Integrated antibiotic resistance surveillance: importance of harmonization and quality assurance of antibiotic susceptibility testing

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Antibiotic resistance (AR) is an underestimated emerging One Health problem. Surveillance systems are the core components of AR management programmes. Integrated harmonized surveillance programmes with active watchfulness on the use of antimicrobials and trends of resistance in bacteria of human, animal and environmental origin are required for exact estimation of the true burden of AR. Harmonized surveillance programmes follow uniformity in antibiotic susceptibility testing protocols, targeted bacterial species, tested antimicrobials, reporting clinical limits, susceptibility interpretation criteria and use of control strains. Harmonization of AR surveillance programmes is crucial for reliable data generation and comparison of AR data at regional, national and global levels. Data generated by such programmes can be used to formulate empirical treatment guidelines and policies for the effective management of AR. Standardization of antibiotic susceptibility testing by adopting quality assurance and quality control programmes is essential for generating valid and reliable data under AR surveillance programmes.

Keywords: Antibiotic resistance, One Health, quality control, surveillance systems.

ANTIMICROBIAL resistance (AMR) has been identified as a major emerging global health problem. It is estimated that worldwide 1.27 million people lost their lives due to infections/diseases caused by antimicrobial-resistant bacteria in 2019 (ref. 1). It is projected that by 2050, 10 million people will die per year due to AMR and may cost the global economy $100 trillion annually[1,2]. AMR occurs when bacteria, viruses, fungi and parasites no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death[3]. Antibiotic resistance (AR) arises due to genetic changes that increase bacterial tolerance to antibiotics, thereby making them less effective during treatment[1,2]. These genetic changes occur in the bacterial genome due to pre-existing mutations and/or the acquisition of foreign DNA. AR is a natural phenomenon, and resistant bacterial strains were present in the environment long before the therapeutic use of antibiotics[4]. The genetic determinants imparting AR evolved in antibiotic-producing environmental microorganisms as an auto-protective measure[5,6]. These resistance determinants were later transferred to other bacteria through natural genetic exchanges, conjugation, transformation and transduction[7]. Around 73% of deaths attributed to AMR are due to six pathogens (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*) associated with resistance. It is projected that 70% of the deaths due to AMR are because of resistance to fluoroquinolone and β-lactam class of antibiotics[1].

The inappropriate use of antibiotics in human beings and livestock, as well as the spread of AMR genes in the environment, are the major drivers of the emergence and rapid evolution of AR. Modern medicine has relied heavily upon antibiotics to treat infectious diseases in humans and animals, which not only changed the dynamics of the evolution of resistant bacterial strains but exerted direct selection pressure on commensal microbiota as well. Over-the-counter sales of antibiotics, under or overdosing, and treatment of non-bacterial infections with antibiotics have aggravated the problem of AR[4]. It is estimated that 73% of all antimicrobials sold globally are used in animals raised for food[8]. Seventy-five per cent of the antimicrobials used in animal production are consumed by China, Brazil, the United States, Thailand, India, Iran, Spain, Russia, Mexico and Argentina[9]. Antimicrobials in livestock are used for therapeutic and non-therapeutic purposes, such as growth promotion and prophylaxis/metaphylaxis (mass prophylaxis) of infectious diseases. Using antibiotics in sub-therapeutic concentrations in livestock for non-therapeutic purposes exerts selective pressure on bacteria and results in the steady evolution and selection of resistant strains. It is important to monitor the use of sub-therapeutic concentrations of antibiotics in animal husbandry as livestock can become reservoirs of AR bacterial strains[10]. The development of AR in livestock poses a threat to humans since the resistant bacteria can be transmitted from animals directly via food (e.g. meat, fish, eggs and dairy products) and contact, or indirectly, through the environment[2].

