Antimicrobial Resistance in Low and Middle Income Countries

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An Analysis of Surveillance Networks

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Executive Summary

The burden of drug-resistant infections is increasing year on year. The largest numbers of lives that will be lost as a result are predicted to be in low- and middle-income countries (LMICs)[1]. As well as shouldering the bulk of the global burden of infectious diseases and drug resistance, surveillance systems in LMICs tend to be weaker, mainly because passive surveillance cannot be integrated into routine case-management of patients in most areas as health systems are too weak. This problem has been circumvented in HIV, tuberculosis (TB) and malaria by designing vertical global surveillance programmes which gather data intermittently to provide a snapshot of the situation. Even with this approach results have been patchy. It is estimated that ~75% of the world's multidrug resistant TB (MDR-TB) cases go undiagnosed and only one third of malaria endemic countries were in compliance with the recommended targets for antimalarial drug efficacy surveillance when last reported [2, 3]. Attempts to kick start global surveillance for resistance to commonly used antibacterial drugs have been made in the past but generally without success [4-6]. The recent catastrophic Ebola epidemic in West Africa has brought the need for surveillance for emerging diseases, in particular those caused by zoonotic pathogens, into sharp focus as experience has shown the majority of these have their origins in LMICs. This argues for adopting a 'One Health' approach to surveillance, taking into account disease transmission dynamics between humans, animals and the environment.

As well as having weaker systems of surveillance for antimicrobial resistance (AMR) LMICs have fewer resources to tackle the problem. The medical and veterinary workforces are smaller and less diversified than in high income countries (HICs) and there is less regulation of antimicrobial drugs which are more likely to be substandard, falsified or unregistered/unlicensed [7]. In the agricultural and farming sectors there has been an increase in intensive production systems for pig and poultry in middle-income countries in response to increased demand for meat accompanying economic growth [8]. These systems are associated with substantial antimicrobial use.

Awareness of AMR and its impact is increasing globally but there is still a long way to go to change ingrained behaviours and attitudes to antibiotic use and infection prevention to bring about the desired impact to slow the spread of AMR. Availability of antimicrobials over-the-counter without prescription is a likely driver for the spread of AMR in many LMICs but at the same time, large swathes of the community, particularly in rural and semirural areas, lack access to antimicrobial drugs and healthcare. This contributes to millions of avoidable deaths, such as the 0.6 million neonates who are estimated to die from sepsis each year [9].

In recognition of the growing threat to health posed by drug-resistant infections, the Fleming Fund was launched in March 2015 with the aim of strengthening surveillance and response capacity in LMICs. The fund is a collaborative effort of the UK Government, the Wellcome Trust, the Bill and Melinda Gates Foundation, the Institut Pasteur International Network and other partners. This report is the output of one piece of scoping work to inform future Fleming activities.

The objective of this scoping work was to identify networks dealing with surveillance, monitoring and analysis of resistance in low and middle income countries, including networks supporting quality assurance, which currently exist or have existed over the last fifteen years and to suggest factors which are important to achieving impact, success and sustainability.

Networks dealing with surveillance, monitoring and analysis of antimicrobial resistance and quality management in LMICs

Through a detailed search of the literature we identified 105 supranational networks concerned with surveillance, monitoring or analysis of drug resistance in bacterial infections, malaria, HIV or TB in humans and animals since 2000. We took an inclusive approach in our definition of networks which were classified as WHO/governmental (n=40), academic (35), pharmaceutical company/contract research organisation led (20), digital disease detection networks (4), and other (6) e.g. an international network for travel-related disease.

In terms of the main pathogens under surveillance, 46 networks were for AMR in bacteria, 18 in malaria, four in TB and nine in HIV. There were 20 general 'disease surveillance' networks, some of which had some AMR surveillance activity and most of these adopted a One Health approach. The remaining networks were a miscellaneous group focused on a variety of individual pathogens or combinations of pathogens e.g. influenza, fungi. The median [range] duration of the networks was 8 years [1-69]. The WHO's Global Influenza Surveillance and Response System (WHO GISRS) was the longest running network, established in 1947, although antiviral resistance was not part of surveillance at the outset. The median [range] number of countries covered by the networks for which information was available was 13 [2-180] and the median [range] number of LMICs covered was 7 [1-121].

From the total of 105 networks 69 are still ongoing. We looked for evidence of activity or functioning of the current networks. Of the current 69, only 34 have published any AMR data in the form of a report or academic publication during the last 3 years and of these six reports were regarding isolates which were collected more than 3 years ago. The other 35 networks did not report any data. We could find no evidence of any activity of any description in the last year for eight networks so it is unclear whether they are still functioning. The reasons networks ceased to exist was usually not available. Fourteen of the current networks operated some kind of external quality assurance scheme which involved LMIC laboratories, seven did not, and for the remainder it was unclear. The data sharing models of the current networks for which this was applicable were open (4), closed (5) and shared or unclear (54).

There is very little coordinated AMR surveillance at regional or global level in animals currently except for surveillance of foodborne infections e.g. by the WHO Global Foodborne Infections network (GFN) and PulseNet International. Pilot projects have taken place in some LMICs with guidance from the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). It is unknown whether a lot more data may exist which is not in the public domain since the health of most animals in the food-production sector, which is a priority for AMR surveillance in animals, is in the hands of large corporations.

Impacts and challenges of the networks

Important impacts of the networks include influencing national treatment policies, informing vaccine development and deployment, improvements in laboratory capacity as a result of establishing networks of reference laboratories and quality management systems, standardisation of surveillance methodologies including data analysis, data sharing, and exchange of information and knowledge between countries. National ownership of surveillance activities was associated with sustainability.

There have also been a number of challenges such as poor coverage of global surveillance programmes, notably over much of sub-Saharan Africa and India. Obtaining representative and comparable data, in particular for drug-resistant bacterial infections has proved extremely challenging. Blood cultures are prioritised as samples for AMR surveillance since they are traditionally thought to be less prone to sampling biases. However in most LMICs blood cultures are not a routine investigation and antimicrobials are chosen empirically without relying on results from diagnostic microbiological tests so it has been difficult to increase uptake of this test in LMIC settings. The more complex the methods for optimum surveillance of drug resistance, the less likely they are to make it into routine protocols e.g. second-line susceptibility testing for TB or *in vivo* surveillance for artemisinin resistance in malaria. Most networks do not have a clear data access policy and reporting delays are common with all networks except the digital disease detection networks.

Supranational laboratory quality management programmes

We identified 32 initiatives (27 still operational) relevant to the quality management of AMR surveillance in LMICs at a regional or global level. More than a third (11) were coordinated by a supranational UN-affiliated body, usually the WHO. The remaining programmes were a mixture of governmental, non-governmental and academic groups or commercial enterprises. Some programmes offered proficiency testing only (15), while many offered different combinations of proficiency testing, standards or policy setting, accreditation, training, assessment and evaluation, or were a repository for/provider of reference material.

Numerous guides, manuals, checklists and other aids to implementation of quality systems in diverse contexts have been developed. These often include recommendations on human resources, infrastructure, safety measures, standards and procedures for specimen collection and testing, QC requirements along with suggested corrective measures, equipment and inventory management and maintenance. These are the topics which are typically included in a quality assurance manual along with measures for quality monitoring and improvement. The WHO has produced several generic and disease-specific resources and tools for quality management in healthcare laboratories such as the Laboratory Quality Stepwise Implementation tool which guides laboratories in the implementation of a comprehensive ISO 15189-compliant quality management system, irrespective of the context. When supplemented by the core technical procedures freely available through EUCAST and various WHO departments, and by the additional technique-specific training, safety and QA measures recommended in those procedures or guides, they complete the information needed to develop a comprehensive quality assurance system for AST.

No global scheme is being proposed currently by the Global Antimicrobial Resistance Surveillance System (GLASS). There are programmes able to offer reference materials or proficiency testing worldwide e.g. ATCC, UK-NEQAS, the College of American Pathologists but the associated costs may be a barrier to widespread participation by laboratories in LMICs. Other obstacles hindering standardisation of surveillance methods are the usage of two different standards for antimicrobial susceptibility testing internationally, EUCAST and CLSI, and the lack of agreement on AST breakpoints in veterinary microbiology [10, 11].

Implications of networks analysis for GLASS

GLASS differs from the other leading global initiatives for AMR surveillance in TB, malaria and HIV by taking a less prescriptive approach to surveillance. The system is based on building up or strengthening traditional models of passive case-based surveillance to generate data, as used in HICs. Priority pathogens, drugs and specimens for surveillance are named but, unlike the other networks, GLASS avoids specifying minimum sample sizes or detailed selection criteria for target populations. Responsibility for quality management is devolved to national reference centres rather than a supranational body. Member States are requested to submit their AMR data to the WHO global antimicrobial susceptibility database (WHONET). It is reasonable to assume that many upper middle income countries may be able to increase their surveillance capacity with a concerted effort; however it is likely that it will be many more years before most low-income countries have a well-functioning system for routine bacteriological surveillance. As a result this approach risks generating non-representative data, as has happened so far and making inter-country comparisons will be difficult. It also means that those communities at the peripheries of health systems will continue to be neglected.

Conclusions

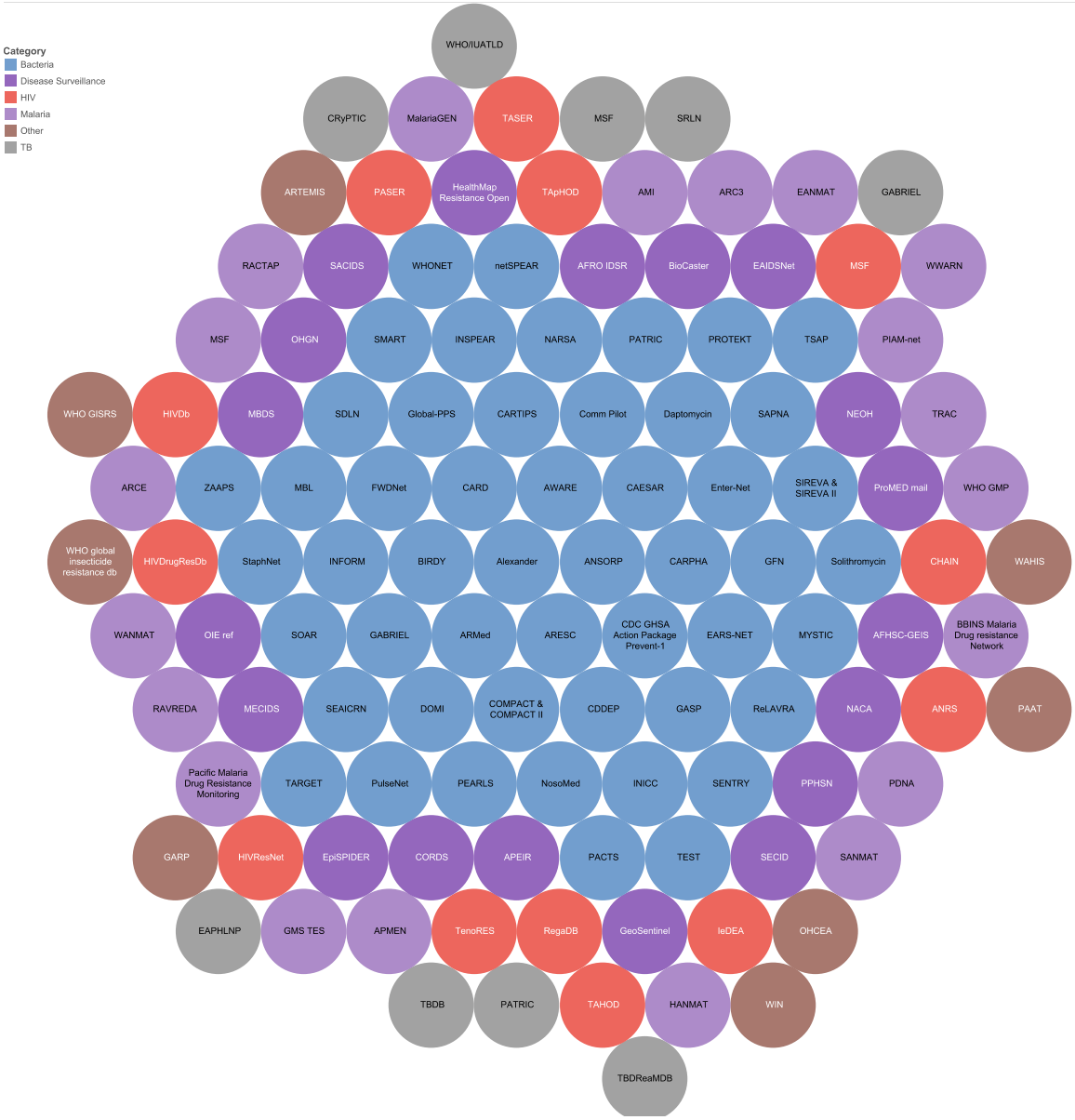
A successful AMR surveillance network should generate comparable, representative, high quality data on pathogens of concern from the target population(s). It should be able to detect and track outbreaks in real time, have rapid, effective mechanisms for communication and reporting and a responsible data sharing policy. A network needs strong leadership and coordination, and it should influence guidelines and policy and ultimately impact on human and animal health. None of the networks we have described has managed to fulfil all of these criteria. Pharma networks produce high quality data but they may not be representative and these networks do not usually support laboratory capacity building in LMICs or influence policy and guidelines. Academic networks also produce high quality data which often targets a clinical or policy question but they too have limited influence on policy and their sustainability is reliant on external funding. All of the networks are slow to report their findings, except for the digital data detection networks, and only a small number have a data access policy. Having a supranational proficiency testing programme linked to networks has been associated with improved laboratory performance. With the exception of the European and Latin American networks, most LMICs take an active approach to AMR surveillance rather than combining it with routine case-management. The aim to strengthen hospital-based surveillance may be too ambitious for most low-income countries at present. Progress in developing molecular and genomic methods to simplify AMR surveillance may solve this problem in the longer term. In the meantime complementary approaches to gather comparable representative data which also reflect the burden of disease in LICs could be considered, such as

community survey approaches looking at respiratory tract and enteric carriage of indicator bacteria. There are opportunities to share molecular technologies used by TB and HIV AMR surveillance networks with antibacterial resistance networks.

For LMICs with very little AMR surveillance activity there is an opportunity to design an integrated system from the outset. This is a complex undertaking and the priorities for designing a system will depend on a number of factors e.g. which animals are farmed in the country and the farming methods, presence of aquaculture, importance of companion animals, etc. Funders could play a role in influencing countries to work on integration of human, animal and environmental surveillance. Surveillance in animals will need the cooperation of the large food-producing corporations in LMICs and will need to be regulated. Incorporating economic and social considerations into the design of programmes will facilitate targeting where in the food production chain surveillance should be performed in order to influence patterns of antimicrobial use. A number of new initiatives and networks have been created in the last decade with a One Health approach to disease surveillance. These networks could be linked to AMR surveillance efforts. The roles and responsibilities of different surveillance networks operating in the same geographical regions need to be defined clearly and opportunities to cooperate identified.

Academic groups, professional bodies, NGOs and other technical support organisations can support regional surveillance activities. Many unanswered questions regarding the optimum methods for AMR surveillance remain and new resistance mechanisms are emerging all the time. An operational research agenda tailored to different contexts could provide evidence to guide and prioritise surveillance activities. In low-income countries public health leaders and programme managers are frequently involved in research, or work very closely with academics and this partnership can be very influential in generating policies and guidelines. Many high income countries use a model whereby an executive agency of the government is charged with the responsibility of setting public health priorities, implementing surveillance and communicating with the public. These agencies are staffed by public health specialists, scientists and researchers. Adapting this model to low income countries could be a means to reduce the number of parallel diseases surveillance networks and disease control initiatives which are operating or to provide better coordination.

Maintaining an up-to-date registry of networks would promote a more coordinated approach to surveillance, reduce duplication of efforts, optimise funding investment and improve sustainability if new initiatives could be channeled through existing well-functioning networks.



Bubble plot of AMR and One Health networks in LMICs since 2000

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List of contributors

Elizabeth A Ashley	Clinician-Scientist, Centre for Tropical Medicine and Global Health, University of Oxford, UK
Arlene Chua	Consultant, Geneva, Switzerland
David Dance	Consultant Microbiologist, Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Vientiane, Laos
Nicholas P Day	Director, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand & Centre for Tropical Medicine and Global Health, University of Oxford, UK
Mehul Dhorda	Head, Asia Regional Centre & EQA Programme, WorldWide Antimicrobial Resistance Network (WWARN), MORU, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
Philippe Guerin	Director, Infectious Diseases Data Observatory (IDDO) and WWARN, Centre for Tropical Medicine and Global Health, University of Oxford, UK
Nisha Ranganathan	Trainee in Infectious Diseases & Microbiology, Imperial College, London, UK
Judith Recht	Consultant, Recife, Brazil
Jonathan Rushton	Professor of Animal Health Economics and Norbrook Endowed Chair in Veterinary Business Management, Royal Veterinary College, London, UK
Ceri Smith	GP trainee, London, UK
Nigel Thomas	Consultant & Software Engineer, WWARN, Centre for Tropical Medicine and Global Health, University of Oxford, UK
Paul Turner	Director of the Cambodia-Oxford Medical Research Unit (COMRU) and Clinical Microbiologist
Nicholas J White	Chairman of the Wellcome Trust South-east Asia Major Overseas Programme, MORU, Bangkok, Thailand & Centre for Tropical Medicine and Global Health, University of Oxford, UK

Cover photograph courtesy of Mehul Dhorda

List of Abbreviations

ACT	artemisinin based combination therapy
AHC	Angkor Hospital for Children
AMI	Amazon Malaria Initiative
AMR	antimicrobial resistance
AMU	antimicrobial use
ANLIS	Servicio de Antimicrobianos del Instituto Nacional de Enfermedades Infecciosas
ANSORP	Asian Network for Surveillance of Resistant Pathogens
APFID	Asia Pacific Foundation for Infectious Diseases
AST	antimicrobial susceptibility testing
ATCC	American Type Culture Collection
BMGF	Bill & Melinda Gates Foundation
CAESAR	Central Asian and Eastern European Surveillance for AMT
CAREC	Centro de Epidemiología del Caribe
CARPHA	Caribbean Public Health Agency
CARSS	China Antimicrobial Resistance Surveillance System
CLSI	Clinical and Laboratory Standards Institute
COMRU	Cambodia-Oxford Medical Research Unit
CPO	carbapenemase-producing organism
CRO	carbapenem-resistant organism
DDD	Digital disease detection
DRI	drug resistant infection
E	ethambutol
ECCMID	European Congress of Clinical Microbiology and Infectious Diseases
ECDC	European Centre for Disease Prevention & Control
EQA	external quality assessment
ESBL	Extended spectrum beta lactamase
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.
EUCAST	The European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agricultural Organisation of the United Nations
GASP	The Gonococcal Antimicrobial Surveillance Programme
GAVI	Global Alliance for Vaccines and Immunisation
GFN	Global Foodborne Infection Network
GLASS	Global Antimicrobial Resistance Surveillance System
GMP	Global Malaria Programme
GREBO	Grupo Para el Control de la Resistencia Antimicrobiana en Bogotá
HCAI	Healthcare associated infection
HIC	high-income country
HIV	Human immunodeficiency virus
HIVDR	HIV drug resistance
IAAS	Infecciones Asociadas a la Atención en Salud
ICU	intensive care unit
IDDO	Infectious Diseases Data Observatory
IPC	Infection prevention and control
H	isoniazid
KPC	*Klebsiella pneumoniae* carbapenemase

LAC	Latin American and Caribbean
LA-EQAS	Programa Latinoamericano de Control de Calidad en Bacteriología y Resistencia a los Antimicrobianos
LIC	low-income country
LMIC	low- or middle- income country
MDR	multidrug resistant
MIC	minimum inhibitory concentration
M&E	monitoring and evaluation
MoH	Ministry of Health
MRSA	Meticillin-resistant *Staphylococcus aureus*
MSF	Médecins sans Frontières
MYSTIC	Meropenem Yearly Susceptibility Test Information Collection
NCD	non-communicable disease
NGO	non-governmental organisation
OIE	World Organisation for Animal Health
OPS	Organización Panamericana de la Salud
PAHO	Pan American Health Organisation
PFGE	pulse-field gel electrophoresis
PNLAC	PulseNet Latin America and the Caribbean
PROTEKT	Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
PT	proficiency testing
QA	quality assessment
QC	quality control
QM	quality management
RAVREDA	Red Amazónica de Vigilancia de la Resistencia a las Drogas Antimaláricas
ReLAVRA	Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos
R	rifampicin
SARI	South America Regional Infectious Diseases Programme
SIREVA	Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas
SLIPTA	Stepwise Laboratory Improvement Process Towards Accreditation
SLMTA	Strengthening Laboratory Management Toward Accreditation
S	streptomycin
TB	tuberculosis
USAID	U.S. Agency for International Development
GRE	glycopeptide resistant enterococci
WGS	whole genome sequencing
WWARN	WorldWide Antimalarial Resistance Network
WHO	World Health Organisation
WHO GISRS	WHO's Global Influenza Surveillance and Response System

Introduction

Antimicrobial resistance (AMR) poses a serious threat to human and animal health worldwide. The Global Action Plan to tackle antimicrobial resistance was endorsed by the World Health Assembly, the Food and Agricultural Organisation of the United Nations (FAO) and the World Organisation for Animal Health (OIE) in 2015 [12, 13]. The plan focuses on antibiotic resistance in commonly encountered bacteria but defines AMR as encompassing drug resistance in fungal infections, tuberculosis, HIV and malaria as well. In terms of complexity of global health challenges, AMR, and particularly *antibiotic* resistance, is hard to match, and grappling with the problem has forced the realisation that a coordinated, cross-sector approach to tackle AMR on a global scale is needed. This has to take into account such diverse factors as the interplay between human and animal hosts for transmission of drug-resistant bacteria, food safety, environmental contamination, antimicrobial usage and quality, and infection prevention and control practices [14, 15].

There is no readily accessible, comprehensive source of reliable surveillance data on antimicrobial resistance. Some well-functioning networks exist for certain pathogens but most do not have a global reach. It is generally accepted that we need good surveillance data to be able to assess the scale of the problem accurately and to target interventions to address AMR. In order to gather such data in many low- and middle- income countries (LMICs) an increase in laboratory capacity will be required. The UK Fleming Fund has been set up by the UK government, the Wellcome Trust, the Bill and Melinda Gates Foundation and the Institut Pasteur International Network with the goal of strengthening surveillance, laboratory and response capacity for drug-resistant infections (DRIs) in LMICs in the next 5 years [16]. This report is the output of one of several pieces of scoping work commissioned to inform the strategy for gathering these data.

Considerations when implementing AMR surveillance in LMICs

According to the 2015 World Bank classification 135 countries are low or middle income. They form a heterogeneous group, but some useful generalisations about the LMIC context which may affect implementation of AMR surveillance compared to high income countries (HICs) can be made:

- **Higher infectious disease burden**. In general LMICs have a higher infectious disease burden than HICs. This is often one of the reasons they remain economically disadvantaged. The spectrum of infectious disease also differs, related to the environment and prevailing vectors as well as socio-economic factors e.g. malaria is almost exclusively a disease of LMICs. Infectious diseases remain a major cause of childhood death in LMICs. All of the declared Public Health Emergencies of International Concern have either had their origins in LMICs (Ebola Virus Disease and polio resurgence in 2014, Zika virus in 2015), or were first reported from a LMIC (H1N1 influenza in Mexico in 2009; virus origin not confirmed). Other serious global epidemics and pandemics such as HIV and Severe Acute respiratory syndrome (SARS) all started in LMICs.
- **Weaker health and pharmacovigilance systems.** Public health systems tend to be weaker in LMICs and people with medium-high income levels are more likely to access health care through the informal private sector, whereas people in poor and/or rural communities may either have access to care from community health workers with limited training, or no ready access at all.
- **Less regulation of medicines.** Antimicrobial drugs are more freely available in LMICs and are dispensed without prescription in many countries. There are often financial incentives for

physicians to prescribe expensive medicines such as newer broad spectrum antibiotics. There is also a higher burden of substandard, falsified and unregistered/unlicensed medical products in LMICs which may play a role in the emergence of AMR [14, 17] [7].

- **Lack of human resources.** In most LMICs human resources are scant by comparison with HICs. The UK has 2.8 doctors and 8.8 nurses or midwives per 1000 population. The corresponding figures for Myanmar are 0.6 and 1 [18]. There is a complete lack of microbiology or infection sub-specialisation amongst physicians in many LMICs. The Democratic Republic of Congo (DRC) has 308 licensed pharmacists compared to 78,322 pharmacists and 52,882 pharmacy technicians in Germany which has a similar population size [19]. The corresponding numbers of veterinarians or para-professionals in DRC and Germany in 2014 were 3453 and 29,518 [20].
- **Reliance on external funding** to support disease-control programmes. This includes both surveillance and health care delivery. External funding is vital and has saved millions of lives. However the short to medium term nature of most grants threatens sustainability of programmes and hinders self-determination by countries in terms of policy direction. Disease-focused Global Health Initiatives have been shown to sometimes have the unwanted effect of further weakening health systems [21].
- **Farming & Agricultural practices**. The increase in new livestock systems in middle-income countries, in particular landless pig and poultry systems, and aquaculture, related to the increased demand for meat and fish accompanying economic prosperity, is associated with greater antimicrobial use and risk of AMR. Regulation around keeping livestock and use of antibiotics is weaker in LMICs than most HICs and there is a higher risk of foodborne diseases with weak reporting systems in some countries [8]. Intensification of livestock production and extension of farming into wild-life habitats are also associated with increased risk of zoonosis emergence [22].
- **Conflict and insecurity** are more frequent in LMICs (and can be related to food insecurity).
- **Poorer sanitation** increasing the risk of propagation of drug resistant infections.
- **Weaker information technology infrastructure** with lower coverage, delay in adoption of new technologies, poorer communication channels.

The final O' Neill report estimated that death rates from AMR could reach 10 million lives per year by 2015 if resistance rates for 6 key pathogens continue to rise [23]. Drug resistance has already had a major impact on the health and wealth of many LMICs, a prime example being the millions of deaths in young children from malaria as first chloroquine and then sulfadoxine-pyrimethamine resistance rates soared in the 1990s [24, 25].The list of high burden MDR-TB countries is dominated by LMICs and emergence of MDR-TB and antiretroviral resistance in HIV has more serious implications for LMICs than HICs because of the prohibitive costs of second and third line drugs.

On the bright side, the high burden of infectious diseases and drug resistance in LMICs has led to innovation and adaptation, both by the countries themselves and the world-at-large e.g. re-discovery of qinghaosu (artemisinin), a potent antimalarial, by Chinese scientists in the 1970s, production of generic antiretroviral medicines by Indian and Brazilian manufacturers which opened up access to inexpensive treatments to millions of HIV-infected individuals worldwide, recent production of low cost pan-

genotype Hepatitis C treatments in Egypt, new models of drug and vaccine development for neglected diseases e.g. Drugs for Neglected Disease Initiative (DNDi), Medicines for Malaria Venture, the Access to Medicines Department of Sanofi-Aventis, the International Vaccine Institute and others.

AMR surveillance in animals is much less frequent than in humans, even in HICs, with a few exceptions e.g. Denmark, Canada. The focus for any AMR surveillance in animals until now has been foodborne infection surveillance or monitoring antibiotic use in feed and antibiotic residues in foods; however unpicking the routes of AMR transmission between humans, food and non-food animals and the environment will not be possible without understanding what animals are colonised or infected with. Livestock production is a multi-million dollar industry and the health of food-producing animals is usually the responsibility of corporations rather than the public sector, bound by global standards for food safety. This has implications for AMR surveillance planning since a collaborative approach between public and private sectors will be needed.

AMR is not a new problem and this is not the first time that attempts have been made to strengthen global surveillance. The 1996 World Health Report called AMR 'a major public health problem worldwide', discussed the problem of antibiotic use in animal feed and stated 'disease control strategies will be seriously threatened by mounting drug resistance levels… Developing countries where the burden of infectious disease is the highest will be facing the impossible task of controlling diseases with only scarce expensive drugs"[26]. The report highlighted surveillance efforts launched around that time such as the WHONET programme and the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. In 2001 a WHO Global Strategy for Containment of Antimicrobial Resistance was published [5]. Now, almost twenty years on, there is a sense of urgency to renew efforts to try to tackle AMR with the launch of the Global Antimicrobial Resistance Surveillance System (GLASS) and the Global Action Plan on Antimicrobial Resistance. The WHO Global Action Plan calls upon member countries to formulate national plans to tackle the growing problem of AMR. Setting up sustainable surveillance systems is one key component of the plan, but there are several others such as societal engagement, education, infection prevention and control and ensuring appropriate access to antimicrobial drugs.

In this report we map and summarise networks and global databases concerned with AMR surveillance in humans, animals or using a One Health approach in LMICs since 2000. We look at surveillance methodology, approaches to quality management, duration of the networks, factors associated with impact, challenges and sustainability and funding. We review contributions of the non-governmental organisation (NGO), academic and other sectors to strengthening AMR surveillance.

An Analysis of AMR surveillance networks in LMICs

The WHO published the 'Antimicrobial Resistance Global Report on Surveillance' in 2014 which gives a baseline assessment of AMR reporting by Member States. The report summarises which countries have antimicrobial susceptibility data for the target pathogens of interest, and the source of this information e.g. from surveillance networks, publications, individual Ministries of Health [27]. The report shows widespread evidence of resistance in all key pathogens but acknowledges problems with lack of representativeness of the data and the fact that use of different laboratory methodologies means results are often not comparable.

A **Global Antimicrobial Resistance Surveillance System** manual for early implementation has been created to guide countries planning AMR surveillance in humans [28]. The priority specimens and pathogens for surveillance in GLASS are shown in Table 1.1:

Table 1.1: Priority pathogens and specimens for AMR surveillance in GLASS

Specimen	Laboratory case definition	Surveillance type and sampling setting	Priority pathogens for surveillance
Blood	Isolation of pathogen from blood	Selected sites or national coverage Continuous Patients in hospital and community	*E.coli* *K.pneumoniae* *A baumannii* *S.aureus* *S. pneumoniae* *Salmonella* spp.
Urine	Significant growth in urine specimen	Selected sites or national coverage Continuous Patients in hospital and community	*E. coli* *K. pneumoniae*
Faeces	Isolation of *Salmonella* spp.or *Shigella* spp. from stools	Selected sites or national coverage Continuous Patients in hospital and community	*Salmonella* spp. *Shigella* spp.
Urethral/cervical swabs	Isolation of *N.gonorrhoeae*	Selected sites or national coverage Continuous Patients in hospital and community	*N.gonorrhoeae*

Reproduced from the GLASS manual for early implementation[28]

As shown the focus for blood culture surveillance is on two pathogens causing a high burden of disease in LMICs (*Streptococcus pneumoniae* and *Salmonella* spp.), *Escherichia coli*, and three of the six so-called ESKAPE nosocomial pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.) [29]. The manual also lists the pathogen-antimicrobial combinations which should be evaluated. In addition to submitting aggregated

susceptibility data for the key pathogens annually, countries are asked to collect basic demographic data about the patients sampled and the size of the population from which they were sampled. This should include whether the sampling was taken more than two calendar days after admission to identify hospital acquired isolates. Data should be entered using the WHONET platform which facilitates management, sharing and reporting of laboratory data.

Stepwise participation to GLASS by Member States is envisaged, with a target of 40% participation by 2019, and it is acknowledged that participants may start with a more restricted list of pathogens than the full list, with limited population coverage and increase both over time. GLASS suggests making links with animal networks but the recommendations for how to conduct AMR surveillance in animals come directly from FAO and OIE. They are embedded in the Codex Alimentarius and the Terrestrial Animal Health Code.

For animals there is a clear expectation than surveillance of antimicrobial use goes hand in hand with surveillance for resistance. The **Codex Alimentarius**, created in 1963, issues a series of international standards relating to food production to promote harmonisation and to facilitate food trade by setting international standards for food safety. These guidelines recommend surveillance of antimicrobial use and of AMR in microorganisms in food animals, crops or food itself. In terms of how to implement surveillance in practice this is covered by a section in the Terrestrial Animal Health Code on "Harmonisation of national AMR surveillance and monitoring programmes." The Code lays out structured advice on the general principles of conducting active targeted surveillance and includes sample size calculations and guidance on where and what to sample, as well as suggested pathogens of interest, but stops short of issuing detailed guidance on laboratory methods and choice of antimicrobials for testing [30]. There is a separate OIE Aquatic Animal Health Code. The AMR focal points from FAO and OIE are members of AGISAR, the **WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance** which was created in 2008. AGISAR is a group of experts promoting harmonisation in AMR surveillance using an integrated approach.

Definitions

For the purposes of this analysis AMR is defined as resistance to antimicrobial agents in bacteria, protozoa, fungi and viruses. We have also included insecticide resistance in arthropod vectors. Countries have been categorised into income groups using the World Bank 2015 classification [31].

Search Strategy

We searched for supranational networks involved in the surveillance of antimicrobial drug resistance in low or middle income countries from January 2000 to May 2016 in Embase, PubMed and Global Health databases. The complete list of search terms is in Appendix 1. This generated 16,629 hits. The titles and abstracts ± full text of the articles were screened to identify AMR surveillance networks. Networks did not have to collect primary samples to be included. Networks were defined by type (WHO/governmental, academic, pharmaceutical company/contract research organisation led, digital disease detection network (i.e. based on text-mining) or other), target pathogen grouping (bacteria, TB, Malaria, HIV, Disease Surveillance network, other), target population (human, animal, One Health, other), data-sharing model (open, closed, shared), coordinating organisation, and funding. Global or

multi-national data repositories containing AMR data or global resistance gene libraries were also included as were One Health disease surveillance networks. We included the disease surveillance/One Health networks even if they were not collecting any AMR surveillance data currently as AMR could fall under their remit in the future and there is overlap between the objectives of disease surveillance and AMR surveillance e.g. zoonotic pathogen transmission. We noted the approaches to quality management taken by the networks. Start and stop dates were recorded and reason for stopping if available.

To try to get some measure of the activity or functioning of the networks we noted whether any AMR data had been published in the last three years (since 2013) in any format, and if so, whether the data was from isolates collected within the last three years. We also documented whether there was evidence the network was still active during the last year, irrespective of whether AMR data had been collected or reported. This could be a meeting report, news item or a publication on any topic by the network or an update on the network website. The literature search strategy was complemented by a review of AMR activity in the NGO sector and a case study of networks in Latin America. Information on these topics was obtained by web-based searching and when possible by direct contact with key members of these organisations for additional in-depth and up to date information.

Data entry and mapping the networks

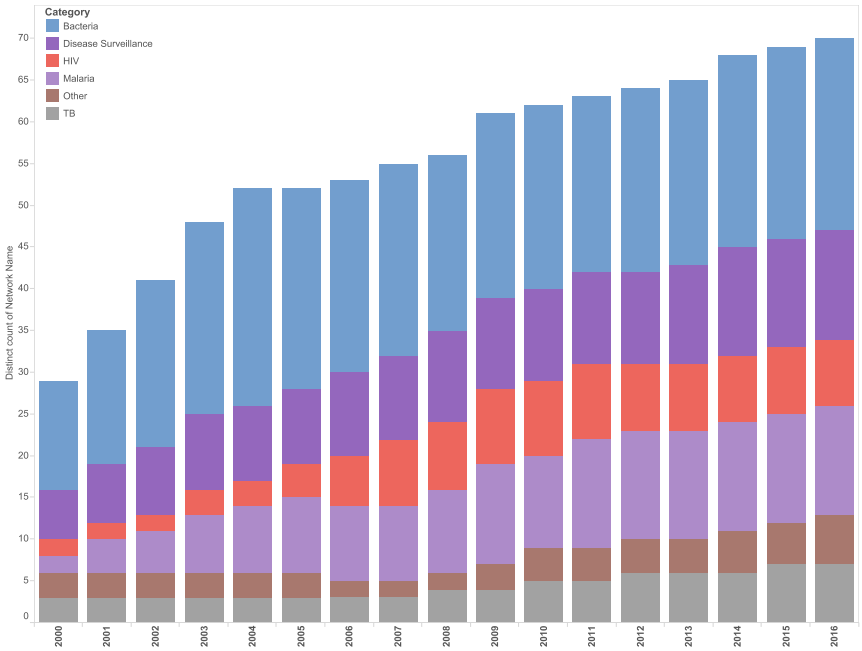
Network information was entered into Excel® and the countries participating to the networks were mapped using Tableau® software.

Findings

We identified 105 supranational networks concerned with AMR surveillance since 2000, of which 40 were WHO/governmental (global or regional), 35 academic, 20 Pharma initiated, and four were digital disease detection networks. Five of the academic networks also hosted a data repository. The remaining six networks were made up of a military network, an NGO network, a global travel associated disease surveillance network, a reference laboratory network, a US CDC coordinated global health security network and a One Health 'network of networks'. In addition there were 12 data repositories for resistance data (usually sequence data). A table containing the full list of networks and databases with individual participating countries named is in Appendix 2.

In terms of the pathogens under surveillance, 46 networks were for AMR in bacteria, 18 in malaria, four in TB, nine in HIV, one influenza, one fungi, one bacteria+fungi, one bacteria+TB, one malaria+HIV+TB, and one trypanosomiasis in animals. We also included one network for insecticide resistance, an infectious disease academic network and 20 general disease surveillance networks with some AMR surveillance activity or a One Health focus. The median [range] duration of the networks was 8 years [1-69]. The WHO's Global Influenza Surveillance and Response System (WHO GISRS) was the longest running network, established in 1947, although antiviral resistance was not part of surveillance at the outset.

Figure 1.1 Number of networks sub-categorised by disease under surveillance 2000-2016



As shown in Figure 1.1 the number of networks has increased over time in each category. Below the networks and data repositories are shown as a Treemap, classified by disease category and type of network e.g. WHO/governmental, academic, pharma, DDD.

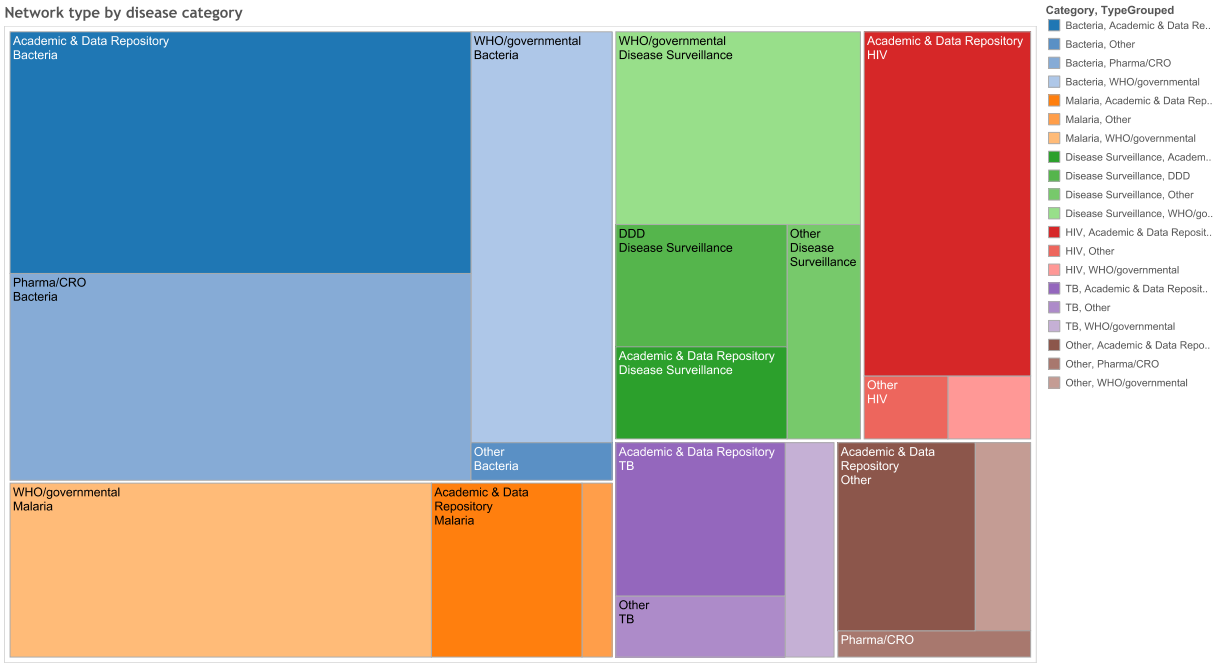


Figure 1.2 Treemap of networks by type and object of surveillance

The funding sources for the networks were corporate (n=24), public or WHO (n=47), Trust or Foundation (n=18) and the remainder from more than one source. One network was not funded.

Of the 46 networks focused on AMR in bacteria six reported data on the GLASS priority pathogens (with the exception of *Salmonella* spp. in four), three networks were for *S.aureus*, nine were for respiratory pathogens (two of these also included *N.meningitidis* and one enteric pathogens), six were for enteric pathogens only, one was for *N.gonorrhoeae* and the remainder included a range of Gram-negative (four) or Gram-positive (two) organisms or a mixture of the two. Six networks collected or reported data on invasive isolates only, four non-invasive and the remainder a combination of the two. For networks which specified the patient populations the isolates came from, six were community-acquired, five hospital-acquired, one was in women only and four in children. The remainder collected both or the information was not available.

