat / cough / Flu / headache / Pain / Weakness / Wound / Dental / dyspnoea / ear / eye / nose / throat / fever / boil /

gastrointestinal / Sexually Transmitted Infection / gynaecological / male genital / urinary tract infection / Chest pain / musculoskeletal / preventive / skin and soft tissue / surgery-related / HIV related opportunist infections / other (specify) / unknown.

12) Today is [*select one option*] the expiry date. before / after / unknown

13) Did you receive written instructions for use? yes / no

14) Did you receive verbal instructions for use? yes / no

15) How do you rate your overall experience with the medicine supplier attended?

Visual analogue scale

We have finished the interview. Thank you for your participation.