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The majority of antibiotics are not completely metabolized by animals and human beings, and 60–90% of doses of the administered antibiotics are excreted in urine and faeces. These residues accumulate in water or soil through wastewater, animal manure, sewage or biosolids. Wastewater treatment plants cannot degrade the antibiotics completely. In soil, abiotic (hydrolysis, photo-degradation and sorption–desorption) and biotic (microbial degradation) processes contribute to the degradation of the antibiotics. It also depends upon soil properties, such as organic matter content, pH, moisture, temperature, oxygen status and soil texture. All these factors contribute to the variable persistence of antibiotics in the soils. Fluoroquinolones, macrolides and tetracyclines have higher half-life values in soil compared to other antibiotics[11].

The presence of antibiotics or their residues exerts indirect weak selection pressure on microbes in the soil, water and other environmental sites[3]. Resistant bacteria can be selected in natural environments at antibiotic concentrations several hundred-fold below lethal concentrations[12]. This selection pressure is more intense in hospitals, medical/veterinary facilities and animal farms where antibiotics or their residues are present in relatively higher environmental concentrations and facilitate the emergence of multi-drug or extensively drug-resistant nosocomial bacterial strains[13,14]. Exposure to antibiotics or their residues eliminates the susceptible bacterial populations and selects resistant bacterial strains with elevated mutation rates and increased survival fitness and persistence[15]. The antibiotic resistance genes (ARGs) can be horizontally transferred to other pathogenic and commensal bacteria. The gradual accumulation of these resistance determinants in certain bacteria results in their evolution as reservoirs of drug-resistant strains. The evolution of antibiotic-resistant pathogenic strains results in shifting treatment regimens from first-line drugs to more expensive second- and third-line regimens[4].

AR is a health and socioeconomic problem, especially in resource-limiting settings. Marginalized human populations cannot access effective recommended treatments for bacterial infections[2]. Animal production under a resource-limiting setting also depends upon antimicrobials, which are used for disease prevention and growth promotion to compensate for poor hygiene standards and ill-organized animal husbandry systems[16]. The demand for high animal proteins in low and middle-income countries has shifted livestock production into an intensive farming system, eventually fuelling a higher use of antibiotics for animal disease prophylaxis and growth promotion[17].

The AR problem is aggravated by an ever-decreasing supply of novel antibiotics, thereby limiting the treatment options for resistant bacterial infections. It is believed that the current antibiotic development ecosystem is fragile and insufficient to meet the growing threat of antibiotic-resistant pathogens. Most antibiotics used to treat resistant bacterial infections are losing their effectiveness[1]. Unlike other new drugs, new antibiotics are reserved for the treatment of only those infections which cannot be treated with older antibiotics and are not available for general treatment. Thus, investment in developing novel antibiotics is not considered economically viable. It is important to incentivize the companies involved in developing antibiotics by awarding them grants or manufacturing contracts by the governments to ensure the economic viability of such projects[18,19]. The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act, introduced in the US Senate and House of Representatives in 2021, is the right step in this direction, ensuring economic returns and thereby keeping the antibiotic development financially viable for developers/manufacturers[20]. Health systems, especially in developed countries, had over the years imposed restrictions and penalties on treatment reimbursement to prevent the misuse of antibiotics. In order to encourage antimicrobial research and development, health systems are now focusing on adopting relaxed reimbursement policies for new, particularly reserve antimicrobials[21].

Antibiotic development ecosystems lack innovation, and it is important to note that many new antibiotics approved in recent years have mechanisms/structures similar to earlier ones. Bacteria may develop resistance to these new drugs in a quick span of time. Therefore, novel antibiotics with new mechanisms of action and chemical structures are the need of the hour[22]. According to World Health Organization (WHO), there are major gaps in the development of antibacterial agents, and the present antibacterial pipeline cannot counter the threat of drug resistance. Of the 27 traditional antibiotics under development against WHO-priority pathogens, the majority are derivatives of existing antibiotic classes. Only six of these 27 antibiotics fulfil at least one of the WHO innovation criteria (absence of known cross-resistance, new target, new mode of action and/or new class). Over 80% (10/12) of the newly approved antibiotics belong to existing antibiotic classes for which resistance mechanisms are established[23].