After excluding the digital disease detection networks the median [range] number of countries covered by the networks for which information was available was 13 [2-180] and the median [range]number of LMICs covered was 7 [1-121]. The OIE reference laboratory network covered the most LMICs but it should be noted that only one of the laboratories was designated as the AMR reference laboratory. The second highest LMIC coverage was by the WHO Global Foodborne Infections network (approximately 104) and then WHO GISRS (67). The median [range] number of participating centres for the 41 networks for which this information was available was 46[5-2000]. The International Nosocomial Infection Control Consortium had the highest number of centres.

Current networks and their functioning

From the total of 105 networks 69 are ongoing. The reasons networks ceased to exist was usually not available. In the case of one malaria network it was documented that inability to secure sustainable funding was one reason for the network's collapse [32]. Of the 69 existing networks, 34 have published any AMR data in the form of a report or academic publication during the last 3 years (since January 2013) and of these six reports were regarding isolates which were collected more than 3 years ago. The other 35 networks did not report any data. We could find no evidence of any activity of any description in the last year for eight networks so it is unclear whether these networks are still functioning. Fourteen of the current networks operated some kind of external quality assurance scheme which involved LMIC laboratories, seven did not, and for the remainder it was unclear. The data sharing models of the current networks for which this was applicable were open (4), closed (5) and shared or unclear (54) (see assessment of current networks functioning in Appendix 3).

The networks are summarised according to disease category and type in the following section with data-repositories and disease-detection networks presented separately.

Surveillance for AMR in bacterial isolates in human health

Here we present the main WHO or governmental global and regional networks performing AMR surveillance in bacteria (excluding *M.tuberculosis*) with participation by LMICs first. All of the WHO Regions have committed to AMR surveillance but only Europe and the Americas have ongoing coordinated data collection at Regional level currently. Some member countries of the other WHO Regions are active in performing surveillance and collating the data nationally such as Viet Nam, Nepal, China and these examples will be highlighted[33, 34].

There is one global network performing routine antibiotic resistance surveillance in a single pathogen (*Neisseria gonorrhoeae*).

Gonococcal Antimicrobial Surveillance Programme (GASP)

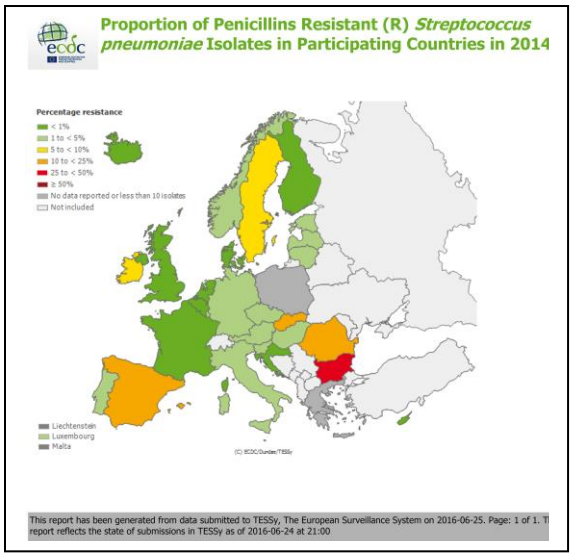
The Gonococcal Antimicrobial Surveillance Programme of the WHO began in 1992 and has participants from round 67 countries. The way the network functions is to designate reference laboratories or centres in participating WHO Regions (Americas, Eastern Mediterranean, Europe, Southeast Asia, Western Pacific). According to the WHO website GASP has had no regional focal point in Africa since 2012, and as a result submitted no data. These laboratories participate to an external quality assessment (EQA) programme and collate the data in collaboration with their WHO Regional Office. The last global report on the WHO website was published in 2012. Not all countries submit data on all antibiotics of interest. The number of isolates submitted by country varies by several orders of magnitude. In 2008 the WPRO and SEARO issued a joint GASP report of quinolone resistance in 8731 strains of *N.gonorrhoeae* from 20 countries. Australia reported resistance in 1685/3110 (53%) strains while Lao PDR reported 1/9 (11%) tested strains as resistant [35]. The WHO 2014 Global Report on Surveillance obtained data on antimicrobial susceptibility in *N.gonorrhoeae* from only 42/194 (22%) Member States and noted that coverage was poorest from presumed high-burden countries. Thus, while GASP provides some data and has helped to raise awareness about drug resistance in *N.gonorrhoeae* around the world it is only a partially functional network [27].

Regional Networks performing routine surveillance for AMR in human health

There are three regional networks with LMIC participation reporting routine AMR surveillance data on the GLASS target pathogens (two in Europe and one in Latin America).

1. The European Antimicrobial Resistance Surveillance Network (EARS-Net)

The European Antimicrobial Resistance Surveillance Network (EARS-Net) is a publicly-funded network of national surveillance systems of EU countries which started in 1998.



It is included in this report as two middle-income countries participate to this network (Bulgaria, Romania). EARS-Net collects data on invasive isolates of seven key pathogens. Data are uploaded to a central database at ECDC. Annual reports are posted on the website and the database is interactive and open access, allowing users to generate maps and reports, but only at country level.

Figure 1.3 EARS-Net generated report on penicillin resistance in *S.pneumoniae* in 2014

2. Central Asian and Eastern European Surveillance for antimicrobial resistance

In 2012 the Central Asian and Eastern European Surveillance (CAESAR) for antimicrobial resistance network was set up to strengthen AMR surveillance in non-EU Member states in close collaboration with ECDC to ensure compatibility of the approach with that of EARS-Net. Seventeen of the 20 participating countries are classified as middle-income. There are no low-income countries. The first report from 2014 listed the key challenges identified at the outset which were

- *"limited human and financial resources to address the need for laboratory capacity building*
- *continuing need to educate laboratory personnel*
- *the need for implementation of updated guidelines on the standardisation of antibiotic susceptibility testing (AST) (from CLSI and EUCAST), laboratory methods for species identification and blood culturing*
- *the need for standard operating procedures and quality control in laboratory practice*
- *the need to improve sampling habits and utilisation of medical microbiologic diagnostics in hospitals*
- *the need to improve laboratory information management and setting up an infrastructure for central data collection at a national reference laboratory*." (Quoted from [36])

Country support provided included training, quality management and ''twinning" with established laboratories. The 2014 CAESAR report summarises the data generated from one high income country (Switzerland) and four low income countries (Belarus, FYR Macedonia, Serbia, Turkey). The data generated by Switzerland and Turkey were assessed to be representative and accurate. Those generated by the other three LMICs were judged to be accurate but non-representative of the target population. Problems included low number of blood cultures, cultures more likely to be drawn from complex patients, low volume blood draws [36]. Table 1.2 summarises the surveillance data reported for two pathogens from a range of countries participating to both European networks in 2013. It illustrates the variation in the number of isolates submitted by different countries using this approach.

Table 1.2 National AMR surveillance data for 2013 from the WHO European Region

Network	Country	Income status/ HDI ranking[1]	Population	N labs	*E.coli* N invasive isolates	*S.pneumoniae* N invasive isolates
EARS-NET	UK	High/14	64.5 M	31-54	6481	1301
EARS-NET	Poland	High/36	38 M	38	1072	170
EARS-NET	Bulgaria	Upper middle/59	7.2 M	14-17	187	29
EARS-NET	Romania	Upper middle/52	19.9M	8-14	302	44
CAESAR	Turkey	Upper middle/72	75.9 M	77	3286	147
CAESAR	FYR Macedonia	Upper middle/81	2.1 M	6	50	5
CAESAR	Serbia	Upper middle/66	7.1 M	14	199	42

[1]HDI ranking: Human development Index ranking (lowest = 188). HDI is a composite index measuring average achievement in three basic dimensions of human development—a long and healthy life, knowledge and a decent standard of living. From UNDP HD reports 2015 http://hdr.undp.org/en/composite/HDI; Turkey use predominantly automated systems for AST and before joining CAESAR had established a National AMR surveillance system in 2011 (http://www.slideshare.net/balbiger/caesar-the-example-of-turkey).

Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA)

ReLAVRA is a Latin American regional surveillance system operating since 1996 which was influential in

the development of GLASS. Fifteen of the 19 participating countries in this long-standing network are from the middle-income bracket, with coordination coming from PAHO and Argentina (training, EQA). A detailed description of how ReLAVRA and other Latin American AMR surveillance networks function is presented in Appendix 4. Countries report a mixture of invasive and non-invasive community and hospital-acquired isolates. An example from the 2010 annual report (of data collected in 2009) is shown in Table 1.3. The high-income countries tend to have a higher number of laboratories participating relative to the population size and submit more invasive isolates. The network is active currently but has not published an annual report since 2010.

Table 1.3 Selected surveillance data reported from ReLAVRA countries in 2009

Country	Income Status[1]	HDI ranking	Population (millions)	Labs (N)	Isolates (N) reported per species						
					Spn I	S.aur	*E.coli* C,U	*E.coli* H	K	A	Nm
Argentina	H	40	43.4	72	458	6058	10766	1873	1356	2216	145
Bolivia	LM	119	10.7	30	33	2291	6107	2904	1014	516	-
Brazil	UM	75	207.8	35	765	-	-	-	-	-	490
Chile	H	42	18.0	266	811	51	-	-	-	33	60
Colombia	UM	97	48.2	124	325	-	-	-	-	-	22
Costa Rica	UM	69	4.8	30	70	-	-	-	-	-	7
Cuba	UM	67	11.4	14	26	79	179	136	39	1	7
Ecuador	UM	88	16.1	15	46	2687	6361	2317	967	348	5
El Salvador	LM	116	6.1	33	42	137	320	949	258	328	-
Guatemala	LM	128	16.3	5	8	2493	-	3682	2435	2455	-
Honduras	LM	131	8.1	7	11	940	1433	817	559	46	-
Mexico	UM	74	127.0	31	-	-	-	-	-	-	-
Nicaragua	LM	125	6.1	11	9	39	406	714	172	393	1
Paraguay	UM	112	6.6	21	169	1519	1798	915	964	109	13
Panama	UM	60	3.9	24	43	1005	-	2910	1721	2018	28
Peru	UM	84	31.4	40	38	621	3017	1347	595	26	1
Dominican Republic	UM	101	10.5	14	78	1210	-	2812	2021	85	5
Uruguay	H	52	3.4	17	65	435	718	195	124	47	32
Venezuela	H	71	31.1	ND	122	3043	8491	1193	1452	466	26

[1] H: High, LM: Lower middle, UM: Upper middle (classification from the World Bank). Population data from World Bank 2015
HDI: Human Development index
Spn I: *Streptococcus pneumoniae* (invasive); Saur: *Staphylococcus aureus*; *E.coli* C,U: *Escherichia coli* (community acquired urine); *E.coli*, H: *Escherichia coli* (hospital acquired); K: *Klebsiella* spp;, A: *Acinetobacter* spp; Nm: *Neisseria meningitidis.*

Data taken from [37]

Regional networks are based on a foundation of well-functioning national networks, some of which can take the lead in training, harmonising laboratory procedures and quality management in the region. Despite the benefits of regional cooperation GLASS does not depend on this and is designed for countries to submit data independently.

Selected National AMR surveillance programmes

National networks can develop in different ways with different partners and funders. Describing all the national surveillance systems in LMICs is beyond the scope of this review. This information has been summarised in a CDDEP discussion paper and the WHO Global Report on Surveillance [34, 38]. We include brief summaries of three national networks to highlight different approaches to set up successful national surveillance systems.

Viet Nam

An initiative in Viet Nam (population 90 million; HDI ranking 116/188) called **VINARES** has boosted national AMR laboratory surveillance as part of an integrated programme to introduce antibiotic stewardship and infection prevention and control strategies to the country at various levels of the health system, with an additional focus to strengthen national policy to tackle AMR. The strategy includes a programme of operational research. Collaborating partners since the study's inception include Vietnamese healthcare professionals and researchers from the Oxford University Clinical Research Unit in Viet Nam, and Linköping University, Sweden [39]. Another academic/ technical support group- the Global Antibiotic Resistance Partnership (GARP) of the Centre for Disease Dynamics, Economics and Policy (CDDEP) was involved in helping the Vietnamese government to formulate their national AMR action plan.

Nepal

The national AMR surveillance system in Nepal (population 28 million; HDI ranking 145/188) originated from a collaboration between the Ministry of Health and the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) in 1998, with funding from USAID. Ten training workshops took place in the first five years with annual refresher training thereafter. Diarrhoeal and respiratory pathogens predominated as the target organisms initially with subsequent addition of extended spectrum beta lactamase (ESBL) producing *E.coli*. After 5 years of joint working the activity was taken over fully by the National Public Health laboratory [40].

China

China, with a population of more than 1.3 billion (HDI ranking 90/188), has incrementally improved its AMR surveillance network, expanding from a small number of regional sites to a nationwide system (Table 1.4). The major driver for the expansion of their surveillance system is the political will to address AMR. In 2011, China started a new round of health-care reform and with that the MoH issued new legislation and implemented a special campaign to promote rational use of antibiotics. China has also been part of the development of GLASS. In 2015, UK and China announced the establishment of a Global Antimicrobial resistance (AMR) research innovation fund [41].

Data from the Chinese surveillance networks have been published in several scientific journals, including resistance phenotypes and molecular mechanisms of resistance. In 2005, the Ministry of Health also started hospital antibiotic consumption surveillance to link the prevalence of resistance to rational use of antibiotics [42]. The current network does not include primary health care and community hospitals and only includes tertiary and secondary hospitals.

Table 1.4 Evolution of the China AMR national surveillance system

Year established (no. of hospitals)	Name of surveillance network	Pathogens
1998 (10 hospitals) 2005 (up to 20 tertiary hospitals nationwide)	Shanghai antibacterial resistance surveillance network (established by Fudan University) Renamed CHINET	
1999 (15-17 member hospitals) 2005 (replaced by Mohnarin – 50 to 80 hospitals 2010 Mohnarin (increased to 150 member hospitals) 2012 CARSS www.CARSS.cn (in Chinese) 2014 – coverage of CARSS had expanded to 1,427 hospitals in the country	Peking University Renamed Mohnarin (MoH National Antibacterial Resistance Investigation Net) Zhejiang University oversees Mohnarin Due to slow development and coverage of the surveillance network (around 100 hospitals), the network was transferred to the Committee of Experts on Rational Drug Use and renamed as the Chinese Antimicrobial Resistance Surveillance System (CARSS). Selection of hospitals by MoH. Enrolment was mandatory.	Target bacteria, monitored every other year 1. MRSA, CA-MRSA, VISA, hVISA 2. Penicillin and macrolide-resistant *S. pneumoniae* 3. GRE 4. Enterobacteriaceae: ESBL, CRE, resistance to quinolones, aminoglycosides or multidrug resistant 5. *Pseudomonas aeruginosa* 6. MDR *Acinetobacter* spp.
2005-	Surveillance by Etest and Agar Dilution of Nationwide Isolate Resistance (SEANIR). Led by the Peking Union Medical College Hospital	Collected mainly target bacteria from member hospitals and determined collective MICs for a relatively small number of strains

Limitations of the two networks (Mohnarin and CHINET) were that they did not include non-teaching hospitals and primary health centres, but coverage before the national CARSS – surveillance expansion was good except for western and northern parts of China, with the two prevailing AMR surveillance networks.

Dr. Zhang Bo, Deputy Director of Academic Committee of CARSS identified the three key factors leading to the successful expansion of CARSS as: enforcement of administrative management, continuous provision of training, and implementation of stringent data quality control procedures. He identified poor quality of equipment in some hospitals as being a barrier to effective implementation. Government

funding for CARSS is gradually increasing but the majority still comes from individual laboratories (see interview transcript in Appendix 5).

These examples of national networks show the role that academic partnerships can play in starting up national surveillance as well as the importance of national ownership for sustainability.

Pharmaceutical company/Contract Research Organisation led networks

There have been a number of global networks examining antibacterial resistance over the years initiated and sponsored by pharmaceutical companies, summarised in Table 1.5 below. The number of LMICs included in these networks ranged from 2-34 and included countries in the low-income bracket. The motivation for setting up these networks was usually to evaluate drug performance (registered drugs or new compounds). Typically, they perform confirmatory testing of identification and antimicrobial susceptibility of isolates in a central laboratory in a high-income country, with the exception of the COMPACT & COMPACT II studies which used a laboratory in Siriraj teaching hospital in Bangkok, Thailand as the reference laboratory. A contract research organisation or the central laboratory usually coordinates the study and the findings are published in peer-reviewed journals and presented at international meetings. Data are held by the sponsor. The bank of isolates generated as a result of the surveillance has been used to test for susceptibility of new drugs or for research purposes, e.g. JMI laboratories in the US has published reports of the results of testing dalbavancin, telavancin, garenoxacin [43-45]. A variety of pathogens are collected including community and hospital acquired from both sterile and non-sterile sites.

One impact of these networks has been the discovery of new resistance mechanisms e.g. macrolide resistance in *H.influenzae* as a result of The Alexander Project [46, 47]. Retrospective analysis of SENTRY isolates after the first report of New Delhi Metallo-beta-lactamase-1 (NDM-1) in 2008 enabled identification of the gene from Indian isolates collected in 2006. Some Pharma networks are prolific in terms of publication output e.g. the SENTRY programme has produced more than 300 publications in peer-reviewed journals. It is hard to assess how representative the samples are of the populations they are obtained from.

An interesting analysis comparing trends in *Escherichia coli* resistance from 1997 to 2001 reported by the MYSTIC and SENTRY surveillance networks showed that, despite collecting isolates from similar geographical areas, estimates of non-susceptibility from MYSTIC were consistently higher than those from SENTRY. However in a multivariable analysis controlling for site, age, sex, year of specimen and ICU admission neither network was associated with susceptibility [48]. This underlines the importance of defining the population being sampled as much as possible.

Table 1.5 Pharmaceutical Company initiated networks since 2000

Name/acronym	Sponsor/Leading institution	Years active & (N LMICs/N HICs)
The Alexander Project	GlaxoSmithKline	1992-2002 (8/28)
Assessing Worldwide Antimicrobial Resistance and Evaluation Program/AWARE	Astra-Zeneca/IHMA	2008-ongoing (3/4)
Community-Acquired Respiratory Tract Infection Pathogen Surveillance/CARTIPS	Bayer HealthCare Pharma	2009-2010 (2/2)
The Comparative Activity of Carbapenem Testing/COMPACT & COMPACT II	Janssen Asia Pacific, a division of Johnson & Johnson Pte Ltd	2008-2010 (3/2)
International daptomycin surveillance programs	JMI Laboratories, North Liberty, IA, USA	2011-2011 (12/21)
International Network For Optimal Resistance Monitoring/INFORM	Astra-Zeneca/IHMA	2012-2014 (not specified)
Multiyear, Multinational Survey of the Incidence and Global Distribution of Metallo-Beta Lactamase-Producing Enterobacteriaceae and *Pseudomonas aeruginosa*	Astra-Zeneca/IHMA	2012-2014 (12/19)
Meropenem Yearly Susceptibility Test Information Collection/MYSTIC	Astra-Zeneca	1997-2008 (4/9)
Program to Assess Ceftolozane/Tazobactam susceptibility/PACTS	Cubist Pharmaceuticals	2012-2012 (2/14)
Pan-European Antimicrobial Resistance Using Local Surveillance/PEARLS	Wyeth Pharmaceuticals	2001-2002 (3/13)
Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin/PROTEKT	Sanofi-Aventis	1999-2004 (10/26)
SENTRY Antimicrobial Surveillance program/SENTRY	Bristol-Myers Squibb	1997-ongoing (8/32)
Survey of Antibiotic Resistance/ SOAR	GlaxoSmithKline	2002-ongoing (34/14)
Study on Antimicrobial Resistance in Staphylococcus aureus/SARISA	LEO Pharma (Copenhagen, Denmark)	1996-1996 (2/16)
Study for Monitoring Antimicrobial Resistance Trends/SMART	Merck & Company, Inc.	2002-2011 (23/30)
International solithromycin surveillance programs	GlaxoSmithKline	2011-2011 (5/22)
TARGETed Surveillance Study	Bayer/GR Micro Ltd.	2003-2007 (2/5)
Tigecycline Evaluation and Surveillance Trial/ TEST	Pfizer/International Health Management Associates, Inc. (IHMA) (Schaumburg, IL)	2004-2011 (24/40)
Zyvox Annual Appraisal of Potency and Spectrum/ZAAPS	Pfizer/JMI Laboratories, USA, Pfizer	2004-ongoing (12/30)

The pharmaceutical industry has funded some surveillance projects led by academic networks which are discussed separately.

Academic networks collecting surveillance data on antibiotic resistance

There are different models for the involvement of academic networks in AMR surveillance. Networks such as GABRIEL founded by Fondation Mérieux and the US CDC Global Health Security Agenda Antimicrobial Resistance Action Package may initiate some projects, but their focus is on increasing technical capacity in LMICs. CDDEP does not collect primary data but hosts a data repository where partners can share data which is analysed and mapped using ResistanceMap. SRL Diagnostic Laboratories Network, a large private laboratory network in India, has shared data with CDDEP.

Other academic networks tend to focus collection of AMR surveillance around a specific clinical question, for example:

- Asian Network for Surveillance of Resistant Pathogens (ANSORP). This academic network, created in 1996, is linked to the Asia Pacific Foundation for Infectious Diseases (APFID) and coordinated by a group from Sungkyunkwan University in the Republic of Korea. Study groups are formed around particular topics e.g. trends in *S.pneumoniae* resistance and funding is sought for individual projects. APFID and ANSORP members have more than 130 peer-reviewed publications since 2000 (http://www.ansorp.org/). More than 120 hospitals in 14 countries participate to the network.
- The Typhoid Fever Surveillance in Africa Programme (TSAP) was funded by the Bill & Melinda Gates Foundation, and either set up or strengthened passive surveillance for bloodstream infections with *Salmonella enterica* serovar Typhi at 13 centres in 10 countries. Each centre had a local Principal Investigator and the programme was coordinated by the International Vaccine Institute in the Republic of Korea [49].
- The International Nosocomial Infection Control Consortium (INICC) is a global academic network with participants in more than 2,000 ICUs from 500 cities in 66 countries. The network collects data on all aspects of healthcare associated infections including antimicrobial resistance data (http://www.inicc.org/). The intensive care unit (ICU) is an obvious target for AMR surveillance since these units are high users of broad spectrum antimicrobial agents, medical devices and assisted ventilation in patients who are very vulnerable to infection. Multidrug resistant organisms such as *Acinetobacter baumannii* are notorious for contaminating the ICU environment, putting patients at greater risk. INICC has more than 200 peer-reviewed publications.
- The Global Point Prevalence Survey (Global-PPS), funded by Biomérieux and coordinated by the University of Antwerp collected data on antimicrobial prescriptions and microbiology data on a single day between February and June 2015 from participating centres in 335 hospitals in 53 countries. While only providing a snapshot, Global-PPS identified large variations in practice across countries [50].

A full list of the academic networks is shown in Table 1.6.

Table 1.6 Academic networks concerned with antibacterial resistance surveillance

Name/acronym	Sponsor/Leading institution	Years active

Asian Network for Surveillance of Resistant Pathogens (ANSORP)	Corporate (project-specific)/ Sungkyunkwan University, Korea	1996-ongoing
Antibiotic resistance in the Mediterranean region (ARMed)	European commission/ Infection Control Unit, Mater Dei Hospital, Msida, Malta	2003-2007
Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries: an international cohort study (BIRDY)	Monaco Department of International Cooperation, Total Corporate Foundation, MSDAvenir/Institut Pasteur International Network	2012-ongoing
Global Health Security Agenda Antimicrobial Resistance Action Package (CDC GHSA Action Package Prevent-1)	US CDC	2014-ongoing
Centre for Disease Dynamics, Economics and Policy (ResistanceMap/CDDEP) [1]	BMGF (+other donors) /CDDEP	1999-ongoing
Community-Based Surveillance of Antimicrobial Use & Resistance in Resource-Constrained Settings Project Group	USAID/WHO	2002-2005
Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL)	Fondation Mérieux	1999-ongoing
The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS)	bioMERIEUX/University of Antwerp	1992-ongoing
International Nosocomial Infection Control Consortium (INICC)	International Nosocomial Infection Control Consortium, Argentina	2015-2016
International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR)	CDC USA	2002-no longer active
Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR)	GAVI Alliance and The Vaccine Fund/netSPEAR	1998-no longer active
South Asian Pneumococcal Alliance (SAPNA)	Pneumococcal vaccines Accelerated Development and Introduction Plan (PnemoADIP)/GAVI	2004-2009
Typhoid Fever Surveillance in Africa (TSAP)	BMGF/International Vaccine Institute	2009-ongoing
Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC)	Zambon S.p.A., Bresso (MI), Italy/European Society for Infection in Urology	2003-2006
DOMI Typhoid Study Group & multicentre shigellosis surveillance study	BMGF/International Vaccine Institute, Republic of Korea	2001-2004
NosoMed pilot survey in the Eastern Mediterranean Area	EU/Université Claude Bernard Lyon I	2003-2004
African-German StaphNet consortium	Deutsche Forschungsgemeinschaf/ University of Saarland, Germany	2010-ongoing

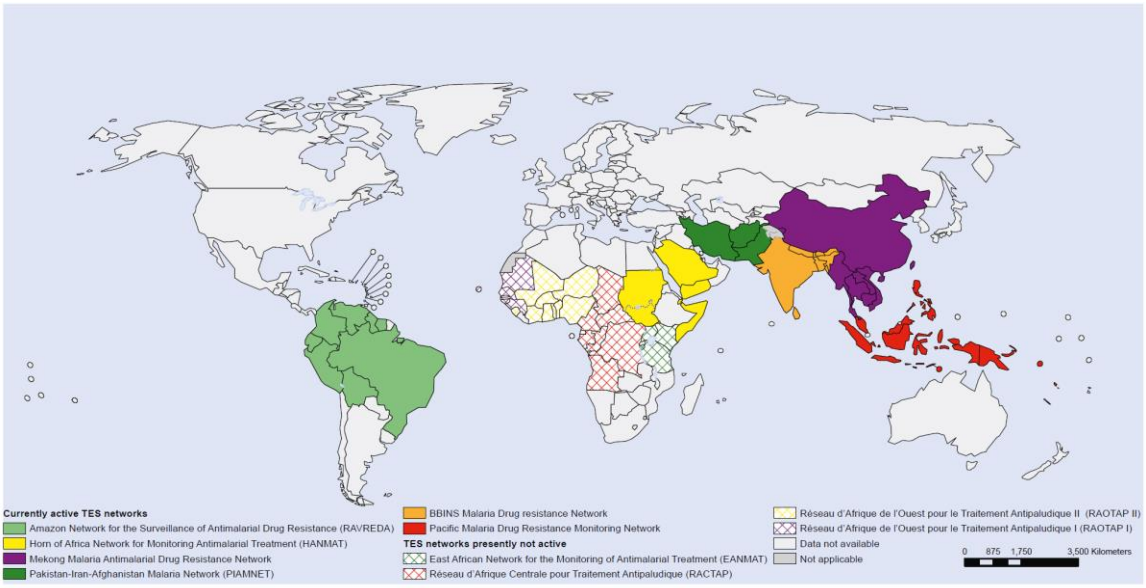
The academic networks have had much more impact to improve laboratory and clinical capacity in LMICs compared to the pharma networks. A reported positive impact of the ARMed network was improvement in participating laboratories' capacity to perform bacterial identification and antimicrobial susceptibility testing (AST), as a result of the EQA programme attached to the network[51]. The INICC

provides countries with tools to prevent healthcare associated infections (HCAIs) as well as collecting microbiological data and has reported decreases in HCAIs in countries using these tools[52, 53]. TSAP incorporated population surveillance into the programme and was able to obtain typhoid incidence data for the regions it was operating in which revised estimates of disease burden. APFID maintains a biobank of bacterial isolates from previous studies (Asian Bacterial Bank) which can be used to screen new drugs or to evaluate for drug resistance mechanisms.

Malaria drug resistance surveillance networks

The Global Malaria Programme (GMP) of WHO provides policy guidance to national malaria control programmes on how to monitor antimalarial drug efficacy. Member countries report their data to WHO GMP directly. Ten regional networks were set up with WHO support in the late 1990s, a time when chloroquine and sulfadoxine-pyrimethamine (SP) resistance rates were rising sharply, malaria was out of control and death rates from malaria were going up in children in sub-Saharan Africa (Figure 1.4). These networks re-energised surveillance and also played a role in advocacy for policy change, acting as a bridge between research groups and national control programmes. Most networks relied on external funding. The successful East African Network for Monitoring Anti-Malarial Treatment (EANMAT), which was made up of programme-managers and researchers, collapsed after the UK Department for International Development withdrew funding in 2006, although other factors contributed to its demise. In 2011 a meeting of former EANMAT member countries resulted in a Kigali Call for Action to revive the network but this has not happened [54].

Figure 1.4 Malaria Regional and sub-Regional Therapeutic Efficacy Surveillance Networks



Reproduced from [27] with permission

Malaria surveillance is linked to clinical outcome and requires patients with malaria to be followed up for 4-6 weeks in a therapeutic efficacy study to assess treatment responses. The very standardised approach to conducting therapeutic efficacy studies is almost universally adhered to. Numerous

documents are available on the WHO website which cover study methodology, laboratory procedures and quality management [55, 56]. In high transmission areas studies are conducted in children under 5 years old who are less immune to malaria. This enables a 'worst-case scenario' estimate of antimalarial drug efficacy to be made and also assesses the main target patient group. The WHO Global Malaria Programme has created an Excel spreadsheet template which can be used to calculate the required estimates of drug efficacy if needed[57]. The 2011 Report of the WHO Global Programme for Artemisinin Resistance Containment (GPARC) reported that compliance with the requirements for antimalarial therapeutic efficacy monitoring by national malaria control programmes was poor with only 31/106 countries in compliance[3]. It is unclear how much this is linked to lack of funding and how much a degree of complacency with the perception that artemisinin based combination therapies (ACTs) are still performing well throughout most of sub-Saharan Africa.

Current antimalarial treatment relies upon the artemisinin derivatives. In 2002, the first signals of artemisinin resistance came from routine surveillance activities by the National Malarial Control Programme in Battambang in Cambodia, when the results of a survey at one sentinel site reported a reduction in efficacy of artemether-lumefantrine. However it was only in 2009 that sufficient evidence accrued from detailed *in vivo* studies by academic groups in which pharmacokinetic data collection, *in vitro* susceptibility testing and evaluation of known molecular markers were performed that resistance was confirmed [58]. Artemisinin resistance is characterised by a phenotype of slow parasite clearance and this may go undetected in standard therapeutic efficacy studies. Molecular markers for artemisinin resistance were identified in 2013 but they are not thought to be sufficiently robust to replace detailed clinical studies in which parasite density is measured every 6 hours for at least the first 48 hours of therapy [59]. These types of study are viewed as being too complicated to implement into routine surveillance and are performed by research groups.

The malaria networks are shown in Table 1.7. As mentioned, many of the supposedly active networks are not compliant with recommendations for efficacy monitoring. Médecins sans Frontières has the expertise to perform AMR surveillance in malaria and was very active in the 2000s when MSF was campaigning for the introduction of ACTs into programmes, but since this has happened they have not kept up routine surveillance[60]. The Asia-Pacific Malaria Elimination Network is also listed. This network does not carry out routine surveillance but is a forum for endemic countries to exchange information with the primary objective of malaria elimination, thus they monitor the situation of resistance emergence in the region. The WorldWide Antimalarial Resistance network is another academic network which does not collect primary data but hosts a data repository for data sharing and analysis by partners and provides tools to facilitate surveillance. The West African Network for Monitoring Antimalarial Treatment (WANMAT) is no longer active and there are no plans to revive it. West Africa is moving towards integrated disease surveillance and recently has set up the West African Network for Infectious Disease Surveillance (WANIDS).

Table 1.7 Supranational Networks involved in surveillance of antimalarial drug resistance

Name/acronym	Sponsor/Leading institution	Years active
Amazon Malaria Initiative (AMI)	USAID and PAHO	2001-ongoing
Asia-Pacific Malaria Elimination Network (APMEN)	Australian Department of foreign affairs and trade	2009-ongoing
Artemisinin Resistance Confirmation, Characterisation, and Containment collaboration (ARC3)	BMGF/WHO GMP	2009-2010
Artemisinin Resistance Containment and Elimination collaboration (ARCE)	WHO GMP	2010-2011
Greater Mekong Sub-region Therapeutic Efficacy Studies (TES) network (GMS TES)	WHO GMS	2007-ongoing
The East African Network for Monitoring Antimalarial Treatment (EANMAT)	DFID/EANMAT secretariat	1997-2006
Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT)	USAID/HANMAT secretariat	2004-ongoing
Pakistan-Iran-Afghanistan Malaria Network (PIAM-net)	Global Fund/PIAM-net secretariat	2008-ongoing
BBINS Malaria Drug resistance Network	USAID/BBINS secretariat	2011-ongoing
Pacific Malaria Drug Resistance Monitoring Network	USAID/PMDRMN secretariat	20011-ongoing
Malaria Genomic Epidemiology Network (MalariaGEN)	Wellcome Trust, BMGF/MalariaGEN, University of Oxford & Sanger Institute, UK	2005-ongoing
Médecins sans Frontières/Epicentre (MSF)[1]	MSF	1999-ongoing
Plasmodium Diversity Network Africa (PDNA)	Wellcome Trust, MRC/University of Science, Techniques and Technologies, Bamako, Mali	2012-ongoing
Réseau d'Afrique Centrale pour traitement anti-paludisme (RACTAP)	WHO, World Bank, USAID	2003- no longer active
Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA)[2]	USAID/PAHO	2001-ongoing
South African Network for the Monitoring of Antimalarial drug resistance (SANMAT)	unknown/SANMAT secretariat	2002-ongoing
Tracking Resistance to Artemisinin Collaboration (TRAC I & II)	DFID/MORU	2011-ongoing
West African Network for Monitoring Antimalaria Treatment (RAOTAP I & II/ WANMAT I & II)	unknown/WANMAT secretariat	2003-no longer active

[1] This network also reports on HIV and TB

[2] see Appendix 4 for more details on RAVREDA

In terms of impact, the routine antimalarial drug efficacy monitoring by the regional networks was influential for advocacy for a change in national policies to the artemisinin-based combination therapies, although policy change was still very slow in coming.

Academic networks have generated a lot of data on the efficacy of antimalarial drugs, much of which has been shared with WWARN which now holds >70% all ACT clinical trial data and provides on-line access to clinical, in-vitro, molecular, pharmacological and drug quality information relevant to antimalarial drug resistance. Pooled analyses coordinated by WWARN have led to policy recommendations to change antimalarial drug dosing. Another impact of the academic malaria drug efficacy surveillance networks has been the establishment of successful North-South scientific partnerships. There are a few examples where the scientific leadership now comes from the South e.g. Plasmodium Diversity Network Africa, a molecular surveillance network [61]. WWARN has created Regional Centres, e.g. in West Africa, led by local senior researchers.

The development of simple, point-of-care rapid diagnostic tests for malaria, while not able to detect drug resistance, has been a major achievement in improving malaria case detection and surveillance and is a powerful tool to improve appropriate antimalarial drug use. Malaria microscopy, while seemingly relatively straightforward, frequently has no mechanism to assure quality in LMIC routine clinics and there is plenty of evidence showing that clinicians pay little heed to the result [62].

Tuberculosis drug resistance surveillance networks

The example of tuberculosis drug resistance surveillance is notable for having a high profile global monitoring system led by the WHO/ International Union against Tuberculosis and Lung Disease (IUATLD) **Global Project on Anti-tuberculosis Drug Resistance Surveillance**. There are very few networks performing AMR surveillance not linked to this global initiative (Table 1.8).

Table 1.8 Supranational networks concerned with drug resistance surveillance in TB

Name/acronym	Sponsor/Leading institution	Years active
Médecins sans Frontières/Epicentre (MSF)[1]	MSF	1999-ongoing
Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL)[2]	Fondation Mérieux	2008-ongoing
Comprehensive Resistance Prediction for Tuberculosis International Consortium (CRyPTIC)	BMGF/University of Oxford	2015-ongoing
East Africa Public Health Laboratory Networking Project (EAPHLNP)	World Bank/EAPHLNP	2010-ongoing
Global TB Supranational Reference Laboratory Network (SRLN)	WHO	1994-ongoing
WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance	WHO	1994-ongoing

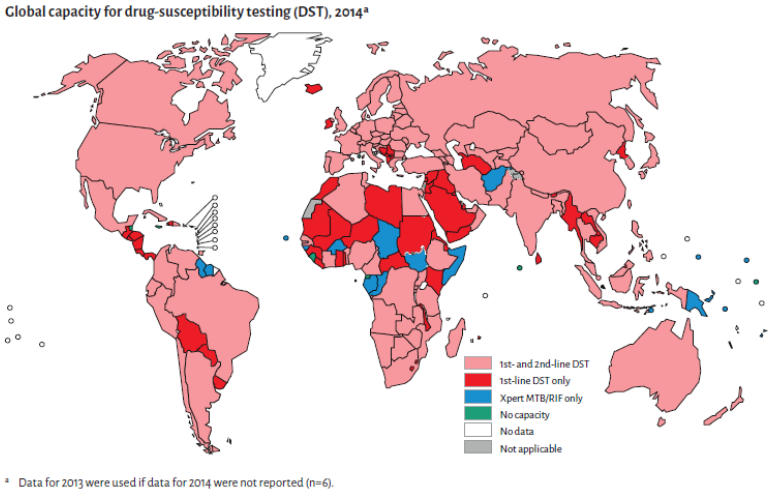
[1] This network also reports on HIV and malaria

[2] This network also reports on bacteria

CRyPTIC is an academic network looking to harness the power of whole genome sequencing of isolates from multiple locations to investigate genomic variation associated with resistance to all drugs. The East Africa Public Health Laboratory Networking Project (EAPHLNP) is a World Bank funded project supporting 25 laboratories in Uganda, Tanzania, Kenya and Rwanda with the aim of increasing capacity for the diagnosis of tuberculosis and other infectious diseases. The role of MSF in supporting AMR surveillance in TB is described later in the report in the section on the role of NGOs in AMR surveillance.

Routine surveillance for drug resistance in TB has been transformed in the last 10 years by the development of robust molecular detection methods, in particular the roll-out of GeneXpert®, a PCR based technology which can be performed directly on primary specimens without an intermediate culture step. Almost 5 million test cartridges were procured in 2014, a tenfold increase over a 3 year period and almost 4000 machines have been procured under a preferential pricing initiative. Despite this progress coverage of surveillance programmes is still not universal with an estimated 1/3 of global TB cases going undiagnosed or unreported and current surveillance for MDR-TB only detecting about one in four cases [2]. Since 2007 WHO has recommended national prevalence surveys to estimate disease prevalence in selected, predominantly high burden, focus countries. The WHO Handbook lists 11 essential prerequisites for eligibility to become a focus country, ranging from strong leadership by the national TB programme, to securing funding, to ensuring community participation [63]. There is a long term goal to move to a global case-notification surveillance system. A key strength of the global TB resistance surveillance network is the WHO TB Supranational Reference Laboratory (SRL) network which was created in 1994 and supports laboratory capacity strengthening in countries. This network runs a successful EQA programme. Challenges remain with less a quarter of high burden countries implementing a comprehensive quality assurance programme for their smear microscopy and limited capacity to perform culture and drug susceptibility testing in several member states (Figure 1.5).

Figure 1.5 Map of drug-susceptibility testing capacity for *Mycobacterium tuberculosis*



Reproduced from [2]with permission

Results of TB AMR surveillance are used to guide countries' second line treatment policies. AMR data from the global programme is available for download from the WHO website.

HIV drug resistance surveillance networks

Global drug resistance surveillance in HIV is still relatively young and there are not many networks (Table 1.9). The World Health Organisation's global network, **HIV ResNet**, was created in 2007 to address concerns regarding HIV drug resistance (HIVDR) and to develop strategies to monitor its emergence and transmission. HIV ResNet is a group of around 50 international experts from academic institutions, laboratories, international and non-profit organisations. HIVResNet has a laboratory strategy to support WHO recommendations for countries to conduct HIV drug resistance surveys. This strategy is to enable countries to have access to quality assured genotyping laboratory services accredited by WHO[64]. As of July 2015, there was a total of 31 accredited laboratories worldwide supporting HIV genotypic resistance testing. The countries performing surveys are not all part of HIV ResNet and tend to publish their findings on their own. The last WHO HIV resistance report was published in 2012[65]. Aside from conducting surveillance on HIV resistance (prevalence of HIV DR in newly infected individuals, surveys on emergence of HIVDR under treatment pressure), WHO also incorporates other data called Early Warning Indicators (EWI) to monitor programme factors linked to the emergence of HIVDR. These include antiretroviral treatment coverage, retention in care, treatment interruption, viral load suppression. Technical guidance is available on the frequency of the surveillance as well as the budget and resources needed for countries to implement surveillance activities [66].

It should be noted that WHO's HIV public health approach does not recommend individual HIV drug resistance testing for patients who fail treatment. Current access to individualised HIV resistance testing remains very limited. WHO does recommend routine HIV viral load monitoring and plans to incorporate these data into analysing trends in HIV drug resistance. A proposed tiered approach to using routine programme data for surveillance based on coverage of HIV viral load and HIV resistance testing is being considered by WHO [67]. WHO is in the process of developing a global action plan for HIV drug resistance 2016-2021 [68].

