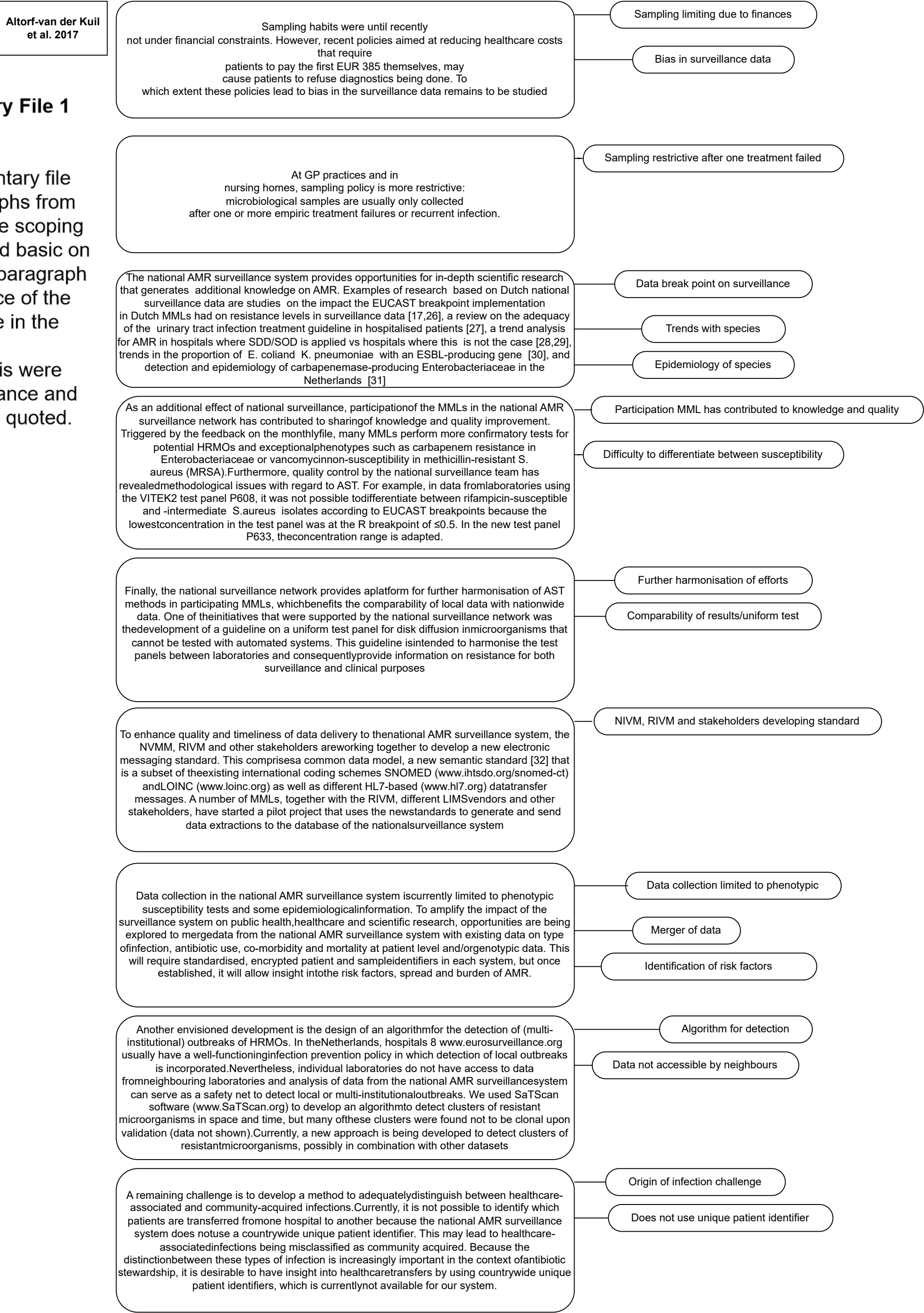
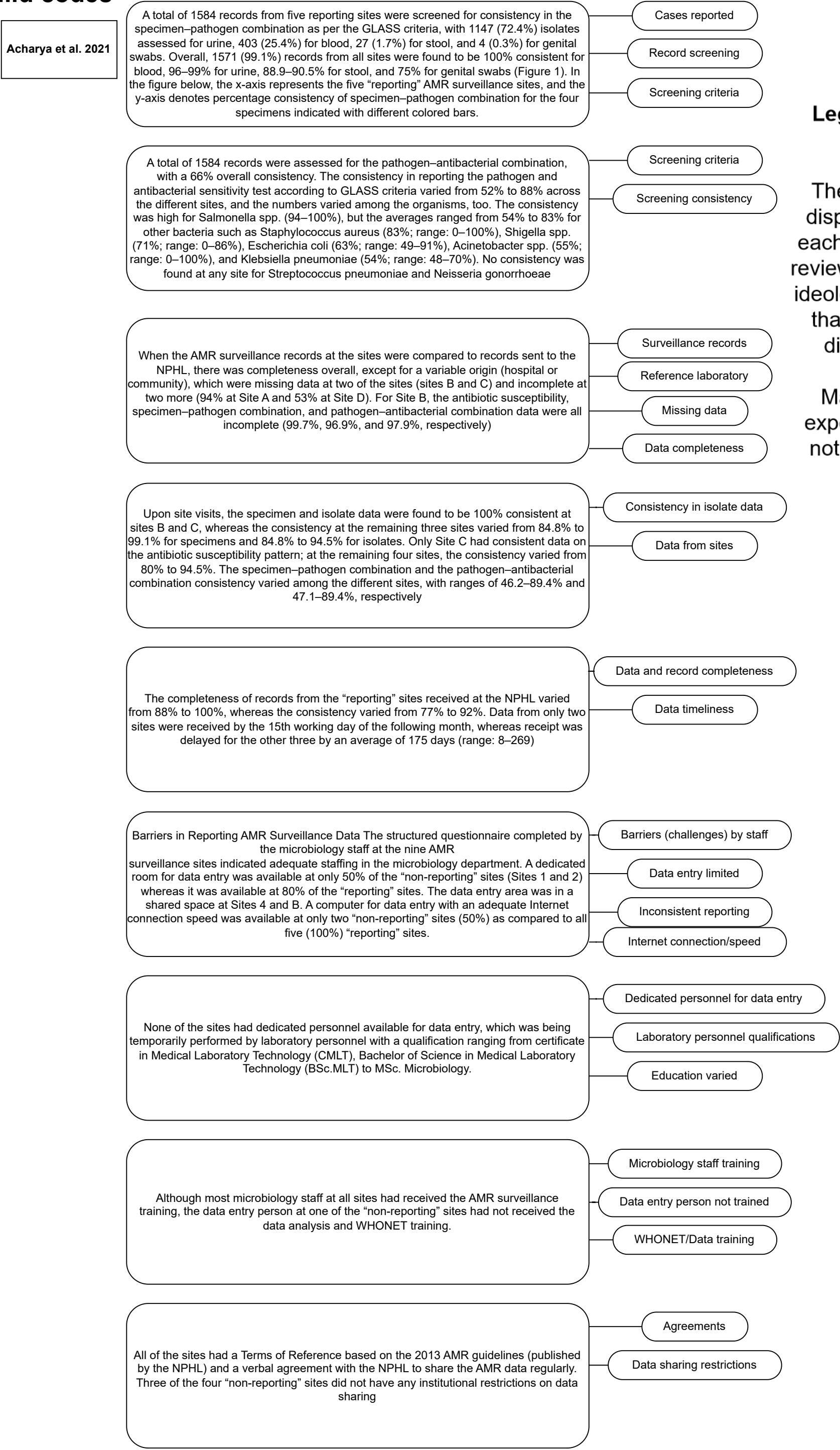


Child codes



Ashley et al. 2018a

In terms of the pathogens under surveillance, 45 networks were for AMR in bacteria or fungi (Table 1), 18 in malaria, 2 in TB, 6 in HIV and 1 for influenza (Table 2). The median (range) duration of the networks was 6 years (1–70). In the case of the discontinued malaria networks, inability to secure sustainable funding was an important reason for their collapse. Coverage of LMICs by the networks varied greatly. The median (range) number of LMICs included in the AMR surveillance networks for which the information was available was 8 (1–67). The WHO Global Influenza Surveillance and Response System (WHO GISRS) was the longest running network, established in 1947, and included the greatest number of LMICs (67), although antiviral resistance was not under surveillance at the outset.

Coverage of LMIC varied

Sustainable funding needed

Collapse due to funding

The networks were a heterogeneous group with different approaches to surveillance reflecting different objectives. The greatest diversity was found in the antibacterial surveillance group. Most global networks initiated and sponsored by pharmaceutical companies had the objective of evaluating susceptibility to specific drugs (registered drugs or new compounds). A variety of bacterial or fungal pathogens were collected by the pharmaceutical networks including community- and hospital-acquired isolates from both sterile and non-sterile sites. Academic networks tended to focus AMR surveillance around a specific clinical question, e.g. one project of the Asian Network for Surveillance of Resistant Pathogens (ANSORP) evaluated susceptibility of ESBL-producing isolates collected in the region to different antimicrobials (Tables 1 and 2). Other academic networks such as the WorldWide Antimalarial Resistance Network (WWARN) part of the newly established Infectious Diseases Data Observatory (IDDO) and International Epidemiologic Databases to Evaluate AIDS (IeDEA) have led analyses of individual patient data collected by other research groups.

Heterogeneous approaches

Global networks are sponsored

Academic networks - clinical

Pharmaceutical - susceptibility

There is one supranational European network for surveillance of food- and waterborne diseases and zoonoses that collects data on antimicrobial susceptibility in humans, animals and food. Larger networks that monitor foodborne infections [WHO Global Foodborne Infections network (GFNI) and PulseNet International], including animal and environmental isolates, do not report AMR data although GFNI does support an external quality assurance (EQA) programme for participating laboratories, which includes antimicrobial susceptibility testing (AST). No other supranational networks for AMR surveillance in animals were identified.

Supranational European network

Food, animals, and human

No other identified

The networks had different approaches to quality management (Table 4). The pharmaceutical-led networks typically did not involve LMIC laboratories in EQA programs but sent all isolates to a central laboratory for confirmatory testing. The global surveillance programs for AMR in TB, HIV, influenza, and gonorrhoea all had proficiency testing programs delivered via supranational networks of reference laboratories. Among the networks for AMR surveillance in bacteria, the Latin-American network, Red Latin-Americana de Vigilancia de la Resistencia a los Antimicrobianos (ReLAVRA) has been running an EQA scheme (LA-EQAS) since 2000 and provides proficiency testing services at no cost to participating laboratories. The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR), the non-EU European network, has used the UK National External Quality Assessment Service (UKNEQAS) for EQA. WHO-sponsored EQA efforts for AST included the discontinued WHO EQAS AST (1998–2001) and the WHO-AFRO/NICD-SA EQAP for countries within the WHO-AFRO region. Currently, GLASS recommends national reference laboratories take responsibility for quality management.

Proficiency testing programs via supranational networks

AMR networks - Latin American, non-European, and Central and East Asian networks have EQA schemes to laboratories

Table 5. Impacts and challenges of the AMR surveillance networks in LMICs with examples

Impacts	Challenges
• Led to changes in treatment policy (malaria networks) • Improved laboratory capacity by establishing networks of reference laboratories and quality management systems (ARMed, WHO/IUATLD, GASP, ReLAVRA, CAESAR) • Standardization of surveillance methodologies and data analysis (WHO Global Malaria Programme, ReLAVRA, WHO/IUATLD, HIVResNet, WHONET, WWARN) • Reduction in healthcare-associated infections in countries (INICC)^{21,22} • Exchange of information, training and knowledge between countries (WHO, ReLAVRA, WWARN, netSPEAR) • Data sharing with secondary benefits to inform treatment guidelines (WWARN, IeDEA) • Created global repositories of bacterial isolates; these can be used to screen new drugs (SENTRY, ANSORP) • Discovery of new resistance mechanisms (The Alexander Project)	• Low coverage, particularly in sub-Saharan Africa and India (GASP, GISRS) • Lack of representativeness of data, e.g. due to selective sampling (HIV, GASP, some CAESAR sites) • Difficulties of implementing routine blood culture/diagnostic microbiology in clinical practice (CAESAR) • 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 TB • Lack of engagement by some partners (netSPEAR) • Reporting delays • Sustainability due to underfunding with consequent understaffing; surveillance has generally not been given high priority by external donors (EANMAT, netSPEAR)

Low coverage

Lack of data representativeness

Difficulty in routine implementation

Difficulty in method integration

Lack of engagement

Reporting delays

Sustainability

The biggest challenges faced by the global networks have been achieving high coverage across LMICs and complying with the recommended frequency of reporting. The Global Project on Anti-Tuberculosis Drug Resistance Surveillance has collected resistance data from 155/194 member states since its inception in 1994. For 72 countries without routine drug susceptibility testing of cases, these data come from surveys, which are ideally performed every 5 years. The biggest gaps in surveillance in the most recent report were over West and central Africa. At an individual level, it was estimated that 33% of new TB cases and 60% of cases treated previously underwent rifampicin susceptibility testing in 2016.⁷ Only one-third of 106 malaria endemic countries were in compliance with the recommended targets for antimalarial drug efficacy surveillance (monitoring at three-yearly intervals) when last reported, although the Global Malaria Programme has recently updated its website with aggregate data from more studies.^{8,9} The Gonococcal Antimicrobial Surveillance Programme (GASP) has had no regional focal point in Africa since 2012. 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. WHO GISRS reported resistance to the neuraminidase inhibitors of influenza viruses in 2016.

Challenge in coverage

Complying with frequency of reporting

No routine susceptibility testing of cases

Coverage poor in high burden countries

In a detailed account of the experience of setting up the Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR), an East African network funded by the GAVI Alliance, in which routine surveillance for pneumococcal disease in public hospitals was strengthened, key challenges noted were difficulty in engaging the government or one of the participating countries in the network, poor performance of some sites despite training and problems with attracting funding. The importance of national and institutional ownership of surveillance activity and of framing it as part of routine activity rather than extra work was stressed. The benefits of collaboration between policymakers, academics and service providers were highlighted, as sentiment echoed by the experience of the malaria regional networks, which energized surveillance and also played a role in advocacy for policy change, acting as a bridge between research groups and national control programmes. Individual patient data meta-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.

netSPEAR strengthened

Difficulty in engaging government

Difficulty in sourcing funding

Collaboration as a bridge between sectors

Burns et al. 2018

The time and technical challenges to retrieve data from the AHC laboratory information system (LIMS) were identified as barriers that had precluded previous analysis and reporting. These barriers might also exist in other provinces. CAHSN provided an easier way to use alternative to the provincial LIMS system, and CAHSN could be quickly and reliably queried to retrieve real-time data (24). In addition, the CAHSN system allowed retrieval of anonymized data, eliminating the need for post-retrieval anonymization, thereby further reducing data security concerns.