Antimicrobial/antibiotic resistance surveillance

AMR/AR remains an underestimated public health problem because of limited testing, underdeveloped laboratory and communication infrastructure, lack of trained and qualified staff and ill-defined integrated population-based surveillance programmes[24]. Information on the current burden of AR and its trends and antibiotic consumption is crucial to design AR combating strategies. Surveillance systems are the core component of AR management programmes[25]. An accurate and reliable surveillance system is a prerequisite for assessing the actual burden of AR on humans, animals and the environment[24]. Surveillance is an intensive form of data recording and involves gathering, recording and analysis of data with the dissemination of information to stakeholders so that effective actions can be taken[26].

AR surveillance maintains continuous watchfulness over the distribution and trends of resistance and can provide

information on the success of a newly introduced intervention strategy[27]. AR surveillance systems are defined as structured and systematic procedures to measure the prevalence or incidence of AR through continuous or periodical surveillance performed with a defined methodology and with specified indicators[28,29]. The Global Antimicrobial Resistance Surveillance System (GLASS), launched by WHO in 2015, is a global collaborative effort to regulate AMR surveillance programmes to support global action on this emerging public health threat[30].

As per the World Organization for Animal Health, surveillance of AR is necessary to: (i) assess and determine the trends and sources of antimicrobial resistance in bacteria; (ii) detect the emergence of new AMR mechanisms; (iii) provide the data necessary for conducting risk analyses as relevant to animal and human health; (iv) provide a basis for policy recommendations for animal and human health; (v) provide information for evaluating antimicrobial prescribing practices and for prudent use recommendations, and (vi) assess and determine effects of actions to combat AMR[31].

Types of antimicrobial/antibiotic resistance surveillance

The data collected by the various AMR/AR surveillance systems can provide information on the actual burden of resistance at the local, national and international levels[28]. Depending upon the requirements, the AR surveillance data can be collected at regional, national and international levels. After analysis and interpretation, AR surveillance data collected at the local level can assist clinicians in rationally choosing antibiotics. AR data collected at regional or national level can be used to elucidate the trends of AR over time and formulation of empirical treatment guidelines. It is important that the objectives of surveillance should be clearly defined, and methods used should fulfil the objectives of the programme. Preference should be given to those programmes with the least investment having a major impact on AR[27].

AR surveillance approaches can be comprehensive or sentinel. The comprehensive approach focuses on surveillance of all the cases of a specified disease (or pathogen) in population at risk. It requires the involvement of a wide range of clinicians or laboratories. Comprehensive surveillance is useful for the collection of limited sets of data, e.g. type of specimen and resistance pattern. In sentinel surveillance, indicator data is collected from representative or sentinel populations and is more suitable for prolonged, continuous and detailed data collection, e.g. long-term trends or the emergence of AR. Depending on the availability of the resources, the surveillance can be continuous or episodic (limited periods). Under AR surveillance, data collection can be active (reports are sought regularly from primary data collectors) or passive (reports are a waited from primary data collectors)[32].

Need for integrated harmonized AR surveillance

AR is a One Health problem and requires integrated surveillance programmes[33]. An integrated surveillance system involves collecting, validating, analysing, and reporting of relevant microbiological and epidemiological data on AMR in bacteria from humans, animals, and environment, as well as relevant antimicrobial use in humans and animals[34]. An integrated surveillance programme requires holistic, multisectoral, and multi-disciplinary approaches across academic institutions, and government and non-government agencies[35]. International collaborations between different AR surveillance networks are required to estimate the burden of AR and the prudent use of antibiotics in humans and animals[36].

Implementation of integrated international and national AR surveillance programmes requires uniformity in methods (sampling, testing and reporting), antibiotic susceptibility testing (AST) protocols, targeted bacterial species, tested antimicrobials, clinical breakpoints, interpretation criteria (resistant, intermediately susceptible and susceptible) and control strains used. This harmonization of AR surveillance programmes is crucial for reliable data generation and comparison of AR data on regional, national and global levels[16].