In terms of impact, the global HIV surveillance strategy has led to incremental improvements in building laboratory networks to support surveillance activities, availability of funding, and incorporation of other indicators of resistance such as the EWI. Policy guidance from WHO on HIV is strong and influential compared to antibiotic resistance. This ranges from treatment guidelines to support from the WHO Prequalification programme on regulatory approval of HIV diagnostic tests and antiretroviral drugs. There is also a relatively clear path for funding for all HIV related activities for various stakeholders.

Two big academic networks for HIV resistance surveillance in LMICs are PASER (Pan African Studies to evaluate resistance) and TASER (TREAT Asia Studies to Evaluate Resistance) [69, 70]. The TASER core data collection has stopped since 2012 due to lack of funding. The EQA part of the programme is still functioning (TAQAS) with some labs still participating. PASER has secured funding to continue its work in 6 countries. MSF is collecting resistance data as part of its HIV programme activities across several countries. The French agency ANRS is also actively involved in a number of HIV research programmes concerned with resistance monitoring. IeDEA is a platform for data-sharing from different sites, used to address research questions. There is overlap of the networks with TASER, TAHOD and TApHOD all sharing data with IeDEA.

Table 1.9 Supranational networks concerned with collection of HIV resistance data

Name/acronym	Sponsor/Leading institution	Years active
Médecins sans Frontières/Epicentre (MSF)[1]	MSF	1999-ongoing
l'Agence nationale de recherches sur le sida et les hépatites virales (ANRS)	ANRS/ Groupe Résistance AC12	1992-ongoing
Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)	European Commission/ University College London UK	2009-2014
Global HIV drug resistance network (HIVResNet)	WHO	2007-ongoing
International Epidemiologic Databases to Evaluate AIDS (IeDEA)	The NICHD Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch, The National Cancer Institute (NCI), Office of HIV & AIDS Malignancy (OHAM)/NIAID	2005-ongoing
PharmAccess African Studies to Evaluate Resistance (PASER)	The Dutch Ministry of Foreign Affairs in partnership with Stichting Aids Fonds, PharmAccess Foundation, TREAT Asia, International Civil Society Support/TREAT Asia	2006-ongoing
TREAT Asia Studies to Evaluate Resistance (TASER)[2]	The Dutch Ministry of Foreign Affairs in partnership with Stichting Aids Fonds, PharmAccess Foundation, TREAT Asia, International Civil Society Support /TREAT Asia	2007-2011 (no prospective data collection but still reporting data analyses)
Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) HIV Observational Database/TAHOD[2]	amfAR, The Foundation for AIDS Research, US NIH/TREAT Asia	2003-ongoing
TREAT Asia Pediatric HIV Observational Database/TApHOD	amfAR, the Australian AIDS Life Association, US NIH/TREAT Asia	2006-ongoing
Tenofovir Resistance Study group (TenoRES)	Wellcome Trust/TenoRES study group	2015-2016

[1]This network also reports on malaria and TB; [2] TASER-M merged with TAHOD in 2012

Surveillance networks for other drug resistant infections in humans

WHO's **Global Influenza Surveillance and Response System (GISRS)** started in 1947 and is primarily concerned with virus surveillance to inform vaccine strains selection. There are six collaborating centres in the network, all bar one (China) in HICs, and four Essential Regulatory Laboratories. An advisory group issues recommendations for antiviral resistance testing and reference viruses are made available to collaborating centres on request. Unlike the other networks the GISRS has high global coverage with very good representation in the African Region (15 participating national influenza centres). National Influenza Centres collect specimens and identify them locally using WHO-provided reagents and forward

representative virus strains plus low-reacting or unidentified viruses to their collaborating centre. **ARTEMIS** was a global pharma-sponsored network concerned with surveillance for resistance in fungi set up in 1997 which ran for approximately 10 years. Nine LMICs participated to the network and geographical differences in susceptibility of *Candida* species to the azole drugs were reported[71].

Animal and One Health AMR surveillance networks

There are far fewer supranational networks concerned with AMR surveillance in animals than in humans. The World Organisation for Animal Health (OIE) has a network of collaborating centres and a network of 252 reference laboratories globally. These laboratories focus on different specialist areas. OIE lays down criteria for laboratories to meet in order to participate to the network e.g. provision of evidence of ISO 17025 accreditation. However only one lab is named as the AMR reference laboratory currently, based at the Animal and Plant Health Agency in the UK. The terms of reference for these reference laboratories are broad and include developing standards, proficiency testing, provision of diagnostic testing, training, and building laboratory networks in the same specialist area but these activities have not taken off internationally for the AMR reference laboratory as yet [72, 73]. The emphasis on AMR surveillance in animals is on food safety and this is the area which has the most systematic approach to surveillance with 2 initiatives operating at a global scale.

Global Foodborne Infections network (GFN)

WHO Global Salm-Surv was created in 2001 and changed its name to the Global Foodborne Infections network (GFN) in 2009. As well as collecting aggregated data on Salmonella isolates (animal and human) annually from participating institutions in 165 countries it acts as a reference laboratory for member countries, supports outbreak investigation, and collaborates on research projects in LMICs in a technical advisory capacity. GFN is committed to capacity building and has an active training programme. There are GFN Regional Centres in Argentina, Cameroon, Costa Rica, South Africa, and Thailand and a free- of-charge EQAS system for GFN reference laboratories coordinated by the National Food Institute in Denmark. Surveillance data are held in a web-based country databank.

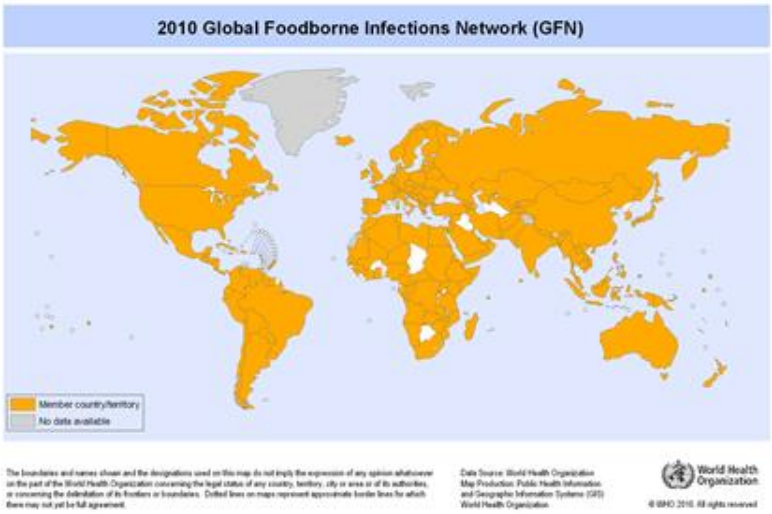


Figure 1.6 Map showing the coverage of the Global Foodborne Infections Network in 2010

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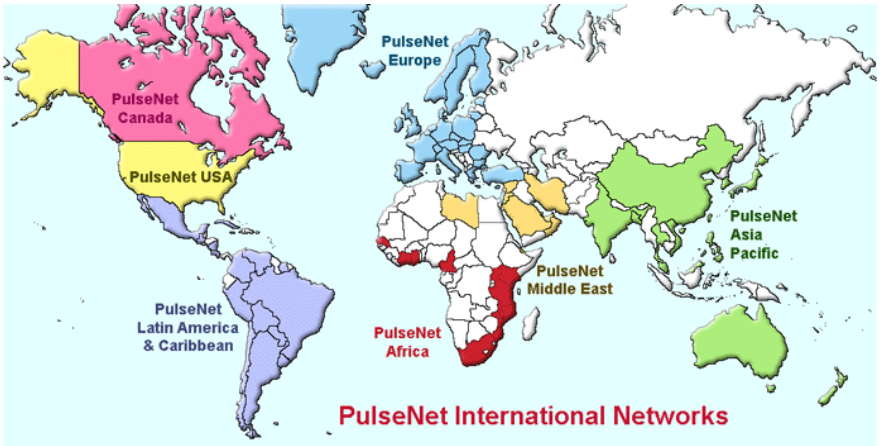
There is a separate International Food Safety Authorities Network (INFOSAN) which permits the rapid dissemination of information about food-safety alerts between member countries[75]. The INFOSAN Secretariat is based in WHO.

PulseNet International

PulseNet is another international laboratory network of networks at regional and national level for foodborne disease surveillance which relies on implementation of standardised molecular methods to perform surveillance for global foodborne disease outbreaks (http://www.pulsenetinternational.org/). AMR surveillance is not the focus of the network but may be a by-product in the event of an outbreak of a drug-resistant infection. It is sub-divided into a series of regional networks as shown in Figure 1.7.

Figure 1.7 Location of the PulseNet International Networks



The network has developed standardised protocols for laboratory procedures which are available on the website. Regional databases exist, accessible to network participants.

Other animal or One Health Networks

Apart from these two major international networks for foodborne infection surveillance, most information on antimicrobial resistance in animals, retail meat products or the environment in the public domain comes from national data collection efforts. Some LMICs have national systems of disease surveillance in animals e.g. Ethiopia but the focus is on other important diseases affecting animals e.g. brucellosis, rather than AMR.

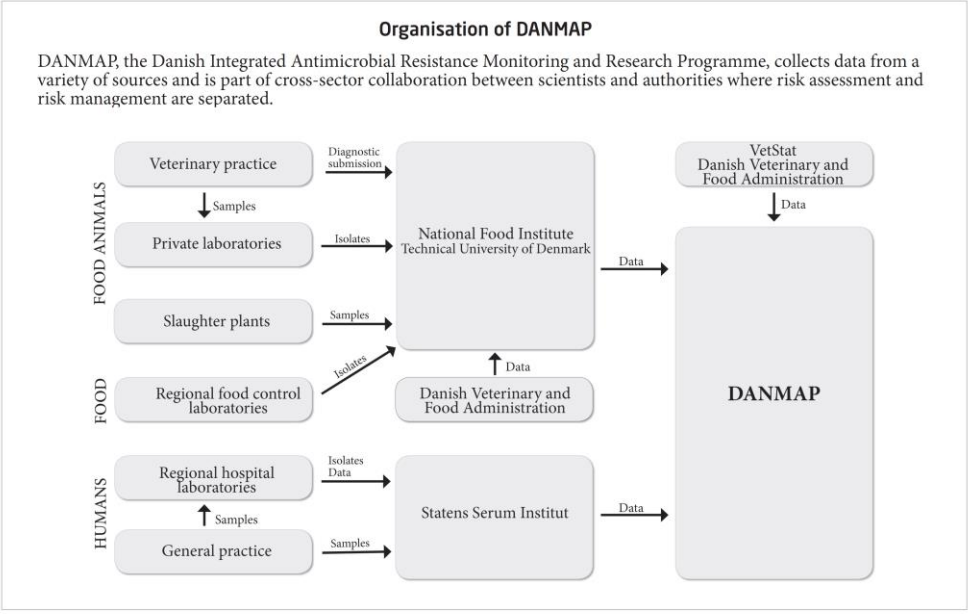
ECDC has a separate food and waterborne diseases surveillance network (ECDC FWD) which cooperates closely with PulseNet. The European Society for Clinical Microbiology & Infectious Diseases set up a study group in 2015 called the ESCMID Study Group for Veterinary Microbiology (ESGVM) which plans to create a network for the surveillance of AMR and zoonoses in animals. Antimicrobial use in animals in the European Union is already monitored through the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. Two other European programmes monitor antimicrobial resistance in animals: the European Food Safety Authority (EFSA) and the veterinary pharmaceutical industry's European Antimicrobial Susceptibility Surveillance in Animals (EASSA) programme.

Integrated human, animal and environmental AMR surveillance

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) has supported a number of pilot projects which have evaluated a 'value chain' analysis approach to microbiological sampling in food production. This approach breaks down meat production into a series of steps from the animals being on the farm, to slaughter points, to the retail step. They promote a cross-sector approach with sampling of animals/meat at each stage, plus environmental sampling e.g. abattoir waste-water and sampling of patients with diarrhoea attending health centres in the locality. These results are combined with antibiotic usage surveys.

For LMICs with very little AMR surveillance activity there is an opportunity to design an integrated system from the outset. There is a consensus that AMR surveillance in animals needs to be active and slaughter-point surveillance is a convenient time-point to sample. There are several HICs which have national integrated surveillance systems in place e.g. DANMAP in Denmark (see Figure 1.8). Denmark also has a surveillance system for veterinary use of drugs for production animals known as VETSTAT.

Figure 1.8 Organisational structure of DANMAP- the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme



Taken from 'Data for Action' http://www.danmap.org/ (with permission)

Thailand is an example of a middle-income country starting to implement integrated surveillance. In 2012 Thailand launched their Antimicrobial Resistance Containment and Prevention Programme. There was no national reference for AMR surveillance in animals at that time. A working group has been set up to address this and to implement active surveillance in poultry and swine [76].

Different models of AMR and AMU surveillance in 19 countries were reviewed in detail in 2014 by an academic group from Griffith University and the University of Adelaide, commissioned by the Australian Department of Agriculture, with the aim of making national recommendations for surveillance in animals and agriculture. The 209 page report discusses myriad considerations when designing an integrated AMR surveillance system, including types of animal or animal products in a country, use of intensive farming methods, importance of small scale animal production, numbers of companion animals, priority pathogens and antimicrobials, the surveillance period for each species/product combination (e.g. for meat production this is from birth until death of the animal while for eggs it would be the layers' life-cycle on the farm), sampling designs, laboratory methods, animal feed surveillance, antimicrobial use recording and cost-effectiveness. In terms of pathogens there needs to be surveillance for commensal bacteria in animals, e.g. coliforms and Enterococci, which may transmit AMR

genes into humans, and not just zoonotic bacteria/foodborne pathogens. The report stressed the importance of engaging all stakeholders in a surveillance effort [77]. Commercial interests will have much more of an influence on design of AMR surveillance compared to setting up surveillance in the human health sector.

All of these considerations listed are highly relevant for LMICs and show that is not possible to design a surveillance plan which can be used by any country but each one will need to be adapted to the context, setting priorities for surveillance. Sampling strategies will be guided by a risk assessment for animal species/pathogen combinations. Microbiological testing of food-producing animals or companion animals has a cost attached which is usually passed on to the owner. Different funding models will need to be explored for LMICs where there may be more small-holders who are unable to meet these costs.

Non-AMR focused animal/veterinary/One Health networks

Other networks concerned with animal health not included in the analysis are mentioned here to highlight laboratory capacity or networks which could be leveraged for AMR initiatives. **OFFLU** is a global animal influenza network which has laboratories specialising in avian, swine and equine influenza. These laboratories are mainly in HICs with a few exceptions (India, China, Brazil, Viet Nam). **ASEAN** countries have a strong animal health regional network with an active veterinary laboratory Technical Advisory Group and Regional proficiency resting and biosafety programmes. The **Companion Animals Parasite Council** has proposed to set up a council for the Tropics [78].

Aquaculture networks

There has been no coordinated surveillance of AMR in the aquatic environment/aquaculture until now. New recommendations have been published under the 18th edition of the OIE Aquatic animal code. Article 6.4.2 states that "Competent Authorities should conduct active antimicrobial resistance surveillance and monitoring programmes for aquatic animals." A 'competent authority' would be a National Veterinary Authority or other governmental body responsible for aquatic animal welfare. Inter-country collaboration at Regional level is encouraged and data should be shared at Regional and international level [79]. There is one active regional aquaculture network- the Network of Aquaculture Centres in Asia-Pacific (NACA) which is primarily concerned with promoting sustainable aquaculture practices in the 12 participating countries. It has an active training and education programme but is not collecting AMR susceptibility data currently.

The private sector

The global meat market is a multi-billion dollar industry controlled by large corporations who thus bear the responsibility for the health of the animals they produce. LMICs have an important role in global food production from animals. Brazil and China are leading beef, pork and broiler meat producers. China, Thailand and Viet Nam occupied positions 1,3 and 4 respectively in the top ten fish exporters in the world in 2012 with their combined exports estimated as being worth more than 32 billion USD [80]. The extent of untapped sources of AMR surveillance data in the private sector in LMICs is unknown.

Initiatives to promote standardised AMR surveillance in animals

Standardisation of antimicrobial testing methods for animals is quite far behind the progress made in humans. A syndromic approach is usually taken when deciding to treat sick animals with antimicrobials.

Suspicion of disease in an animal may precipitate a decision to treat all animals in close proximity presumptively, because of the potential for dire consequences if the infecting agent is transmitted. Thus, in theory, antimicrobial stewardship could be improved in animals by adopting a test and treat approach in sick animals, enabling more effective targeted therapy to be initiated and reducing secondary preventive use. However, this would have significant cost implications. When testing does occur, breakpoints indicating susceptibility or resistance to a particular antimicrobial agent in different animal species are poorly defined [81]. VetCAST is a subcommittee of EUCAST working to harmonise antimicrobial susceptibility testing in isolates from animals in the European Region[11]. CLSI also has a Subcommittee on Veterinary Antimicrobial Susceptibility Testing (VAST).

Supranational Disease Surveillance networks with a One Health Approach

A number of regional disease surveillance networks with a One Health Approach have been created in the response to the threat of emerging diseases and epidemics (Table 1.10).

Table 1.10 Disease-surveillance networks adopting a One Health approach

Name/acronym	Sponsor	Years active
WHO African Region Integrated Disease Surveillance Programme /AFRO-IDSR	WHO	2002-ongoing
Asia Partnership on Emerging Infectious Diseases Research/APEIR	International Development Research Centre (Canada)	2006-ongoing
Connecting Organisations for Regional Disease Surveillance/CORDS	The Rockefeller Foundation, Skoll Global Threats Fund, Bill & Melinda Gates Foundation	2009-ongoing
East African Integrated Disease Surveillance Network/EAIDSNET	Rockerfeller Foundation	2000-ongoing
Pacific Public Health Surveillance Network /PPHSN	Voluntary network	1996-ongoing
The Middle East Consortium on Infectious Disease Surveillance/MECIDS	Unspecified donors	2003-ongoing
Mekong Basin Disease Surveillance /MBDS	Various trusts, foundations, public & corporate sponsors	2001-ongoing
Network for the Evaluation of One Health/NEOH	European Cooperation in Science & Technology	2014-ongoing
One Health Global Network/OHGN	Voluntary support	2011-ongoing
The Southern African Centre for Infectious Disease Surveillance/SACIDS	Various trusts, foundations, public & corporate sponsors	2008-ongoing
Southeast European Centre For Surveillance And Control Of Infectious Disease/SECID	CORDS, WHO, CDC, UNFPA	2013-ongoing
One Health Central and Eastern Africa/OHCEA	USAID	2010-ongoing
West African Network for Infectious Disease Surveillance/WANIDS[1]	Not yet funded	Not yet active

[1] Not included in overall networks analysis as not yet active

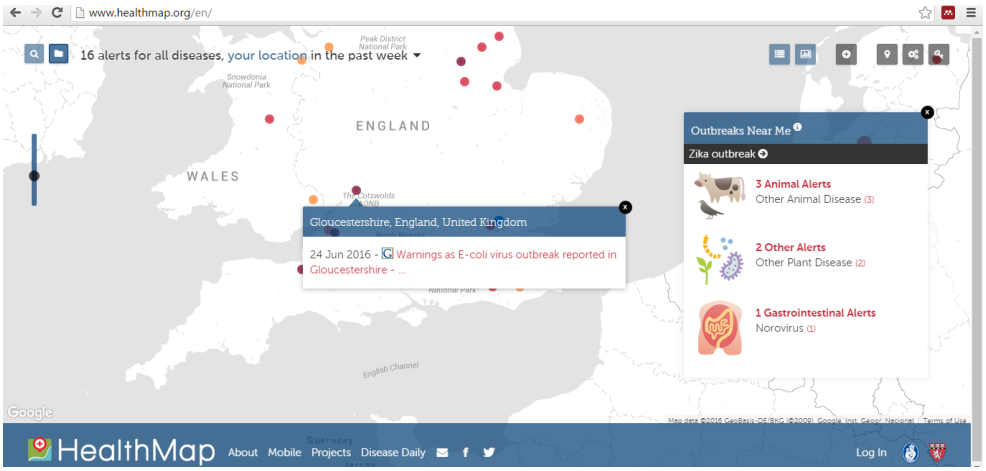
They are mainly academic networks and the scope of activities varies depending on location, for example the stimulus for creating two of the Asian networks was the threat of avian influenza. The Middle-Eastern network, MECIDS focuses on leishmaniasis, foodborne infections and avian influenza. Several of these networks are linked e.g. APEIR, EAIDS, MBDS, MECIDS, SECID, SACIDS and WANIDs are linked and come under the umbrella of CORDS, which has its headquarters in Lyon in France. CORDS acting as an overarching network of networks to promote exchange of information and expertise. There is some overlap between the activities of different integrated disease surveillance initiatives in the African Region. The WHO AFRO Integrated Disease Surveillance Programme states its aim as being provision of technical support to countries, networks and centres of excellence in the region. It has produced a number of technical documents outlining how to implement integrated disease surveillance. EAIDSNET is a collaboration between governments in East African Region and has one of its aims as being to harmonise integrated disease surveillance. The original vision for SACIDS was that it would function as an African CDC. However the US CDC launched the African CDC in 2015 following the Ebola epidemic. Planned activities of CDC Africa are centred around emerging disease response [82].

Some of the disease surveillance networks highlight AMR as a priority One Health issue (APEIR, SACIDS) but none appear to be actively engaged in AMR surveillance. MBDS undertook a laboratory mapping exercise in 2009 and it is possible that the other networks have information on regional laboratories which would be useful when planning laboratory capacity strengthening for AMR in LMICs. The feasibility of integrating AMR surveillance into the activities of these other disease surveillance networks should be explored.

Digital Disease Detection networks

Internet-based disease reporting systems like ProMED and HealthMap use a mixture of text-mining and verified reporting from individuals in the network. Currently their main focus is on emerging diseases or outbreaks but they also report on drug-resistant infections. A strength of digital disease detection (DDD) networks is their ability to disseminate information very rapidly. A disadvantage is they rely on sources such as news reports which may not always be accurate or verifiable (see Figure 1.9).

Figure 1.9 Screenshot of HealthMap and an 'E.coli virus' alert



The role of other networks to support AMR Surveillance in LMICs

In some LMICs non-governmental organisations, academic networks, professional bodies, not-for-profit organisations/technical support agencies, and governmental organisations including the military are supporting either AMR surveillance activities or could play a role as countries participate in GLASS.

1. Non-governmental Organisations and AMR surveillance

NGOs can play an important role in settings where no surveillance data on antimicrobial resistance exists, for example due to a breakdown in health services following a humanitarian emergency, with the caveat that they will usually last only as long as the NGO is present and deems it a priority. The AMR-related activities of two prominent NGOs are outlined in the following section.

a. Médecins sans Frontières (MSF)

MSF is an international medical humanitarian organisation founded in 1971 that delivers emergency aid to people affected by armed conflict, epidemics, natural disasters and exclusion from healthcare. In 2014, the organisation had projects in 63 countries worldwide [83]. Examples of the activities carried out by MSF include treatment of malaria, HIV, TB including MDR-TB, feeding programmes for severely malnourished children, maternal and child care programmes, surgical programmes including obstetric surgery, medical treatment of patients of sexual violence, mental health programmes, infectious diseases outbreak interventions including Ebola, cholera, meningitis, measles as well as vaccination programmes.

Except for their drug resistant TB programmes, MSF has no specific programme designated as an 'antimicrobial resistance programme'. However, in the past few years, MSF has documented the presence of resistant bacteria in several research studies. They also have a handful of programmes with microbiology laboratory support.

Several individuals within MSF have raised concerns about the continued practice of using certain first-line antibiotics (such as amoxicillin, trimethoprim-sulfamethoxazole) for empiric treatment of infectious syndromes. MSF publishes a Clinical guideline (Diagnosis and treatment manual), also known as the MSF green book, designed for use by medical professionals involved in curative care at the dispensary and hospital levels [84]. There is recognition by MSF that the presumptive antibiotic treatment recommended for various infectious syndromes in the guidelines is not ideal given that antibiotic prescribing practices should be based on local data [85]. However, the extent and burden of antibiotic resistance in MSF programmes is currently unknown. Because of this growing concern, MSF has invested in microbiology capacity to mainly improve clinical care. Priority has been given to improving management of sepsis, pediatric infections, infections in trauma and burns and surgical site infections. Surveillance is deemed to be a secondary activity but MSF has expressed its willingness to share any data on antibiotic resistance it collects to WHONET [86].

i. MSF Experience in setting up a microbiology laboratory

In programmes requiring microbiology laboratory support, the approach of MSF is to first try to identify an existing reliable local microbiology laboratory. MSF is currently developing a standardised checklist to guide their laboratory advisors in identifying a reliable laboratory. This will include storage conditions of

reagents, participation to external quality assurance schemes, procedures for doing blood culture, etc. In the past, the decision to choose a referral laboratory was dependent on the referent laboratory advisor who, in most cases, was not a trained microbiologist.

Some of the disadvantages of relying on an external laboratory include delays in results reporting, lack of communication between the medical team and the laboratory, not providing MICs, etc. Aside from these factors, MSF works in remote areas and it is usually just not practical to send out specimens. However, the most important factor for MSF in deciding whether to set up its own microbiology lab is its eventual impact to patient care. In particular, these are programmes in remote areas where access to laboratory results is needed urgently for clinical decision-making.

To give an example, there is a 200 bed pediatric hospital with a separate nutrition ward, ICU, burns and isolation unit in Koutiala, Mali. The existing laboratory staff was made up of 5 technicians, most of whom had knowledge of only basic techniques. An expatriate microbiologist was brought in to strengthen the laboratory and then continue to support the laboratory staff remotely. All abnormal laboratory test results are sent for verification. According to the laboratory advisor, the most important thing to invest in is the quality of training (laboratory technicians, doctors and nurses). The other main challenge is the availability and supply of reagents and consumables. Most of the time, external laboratories would use the cheapest reagents and consumables. MSF imports quality reagents and consumables into the country when there is no local and reliable supply. However, this is not sustainable long term, and the ability of countries or regions to manufacture good quality reagents and consumables will be a key factor in scaling up microbiology, including validation of these reagents and consumables. This factor is often overlooked with most of the emphasis put on proficiency testing when laboratory quality management is discussed.

From the MSF experience, setting up a microbiology laboratory generally takes at least 2 years. Aside from the issue of logistics, the main challenge once the lab has been set up is addressing the lack of awareness of the doctors and nurses on how to use the laboratory service (i.e., from when to order cultures to interpretation of results). Training and continuing education is important. For the laboratory in Koutiala, Mali, the team worked with the paediatricians to develop a testing algorithm, including when to call a culture a real positive and when to call it a contaminant. This process of engaging with the clinicians can take a lot of time [87, 88].

ii. Mapping of a network of quality microbiology laboratories is needed

There is a need to identify good quality microbiology laboratories that can be used for referral of clinical samples. One observation noted by MSF was that when microbiology laboratories do exist, they are only used for research and the services are not available for individual patient management.

iii. Development of a "Mini Lab" as a possible solution

In many settings where MSF work, there are many constraints to scaling up microbiology capacity, including lack of expertise (trained medical staff to know when to order tests and to interpret lab results); funding (infrastructure, instruments, consumables); logistical capacity (need for reagents, waste management); human resources (lack of trained lab technicians). In order to address this, MSF has

developed a project called “Mini Bacterio Lab” or “Mini Lab”[89]. There are a few models of a primary microbiology culture laboratory in resource-limited settings that have been described in the literature, e.g. mobile microbiology as part of a field hospital in Israel [90].The initial strategy of MSF was to establish a standard protocol for a primary microbiology culture laboratory to expand routine access to microbiology for patients. This microbiology lab will provide basic identification of bacteria and sensitivity testing to commonly used antibiotics and will be limited to a selection of specimen types. This primary microbiology culture laboratory will be complemented by development of an advanced bacteriology culture laboratory. The latter is designed to handle more specimen types as it is intended also to identify causes of STIs, osteomyelitis, surgical infections, etc. with more complete identification of the bacteria and antibiotic susceptibility. The plan consists of validating this primary culture laboratory in resource-limited settings before expansion to additional MSF sites. The goal of the project will be a standardised bacteriology culture manual describing the infrastructure and human resources requirements, sample collection and analysis, SOPs of various culture methods, reporting and data analysis including submission to WHONET as well as EQA. Another output of the project is a laboratory culture catalogue to standardise equipment, reagents and other consumables needed in the laboratory to facilitate ordering and set up of laboratories.

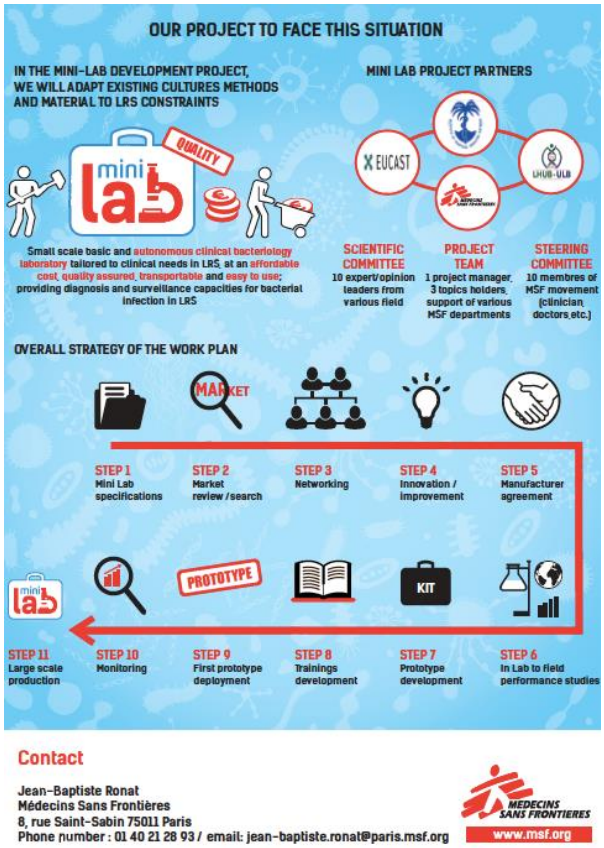


Figure 1.10 MSF mini lab project

In a recent update of the mini lab project, the work plan mentions plans to adapt current culture methods to LMICs and appears to have a product development component to it. It remains to be seen whether this project can help scale up laboratory capacity in resource-limited settings. The illustration in Figure 1.10 was presented at the last ECCMID meeting (2016) and provides details of the partnership as well as the work plan for the mini lab project.

The operational research studies documenting antibiotic resistance in MSF contexts and relevant programmes are summarised in Table 1.11.

Table 1.11 List of MSF operational research and programmes where antibiotic resistance to various bacteria has been documented

Country (Year started)	Programme (i.e. special population, syndromes)	Pathogens
Uganda (Mbarara Regional Referral Hospital) 2009-2012	Epicentre –Central Nervous System (CNS) infection study (*unpublished*)	Common causes of CNS infections. Bacteria isolated: *S.pneumoniae*, *H.influenzae*, S. Typhi, *Salmonella* spp. Antibiotic resistance noted in study: ESBL producing *E.coli* and *Klebsiella pneumoniae*, Ciprofloxacin resistant S.Typhi
Niger (Niamey and Maradi) - 2009	Epicentre study: severe diarrhoea [91]	Diarrhoea pathogens Resistant organisms detected – ESBL producing *Salmonella* spp.; 1/3 of bacteria were resistant to all antibiotics available in Niger
Niger – 2008	Epicentre sub study: Hospitalised children with severe acute malnutrition [92]	Stool carriage rates of ESBL (entry and exit); only genetic study – CTX-M beta lactamase
Programme in Jordan Patients coming from Syria (2011- ongoing)	Chronic wounds from trauma (blast injury, gunshot wounds, motor vehicle trauma) Chronic osteomyelitis	MRSA, resistant Gram-negative infections, ESBLs, CPO , resistant *Pseudomonas* spp.
Iraq (2006-2009)	Chronic osteomyelitis post trauma [93]	MRSA, ESBL, resistant Gram-negative infections.
Iraq Suleimaniyah, north Iraq(2008-2009) – burn hospital	Burns and sepsis, bacteremia *(unpublished)*	ESBL producing Enterobacteriaceae, MRSA
Afghanistan (2013)	Colonisation study of inpatient and outpatients *(unpublished)*	MRSA, GRE, ESBL
Yemen (ongoing)	Trauma patients	
Mali (ongoing)	Pediatric sepsis	
Haiti (ongoing)	Trauma and burn patients	
CAR (ongoing)	Surgical programme	

iv. MSF's experience on conducting surveillance of TB drug resistance:

The decision of MSF to conduct TB resistance surveillance studies was because there was no up to date national data in the TB projects where they were working. These studies were done from 2007 to 2010 in Swaziland, Uganda, Malawi and Kenya in collaboration with national authorities (Table 1.12)[94, 95]. In general, these surveillance activities were viewed as successful in terms of filling a gap in information

as well as engaging the national authorities to set up and conduct national TB surveillance. Other efforts to conduct surveillance activities in countries such as India were not so successful [96].

Table 1.12 MSF programmes collecting TB drug resistance data

Country (Year started)	Description
Swaziland (2009-2010) Nationwide	Cross sectional survey using WHO guidelines for surveillance of drug resistance in TB 15 TB diagnostic centres of 4 regions in Swaziland [95]
Swaziland (2009)	From same study above; a genotypic study of Rifampicin resistance using Cepheid GeneXpert® test [97]
Kenya (2007 to 2009) Homa Bay	Cross sectional survey using WHO guidelines for surveillance of drug resistance in TB TB referral centre for 3 districts (total population of >600,000; HIV prevalence 21%) [94]
Uganda (2007 to 2010) West Nile region	Regional referral hospital for 9 districts of the region (total population of around 2 [94]million; HIV prevalence 2.3%)
Malawi (2008-2009) Chiradzulu	District hospital (covers population of 252,000; HIV prevalence of 25%)

b. EPN – Ecumenical Pharmaceutical Network [www.epnetwork.org]

EPN is an international non-profit Christian network. EPN was first established in 1981 as the Pharmaceutical Advisory Group at the World Council of Churches. Since then, it has evolved to become an independent network of members known as EPN, an international non-profit organisation based in Kenya. The network currently has 92 members including 35 countries in Africa, Asia, Europe and the Americas. Their main goal is to improve the quality of pharmaceutical service delivery and the access to essential medicines. This network is considered one of the major providers of care in Africa. Since 2008, EPN has worked on AMR issues (i.e. education campaigns, random testing of antibiotics entering church health systems in 15 countries to assure the quality of drugs, research on knowledge on antibiotic use and resistance).

The strength of this network is its access to information on antibiotic use, which is the other arm of surveillance. This was discussed in one of the workshops in their recent annual meeting. It was noted that data on antibiotic use already exists in many settings and as pharmacists they have easy access to this [98].

Analysis of the role of NGOs in AMR surveillance:

NGOs can play an important role in settings where no surveillance data on antimicrobial resistance exists. In the case of MSF and TB DR, the work was a catalyst for the national authorities to set up a surveillance system in the country. Because of the nature of their activities, MSF is able to highlight the needs of certain populations (malnutrition, high burden HIV population, as well as difficult to reach populations – war and conflict). MSF's work on antibiotic resistance is focused on addressing clinical demands (patient-centred) and not surveillance (population–centred). It remains to be seen whether such data could be incorporated into national surveillance programmes usefully, as the data are often from non-representative populations.

The bottleneck in understanding the extent of antibiotic resistance in many settings is the difficulty of scaling up microbiology capacity in the field. MSF is in a unique position to share its experiences on setting up a laboratory in LMICs (i.e., mapping of 'quality assured labs' and SOPs on simple microbiology, outcome and implementation of the 'mini lab' project). MSF could potentially develop their experience of having a 'remote microbiology expert' and incorporate that into their MSF tele-expertise system. This could be an educational model for supporting laboratory technicians. Strengths of other NGOs include their networking capability and engagement with national governments and other partners.

2. Academic networks

Research networks based in LMICs who could play a role in supporting countries setting up AMR surveillance are:

- International Centre for Diarrhoeal Disease Research, Bangladesh. ICDDR,B is based in Bangladesh but has strong links with collaborators in other South Asian countries and was instrumental in setting up Nepal's national surveillance programme.
- Institut Pasteur International network has research centres in Brazil, Cambodia, Cameroon, Central African Republic, Cote d'Ivoire, Iran, Laos, Madagascar, Niger, Senegal, Viet Nam
- UK Medical Research Council: Gambia
- The Wellcome Trust Major Overseas Programmes have established units or research bases in Cambodia, DRC, Indonesia, Kenya, Laos, Malawi, Myanmar, Nepal, South Africa, Thailand and Viet Nam and collaborate with partners in a larger number of LMICs.

There are also professional bodies, foundations and universities not based in LMICs but with overseas collaborations e.g.

- US CDC Global Disease Detection programme
- American Society of Microbiologists (ASM) e.g. The LabCap Scheme
- Fondation Mérieux
- Royal College of Pathologists (LabSkills Africa)
- Universities and postgraduate institutions e.g. London School of Hygiene & Tropical Medicine
- Veterinary schools worldwide e.g. Royal Veterinary College, Cambridge and Liverpool Universities in UK

- UK Centre for Environment, Fisheries and Aquaculture Science (CEFAS) has a strong international presence. CEFAS is involved in projects looking at improving sustainable aquaculture practices in countries such as India and thus could support countries wanting to implement AMR surveillance.

3. Governmental organisations

Organisations like CDC and the military in the US are actively involved in AMR projects and building laboratory capacity e.g.

- CDC Global Health Security Agenda Antimicrobial Resistance Action Package
- Armed Forces Health Surveillance Center, Global Emerging Infections Surveillance and Response System (AFHSC-GEIS).

4. Not-for-profit human development/technical support organisations

- FHI-360 (https://www.fhi360.org/us-and-global-reach) is a development organisation which has expertise enabling it to fulfil a wide range of roles e.g. laboratory capacity strengthening including quality assurance, behavioural surveillance surveys in HIV and clinical trials monitoring.
- Malaria Consortium (http://www.malariaconsortium.org/) works in LMICs to deliver programmes on malaria and a range of other diseases by providing technical support and capacity building.
- PSI (http://www.psi.org/) worked on reproductive health projects when it was founded but has now expanded its activities. PSI has been working with partners in Southeast Asia in countries with artemisinin-resistant malaria to support prevention and treatment programmes.
- SORT-IT (http://www.who.int/tdr/capacity/strengthening/sort/en/). The Structured Operational Research and Training IniTiative, is a collaboration between TDR, The Union, and MSF and provides training and capacity building to organisations in LMICs in operational research.
- SIAPS (http://siapsprogram.org/approach/) stands for Systems for Improved Access to Pharmaceuticals. The programme supports countries in strengthening policies related to drug use, procurement of essential medicines and medicines quality.

5. Advocacy groups

The role of advocacy groups to raise awareness and bring about action to tackle AMR should not be underestimated.

- **ReAct – Action on Antibiotic resistance [www.reactgroup.org]** is a global network working specifically on AMR located in five continents and has taken both regional and global approaches to mobilise policy action on antibiotic resistance. ReAct's strategy has been to raise awareness on antibiotic resistance to a range of constituencies, develop networks with interested parties, and move forward towards developing national policy platforms with social mobilisation in selected countries. The group is currently developing a pilot project that includes three countries in three continents using point prevalence surveys to raise awareness. This is currently in the planning phase and they plan to engage their academic partners and NGOs such as MSF[99].

- **HAI – Health Action International [http://haiweb.org]** is a non-governmental organisation whose main work is to improve access to essential medicines in LMICs. HAI has a network of international partners and collects data and conducts research in more than 70 countries. HAI has worked with WHO on mapping the prices and availability of drugs and co-authored a manual for national drug price surveys. More recently, HAI has started to develop an antibiotic resistance portfolio. The group aims to address antibiotic resistance through a project on STD, working with national partners. Country selection and discussion is ongoing [100, 101].
- **The Center for Disease Dynamics, Economics & Policy (CDDEP)** is a research and advocacy organisation, which works on a range of public health threats, including AMR. CDDEP started the **Global Antibiotic Resistance Partnership (GARP)**, to create a platform for developing policy proposals on antibiotic resistance in LMICs. GARP has conducted national situational analyses focusing on antibiotic resistance and use, and developed recommendations in each country. GARP's work includes the following countries: India, Kenya, South Africa, Viet Nam, Mozambique, Nepal, Tanzania and Uganda.
- **The Alliance for the Prudent Use of Antibiotics** (**APUA**) is a non-profit organisation which was founded in 1981 and advocates for appropriate antibiotic use. APUA works in countries and supports education and research [102].
- **The World Alliance against antibiotic resistance (WAAR)** is another global advocacy organisation, committed to raising awareness about AMR [103].

AMR Data Repositories

In this final section of the networks analysis we include a table of the global repositories for AMR data (Table 1.13). We summarise standalone databases only and not academic networks already presented in the earlier sections which also have a data repository, i.e. WWARN/IDDO, IeDEA, TAHOD, TApHOD, CDDEP. Several of these databases contain genetic data e.g. resistance gene sequences. Some provide tools to facilitate the analysis of genetic data (Stanford HIV drug resistance database, PATRIC). NARSA is a repository of staphylococcal isolates which participants can donate strains to or request to use some of the reference strains available. The global database created to manage AMR data, WHONET, is highlighted below.

WHONET is a computer software developed in 1989 by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance based at the Brigham and Women's Hospital in Boston. Countries use WHONET to upload their antimicrobial susceptibility data which then generates automated reports. It can be used as a Laboratory information Management System or receive files transferred from other databases. Laboratories in more than 90 countries submit data to WHONET already and reporting AMR surveillance data via WHONET is expected of countries participating to GLASS. The plan is to collect data aggregated at national level with individual level data kept locally. WHONET has been adapted for GLASS data entry and report generation [28].