Time challenges to retrieve data from LIMS

Technical challenges to retrieve data

CAHSN system allowed for faster and more secure retrieval

Robust surveillance systems include multiple surveillance components. Examining passively acquired AHC data with actively and passively acquired CIPARS data provided a comparatively low-cost method to use existing data to increase AMR surveillance in BC. When interpreting the data obtained from the CIPARS and AHC components, it is important to note differences between CIPARS and AHC data, which include: i) CIPARS implements an active, random sampling strategy, while AHC relies on passive sample procurement; ii) CIPARS samples are obtained from a larger portion of the food production continuum (live animals through abattoir to retail meat); iii) some CIPARS results are national and not specific to BC; and iv) AHC isolates are more likely than CIPARS isolates to originate from individuals that are sick or unthrifty, and might be more likely to have received antimicrobial treatment.

Low cost method to use existing data to increase AMR surveillance

CIPARS - random sampling strategy

AHC relies on passive sample procurement

CIPARS national and not specific to BC

AHC isolates more likely to originate from individuals that are sick

Preliminary findings from examining the AHC and CIPARS components together by food chain value, provide new information, which might be valuable for future surveillance activities. For example, during the survey of experts, interviewees expressed a common concern that using data from sick animals might lead to erroneously high estimates of AMR. Given the limitation of small sample sizes for some sample types, general similarities between AHC and CIPARS AMR for commodity chains indicate that this assumption warrants further examination. In humans, most AMR samples come from diagnostic samples. As another example, AHC data added evidence to support CIPARS data showing very low resistance to fluoroquinolones in Enterobacteriaceae. However, the lack of AHC AMR data for Campylobacter was an important limitation to interpretation. Improving capacity for assessing and reporting AMR in Campylobacter might add public health value to AHC's work. As a final example, examining AHC and CIPARS data side-by-side graphically illustrates that ceftriaxone resistance appears higher in AHC than in CIPARS Enterobacteriaceae isolates from turkeys, as well as that the CIPARS program was restricted to retail meat during 1 year (2013). The comparison suggests that if a detailed review of AHC data shows limited sampling bias (i.e., AHC data represent multiple premises over many years), increasing active surveillance for ceftriaxone AMR in turkeys in BC might be of comparative priority.

Data from sick animals leads to high estimates of AMR

Small sample sizes for some sample types

Improving capacity for assessing and reporting of AMR

Limited sampling bias

Collineau et al. 2019

Yet, there are a number of challenges that need to be addressed before the transition can be effective. There is still a lack of knowledge translation between bioinformaticians and risk assessors, with bioinformaticians having a limited understanding of the type of

Knowledge translation gap between parties

LMICs shoulder the bulk of the global burden of infectious diseases and drug resistance but their surveillance systems tend to be weaker than those in high-income countries (HICs), because passive surveillance cannot be integrated with routine casemanagement of patients easily in many areas. This problem has been circumvented to an extent in TB, malaria and HIV AMR surveillance by using active approaches to surveillance in LMICs and gathering data intermittently to provide a snapshot of the situation. However, achieving high coverage of all LMICs and complying with the recommended frequency of surveillance has been difficult. A review of the HIV, TB and malaria surveillance systems in 2011 suggested that one risk of integrating surveillance into routine activities was that high-quality implementation was less likely.¹⁷ By contrast, GLASS is based on building up or strengthening traditional models of passive case-based surveillance to generate data, as in HICs. Priority pathogens, drugs and specimens for surveillance are named but, unlike the other networks, GLASS does not specify 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 directly on primary TB specimens without an intermediate culture step.¹⁸ Molecular surveillance for drug resistance in other bacteria remains some way off but should be a high priority in order to simplify surveillance in LMICs

Difficulty in recommended frequency of surveillance

Responsibility given to national reference centres rather than supranational

No intermediate culture set up

Assessing the representativeness of AMR surveillance data presents a particular challenge. This will be affected by the geographical location and number of sentinel sites, the number and characteristics of individuals sampled, prior treatment history, the incidence of the target pathogen and the methods of detection. WHO/IUATLD has developed its surveillance methodology to the point where it uses survey data to estimate MDR-TB incidence worldwide but this is exceptional for the global programmes. The global report on early warning indicators of HIV drug resistance states that data from most countries cannot be considered as representative due to the way in which the clinics sampled were selected.¹¹ In malaria therapeutic efficacy studies in high transmission settings, children less than five years of age are studied since they have the lowest levels of acquired immunity to malaria to give a 'worst-case scenario' depiction of drug efficacy. AMR surveillance for the most commonly encountered bacteria, as it has been practised to date, presents more problems than for other pathogens because of the lack of agreed case definitions and standardized sampling methods. An analysis comparing trends in *Escherichia coli* resistance from 1997 to 2001 reported by the global Meropenem Yearly Susceptible Test Information Collection (MYSTIC) and SENTRY pharma networks showed that, despite collecting isolates from similar geographical areas, estimates of nonsusceptibility from MYSTIC were consistently higher than those from SENTRY. However, further analysis revealed this was due to a higher proportion of isolates from patients in ICUs in MYSTIC

Representativeness of AMR data is a challenge

Characteristics not taken into account

Characteristics not taken into account

AMR surveillance in animals is still in its infancy, with the exception of foodborne infections, but some strategies have been piloted in LMICs under the guidance of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). The challenges are great, e.g. progress towards standardizing AST breakpoints in veterinary microbiology is far behind that made in humans.

Standardization still being deliberated

A successful AMR surveillance network should generate up-to-date comparable, representative, high-quality data on pathogens of concern from the target population(s). It should be able to detect and track unexpected events including outbreaks in real time, have rapid, effective mechanisms for communication and reporting, and have 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. Very few networks were instigated to specifically monitor intervention programmes, e.g. the International Nosocomial Infection Control Consortium. Linking surveillance activity to interventions to combat drug resistance has the potential to increase their impact

Surveillance should generate representative high quality data

Effective mechanisms for data sharing

Strong leadership

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. Purely academic networks also produce high-quality data; they often target a clinical or policy question, but they too have limited influence on policy and their sustainability is reliant on external funding. Most of the networks are slow to report their findings and do not give unrestricted access to their data. The experience of the larger global programmes for AMR surveillance in TB, malaria and HIV suggests that options for more active surveillance may need to be considered in order to gather comparable useful data from low-income countries before reliable case-based surveillance can be established.

Pharma may not produce representative data

Limited laboratory capacity in LMICs

Limited influence on policy

Limited scope of surveillance

Chandrasekera et al. 2015

Limited sustainability

Implementing MHS-wide AMR surveillance has proven more challenging due in part to the sheer size of the system (more than 230 MTFs) and the stovepipe approach to data handling. Two strategies have been taken to address the need for AMR surveillance across the MHS: one by the Walter Reed Army Institute of Research with the Multidrug-Resistant Organism Repository and Surveillance Network and the other by the Navy Marine Corps Public Health Centers EpiData Center (NMCPHC-EDC). Together, the Multidrug-Resistant Organism Repository and Surveillance Network (MRSN) and EpiData Center (EDC) form the Antimicrobial Resistance Monitoring and Research Program (ARMoR).

Implementing surveillance difficult due to size

Collaboration between sectors

Bale et al. 2010

Our study illustrates important improvements in individual laboratory and network capability achievable through application of these established principles over time when the 'correct' result was ultimately obtained for 95.6% of tests performed in the Indian GASP in 2007. This highly satisfactory outcome was achieved through continuing close collaboration between the WHO collaborating centre and the SEAR regional reference laboratory on the one hand, and the liaison of this same laboratory, in its role as the Indian GASP coordinating laboratory, with Indian GASP participants on the other. A single proficiency survey for AMR in *N. gonorrhoeae* in the UK with six gonococcal strains sent to 411 laboratories in 1986 saw an 11% error rate [14] for gonococcal sensitivity tests. In a survey from 14 laboratories from Western Europe [15], overall concordance using all methods (disc diffusion, agar dilution, E test) was highest for ceftriaxone (93%) and lowest for tetracycline (72%) which is in contrast to our study. Disc diffusion gave the lowest overall concordance (72%) compared to MIC determination (>88%) by either method in the study from Western Europe [15]

Improvements in capability through principle

Collaboration between WHO and SEAR

The Indian GASP EQAS also confirmed the value of repeat challenges with identical but anonymized strains accompanied by general anonymous feedback to participants and detailed comment to individual centres. The importance of this feedback, including that in relation to technically correct, but wrongly interpreted laboratory data was especially noted. The outcome of this study suggests that this continuing educative process, conducted anonymously by dialogue between the coordinating centre and participants on an individual basis, means that the Indian EQAS has extended its programme beyond that of proficiency testing to establish a viable network forum that has substantially strengthened the Indian GASP. Other national and regional GASP EQAS programmes obtained similar results using, initially, monthly challenges accompanied by similar feedback and network-based educative processes [4, 16]. However, the Indian GASP EQAS was restricted to annual evaluations because of limited resources. Improved laboratory performance may have been achieved earlier if more frequent challenges, accompanied by education and consultation, had been possible.

Feedback from participants

Anonymous educative process

Dialogue between coordinating centre and participants

Network based educative process.

Limited resources

One major limitation of the disc-diffusion method revealed here was the failure to distinguish strains with 'decreased susceptibility' to ceftriaxone in a high proportion of tests. This finding provided valuable field data on the lack of utility in peripheral centres of the proposed system for ceftriaxone disc-diffusion testing that had worked well in a central reference laboratory. Recently additional published information provided further insights into the possible reasons for the failure of this trial of ceftriaxone disc diffusion testing. A number of inter-related molecular changes occurred in multiple genes that are responsible

Failure to distinguish strains

Lack of utility in peripheral centres

information required for QMRA modeling, and risk assessors having poor comprehension of how WGS data are analyzed, including what type of information can be generated and any limitations on these analyses. Risk assessors and epidemiologists need to be better trained in next generation sequencing techniques and molecular epidemiology (De Lamballerie, 2009; Arts and Weijnenberg, 2013). Risk assessors also have to be proactive and should be involved from the early stages of development of WGS databases and bioinformatics tools, so that they can make their needs more explicit and influence the type and format of data being generated, rather than simply acting as 'end-users' of WGS data. Input from both bioinformaticians and risk assessors should also be considered while designing surveillance programs and data collection initiatives to ensure these are capturing the data needed to perform the types of analyses described in this review.

Poor comprehension of data/analysis

Better training regarding techniques

Both be considered in designing surveillance programs

The different procedures through which WGS data are generated and analyzed have a strong influence on the results. For example, the choice of different sequencing platforms introduces systematic biases that have an impact on the inferred phylogenies (Kaas et al., 2014). With foodborne AMR pathogens easily traversing jurisdictions or countries, it can be problematic when different laboratories use different procedures and do not arrive at identical conclusions (Pightling et al., 2018).

Different procedures in WGS data

Problematic as different laboratories use different procedures

Efforts toward harmonization and standardization of WGS techniques are ongoing, for example under the Global Microbial Identifier (Moran-Gilad et al., 2015) and the PulseNet International initiatives (Nadon et al., 2017), but a consensus on methods, quality measures and thresholds for data generation and analysis of foodborne AMR pathogens has yet to be established (Lüth et al., 2018). In the absence of a current consensus, it is important to ensure all sequenced genomes are made publicly available where possible, or available privately across jurisdictions, as to allow researchers to repeat analyses within their pipelines or under their parameters. Standardization of epidemiological data (also referred to as 'metadata') accompanying WGS data is also critical to provide requisite contextual information necessary to any microbial risk assessment activity (Hill et al., 2017). The Genomic Epidemiology Ontology (GenEpiO) Consortium seeks a global standard for the metadata associated with WGS data, including laboratory, clinical and epidemiological data fields (e.g., strain names harmonized and compatible with previous classification schemes), as well as existing food categories (Griffiths et al., 2017). Data sharing and inter-operability (e.g., between laboratory and epidemiological databases) should also be addressed as <http://www.genomicsepidemiology.org/> key priorities to ensure the efficient use of WGS data (Pightling et al., 2018).

Harmonization through Global Microbial Identifier and other International initiatives

Consensus has yet to be made

Standardization of epidemiological data accompanying WGS

Consortium for global standard

Data sharing and interoperability

Global standard

for the alterations in susceptibility to extended-spectrum cephalosporins [18, 19]. However, the impact of these changes (both known and unknown) affects the extended-spectrum cephalosporins unequally. The injectable antibiotic ceftriaxone is least affected in terms of MIC increases and clinical treatment failure. The orally administered members of the group, such as cefixime and ceftibuten, are associated with greater relative MIC change and treatment failure [9, 18]. Consequently, results of susceptibility testing for ceftriaxone cannot represent the susceptibility status of all members of this group of antibiotics. Alternative testing methods relevant to all the different cephalosporins have therefore been developed and will be re-evaluated under peripheral centre conditions. Until these methods have been fully verified, the importance of using accurate MIC methods and appropriate internal controls for detecting reduced susceptibility to cephalosporins should be restated [11]. Finalization of these methods is relevant not only to India because of the detection of cephalosporin 'non-susceptible' strains of *N. gonorrhoeae* there [20], but also more widely because of the increasing spread and prevalence of these gonococci earlier if more frequent challenges, accompanied by education and consultation, had been possible.

Alternative methods for verification

Education and consultation

AMR surveillance of *N. gonorrhoeae* is critical for public health purposes [1, 6], but the data must be rigorously validated by ongoing appraisal of the quality of the results of the surveillance if it is to be used with confidence to alter treatment schedules [1, 6]. While the results of the Indian GASP EQAS challenges were encouraging, there is a clear need for continuing network-based educational programmes that emphasize adherence to proper laboratory testing methods, the importance of quality control, and the basic concepts of quality assurance, the latter including increased frequency of challenges accompanied by relevant feedback [6]. The lessons from the Indian GASP EQAS can provide helpful information in other settings at a time when there is a demonstrated need for more and better quality AMR data to assist in the control of gonorrhoea.