All AR surveillance systems do not follow the same AST interpretation criteria and generate heterogeneous data. This heterogeneity also arises due to a lack of uniformity in bacterial species targeted, selection of antibiotics, AST methods, susceptibility interpretation criteria/breakpoints, lot numbers of culture media used and resistance phenotypes to be monitored[16,28]. The heterogeneous data generated by the different AR surveillance systems becomes difficult to compare (between laboratories across different geographical regions), analyse and interpret. AST criteria recommended by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are the most commonly followed guidelines by different AR surveillance programmes around the world[37,38]. However, the interpretation criteria suggested by these two agencies are not the same. A change in interpretation criteria from CLSI to EUCAST increases the number of strains classified as multidrug-resistant and has different levels of agreement. Harmonization of clinical minimum inhibitory concentrations (MIC) breakpoints or zones of inhibition (ZOI) is important for epidemiological purposes to compare resistance rates[39].

The heterogeneity between methods or functioning of different laboratories can be overcome by adopting a centralized approach for collecting and testing the isolates[40]. Under this approach, isolates collected by different centres (hospitals, diagnostic laboratories, etc.) are processed at a central laboratory, thereby ensuring uniformity in organism collection, storage, transportation and application of recommended methods of AST. Under this system, tested isolates are easily available for further studies, such as

determining resistance mechanisms or epidemiological typing. Centralized laboratory-based surveillance has a major limitation of low throughput, and only a restricted number of isolates can be tested. These kinds of studies rely on the performance of control/reference strains for the accuracy of laboratory methods and procedures. An external quality assurance involving periodic (once/twice a year) testing of strains of undisclosed antibiotic susceptibility supplied by an external reference laboratory must be applied for AR surveillance programmes with a centralized approach.

Surveillance systems relying on AST data generated by participating laboratories need to be harmonized, and such laboratories have to give up their own methods. All the participating laboratories must use reference strains with known antimicrobial susceptibility as controls and should be provided with culture media of the same make and lot numbers to minimize variations in the results. Reference collection of control strains should include organisms with different resistance mechanisms and degrees of susceptibility to different classes of antibiotics. Such surveillance systems must run a periodic (once/twice a year) quality assurance programme between participating laboratories to assess the validity and reliability of the results[40]. Under this quality assurance programme, the same bacterial strains with undisclosed antibiotic susceptibility are tested by all participating laboratories using recommended AST methods and results are compared. A high level of agreement (≥90%) between the results of different participating laboratories is desirable under the quality assurance programme[41].

Surveillance systems based on routine susceptibility testing access to already collected extensive data and include clinical laboratories. However, such data based on routine susceptibility testing methods differ between laboratories in AST procedures, antimicrobial agents used and susceptibility interpretation criteria. Online or software-based database solutions are required to collect routine susceptibility testing data. The accuracy and validity of such data remain under question for the surveillance systems with non-centralized testing[42]. AST programmes, along with proficiency in testing, must also assess the reporting accuracy[43].

Importance of quality assurance and quality control in AR surveillance

The primary role of AST laboratories is to provide accurate and timely results to choose the optimum therapy/treatment guidelines for treating infectious diseases. AST also provides options to choose safe, least toxic, cheap and most effective antibiotics from available drugs. AST procedures are susceptible to changes in laboratory conditions/chemicals/bacteriological media. It is crucial that AST procedures should be standardized and must have rigorous quality controls for accurate and reproducible results. AST results help in elucidating the emerging resistance and novel resistance patterns. These can be applied to define the agents of choice for empirical therapy, establish policies for prescribing antibiotics, conduct epidemiological studies or resistance surveillance and evaluate the efficacy of newly developed agents[27].

Standard processes required to establish quality measures in the laboratory are the functions of quality assurance (QA) and quality control (QC) programmes. QA can be defined as the overall programme by which the quality of the test results can be guaranteed. QA monitors the overall performance of the laboratory and covers pre-analytical, analytical and post-analytical phases of testing. QC monitors the analytical phase of testing and guarantees the proper working of the test. Standardization of AST by adopting the QA and QC programmes is essential for generating valid and reliable antimicrobial testing data. CLSI/EUCAST guidelines help laboratories to perform QC tests, measure and record results, prepare bacterial inoculum, choose control strains, interpret results and provide corrective measures for errors in AST procedures[44].