Table 1.13 Global Repositories for AMR data

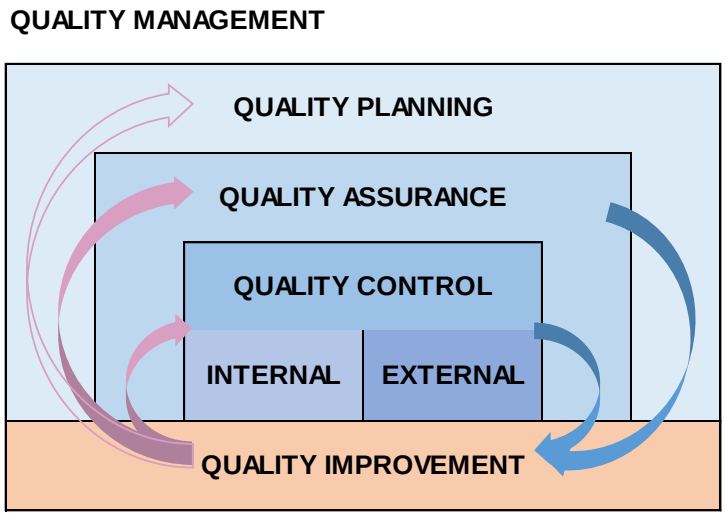
Name/acronym	Sponsor/Leading institution	Years active & (access policy)
HIV databases	NIAID	1987-ongoing
HIV drug resistance database	NIH/NIAID & other sponsors/Stanford University	1997-ongoing
Pathosystems Resource Integration Centre/PATRIC	NIH NIAID/University of Chicago	2012-ongoing
RegaDB : A Viral Data and Analysis Management Environment	Rega Institute, Katholieke Universiteit Leuven and MyBioData Biomedical IT Solutions	2007-ongoing
Surveillance Data Link Network/ SDLN	IHMA (coordinates Pharma sponsored initiatives)	1993-ongoing
TBDatabase/TBDB	BMGF/Broad Institute & Stanford School of Medicine	2008-ongoing
The Comprehensive Antibiotic Resistance Database/CARD	Various donors/ McMaster University's Department of Biochemistry & Biomedical Sciences (Hamilton, Ontario, Canada)	2013-ongoing
The Network on Antimicrobial Resistance in Staphylococcus aureus/NARSA	NIAID The Network on Antimicrobial Resistance in Staphylococcus aureus/NARSA	1997-2016
Tuberculosis Drug Resistance Mutation Database/TBDReaMDB	Ellison Foundation, Swedish Research Council/Harvard University	2008-ongoing
WHO global antimicrobial susceptibility database/WHONET	NIH/Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA	1989-ongoing
WHO global insecticide resistance database	WHO	2014-ongoing
World Animal Health Information System/WAHIS	OIE (no AMR data currently)	2004-ongoing

This completes the description of the main networks and groups which have been involved in AMR surveillance to any extent (including sharing information) since 2000 and the global repositories for resistance data. In the following section of the report we go on to describe initiatives concerned with laboratory quality management in LMICs.

Quality management

Implementation of global surveillance for AMR across multiple countries and healthcare contexts requires standardisation of the types of data which are collected as well as the way in which they are interpreted, analysed and reported. Robust, systematic approaches will be needed to attain these standards or specifications, i.e., to ensure that these data and intelligence are of 'high quality'. Quality Management (QM) systems, encompassing quality planning, assurance, control and improvement, were developed when similar needs became evident during the industrial revolution (Figure 1.11).

Figure 1.11 The elements of a Quality Management System



Definitions

Quality planning: Defining the minimum standards and resources and the recommended processes and procedures required to obtain, analyse, interpret and report AST data[104].

Quality assurance (QA): Translation of pre-defined standards and specifications into requirements for human resources, training, procedures, equipment and materials and into systems designed to ensure that all the required components of a process are performing as expected.

Quality control (QC): Use of reference materials or strains to confirm that test results are within expected limits and/or by re-testing a specimen to verify that the variance between repeated test results is within acceptable limits. QC can be internal, i.e., a routine check to verify correct functioning of an analytical procedure, or external wherein a specimen tested within a laboratory is re-tested in a reference environment. A particular case of external QC is that of Proficiency Testing (PT) which involves analysis of blinded specimens and comparison with expected results and/or those from other laboratories.

Quality Improvement: Using information from QA and QC to improve adherence to standards and specifications, to make the process of attaining them more efficient or even to update the standards where appropriate.

Assessment of tools and resources for quality assurance of AST

A critical early step in quality management is to define clearly the specifications to which the inputs and outputs as well as the process must conform, i.e., to define what 'quality' means in a given context. In the case of AMR, this translates into defining which specimens are tested, which testing methods are acceptable and how the results need to be interpreted and reported. The GLASS Manual clearly defines a list of specimens and the populations or settings from which data are to be reported as well as the pathogen–antimicrobial combinations which are to be prioritised [28]. However the manual covers neither HIV, TB and malaria nor veterinary or foodborne diseases as they are covered under specific WHO programmes. Detailed recommendations on quality assurance of the laboratory investigations used to detect AMR are not included in the manual either as responsibility for these measures is devolved to national or regional initiatives.

Programmes or institutions involved in quality management in AMR surveillance in LMICS were identified from the networks search. We included global initiatives to support development and dissemination of standards as well as those supporting implementation of quality management in laboratories reporting AMR data, including those on HIV and other viral diseases, TB, malaria and animal or foodborne diseases.

Criteria used to assess laboratory quality management programmes

The assessment was performed using a standard form. Apart from collecting information on the geographical and temporal coverage of their activities, programmes were assessed according to the following criteria, chosen to identify programmes or elements which could serve as models for laboratory quality management in a global AMR surveillance effort as well as challenges for widespread implementation:

- **Scope of the activities:** pathogens and assays covered in the programme, materials (known isolates or other reference materials, manuals and procedures) or services (accreditation, proficiency testing, quality improvement, trouble-shooting) available
- **Access to materials or services:** Whether the QA activities covered specific regions or projects, cost of participation
- **Indicators of quality of the programme:** Whether the materials and/or services took into account and/or were updated in accordance with the relevant standards and policies, feedback from public health officials and infectious disease practitioners, whether the programme itself was accredited

Summary of Quality management programmes

We identified 32 programmes (27 still operational), of which 21 had global coverage, ten regional, and one was a country-specific programme (an example of EQA provided by URC/CDC to an LMIC which could be replicated in other countries). The median [range] duration of the programmes was 16[3-91] years with the top spot occupied by ATCC in the US, a standards organisation which provides reference isolates/material worldwide. More than a third of the programmes (11) were coordinated by a supranational UN- affiliated body, usually the WHO. The remainder was a mixture of governmental, non-governmental and academic groups or commercial enterprises. The business model was one of no cost to participants in the majority of cases (20), cost-recovery in five cases, commercial-for-profit in three cases and unknown for the remainder. Some programmes offered proficiency testing only (15), while many offered different combinations of proficiency testing, standards or policy setting, accreditation,

training, assessment and evaluation, or were a repository for/provider of reference material. A range of diagnostic methods (culture, serology, molecular), and pathogens was covered by the programmes (e.g. *N.gonorrhoeae*, HIV, *M.tuberculosis*, *Coryneform diphtheriae*, or all commonly encountered bacteria, viruses and fungi). The programmes are summarised briefly in Table 1.14, with full details given in Appendix 6.

Table 1.14 Supranational quality management programmes used in relation to AMR surveillance in LMICs

Name (acronym) of Programme/ Country location of Head Office	url	Years active
ATCC/ United States	http://www.lgcstandards-atcc.org/	1925-ongoing
Clinical & Laboratory Standards Institute (CLSI)/ United States	www.clsi.org	1968-ongoing
College of American Pathologists/ United States	www.cap.org	1946-ongoing
Diphtheria Surveillance Network (DIPNET)/ United Kingdom	http://www.dipnet.org/	1998-ongoing
European Committee for Antimicrobial Susceptibility Testing (EUCAST)/ Sweden	www.eucast.org	1997-ongoing
European Network for Imported Viral Diseases (ENIVD)/ Germany	http://www.enivd.de/index.htm	2013-2014
WHO Global Foodborne Infections Network External Quality Assurance System (GFN-EQAS)/ Denmark	http://www.who.int/gfn/activities/eqas/en/	2000-ongoing
Global Laboratory Initiative/ Switzerland	http://www.stoptb.org/wg/gli/default.asp	2008-ongoing
WHO HIVResNet Laboratory Accreditation Scheme/ Switzerland	http://www.who.int/hiv/topics/drugresistance/laboratory/en/index2.html	2007-ongoing
Integrated Quality Laboratory Services/ France	http://www.iqls.net/	2010-ongoing
ReLAVRA Latin America External Quality Assessment (LA-EQAS)/ Argentina	no weblink available	2000-ongoing
National Health Laboratory Service/ South Africa	http://www.nhls.ac.za/?page=eqa_program_for_the_xpert_mtb/rif_assay&id=76	1998-ongoing
NRL/ Australia	www.nrl.gov.au	1985-ongoing
One World Accuracy/ Canada	http://www.oneworldaccuracy.com/	2000-ongoing
Pacific Paramedical Training Centre Regional External Quality Assessment (REQA) Programme/ New Zealand	http://pptc.org.nz/regional-external-quality-assurance-programme/	1985-status unknown
Quality Control for Molecular Diagnostics (QCMD)/ United Kingdom	www.qcmd.org	2001-ongoing
Royal College of Pathologists of Australasia Quality Assurance Programs Pty Ltd (RCPAQAP)/ Australia	http://www.rcpaqap.com.au/	1988-ongoing
Name (acronym) of Programme/ Country location of Head Office	**url**	**Years active**

Strengthening Laboratory Management Toward Accreditation (SLMTA)/ United States (linked to WHO-AFRO)	http://slmta.org/	2009-ongoing
The East African Regional External Quality Assessment Scheme (EA-REQAS)/ Kenya	http://www.eareqas.org/	2000-ongoing
TREAT Asia Quality Assessment Scheme(TAQAS)/ Australia	No web-link available	2006-ongoing
United Kingdom External Quality Assurance Scheme (UK NEQAS)/ United Kingdom	http://www.ukneqas.org.uk/	1969-ongoing
University Research Co URC/CDC Lab Project/ United States	No web-link available	Jan 2013- Dec 2013
HIV/AIDS Network Coordination Virology Quality Assurance (hanc VQA)/ United States	https://www.hanc.info/labs/labresources/vqaResources/ptProgram/Pages/default.aspx	2007-ongoing
The World Health Organisation (WHO)/ Switzerland	http://www.who.int/drugresistance/publications/WHO_CDS_CSR_RMD_2003_6/en/	2003- ongoing
WHO African Region External Quality Assurance Programme (WHO AFRO EQAP)/ South Africa	http://www.who.int/bulletin/volumes/90/3/11-091876/en/	2002-ongoing
WHO Asia-Pacific EQA Programme/ Indonesia	no web link available	2005- status unknown
WHO External Quality Assessment Project for the Detection of Subtype Influenza A Viruses by PCR/ Switzerland	http://www.who.int/influenza/gisrs_laboratory/external_quality_assessment_project/en/	2007-ongoing
WHO Gonococcal Surveillance Programme EQAS	none	1992-ongoing
WHO Laboratory Quality Stepwise Implementation Tool/ The Netherlands	https://extranet.who.int/lqsi/	2011-ongoing
WHO Mycobacterial Supranational Reference Laboratory (SRL) network/ Switzerland	No web link www.who.int/tb/laboratory/srln-list.pdf	1991-ongoing
Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA)/ WHO-AFRO, Republic of Congo	WHO Guide for the Stepwise Laboratory Improvement Process Towards Accreditation (SLIPTA) in the African Region (with checklist)	2011-ongoing
World Health Organisation's External Quality Assurance System for Antimicrobial Susceptibility Testing (EQAS-AST)/ Switzerland	no link available on WHO website [105]	1998-2006

The programmes are discussed below in relation to the key themes of quality management to detect AMR.

AST methods and interpretation

The gold standard for detection of AMR in bacteria and fungi is determination of the phenotype of a given isolate by culture-based *in vitro* AST (CLSI, EUCAST). Well-defined reference methods for AST for based on disk-diffusion or microdilution are available alongside regularly updated guides on interpretation of

susceptibility data generated using such methods. Progress has been made in harmonising methods and breakpoints to define antimicrobial susceptibility internationally, but differences in the two main standards, CLSI and EUCAST, remain. Before data aggregation at national or international level they will need to be harmonised [10]. This process is already underway [106] and needs to be actively encouraged as it will be a critical determinant of the 'quality' and comparability of AMR data generated globally over time.

Validated nucleic acid amplification-based tests (NAATs) are considered as being sufficient evidence for confirming resistance and to guide treatment of viral diseases. In the case of bacterial diseases however, molecular tests are of limited use currently since resistance genes, even if present in an isolate, may not be expressed into a corresponding resistance phenotype. Resistance genotyping tests are hence not used routinely for treatment decisions or surveillance of AMR with a few notable exceptions e.g. rifampicin-resistant *M.tuberculosis* and meticillin-resistant *S.aureus*. The lack of correlation between genotype and phenotype is likely to be a result of a multitude of factors, not the least of which may be differential expression of the resistance genes [107]. Nonetheless, given the rapid advances in 'omics-related data generation and analysis, it is likely that practical applications will be found. A methodology to validate or reject candidate molecular markers or assays currently in development by comparison with existing validated methods will be required [108-110]. This is in addition to clear guidelines on the contexts, pathogens and antimicrobials for which the use of currently available knowledge, i.e., markers and the assays to detect them, is acceptable and appropriate for reporting AMR.

Various molecular typing methods based on nucleic acid typing or on mass spectrometry are being applied increasingly in pathogen identification and serotyping, e.g. outbreak investigations [111, 112]. In malaria, molecular markers of drug resistance can be used for surveillance but the gold standard of evidence to change treatment policies at the public health level remains *in vivo* studies [55]. This is also because it has been difficult to standardise methods and breakpoints of *in vitro* assays for antimalarial susceptibility testing thus hindering its widespread deployment.

Quality assurance of AST

Awareness of the benefits of quality management has led to the development of numerous guides, manuals, checklists and other aids to implementation of quality systems in diverse contexts. These often include recommendations on human resources, infrastructure, safety measures, standards and procedures for specimen collection and testing, QC requirements along with suggested corrective measures, equipment and inventory management and maintenance. These are all topics which are typically included in a quality assurance manual along with measures for quality monitoring and improvement. The exact measures and how or when they are implemented may differ between various applications of such manuals but the basic premise remains the same – to ensure that the inputs, the outputs and the process producing one from the other is performing within acceptable limits of variation or tolerance and that there are adequate controls to signal deviations from such limits. The WHO has produced several generic and disease-specific resources and tools for quality management in healthcare laboratories. The WHO Laboratory Quality Management System handbook accompanied by training materials and generic quality manual as well as the WHO Laboratory Quality Stepwise Implementation tool provide the information required to implement a comprehensive ISO 15189-compliant quality

management system, irrespective of the context. When supplemented by the core technical procedures freely available through EUCAST, GLI, GFN, HIV-DR, WHO-GMP, WHO-TDR and by the additional technique-specific training, safety and QA measures recommended in those procedures or guides, they complete the information needed to develop a comprehensive quality assurance system for AST. It would be worthwhile to review available materials for coherence with harmonised testing and reporting guidelines and for completeness before promoting further dissemination as a complete package to end users. Such a package would serve as a ready reference for laboratories already reporting AMR data and provide a head start to laboratories in the process of setting up AST.

Quality control of AST

Systematic checks to verify adequate performance of an assay are performed at the time of assay optimisation or validation, as part of quality control once an assay has been introduced into routine use and to re-verify performance when there is a change in the way the assay is performed. Such checks are accomplished through the use of well characterised 'reference' materials to test whether the assay produces expected results. In AST, reference materials could mean the reagents used in the assay (e.g., media or antibiotic disks for culture-based assays, primers, probes or pathogen nucleic acids for NAATs, etc.) or reference strains with well-defined drug resistance phenotypes or genotypes. Reference strains or other materials for internal quality control of culture-based AST or synthetic/extracted nucleic acids for NAATs are readily available from ATCC but on a cost recovery basis; shipping costs, which may be significant in some cases, must also be borne by the laboratory requesting the materials. These material or shipping costs are likely to pose barriers to their use in LMICs and may in some cases be prohibitive.

External quality assessments and accreditation

External quality assessments can be performed through re-checking of specimens already tested in a laboratory in a reference laboratory or through proficiency testing. The Latin America EQA Scheme (LA-EQAS) of ReLAVRA has been running since 2000 and provides proficiency testing services at no cost to participants in South America (see Appendix 4). WHO-GFN offers proficiency testing for detection and AST in foodborne pathogens at no cost to laboratories worldwide. The Supranational Reference Laboratory Network was set up in 1994 as a platform to support WHO initiatives for the diagnosis, treatment and surveillance of drug resistance in TB. It supports quality assurance of AST for TB through specimen exchanges for rechecking or proficiency testing and quality improvement through training, on site evaluations and supervision [113]. Similarly, laboratories affiliated with the US Division of AIDS (DAIDS) can obtain free quality assurance, EQA and assay support services from Virology Quality Assurance (VQA) which has been contracted by DAIDS to provide these services. In addition, several other pathogen-specific quality assurance schemes and services exist (ENIVD for dengue serology, DIPNET for diphtheria diagnosis and serotyping, WHO GASP for *N. gonorrhoeae*, and others). WHO-sponsored EQA efforts for AST include the WHO EQAS AST (1998-2001)[105] and the WHO-AFRO / NICD-SA EQAP for countries within the WHO-AFRO region [114]. However, none of these quality assurance initiatives are geared to support EQA for a global network of AMR surveillance centres. Non-profit organisations like the College of American Pathologists and UK-NEQAS do provide proficiency testing (but not re-checking) services globally (e.g. 8,000 labs from over 140 countries participate to UK-NEQAS), but here again, there is an associated cost which can be a barrier to participation for laboratories in LMICs.

Accreditation

Accreditation of systems or processes in a laboratory i.e., objective verification of the conformity of the system to pre-defined standards and specifications, alongside regular external quality assessments provides additional confirmation of the comparability of the results generated in a given lab with those from its peers. The WHO LQSI and GLI provide aids to help laboratories implement quality management systems compliant with the ISO 15189 standard. SLMTA (Strengthening Laboratory Management Toward Accreditation) and SLIPTA (Stepwise Laboratory Improvement Process Towards Accreditation) are successful complementary programmes to assist laboratories in the implementation of ISO 15189-compliant quality management systems. While many laboratories are capable of producing good quality results and/or operate quality management systems developed in-house, formal accreditation must be a goal of all laboratories aiming for sustained participation in global AMR surveillance.

What can we learn from past and current AMR networks and what are the implications for future surveillance?

Goals of AMR surveillance are to obtain representative data on the status of AMR, detect outbreaks, monitor trends and use this information to guide policy. In this report we have described 105 networks involved in AMR or One Health surveillance in humans and animals in LMICs since 2000. Of the global networks the influenza and Global Foodborne Infections networks have the highest coverage of LMICs, but resistance surveillance is only a secondary part of their activities. The global networks involved in surveillance for AMR in TB, HIV and gonorrhoea show gaps in coverage over much of sub-Saharan Africa, also noted by other reviews of surveillance efforts [27, 34].

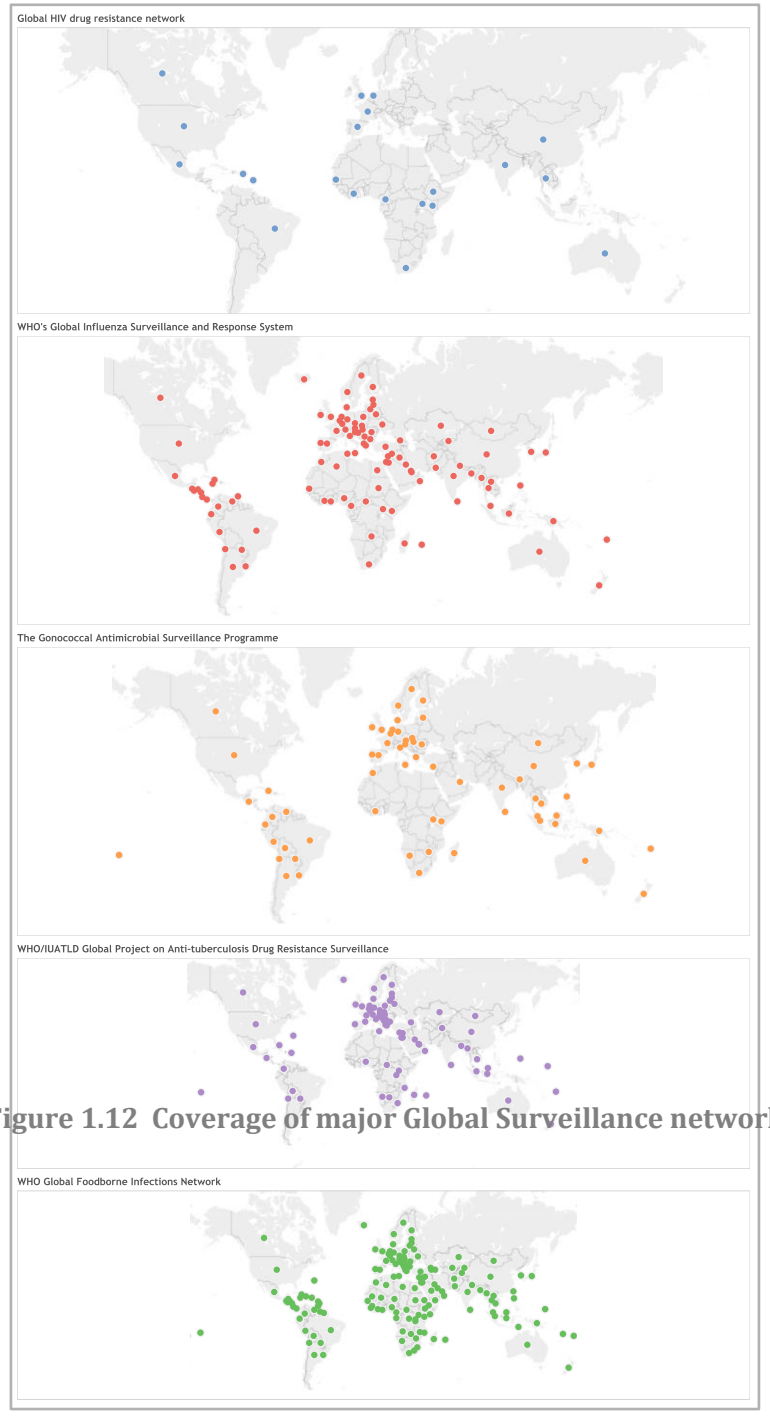


Figure 1.12 Coverage of major Global Surveillance networks

The WHO Regional networks for antibacterial resistance surveillance are not yet off the ground except for the Americas and Europe. China and India, the countries with the highest population counts (approximately 18% of the total world population apiece) are at different stages with regard to developing national systems. China has expanded its national surveillance significantly in the last two years and has more than 1400 hospitals participating nationwide. India has not yet set up coordinated nationwide surveillance but this is planned using the HealthMap platform [115]. Almost no coordinated AMR surveillance is taking place in animals globally; however there may be surveillance data from food-producing animals which are not in the public domain.

In terms of the target pathogens the majority of networks for HIV, TB and malaria are either WHO/governmental or academic networks and most conform to the recommendations for surveillance set by WHO. Coverage and functioning of these networks is often poor in the poorest countries. In the case of networks which have surveyed

resistance of bacteria to antibiotics there are a much greater number and they are more diverse in terms of leadership, target pathogens and surveillance methodology. A large number of these networks have been initiated by the pharmaceutical industry and some of these networks cover similar geographical regions, but differences in patient selection and methodologies mean the data are often not comparable. One review of predominantly Pharma-led AMR surveillance networks has identified a number of potential biases in the data reported, related to sampling, multiple counting and laboratory methods [116]. The main impacts and challenges of the AMR surveillance networks described are shown in Table 1.15.

Table 1.15 Main impacts and challenges in AMR surveillance

Impacts	Challenges
• Led to changes in treatment policy (e.g. malaria in sub-Saharan Africa in the early 2000s) • Informed vaccine development (influenza, pneumococcus) • Improved laboratory capacity by establishing networks of reference laboratories and quality management systems in some networks (ARMed, TB, GFN, GASP) • Standardisation of surveillance methodologies and data analysis (malaria, ReLAVRA, TB, HIV, PulseNET, WHONET) • Exchange of information, training and knowledge between countries e.g. ReLAVRA, WWARN, GFN • Data sharing with secondary benefits to inform treatment guidelines (malaria and WWARN) • Created global repositories of bacterial isolates. These can be used to screen new drugs (SENTRY, ANSORP).	• Poor coverage in Sub-Saharan Africa and India with the exception of the Global Influenza Surveillance & Response System. • Lack of representativeness of data: e.g. low numbers of isolates, bias towards taking samples from patients who have already failed therapy • Difficulties of implementing routine blood culture/diagnostic microbiology in clinical practice, including financial disincentives to take microbiology samples • Difficulties in implementing complex surveillance methodologies e.g. optimal in vivo methods for surveillance for artemisinin resistance in malaria, second line drug susceptibility testing for tuberculosis • Reporting delays • Sustainability due to underfunding with consequent understaffing. Surveillance has generally not been given high priority by external donors

Comparison of AMR surveillance by the major disease programmes

Existing major global AMR surveillance programmes for TB, malaria and HIV have been developed over several years and are not at the stage where surveillance is integrated into routine case management, although this is the long-term goal for TB and HIV. Instead surveillance is approached as a separate population level activity in many countries with survey and research methods employed to gather representative data. While this approach is expensive and labour intensive these intermittent concerted efforts remain the most practical way to obtain the information required in many LMICs with limited human and financial resources. This 'active surveillance' is still not functioning perfectly with only 30% of countries compliant with requirements for surveillance for malaria and three-quarters of global MDR-TB cases going undetected.

Guidance for surveillance for AMR in malaria, TB, and HIV is more prescriptive than GLASS in terms of specifying the number of samples or patients needing to be evaluated (Table 1.16). GLASS proposes a more flexible approach based on local needs which, while laudable, risks countries generating non-comparable data. Standardisation allows comparisons to be made between countries more easily e.g. to determine which are high-burden countries and prioritise interventions.

Table 1.16 Comparison of WHO global AMR surveillance networks

	TB	Malaria	HIV	Bacteria (GLASS)
Type(s) of surveillance	Case-notification & national Surveys	Therapeutic efficacy studies & molecular marker surveys	EWI[1] and Molecular marker surveys	Routine invasive isolate surveillance (with scope to expand)
Technology/ laboratory methods	Culture and susceptibility testing GeneXpert® Other molecular methods	Microscopy and PCR-based technologies	PCR-based	Culture and susceptibility testing
Selection criteria & for population of interest + sample size	Yes	Yes	Yes	No
Data sharing mechanism	WHO global TB database	WHO GMP database	WHO HIVDR database	WHONET
Reference laboratory network	Yes	No	Yes	No
Global proficiency testing scheme	Yes	No	Yes	No
Guidance on use of surveillance data	Individual case-management & may guide design of new 2nd line treatment regimens	Defined cut-offs for considering national treatment policy change	Survey results used to support choice of nationally recommended second- and third-line ART regimens	No

[1]EWI= Early Warning Indicators e.g. ARV coverage, retention in care, treatment interruption, viral load suppression

A review of the HIV, TB and malaria surveillance systems in 2011 described how the standardised protocols lead to comparable outputs without undue strain on national programmes. The risks of

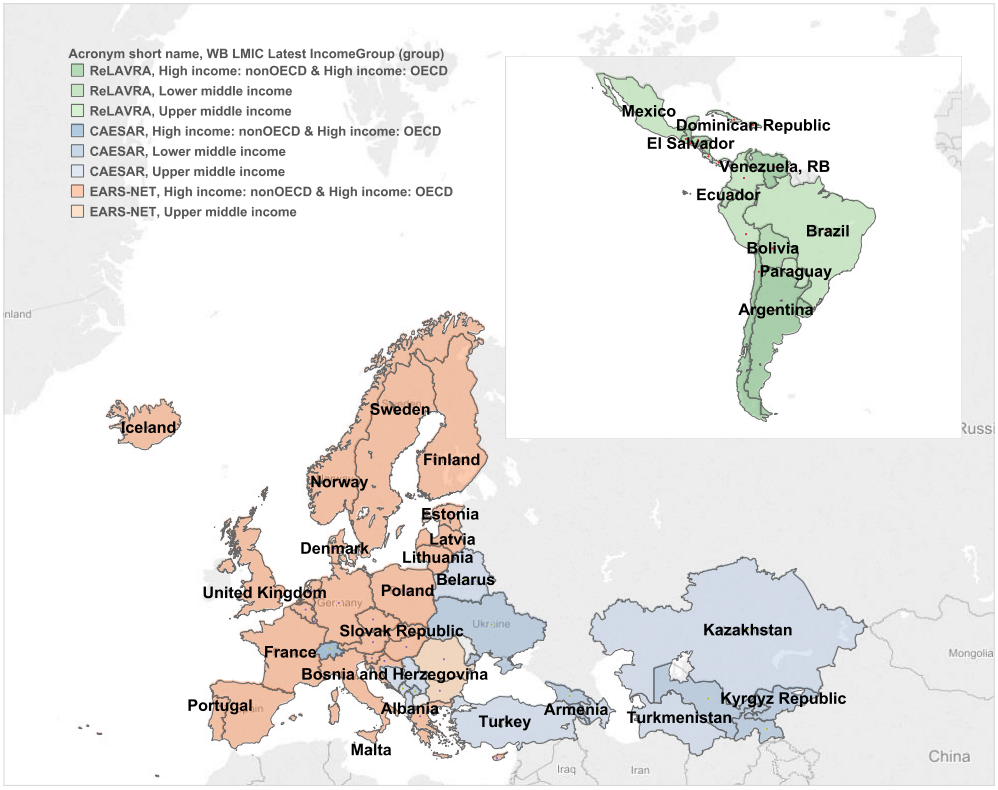
integrating surveillance into routine activities were highlighted as high-quality implementation was less likely [117].

Implementation of GLASS in LMICs

In high income countries routine AMR surveillance is usually built on a foundation of a strong health system where diagnostic microbiology is part of routine care. Even then, sentinel surveillance systems in HICs may miss emerging resistance to antimicrobials [118]. A small number of upper middle income countries participate to the European networks, EARS-Net and its younger sibling, CAESAR which rely on surveillance of invasive isolates, which are priority specimens in GLASS. Building laboratory capacity in CAESAR has been successful; however changing how diagnostic microbiology services are used in countries where healthcare workers are not accustomed to incorporating them into their clinical practice has been more challenging.

In Latin America diagnostic microbiology is more established and participating countries are active in surveillance within the ReLAVRA network. A broader range of pathogens are reported from both sterile and non-sterile sites. The Latin American networks have a point person in PAHO who plays a coordinating role. Institutions in Argentina, a high income country, take the lead in organising training and proficiency testing.

Figure 1.13 Map showing existing Regional AMR surveillance networks by country income status



Limitations of antibacterial resistance surveillance focus on invasive isolates

Blood cultures are often considered as being less likely than other samples to be affected by sampling bias between sites [119]. However, particularly in LMICs, there are disadvantages to relying on blood cultures for surveillance such as:

1. Difficulties to obtain a representative sample of the population. Empiric antimicrobial therapy without taking a blood culture is standard practice in many LMICs. There is anecdotal evidence that patients who have a blood culture taken are more likely to have been in hospital for some time or to have failed treatment [28].
2. Low yield of significant isolates and GLASS priority pathogens. A higher proportion of non-bacterial pathogens cause fever in LMICs compared to HICs, lessening the proportion of positive results obtained from blood culture of febrile patients. In countries with little laboratory capacity the end-result may be very few data-points for the GLASS priority pathogens. In Mahosot Hospital in Vientiane in Laos where blood cultures are encouraged and provided free-of-charge the typical monthly yield of significant positive results in 2015 was 20 [120]. In a hospital in Thakhek, a town in south-central Laos there were between 1 and 4 positive blood cultures per month in 2015. Two studies of community acquired sepsis from Kilifi in Kenya have reported blood culture positivity rates of 6.6% and 2% which illustrates the numbers of blood samples which will need to be taken to yield reasonable numbers of positive results [121, 122]. High rates of antibiotic pre-treatment in the community will also decrease the yield of blood culture. In a blood culture surveillance study conducted in 35,639 patients in Thailand over a 3 year period, 27% reported having taken antibiotics already. Serum antibiotic activity was detected in 24% samples (24,538 tested). Isolation of any pathogen was half as common in patients who had taken antibiotics with detection of *S.pneumoniae* being 4 to 9 fold less common [123].
3. Low sensitivity for detection of emerging or MDR pathogens, e.g. in the UK in 2012 only 9% of the carbapenemase-producing organisms isolated were from blood cultures [124, 125].

In countries unaccustomed to using diagnostic microbiology, provision of a more comprehensive service is more likely to result in microbiology being perceived as useful, with potential to influence patient management and facilitate antibiotic stewardship and infection prevention and control decisions, rather than focusing on blood cultures which may only yield a 2-5% positivity rate for significant pathogens. But the cost for diagnostic pathology tests in LMICs is usually passed on to the patients who may not be able to pay. Persuading them to pay for a test which may lead to information that they require second line antibiotics which are either unavailable or unaffordable presents additional ethical problems which need to be thought through before implementing patient level surveillance strategies.

Complementary approaches to AMR surveillance in LMICs

There have been numerous reviews of, and proposals for, different models of AMR surveillance in recent years [119, 126-135]. Suggestions for surveillance in LMICs have included using Health and Demographic Surveillance sites to collect AMU data, monitoring of sentinel populations for febrile illness, and integrating surveillance activities with other initiatives such as vaccination [126]. Grundmann described different surveillance objectives which may determine how a system is designed e.g. a

patient-centred approach to address clinical demands, a population-based approach to address policy demands or a pathogen-based approach to address infection prevention and control demands [133].

Setting up AMR surveillance unlinked to clinical outcomes or treatment protocols in LMICs and achieving low coverage risks failing to have any impact on the disease burden caused by AMR. What constitutes representativeness and adequate coverage in terms of AMR surveillance requirements in LMICs needs to be defined. This is not an easy task without a better understanding of the amount of variation that occurs within countries which could relate to population density, access to healthcare and antimicrobial drugs, proximity to animals and sanitation. There are also practical considerations. If a health system is weak it will be difficult to create a well-functioning laboratory network capable of obtaining representative routine surveillance data. In 2002 the WHO published 'Surveillance standards for antimicrobial resistance' which included sample size estimates to enable detection of resistance isolates [6]. This has been replaced by the GLASS manual which does not include sample sizes as the emphasis is on a phased approach to increasing passive surveillance. GLASS includes a statement that alternative approaches of more complex case-based surveillance of clinical syndromes should be explored and proposes evaluations of this strategy at selected sites in 2018.

There is a range of expertise and experience in LMICs with respect to laboratory capacity for AMR surveillance so it is unfair to assume that having a focus on invasive isolates only in many low-income countries will never produce useful results. However for many countries, with little capacity at present, this approach is unlikely to produce representative comparative data in the short- to medium- term.

Other complementary approaches could be evaluated to supplement the information that routine surveillance of invasive isolates will yield, such as:

a) Active surveillance for target pathogens in other samples or in asymptomatic carriers
b) Hospital-based surveillance in target groups
c) Surveillance focused on front-line antimicrobial therapies
d) Population level genomic based surveillance

a. Target pathogen active surveillance approach:

i. *Escherichia coli*. Urinary isolates could be obtained for surveillance e.g. from out-patients or antenatal clinics. Targeting urinary isolates was found to be a practical solution in a WHO AMR surveillance community pilot study which used a mixture of mid-stream, clean-catch and samples deliberately contaminated with faecal flora to increase the yield of *E.coli*. For sites who had data on both carriage and significant isolates causing urinary tract infection the latter were more drug resistant [136].

ii. ESBL- and carbapenemase-producing organism screening from rectal swabs/faeces samples. The relevance of carriage rates of ESBL/carbapenemase producers to community acquired sepsis is uncertain and would need further evaluation. Some studies from Southeast Asia have suggested that carriage rates and rates in clinical isolates are similar ([137]. These kinds of surveys could also provide useful baseline information on susceptibility of ESBL producing organisms to gentamicin, which is widely used in LMICs. Low carriage rates could

provide some reassurance about the safety of empirical regimens for community acquired severe sepsis presenting to healthcare facilities.

iii. *Streptococcus pneumoniae*: children in LMICs are frequently colonised asymptomatically by *S.pneumoniae.* Nasopharyngeal swabs collected from asymptomatic children and those with pneumonia can be used to monitor circulating pneumococcal serotypes and associated antimicrobial resistance. Whilst there are wide serotype-specific variations in invasiveness, colonisation data has been used to predict the impact of pneumococcal conjugate vaccine introduction on invasive pneumococcal disease successfully [138, 139].

iv. Meticillin-resistant *Staphylococcus aureus*: MRSA screening could be considered on a sample of patients admitted to a health-care facility annually using a cross-sectional survey approach. This can be performed using standard culture methods, or chromogenic agar, or using molecular methods e.g. GeneXpert® MRSA directly from swabs.

v. *Neisseria gonorrhoeae*. Screening using nucleic acid amplification tests of larger numbers of specimens (urethral/throat/rectal/cervical swabs) could give more information on the burden of disease and enable better targeting of culture and susceptibility testing which are difficult to set up. In terms of progress towards molecular surveillance of resistance, some important resistance mechanisms can be targeted by PCR-based tests e.g. quinolones, penicillinases although they still require a culture step. Multi-antigen sequence typing (NG-MAST) has been evaluated in pilot projects and shown to be predictive of drug resistance [140]. Some point of care assays have been developed for STI diagnosis. GeneXpert® CT/NG is one which has been shown to be highly sensitive and specific for gonorrhoea and chlamydia diagnosis [141]. Latin America used their routine AMR surveillance channels to boost GC surveillance for *N.gonorrhoeae* and a long term plan to combine reporting to GASP and GLASS rather than maintaining two separate networks would make sense if GLASS is functioning well [142].

Some of the approaches above propose screening in asymptomatic individuals. While the clinical relevance of these findings is less clear than for results from sampling symptomatic patients this approach presents a method for generating useful amounts of comparable AMR data at sites where it will take time to build up a fully-functional diagnostic service. Operational research could help answer questions on applicability to patients with confirmed infections. With this model, survey samples from different areas could be sent to a national reference laboratory for processing. Using molecular methods would minimise the increased risk of losing isolates in adverse transit conditions when culture-based techniques are used. Optimum sampling frames would need to be defined based on desired representativeness, feasibility and cost.

b. Example of an active hospital-based surveillance approach targeting patient groups:

Improving existing laboratory capacity in hospitals provides an opportunity to strengthen infection prevention and control (IPC) and antimicrobial stewardship programmes simultaneously. One approach would be to target specific patient groups in the hospital e.g.:

i. Intensive care unit patients. It is known that LMICs have a high burden of healthcare associated infections in high-dependency settings [143]. Diagnostic blood cultures and

tracheal aspirates taken when clinically indicated could be supplemented by weekly superficial skin swabs and rectal swabs to monitor for ESBL, CPO, GRE, and MRSA carriage.

ii. Neonatal Units- using the same approach as (i).

iii. Surgical patients- as part of a surgical site surveillance programme.

iv. Cross-sectional surveys of all inpatients. This approach has been used as one of a package of interventions to tackle healthcare associated infections in Angkor Hospital for Children in Cambodia. Nose swabs were taken to screen for *S.aureus* and faecal samples for resistant Gram-negative bacteria) as well as collecting data on antimicrobial usage, use of medical devices and HCAI incidence [144].

These types of surveillance approaches feed into antimicrobial stewardship/IPC programmes naturally and will increase their effectiveness. It is difficult to advocate for changes in therapy or IPC practices without good microbiological data to support the advice. Hospitals with limited human resources and laboratory capacity could rotate surveillance target groups throughout the year. A disadvantage of this type of programme is that it risks missing outbreaks occurring when there is no surveillance going on.

c. Surveillance focused on efficacy of community front-line antimicrobial therapies

A different approach to AMR surveillance which is more relevant to tackling the burden of disease in LMICs would be to focus on the common causes of community acquired infection in LMICs e.g. *Streptococcus pneumoniae* and *Salmonella enterica var* Typhi and to assess the efficacy of the front-line empirical regimens given in out-patient centres, by community health workers or local pharmacies/drug shops. For the pneumococcus the molecular based- screening approach described in (a) could be used. Diagnosis of enteric fever is more difficult as it still relies on blood culture.

d. Population level versus individual level surveillance

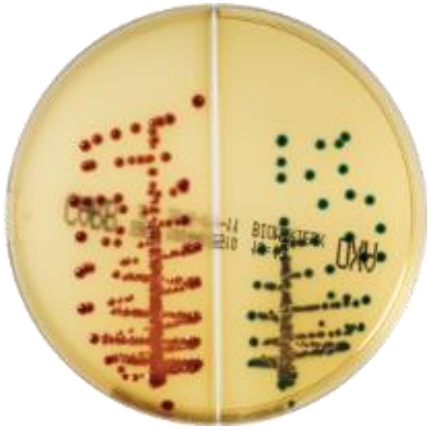
The power of whole genome sequencing as a surveillance tool is being explored, with real-time monitoring of outbreaks as well as evaluation of approaches which move away from examining single bacterial isolates to sequencing the resistome in a range of human, animal and environmental samples. Results can be difficult to put into a health context due to the fact that many non-pathogenic bacteria carry resistance genes so, while knowledge in this area is increasing rapidly, this is a research tool for LMICs at present, with the possible exception of foodborne outbreak investigation.