Data validation by appraisal

Clear need for educational programmes

Adherence to testing methods

Quality control and assurance with feedback

Bennani et al. 2021

We identified 30 key organisations directly involved in the national surveillance system (Table 1). Out of these, 15 belong to government organisations, nine to the private sector and six to international institutions.

30 organisations involved in surveillance

Planning, data collection, analysis, interpretation and reporting are conducted by each sector separately with the exception of Scotland where there is an OH surveillance report (Scottish One Health Antimicrobial Use and Antimicrobial Resistance Report [SONAAR]).¹⁹ There are also variations in the surveillance systems in the four UK countries, especially in humans where the implementation of the AMR strategy is fully developed. In animals, there is a UK wide annual surveillance report for AMR and AMU, which is the Veterinary Antimicrobial Resistance Surveillance (VARSS) report, while in humans there are separate surveillance reports in each UK nation.

Separation of activities

OH surveillance report

Variation in AMR system

In terms of cross-sectoral collaboration, the most important activity is the ResAlert contingency plan, which refers to the response upon identification of a resistant bacterial isolate from an animal considered to pose a potential risk to human and/or animal health.²⁰ This is a UK wide plan initiated in 2015 and coordinated by the VMD in collaboration with government agencies covering human and animal health, food safety and the devolved administrations. Depending on the hazard identified, relevant advisory committees are notified by the relevant agencies.^{20,21} Other examples of cross-sectoral collaborations include the UK OH reports and the DEFRA Antimicrobial Resistance Coordination (DARC) group. The UK OH report on human and animal antibiotic use, sales and resistance was produced by PHE and the VMD for the first time in 2015 and this helped to align the data across sectors and included also recommendations to address data limitations and to improve integrated analyses.²² A second report was published in 2019, which in addition to the data included in the first report had also data on AMR in isolates from retail meat.²¹ The DARC group coordinates, advises and reviews DEFRA activities on AMU in animals and AMR Veterinary Record 5 of 12 In micro-organisms from feedingstuffs, animals and food. This advisory group has representatives from science and policy from England, Northern Ireland, Scotland and Wales covering human and animal health and the environment.³

ResAlert contingency plan

UK wide plan

Different sectors encompassed

UK OH report aligned data across sectors

Addressed data limitations and integrated analyses

DARC group coordinates DEFRA activities

Advisory group has representatives from science and policy

The UK contributes to European and Global surveillance through different programmes that are represented as follows: 1. The European Antimicrobial Resistance Surveillance Network (EARS-Net): Run by ECDC and collects data on AMR in eight bacterial pathogens from invasive infections in humans (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp.).²³ 2. The European Surveillance of Antimicrobial Consumption Network (ESAC-Net): Run by ECDC and collects data on the consumption of antimicrobial agents in humans.²³ 3. The European Food and Waterborne Diseases and Zoonoses Network (FWD-Net): Run by ECDC and collects data on AMR in *Salmonella* spp., *Campylobacter* spp. and Shiga toxin/verocytotoxin-producing *E. coli* (STEC/VTEC). The data contribute to the EFSA/ECDC annual summary report. To facilitate comparison of the data between countries and with results from the AMR monitoring performed in isolates from animals and food products, EU protocol for harmonised monitoring of AMR in human *Salmonella* and *Campylobacter* isolates was developed by the ECDC.^{24,25} 4. The EU harmonised monitoring of antibiotic resistance in zoonotic and commensal bacteria from healthy FPs and food: Run by EFSA and collects resistance data on *Salmonella* spp. and *Campylobacter* spp. and indicator *E. coli* and *Enterococcus* spp.²⁴ 5. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC): Run by EMA and collects data on the use of antimicrobial agents in animals.²⁶ 6. The Global Antimicrobial Resistance Surveillance System (GLASS): Run by WHO and collects information on resistance among human priority bacterial pathogens from clinical specimens considered a threat globally.¹⁸

European and global contribution

Surveillance network ran by ECDC

Data collection of agents, food, and disease

Summary reports

Comparability of data

GLASS ran by WHO collects information on AMR

In animals, the veterinary antibiotic resistance and sales data monitoring programme is commissioned³ <https://www.gov.uk/government/groups/defra-antimicrobial-resistancecoordination-darc-group>. and funded by the VMD, which is an executive agency of DEFRA. The VMD is also responsible for the publication of the VARSS report, which includes data on antibiotic consumption (sales data and usage data), and antibiotic resistance from animals in the UK.^{9,27,28}

Funding by VMD

Fluit et al. 2006

A certain sample bias is present in every surveillance system, because different criteria are used by different physicians when selecting patients for microbiological investigation [8,9]. In addition, since isolates or data may be used in several studies, there are dangers in concatenating results or comparing the studies [10]. The longitudinal component of these studies may also be a problem, in that some centres may withdraw from a multicentre study. The problem of biased isolate inclusion is even greater for surveys of antibiotic resistance in the community. Usually, only samples from patients with persistent infections or infections refractory to treatment are referred to a central laboratory by a general practitioner, and it is not clear how representative these isolates are of strains causing community-acquired infections in general. Therefore, neither hospitals nor isolates may give a clear representative perspective of the global danger of resistance. Although longitudinal studies that include the same hospitals and types of isolates give some indication concerning trends, it is risky to provide guidance to clinicians for empirical antibiotic therapy based on this information, because of differences at the local level. Therefore, local resistance data must be available to physicians working in hospitals; regional data concerning community pathogens must be available to general practitioners; and national data must be available to healthcare policy-makers. Moreover, European and worldwide data must be freely available to all to provide early warning signs. One example of the need for a global information system is vancomycin-resistant *Staphylococcus aureus*. To date, there have been three reports of true vancomycin-resistant *S. aureus* [11–13], and because such bacteria pose a serious health-threat, early warning is very important.

Sampling bias in surveillance systems

Samples from persistent patients

Isolates may not give a clear representative perspective of the global danger of resistance

Good-quality susceptibility data are essential to detect trends, as well as new and rare resistance phenotypes. Unfortunately, the quality of resistance data, especially from clinical laboratories, is often questionable [13–16]. Quality control of the susceptibility data is therefore crucial. A further complication in Europe is the use of different definitions for 'resistant': i.e., when is an isolate 'susceptible', 'intermediately-resistant' or 'resistant' to an antibiotic?

Good quality susceptibility data needed

Questionable quality of data

Definitions differ for resistance

With few exceptions, surveillance efforts in the veterinary sector are limited and the different programmes are not coordinated. Furthermore, the criteria for testing isolates differ widely among countries, as do the antimicrobial agents tested. As a result, there is no clear picture of the extent of antibiotic resistance among isolates of veterinary origin [9]. The same is true for isolates from food; in many cases, it is only in following cases of food poisoning that an attempt is made to track antibiotic-resistant isolates to their source. The cost of adequate surveillance, despite the issue of food safety, and the small profit margins in the veterinary sector make the financing of surveillance in the veterinary and agriculture sectors difficult. Finally, although antibiotic resistant isolates have been described, no major efforts have been made to assess the reservoirs formed by pets and the environment.

Veterinary sector limited

Criteria differ from country to country

Between sectors there is overall difference

Cost of adequate surveillance

An additional problem is the limited availability of genetic data concerning antibiotic resistance. In most cases, it is unknown whether the spread of resistance is caused by the clonal spread of a resistant strain, or by the horizontal transfer of resistance determinants among different strains and species. Reference centres have responsibility in this area, but are often not well-equipped or supported to perform such research. Despite (e.g.) the HARMONY [17], GENE [18], CAMPYNET (<http://campynet.vetinst.dk>) and PULSENET (<http://www.cdc.gov/pulsenet/>) projects, in which a start has been made on the development and implementation of standardised and exchangeable typing methods to monitor clonal expansion, more work needs to be done in this field. A major problem is that standardised protocols are not implemented in all studies, and that testing for clonal spread is limited because it is costly and time-consuming. Another problem is that the spread of antibiotic resistance through horizontal transfer is rarely monitored. This includes spread among different reservoirs. Some surveillance programmes have reported data on a limited number of isolates and resistance determinants, but no large-scale structured efforts have been made to study such spread. The WHO recently identified this lack of information concerning microbial genetics and ecology in antimicrobial-resistant bacteria as a gap in current knowledge and hence a key need [3].

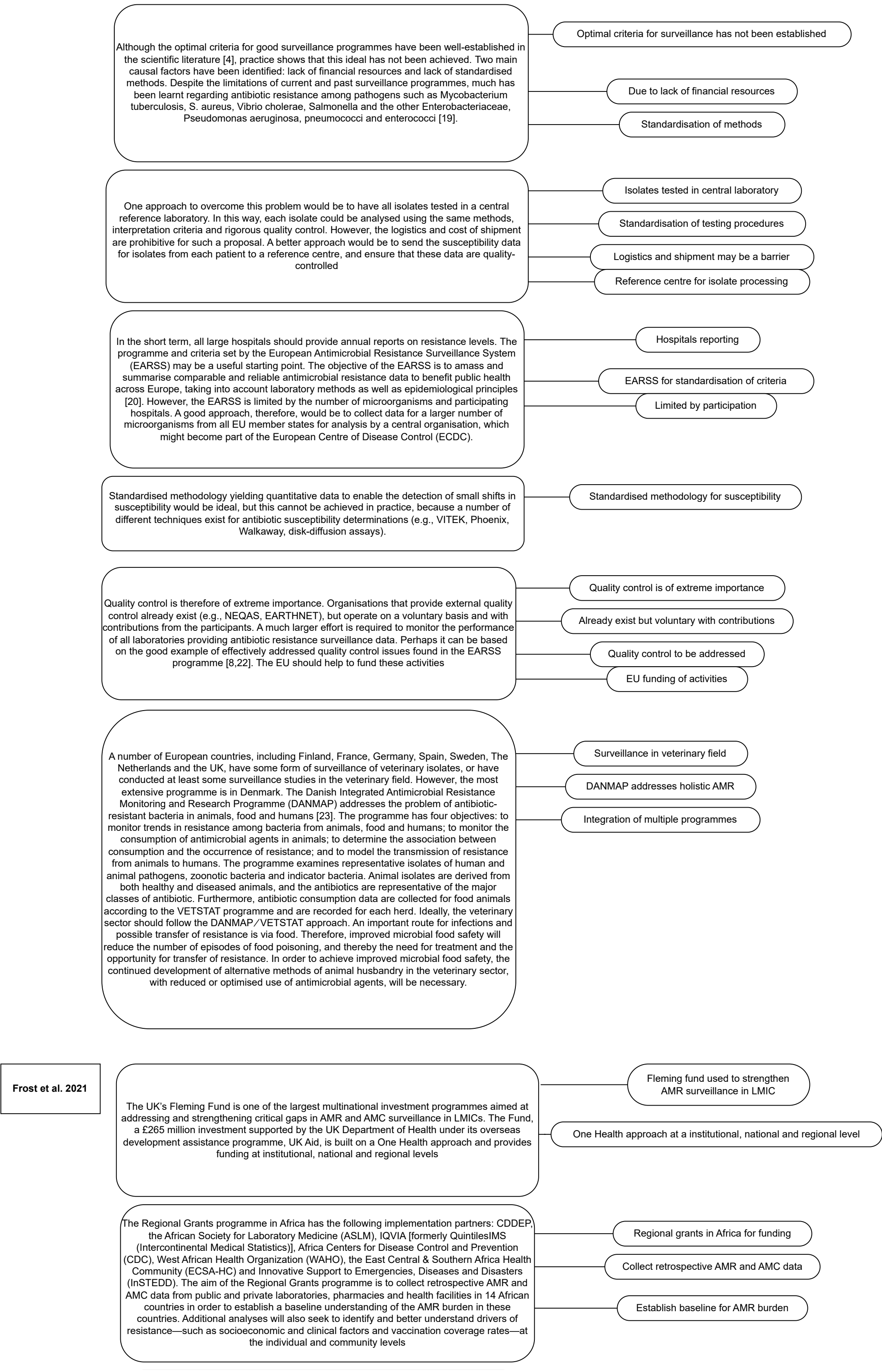
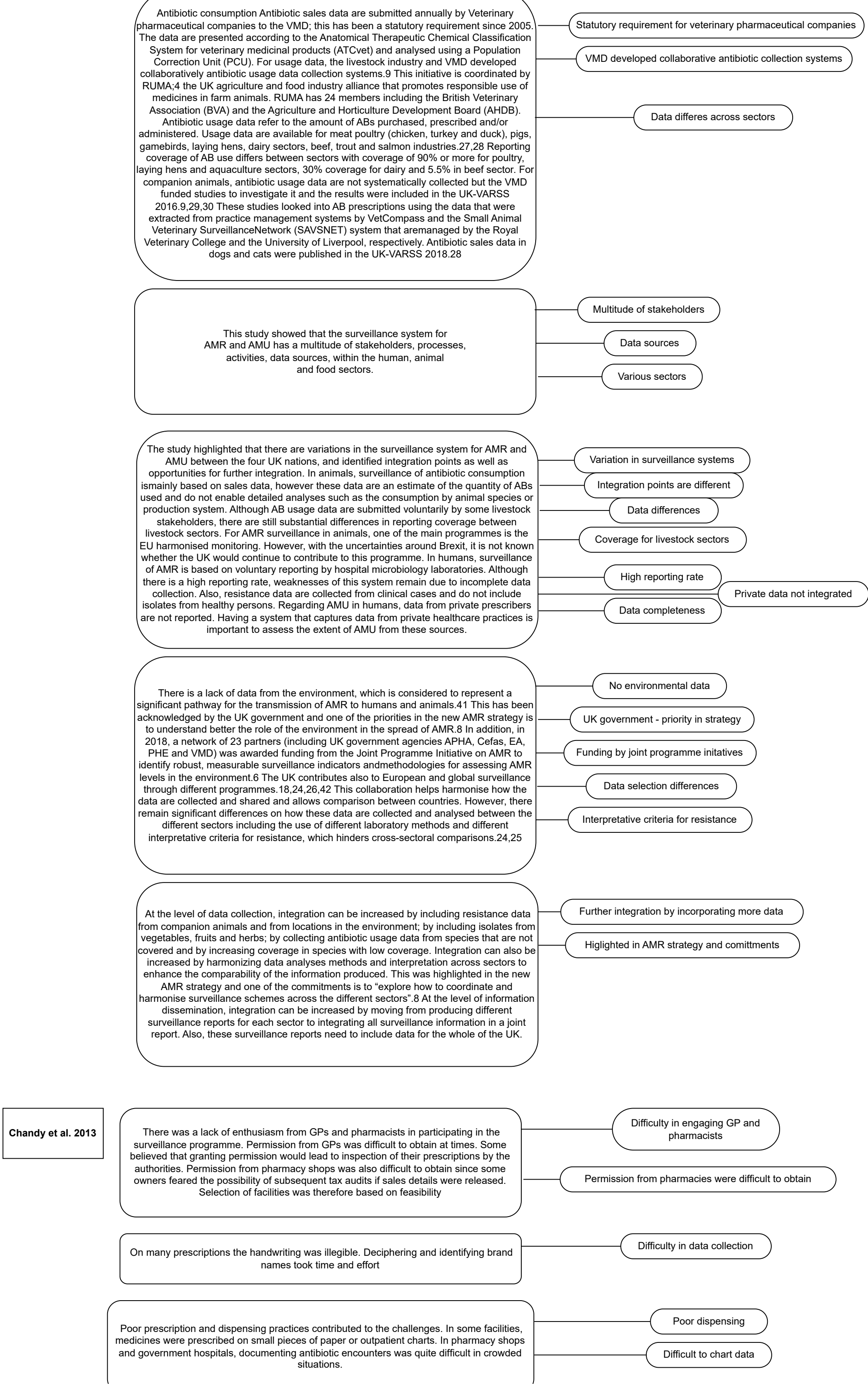
Limited availability of genetic data