AST methodology requires standardization of bacterial inoculum size, growth media, growth/incubation conditions (atmosphere, temperature, duration) and antimicrobials to be tested and their concentrations[38]. Direct colony suspension method is the most frequent method used to prepare inoculum from an 18–24 h grown bacterial culture. The turbidity of bacterial suspension is adjusted to 0.5 McFarland standard, which corresponds to $1–2 \times 10^8$ colony forming units (cfu)/ml. After turbidity adjustment, this inoculum suspension should be used within 15 min of preparation. Muller Hinton agar (MHA) is the recommended medium for AST[37,45]. In disc diffusion or *E*-test method, 100 µl (approximately 10^7 cfu/ml) of inoculums is spread uniformly on petri plates containing sterile MHA. In MIC determination by agar dilution method, 2 µl of the 1 : 10 bacterial suspension containing approximately 200 cfu/ml is delivered onto antibiotic-containing and control plates using a multi-spot inoculator[46]. CLSI/EUCAST guidelines should be followed to determine the incubation conditions, panel antimicrobials and their concentrations for bacterial species under investigation[37,38].

Bacterial strains used as controls in AST procedures must be carefully monitored for their MIC or ZOI ranges and loss of resistance mechanisms. These strains should be stored on recommended media under optimum storage conditions. The cultures should be stored at –80°C in 20% glycerol stocks. The control strain panel should include genetically stable isolates with different phenotypes. It should include both susceptible and resistant strains to previously and currently recommended antibiotics[47]. WHO recommends a panel of genotypically and phenotypically well-characterized 14 reference *Nessieria gonorrhoeae* strains as controls for gonococcal AST programmes. Antimicrobial susceptibility profiles and molecular mechanisms of AMR of this panel were determined for 20 different antimicrobials, including new or not previously recommended antibiotics, which can be used for gonorrohea treatment in the future[48].

The working cultures should be stored on nutrient agar (non-fastidious bacterial strains) or chocolate agar (fastidious bacterial strains) slants at 4°–8°C. The control strains should be checked regularly for purity by culture characteristics, morphology and biochemical reactions. Any changes in MIC or ZOI of the control strains indicate contamination of the culture or genetic changes[47]. New batches of the media should be tested in parallel with old media using routine control strains against all the antimicrobial agents regularly used in susceptibility testing. The results of AST with new and old media should be comparable.

Antibiotics used for AST should be stored properly to preserve their potency. Stocks of antibiotic discs (used in disc diffusion assay) and antibiotic gradient strips (used in *E*-test) should be stored below 8°C and preferably at –20°C or as per manufacturer's recommendations. Antibiotic discs/strips and powder should not be used after the expiry date. Antibiotic powders used in agar dilution methods should be stored at –20°C. Stock solutions of the antibiotic powders prepared for future use can be stored at –80°C indefinitely without losing potency. These stock solutions are meant for one time use as repeated freezing and thawing reduces the potency of the antibiotic.

Control strains should be tested routinely for their ZOI or MIC values. Two consecutive results, either above or below the recommended limits, indicate a systematic error. More than two results outside the limits in a series of 20 tests also indicate the error. AST results consistently above or below the recommended breakpoints for several antimicrobial agents require a review of methodology. It includes checking of storage conditions for control strains and antibiotics, purity of the bacterial culture, consistency of bacterial media, depth of agar, time between inoculation and application of discs/strips, the temperature of the agar at which antibiotic is dissolved for agar dilution assay and storage conditions for the storage of Petri dishes, the potency of antibiotic (discs/strips or powder) and incubation conditions[47].