Use of newer technologies to facilitate AMR surveillance

The potential impact of development of simpler field-adapted molecular tools to boost surveillance capacity cannot be overstated. While progress is being made to define molecular markers in bacteria which correlate with MIC based epidemiological cut-offs separating wild-type from non-wild-type isolates, they are some way off being usable for surveillance and may never replace MIC for individual patient management. Some good predictive molecular assays are available, including some which use the GeneXpert® platform which a number of countries may already have access to for their TB programmes.

In high income countries there has been investment in automation and expensive technologies such as Matrix Assisted Laser Desorption/Ionization-Time-of-flight (MALDI-TOF) Mass Spectrometry to improve

efficiency of diagnostic microbiology services. They represent a significant advance in identification methods for bacteria and fungi but cannot be used on many primary specimens reliably at the moment. Identification of resistance with MALDI-TOF is under development and will have the same limitations as identification of genotypic resistance. They are unlikely to be rolled out at scale unless they come down in price and are adapted to field conditions but their use in national reference laboratories in LMICs should be evaluated.



There are other simple tools used routinely in HICs when screening large numbers of samples for antimicrobial resistance such as chromogenic agar (see Figure 1.14). The cost of these tools compared to more laborious conventional methods of identification and susceptibility testing makes it unlikely that these will be introduced in many LMICs in the foreseeable future and presents another barrier to simplifying AMR surveillance in LMICs.

Figure 1.14 Example of chromogenic media to detect carbapenemase-producing bacteria
http://www.biomerieux-diagnostics.com/chromid-carba-smart

Veterinary and Integrated surveillance

Integrated surveillance of AMU and AMR using a One Health Approach is being promoted but this is still not embedded in many HICs and there is no clear guidance on how to implement this in LMICs yet. There is very little AMR surveillance taking place routinely on a global scale in animals but a number of disease surveillance networks and One Health networks have been created. Classical foodborne pathogens causing gastroenteritis in humans are prioritised for veterinary AMR surveillance, however this will not further our understanding of routes of transmission of other drug resistance genes between animals, humans and the environment. Active surveillance in animals needs to be extended to commensal organisms such as MRSA, coliforms and Enterococci. There is insufficient evidence currently to inform the optimum approach to integrated surveillance. WHO, FAO and OIE are collaborating at a strategic level but without explicit guidance on how to integrate surveillance in a coherent manner it is unlikely to happen. The AGISAR expert group is providing leadership in promoting the best ways to perform AMR surveillance in animals and the environment and is in the process of updating their recommendations [145]. Pilot projects have assessed sampling of animals and food at critical points along the production chain with contemporaneous samples of humans with gastrointestinal symptoms in the same locality. Standardisation of laboratory methods in veterinary bacteriology is lagging behind the progress made in humans and it is a more complex issue as standards need to be developed for different animal species/pathogen/antimicrobial combinations.

Priorities for veterinary AMR surveillance will vary between LMICs depending on the variety of animals and animal products in the country, farming methods, importance of aquaculture and companion animals as well as considerations of feasibility and cost. In terms of strategies for surveillance of antimicrobial use a better understanding of current patterns of use and antimicrobial residues in LMICs

would help identify practical approaches to antimicrobial use surveillance. Surveillance protocols need to be developed in consultation with key stakeholders responsible for animal health which, in LMICs with significant revenue from food production, will often be the private sector, so there will need to be regulation and agreements on data-sharing. Incorporating economic and social considerations into the design of surveillance programmes will facilitate targeting where in the food production chain surveillance should be performed in order to influence patterns of antimicrobial use.

Quality management and Laboratory accreditation

Given the scope and scale of GLASS, it would be very hard or impossible to impose a complete and comprehensive quality assurance manual for implementation at all participating surveillance centres. It may indeed even be counter-productive in that it would delay the implementation of such surveillance activities given the time and resources needed to change or to adapt any existing quality management systems. There are good examples of successful implementation of quality management strategies in AMR surveillance in LMICs. The HIV, TB, Influenza and the Global Foodborne Infections networks each have a supranational network of reference laboratories to support national programmes and coordinate quality management activities such as EQA. For bacteriological surveillance GLASS is recommending the national reference laboratory takes responsibility for these activities. Several LMICs do not have a national reference laboratory with expertise in diagnosing drug resistant infections at the moment. A similar strategy to the other reference laboratory networks could be envisaged with the scope of the proposed interventions aimed at quality assurance limited to those likely to have a significant impact within relatively short time-frames.

Proposed strategy for quality assurance of AST

The process of defining which specimens/pathogen-antimicrobial combinations are to be tested, which testing methods are acceptable and how the results need to be interpreted/reported is the first and critical of the steps towards quality assured AMR data generation. Then, as with previous efforts to build global networks of surveillance laboratories (WHO HIV RESNET, WHO TB SRLN), the most efficient way to select reporting centres and laboratories is likely to be to invite applications from candidate centres along with completed self-assessment checklists requesting information on available human resources, infrastructure, equipment, which AST assays are already implemented and whether or not the laboratory is accredited. Accredited labs would be given priority, but labs meeting other requirements would be required to submit data on rigorous QC for their data to be accepted and would be required to demonstrate adequate performance in formal PT as per pre-determined rules to maintain their affiliation to the network. This presupposes that such labs would have free access to reference strains and possibly other materials as well as to a PT scheme. Finally all non-accredited labs would be encouraged and supported to participate in mentoring schemes such as SLMTA and to use quality management implementation tools such as SLIPTA and WHO-LQSI with the goal of attaining full accreditation within a maximum of 3 years of joining the network. Training on assays not already implemented in participating labs and on newer techniques would also be part of the network activities. If a model like this is adopted, it implies investment in the following activities related to quality assurance:

Meetings and workshops

- Group of experts to define which data are to be collected and the recommended methods
- Quality assurance scheme development – define reference materials, QC recommendations, etc.
- Training on quality management, AST assays and techniques
- Periodic meetings to select new laboratories for inclusion within the network and to review performance of existing network laboratories as well as to review technical or QA/QC recommendations

EQA scheme

- Ensure free availability of reference materials – reference strains for routine QC, quality assured materials for assay validation (small quantities of media with or without antibiotics, disks, primers, probes, nucleic acid extracts, etc.)
- Operate PT scheme - procure and distribute reference strains or other reference materials for blinded testing, 2-4 cycles per year; compile, analyse data from all labs and provide feedback – corrective measures, suggested training or re-training
- Operate training and mentoring programme to make available technical expertise and mentorship to implement and sustain production of high quality AST data

Human resources

- Administrative staff
- Trainers
- Mentors/auditors

Data management and data-sharing

AMR surveillance data need to be recorded accurately and transferred easily. For countries without laboratory information management systems WHONET is available and provides a simple way to standardise data collection and comply with the GLASS recommendations. Most networks collect aggregated data but individual isolate data would allow for more meaningful comparisons across sites to be made. Several other platforms for sharing resistance data exist e.g. WWARN, IDDO, CDDEP which present resistance data in different ways. Different groups have also proposed different drug resistance or effectiveness indices [146, 147]. Commitment to a standardised approach to interpreting and displaying resistance data is needed with data sharing governance, security policies and an ethical framework to ensure continuous engagement of data contributors from LMICs.

Timely reporting

Reliance of publication of network annual reports or publications in peer-reviewed journals is an important source of delay in making new information available. Digital disease detection networks are able to disseminate information rapidly and could perhaps play a role in dissemination of verified information from laboratories.

The role of other groups to support surveillance activities

There are many examples of the contribution that other organisations have made to strengthen AMR surveillance in LMICs e.g. academic groups, NGOs, industry, professional organisations, the military.

They are likely to continue to have a key role in supporting the design, laboratory capacity strengthening and quality management aspects of surveillance but there is a risk of duplication of effort with parallel initiatives being set up without more standardisation and coordination. Any initiatives conducted by these entities and institutions should at a minimum be in line with the national action plan or WHO recommendations if there is no national action plan.

Many high income countries use a model whereby an executive agency of the government is charged with the responsibility of setting public health priorities, implementing surveillance and communicating with the public. These agencies are staffed by public health specialists, scientists and researchers. Adapting this model to low income countries could be a means to reduce the number of parallel diseases surveillance networks and disease control initiatives which are operating or to provide better coordination.

Research agenda

Research is needed to optimise surveillance methods, including sampling strategies, developing new diagnostic tools and importantly linking surveillance outputs with clinical outcome data which are likely to be too burdensome for countries to collect apart from simple metrics like length of stay or mortality. Without clinical data the impact of AMR on morbidity and mortality is less visible and the chances of concerted action are lower if the detrimental effects to health are not obvious. If a child dies of a severe pneumonia because of penicillin resistance in *S.pneumoniae* this critical piece of information needs to be captured [148].

Gaps in the proposed AMR surveillance strategy

There are a number of infections with a significant global disease burden for which there is no routine surveillance for resistance and which are not mentioned in GLASS e.g. rickettsial diseases, fungal infections, drug resistant *Helicobacter pylori*, anthelmintic resistance in both animals and humans. There are now numerous case series reporting resistance in *H.pylori* which is the most important risk factor for gastric carcinoma, estimated to have killed more than 700,000 people in 2012, with the highest burden of disease in Asia and Eastern Europe [149].

Cost and cost-effectiveness

Strengthening laboratory capacity and maintaining diagnostic and surveillance activities has significant costs attached. For England alone it has been estimated that all NHS pathology services cost approximately £2-3 billion per year, the majority being workforce costs [150]. The East Africa Public Health Laboratory Networking Project, funded by the World Bank in 2010, with the aim of scaling up a laboratory network in four East African countries, was awarded 63.66 million USD over 10 years [151]. Rwanda was one of the countries and used a modified performance-based financing approach with success, linking payments to laboratories to evidence of quality improvement [152]. AMR surveillance may increase other costs apart from those associated with bacteriological testing e.g. costs of treatment if resistance rates are high and more second-line drugs are indicated. A prime example of this secondary cost impact is the move to improved diagnosis of MDR-TB. A cost-analysis assessing the impact of introducing GeneXpert® in South Africa, which has a high MDR-TB burden, estimated an incremental capital cost of 222 million US dollars plus an incremental recurrent cost of around 300 million dollars

over 6 years [153]. Combining AMR surveillance with other disease surveillance activities and sharing laboratory infrastructure may be one way to increase cost-effectiveness.

No one left behind?

The slogan "access not excess" is quoted frequently- referring to the need to curb excessive use of antimicrobials without impeding access in areas where they are most needed. More people die due to lack of antimicrobials than as a consequence of drug resistance [154]. There is a risk that the countries with the greatest need to improve access to antibiotics will be the ones with the weakest health systems who will struggle to implement high quality AMR surveillance. This presents an opportunity to try to integrate AMR surveillance with improving access to diagnosis and antimicrobial treatments. Improved diagnosis, close to the point of care, even without detection of drug resistance, could have a big impact to improve rational drug use. Not addressing this risks increasing inappropriate antimicrobial use since so many patients present with undifferentiated fever for which only malaria can be excluded with current affordable point-of-care tests. While this has led to more appropriate antimalarial drug use, the remaining children without malaria but no other confirmed diagnosis are likely to receive an antimicrobial drug when this is not warranted [155]. Unless these countries are prioritised for assistance to improve disease and concomitant AMR surveillance they risk being left behind in the global AMR surveillance effort.

Options for increasing access to measures which will lead to appropriate antimicrobial use in LMICs, including access to affordable high quality drugs have been reviewed by Mendelson and colleagues. They include strategies such as subsidising provision of quality assured medicine, as was trialed for malaria, acceleration of drug registration, increased access to diagnostic or biomarker-based tests and to vaccines, and, in the longer term, better regulation and health systems strengthening [156]. The Affordable Medicines Facility – malaria (AMF-m) was piloted in seven LMICs in 2010 and involved delivery of heavily subsidised, high quality antimalarials through the private and public sectors with good success in some countries but the cost of the programme and political opposition from some quarters led to withdrawal of support from major donors [157].

The accredited drug dispensing outlet (ADDO) programme was a separate initiative launched in Tanzania, and later in Liberia and Uganda, with the goal of improving access to affordable quality medicines in drug shops in areas where there was limited access to registered pharmacies. This was achieved through training, regulation and provision of some incentives such as access to loans to the shop owners. Consumers were sensitised to the programme through public awareness campaigns. There was an education programme for dispensers and appropriate antimicrobial prescribing and AMR were included in this [158]. There is some evidence that the ADDO programme has increased access to antimicrobials in Tanzania but not that appropriate use was associated with participation to the programme, when compared with non-accredited dispensaries [159-161]. Initiatives to facilitate prescribing decisions such as simplified versions of decision making algorithms using mobile technology that have been trialed in healthcare settings could be one way of improving prescribing [162].

Limitations of this network analysis

Limitations of this analysis include reliance on published data and network websites to obtain most of the information about network functioning. If networks do not maintain a web presence or update information on their activities we will have assumed they were not active in a particular area unless we received information to the contrary. One clear example where this was not the case was ReLAVRA which we know to be active from direct contact with the coordinator but which has not published a report since 2010.

Conclusion

For a network to be worthwhile its value should be 'greater than the sum of its parts' but how can this be measured? We can define the success of an AMR surveillance network by:

- Generation of comparable, representative, high quality data on pathogens of concern
- Collaboration between partners e.g. training, shared protocols, data sharing
- Strong coordination from a central body
- Geographical coverage
- Able to detect and track outbreaks in real time
- Rapid effective reporting
- Active communication systems e.g. updated website, newsletter, publications
- Sustainability
- Impact on guidelines or policy
- Impact to improve human and animal health
- Other impacts such as scientific discoveries e.g. new resistance mechanisms, modes of transmission of AMR.

None of the networks we have described has managed to fulfil all of these criteria. Their relative strengths and weaknesses are shown in Table 1.17.

Table 1.17 Strengths and weaknesses of the different types of AMR surveillance networks

	WHO/ governmental	Academic	Pharma/ CRO	Digital Disease Detection
Generate high quality data	✓✓	✓✓✓	✓✓✓	✓
Collaboration[1] between partners	✓✓✓	✓✓✓	✓	✓
Outbreak detection	✓	-	-	✓✓✓
Rapid reporting	✓	✓	✓	✓✓✓
Geographical coverage	✓	✓	✓✓	✓✓✓
Impact on guidelines or policy	✓✓	✓	-	–
Sustainability	✓✓	✓	✓	✓✓

[1] e.g. training, quality management, information exchange

Pharma networks produce high quality data but it may not be representative and they do not tend to support laboratory capacity building in LMICs or influence policy and guidelines. Academic networks produce high quality data which often targets a clinical or policy question but they too have limited influence on policy and their sustainability is reliant on external funding. All of the networks are slow to report resistance data, except for the digital data detection networks such as ProMed, and only a small number have a clear data access policy. Having centralised detailed guidance on how to perform surveillance is associated with having a smaller number of networks working in a more coordinated manner e.g. HIV, malaria, TB, although there are other factors at play such as lack of vested interests by pharmaceutical companies in drug or vaccine development for these diseases. Having a supranational proficiency testing programme linked to networks has been associated with improved laboratory performance. With a few notable exceptions e.g. ReLAVRA, most AMR surveillance networks in LMICs take an active approach to surveillance rather than combining it with routine case-management. A number of new disease surveillance networks have been created which take a One Health Approach. These networks could be linked to AMR surveillance efforts. There may be opportunities to share molecular technologies in use across networks for different diseases. Academic groups, professional bodies, NGOs and other technical support organisations can support regional surveillance activities or could even be sub contracted to do so on behalf of governmental organisations. Surveillance in animals will need the cooperation of the large food-producing corporations in LMICs and will need to be regulated. The biggest challenge is to make surveillance count in LMICs and to lead to concrete improvements in human and animal health.

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Figure: Leaflet used as part of the Cambodian antibiotic awareness campaign

Appendix 1 AMR Networks Search Strategy

05/05/16

Networks involved in the surveillance of antimicrobial drug resistance in low-middle income countries

Database: Embase <1974 to 2016 May 04>
Search Strategy:
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1 antibiotic resistance/ (126544)
2 drug resistance/ or exp antibiotic resistance/ or exp antifungal resistance/ or exp antimalarial drug resistance/ or exp antiviral resistance/ or exp cross resistance/ or exp multidrug resistance/ or exp penicillin resistance/ or exp pesticide resistance/ (239457)
3 exp drug resistant tuberculosis/ (5477)
4 ((antibiotic* or anti-biotic*) adj3 resistan*).ti,ab. (42435)
5 (bacterial adj3 resistan*).ti,ab. (11939)
6 ((anti-fungal* or antifungal*) adj3 susceptib*).ti,ab. (3080)
7 ((anti-fungal* or antifungal*) adj3 surveillan*).ti,ab. (72)
8 ((anti-fungal* or antifungal*) adj3 resistan*).ti,ab. (1969)
9 (HIV* adj3 resistan*).ti,ab. (7753)
10 ((antiretroviral* or anti-retroviral*) adj3 resistan*).ti,ab. (1780)
11 ((antimalarial* or anti-malarial*) adj3 resistan*).ti,ab. (1191)
12 ((anti-tuberculosis or antituberculosis) adj3 resistan*).ti,ab. (571)
13 "MDR tuberculosis".ti,ab. (345)
14 (((multidrug* or multi-drug*) and tuberculosis) adj3 resistan*).ti,ab. (7303)
15 ((antimicrobial* or anti-microbial*) adj3 resistan*).ti,ab. (18931)
16 ((antimicrobial* or anti-microbial*) adj3 surveillan*).ti,ab. (1700)
17 ((antimicrobial* or anti-microbial*) adj3 susceptib*).ti,ab. (14093)
18 AMR.ti,ab. (3179)
19 ((antibacterial* or anti-bacterial*) adj3 resistan*).ti,ab. (1444)
20 OR/ 1-19 (281488)
21 surveillan*.ti,ab. (163513)
22 exp drug surveillance program/ (21554)
23 exp prevalence/ (497896)
24 exp health survey/ (183834)
25 OR/ 21-24 (802958)
26 developing country/ (83513)
27 exp "Africa south of the Sahara"/ or exp Africa/ (249775)
28 exp Asia/ (758868)
29 exp South America/ (143140)
30 exp "South and Central America"/ (167411)
31 (Africa or Asia or South America or Latin America or Central America).tw. (158960)
32 (American Samoa$ or Beliz$ or Botswana$ or Brazil$ or Bulgaria$ or Comoro$ or Costa Rica$ or Croatia$ or Dominica$ or Equatorial Guinea$ or Gabon$ or Grenada$ or Kazakh$).tw. (128433)
33 (Leban$ or Libya$ or Lithuania$ or Malaysia$ or Mauriti$ or Mexic$ or Micronesia$ or Montenegr$ or Palau$ or Panama$ or Romania$).tw. (97345)

34 (Seychelles$ or South Africa$ or Saint Lucia$ or "Saint Vincent and the Grenadines" or Turk$).tw. (98504)
35 (Yugoslavia$ or Guinea$ or Libia$ or Mayotte or Northern Mariana Island$ or Russian Federation or Samoa$ or Serbia$ or Slovak Republic$).tw. (126207)
36 (St Lucia$ or "St Vincent and the Grenadines").tw. (295)
37 (Albania$ or Algeria$ or Angol$ or Armenia$ or Azerbaijan$ or Belarus$ or Bhutan$ or Bolivia$ or "Bosnia and Herzegovina" or Bosnian$).tw. (18448)
38 (Cameroon$ or China or Chinese or Colombia$ or Congo$ or Cuba$ or Djibouti$ or Dominican Republic$ or Ecuador$ or Egypt$ or El Salvador$ or Fiji$).tw. (345372)
39 ("Georgia (Republic)" or Goergian$ or Guam$ or Guatemal$ or Guyana$ or Hondur$ or Indian Ocean Island$ or Indonesia$ or Iran$ or Iraq$ or Jamaica$ or Jordan$ or Lesotho).tw. (77648)
40 ("Macedonia (Republic)" or Marshall Island$ or Micronesia$ or Middle East$ or Moldova$ or Morocc$ or Namibia$ or Nicaragua$ or Paraguay$ or Peru$ or Philippin$).tw. (46055)
41 (Samoa$ or Sri Lanka$ or Suriname$ or Swaziland$ or Syria$ or Thai$ or Tonga$ or Tunisia$ or Turkmen$ or Ukrain$ or Vanuatu).tw. (72724)
42 (Bosnia$ or Cape Verd$ or Gaza or Georgia$ or Kiribati$ or Macedonia$ or Maldives or Marshall Island$ or Palestin$ or Syrian Arab Republic$ or West Bank).tw. (17626)
43 (Afghan$ or Bangladesh$ or Benin$ or Burkina Faso$ or Burundi$ or Cambodia$ or Central African Republic$ or Chad$ or Comoros or "Democratic Republic of the Congo").tw. (36779)
44 (Cote d'Ivoire or Eritrea$ or Ethiopia$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Haiti$ or India$ or Kenya$ or Korea$ or Kyrgyz$ or Laos or Laot$ or Liberia$).tw. (391775)
45 (Madagascar or Malagasy or Malawi$ or Mali$ or Mauritania$ or Melanesia$ or Mongolia$ or Mozambi$ or Myanmar or Nepal$ or Niger$ or Nigeria$).tw. (704503)
46 (Pakistan$ or Papua New Guinea$ or Rwanda$ or Senegal$ or Sierra Leone$ or Somalia$ or Sudan$ or Tajikistan$ or Tanzania$ or East Timor$ or Togo$).tw. (55448)
47 (Uganda$ or Uzbek$ or Viet Nam$ or Yemen$ or Zambia$ or Zimbabw$).tw. (38488)
48 (Burm$ or Congo$ or Lao or North Korea$ or Solomon Island$ or Sao Tome or Timor$ or Viet Nam).tw. (21555)
49 ((developing or less$ developed or third world or under developed or middle income or low income or underserved or under served or deprived or poor$) adj (count$ or nation? or state? or population?)).tw. (78367)
50 (lmic or lmics).tw. (1460)
51 OR/ 26-50 (2572745)
52 20 and 25 and 51 (10122)
53 52 (10122)
54 limit 53 to yr="2000 -Current" (9525)

Database: Global Health <1973 to 2016 Week 16>
Search Strategy:
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1 exp drug resistance/ (78375)
2 drug resistance/ or exp antibiotic resistance/ or exp antifungal resistance/ or exp antimalarial drug resistance/ or exp antiviral resistance/ or exp cross resistance/ or exp multidrug resistance/ or exp penicillin resistance/ or exp pesticide resistance/ (72384)
3 ((antibiotic* or anti-biotic*) adj3 resistan*).ti,ab. (17385)
4 (bacterial adj3 resistan*).ti,ab. (3476)
5 ((anti-fungal* or antifungal*) adj3 susceptib*).ti,ab. (2153)
6 ((anti-fungal* or antifungal*) adj3 surveillan*).ti,ab. (49)

7 ((anti-fungal* or antifungal*) adj3 resistan*).ti,ab. (1240)
8 (HIV* adj3 resistan*).ti,ab. (3265)
9 ((antiretroviral* or anti-retroviral*) adj3 resistan*).ti,ab. (1007)
10 ((antimalarial* or anti-malarial*) adj3 resistan*).ti,ab. (844)
11 ((anti-tuberculosis or antituberculosis) adj3 resistan*).ti,ab. (337)
12 "MDR tuberculosis".ti,ab. (200)
13 (((multidrug* or multi-drug*) and tuberculosis) adj3 resistan*).ti,ab. (3858)
14 ((antimicrobial* or anti-microbial*) adj3 resistan*).ti,ab. (10807)
15 ((antimicrobial* or anti-microbial*) adj3 surveillan*).ti,ab. (962)
16 ((antimicrobial* or anti-microbial*) adj3 susceptib*).ti,ab. (8418)
17 AMR.ti,ab. (317)
18 ((antibacterial* or anti-bacterial*) adj3 resistan*).ti,ab. (619)
19 OR/ 1-18 (90507)
20 surveillan*.ti,ab. (56704)
21 (monitoring or surveillance).sh. (36622)
22 20 OR 21 (76845)
23 exp Developing Countries/ (625454)
24 exp "Africa south of the Sahara"/ or exp Africa/ (154943)
25 exp Asia/ (427221)
26 exp South America/ (94870)
27 (South and Central America).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes] (2568)
28 exp Central America/ (7677)
29 (Africa or Asia or South America or Latin America or Central America).tw. (703297)
30 (American Samoa$ or Beliz$ or Botswana$ or Brazil$ or Bulgaria$ or Comoro$ or Costa Rica$ or Croatia$ or Dominica$ or Equatorial Guinea$ or Gabon$ or Grenada$ or Kazakh$).tw. (84768)
31 (Leban$ or Libya$ or Lithuania$ or Malaysia$ or Mauriti$ or Mexic$ or Micronesia$ or Montenegr$ or Palau$ or Panama$ or Romania$).tw. (46386)
32 (Seychelles$ or South Africa$ or Saint Lucia$ or "Saint Vincent and the Grenadines" or Turk$).tw. (50066)
33 (Yugoslavia$ or Guinea$ or Libia$ or Mayotte or Northern Mariana Island$ or Russian Federation or Samoa$ or Serbia$ or Slovak Republic$).tw. (28623)
34 (St Lucia$ or "St Vincent and the Grenadines").tw. (308)
35 (Albania$ or Algeria$ or Angol$ or Armenia$ or Azerbaijan$ or Belarus$ or Bhutan$ or Bolivia$ or "Bosnia and Herzegovina" or Bosnian$).tw. (9286)
36 (Cameroon$ or China or Chinese or Colombia$ or Congo$ or Cuba$ or Djibouti$ or Dominican Republic$ or Ecuador$ or Egypt$ or El Salvador$ or Fiji$).tw. (195257)
37 ("Georgia (Republic)" or Goergian$ or Guam$ or Guatemal$ or Guyana$ or Hondur$ or Indian Ocean Island$ or Indonesia$ or Iran$ or Iraq$ or Jamaica$ or Jordan$ or Lesotho).tw. (53920)
38 ("Macedonia (Republic)" or Marshall Island$ or Micronesia$ or Middle East$ or Moldova$ or Morocc$ or Namibia$ or Nicaragua$ or Paraguay$ or Peru$ or Philippin$).tw. (88185)
39 (Samoa$ or Sri Lanka$ or Suriname$ or Swaziland$ or Syria$ or Thai$ or Tonga$ or Tunisia$ or Turkmen$ or Ukrain$ or Vanuatu).tw. (34452)
40 (Bosnia$ or Cape Verd$ or Gaza or Georgia$ or Kiribati$ or Macedonia$ or Maldives or Marshall Island$ or Palestin$ or Syrian Arab Republic$ or West Bank).tw. (8159)
41 (Afghan$ or Bangladesh$ or Benin$ or Burkina Faso$ or Burundi$ or Cambodia$ or Central African Republic$ or Chad$ or Comoros or "Democratic Republic of the Congo").tw. (22192)

42 (Cote d'Ivoire or Eritrea$ or Ethiopia$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Haiti$ or India$ or Kenya$ or Korea$ or Kyrgyz$ or Laos or Laot$ or Liberia$).tw. (176846)
43 (Madagascar or Malagasy or Malawi$ or Mali$ or Mauritania$ or Melanesia$ or Mongolia$ or Mozambi$ or Myanmar or Nepal$ or Niger$ or Nigeria$).tw. (82145)
44 (Pakistan$ or Papua New Guinea$ or Rwanda$ or Senegal$ or Sierra Leone$ or Somalia$ or Sudan$ or Tajikistan$ or Tanzania$ or East Timor$ or Togo$).tw. (38106)
45 (Uganda$ or Uzbek$ or Viet Nam$ or Yemen$ or Zambia$ or Zimbabw$).tw. (23056)
46 (Burm$ or Congo$ or Lao or North Korea$ or Solomon Island$ or Sao Tome or Timor$ or Viet Nam).tw. (18038)
47 ((developing or less$ developed or third world or under developed or middle income or low income or underserved or under served or deprived or poor$) adj (count$ or nation? or state? or population?)).tw. (636179)
48 (lmic or lmics).tw. (648)
49 OR/ 23-48 (875208)
50 19 and 22 and 49 (4378)
51 limit 50 to yr="2000 -Current" (4125)

PubMed – search date 05/05/16

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Sri Lanka$[Text Word] OR Suriname$[Text Word] OR Swaziland$[Text Word] OR Syria$[Text Word] OR Thai$[Text Word] OR Tonga$[Text Word] OR Tunisia$[Text Word] OR Turkmen$[Text Word] OR Ukrain$[Text Word] OR Vanuatu[Text Word])))) OR (("Macedonia (Republic)"[Text Word] OR Marshall Island$[Text Word] OR Micronesia$[Text Word] OR Middle East$[Text Word] OR Moldova$[Text Word] OR Morocc$[Text Word] OR Namibia$[Text Word] OR Nicaragua$[Text Word] OR Paraguay$[Text Word] OR Peru$[Text Word] OR Philippin$[Text Word])))) OR (("Georgia (Republic)"[Text Word] OR Goergian$[Text Word] OR Guam$[Text Word] OR Guatemal$[Text Word] OR Guyana$[Text Word] OR Hondur$[Text Word] OR Indian Ocean Island$[Text Word] OR Indonesia$[Text Word] OR Iran$[Text Word] OR Iraq$[Text Word] OR Jamaica$[Text Word] OR Jordan$[Text Word] OR Lesotho[Text Word])))) OR ((Cameroon$[Text Word] OR China[Text Word] OR Chinese[Text Word] OR Colombia$[Text Word] OR Congo$[Text Word] OR Cuba$[Text Word] OR Djibouti$[Text Word] OR Dominican Republic$[Text Word] OR Ecuador$[Text Word] OR Egypt$[Text Word] OR El Salvador$[Text Word] OR Fiji$[Text Word])))) OR ((Albania$[Text Word] OR Algeria$[Text Word] OR Angol$[Text Word] OR Armenia$[Text Word] OR Azerbaijan$[Text Word] OR Belarus$[Text Word] OR Bhutan$[Text Word] OR Bolivia$[Text Word] OR "Bosnia[Text Word] AND Herzegovina"[Text Word] OR Bosnian$[Text Word])))) OR ((St Lucia$[Text Word] OR "St Vincent[Text Word] AND the Grenadines"[Text Word])))) OR ((Yugoslavia$[Text Word] OR Guinea$[Text Word] OR Libia$[Text Word] OR Mayotte[Text Word] OR Northern Mariana Island$[Text Word] OR Russian Federation[Text Word] OR Samoa$[Text Word] OR Serbia$[Text Word] OR Slovak Republic$[Text Word])))) OR ((Seychelles$[Text Word] OR South Africa$[Text Word] OR Saint Lucia$[Text Word] OR "Saint Vincent[Text Word] AND the Grenadines"[Text Word] OR Turk$[Text Word])))) OR ((Leban$[Text Word] OR Libya$[Text Word] OR Lithuania$[Text Word] OR Malaysia$[Text Word] OR Mauriti$[Text Word] OR Mexic$[Text Word] OR Micronesia$[Text Word] OR Montenegr$[Text Word] OR Palau$[Text Word] OR Panama$[Text Word] OR Romania$[Text Word])))) OR ((American Samoa$[Text Word] OR Beliz$[Text Word] OR Botswana$[Text Word] OR Brazil$[Text Word] OR Bulgaria$[Text Word] OR Comoro$[Text Word] OR Costa Rica$[Text Word] OR Croatia$[Text Word] OR Dominica$[Text Word] OR Equatorial Guinea$[Text Word] OR Gabon$[Text Word] OR Grenada$[Text Word] OR Kazakh$[Text Word])))) OR ((Africa[Text Word] OR Asia[Text Word] OR South America[Text Word] OR Latin America[Text Word] OR Central America[Text Word])))) OR ((((((("Developing Countries"[Mesh]) OR ("Africa"[Mesh] OR "Africa South of the Sahara"[Mesh])) OR "Asia"[Mesh]) OR "South America"[Mesh]) OR "Latin America"[Mesh]) OR "Central America"[Mesh])))) AND ((surveillan*[Title/Abstract]) OR ((("Prevalence"[Mesh]) OR "Health Surveys"[Mesh]) OR "Guideline Adherence"[Mesh])))) AND ((((((((((((((("Tuberculosis, Multidrug-Resistant"[Mesh]) OR ("Drug Resistance, Microbial"[Mesh]) OR "Drug Resistance, Multiple"[Mesh])) OR ((resistan*[Title/Abstract]) AND ((anti-biotic*[Title/Abstract] OR antibiotic*[Title/Abstract])))) OR ((resistan*[Title/Abstract]) AND ((bacterial[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibacterial*[Title/Abstract])))) OR ((resistan*[Title/Abstract]) AND ((anti-fungal*[Title/Abstract] OR antifungal*[Title/Abstract])))) OR ((resistan*[Title/Abstract]) AND HIV*[Title/Abstract])) OR ((surveillan*[Title/Abstract]) AND ((anti-fungal*[Title/Abstract] OR antifungal*[Title/Abstract])))) OR ((((anti-fungal*[Title/Abstract] OR antifungal*[Title/Abstract])))) AND susceptib*[Title/Abstract])) OR ((resistan*[Title/Abstract]) AND ((anti-retroviral*[Title/Abstract] OR antiretroviral*[Title/Abstract])))) OR ((resistan*[Title/Abstract]) AND ((antimalarial*[Title/Abstract] OR anti-malarial*[Title/Abstract])))) OR ((resistan*[Title/Abstract]) AND ((anti-tuberculosis[Title/Abstract] OR antituberculosis[Title/Abstract])))) OR (((resistan*[Title/Abstract])

AND (multidrug*[Title/Abstract] OR multi-drug*)[Title/Abstract]) AND tuberculosis[Title/Abstract])) OR ((resistan*[Title/Abstract]) AND ((anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract]))))) OR ((((anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract])))) AND surveillan*[Title/Abstract])) OR ((susceptib*[Title/Abstract]) AND ((anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract]))))) OR MDR tuberculosis[Title/Abstract]) OR AMR[Title/Abstract])

Filters activated: Publication date from 2000/01/01 to 2016/12/31.

= 7102

Search results

Embase	9525
Global Health	4125
PubMed	7102
Total	20752
Deduplicated total	16629

Appendix 2 Tables of networks and data repositories

2.1 Bacteria networks

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-Funding	
The Alexander Project	Pharma/CRO	Human, all ages, community acquired infections	J Antimicrob Chemother. 2005 Oct;56 Suppl 2:ii3-ii21. http://jac.oxfordjournals.org/content/56/suppl_2/ii3.full.pdf	Brazil, Mexico, South Africa, Kenya	Argentina, Austria, Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Luxembourg, Netherlands, Poland, Portugal, Ireland, Russian Federation, Slovak Republic, Slovenia, Spain, Switzerland, United Kingdom, United States, Saudi Arabia, Hong Kong, Singapore, Japan	1992-2002	Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis	both	Corporate (GlaxoSmithKline)
Asian Network for Surveillance of Resistant Pathogens (ANSORP)	Academic	Human,all ages	http://www.ansorp.org/06_ansorp/ansorp_01.htm	China, Thailand, India, Sri Lanka, Malaysia, Indonesia, Viet Nam, Philippines	Korea, Republic of, Hong Kong, Taiwan, Singapore, Japan, Saudi Arabia	1996-ongoing	Streptococcus pneumoniae, Community acquired Meticillin resistant Staphylococcus aureus, Shigella spp., Salmonella spp.	both	Corporate (project specific)
Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC)	Academic	Women	no web link available	Brazil	Austria,France, Germany, Hungary,Italy, Poland, Russian Federation, Spain, Netherlands	2003-2006	Escherichia coli, other urinary pathogens	non-invasive (urine)	Corporate (Zambon S.p.A., Bresso (MI), Italy)
Antibiotic resistance in the Mediterranean region (ARMed)	WHO/governmental	Human,all ages	http://www.jidc.org/index.php/journal/article/view/19858565/296	Turkey, Tunisia, Egypt, Jordan, Morocco, Algeria, Lebanon	Malta, Cyprus	2003-2007	Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Enterococcus faecium, Enterococcus faecalis	invasive	Public (EC)
Assessing Worldwide Antimicrobial Resistance and Evaluation Program (AWARE)	Pharma/CRO	Human	http://aac.asm.org/content/60/1/343	China, Philippines,Thailand	Australia, Japan, Korea, Republic of, Taiwan	2008-ongoing	Staphylococcus aureus	both	Corporate (Astra-Zeneca)
Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries: an international cohort study by the Institut Pasteur International Network(BIRDY)	Academic	Children (community acquired and HCAIs)	http://www.charliproject.org/	Madagascar, Senegal, Cambodia		2012-ongoing	unselected	both	Public,Corporate (Monaco Department of International Cooperation, Total Corporate Foundation, MSDAvenir)
The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR)	WHO/governmental	Human, all ages	http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/antimicrobial-resistance/central-asian-and-eastern-european-surveillance-on-antimicrobial-resistance-caesar	Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Republic of, Serbia, Tajikistan, Macedonia, the Former Yugoslav Republic of, Turkey, Turkmenistan, Ukraine, Uzbekistan, Kosovo	Montenegro, Russian Federation, Switzerland	2013-ongoing	Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter spp.	invasive	Public
The Comprehensive Antibiotic Resistance Database (CARD)	Data repository, Ontario, Canada	Human, all ages	http://arpcard.mcmaster.ca			2013-ongoing	Unselected	NA	Public,Corporate (Canadian Foundation for Innovation, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Medical Research Council (UK), and Ontario Research Fund)

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
Caribbean Public Health Agency (CARPHA)	WHO/governmental	all ages	http://carpha.org	Anguilla, Belize, Dominica, Grenada, Haiti, Guyana, Jamaica, Saint Vincent and the Grenadines, Suriname, Montserrat	Antigua and Barbuda, Aruba, Bahamas, Barbados, Bermuda, Bonaire, Sint Eustatius and Saba, Virgin Islands, British, Cayman Islands, Curacao, Saint Kitts and Nevis, Saint Lucia, Saint Maarten, Trinidad and Tobago, Turks and Caicos Islands	2013-ongoing	M.tuberculosis, other bacterial pathogens such as ESBLs, Meticillin Resistant Staphylococcus aureus	both	Trust or Foundation (CARPHA Foundation)
Community-Acquired Respiratory Tract Infection Pathogen Surveillance	Pharma/CRO	Adults (community and hospital acquired)	No web link available	China, Indonesia	Taiwan, Singapore	2009-2010	Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Klebsiella pneumoniae, meticillin-susceptible Staphylococcus aureus, Streptococcus spp	both	Corporate (Bayer HealthCare Pharma)
CDC Global Health Security Agenda Antimicrobial Resistance Action Package	Other	One Health	http://www.cdc.gov/globalhealth/security/actionpackages/antimicrobial_resistance.htm	India, Thailand	Canada, Germany, Netherlands, Sweden, United Kingdom, Indonesia, Australia,Italy, Japan, Norway, Portugal, Switzerland, United States	2014-ongoing	not specified	not known	Public (US CDC)
Centre for Disease Dynamics, Economics and Policy (CDDEP)/ResistanceMap	Academic, Data repository, Washington DC, USA	One Health	http://cddep.org/			1999-ongoing	Escherichia coli, Klebsiella pneumoniae, P.aeruginosa, A.baumannii, Proteus mirabilis, Staphylococcus aureus, CoNS, Enterococcus spp, Streptococcus pneumoniae	invasive	Trust or Foundation (BMGF & other donors)
Community-Based Surveillance of Antimicrobial Use and Resistance in Resource-Constrained Settings Project Group	Academic	all ages, community acquired infections	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2010.02696.x/full	India, South Africa		2002-2005	Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae	non-invasive	Public (USAID)
The Comparative Activity of Carbapenem Testing (COMPACT & COMPACT II)	Pharma/CRO	Hospitalised patients (including ICU)	no web link available	Philippines, Thailand, Viet Nam	Singapore, New Zealand	2008-2010	Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Acinetobacter baumannii, other Gram negative	both	Corporate (Janssen Asia Pacific, a division of Johnson & Johnson Pte Ltd)
International daptomycin surveillance programs	Pharma/CRO	Human	No web link available	Bulgaria, Romania, Turkey, Ukraine, Brazil, Colombia, Ecuador, Guatemala, India,Mexico, Panama , Peru	Argentina, Chile, Australia, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, New Zealand, Poland, Portugal , Russian Federation, Slovenia, Spain, Sweden, United Kingdom, Venezuela	2011-2011	Gram positive (except Streptococcus pneumoniae)	both	Corporate (Pharma & JMI Laboratories, North Liberty, IA, USA)
Diseases of the Most Impoverished (DOMI) Typhoid Study Group & multicentre shigellosis surveillance study	Academic	Children (Except China),Community acquired	http://www.who.int/bulletin/volumes/86/4/06-039818.pdf?ua=1	China, India, Indonesia, Pakistan, Viet Nam		2001-2004	Salmonella Typhi, Shigella spp	both	Trust or Foundation (BMGF)
European Antimicrobial Resistance Surveillance Network (EARS-Net)	WHO/governmental	Human	http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx	Bulgaria, Romania	Austria, Belgium, Croatia, Cyprus, Czech Republic , Denmark, Estonia, Finland, France, Germany , Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom	1999-ongoing	Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa	invasive	Public (ECDC)