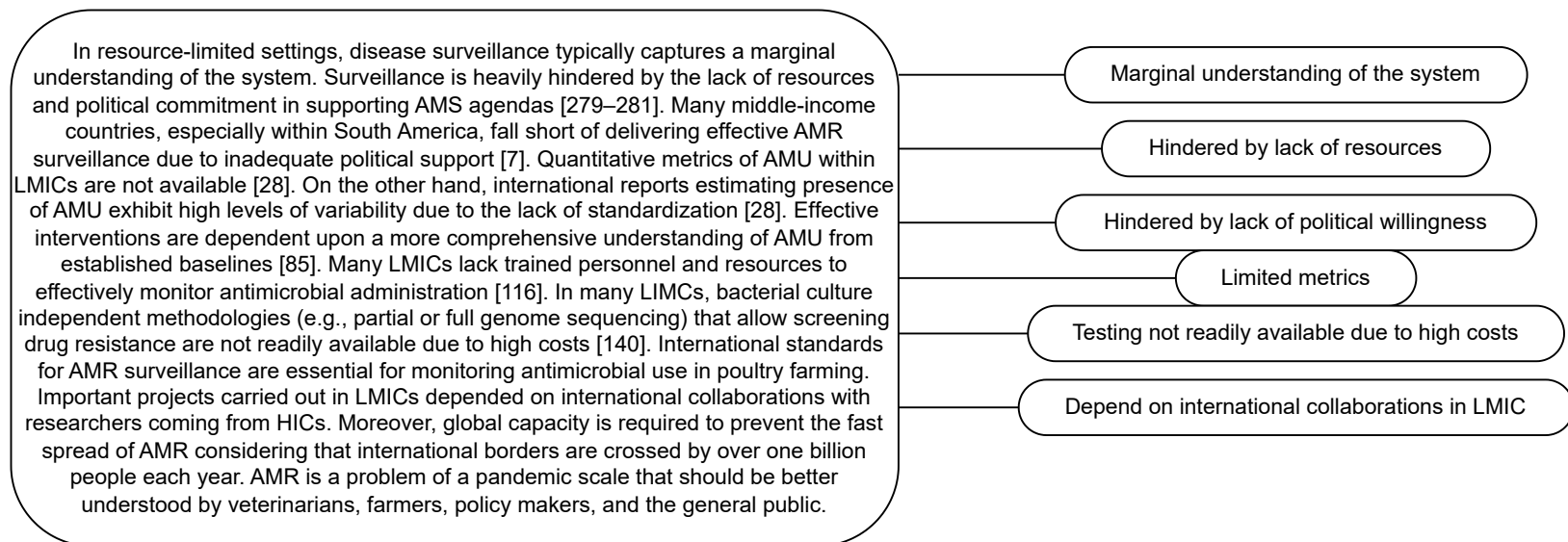
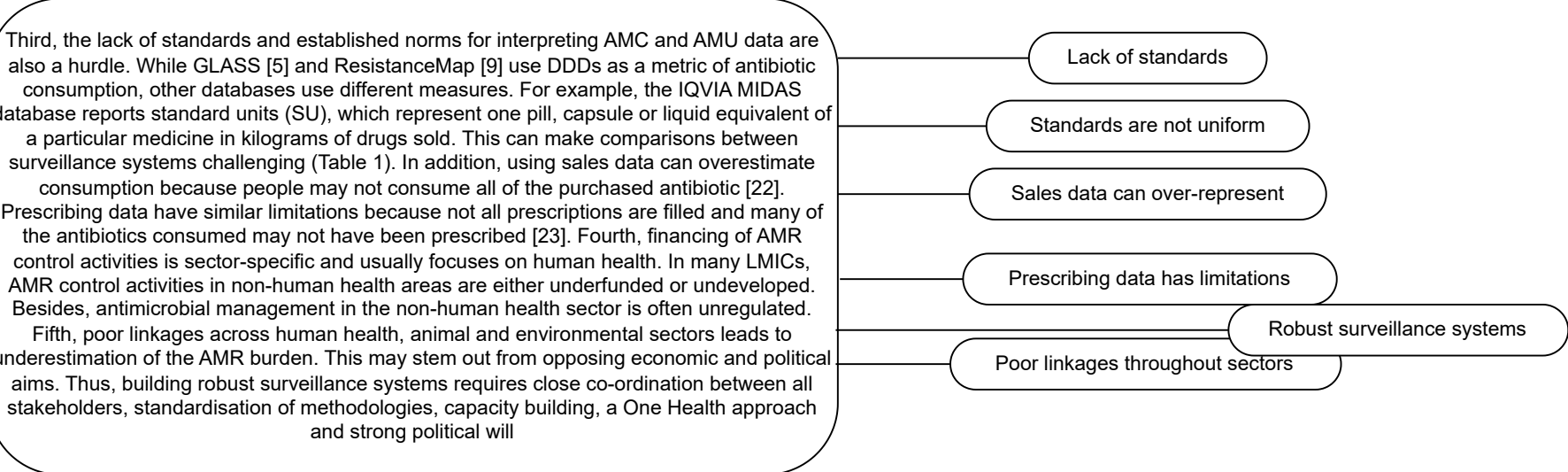
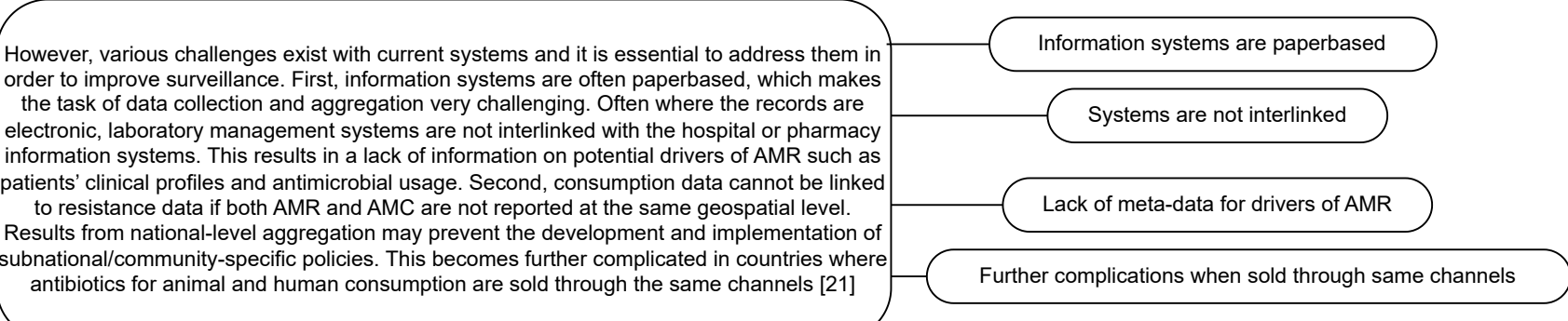
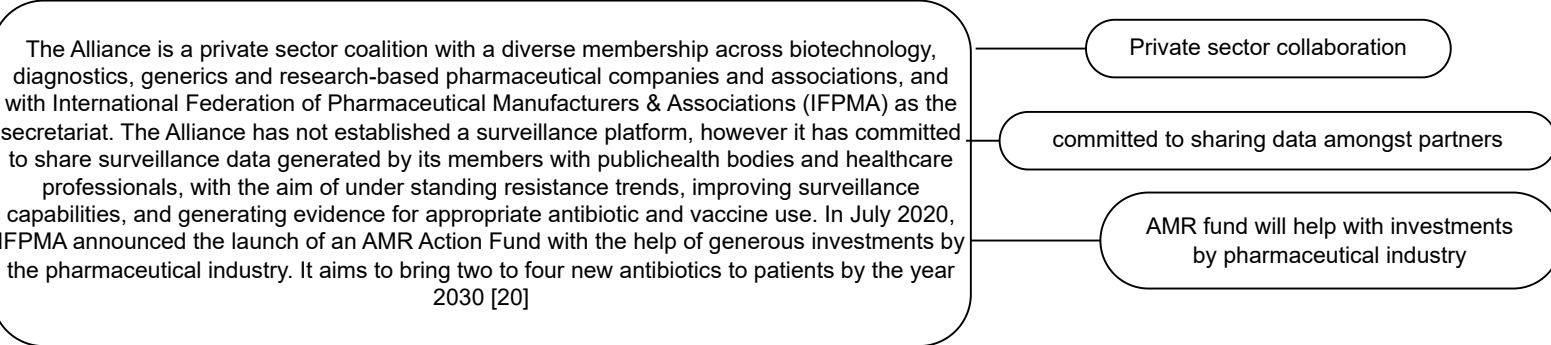
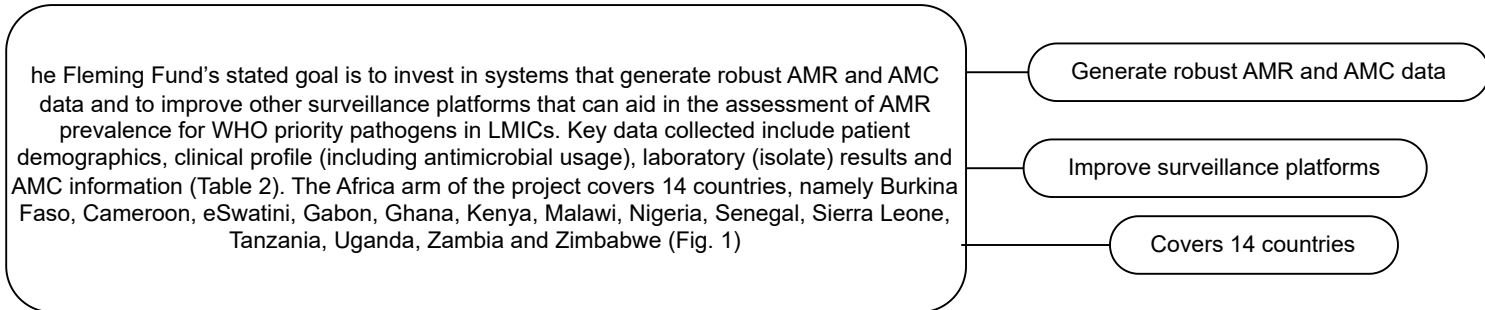
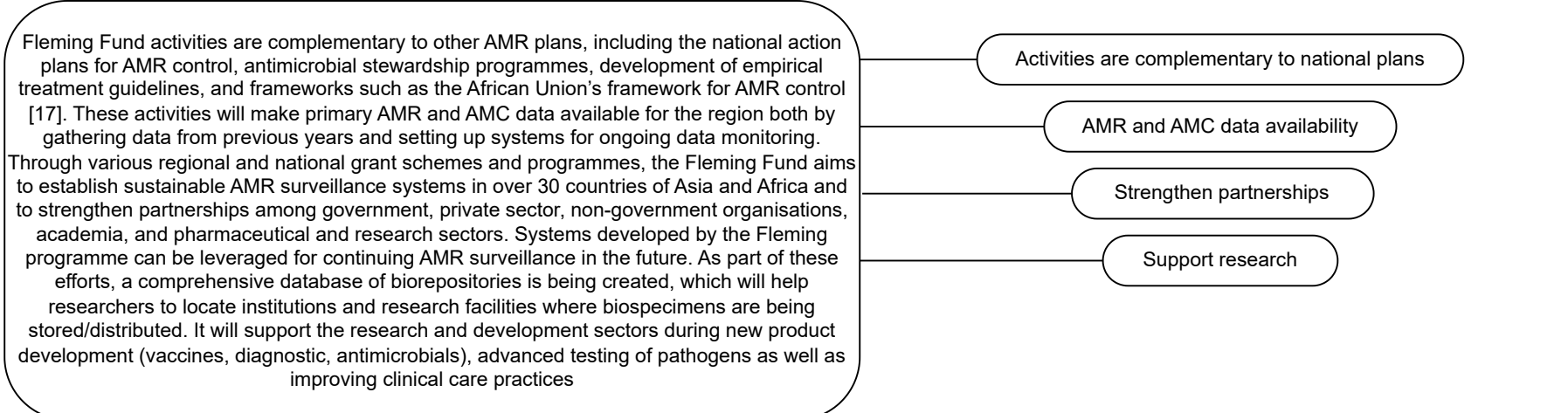
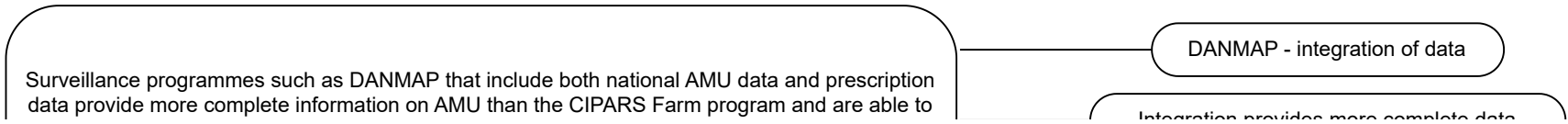
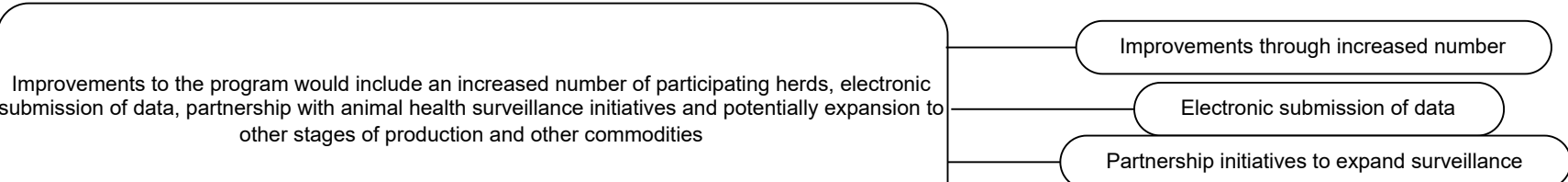
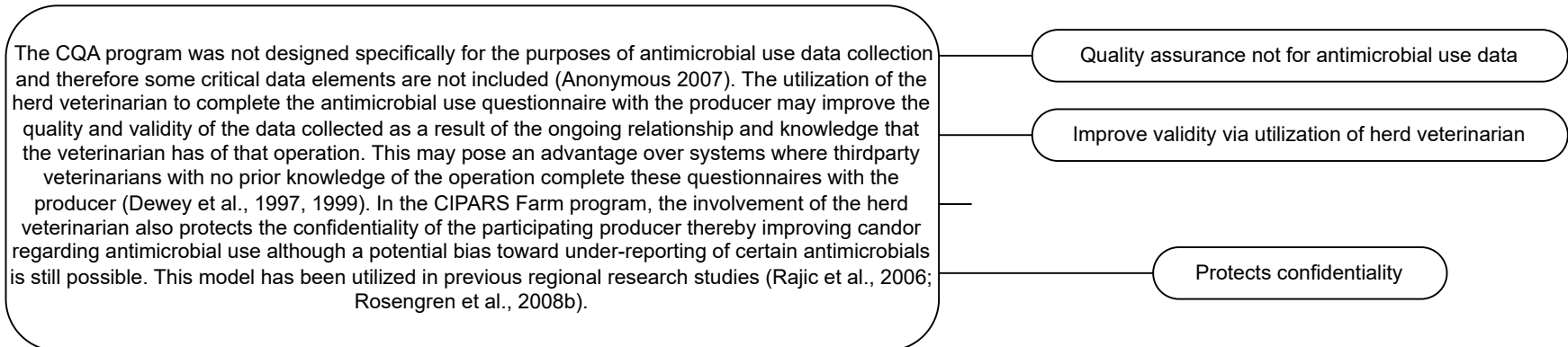
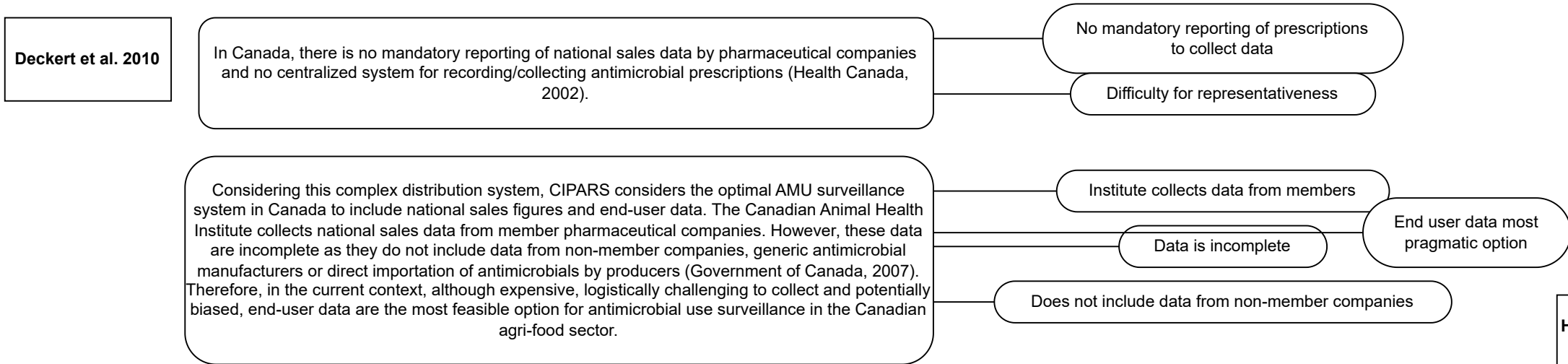
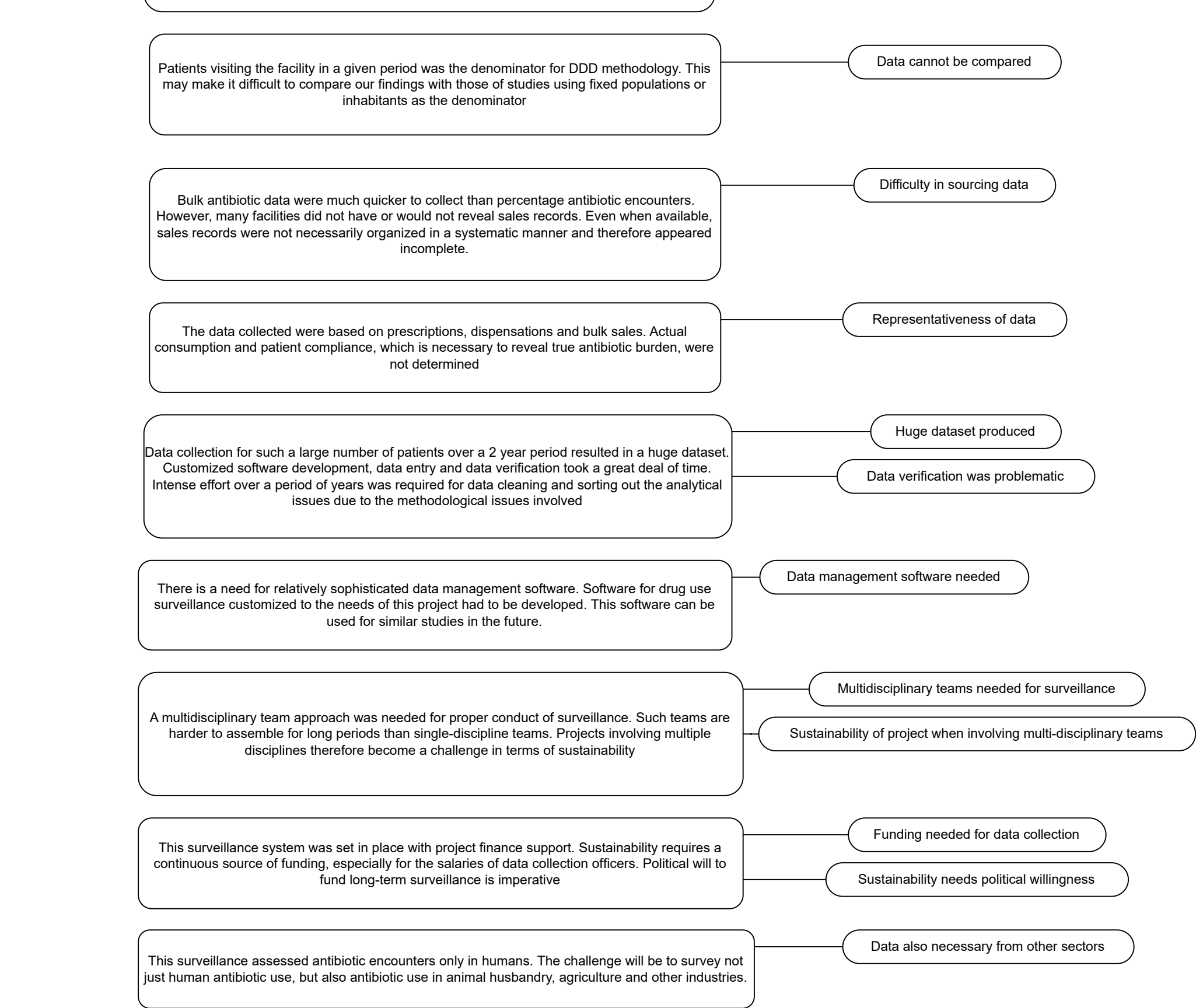
Reference centres have responsibility but are not well equipped