A good QC programme increases the precision and accuracy of AST results. QC programmes include both external quality and internal quality assessment. In external quality assessment (EQA), bacterial strains with defined susceptibility are distributed from a central laboratory to the participating laboratories (Figure 1). AST results from participating laboratories are submitted to the central laboratory for comparison and are analysed in relation to methods (disc diffusion, *E*-test or agar dilution) used. After analysing the results, the central laboratory provides feedback to the participating laboratories on their performance. This analysis allows a comparison of the accuracy of results with central laboratories and between participating laboratories. Such programmes help in providing the participating laboratories opportunities to identify discrepancies and improve AST protocols[47]. EQA should be a part of any AMR surveillance system as it not only cross-validates the data generated by participating laboratories but also establishes the comparability of data generated from different geographical areas[34].

The National Microbiology Laboratory (NML) of the Public Health Agency of Canada has been running one such proficiency and accuracy testing programme to monitor antimicrobial susceptibilities of *N. gonorrhoeae* isolates as part of the National *N. gonorrhoeae* Antimicrobial Surveillance Program since 1985. Under this programme, the participating laboratories are provided with a panel of *N. gonorrhoeae* strains with undisclosed antimicrobial susceptibilities comprising four isolates currently circulating in Canada and one blinded reference strain. The participating laboratories test these isolates with the recommended antimicrobials and testing methods routinely used in their laboratory. The NML also tests all the isolates sent to the participating laboratories. The AST results of all the participating laboratories and those of NML are analysed and compared. The agreement of the results for MICs of different antibiotics should be ≥90% (refs 41, 49). A similar QC comparison programme was initiated in the 1990s under WHO approved Gonococcal Antimicrobial Susceptibility Programme in Latin America and the Caribbean (GASP-LAC) for antimicrobial susceptibility testing of *N. gonorrhoeae* in Latin American and Caribbean countries[50,51].

Internal QC pertains to the proper functioning of the AST laboratory (Figure 1). It is mainly dependent upon the performance of control reference strains. In this, the bacterial strains are subjected to AST again on the same day as they were tested previously for the first time, but the identity of the bacterial strains is blinded during the second testing. The results of the two tests are compared, and discrepancies are noted. This assessment system should be adopted in those laboratories where the EQA system is absent, and the number of tested bacterial isolates is low[47].

Integrated surveillance of AMR across the One Health sector is critically important for formulating effective evidence-based policies to control and prevent AMR. GLASS was the first global collaborative effort to standardize AMR surveillance. GLASS provides a standardized approach to the collection, analysis, interpretation and sharing of data by countries and seeks to actively support capacity building, and monitor the status of existing and new national surveillance systems. GLASS collaborates with large regional networks, the European Antimicrobial Resistance Surveillance Network (EARS-Net), Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR), the Latin American Network for Antimicrobial Resistance Surveillance (Rede Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA)), and the Western Pacific Regional Antimicrobial Consumption Surveillance System (WPRACSS)[52]. The EARS-Net was started in 1998 and is a publicly funded network of national AMR surveillance systems of European Union countries. It is a multicountry surveillance network and collects routine clinical antibiotic susceptibility data from national surveillance systems[53]. CAESAR is a network of national AMR