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
The Enter-Net International Surveillance Network	WHO/governmental	Human, food-borne infection	http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=73	Romania	Austria, Belgium, Denmark, United Kingdom, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Luxembourg, Netherlands, Portugal, Scotland, Spain, Sweden, Norway, Switzerland, Cyprus, Czech Republic, Estonia, Hungary, Malta, Iceland, Slovakia, Slovenia	1993-2007	Salmonella spp., Verocytotoxin producing Escherichia coli	both	Public (EC DG SANCO under the Public Health Programme 1996–2002)
Food- and waterborne diseases and zoonoses Network (FWDNet)	WHO/governmental	Human	http://ecdc.europa.eu/en/healthtopics/food_and_waterborne_disease/fwd-network/Pages/fwd-network.aspx	Bulgaria, Romania	Austria, Belgium, Croatia, Cyprus, Czech Republic , Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom	2007-ongoing	Salmonella spp., Escherichia coli, Campylobacter spp.	both	Public
Global Antibiotic Resistance Partnership (GARP)	Academic	One Health	http://www.cddep.org/garp/home	India, Kenya, Mozambique, Nepal, South Africa, Tanzania, United Republic of, Uganda, Viet Nam		2009-ongoing	not applicable	both	Trust or Foundation (BMGF)
The Gonococcal Antimicrobial Surveillance Programme (GASP)	WHO/governmental	Human, all ages	http://www.who.int/reproductivehealth/topics/rtis/gonococcal_resistance/en/	Bolivia, Brazil, Bhutan, Cambodia, China, Colombia, Cote d'Ivoire, Cuba, Ecuador, El Salvador, Fiji, India, Indonesia, Kenya, Madagascar, Malaysia, Mongolia, Morocco, Namibia, Papua New Guinea, Paraguay, Peru, Philippines, Romania, South Africa, Sri Lanka, Tanzania, United Republic of, Thailand, Tonga, Uganda, Viet Nam, Zimbabwe	Australia, Austria, Argentina, Bahrain, Belgium, Brunei Darussalam, Canada, Chile, Hong Kong, Cyprus, Denmark, Ecuador, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Latvia, Korea, Republic of, Malta, New Zealand, Paraguay, Portugal, Russian Federation, Singapore, Slovakia, Slovenia, Spain, Sweden, Netherlands, Norway, Uruguay, United Kingdom, United States, Venezuela	1992-ongoing	Neisseria gonorrhoeae	non-invasive	WHO
WHO Global Foodborne Infections Network	WHO/governmental	One Health	http://www.who.int/gfn/en/	Afghanistan, Albania, Algeria, American Samoa, Angola, Armenia, Azerbaijan, Bangladesh, Belarus, Belize, Bolivia, Bosnia and Herzegovina, Brazil, Bulgaria, Burundi, Cambodia, Cameroon, Central African Republic, China, Colombia, Costa Rica, Cote d'Ivoire, Congo, Congo, the Democratic Republic of the, Cuba, Djibouti, Ecuador, Egypt, Guinea, Ethiopia, Eritrea, El Salvador, Fiji, Gabon, Gambia, Georgia, Ghana, Guatemala, Guyana, Haiti, Honduras, India, Indonesia, Iran, Islamic Republic of, Jamaica, Kazakhstan, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Lesotho, Libya, Macedonia, the Former Yugoslav Republic of, Madagascar, Malawi, Malaysia, Mali, Mauritania, Mauritius, Mexico, Micronesia, Federated States of, Moldova, Republic of, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Puerto Rico, Romania, Rwanda, Senegal, Serbia, Sierra Leone, Somalia, South Africa, Sri Lanka, Sudan, Suriname, Swaziland, Syrian Arab Republic, Tajikistan, Thailand, Timor-Leste, Tunisia, Turkey, Uganda, Ukraine, Uzbekistan, Tanzania, United Republic of, Vanuatu, Viet Nam, Yemen, Zambia, Zimbabwe	Argentina, Australia, Austria, Bahrain, Barbados, Belgium, Bermuda, Bolivia, Brazil, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Jordan, Korea, Republic of, Kuwait, Latvia, Lithuania, Luxembourg, Macao, Malta, Martinique, Montenegro, Morocco, Netherlands, New Zealand, Norway, Oman, Palestine, State of, Poland, Portugal, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Trinidad and Tobago, United Arab Emirates, United Kingdom, United States, Uruguay, Venezuela	2001-ongoing	Salmonella spp.	both	WHO

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS)	Academic	All patients on 1 day	http://www.global-pps.com/	Bulgaria, Albania, Bosnia and Herzegovina, Georgia, Kosovo, Kyrgyzstan, Macedonia, the Former Yugoslav Republic of, Moldova, Republic of, Serbia, India, Viet Nam, Iraq, Jordan, Lebanon, Pakistan, Palestine, Brazil, Costa Rica, Mexico, Egypt, South Africa, Nigeria, Senegal, Namibia	Belgium, Chile, Croatia, Cyprus, Czech Republic, Denmark, United Kingdom, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Northern Ireland, Portugal, Slovenia, Spain, Sweden, Belarus, Russian Federation, Switzerland, Japan, Singapore, Taiwan, Bahrain, Israel, Kuwait, Qatar, Saudi Arabia, United States, Canada, Argentina, Venezuela	2015-ongoing		both	Corporate (bioMERIEUX)
International Network For Optimal Resistance Monitoring (INFORM)	Pharma/CRO	Human	http://aac.asm.org/content/60/5/2849.full.pdf+html			2012-2014	Proteus mirabilis, Proteus vulgaris, Morganella morganii, Escherichia coli, Klebsiella oxytoca, Citrobacter spp., Serratia marcescens, Providencia spp., Enterobacter spp., Klebsiella pneumoniae	both	Corporate (Astra-Zeneca)
International Nosocomial Infection Control Consortium (INICC)	Academic	Human, all ages, nosocomial infections, ICU bias	http://www.inicc.org/	Bolivia, Brazil, Bulgaria, China, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Egypt, India, Iran, Islamic Republic of, Jordan, Kosovo, Lebanon,Macedonia, the Former Yugoslav Republic of, Malaysia, Mexico, Morocco, Pakistan, Panama, Peru, Philippines, Romania, El Salvador, Serbia, Sri Lanka, Sudan, Thailand, Tunisia, Turkey, Viet Nam	Argentina, Greece, Lithuania, Poland, Puerto Rico, Saudi Arabia, Singapore, Slovakia, United Arab Emirates, Uruguay, Venezuela	2002-ongoing	Unselected	both	Trust or Foundation (run as a not-for-profit foundation)
International Network for the Study and Prevention of Emerging Antimicrobial Resistance	Academic		http://wwwnc.cdc.gov/eid/article/7/2/70-0319_article	Bosnia and Herzegovina, Brazil, Bulgaria, China, Cote d'Ivoire, Morocco, Romania, Senegal, Tunisia	Argentina, Austria, Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Luxembourg, Netherlands, Poland, Russian Federation, Slovenia, Spain, Switzerland, United Kingdom, United States	1998-2010(?)	Streptococcus spp., Streptococcus pneumoniae, Staphylococcus spp., Enterobacteriaceae, Neisseria meningitidis, Acinetobacter baumannii, Salmonella Typhi, Haemophilus influenzae, Brucella spp.,Clostridium difficile, Clostridium perfringens	both	Public (CDC)
Multiyear, Multinational Survey of the Incidence and Global Distribution of Metallo- Beta Lactamase-Producing Enterobacteriaceae and Pseudomonas aeruginosa	Pharma/CRO	Human	no web link available	Brazil, Colombia, Mexico, Philippines, Nigeria, Romania, South Africa,Thailand, Kenya, Malaysia, China, Turkey	Argentina, Chile, Czech Republic, Italy, Hungary, Portugal, Poland,United States,Russian Federation, Kuwait, Greece, Venezuela, Taiwan, Korea, Republic of, Spain, United Kingdom, Australia, Austria, Belgium	2012-2014	Pseudomonas aeruginosa, Klebsiella spp., Enterobacter spp., Proteus spp., Citrobacter freundii, Escherichia coli, Serratia marcescens	both	Corporate (Astra-Zeneca, IHMA)
Meropenem Yearly Susceptibility Test Information Collection (MYSTIC)	Pharma/CRO	Human including ICU, neutropenic, cystic fibrosis	Diagn Microbiol Infect Dis. 2009 Feb;63(2):217-22. doi: 10.1016/j.diagmicrobio.2008.11.004.	Turkey, Brazil, Mexico, Thailand	United Kingdom, Belgium, Czech Republic, Italy, Germany, Poland, Hong Kong, Israel, Russian Federation	1997-2008	Broad range of Gram positive and Gram negative organisms	both	Corporate (Astra-Zeneca)
The Network on Antimicrobial Resistance in *Staphylococcus aureus (NARSA)*	Data repository, Virginia, USA		https://www.beiresources.org/Home.aspx			1997-2016	Staphylococcus aureus	both	Public (NIAID)

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR)	Academic	Children <5y	https://cid.oxfordjournals.org/content/48/Supplement_2/S147.full	Kenya, Uganda, Tanzania, United Republic of, Ethiopia		2003-2007	Streptococcus pneumoniae, Haemophilus influenzae	invasive	Trust or Foundation (GAVI Alliance and The Vaccine Fund)
NosoMed pilot survey in the Eastern Mediterranean Area	Academic	Hospital acquired infection	no web link available	Algeria, Tunisia	France	2003-2004	MRSA, Ceftazidime-resistant Psuedomonas aeruginosa,Imipenem-resistant Acinetobacter baumannii , third-generation cephalosporin-resistant Enterobacteriaceae	both	Public (EU)
Program to Assess Ceftolozane/Tazobactam susceptibility (PACTS)	Pharma/CRO	Human, all ages	No web link available	Turkey, Ukraine	Israel, Poland, United States, Belgium, Greece, Portugal, Germany, Ireland, Russian Federation, United Kingdom, Italy, Spain, France, Sweden	2012-2012	Pseudomonas aeruginosa, Enterobacteriaceae	both	Corporate (Cubist Pharmaceuticals)
Pan-European Antimicrobial Resistance Using Local Surveillance (PEARLS)	Pharma/CRO	All ages, nosocomial infections	No web link available	Lebanon, South Africa, Turkey	Austria, Belgium, France, Germany, Switzerland, Netherlands, Croatia, Greece, Italy, Portugal, Slovenia, Spain, Saudi Arabia	2001-2002	Enterococcus faecium, Enterobacter cloacae, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus	both	Corporate (Wyeth Pharmaceuticals)
Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT)	Pharma/CRO	Human, all ages, community acquired infections	No web link available	Brazil, Colombia, China, Ecuador, Guatemala, Indonesia, Mexico, Turkey, Peru, South Africa	Australia, Argentina, Belgium, Canada, Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Ireland, Israel, Japan, Netherlands, Poland, Portugal, Russian Federation, Korea, Republic of, Sweden, Spain, Slovak Republic, Switzerland, Taiwan, United Kingdom, United States, Venezuela	1999-2004	Streptococcus pneumoniae, Legionella spp.	both	Corporate (Sanofi-Aventis)
PulseNet International	WHO/governmental	One Health, food-borne infection	http://www.pulsenetinternational.org/protocols/	South Africa, Kenya, Gambia, Senegal, Cameroon, Malawi, Tanzania, United Republic of, Cote d'Ivoire, Ghana, Uganda, Mozambique, South Africa, Bangladesh, China, India, Malaysia, Philippines, Thailand, Viet Nam, Bulgaria, Romania, Turkey, Bolivia, Brazil, Colombia, Costa Rica, Cuba, Guatemala, México, Nicaragua, Paraguay, Peru, Iran, Islamic Republic of, Jordan, Lebanon, Libya	United States, United Kingdom, Australia, Korea, Republic of, Hong Kong, Japan, New Zealand, Taiwan, Canada, Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Argentina, Chile, Uruguay, Venezuela, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia	1998-ongoing	Campylobacter jejuni, Escherichia coli 0157, Clostridium botulinum, Salmonella spp., Shigella sonnei, Shigella flexneri, Listeria monocytogenes, Vibrio cholerae, Vibrio parahaemolyticus, Yersinia pestis	both	Public

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA)	WHO/governmental	Human, all ages, hospital and community-acquired	new.paho.org	Bolivia, Brazil, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic	Argentina, Chile, Venezuela, Uruguay	1996-ongoing	Community Acquired: Salmonella spp., Shigella spp., Vibrio cholerae, Neisseria meningitidis, Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae, Campylobacter spp., Neisseria gonorrhoeae, Beta Haemolytic Streptococcus spp. Hospital-acquired: Enterococcus spp., Klebsiella pneumoniae, Acinetobacter spp., Pseudomonas aeruginosa Escherichia coli, Staphylococcus aureus, Enterobacter spp.	both	Public (PAHO)
South Asian Pneumococcal Alliance (SAPNA)	Academic	Children<5y	No web link available	India, Sri Lanka, Nepal		2004-2009	Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitis	invasive	Public,Corporate (GAVI Alliance and The Vaccine Fund)
Study on Antimicrobial Resistance in Staphylococcus aureus (SARISA)	Pharma/CRO	Human, all ages	No web link available	South Africa, Malaysia	Denmark, Norway ,Sweden, Germany, Lithuania, United States, New Zealand, Australia, France, United Kingdom, Spain, Belgium, Kuwait, Poland, Greece,	1996-1996	Staphylococcus aureus	both	Corporate (LEO Pharma (Copenhagen, Denmark))
Surveillance Data Link Network (SDLN)	Data repository, Illinois, USA	Human, all ages	http://www.ihmainc.com/pages/surveillance_data_link_network/16.php			1993-ongoing	Unselected	both	Corporate (International Health Management Associates, Inc. (IHMA))
Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas (SIREVA & SIREVA II)	WHO/governmental	Human, all ages	http://www.paho.org/hq/index.php?option=com_content&view=category&layout=blog&id=3609&Itemid=3953	Bolivia, Brazil, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Honduras, México, Nicaragua, Panamá, Paraguay, Peru, Dominican Republic	Argentina, Chile, Venezuela, Uruguay	1993-ongoing	Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis	both	Public (PAHO)
Study for Monitoring Antimicrobial Resistance Trends (SMART)	Pharma/CRO	Human, all ages	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3854014/pdf/pharmaceuticals-06-01335.pdf	China, Colombia, Guatemala, India, Jordan, Lebanon, Malaysia, Panama, Philippines, Thailand, Tunisia, Viet Nam, Turkey, India, Kazakhstan, Dominican Republic, Panama, Ecuador, Romania, Serbia, Mexico, South Africa, Georgia	Australia, Argentina, Canada, Chile, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Lithuania, Saudi Arabia, Slovenia, Korea, Republic of, Spain, Portugal, New Zealand, Puerto Rico, Singapore,Taiwan, Germany, United Arab Emirates, United Kingdom, United States,	2002-2011	Gram Negatives	both (intra-abdominal + urine)	Corporate (Merck & Company, Inc.)

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
Survey of Antibiotic Resistance (SOAR)	Pharma/CRO	Human, community-acquired respiratory infection	http://www.gsk.com/en-gb/research/what-we-are-working-on/antibiotics-research/#how-we-help-track-antibiotic-resistance	Cote d'Ivoire, Kenya, Congo, the Democratic Republic of the, Senegal, Nigeria, Thailand, India, China, Ukraine, Turkey, Viet Nam, Pakistan, Lebanon, Bulgaria, Philippines, Romania,Serbia, Brazil, Mexico, Costa Rica, Jamaica, Pakistan, Turkey, Egypt, South Africa, Morocco, Tunisia, Lebanon,	United Arab Emirates, Singapore, Bahrain, Oman, Argentina, Chile, Croatia, Czech Republic, Greece,Russian Federation, Slovak Republic, Trindad and Tobago, Saudi Arabia, Kuwait	2002-ongoing	Streptococcus pneumoniae, Haemophilus influenzae	non-invasive	Corporate (GlaxoSmithKline)
International solithromycin surveillance programs	Pharma/CRO	Human	No web link available	Brazil , Mexico, Ukraine, Romania, Turkey	Argentina, Australia, Belgium , Chile, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, New Zealand, Poland, Portugal, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, United States	2011-2011	Gram positive (except Streptococcus pneumoniae)	both	Corporate (JMI Laboratories, North Liberty, IA, USA)
African-German StaphNet consortium	Academic	Human, symptomatic patients and carriers	http://eurocryo-portal.ibmt.fraunhofer.de/StaphPortal/welcome.do	Tanzania, United Republic of, Gabon, Mozambique	Germany	2010-ongoing	S.aureus	both	Public (Deutsche Forschungsgemeinschaf)
TARGETed Surveillance Study	Pharma/CRO	Human, community acquired respiratory tract infection	no web link available	Mexico, South Africa	France, Germany, Italy, Spain, United States	2003-2007	S.pneumoniae	both	Corporate (Bayer)
Tigecycline Evaluation and Surveillance Trial (TEST)	Pharma/CRO	Human, all ages	http://www.testsurveillance.com/	Mauritius, Morocco, Namibia, South Africa, Tunisia, China, India, Indonesia, Malaysia, Pakistan, Philippines, Thailand, Lebanon, Turkey, Jordan, Brazil, Colombia, El Salvador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Puerto Rico	Australia, Austria, Belgium, Bulgaria, Chile, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Latvia,Lithuania, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Taiwan, Netherlands, United Kingdom, Argentina, Singapore, Korea, Republic of, Israel, Kuwait, Oman, Saudi Arabia, Canada, United States, Venezuela	2004-2011	Streptococcus pneumoniae, Enterococcus spp., Staphylococcus aureus, Streptococcus agalactiae, Haemophilus influenzae, Acinetobacter spp., Escherichia coli, Enterobacter spp., Pseudomonas aeruginosa, Serratia spp., Klebsiella spp., Bacteroides, Prevotella, Anaerococcus, Clostridium spp., Finegoldia, Peptostreptococcus	both	Corporate (Pfizer)
The Typhoid Fever Surveillance in Africa Program (TSAP)	Academic	Human, all ages	http://cid.oxfordjournals.org/content/62/suppl_1/S9.full	Burkina Faso, Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar, Senegal, South Africa, Sudan, Tanzania, United		2009-ongoing	Salmonella enterica var Typhi	invasive	Trust or Foundation (BMGF)

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Pathogen	Invasive/non-	Funding
WHO global antimicrobial susceptibility database (WHONET)	Data repository, Boston, USA	One Health	whonet.org	Algeria, Armenia, Cameroon, Gambia, Ghana, Kenya, Madagascar, Mozambique, Namibia, Nigeria, Senegal, Somalia, Sudan, South Africa, Tanzania, United Republic of, Uganda,Iran, Islamic Republic of, Jordan, Lebanon, Libya, Morocco, Oman, Pakistan, Tunisia, China, Malaysia, Mongolia, Philippines, Viet Nam, Bangladesh, Bhutan, India, Indonesia, Myanmar, Nepal, Sri Lanka, Thailand, Romania, Bosnia and Herzegovina, Serbia, Kazakhstan, Turkey, Kosovo, Ukraine, Mexico, Bolivia, Belize, Nicaragua, Brazil, Panama, Paraguay, Peru, Colombia, Suriname, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras	United Arab Emirates, Oman, Kuwait, Saudi Arabia, Australia, Brunei Darussalam, Hong Kong, Japan, Korea, Republic of, Singapore, Taiwan, Latvia, Austria, Lithuania, Belarus, Luxembourg, Belgium, Malta, Moldova, Bulgaria, Netherlands, Croatia, Norway, Cyprus, Denmark, Poland, Estonia, Portugal, Finland, France, Russian Federation, Germany, Greece, Slovakia, Ireland, Slovenia, Israel, Spain, Italy, Sweden, Argentina, Canada, Chile, Trinidad and Tobago, United States, Uruguay,Venezuela	1989-ongoing	All culture results	both	Public (NIH and others)
Western Pacific Regional Programme for Surveillance of Antimicrobial Resistance	WHO/governmental	Human	http://apps.who.int/medicinedocs/documents/s16877e/s16877e.pdf	Malaysia, China, Viet Nam, Philippines, Fiji, Tonga	Australia, Brunei Darussalam, New Zealand, Singapore, Hong Kong, Japan, Korea, Republic of	1991-1998	unselected (>20 species)	both	WHO
Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS)	Pharma/CRO	Human, all ages	No web link available	Brazil, China, Ecuador, Guatemala, Indonesia, Malaysia, Mexico, Thailand, Turkey, Peru, South Africa, Ukraine	Australia, Argentina, Belgium, Canada, Chile, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Italy, Ireland, Israel, Japan, Netherlands, Poland, Portugal, Russian Federation, Singapore, Korea, Republic of, Sweden, Spain, Slovenia, Switzerland, Taiwan, United Kingdom, United States, Venezuela	2004-ongoing	Gram positive	both	Corporate (Pfizer)
SENTRY Antimicrobial Surveillance program	Pharma/CRO	Human, all ages	No web link available	Albania, Brazil, Colombia, Mexico, China, Philippines, South Africa, Romania	Australia, Austria, Argentina, Chile, Uruguay, Hong Kong, Japan, Latvia, Singapore, Taiwan, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Russian Federation, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States, Canada, Venezuela	1997-ongoing	unselected bacteria and fungi	both	Corporate (Bristol-Myers Squibb)
Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL)	Academic	Human, all ages	http://www.fondation-merieux.org/gabriel-network	Brazil, Haiti, Paraguay, Georgia,Ukraine, Cameroon, Lebanon, Mali, Madagascar, Bangladesh, Cambodia, China, Mongolia	France	2008-ongoing	unselected	both	Trust or Foundation (Fondation Mérieux)
Pathosystems Resource Integration Centre (PATRIC)	Data repository, Illinois, USA	Human	https://www.patricbrc.org/portal/portal/patric/Home	South Africa, Brazil, China, Kazakhstan, Peru, Colombia, Malaysia, Philippines	Russian Federation, Argentina, Korea, Republic of, United States, Uruguay, Sweden,United Kingdom	2012-ongoing	unselected (including mycobacteria)	both	Public (NIH/NIAID)

2.2 Malaria networks

NETWORK NAME (Acronym)	Type	Link	LMIC(s) covered)	HICs	Duration	Funding
Amazon Malaria Initiative (AMI)	WHO/governmental	http://www.usaidami.org/#sthash.LIqsdRzC.dpbs	Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, Suriname, Panama, Nicaragua, Honduras, Guatemala	Venezuela	2001-ongoing	Public (USAID/PAHO)
Asia-Pacific Malaria Elimination Network (APMEN)	WHO/governmental	http://apmen.org/	Bangladesh, Bhutan, Cambodia, China,Korea, Democratic People's Republic of, India, Indonesia, Lao People's Democratic Republic, Malaysia, Nepal, Papua New Guinea, Philippines, Solomon Islands, Sri Lanka,Thailand, Vanuatu, Viet Nam	Korea, Republic of	2009-ongoing	Public (Australian Department of foreign affairs and trade)
Artemisinin Resistance Confirmation, Characterization, and Containment collaboration (ARC3)	WHO/governmental	No web link available	Cambodia, Thailand, Bangladesh		2009-2010	Trust or Foundation (BMGF)
Artemisinin Resistance Containment and Elimination collaboration (ARCE)	WHO/governmental	No web link available	Lao People's Democratic Republic, Myanmar,Viet Nam		2010-2011	WHO
BBINS Malaria Drug resistance Network (BBINS)	WHO/governmental	No web link available	India, Sri Lanka, Bangladesh, Bhutan, Nepal		2011-ongoing	Public (USAID)
The East African Network for Monitoring Antimalarial Treatment (EANMAT)	WHO/governmental	No web link available	Kenya, Uganda, Tanzania, United Republic of, Rwanda, Burundi		1997-2006	Public (DFID)
Greater Mekong Sub-region Therapeutic Efficacy Studies (TES) network	WHO/governmental	No web link available	Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand, Viet Nam, Bangladesh, India		2007-ongoing	WHO
Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT)	WHO/governmental	No web link available	Somalia, Ethiopia, Sudan, South Sudan, Yemen	Saudi Arabia	2004-ongoing	Public (USAID)
MalariaGEN Genomic Epidemiology Network	Academic	http://www.malariagen.net/home?destination=node/1	Bangladesh, Brazil, Burkina Faso, Cambodia, Cameroon, China, Colombia, Congo, the Democratic Republic of the, Ghana, Guinea, India, Indonesia, Kenya, Laos, Madagascar, Malawi, Malaysia, Mali, Myanmar, Nigeria, Papua New Guinea, Peru, Senegal, Sri Lanka, Tanzania, United Republic of, Thailand, Gambia, Uganda, Viet Nam		2005-ongoing	Trust or Foundation (Wellcome Trust, BMGF)

NETWORK NAME (Acronym)	Type	Link	LMIC(s) covered)	HICs	Duration	Funding
Plasmodium Diversity Network Africa (PDNA)	Academic	http://www.cggh.org/collaborations/plasmodium-diversity-network-africa	Gambia, Mali, Ghana,CÃ´te d'Ivoire, Cameroon, Gabon, Ethiopia, Congo, the Democratic Republic of the, Kenya, Tanzania, United Republic of, Madagascar, Cabo Verde, Angola, Mozambique, South Africa		2012-ongoing	Public, Trust or Foundation (Wellcome Trust, MRC)
Pacific Malaria Drug Resistance Monitoring Network	WHO/governmental	No web link available	Malaysia, Papua New Guinea, Philippines, Solomon Islands, Vanuatu, Indonesia, Timor-Leste	Korea, Republic of	2011-ongoing	Public (USAID)
Pakistan-Iran-Afghanistan Malaria Network (PIAM-net)	WHO/governmental	No web link available	Afghanistan, Iran, Islamic Republic of, Pakistan		2008-ongoing	Public (Global Fund)
Reseau d'Afrique Centrale pour traitement anti-paludisme (RACTAP)	WHO/governmental	No web link available	Chad, the Central African Republic, Equatorial Guinea, Cameroon, Gabon, Angola, the Republic of Congo, Congo, the Democratic Republic of the		2003-2009	Public (WHO, World Bank, USAID)
Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA)	WHO/governmental	http://www.paho.org/hq/index.php?option=com_content&view=article&id=2231&Itemid=1922&lang=en	Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, Suriname, Panama, Nicaragua, Honduras, Guatemala, Belize	Venezuela	2001-ongoing	Public (USAID/PAHO)
South African Network for the Monitoring of Antimalarial drug resistance (SANMAT)	WHO/governmental		South Africa, Botswana, Zimbabwe, Malawi, Mozambique, Swaziland, Zambia		2002-ongoing	NK
Tracking Resistance to Artemisinin Collaboration (TRAC)	Academic (MORU coordinated)	http://www.wwarn.org/working-together/partner-projects/tracking-resistance-artemisinin-collaboration-ii, DFID	Cambodia, Thailand, Viet Nam, Myanmar, Lao People's Democratic Republic, Bangladesh, India, Congo, the Democratic Republic of the, Kenya, India		2011-ongoing	Public (DFID)
West African Network for Monitoring Antimalaria Treatment (WANMAT)	WHO/governmental		Mauritania, Senegal, Gambia, Guinea, Guinee-Bissau, Liberia, CÃ´te d'Ivoire, Ghana, Mali, Burkina Faso, Niger, Nigeria, Benin, Togo, Ghana		2003-2009	NK
WorldWide Antimalarial Resistance Network (WWARN)	Academic, Data repository (Oxford, UK)	http://www.wwarn.org			2009-ongoing	Public, Corporate, Trust or Foundation (various)

2.3 HIV networks

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding
l'Agence nationale de recherches sur le sida et les hépatites virales (ANRS)	Academic	Human	http://www.hivfrenchresistance.org/	Burkina Faso, Cambodia, Cameroon, CÃ´te d'Ivoire, Senegal, Thailand, Viet Nam, Republic of Congo, Central African Republic, Chad		1992-ongoing	Public (ANRS)
Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)	Academic (University College, London)	Human	http://www.irsicaixa.es/en/fp7223131-collaborative-hiv-and-anti-hiv-drug-resistance-network-chain	Cameroon, Senegal	Netherlands, Greece, Denmark, Italy, Belgium, Spain, Portugal, Germany, Sweden, Switzerland, Slovenia, Russian Federation, United Kingdom	2009-2014	Public (EC)
HIV databases	Data repository, New Mexico, USA	Human	http://www.hiv.lanl.gov/content/index			1987-ongoing	Public (NIAID)
HIV drug resistance database	Data repository, California, USA	Human	http://hivdb.stanford.edu/			1997-ongoing	Public (NIAID),Corporate
Global HIV drug resistance network (HIV ResNet)	WHO/governmental	Human	http://www.who.int/hiv/topics/drugresistance/hivresnet/en/	China, Viet Nam, Thailand, India, Puerto Rico, Mexico, Brazil, Uganda, Kenya, Senegal, South Africa, CÃ´te d'Ivoire, Ethiopia, Cameroon, Mexico	Australia, United Kingdom, Spain, Netherlands, France, United States, Canada, Martinique	2007-ongoing	WHO
International Epidemiologic Databases to Evaluate AIDS	Academic, Data repository	Human	http://www.iedea.org/who-we-are	Brazil, Haiti, Honduras, Mexico, Peru, Cambodia, China, India, Indonesia, Malaysia, Philippines, Thailand, Viet Nam, Benin, Burkina Faso, CÃ´te d'Ivoire, Ghana, Guinea-Bissau, Mali, Nigeria, Senegal, Togo, Burundi, Cameroon, Congo, the Democratic Republic of the, Rwanda, Kenya, Tanzania, United Republic of, Uganda, Botswana, Lesotho, Malawi, Mozambique, South Africa,Zambia, Zimbabwe	Canada,United States, Argentina, Chile, Australia, Hong Kong, Japan, Singapore, Taiwan, Korea, Republic of,	2005	Trust or Foundation (The NICHD Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch, The National Cancer Institute (NCI), Office of HIV and AIDS Malignancy (OHAM))

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding	Funder name(s)
PharmAccess African Studies to Evaluate Resistance	Academic	Human	http://www.pharmaccess.org/RunScript.asp?Page=126&p=ASP%5CPg126.asp	Kenya, Nigeria, Uganda, South Africa, Zambia , Zimbabwe		2006	Trust or Foundation (The Dutch Ministry of Foreign Affairs in partnership with Stichting Aids Fonds, PharmAccess Foundation, TREAT Asia, International Civil Society Support)	The Dutch Ministry of Foreign Affairs in partnership with Stichting Aids Fonds, PharmAccess Foundation, TREAT Asia, International Civil Society Support
RegaDB : A Viral Data and Analysis Management Environment	Data repository	Human	http://rega.kuleuven.be/cev/regadb			2007	Public,Corporate	
Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) HIV Observational Database (TAHOD)	Academic, Data repository	Human	http://kirby.unsw.edu.au/projects/treat-asia-hiv-observational-database-tahod	Indonesia, Japan, Malaysia, Papua New Guinea, Philippines, Thailand	Korea, Republic of, Australia, Japan, Hong Kong, Taiwan, Singapore	2003-ongoing	Public (TREAT Asia, a program of amfAR, The Foundation for AIDS Research, US NIH)	TREAT Asia, a program of amfAR, The Foundation for AIDS Research, US NIH
TREAT Asia Pediatric HIV Observational Database (TApHOD)	Academic, Data repository	Human	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3106968/	Cambodia, India, Indonesia, Malaysia, Thailand, Viet Nam		2006-ongoing	Public (amfAR, the Australiian AIDS Life Association, US NIH)	amfAR, the Australiian AIDS Life Association, US NIH.
TREAT Asia Studies to Evaluate Resistance(TASER)	Academic	Human	http://kirby.unsw.edu.au/projects/treat-asia-studies-evaluating-resistance-taser	China, Indonesia, Malaysia, Philippines, Thailand	Korea, Republic of	2007-2011	Public, Trust or Foundation (The Dutch Ministry of Foreign Affairs in partnership with Stichting Aids Fonds, PharmAccess Foundation, TREAT Asia, International Civil Society Support)	The Dutch Ministry of Foreign Affairs in partnership with Stichting Aids Fonds, PharmAccess Foundation, TREAT Asia, International Civil Society Support
Tenofovir Resistance Study group	Academic	Human	http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(15)00536-8/abstract	Thailand, Uganda, Brazil, Kenya, Mexico, Malawi, South Africa, Zimbabwe, Swaziland, Nigeria	Argentina, Canada, United States, Luxembourg, France, Italy, Sweden, Belgium, Germany, Spain, Portugal, Netherlands, United States	2015-2016	Trust or Foundation (Wellcome Trust)	Wellcome Trust

2.4 Tuberculosis networks

NETWORK NAME (Acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding
Comprehensive Resistance Prediction for Tuberculosis International Consortium (CRyPTIC)	Academic	Human, all ages	No web link available (coordinated by University of Oxford)	Brazil, China, India, South Africa, Viet Nam	France, Germany, Italy, United Kingdom, United States	2015-ongoing	Trust or Foundation (BMGF)
East Africa Public Health Laboratory Networking Project (EAPHLNP)	WHO/governmental	Human, all ages	http://www.eac.int/~eacint/health/index.php?option=com_content&view=article&id=134&Itemid=167	Uganda, Tanzania, United Republic of, Rwanda, Kenya		2010-ongoing	Public World Bank)
Global TB Supranational Reference Laboratory Network (SRLN)	Other	Human, all ages	http://www.stoptb.org/wg/gli/srln.asp	Uganda, Pakistan, Egypt, India, Thailand, China, Mexico,Algeria, Benin, South Africa	Belgium, Italy, Germany, Sweden, Croatia, Latvia, Australia, Guadeloupe, Korea, Republic of, United States, Argentina, Chile, Portugal,Denmark, Japan, United Kingdom, Spain, Czech Republic	1994-ongoing	NK
TBDatabase (TBDB)	Data repository, Massachusetts, USA	Human, all ages	http://www.tbdb.org/			2008-ongoing	Trust or Foundation
Tuberculosis Drug Resistance Mutation Database (TBDReaMDB)	Data repository, Massachusetts, USA	Human, all ages	http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000002			2008-ongoing	Trust or Foundation (Ellison Foundation, Swedish Research Council)
WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance	WHO/governmental	Human	http://www.who.int/tb/publications/global_report/gtbr14_supplement_web_v3.pdf	Albania, Bangladesh, Belarus, Benin, Bolivia, Bosnia and Herzegovina, Botswana, Brunei Darussalam, Bulgaria, Cambodia, Central African Republic, China, Colombia, El Salvador, Fiji, Georgia, Indonesia, Jordan, Kazakhstan, Lebanon, Madagascar, Mexico, Mongolia, Marshall Islands, Mauritius, Montenegro, Mozambique, Myanmar, Namibia, Paraguay, Puerto Rico, Moldova, Republic of, Rwanda, Serbia, Sri Lanka, Swaziland, Tajikistan, Macedonia, the Former Yugoslav Republic of, Uganda	Andorra, Australia, Austria, Bahamas, Bahrain, Belgium, Bermuda, Brunei Darussalam, Canada, Hong Kong , Macao, Chile, Curaçao, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, French Polynesia, Germany, Greece, Guam, Hungary, Iceland, Ireland, Israel, Italy, Kuwait, Latvia, Lithuania, Luxembourg, Malta, New Zealand, Netherlands, Northern Mariana Islands, Norway, Oman, Palau, Poland, Portugal, Qatar, Russian Federation, Singapore, Slovakia, Slovenia, Sweden, Switzerland, United Kingdom, United States	1994-ongoing	WHO

2.5 Disease Surveillance networks

NETWORK NAME (Acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding
Armed Forces Health Surveillance Center, Global Emerging Infections Surveillance and Response System (AFHSC-GEIS)	Other	Human, all ages	Meyer et al. BMC Public Health 2011, 11(Suppl 2):S8 http://www.biomedcentral.com/1471-2458/11/S2/S8	Bhutan, Cambodia, Lao People's Democratic Republic, Nepal, Thailand, Cameroon, Kenya, Tanzania, United Republic of, Uganda, Benin, Burkina Faso, Cote d'Ivoire, Ghana, Liberia, Mali, Niger, Nigeria, Sierra Leone, Togo, Afghanistan, Egypt, Iraq, Pakistan, Sudan, Syrian Arab Republic, Philippines, Azerbaijan, Georgia, Mongolia, Romania, Colombia, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru	Japan, Korea, Republic of, Singapore, Jordan, Kuwait, Oman, Poland	1998-ongoing	Public (US Department of Defense)
WHO African Region Integrated Disease Surveillance Programme (AFRO IDSR)	WHO/governmental	Human, all ages	http://www.afro.who.int/en/clusters-a-programmes/dpc/integrated-disease-surveillance.html	Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cabo Verde, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Congo, the Democratic Republic of the, Equatorial Guinea, Ethiopia, Eritrea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, South Sudan, Swaziland, Togo, Uganda, Tanzania, United Republic of, Zambia, Zimbabwe		2002-ongoing	Public
Asia Partnership on Emerging Infectious Diseases Research (APEIR)	Academic	One Health	http://www.apeiresearch.net/new/main.php	Cambodia, China, Indonesia, Lao People's Democratic Republic, Thailand, Viet Nam		2006-ongoing	Public
BioCaster	DDD, Tokyo, Japan	One Health	http://bioinformatics.oxfordjournals.org/content/24/24/2940.full.pdf+html			2006- no longer active	Corporate (Japan Science and Technology Agency (JST); the Japan Society for the Promotion of Science (18049071); Research Organization of Information Systems (ROIS))
Connecting Organizations for Regional Disease Surveillance (CORDS)	Other	One Health	http://www.cordsnetwork.org/			2009-ongoing	Trust or Foundation (The Rockefeller Foundation, Skoll Global Threats Fund, Bill & Melinda Gates Foundation)
East African Integrated Disease Surveillance Network (EAIDSNet)	WHO/governmental	One Health	http://www.eac.int/health/index.php?option=com_content&view=article&id=68:eaidsnet-overview&catid=17:eaidsnet&Itemid=134	Burundi, Kenya, Rwanda, Uganda, Tanzania, United Republic of		2000-ongoing	Trust or Foundation (Rockerfeller Foundation)

NETWORK NAME (Acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding
The EpiSPIDER Project	DDD, USA	One Health	No web link available			2008-2011	Trust or Foundation (Oak Ridge Institute for Science Education, US Department of Energy)
Worldwide communication and data collection network for the surveillance of travel related morbidity (GeoSentinel)	Other	Human, all ages	http://www.istm.org/geosentinel	Thailand, Viet Nam, South Africa, Peru, Nepal		1995-ongoing	Public (CDC, International Society of Travel Medicine)
HealthMap Resistance Open	DDD, Boston, USA	One Health	http://www.healthmap.org/resistanceopen/			2006-ongoing	Public, Corporate, Trust or Foundation
Mekong Basin Disease Surveillance (MBDS)	WHO/governmental	One Health	http://www.mbdsnet.org/	Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand, Viet Nam		2001-ongoing	Public, Trust or Foundation
The Middle East Consortium on Infectious Disease Surveillance (MECIDS)	WHO/governmental	One Health	http://www.mecidsnetwork.org/	Jordan, Palestine	Israel	2003-ongoing	Other (donor)
Network of Aquaculture Centres in Asia-Pacific (NACA)	WHO/governmental	Fish	http://www.enaca.org/	Bangladesh, Cambodia, China, India, Indonesia, Iran, Islamic Republic of, Korea, Democratic People's Republic of, Lao People's Democratic Republic, Malaysia, Myanmar, Nepal, Pakistan, Philippines, Sri Lanka, Thailand, Viet Nam	Australia, Hong Kong, Maldives	1988-ongoing	Public
Network for Evaluation of One Health (NEOH)	Academic	One Health	http://neoh.onehealthglobal.net/	Bosnia and Herzegovina, Macedonia, the Former Yugoslav Republic of, Romania, Serbia, Tanzania, United Republic of	Australia, Belgium, Croatia, France, Germany, Italy, Ireland, New Zealand, Netherlands, Poland, Portugal, Sweden, Spain, Switzerland, United Kingdom	2014-ongoing	Public (European Cooperation in Science & Technology)
One Health Central and Eastern Africa (OHCEA)	Academic	One Health	http://ohcea.org/	Ethiopia, Congo, the Democratic Republic of the, Kenya, Rwanda, Tanzania, United Republic of, Uganda		2010-ongoing	Public (USAID)
One Health Global Network (OHGN)	Academic	One Health	http://www.onehealthglobal.net/introduction/			2011-ongoing	Other (Voluntary support)