Other systems have developed and implemented

Standardised protocols throughout studies

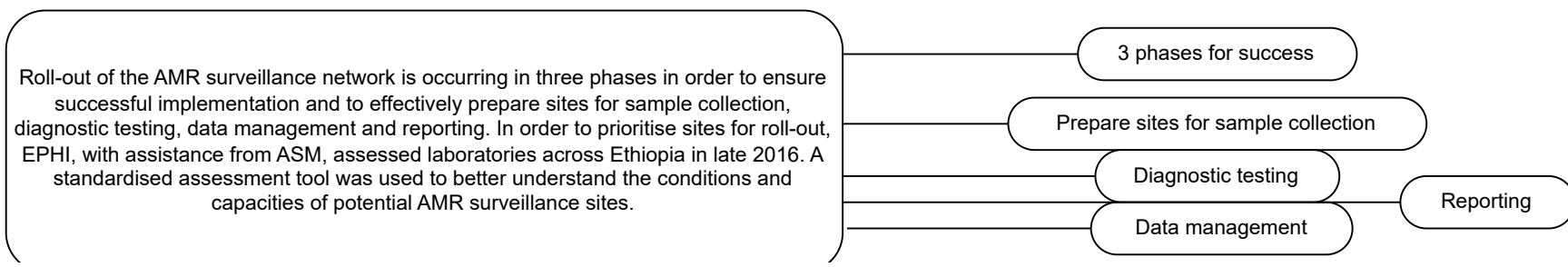
Horizontal transfer rarely monitored

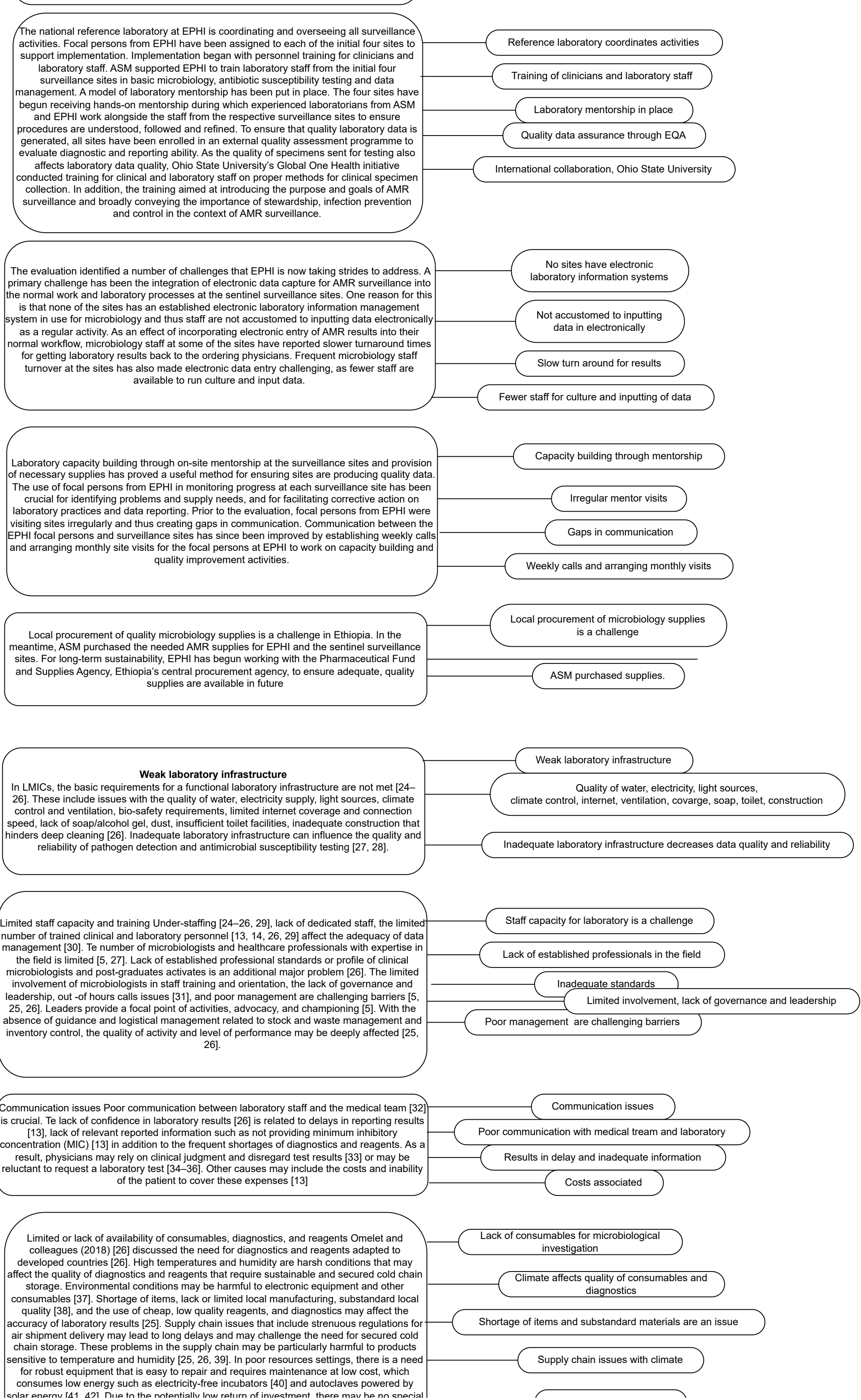
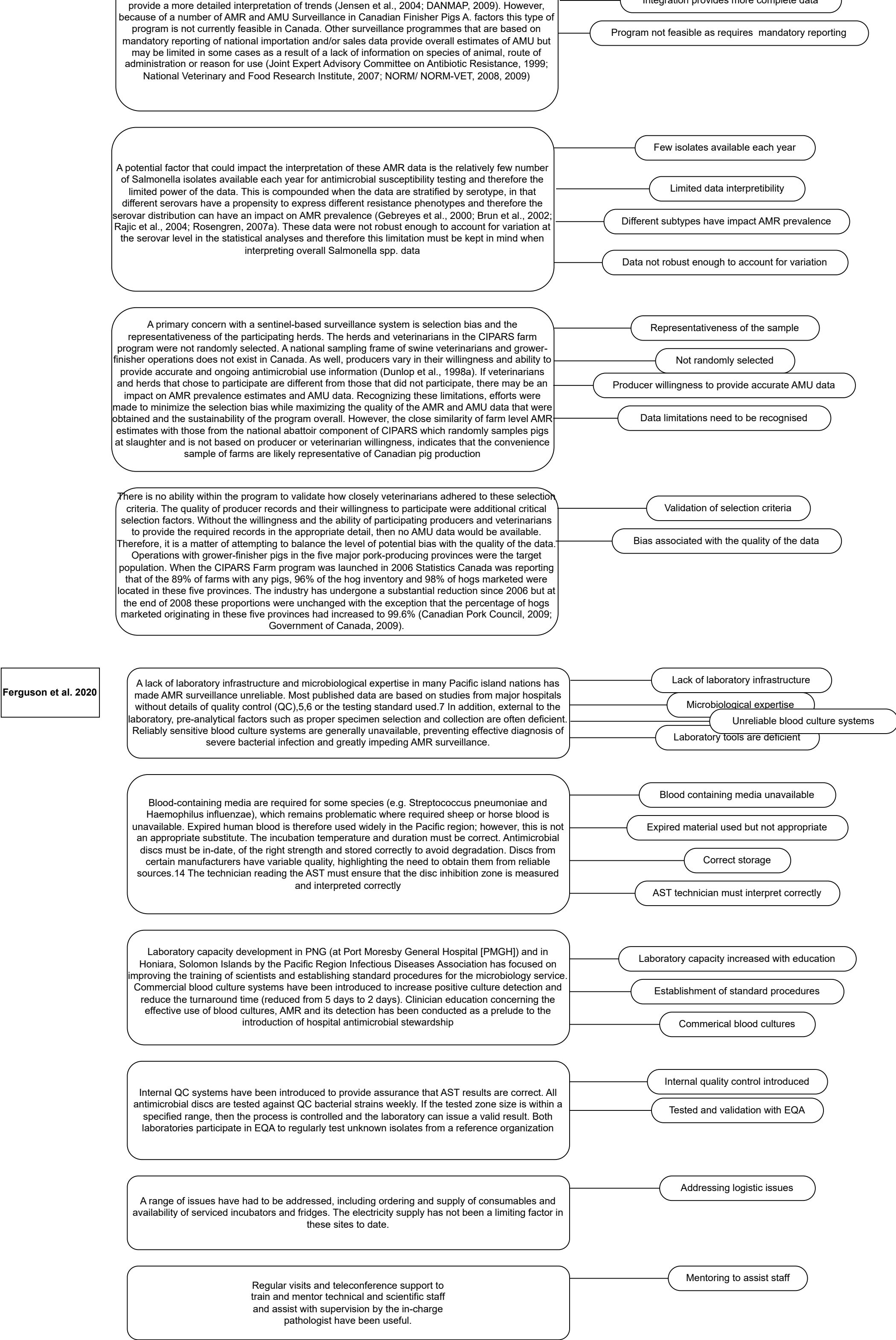