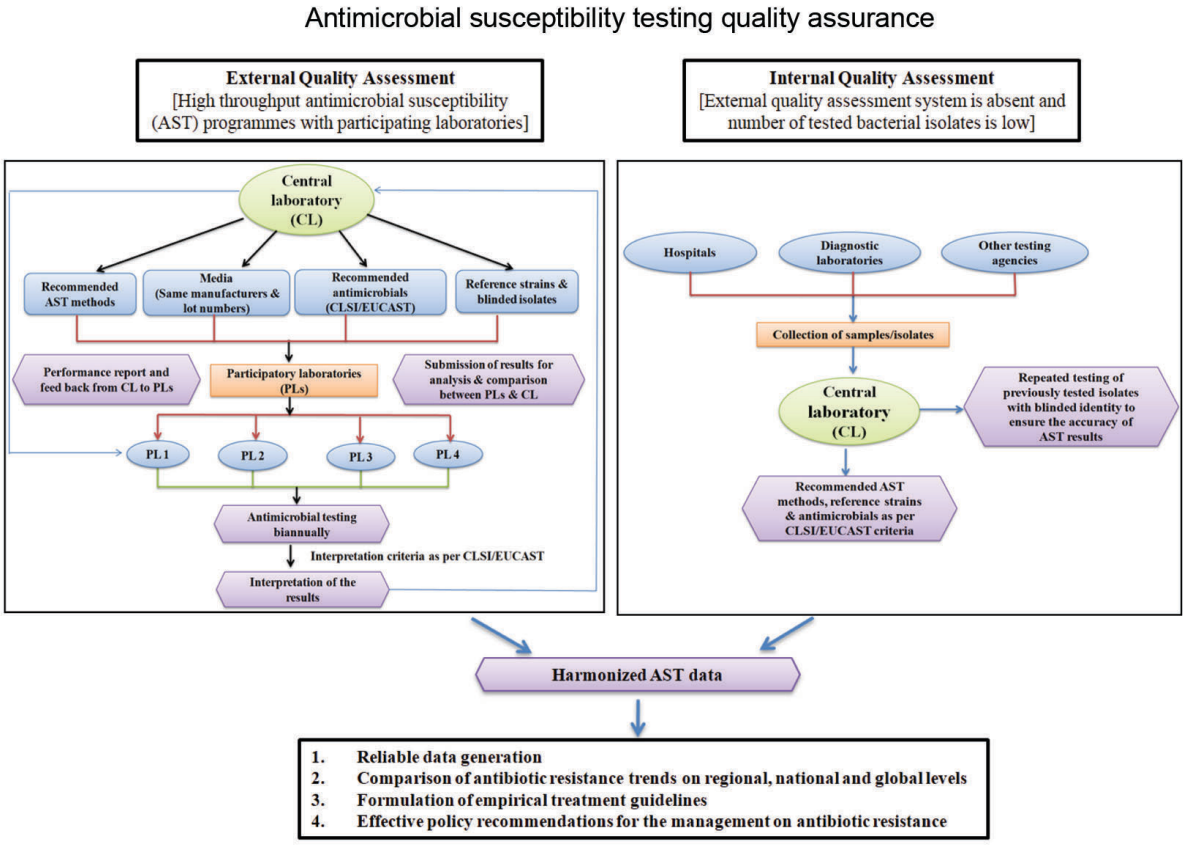

Figure 1. Schematic representation of external and internal quality assurance programmes for harmonized antibiotic resistance data generation.

surveillance systems and includes all countries in the WHO European Region that are not part of the EARS-Net[54]. ReLAVRA was established in 1996 by the Pan American Health Organization (PAHO)/WHO regional office and the partnering member states. The network is one of the oldest and includes 20 countries. Each participating country in the ReLAVRA is represented by a national reference laboratory[55].

In the USA, the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) was established in 1996 and became nationwide in 2003. It is the collaboration among state and local public health departments, the Centers for Disease Control, the US Food and Drug Administration (FDA), and the US Department of Agriculture (USDA). NARMS monitors changes in the antimicrobial susceptibility of certain enteric bacteria from human beings (CDC), retail meats (FDA) and food animals (USDA). It provides information on emerging bacterial resistance, the spread of resistance and the difference between resistant and susceptible infections[56]. In 2016, CDC established the Antimicrobial Resistance Laboratory Network (AR Lab Network). The network aims to provide nationwide laboratory capacity to rapidly detect AMR, inform local responses to prevent the spread of resistance and close the gaps between local capabilities and the data needed to combat AMR in the USA. In 2021, CDC launched Global Antimicrobial Resistance Laboratory and Response Network (Global AR Lab & Response Network). The objectives of this network are to improve the detection of existing and emerging AMR threats outside of the USA and to design global prevention strategies. Both these networks support laboratory testing in health care, community and the environment (e.g. water, soil)[57]. Canadian Nosocomial Infection Surveillance Program and the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) collect data on resistant human nosocomial pathogens, zoonotic food-borne pathogens and antimicrobial utilization in both humans and animals[58].