NETWORK NAME (Acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding
World Organisation for Animal Health (OIE) network of reference centres	WHO/governmental	Aquatic animals	http://www.oie.int/en/our-scientific-expertise/overview/	Afghanistan, Albania, Algeria, Angola, Armenia, Azerbaijan, Bangladesh, Belarus, Belize, Benin, Bhutan, Bosnia & Herzegovina, Botswana, Brazil, Bulgaria, Burkina Faso, Burundi, Cabo Verde, Cambodia, Cameroon, Central African Republic, Chad, China, Colombia, Comoros, Costa Rica, Cote d'Ivoire, Cuba, Democratic People's Republic of the Congo, Republic of Congo, Djibouti, Dominican Republic, Ecuador, Egypt, Equatorial Guinea, Eritrea, El Salvador, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Guatemala, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Iran, Islamic Republic of, Iraq, Jamaica, Jordan, Kazakhstan, Kenya, Korea, Democratic People's Republic of, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Lesotho, Liberia, Libya, Macedonia, the Former Yugoslav Republic of, Madagascar, Malawi, Malaysia, Maldives, Mali, Mauritania, Mauritius, Mexico, Micronesia, Federated States of, Moldova, Republic of, Mongolia, Montenegro, Morocco, Myanmar, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Panama, Papua New	Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belgium, Brunei Darussalam, Canada, Chile, Hong Kong, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Caledonia, New Zealand, Norway, Oman, Poland, Portugal, Qatar, Korea, Republic of, Russian Federation, San Marino, Saudi Arabia, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Trinidad and Tobago, United Kingdom, United Arab Emirates,United States, Uruguay, Venezuela	1987-ongoing	NK
Pacific Public Health Surveillance Network	WHO/governmental	Human	http://www.pphsn.net/index.htm	American Samoa, Micronesia, Federated States of, Fiji, Papua New Guinea, Kiribati, Samoa, Solomon Islands, Vanuatu	Cook Islands, French Polynesia, Guam, Marshall Islands, New Caledonia, Northern Mariana Islands, Nauru, Niue, Palau, Pitcairn, Tokelau, Tonga, Tuvalu, Wallis and Futuna	1996	Public
Program for Monitoring Emerging Diseases	DDD, Boston, USA	One Health	http://www.promedmail.org/			1994	Public, Corporate, Trust or Foundation (Wellcome Trust, Skoll Global Threats Fund, Google.org, the Gates Foundation, the Rockefeller Foundation, the Oracle Corporation, the Nuclear Threat Initiative)
The Southern African Centre for Infectious Disease Surveillance (SACIDS)	WHO/governmental	One Health	http://www.sacids.org/oweb/sacids/home	South Africa, Congo, the Democratic Republic of the , Mozambique, South Africa, Zambia, Tanzania, United Republic of		2008-ongoing	Public, Corporate, Trust or Foundation
Southeast European Center For Surveillance And Control Of Infectious Disease (SECID)	WHO/governmental	One Health	https://www.secids.com/	Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Romania, Serbia, Montenegro, Macedonia, the Former Yugoslav Republic of	Israel	2013-ongoing	Public (various e.g CORDS, WHO, CDC, UNFPA)

NETWORK NAME (acronym)	Type	Population	Link	LMIC(s) covered)	HICs	Duration	Funding
ARTEMIS Global Antifungal Surveillance Program (ARTEMIS)	Pharma/CRO	Human, all ages, hospitalised patients	http://jcm.asm.org/cgi/pmidlookup?view=long&pmid=17442797	Brazil, China, Colombia, Ecuador, India, Malaysia, Mexico, South Africa, Turkey	Argentina, Australia, Belgium, Canada, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Portugal, Russian Federation, Saudi Arabia, Slovak Republic, Korea, Republic of, Spain, Switzerland, Taiwan, United Kingdom, United States, Venezuela	1997-2005	Corporate (Pfizer, Astellas, Merck)
Medecins sans Frontieres/Epicentre (MSF)	NGO	Human	http://www.epicentre.msf.org/e	Congo, the Democratic Republic of the, Myanmar, Uganda, Guinea, Colombia, Angola, Sierra Leone, Mali, Chad, Zambia, Sudan, Liberia, Lao People's Democratic Republic			Public and private donors
Programme Against African Trypanosomiasis (PAAT)	WHO/governmental	Animal	http://www.fao.org/ag/againfo/programmes/en/paat/home.html	Congo, the Democratic Republic of the, Central African Republic, Angola, Burkina Faso, Cameroon, Chad, Congo, Cote d'Ivoire, Gabon, Guinea, Malawi, South Sudan, Uganda, Tanzania, United Republic of, Zambia, Zimbabwe		1999-ongoing	Public, Corporate, Trust or Foundation (various)
South East Asia Infectious Disease Clinical Research Network (SEAICRN)	Academic	Human, all ages	http://www.seaicrn.org/Infobox.aspx?pageID=1	Thailand, Viet Nam, Indonesia		2005-ongoing	Public, Trust or Foundation (NIAID, Wellcome Trust)
World Animal Health Information System (WAHIS)	Data repository, Geneva	Animal	http://www.oie.int/wahis_2/public/index.php/home			2004-ongoing	Public
WHO's Global Influenza Surveillance and Response System (GISRS)	WHO/governmental	Human, all ages	http://www.who.int/influenza/gisrs_laboratory/antiviral_susceptibility/en/	Afghanistan,Albania, Algeria, Bangladesh, Belarus, Brazil, Bulgaria, Cameroon, Central African Republic, China, Colombia, Costa Rica, Cote d'Ivoire, Cuba, Korea, Democratic People's Republic of, Ecuador, Egypt, El Salvador, Fiji, Georgia, Ghana, Guatemala, Honduras, India, Indonesia, Iran, Islamic Republic of, Iraq, Jamaica, Jordan, Kazakhstan, Kenya,Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Madagascar, Malaysia, Mauritius, Mexico, Mongolia, Morocco, Myanmar, Nepal, Nicaragua, Nigeria, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Moldova, Republic of, Romania, Senegal, Serbia, South Africa, Sri Lanka, Sudan, Syrian Arab Republic, Thailand, Tunisia, Turkey, Uganda, Ukraine, Tanzania, United Republic of, Viet Nam, Zambia	Argentina, Australia, Austria, Bahrain, Belgium, Canada, Chile, Hong Kong, Croatia, Czech Republic, Denmark,Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kuwait, Latvia, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Oman, Poland, Portugal, Qatar, Korea, Republic of, Russian Federation, Slovakia, Slovenia, Spain, Sweden, Switzerland, Trinidad and Tobago, United Kingdom, United States, Uruguay, Venezuela	1947-ongoing	WHO
WHO global insecticide resistance database	Data repository, Geneva	Mosquito	http://www.who.int/malaria/areas/vector_control/insecticide_resistance_database/en/	Equatorial Guinea, Eritrea, Mozambique, Rwanda, South Africa, Tanzania, United Republic of, Zambia		2014-ongoing	WHO
Worldwide Insecticide Resistance Network (WIN)	Academic	Insects	https://win-network.ird.fr/	Iran, Islamic Republic of, Thailand, India, Brazil, Mali, Guiana	France, Greece, Portugal, United Kingdom, Singapore, United States	2016-ongoing	Public (IRD)

Appendix 3 Functioning of current networks

The tables below include networks which are still current and summarises them in terms of evidence of activity (publication of up-to-date AMR data, or any other activity e.g. meetings), data-sharing model, proficiency testing or EQA programme in LMIC laboratories.

Network acronym /short name	Network name	Network type	N countries	N LMICs	AMR Data report/publication in the last 3 years	Isolates reported were collected within last 3y	Evidence of any activity in last year, e.g. meeting report, news item, update on website	Data-sharing model	PT/EQA programme for network labs
	African-German StaphNet consortium	Academic	4	3	Yes	Yes	Yes	Unclear/ Shared	Unclear
AMI	Amazon Malaria Initiative	WHO/ governmental	12	11	Yes	Yes	Yes	Unclear/ Shared	Unclear
RAVREDA	Amazon Network for the Surveillance of Antimalarial Drug Resistance	WHO/ governmental	13	12	No	No	Yes	Unclear/ Shared	Unclear
AFHSC-GEIS	Armed Forces Health Surveillance Center, Global Emerging Infections Surveillance and Response System	Other	47	39	No	No	Yes	Closed	Unclear
APEIR	Asia Partnership on Emerging Infectious Diseases Research	Academic	6	6	No	No	No	Unclear/ Shared	NA
ANSORP	Asian Network for Surveillance of Resistant Pathogens	Academic	14	8	Yes	No	Yes	Unclear/ Shared	Unclear
APMEN	Asia-Pacific Malaria Elimination Network	WHO/ governmental	18	17	No	No	Yes	Unclear/ Shared	NA
AWARE	Assessing Worldwide Antimicrobial Resistance and Evaluation Program	Pharma/CRO	7	3	Yes	Yes	Yes	Closed	No
BIRDY	Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries: an international cohort study	Academic	3	3	Yes	Yes	Yes	Unclear/ Shared	Unclear
BBINS Malaria Drug resistance Network	BBINS Malaria Drug resistance Network	WHO/ governmental	5	5	Yes	Yes	Yes	Unclear/ Shared	Unclear
CARPHA	Caribbean Public Health Agency	WHO/ governmental	25	10	Unclear	Unclear	Unclear	Unclear/ Shared	Unclear
CDDEP	Centre for Disease Dynamics, Economics and Policy/ResistanceMap	Academic, Data repository	0	0	Yes	Yes	Yes	Shared	NA
CRyPTIC	Comprehensive Resistance Prediction for Tuberculosis International Consortium	Academic	10	5	No	No	Yes	Open	Unclear
CORDS	Connecting Organizations for Regional Disease Surveillance	Other	0	0	No	No	Yes	NA	NA
EAPHLNP	East Africa Public Health Laboratory Networking Project	WHO/ governmental	4	4	No	No	Yes	Unclear/ Shared	Yes
EAIDSNet	East African Integrated Disease Surveillance Network	WHO/ governmental	5	5	No	No	No	Unclear/ Shared	NA
EARS-NET	European Antimicrobial Resistance Surveillance Network	WHO/ governmental	29	2	Yes	Yes	Yes	Open to participating countries	Yes
FWDNet	Food- and waterborne diseases and zoonoses Network	WHO/ governmental	29	2	Yes	Yes	Yes	Unclear/ Shared	Unclear
GARP	Global Antibiotic Resistance Partnership	Academic	8	8	NA	NA	Yes	NA	NA
GABRIEL	Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries	Academic	14	13	Yes	Yes	Yes	Unclear/ Shared	Yes

Network acronym /short name	Network name	Network type	N countries	N LMICs	AMR Data report/publication in the last 3 years	Isolates reported were collected within last 3y	Evidence of any activity in last year, e.g. meeting report, news item, update on website	Data-sharing model	PT/EQA programme for network labs
CDC GHSA Action Package Prevent-1	Global Health Security Agenda Antimicrobial Resistance Action Package	Other	15	2	No	No	Yes	Unclear/ Shared	Unclear
HIVResNet	Global HIV drug resistance network	WHO/ governmental	23	15	No	No	Yes	Unclear/ Shared	Yes
GMS TES	Greater Mekong Sub-region Therapeutic Efficacy Studies (TES) network	WHO/ governmental	8	8	Yes	Yes	Yes	Unclear/ Shared	Unclear
HealthMap Resistance Open	HealthMap Resistance Open	DDD	2	1	Yes	Yes	Yes	Shared	NA
HANMAT	Horn of Africa Network for Monitoring Antimalarial Treatment	WHO/ governmental	6	5	No	No	No	Unclear/ Shared	Unclear
IeDEA	International Epidemiologic Databases to Evaluate AIDS	Academic, Data repository	47	36	Yes	Yes	Yes	Shared	Unclear
INICC	International Nosocomial Infection Control Consortium	Academic	43	32	Yes	No	Yes	Shared	No
ANRS	l'Agence nationale de recherches sur le sida et les hépatites virales	Academic	10	10	Yes	No	Yes	Unclear/ Shared	Unclear
MalariaGEN	MalariaGEN Genomic Epidemiology Network	Academic	29	29	Yes	Yes	Yes	Shared	NA
MSF	Medecins sans Frontieres/Epicentre	Other	13	13	Yes	Yes	Yes	Unclear/ Shared	Unclear
MBDS	Mekong Basin Disease Surveillance	WHO/ governmental	6	6	No	No	Yes	Unclear/ Shared	Yes
NEOH	Network for Evaluation of One Health	Academic	20	5	No	No	Yes	NA	NA
NACA	Network of Aquaculture Centres in Asia-Pacific	WHO/ governmental	19	16	No	No	Yes	Unclear/ Shared	No
OHCEA	One Health Central and Eastern Africa	Academic	6	6	No	No	Yes	Unclear/ Shared	NA
OHGN	One Health Global Network	Academic	0	0	No	No	Yes	NA	NA
	Pacific Malaria Drug Resistance Monitoring Network	WHO/ governmental	8	7	Yes	Yes	Yes	Unclear/ Shared	Unclear
PPHSN	Pacific Public Health Surveillance Network	WHO/ governmental	22	8	No	No	Yes	Unclear/ Shared	Unclear
PIAM-net	Pakistan-Iran-Afghanistan Malaria Network	WHO/ governmental	3	3	No	No	Yes	Unclear/ Shared	Unclear
PASER	PharmAccess African Studies to Evaluate Resistance	Academic	6	6	Yes	No	Yes	Unclear	Unclear
PDNA	Plasmodium Diversity Network Africa	Academic	15	15	Yes	Yes	Yes	Shared	NA
ProMED mail	Program for Monitoring Emerging Diseases	DDD	0	0	Yes	NA	Yes	NA	NA
PAAT	Programme Against African Trypanosomiasis	WHO/ governmental	16	16	No	No	No	Unclear/ Shared	No
	PulseNet International	WHO/ governmental	80	36	No	No	Yes	Shared	Regional schemes
ReLAVRA	Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos	WHO/ governmental	19	15	No	No	Yes	Unclear/ Shared	Yes
SENTRY	SENTRY Antimicrobial Surveillance program	Pharma/CRO	40	8	Yes	Yes	Yes	Closed	No

Network acronym /short name	Network name	Network type	N countries	N LMICs	AMR Data report/publication in the last 3 years	Isolates reported were collected within last 3y	Evidence of any activity in last year, e.g. meeting report, news item, update on website	Data-sharing model	PT/EQA programme for network labs
SIREVA & SIREVA II	Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas: SIREVA 1993, became SIREVA II in 2004,	WHO/ governmental	19	15	No	No	No	Unclear/ Shared	Yes
SANMAT	South African Network for the Monitoring of Antimalarial drug resistance	WHO/ governmental	7	7	No	No	No	Unclear/ Shared	Unclear
SEAICRN	South East Asia Infectious Disease Clinical Research Network	Academic	4	3	No	No	Yes	Unclear/ Shared	Unclear
SECID	Southeast European Center For Surveillance And Control Of Infectious Disease	WHO/ governmental	9	8	No	No	Yes	Unclear/ Shared	NA
SOAR	Survey of Antibiotic Resistance	Pharma/CRO	48	34	Yes	Yes	Yes	Closed	Unclear
CAESAR	The Central Asian and Eastern European Surveillance of Antimicrobial Resistance	WHO/ governmental	20	17	Yes	Yes	Yes	Unclear/ Shared	Yes
Global-PPS	The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance	Academic	63	24	Yes	Yes	Yes	Unclear/ Shared	No
GASP	The Gonococcal Antimicrobial Surveillance Programme	WHO/ governmental	70	32	Yes	No	No	Unclear/ Shared	Yes
MECIDS	The Middle East Consortium on Infectious Disease Surveillance	WHO/ governmental	3	2	No	No	No	Unclear/ Shared	NA
SACIDS	The Southern African Centre for Infectious Disease Surveillance	WHO/ governmental	6	6	No	No	Yes	Unclear/ Shared	NA
TSAP	The Typhoid Fever Surveillance in Africa Program	Academic	10	10	Yes	Yes	Yes	Unclear/ Shared	Unclear (IQA only)
TAHOD	Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) HIV Observational Database	Academic, Data repository	12	6	Yes	Yes	Yes	Shared	Unclear
TRAC	Tracking Resistance to Artemisinin Collaboration	Academic	10	10	Yes	Yes	Yes	Unclear/ Shared	Yes
TApHOD	TREAT Asia Pediatric HIV Observational Database	Academic, Data repository	6	6	No	No	Yes	Shared	Unclear
TASER	TREAT Asia Studies to Evaluate Resistance	Academic	6	5	Yes	No	Yes	Shared	Unclear
AFRO IDSR	WHO African Region Integrated Disease Surveillance Programme	WHO/ governmental	47	47	No	No	Yes	Unclear/ Shared	NA
GFN	WHO Global Foodborne Infections Network	WHO/ governmental	177	104			Yes	Shared	Yes
	WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance	WHO/ governmental	89	39	Yes	Yes	Yes	Open	Yes
WHO GISRS	WHO's Global Influenza Surveillance and Response System	WHO/ governmental	113	67	Yes	Yes	Yes	Open	Yes
OIE network	World Organisation for Animal Health network of reference centres	WHO/ governmental	180	121	No	No	Yes	NA	Unclear
WWARN	WorldWide Antimalarial Resistance Network	Academic, Data repository	0	0	Yes	Yes	Yes	Shared	NA
GeoSentinel	Worldwide communication and data collection network for the surveillance of travel related morbidity	Other	5	5	No	No	Yes	Shared	NA
WIN	Worldwide Insecticide Resistance Network	Academic	12	6	No	NA	Yes	Unclear	Unclear
ZAAPS	Zyvox Annual Appraisal of Potency and Spectrum	Pharma/CRO	42	12	Yes	Yes	Yes	Closed	No

Appendix 4 AMR surveillance networks in Latin America and the Caribbean- a case study

The Latin American and Caribbean (LAC) countries vary greatly in terms of their level of development and epidemiological profiles. Despite great improvement in the region of some basic health indicators in recent decades, the overall public health situation is deficient and outdated in most countries [163]. Slow progress is due in part to unevenly distributed resources within and between LAC countries, which include human resources and training, deficient information systems, weak institutional and organisational capacity, inadequate health technologies, and insufficient financial resources. In several LAC countries, many communities lack access to essential public health services.

The Pan American Health Organisation (PAHO) is a WHO regional office for the Americas created in 1902 as a specialised international health agency for the Americas to engage in technical cooperation with its member countries to fight communicable and non-communicable diseases (NCDs) and their causes, to strengthen health systems, and to respond to emergencies and disasters. It currently has about 50 member countries and territories, and works in setting regional health priorities, often as a coordinating and funding entity of regional public health networks in different regions in the Americas. It is divided in sub-regions including the Caribbean (Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Bermuda, British Virgin Islands, Cayman Islands, Commonwealth of Dominica, Dominican Republic, French Guiana, Grenada, Guadeloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Netherland Antilles (Curaçao, Saba, St. Eustatius, St. Maarten, Nevis, Saint Lucia, St. Kitts, St. Vincent and The Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos, and the U.S. Virgin Islands), Central America (Belize, Costa Rica, El Paso, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama) and South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, and Venezuela). According to the United Nations classification of 2015, with the exception of Canada, USA, Antigua & Barbuda, Argentina, Aruba, The Bahamas, Cayman Islands, Chile, Curacao, Uruguay, Venezuela, Virgin Islands, Barbados, St Kitts & Nevis, St Maarten, Turks & Caicos, and Trinidad and Tobago, considered high-income countries, all other PAHO members are LMICs.

In addition to ongoing serious epidemics of dengue and chikungunya viruses, currently Latin America is also facing an alarming situation regarding Zika virus. On February first 2016, WHO declared the cluster of microcephaly cases and other neurological disorders related to ZIka a «public health emergency of international concern». In May 2015, PAHO issued an alert regarding the first confirmed Zika virus infections in northeastern Brazil. Currently, outbreaks are occurring in many countries and territories in the Americas. WHO's Regional Office for the Americas (AMRO/PAHO) has been working closely with affected countries since May 2015 including partner specialists that were deployed to help health ministries detect and track the virus, contain its spread, advise on clinical management of Zika and investigate the spikes in microcephaly and Guillain-Barré syndrome in areas where Zika outbreaks have occurred.

The recent emergence and spread of multi-resistant pathogens have jeopardised infectious disease control in the Americas. Antimicrobial resistance (AMR) is the focus of several networks in the region that work on surveillance of infections at national and regional levels. In particular, the rise in the

number of carbapenemase-producing organisms is a serious problem regionally. These resistant microorganisms have already been identified in Argentina, Barbados, Brazil, Colombia, Nicaragua, Panama, Uruguay, and Venezuela. Outbreaks of infections by carbapenem resistant *Klebsiella pneumoniae* have caused increased mortality. Several neonatal outbreaks have taken place in the region, many of them caused by multi-resistant bacteria in 2013 especially in the English-speaking Caribbean countries [164]. A retrospective observational, analytical, multicentre study was conducted in Colombia to compare the frequency of bacterial resistance phenotypes in isolates from patients in intensive care units (ICU) and other (non-ICU) high-complexity public and private hospital services (n=79 hospitals) from January 2007 to December 2009 [165]. Increased percentages of vancomycin-resistant *Enterococcus faecium*, imipenem-resistant *Klebsiella pneumoniae*, ciprofloxacin-resistant *K. pneumoniae*, ceftazidime-resistant *Escherichia coli* and cefotaxime-resistant *Enterobacter cloacae* ($\rho = 1$, $P < 0.01$) were found over time.

Most countries of the Americas have reported cases of MDR-TB, and a few countries have also reported extensively drug resistant (XDR) TB cases. Laboratory services are a major component of surveillance efforts, with a network of laboratories working in coordination and sharing information. Since 2004, surveillance of resistant TB was based on national and subnational surveys and sentinel surveillance. It was hoped that from 2015 it would be primarily based on routine surveillance but this has not been realised yet. There is limited capacity of laboratory services to conduct first- and second-line drug sensitivity tests, due in great part to slow implementation of new diagnostic technologies which are unevenly spread throughout the region. There are also problems related to funding and the development of laboratory information systems.

Here we review AMR surveillance networks in Latin America and the Caribbean. A common theme is the presence of an outside coordinating entity, usually PAHO, that sets up the network initially by contacting countries and funding some activities including external quality assessment (EQA). In some instances there is participation of other US agencies such as USAID. The networks are then featured on the PAHO website, with reports and publications in Spanish and a few in English. These networks use WHONET software and follow standards from the Clinical and Laboratory Standards Institute (CLSI). Independent regional and national surveillance networks have their own websites, with all information and reports in Spanish. Most networks started operating after 2000.

ReLAVRA, a regional network for antimicrobial resistance surveillance in Latin America

The “Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos” (ReLAVRA), created, funded and coordinated by the Pan American Health Organisation (PAHO) or in Spanish Organización Panamericana de la Salud (OPS), is a Latin American regional surveillance system operating since 1996 based on standardised principles and horizontal cooperation between participant countries. Initially established to strengthen capacity for antibiotic susceptibility testing, it uses WHONET software [166] for management and analysis of antimicrobial susceptibility tests as a tool for data collection. Surveillance was first focused on enteric pathogens only: *Salmonella* spp., *Shigella* spp. and *Vibrio cholerae*. Starting in 2000, additional species of pathogens from infections acquired either in the

community or at the hospital were included. Selection of these pathogens to monitor has been a key task of the network. As of 2013, nosocomial bacteria under surveillance were *Enterococcus spp*., *Klebsiella pneumoniae, Acinetobacter spp., Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, and Enterobacter* spp.. Community pathogens include *Salmonella* spp*., Shigella* spp*., Vibrio cholerae, Escherichia coli, Neisseria meningitidis, Neisseria gonorrhoeae, Streptococcus pneumoniae, Haemophilus influenzae, Campylobacter* spp*.,* β -haemolytic *Streptococci*, and *Staphylococcus aureus*.

ReLAVRA interacts with other surveillance systems in Latin America, including SIREVA (Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas) that focuses specifically on pneumonia and meningitis surveillance (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*), the Global Food Network (GFN) that performs surveillance on *Salmonella* spp., *Shigella* spp., *Campylobacter* spp. and *V. cholerae*, and since 2010, the IAAS (Infecciones Asociadas a la Atención en Salud) in 10 countries in the region. SIREVA was created earlier than ReLAVRA by PAHO in 1993 and included 6 countries in the region for surveillance of *S. pneumoniae* in children under 6 years of age. SIREVA was followed by SIREVA II in 2004, when the network incorporated *H. influenzae* and *N. meningitides* surveillance in the same age group. SIREVA II currently includes 19 countries in Latin America.

Nineteen countries currently participate in the ReLAVRA network: Argentina, Bolivia, Brazil, Colombia, Chile, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Uruguay, Venezuela. Argentina plays a crucial role among ReLAVRA participating countries, serving as a reference centre for protocols, training and manuals, as well as the regional laboratory for quality assessment coordinated by PAHO/OPS. The Caribbean Epidemiology Centre (CAREC) which included Trinidad & Tobago, used to participate in some ReLAVRA activities. CAREC became the Caribbean Public Health Agency (CARPHA- see below "The Caribbean" section) in 2013 and there is no current link between the Caribbean states in this network and ReLAVRA, although there was a subsequent attempt to coordinate a joint effort between the Argentinian reference laboratory, PAHO and CARPHA.

Interested countries can apply to join the network after committing to having a **national reference centre** (usually the **coordinating centre**) for sentinel laboratories across the country. This can be a private laboratory if there is no public laboratory capable of fulfilling this role (e.g. Ecuador used a private laboratory for 10 years). This centre has the following functions:

- To organise and coordinate the surveillance programme for susceptibility testing of pathogens of public health importance.
- To serve as a reference laboratory for the national participating laboratories. This includes implementation of QA (internal, external, monitoring and evaluation (M&E)) to guarantee quality of diagnosis and AMR evaluation. Guidelines are issued to ensure these are conducted, and distribution of the American Type Culture Collection (ATCC) reference strains for quality control of antibiograms and evaluating programmes of participating laboratories at national level.

- To standardise methods for diagnosis, serotyping, and antimicrobial susceptibility testing.
- Capacity building: providing training to professionals and technicians of participating institutions
- To organise and maintain a reference strain collection.
- To periodically consolidate the information provided by sentinel institutions, as well as to analyse it and disseminate it.

The **sentinel institutions** in each country commit to the following activities:

- Periodic control and maintenance of equipment
- Compliance with biosafety regulations
- Adherence to quality control guidelines of the Clinical and Laboratory Standards Institute (CLSI), for antibiograms by the Kirby Bauer method, including use of ATCC strains
- Dissemination of findings

An external quality control programme was implemented in 2000 called "Programa Latinoamericano de Control de Calidad en Bacteriología y Resistencia a los Antimicrobianos" (LA-EQAS), with 17 laboratories from 16 countries in the region, coordinated by the "Servicio de Antimicrobianos del Instituto Nacional de Enfermedades Infecciosas" based at INEI-ANLIS "Dr. Carlos G. Malbrán" in Buenos Aires, Argentina (countries in this QA programme and year they joined are shown in Figure 1).

Figure 1. LA-EQAS programme

This coordinating laboratory is also the reference laboratory for antimicrobial susceptibility tests. The 17 national reference laboratories participating in LA-EQAS were evaluated in their ability to detect emerging antimicrobial resistance from three bacterial isolates including resistance of enteric bacteria to carbapenems due to the presence of *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-beta-lactamase (MBL) type IMP, and intermediate resistance of *Staphylococcus aureus* isolates to vancomycin (vancomycin intermediate resistant *S. aureus*—VISA) with results published in 2011 [167]. Interpretation of sensitivity tests, detection of the resistance mechanism, and assessment of either inhibition halo size (disk diffusion method) or minimum inhibitory concentration (MIC) were evaluated, resulting in concordance in the detection of resistance mechanisms of 76.4%, 73.3%, and 66.7% for the *K. pneumoniae* PAHO-161, *E. cloacae* PAHO-166, and *S. aureus* PAHO-165 strains, respectively. Concordance between the

inhibition areas observed by the participating laboratories and the reference laboratory was around 90% [168].

The 2008 annual report from ReLAVRA stated that annual external QA (EQA) of coordinating laboratories at national level (reference centres) is handled by the National Laboratory for Enteric Pathogens (NLEP) in Canada and the "Instituto Nacional de Enfermedades Infecciosas" (ANLIS) in Argentina. These two laboratories conduct EQA; NLEP for enteric pathogens, send unknown samples of *Salmonella*, *Shigella* and *Vibrio cholerae*, and ANLIS sends a panel of 10 enteric and non-enteric unknown strains to the national reference laboratories in ReLAVRA countries. The EQA results were included in the annual ReLAVRA reports available until 2010 (see below). The Argentina-led EQA programme reported a response time of 30 days. The mean response time for participating countries was 34 days (range 16-47 days), much longer than the recommended <15 days for international programs. The recommended time for domestic EQA programs is 10 days, but no data are available for national quality control programs of ReLAVRA countries [164].

The national reference laboratories as well as the sentinel laboratories do not receive funding for their ReLAVRA-specific activities, as they function in their national capacities as they were all along before joining ReLAVRA. The activities related to EQA led by Argentina and coordinated by PAHO are covered by PAHO including mailing of strain panels as well as the time spent by personnel working on EQA in Argentina. Countries cover expenses related to EQA conducted once the strains reach their laboratories. PAHO also provides funding for some of the regional training and traveling related to ReLAVRA that is usually performed by the Argentina INEI-ANLIS team that works with ReLAVRA, led by Drs. Alejandra Corso and Fernando Pasteran.

Scientific publications in peer-reviewed journals of participating laboratories on important drug-resistant microorganisms' prevalence, resistance mechanisms and markers of resistance are evidence of effective collaboration and capacity building at national level in participating countries' laboratories that apply ReLAVRA algorithms for detection of emerging AMR. For example, in 2014 emergence of unrelated NDM1 producing *Acinetobacter pittii* strains in Paraguay was reported from isolates of two patients (both children) that had died in 2012 and who had no history of traveling [169]. Following a ReLAVRA algorithm, the National Health Laboratory of Paraguay confirmed an MBL phenotype in two *Acinetobacter* spp. isolates recovered from a single hospital, a phenotype not previously observed in *Acinetobacter* spp. from Paraguay. The strains were further submitted to the regional reference laboratory and were identified as *A. pittii* by MALDI-TOF. Antimicrobial susceptibility testing revealed a similar resistance profile in both isolates, except for ampicillin/sulbactam and quinolones. Presence of MBLs was suggested based on phenotypic testing (EDTA-based assay).

ReLAVRA published annual reports in Spanish from 2000 until 2010 which are available for download at the PAHO website [170, 171]. There have been no reports published on the website since 2010 (based on 2009 data). The following three years' reports are in preparation and will be published soon in Spanish in a special issue of the Brazilian Journal of Tropical Pathology. SIREVA II annual reports are also available in Spanish from PAHO from 2000 until 2012 [172].

The ReLAVRA annual reports include first a summary of important AMR emerging in the region. This regional section is followed with a per-country detailed report including results for:

1) QA for that year at national level: strains sent, correct diagnosis (genus and species), inhibition halo size, interpretation of results (sensitive or resistant) and error grade (minor, grave or very grave)

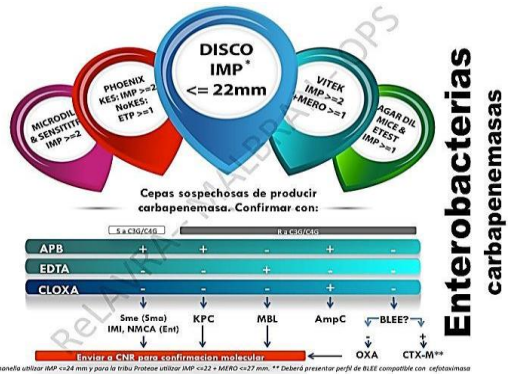
2) Pathogens found, reported in two categories: community- or hospital-acquired, per pathogen genus and serotype with either intermediate or complete resistance per antibiotic. In some cases, AMR is presented per age group, usually for <6, and ≥6 years of age.

After the sections with the data from participating countries, EQA results for the whole region by NLEP (Canada) and INEI (Argentina) are presented (concordance). The annual ReLAVRA reports end with conclusions and recommendations.

Both ReLAVRA and SIREVA contributed to the 2014 WHO "Antimicrobial resistance- global report on surveillance" [38]. The Global Antimicrobial Resistance Surveillance System (GLASS), manual for early implementation of global AMR surveillance acknowledged valuable insight from ReLAVRA into the practical applicability of the manual from a user's perspective [28].

On the PAHO website under SIREVA, two manuals can be also downloaded with procedures for: 1) diagnosis of bacterial pneumonia and meningitis and characterisation of *Streptococcus pneumoniae* and *Haemophilus influenzae* strains (2012), and 2) Laboratory diagnosis of bacterial meningitis caused by *Neisseria meningitidis* (2011). [38].

PAHO supports Spanish translation and dissemination of CLSI standards and other documents to all countries in the network. Translation of 2012 standards (M02-A11, M-100 and M07 A9) was completed and a license agreement allowed distribution of PDF copies to Argentina, Bolivia, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela [164]. Health ministries of several ReLAVRA participating countries issue protocols and methods to assess both AMR of strains as well as quality assurance, many of them based on ReLAVRA and SIREVA guidelines. The Peruvian NIH in 2014 published a protocol for detection of KPC in enterobacteria [173] including an algorithm from ReLAVRA with INEI-ANLIS as the source of the protocol which is shown in Figure 2 below.



IMP: imipenem.
ETP: Ertapenem
MERO: Meropenem
APB: ácido 3 aminofenil borónico.
OXA/CLOXA: oxacilina o cloxacilina según este disponible.

Fuente:
Servicio Antimicrobianos, Instituto Nacional de Enfermedades Infecciosas, INEIANLIS "Dr. Carlos G. Malbrán"

Figure 2 Carbapenemase search consensus protocol/algorithm from ReLAVRA

SAIDI, a short-lived South-American network

SAIDI (South American Infectious Diseases Initiative) started working in 2003 when USAID announced its support for an initiative to address antimicrobial resistance (AMR, including MDR-TB) in Peru, Paraguay, and Bolivia, bringing together USAID-funded international partners previously working on AMR and attempting a "holistic" response involving all stakeholders. SAIDI worked within existing structures to build on in-country efforts to prevent and contain AMR by creating new sets of community-focused activities that worked with all involved groups (patients, health care providers, and organisations working on AMR) at all levels of society in a variety of ways. Formal work plans and strategies were developed in collaboration with key national partners. International partners contributing to SAIDI were PAHO, the U.S. CDC, the Alliance for the Prudent Use of Antibiotics, the Rational Pharmaceutical Management Plus Programme of Management Sciences for Health, the U.S. Pharmacopeia Drug Quality and Information Program, and Links Media.

The effort, which lasted until approximately 2009, provided technical assistance in the areas of infection prevention and control, medicine quality, pharmaceutical management, education for health professionals, and behaviour change communication through a multifaceted, multidisciplinary, and systemic approach. The strategy was initially viewed as a progression through 6 components:

- **Component 1:** preparation: donors and international partners discuss general objectives, select countries for intervention, gather evidence on local problems related to AMR
- **Component 2:** Situational analysis (donor USAID and international partners conduct diagnostic studies to gather additional evidence to identify local needs in target countries)
- **Component 3:** Plan formulation based on evidence with stakeholders, international and national partners
- **Component 4:** Cross-sector implementation of action plan; monitoring and evaluation plan
- **Component 5:** Monitoring and evaluation, dissemination of results and lessons learned
- **Component 6:** Sustainment (post-SAIDI) to control spread of AMR

For SAIDI in Bolivia, Paraguay, and Peru, it took four years from Component 1 through Component 4. In 2010 USAID published a draft report on the SAIDI approach in these three countries presenting local improvements and accomplishments [174] including implementation of South-South collaboration between participant countries and strengthening of epidemiological surveillance by MOHs. It was found that success in each country was directly related to jointly establishing clearly defined goals, roles, and responsibilities (particularly related to project leadership) at the start of the initiative. SAIDI partners created individualised interventions in each of the participating countries based on local contexts. This flexibility was important when working with local partners to develop the framework of what should be achieved and activity work plans. SAIDI included the widest range of stakeholders possible in work plan development including international technical partners, Ministries of Health, academics, professional associations, and consumers. Whenever possible, lessons learned and best practices were shared between counterparts in each of the participating countries through regional conferences and online forums.

The SAIDI programme combated AMR and TB (including MDR-TB) and also facilitated the response to the pandemic H1N1 influenza by improving infection control practices and implementing guidelines for treating respiratory infections. SAIDI training in infection control supported the development of the national plan to contain AMR in Paraguay and decentralised infection prevention and control activities in Bolivia. SAIDI also helped standardise procedures for managing drugs used for treating TB, and performing quality control for these drugs. Bolivia and Peru conducted quality surveillance on private sector pharmacies, resulting in corrective actions including seizure and destruction of medicines.

Due to lack of continued funding from USAID, SAIDI came to an end as an official network, but activities within each of the three countries were not interrupted.

Colombian regional surveillance networks

Colombia was one of the most recent countries to join ReLAVRA in 2010. The country has three regional surveillance networks covering different geographic areas, which are described below; location of these networks is shown in the Figure 3 map. Most networks use WHONET software and CLSI guidelines. Data from hospitals and institutions is sent to the national institute of health (INS) with statistics done by the epidemiological surveillance system (SIVIGILA). In 2012, the Colombian NIH (INS) asked all relevant institutions, universities, research group to participate in a national network for prevention, surveillance and control of infections and AMR.

The "Grupo Para el Control de la Resistencia Antimicrobiana en Bogotá" (**GREBO**) was created in 2001 and currently consists of a network of hospitals including 28 in Bogota and 10 others outside the Colombian capital. They publish annual bulletins on their website (http://www.grebo.org) reporting resistance profiles in adults versus paediatric and neonatal populations (ICU versus non-ICU categories) to different antimicrobials in Gram-negative and Gram-positive microorganisms. Each year the observed profiles are compared to previous years and trend graphs are shown for recent years for important markers of resistance. These reports are produced with funding from Astra Zeneca.

In southwestern Colombia, in 2010 a local surveillance network for nocosomial infections was created (Red de Vigilancia de Eventos Nosocomiales del Valle, **RENOVA**) including hospitals and clinics in the region. A descriptive study that covered the period between January 2010 and December 2012 in 13 institutions in this network collected monthly results from bacterial cultures from samples of hospitalised patients which were analysed with WHONET software [175]. Participating laboratories performed internal QA with ATCC strains, with external by the INS and other institutions. A total of 123,798 isolates were included in the analysis; 48% from outpatients, 22% and 20% respectively from emergency and hospitalisations, and 10% from ICU. A 65% of isolates were *Enterobacteriaceae*, 11.4% *Staphylococcus* spp. and 6.7% non-fermenting Gram-negative bacilli. The most prevalent microorganisms found were *E. coli*, *K. pneumoniae* and *S. aureus. Escherichia coli* showed up to 17% resistance to third generation cephalosporins, while carbapenem resistant *Klebsiella pneumoniae* increased to 2.7% isolates in the ICU. MDR *Pseudomonas aeruginosa* accounted for up to 21% isolates in ICU and in the general wards.

A third regional network in Colombia, located in the city of Medellin (Grupo para el Estudio de la Resistencia a Antibióticos de Medellín, **GERMEN**), that has collected data since 2007 published a descriptive retrospective study in 2014 on antibiotic resistance in their region based on 106,408 isolates from hospitalised patients in 22 institutions for 6 years of surveillance between 2007 and 2012 with funding from Astra Zeneca Colombia, bioMérieux Colombia, PFIZER Colombia and Becton Dickinson [176]. This study reported emergence of *E. faecium* resistant to vancomycin and carbapenem-resistant *Enterobacteriaceae*. Published in their website in Spanish (http://www.grupogermen.org/publicaciones-e-investigaciones.html) there are reports of antibiotic resistance found in the network's area for different time periods as well as a 2015 update for antimicrobial susceptibility tests that included fosfomycin, cefazolin and *Staphylococcus* testing and the new Carba NP test for carbapenemase from CLSI.

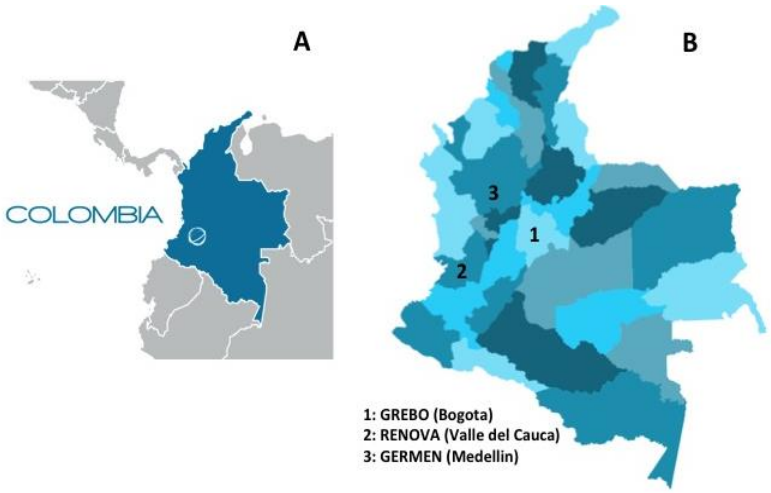


Figure 3 Antimicrobial resistance surveillance networks in Colombia. Colombia is shown in a map of the Americas region bordering four countries in South America and Panama in Central America; it has coastlines on both the Caribbean Sea and the Pacific Ocean (panel A). Locations of the three networks described are shown on the Colombia map (panel B).