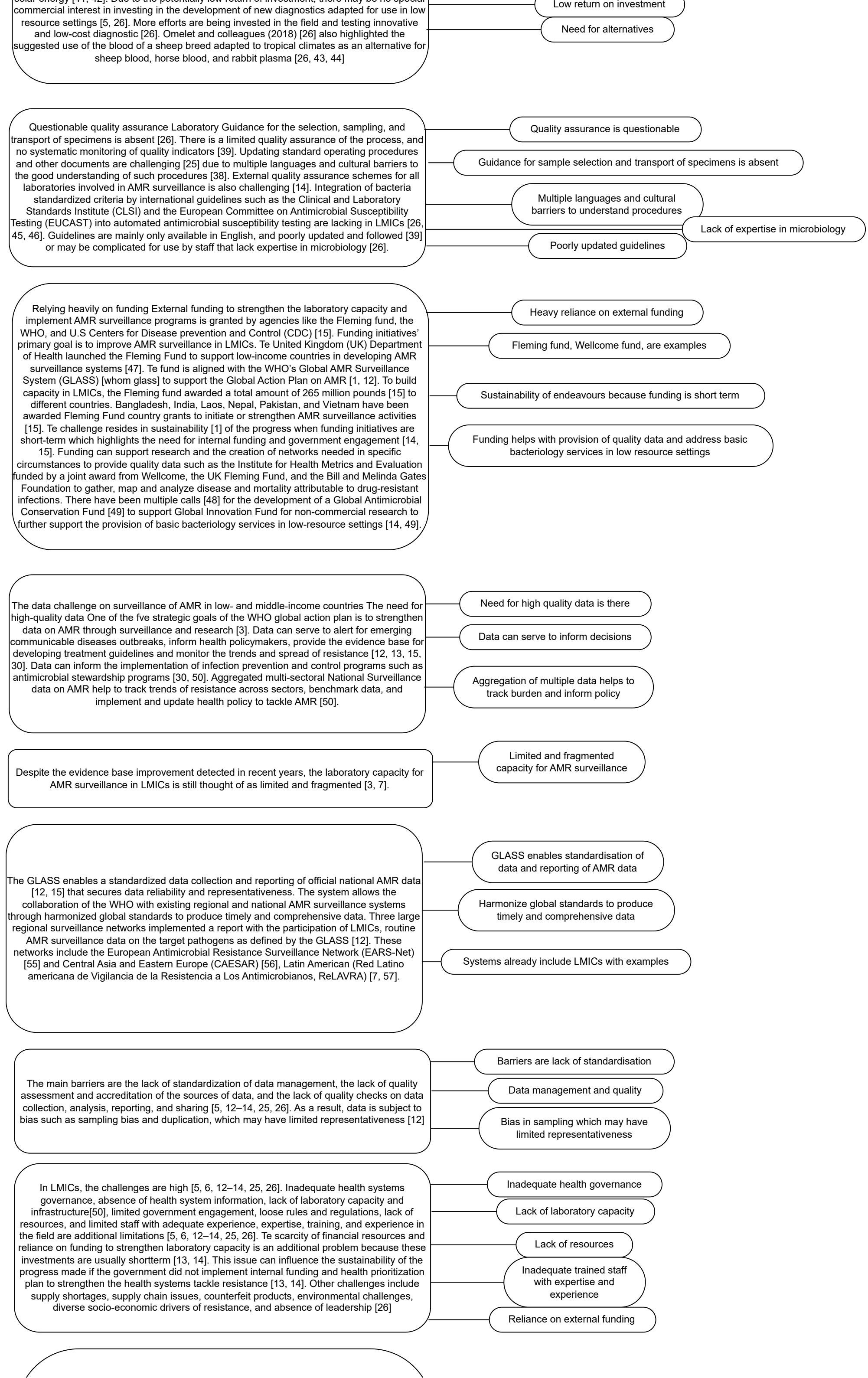
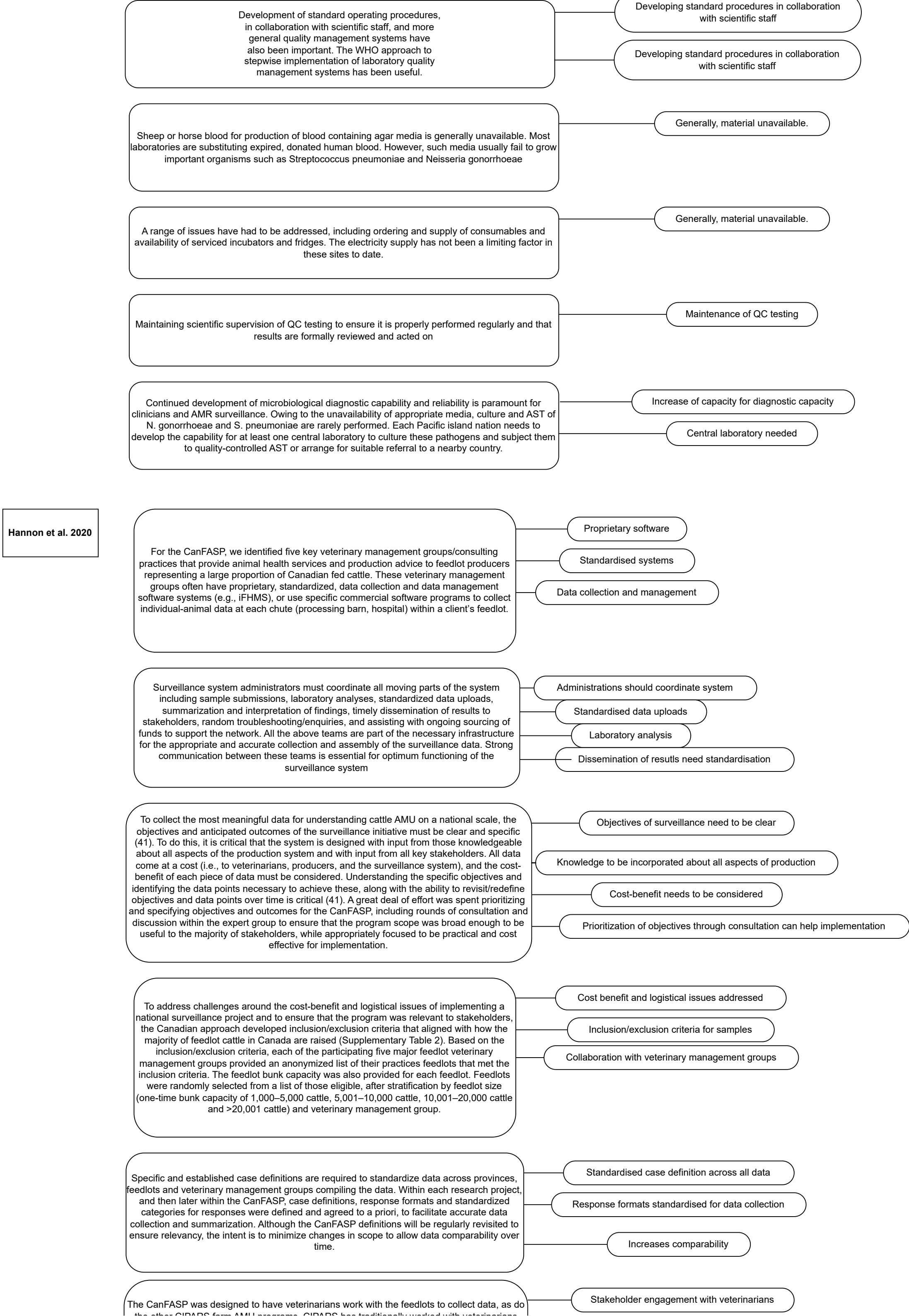