In India, the Indian Council of Medical Research (ICMR), New Delhi, launched Antimicrobial Resistance Surveillance and Research Network (AMRSN) in 2013 to collate AMR data nationally and to elucidate mechanisms of the evolution of AMR. The main goals of ICMR-AMRSN are to: (i) establish a network of hospitals to monitor trends in the antimicrobial susceptibility profiles of clinically important bacteria and fungi limited to human health; (ii) include comprehensive molecular studies for identifying the clonality of drug-resistant pathogens and their transmission dynamics to enable a better understanding of AMR in the Indian context and develop suitable interventions; (iii) disseminate information on AMR in pathogenic organisms to stakeholders to promote interventions that reduce

AMR, and (iv) create data management system for data collection and analysis[59]. ICMR-AMRSN functions through seven nodal centres (NCs) in four tertiary care hospitals and targets seven groups of pathogens for AMR surveillance. These pathogen groups and nodal centres are: (i) enterobacterales causing sepsis (Postgraduate Institute of Medical Education and Research, Chandigarh); (ii) gram-negative non-fermenters (Christian Medical College, Vellore); (iii) gram-positives: staphylococci and enterococci (Jawaharlal Institute of Medical Education and Research, Puducherry); (iv) typhoidal Salmonella (All India Institute of Medical Sciences, New Delhi); (v) diarrhoeagenic bacterial organisms (Christian Medical College, Vellore); (vi) fungal pathogens (Postgraduate Institute of Medical Education and Research, Chandigarh), and (vii) streptococcus pneumoniae (Christian Medical College, Vellore). Twenty regional laboratories/regional centres (RCs) are included from tertiary care hospitals to provide antimicrobial susceptibility data and a fixed number of isolates for each pathogenic group. The RCs perform only antimicrobial susceptibility testing, and NCs carry out detailed molecular studies on the identified resistant organisms (ICMR). ICMR-AMRSN is a harmonized AMR surveillance programme, and the uniformity in antimicrobial susceptibility data is ensured by periodically revising standard operating procedures in bacteriology and mycology and following the CLSI guidelines[60].

In 2016, ICMR agreed with the Indian Council of Agricultural Research (1CAR) to support collaborative research on areas of mutual interest, including AMR. National Action Plan 2017 identified surveillance of AMR in the country as a strategic priority. Implementing a long-term integrated AMR surveillance programme linking human and veterinary sectors similar to ICMR-AMRSN in the country was essential to address the menace of AMR holistically. Eight nationally representative veterinary microbiology laboratories were assessed for participation in an integrated AMR surveillance network. Lack of dedicated funding for AMR surveillance, absence of standard guidelines for antimicrobial susceptibility testing, shortage of reference strains and absence of data sharing mechanisms were identified as the major gaps for implementing integrated AMR surveillance network in veterinary sciences in India[61].

In August 2018, ICAR, with the cooperation of the Food and Agricultural Organization (FAO) and the United States Agency for International Development (USAID), formed the Indian Network of Fisheries and Animal Antimicrobial Resistance (INFAAR). This network aims to verify AMR in animal and fish production systems, describe the spread of resistant bacterial strains and resistance genes, identify trends in resistance and generate hypotheses about sources and reservoirs of resistant bacteria. INFAAR is operational through 18 organizations (15 ICAR institutions and 3 state agriculture universities) in 20 centres (9 centres from fisheries and 11 from the livestock sector) spread across the country[62].

Conclusion

Surveillance programmes on AR must work under the One Health concept with a holistic approach at the animal–human–ecosystems interface. Integrating harmonized surveillance programmes requires reliable AR data generation and formulation of region-specific intervention strategies. A global or national surveillance programme lacking a defined objective and universally accepted epidemiological and microbiological approaches cannot comprehensively analyse the problems of AR. QA and QC programmes contribute significantly to the proficiency and accuracy of AST and, in turn, improve the reliability of data generated by AR surveillance programmes.

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