The Caribbean

CARPHA is the new single regional public health agency for the Caribbean. It was legally established in July 2011 by an inter-governmental agreement signed by Caribbean Community Member States and began operation in January 2013. Currently CARPHA includes the following member states: Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, BES Islands (Bonaire, St. Eustatius, Saba), British Virgin Islands, Cayman Islands, Curacao, Dominica, Grenada, Haiti, Guyana, Jamaica, Montserrat, Saint Kitts and Nevis, Saint Lucia, St Maarten, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands. They work under a wide public health umbrella on issues that require a coordinated regional response (natural disasters, injuries and violence, management of diseases, compliance with international regulations) by combining the functions of five Caribbean Regional Health Institutes (RHIs) into a single agency: The Caribbean Environmental Health Institute (CEHI), CAREC, The Caribbean Food and Nutrition Institute (CFNI), The Caribbean Health Research Council (CHRC), and The Caribbean Regional Drug Testing Laboratory (CRDTL). There are no available publications from CARPHA that we could find on AMR surveillance, and no further information on whether the network is planning to develop capacity in the region towards this aim was obtained by contacting CARPHA's director of Surveillance, Disease Prevention and Control. Some general information

about the organisation is on their website (http://carpha.org). An inaugural report published in 2013 [177] lists several publications, mostly in one peer-reviewed journal (JHPN) regarding acute gastroenteritis in the region.

RAVREDA/AMI, a regional network for antimalarial resistance surveillance in Latin America

The Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA) was created by PAHO and the U.S. Agency for International Development (USAID) in 2001 in response to the challenge of antimalarial drug resistance in the Amazon [178]. As its work progressed, RAVREDA partnered with international institutions and local organisations in the countries to achieve its goals. Most of these countries also participate in the Amazon Malaria Initiative (**AMI**). Since 2008, AMI is managed by USAID Peru as part of its South America Regional Infectious Diseases Programme (SARI). There was an identified need to invest in targeted activities to improve malaria control in countries in the Amazon basin from where 88% of reported malaria cases in Latin America originated. It is sometimes hard to distinguish the roles and participation of these two organisations (RAVREDA and AMI) even for participating countries.

The network was organised in 2001 by Brazil, Colombia, Ecuador, Guyana, Peru, Suriname, along with PAHO and the support of USAID. Venezuela participated in the network from its beginning, but stopped in 2007. Bolivia participated until 2013. The network was expanded in 2008 to include Panama, Nicaragua, Honduras, Guatemala and Belize in Central America. French Guiana; Haiti and Dominican Republic currently join the network as observers. Through AMI, USAID collaborates with a network of national malaria control programs in these countries, addressing priority issues of identified common interests regarding malaria prevention and control through the provision of technical assistance, as opposed to imposing an agenda. USAID also promotes South-South collaboration, sharing of experiences across the region, and working in partnership. USAID utilised a novel business model based on a mix of complementary sources of technical assistance, which has proven more effective than more conventional approaches.

The focus of this network has centred around developing and strengthening reliable and standardised surveillance information on malaria drug resistance and vector control to be used to monitor trends and more effectively target disease control efforts. Considerable efforts were directed towards improving laboratory-based malaria diagnosis as well as developing tools and approaches tested and disseminated in local settings.

RAVREDA established a network of sentinel sites where standardised protocols are used for ongoing *in vivo* surveillance of malarial drug efficacy. Drug resistance surveillance has provided RAVREDA/AMI countries with reliable information on the distribution and intensity of resistance to antimalarial medicines. One of the initials goals was to build the evidence base to support introduction of artemisinin based combination therapy (ACT) for falciparum malaria and to improve access to and quality of malaria diagnosis. Considerable progress was made on this front (Figure 4) by 2006, and the areas of epidemiological surveillance and vector control received further attention.

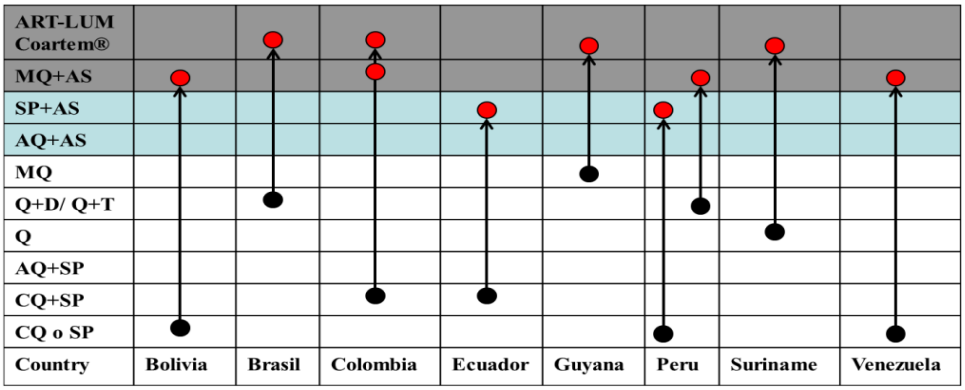


Figure 4 Changes in policies for treatment of non-complicated falciparum malaria in AMI countries 2000-2006.

Black dots and arrows indicate late 1990s, whereas red dots show ACT as policy in 2006 for the indicated AMI countries. ART-LUM: artemether-lumefantrine; AS: artesunate; AQ: amodiaquine; CQ: chloroquine; D: doxycycline; MQ: mefloquine; SP: sulfadoxine-pyrimethamine, Q:quinine; T: tetracycline. From [179].

Treatment policies have been adopted by local governments about a year after completion of efficacy studies, reflecting quick decision-making, and the importance of the issue in affected countries. All RAVREDA countries had modified their official malaria treatment regimens to more effective combination therapies by 2007 while continuing drug efficacy monitoring, therefore providing ongoing means of detecting new forms of resistance. In an external evaluation of AMI/RAVREDA by PAHO published in 2012 [180] the success of the network was highlighted. Although originally conceived to address specifically the mapping of antimalarial drug resistance in the region, the networks have evolved to deal successfully with a wide range of issues related to malaria: diagnosis and treatment; selection, training, qualification and performance monitoring of microscopy technicians; storage and logistics of drugs and insecticides; epidemiological surveillance and information systems, as well as the integration of entomology into epidemiological surveillance.

AMI/RAVREDA publishes a newsletter quarterly in English available on the USAID website (quarterly bulletins), which reports activities and achievements at a regional as well as per-country levels [181]. Also on this website under “reports and fact sheets”, a fact sheet document can be downloaded in English, Spanish or Portuguese on antimalarial drug resistance. Furthermore, the networks have facilitated publication of studies in peer-reviewed journals regarding malaria in participant countries including a review of malaria incidence trends in 21 endemic countries in the Americas [182]. The network has also provided partial funding to studies in the region including the source of *P. falciparum* malaria outbreaks in Ecuador [183], genetic markers for detection of *P. falciparum* infections in Guyana and Suriname [184] and in Honduras [185], molecular basis of resistance to insecticides in mosquito malaria vectors in northwest Peru [186], mosquito responses to human-occupied, insecticide-treated and untreated bed nets [187], and molecular markers of chloroquine and sulfadoxine-pyrimethamine resistance *in P. falciparum* in Nicaragua [188]. Recently identified markers of artemisinin resistance in *P. falciparum* were studied in 98 samples from Guyana to demonstrate independent emergence of these alleles in this region, where resistance alleles to previously used drugs are fixed [189].

Figure 5 Current first-line treatment for uncomplicated *P. falciparum* malaria by country. From AMI/RAVREDA fact sheet on antimalarial drug resistance, this map shows the Guiana shield as a high risk area for emergence of resistance to ACTs.

AMI/RAVREDA holds annual meetings in different LA countries each year to evaluate important regional malaria topics and come up with recommendations. The 2016 (15th annual) meeting was held in Bogota in May and recommendations included a regional action plan for malaria elimination (2016-2020) with support from USAID, preparation of manuals and protocols for adequate response to outbreaks, monitoring efficacy of and resistance to antimalarials (molecular studies), containment and elimination of artemisinin resistance (Guiana shield region, see Figure 5), and sustainability at national level as necessary after external funding ends. The possible use of MDA for malaria elimination was discussed in view of the WHO recommendation for *P. falciparum* in areas moving towards elimination with good health and surveillance coverage and only 2-3 rounds at a time for a short period.

Dr Jaime Chang (Project Management Specialist at USAID/Peru), a key individual in RAVREDA's evolution towards strengthening South-South regional interaction between member countries, explains to us how these networks should progress in his opinion:

"In many cases a network is initiated with the support of "Northern" agencies providing financial and technical assistance, even when South-South collaboration exists. The roles of its members must evolve in time, aiming to decrease dependence on external funding, to change the "North-South technical assistance" to "North-South technical collaboration", and to increase the level of South-South collaboration. Likewise, the network's activities should be increasingly financed by participating countries as these activities become part of their members' routine operations (examples: monitoring antimalarial efficacy, reporting antimalarial stocks, participating in external evaluation of microscopy performance). The latter may require the recognition of networking and of the specific activities as inherent to the functioning of national malaria control programs (NMCP), so they can be planned and budgeted for. The network should not impose activities that are not genuinely important to the NMCP" (April 2016).

Anti-tuberculosis drug resistance surveillance in Latin America

In LA, only Brazil is considered by WHO as a high burden TB country. Most LA countries have reported data on anti-TB DR to WHO as part of the Global Project on Anti-tuberculosis Drug Resistance Surveillance. In the WHO 2015 global report on TB [2], LA countries contributed data on drug susceptibility testing for TB cases, estimated multi-drug resistant (MDR)-TB among notified TB cases, MDR-TB cases detected, and enrolments on MDR-TB treatment.

Argentina, Chile, and Mexico are part of the TB Supranational reference Laboratory Network created in 1994 as a sub-group of the WHO initiative to support a Global Project on TB drug resistance surveillance (http://www.who.int/tb/areas-of-work/laboratory/srl-network/en/). This network is a key technical resource supporting strengthening of the laboratory capacity in countries. Under WHO coordination and support, the network has expanded from initial 14 to actual 30 Supranational Reference Laboratories.

A TB laboratory network in **Cuba** comprises 609 diagnosis centres based on microscopy, of which 48 additionally use cultures. The national reference TB laboratory (LNR-TB) at the Instituto de Medicina Tropical Pedro Kourí (IPK), an official PAHO/WHO collaborator, has adopted a surveillance sentinel system for drug resistance. This network continuously reports results regarding susceptibility testing and LNR-TB conducts longitudinal surveillance on anti-TB drugs since 1982 [190]. A longitudinal cohort study was published on 2,285 *M. tuberculosis* isolates from patients with positive cultures from 15 centres around the country sent to the LNR-TB laboratory during the period from 2000 to 2009 for diagnosis confirmation and susceptibility testing [191]. For anti-TB DR testing the indirect ratio Löwenstein Jensen (L-J) method with 1% threshold was used for isoniazid (H), streptomycin (S), ethambutol (E) and rifampicin (R). A 91.5% of all tested strains that corresponded to new cases, and 0.4% of strains showed multi-drug resistance (MDR). Of strains with previous treatment 9.2% of strains were MDR, predominantly to H-S-R. Isolates resistant to all four anti-TB drugs assayed made up 3.2% of all strains. A subsequent prospective longitudinal study in 657 *M. tuberculosis* isolates from 2010 and 2011 found that MDR was 1.03% in new cases and 10.38% in previously treated cases[192]. Two extensively resistant isolates were found.

In **Chile**, the national TB reference laboratory located at the national health institute conducts *M. tuberculosis* surveillance since 1961, both on new cases of primary resistance (periodically since 1971) and resistance acquired in previously treated cases. Since 2014 the TB programme has expanded surveillance to anti-TB DR on all new pulmonary cases and previously treated with bacterial confirmation. A study on DR was carried out between 2011 and 2012 by the Chilean national reference laboratory as part of the WHO's DR Surveillance Programme [193].

In 1996, the first national survey of anti-TB DR was conducted in **Brazil** with participants from 13 health care facilities throughout the country; rates of primary and acquired MDR-TB were 1.1% and 7.9%, respectively. A second study was conducted between 2006 and 2007 in the city of Porto Alegre, where the efficacy of tuberculosis control programs had decreased significantly, from five primary health care clinics and three public hospitals [194]. From sputum samples, smear microscopy and mycobacterial cultures were done, and samples were also tested for resistance to R and H (due to poor reproducibility of tests for resistance to S and E, those results were not considered), with results suggesting that DR TB

(primary and acquired MDR-TB were 2.2% and 12.0% respectively) was associated with re-treatment and a longer time to diagnosis. GeneXpert® technology, after an initial validation in a few municipalities, is being implemented more broadly and used in Brazil as it is recognised as allowing almost immediate detection (under 2h for results) of susceptible and R resistant *M. tuberculosis* complex (Xpert MTB/Rif). In 2010 this molecular technology was recommended by WHO for initial diagnosis in TB patients with suspected multidrug resistance or HIV infection for whom prompt diagnosis and appropriate treatment initiation is crucial. The main bottleneck for GeneXpert® implementation is cost. Two municipalities in Brazil (Rio de Janeiro and Manaus) were tested in 2012 by introduction of the Xpert® MTB/Rif assay as replacement of sputum smear microscopy in routine health care settings, resulting in increased detection of TB cases by 34%, compared to smear microscopy and good acceptability. In 2014, the Brazilian MoH implemented a "network of rapid TB testing" by distributing 160 pieces of equipment to laboratories in 92 municipalities chosen based on their reporting (annually) of 60% of all national new cases of TB. They plan a further 70 new equipment pieces to be distributed in 2016 with an initial capacity of 250,000 tests (Brazil MoH).

Anti-HIV drug resistance surveillance in Latin America

A WHO HIVDR strategy for prevention and assessment was introduced in Latin American countries in 2006 through a number of regional and subregional capacity-building meetings, workshops and trainings [195]. The need for implementation of national HIVDR control strategies was emphasised. Between 2006 and 2011, direct technical cooperation and in country training for the development and implementation of national plans for HIVDR prevention and assessment were provided to 30 countries: Anguilla, Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Montserrat, Nicaragua, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, and Venezuela.

PAHO currently coordinates the **HIV Drug Resistance Technical Cooperation Network (TCN)** created in 2013 for Latin America and the Caribbean. This network, a regional collaborative initiative that gathers technical expertise and mobilises resources to support implementation of HIVDR surveillance and control in LAC countries, has 3 specialised branches:

1) **Laboratory branch**: provides technical support for lab capacity building and HIV genotyping, including quality assurance

2) **Epidemiology branch**: provides technical support for HIVDR surveillance protocol development and implementation, epidemiological analysis and public health use of data.

3) **Clinical branch:** provides technical support for training of human resources on interpretation and use of HIV genotyping for clinical monitoring and support for discussion of difficult cases, including translation to Spanish of technical documents. Each branch is coordinated by a Network member institution, identified on a voluntary basis and with a 12 month rotation of duty.

In order to monitor the transmission of drug-resistant HIV strains and the subtype profile in the chronically infected drug-naïve population the **Brazilian Network for HIV drug resistance (HIV-BResNet**) was established in 2000 in Brazil. The first survey done by this network in 2001 showed an overall primary resistance rate of 6.6% [196]. In 2009 results of another survey were published on 210 recently diagnosed individuals from six state capitals in different regions in Brazil which indicated 8.1% of isolates containing resistance mutations [197].

Epidemiological surveillance of drug resistance of foodborne pathogens in Latin America

Last year WHO released the first ever global estimates of foodborne diseases, which showed that almost 1 in 10 people fall ill every year from eating contaminated food and 420,000 die as a result [198]. In a recent WHO report, the Americas showed 77 million people falling ill every year from contaminated food (31 million are children under the age of 5 years), with an estimated 9000 deaths (more than 2000 children under 5). *Norovirus, Campylobacter, E. coli* and non-typhoidal *Salmonella* cause 95% of diarrhoeal disease cases. Toxoplasmosis and the pork tapeworm (*Taenia solium*) are very important food safety concerns in Central and South America.

Different sets of pathogens are under surveillance in health facilities and at the community level in Latin America. In the region, WHO-GFN connects clinical, food analysis and veterinary laboratories to build national capacity to detect, control and prevent foodborne and other enteric infections from farm to table. All national reference laboratories for foodborne diseases within the Americas are GFN members. Via this network, training on integrated surveillance systems in all countries has been implemented and integrated surveillance pilot projects and research projects for AMR as well in seven countries, including two active research projects in Peru and Costa Rica. The region has developed workshops to implement national programmes in three countries (Mexico, Brazil and Chile) and a workshop for six Caribbean countries. The WHONET information system is used, and the goal is to introduce WGS in the near future (there is currently a WGS pilot project in Argentina). The objective of the Peruvian project has been to determine the AMR profile of Enterobacteriaceae isolated from faecal samples from children under two years of age and *E. coli* isolated from reservoirs (water, food and animal faeces) in a peri-urban community in Lima. In Costa Rica, the project is to determine the prevalence and characteristics of *Salmonella* in pigs for human consumption, through a cross-sectional study to generate information useful in the design of strategies for the prevention and control of *Salmonella* infections in both human and veterinary public health. Data from 2012-2013 are being collected from the region via a ReLAVRA-GFN call for data.

PulseNet (http://www.cdc.gov/pulsenet/index.html) is a laboratory network that connects foodborne illness cases to detect outbreaks since 1996. The network **PulseNet Latin America and the Caribbean** (PNLAC, http://www.pulsenetinternational.org/networks/Pages/latinamerica.aspx.) started in 2004. PAHO and the Argentine institute INEI-ANLIS “Carlos G. Malbrán” played important roles, as they do for ReLAVRA, in the creation and strengthening of PNLAC. While INEI-ANLIS is in charge of the technical support regarding protocols, analysis, certification and quality control programs (Regional Reference

Laboratory), PAHO provides all the aspects needed for communication among members, server development and maintenance, regional databases and project developments.

Figure 6 PNLAC National and Regional Reference Laboratories. There are 20 national reference laboratories from 16 countries in Latin America and one regional reference centre in the Caribbean (CARPHA). From [199].

Both organisations, together with CDC, share responsibilities for strategic planning and conduction of PNLAC. Member countries are Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Guatemala, Mexico, Nicaragua, Paraguay, Peru, Uruguay, Venezuela, and Caribbean CARPHA countries.

The main goal is to support the Pan American regional strategy approved by the Ministers of Health in the Regional Plan for Food Safety (Resolution CD 42/10) in strengthening surveillance of foodborne diseases and to reinforce communication and technical cooperation among the member countries in relation to food safety and health including detection of early emerging and re-emerging pathogens. The network encourages countries to focus on diagnosis and research of disease burden, to establish national and regional databases, and to actively use the national and regional information provided in coordinated public health actions and interventions.

The network has established the capability in the participating countries for genotyping bacterial pathogens strains with standardised protocols for selected pathogens (*Salmonella* spp, *Vibrio cholerae, Escherichia coli* O157 and STEC no-O157, *Shigella* spp., *Campylobacter* spp., *Listeria monocytogenes)*. A regional shared database of the isolates has been created.

When two or more people get the same illness from the same contaminated food or drink, the event is called a foodborne disease outbreak. A highly precise method commonly used to identify specific bacterial isolates epidemiologically related based on molecular subtyping is pulse-field gel electrophoresis (PFGE). Once a DNA fingerprint is created, the public health laboratory analyses the fingerprint pattern using a software programme known as BioNumerics. After analysis, the laboratory uploads its pattern to the national database, where PulseNet Central's database managers will investigate the pattern to see if it is causing an outbreak or it is part of an ongoing outbreak. If so, these database managers will work with the public health microbiologists and epidemiologists to further investigate the outbreak. Although PFGE is the current "gold standard" fingerprinting method used within PulseNet members, they are transitioning toward using whole genome sequencing (WGS).

Videos produced by the network explaining PFGE are available on YouTube (Spanish). The detailed protocol for standardised PFGE, published in 2012, is available in six parts. The first of these six videos consists of an introduction explaining the purpose and objectives of PNLAC as a network (https://www.youtube.com/watch?v=6JSmSYDC0xk) and emphasises the importance of following standardised and validated protocols, as well as analysis tools.

PNLAC was chosen in 2013 as the recipient of the IHRC Innovations in PulseNet Award for their use of virtual collaboration spaces for meetings and developing online workshop training for analysis and a video with the steps of the PFGE laboratory procedures.

The number of regional and national databases and PFGE patterns by PNLAC members is constantly expanding, with a total of 6637 PFGE patterns available for online consultation and comparison with 54 disease outbreaks in 2015. The network facilitates sharing of information from relevant outbreaks, which is discussed through online meetings. When necessary, international alerts are issued which have proven extremely useful, such as the coordinated response for heightened cholera surveillance following the Haitian cholera outbreak on 2010, still ongoing.

Summary of Latin American AMR Surveillance networks

Most LA countries actively participate in regional networking for AMR surveillance via three main networks (PulseNet Latin-American and Caribbean, GFN, and ReLAVRA/SIREVA). In spite of differences regarding AMR testing capacity and challenges related to resources, these countries contribute AMR data for analysis within the regional networks. Information and technology are exchanged between countries through these networks, and methodologies and protocols are developed and shared by publishing manuals and/or at annual regional courses usually held at a national reference centre in the country with best capacity- a role often fulfilled by Argentina. These protocols are updated when necessary, and the updates are also disseminated to participating countries. For both ReLAVRA and PulseNet, the Argentine institute INEI-ANLIS “Carlos G. Malbrán” is in charge of technical support and regional quality control programmes.

For both ReLAVRA and PulseNet networks, as well as for SAIDI, PAHO has/had a coordinating role. PAHO posts on their website all official information from these networks such as reports, news, events, manuals and protocols whenever they are published. Most of these documents, and event announcements are available in Spanish only, which makes exposure to and possible interaction with other networks based in non-Spanish speaking regions difficult. When manuals and protocols need to be translated from English to Spanish for countries to use, PAHO usually oversees this process. PAHO provides funding for translations as well as for regional events such as meetings, covering mostly traveling costs from staff from one country to another in the region. The PAHO staff in charge of these networks and coordinating activities is quite limited (about one person per network). This becomes critical in cases of regional emergencies such as the one declared for Zika recently, when PAHO individuals in charge of networks shift their focus mostly towards these issues as they take priority over regular network activities. PAHO funding is also limited, and we have noticed annual reports for some networks are currently delayed by a few years, although they are due to come out soon.

Having PAHO and some HICs such as Argentina in LA AMR surveillance networks has been instrumental in coordinating countries that may have remained isolated otherwise, and building capacity especially via regional courses, publication of manuals and training sessions. A crucial element overseen and coordinated via Argentina and PAHO is the EQA, which although still facing challenges regarding response time from laboratories in some countries, keeps them on track and updated on QA procedures. It also has put some pressure on more laboratories in different countries to get certifications and to impose rules such as following CLSI standards.

In LA countries clinicians working on infectious diseases usually specialise in “infectious diseases”, “tropical diseases”, or “tropical medicine” which may have been a critical factor in detecting a need for establishing surveillance systems early on in the region on AMR. In most universities (undergraduate and graduate education) there are several laboratories conducting research on tropical diseases, including neglected diseases.

Appendix 5 Interview with Dr Zhang Bo, Deputy Director of Academic Committee of the China Antimicrobial Resistance Surveillance System

Interview questions prepared by Arlene Chua. Translation courtesy of Henry Li, PhD student from LSHTM

The AMR surveillance in China has evolved and has increased participation of hospital sites over the years, to currently 1,427 sites. In your opinion, what are the key factors for the success of the network? What do you think are its limitations?

There are three key factors for the successful expansion of CARSS:

- Enforcement of administrative management
- Continuous provision of training
- -Implementation of stringent data quality control

The limitations are:

- Too diverse range of equipment being employed in different hospitals
- Lack of quality in some of the equipment

What is the plan for further developing CARSS in the next 3-5 years?

We'll organise training seminars for microbiologists based in hospitals that are judged to be behind in terms of their data quality, and increase their technical capacity. At the same time we're working with manufacturers of the equipment in order to help them improve quality of their products.

Can you tell me a little how the sites are selected by MOH? What are the main criteria for site selection?

More than several dozens of tertiary hospitals and secondary hospitals are selected from each province, and these would certainly include all the biggest hospitals.

(Henry's notes: they told me that some epidemiologists worked out what hospitals to include base on a number of criteria, including regional representativeness, population coverage, ratio of tertiary and secondary hospitals, resistance epidemiology, etc. But they have to be technically equipped (at least having the people and the machines) in order to be considered to be first place. Once selected these hospitals would be informed of the decision)

Can you describe the external quality assurance mechanism that is set up for the laboratories included in CARSS?

In 2015 we set up a centre for quality control. Besides continuously providing training, we also set up local based training camps to increase the provision and coverage of training.

How is the data in CARSS linked to monitoring antibiotic usage and to animal health? Can you describe what other surveillance and monitoring system in China on those issues?

At the moment there isn't a unified network to do that. In China, the surveillance networks for resistance in humans and in animals are managed by different ministries. Talks are on-going to explore mechanisms to potential bring together these networks. Some surveillance networks for resistance are set up by organisations outside the government, for example, by Peking University First Hospital (CARST), and Huashan Hospital of Fudan University. CARST would regularly collect samples of bacteria from hospitals within its network, and drug sensitivity of these bacteria would be assessed centrally to avoid differences in brands of antibiotics and/or methodology used.

How do you see the work of WHO and GLASS? What is the main reason for China's participation/non participation in GLASS? What do you think WHO needs to convey to countries in order for them to participate in GLASS?

GLASS is hugely important to global surveillance of resistance. China absolutely has to get involved—we're the most populous nation in the world, and we're also a WHO member. WHO should provide technical and financial assistance to encourage other countries to participate in building GLASS.

In general, there is a lack of information on the cost of setting up national surveillance systems. Can you describe how China has funded CARSS?

Although the Chinese government is attaching increasing importance to the building of CARSS, and indeed, government funding for CARSS is gradually increasing, the majority of funding at the moment is still raised by individual laboratories.

Finally, many countries don't have any national surveillance system set up. From the experience in China, what would you advise them where to focus on when setting up a surveillance system?

They should focus on the types of drug resistance that have huge impact on human health, e.g. MRSA, VRE and CRE

Appendix 6 Table of Quality Management Programmes

Name of Programme (acronym) / Coordinating Institution/Location of Head Office	Website	Geographical scope of programme activities	Duration	Pathogens included in programme	Materials available to all potential users?	Business model	Type of programme/institution
ATCC/ United States	http://www.lgcstandards-atcc.org/	Global	1925-ongoing	Bacteria, Viruses, Fungi	Yes	Commercial, for-profit	Commercial
Clinical & Laboratory Standards Institute (CLSI)/ United States	www.clsi.org	Global	1968-ongoing	All pathogenic microbes	Yes	Cost-recovery/not-for-profit	Non-governmental organisation/agency
College of American Pathologists/ United States	www.cap.org	Global	1946-ongoing	All pathogenic microbes	Yes	Cost-recovery/not-for-profit	Non-governmental organisation/agency
Diphtheria Surveillance Network (DIPNET)/ United Kingdom	http://www.dipnet.org/	Global	1998-ongoing	Diphtheria	Yes	No cost to participants	Supranational/regional body
European Committee for Antimicrobial Susceptibility Testing (EUCAST)/ Sweden	www.eucast.org	International Region	1997-ongoing	Bacteria, Parasites, Fungi, veterinary pathogens (pilot)	Yes	No cost to participants	Supranational/regional body
European Network for Imported Viral Diseases (ENIVD)/ Germany	http://www.enivd.de/index.htm	Global	2013-2014	Dengue (serology)	Yes	No cost to participants	Supranational/regional body
Global Foodborne Infections Network External Quality Assurance System (GFN-EQAS)/ Denmark	http://www.who.int/gfn/activities/eqas/en/	Global	2000-ongoing	Salmonelle, Shigella, Campylobacter	Yes	No cost to participants	Supranational/UN-affiliated body
Global Laboratory Initiative/ Switzerland	http://www.stoptb.org/wg/gli/default.asp	Global	2008-ongoing	MTB	Yes	No cost to participants	Supranational/UN-affiliated body
HIVResNet Laboratory Accreditation Scheme/ Switzerland	http://www.who.int/hiv/topics/drugresistance/laboratory/en/index2.html	Global	2007-ongoing	HIV (resistance)	Yes	No cost to participants	Supranational/UN-affiliated body

Name of Programme (acronym) / Coordinating Institution/Location of Head Office	Programme activities	Types of available reference materials	Is the inventory of available materials regularly updated per the relevant standards and policy documents?	Types of proficiency testing	Is the test panel regularly updated per the relevant standards and policy documents?	Quality improvement mechanisms	Accreditation standards
ATCC/ United States	Standards and/or Policy setting, Repository / Reference Material	Reference strains / isolates	Yes				ISO 17025, ATCC is an ISO 9001:2008 certified, ISO 13485:2003 certified, ISO 17025:2005 and ISO Guide 34:2009 accredited organization
Clinical & Laboratory Standards Institute (CLSI)/ United States	Standards and/or Policy setting, Accreditation body	na					ISO 15189, ISO 17025, ISO 17043, GCLP, CLSI, EUCAST
College of American Pathologists/ United States	Standards and/or Policy setting, Repository / Reference Material, Proficiency Testing, Accreditation body	Reference strains / isolates, Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Yes	Disk diffusion, MIC, Genetic tests, Pathogen identification	Yes	Suggested corrective actions included in PT report, Hands-on training workshops, generic, Hands-on training workshops, lab or project specific, Troubleshooting or technical support provided on site, Troubleshooting or technical support provided remotely	CAP is itself an accrediting body
Diphtheria Surveillance Network (DIPNET)/ United Kingdom	Standards and/or Policy setting, Proficiency Testing	Reference strains / isolates	Unknown	Pathogen identification, toxin production	Unknown	Hands-on training workshops, generic	
European Committee for Antimicrobial Susceptibility Testing (EUCAST)/ Sweden	Standards and/or Policy setting						
European Network for Imported Viral Diseases (ENIVD)/ Germany	Proficiency Testing, Training, networking	serum	No	Dengue serology	No		
Global Foodborne Infections Network External Quality Assurance System (GFN-EQAS)/ Denmark	Proficiency Testing	Reference strains / isolates	Unknown	MIC, Pathogen identification	Unknown	Suggested corrective actions included in PT report	
Global Laboratory Initiative/ Switzerland	Standards and/or Policy setting, Proficiency Testing, Training			Pilot GeneXpert EQA	Unknown	Training packages (accessible on website)	provides a stepwise plan to guide TB laboratories towards ISO 15189 accreditation
HIVResNet Laboratory Accreditation Scheme/ Switzerland	Accreditation body						HIVResNet

Name of Programme (acronym) / Coordinating Institution/Location of Head Office	Website	Geographical scope of programme activities	Duration	Pathogens included in programme	Materials available to all potential users?	Business model	Type of programme/institution
Integrated Quality Laboratory Services/ France	http://www.iqls.net/	Global	2010-ongoing	not sure. TB	Yes	Commercial, for-profit	Private enterprise
Latin America External Quality Assessment (LA-EQAS)/ Argentina	no weblink available	International Region	2000-ongoing	Bacteria	Yes	No cost to participants	Supranational/UN-affiliated body
National Health Laboratory Service/ South Africa	http://www.nhls.ac.za/?page=eqa_program_for_the_xpert_mtb/rif_assay&id=76	International Region	1998-ongoing	Bacteria, Parasites, Mycology	Yes	Unknown	Research/academic group/consortium
NRL/ Australia	www.nrl.gov.au	Global	1985-ongoing	Bacteria, Viruses	Yes	Cost-recovery/not-for-profit	Governmental/ Regulatory agency
Oneworld Accuracy/Canada	http://www.oneworldaccuracy.com/	Global	2000-ongoing	Bacteria, Viruses, Parasites, Fungi	Yes	Commercial, for-profit	Private company
Pacific Paramedical Training Centre Regional External Quality Assessment (REQA) Programme/ New Zealand	http://pptc.org.nz/regional-external-quality-assurance-programme/	International Region	1985-?	Viruses	Unknown	Unknown	Hospital/laboratory association
Quality Control for Molecular Diagnostics (QCMD)/ United Kingdom	http://www.qcmd.org/index.php?pageId=45&pageVersion=EN	Global	2001-ongoing	All pathogenic microbes	Yes	Commercial, for-profit	Private company
Royal College of Pathologists of Australasia Quality Assurance Programs Pty Ltd (RCPAQAP)/ Australia	http://www.rcpaqap.com.au/	Global	1988-ongoing	Bacteria, Viruses	Yes	Cost-recovery/not-for-profit	Research/academic group/consortium
Strengthening Laboratory Management Toward Accreditation (SLMTA)/ United States (linked to WHO-AFRO)	http://slmta.org/	Project-specific	2009-ongoing	NA	No	No cost to participants	Governmental/ Regulatory agency
The East African Regional External Quality Assessment Scheme (EA-REQAS)/ Kenya	http://www.eareqas.org/	International Region	2000-ongoing	Bacteria, Parasites	Yes	Unknown	Supranational/regional body
TREAT Asia Quality Assessment Scheme(TAQAS)/ Australia	No web-link available	International Region	2006-ongoing	HIV	Yes	No cost to participants	Research/academic group/consortium

Name of Programme (acronym) / Coordinating Institution/Location of Head Office	Programme activities	Types of available reference materials	Is the inventory of available materials regularly updated per the relevant standards and policy documents?	Types of proficiency testing	Is the test panel regularly updated per the relevant standards and policy documents?	Quality improvement mechanisms	Accreditation standards
Integrated Quality Laboratory Services/ France	Proficiency Testing, Training, Assessment & Evaluation, Tool development	unknown	Unknown	Pathogen identification	Unknown	Hands-on training workshops, lab or project specific, Troubleshooting or technical support provided on site	
Latin America External Quality Assessment (LA-EQAS)/ Argentina	Proficiency Testing	Reference strains / isolates	No	Disk diffusion, MIC, Pathogen identification	Unknown	Suggested corrective actions included in PT report	
National Health Laboratory Service/ South Africa	Proficiency Testing	Reference strains / isolates	Unknown	Disk diffusion, MIC, Genetic tests, Pathogen identification	Unknown	Suggested corrective actions included in PT report	ISO 17043
NRL/ Australia	Standards and/or Policy setting, Repository / Reference Material, Proficiency Testing	Reference strains / isolates, Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Yes	Genetic tests, Pathogen identification	Yes	Hands-on training workshops, generic	ISO 15189, ISO 17043
Oneworld Accuracy/Canada	Proficiency Testing	Reference strains / isolates, Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Yes	Disk diffusion, MIC, Genetic tests, Pathogen identification	Yes	Depends on participating organisations	
Pacific Paramedical Training Centre Regional External Quality Assessment (REQA) Programme/ New Zealand	Proficiency Testing, Training					Hands-on training workshops, generic	
Quality Control for Molecular Diagnostics (QCMD)/ United Kingdom	Proficiency Testing	Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Yes	Genetic tests	Yes		ISO 17043, UKAS
Royal College of Pathologists of Australasia Quality Assurance Programs Pty Ltd (RCPAQAP)/ Australia	Proficiency Testing	Reference strains / isolates, Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Yes	Disk diffusion, MIC, Genetic tests, Pathogen identification	Yes	Suggested corrective actions included in PT report	ISO 17043
Strengthening Laboratory Management Toward Accreditation (SLMTA)/ United States (linked to WHO-AFRO)	Standards and/or Policy setting						
The East African Regional External Quality Assessment Scheme (EA-REQAS)/ Kenya	Proficiency Testing	Reference strains / isolates	Unknown	microscopy (malaria, AFB) and serology	Unknown	Suggested corrective actions included in PT report	
TREAT Asia Quality Assessment Scheme(TAQAS)/ Australia	Proficiency Testing	Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Unknown	Genetic tests	Unknown		

Name of Programme (acronym) / Coordinating Institution/Location of Head Office	Website	Geographical scope of programme activities	Duration	Pathogens included in programme	Materials available to all potential users?	Business model	Type of programme/institution
United Kingdom External Quality Assurance Scheme (UK NEQAS)/ United Kingdom	http://www.uknegas.org.uk/	Global	1969-ongoing	Bacteria, Viruses, Parasites, Fungi	Yes	Cost-recovery/not-for-profit	Non-governmental organisation/agency
University Research Co URC/CDC Lab Project/ United States		Country	Jan 2013-Dec 2013	MTB GeneXpert	Yes	No cost to participants	Unknown
HIV/AIDS Network Coordination Virology Quality Assurance (hanc VQA) / United States	https://www.hanc.info/labs/labresources/vqaResources/ptProgram/Pages/default.aspx	Global	2007-ongoing	HIV (resistance)	Yes	No cost to participants	Research/academic group/consortium
The World Health Organisation (WHO)/ Switzerland	http://www.who.int/drugresistance/publications/WHO_CDS_CSR_RMD_2003_6/en/	Global	2003-ongoing	Bacteria	No	No cost to participants	Supranational/UN-affiliated body
WHO African Region External Quality Assurance Program (WHO AFRO EQAP)/ South Africa	None http://www.who.int/bulletin/volumes/90/3/11-091876/en/	International Region	2002-ongoing	Bacteria, Parasites, Cryptococcus spp.	Yes	No cost to participants	Research/academic group/consortium
WHO Asia-Pacific EQA Programme/ Indonesia	no web link available	International Region	2005-?	malaria	Yes	No cost to participants	Supranational/regional body
WHO External Quality Assessment Project for the Detection of Subtype Influenza A Viruses by PCR/ Switzerland	http://www.who.int/influenza/gisrs_laboratory/external_quality_assessment_project/en/	Global	2007-ongoing	Influenza A & B (includes avian)	Yes	No cost to participants	Supranational/UN-affiliated body
WHO Gonococcal Surveillance Program EQAS	none	International Region	1992-ongoing	Neisseria gonorrhoeae	Yes	No cost to participants	Supranational/UN-affiliated body
WHO Laboratory Quality Stepwise Implementation Tool/ The Netherlands	https://extranet.who.int/lqsi/	Global	2011-ongoing	All pathogenic microbes	Yes	No cost to participants	Supranational/UN-affiliated body
WHO Mycobacterial Supranational Reference Laboratory (SRL) network/ Switzerland	No web link www.who.int/tb/laboratory/srln-list.pdf	Global	1991-ongoing	MTB	Unknown	No cost to participants	Supranational/UN-affiliated body
Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA)/ WHO-AFRO, Republic of Congo	http://www.afro.who.int/en/clusters-a-programmes/hss/blood-safety-laboratories-a-health-technology/blt-highlights/3859-who-guide-for-the-stepwise-laboratory-improvement-process-towards-accreditation-in-the-african-region-with-checklist.html	International Region	2011-ongoing	NA	No	No cost to participants	Supranational/UN-affiliated body
WHO External Quality Assurance System for Antimicrobial Susceptibility Testing (EQAS-AST)/ Switzerland	no link available on WHO website http://jcm.asm.org/content/41/6/2372.long	Global	1998-2006	Bacteria	Yes	No cost to participants	Supranational/UN-affiliated body

Name of Programme (acronym) / Coordinating Institution/Location of Head Office	Programme activities	Types of available reference materials	Is the inventory of available materials regularly updated per the relevant standards and policy documents?	Types of proficiency testing	Is the test panel regularly updated per the relevant standards and policy documents?	Quality improvement mechanisms	Accreditation standards
United Kingdom External Quality Assurance Scheme (UK NEQAS)/ United Kingdom	Proficiency Testing	Reference strains / isolates	Yes	Disk diffusion, MIC, Pathogen identification, serology, virus detection/quantification	Yes	Suggested corrective actions included in PT report	CPA and UKAS (against ISO 17043 requirements)
University Research Co URC/CDC Lab Project/ United States	Proficiency Testing	not sure	No	Genetic tests	No	Unclear	na
HIV/AIDS Network Coordination Virology Quality Assurance (hanc VQA) / United States	Proficiency Testing	Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Unknown	Genetic tests	Unknown	Suggested corrective actions included in PT report	
The World Health Organisation (WHO)/ Switzerland	Standards and/or Policy setting	na	No	na	No	na	na
WHO African Region External Quality Assurance Program (WHO AFRO EQAP)/ South Africa	Proficiency Testing	Reference strains / isolates	Unknown	Pathogen identification	Unknown	Suggested corrective actions included in PT report, Hands-on training workshops, lab or project specific	
WHO Asia-Pacific EQA Programme/ Indonesia	Repository / Reference Material, Proficiency Testing	Reference strains / isolates	Unknown	Pathogen identification, microscopy (quantitative)	Unknown	Troubleshooting or technical support provided on site	
WHO External Quality Assessment Project for the Detection of Subtype Influenza A Viruses by PCR/ Switzerland	Proficiency Testing	Genetic materials (whole genome DNA extracts, total NA extracts, plasmids, primers, probes, etc.)	Unknown	Genetic tests, Pathogen identification	Unknown	Suggested corrective actions included in PT report	
WHO Gonococcal Surveillance Program EQAS	Proficiency Testing	Reference strains / isolates	Unknown	Disk diffusion, MIC, Pathogen identification	Unknown		
WHO Laboratory Quality Stepwise Implementation Tool/ The Netherlands	Standards and/or Policy setting	QM implementation tools only	Yes	na	No	Troubleshooting or technical support provided remotely	ISO 15189
WHO Mycobacterial Supranational Reference Laboratory (SRL) network/ Switzerland	Standards and/or Policy setting, Proficiency Testing	Reference strains / isolates	Unknown	MIC, Genetic tests, Pathogen identification	Unknown	Hands-on training workshops, lab or project specific	
Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA)/ WHO-AFRO, Republic of Congo	Standards and/or Policy setting, Accreditation body	na	na	na	na	na	SLIPTA Certificate of Recognition (this is not a certificate of laboratory accreditation)
WHO External Quality Assurance System for Antimicrobial Susceptibility Testing (EQAS-AST)/ Switzerland	Proficiency Testing	Reference strains / isolates	No	Disk diffusion, MIC, Pathogen identification	No	Suggested corrective actions included in PT report	