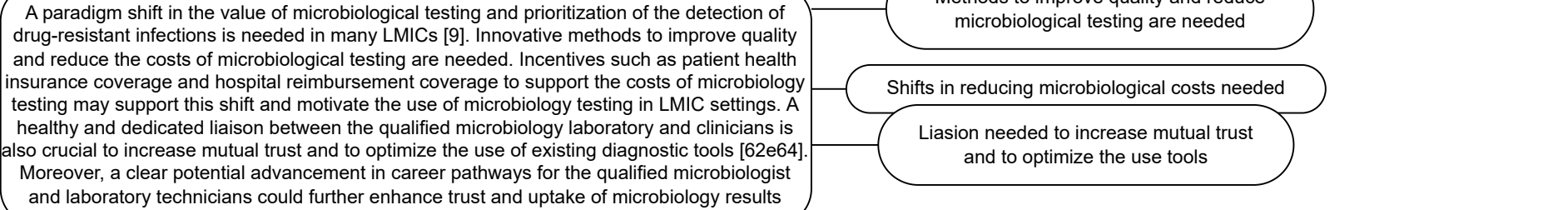
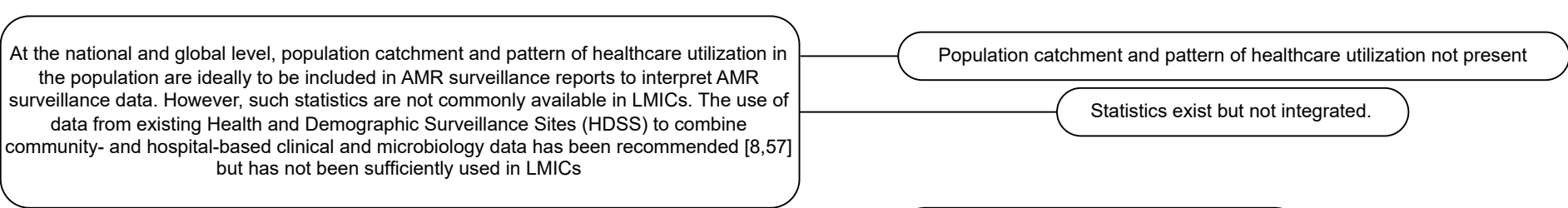
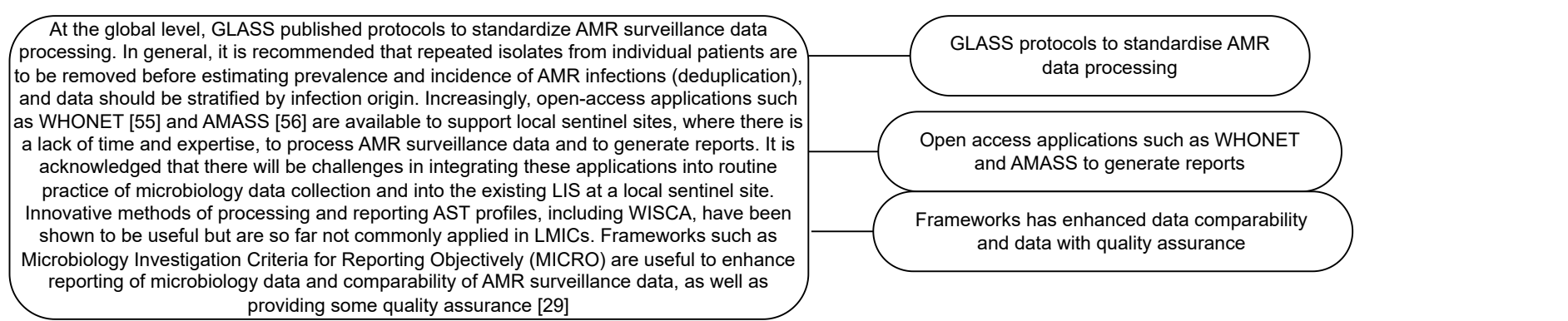
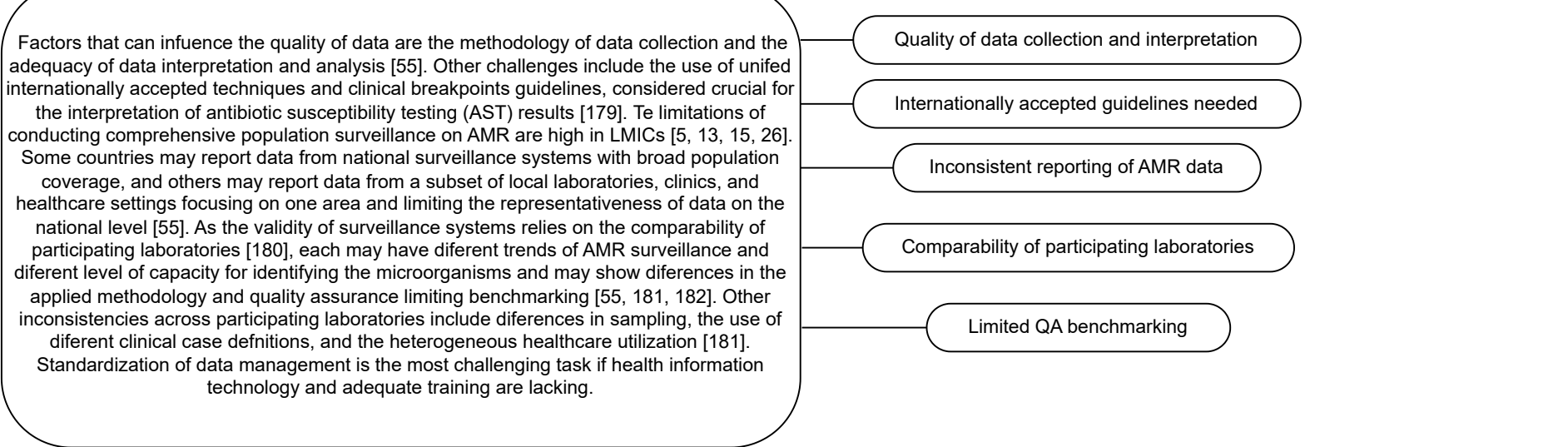
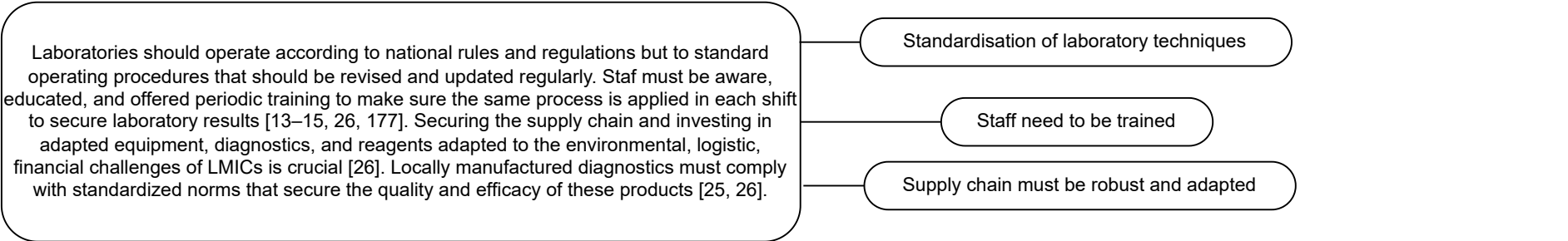
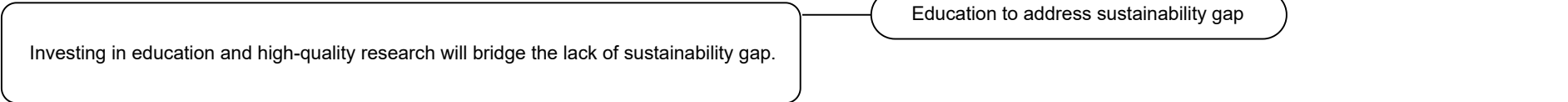
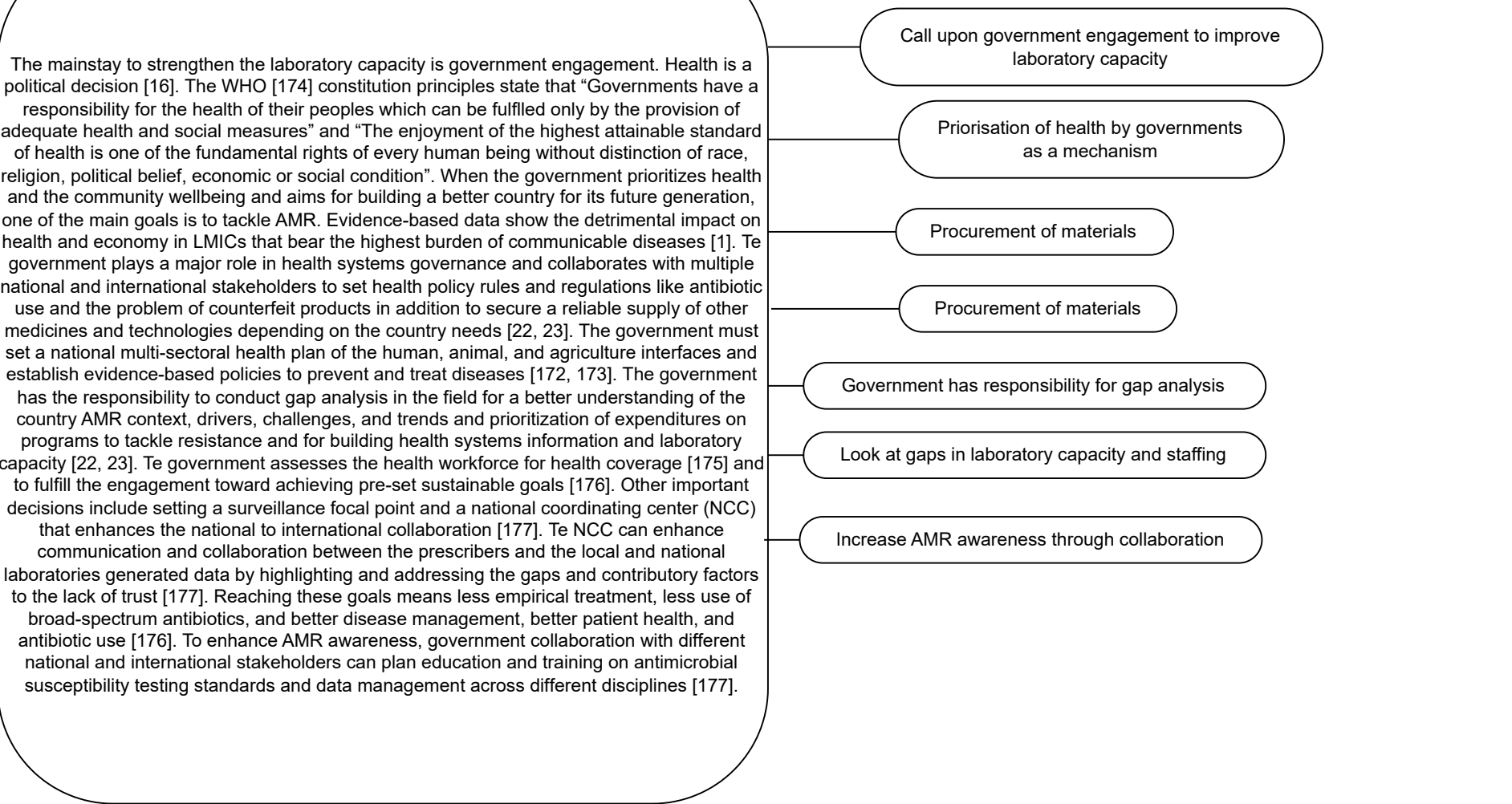
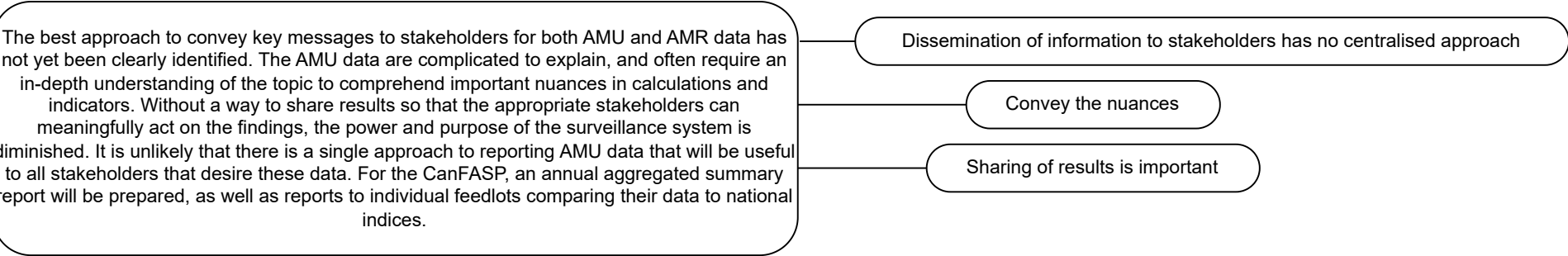
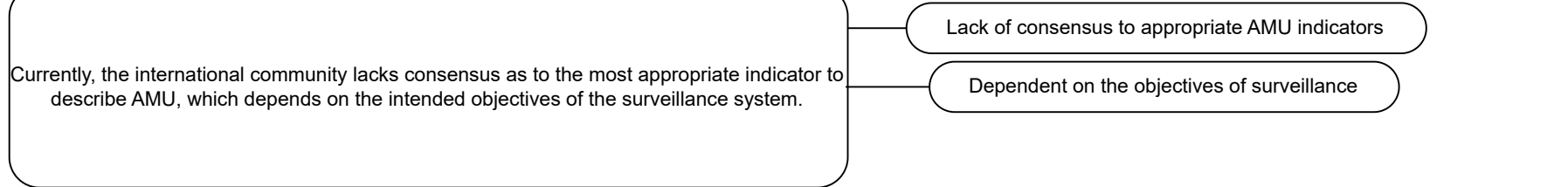
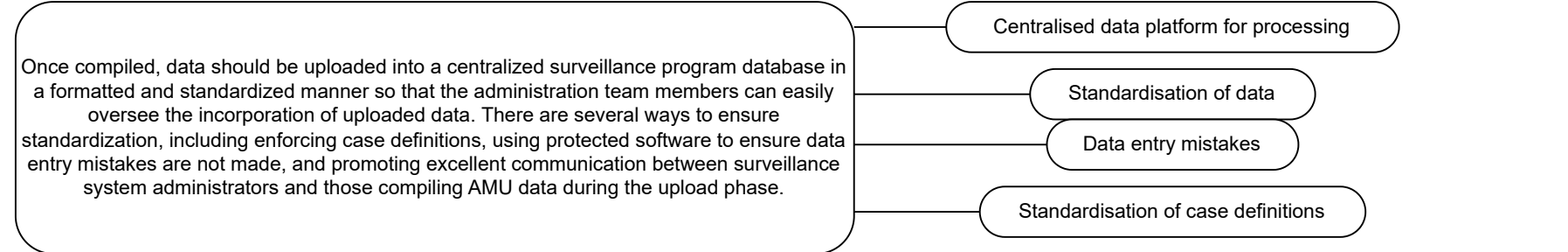
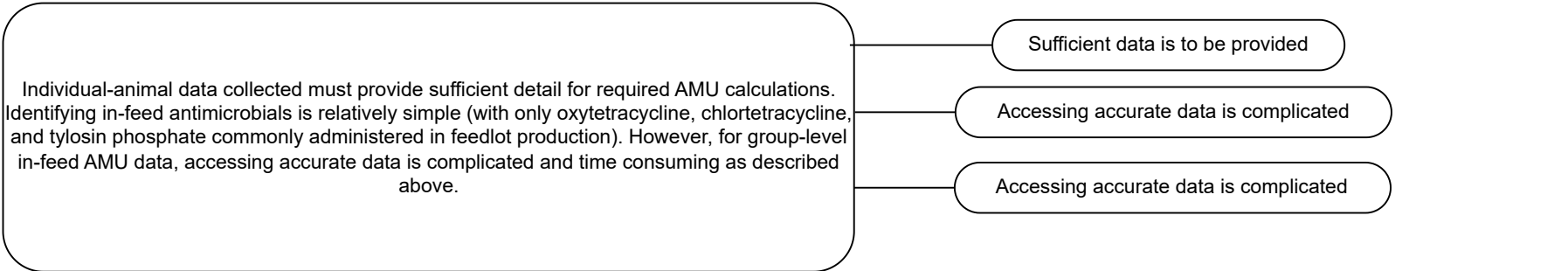
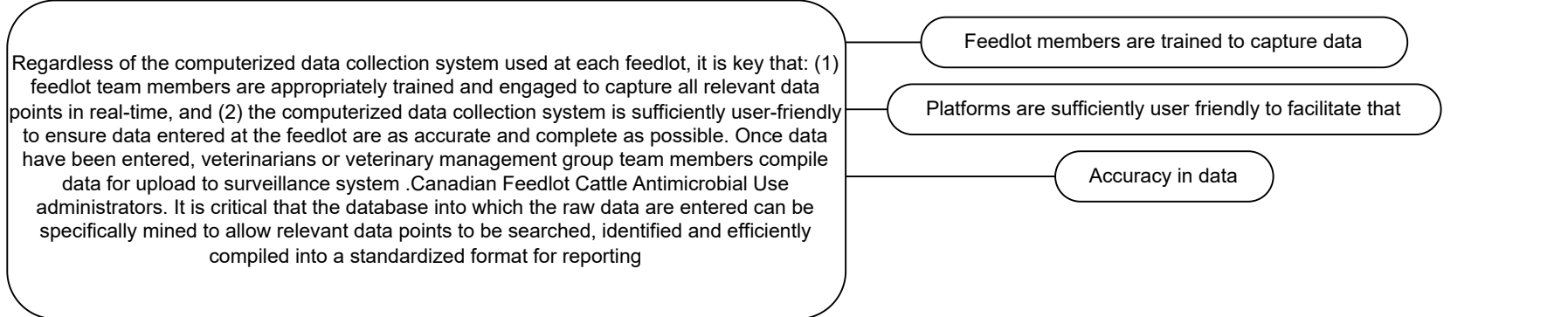
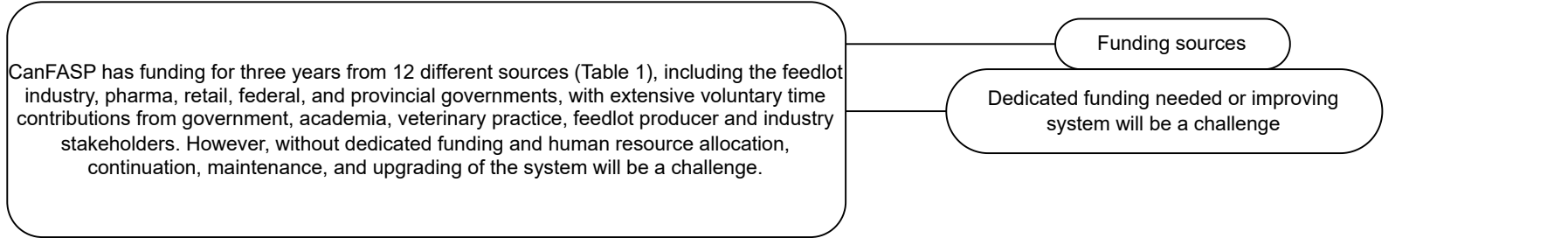
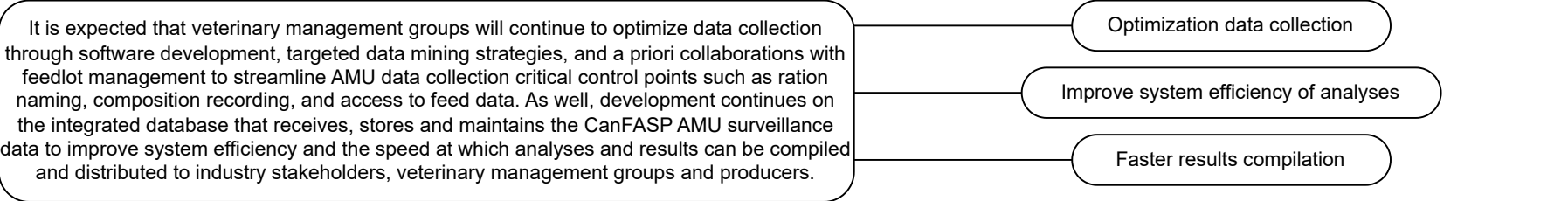
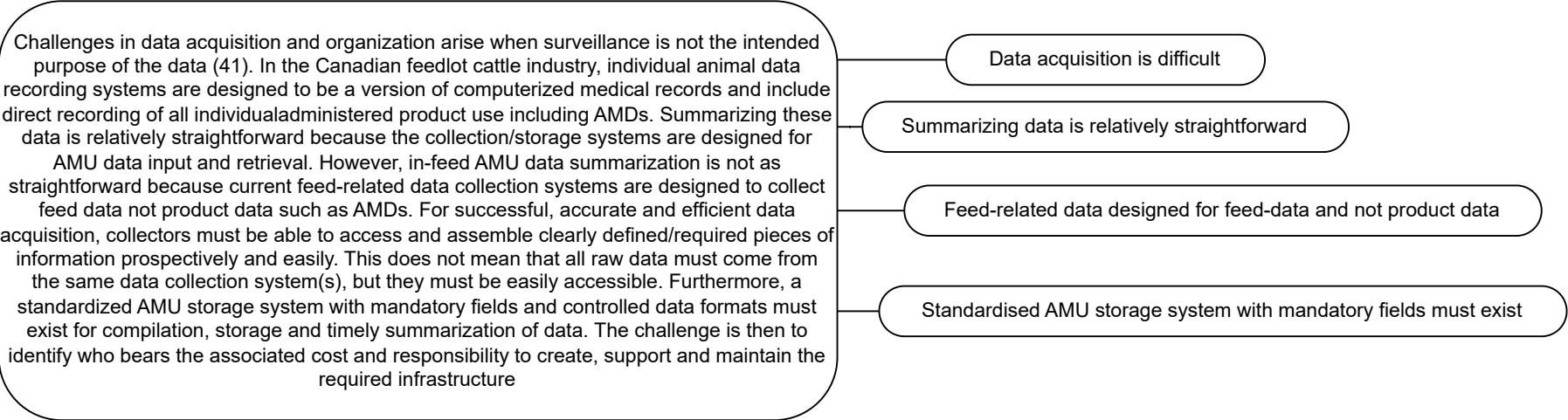
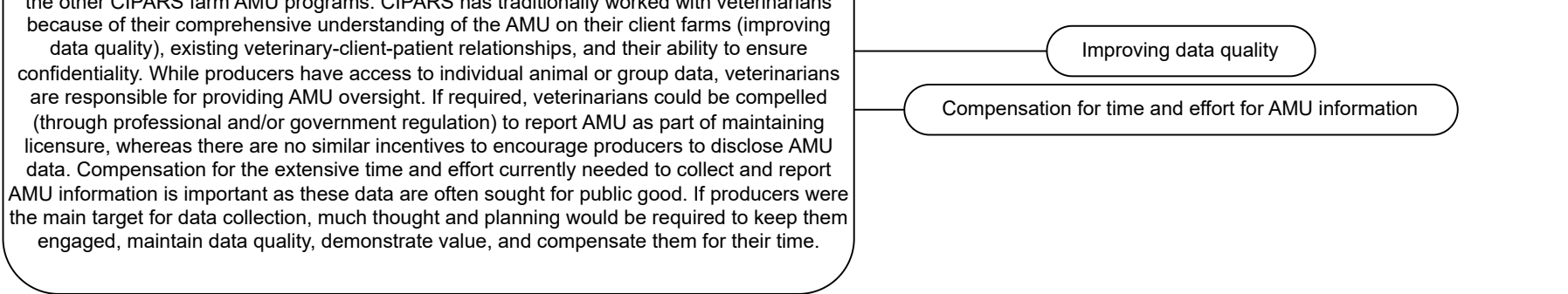
Hedman, Vasco and Zhang 2020

Ibrahim et al. 2018



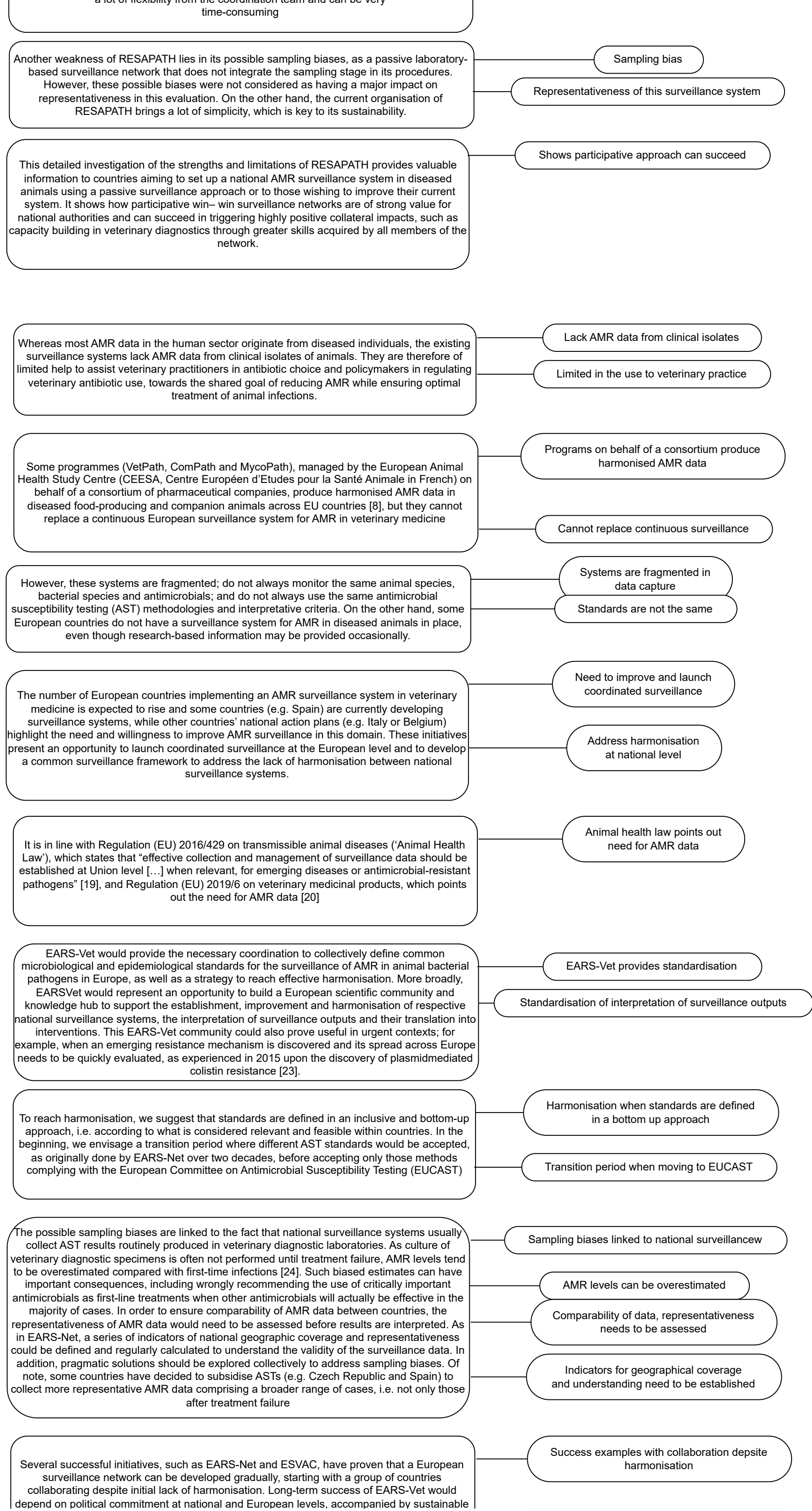
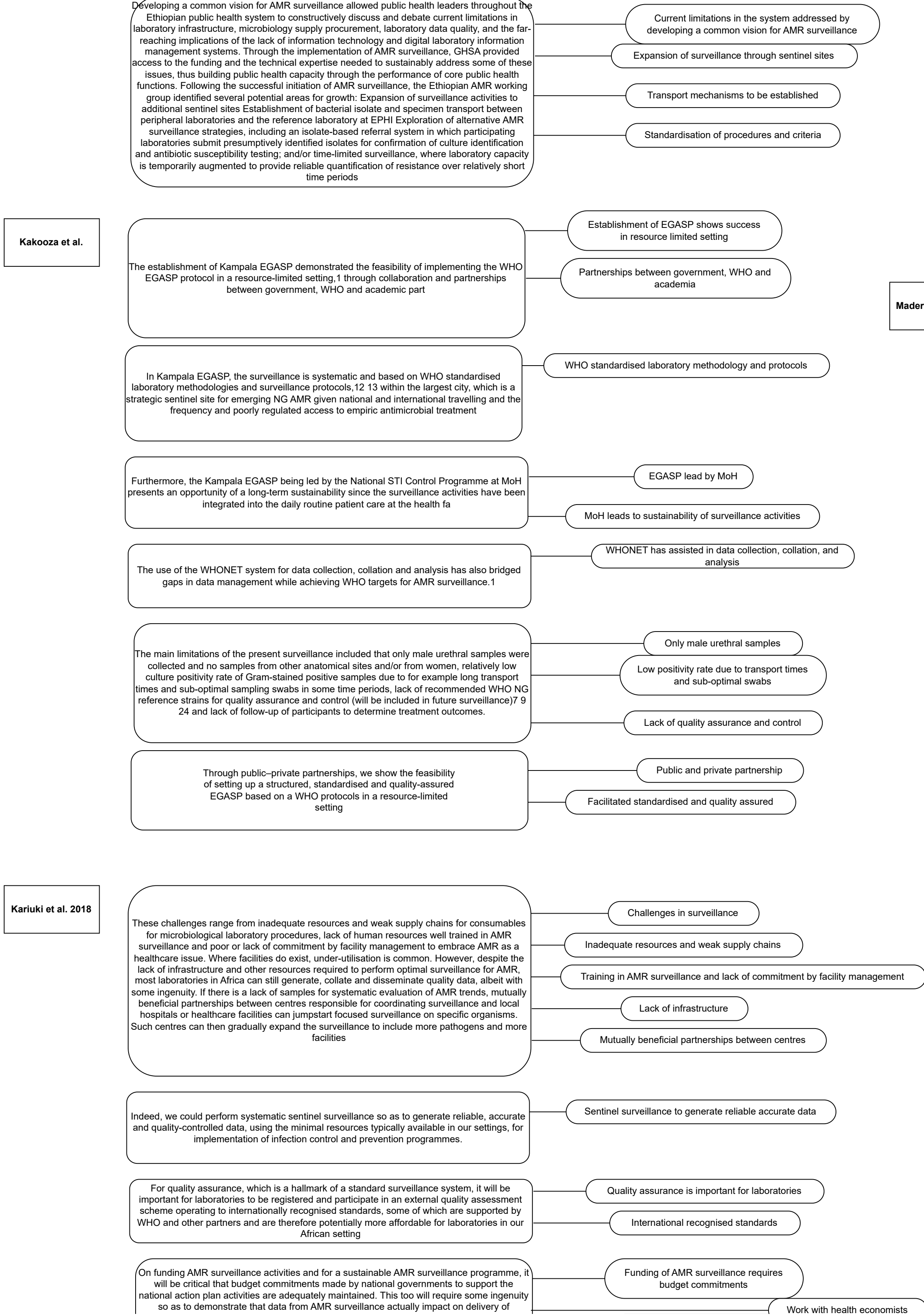


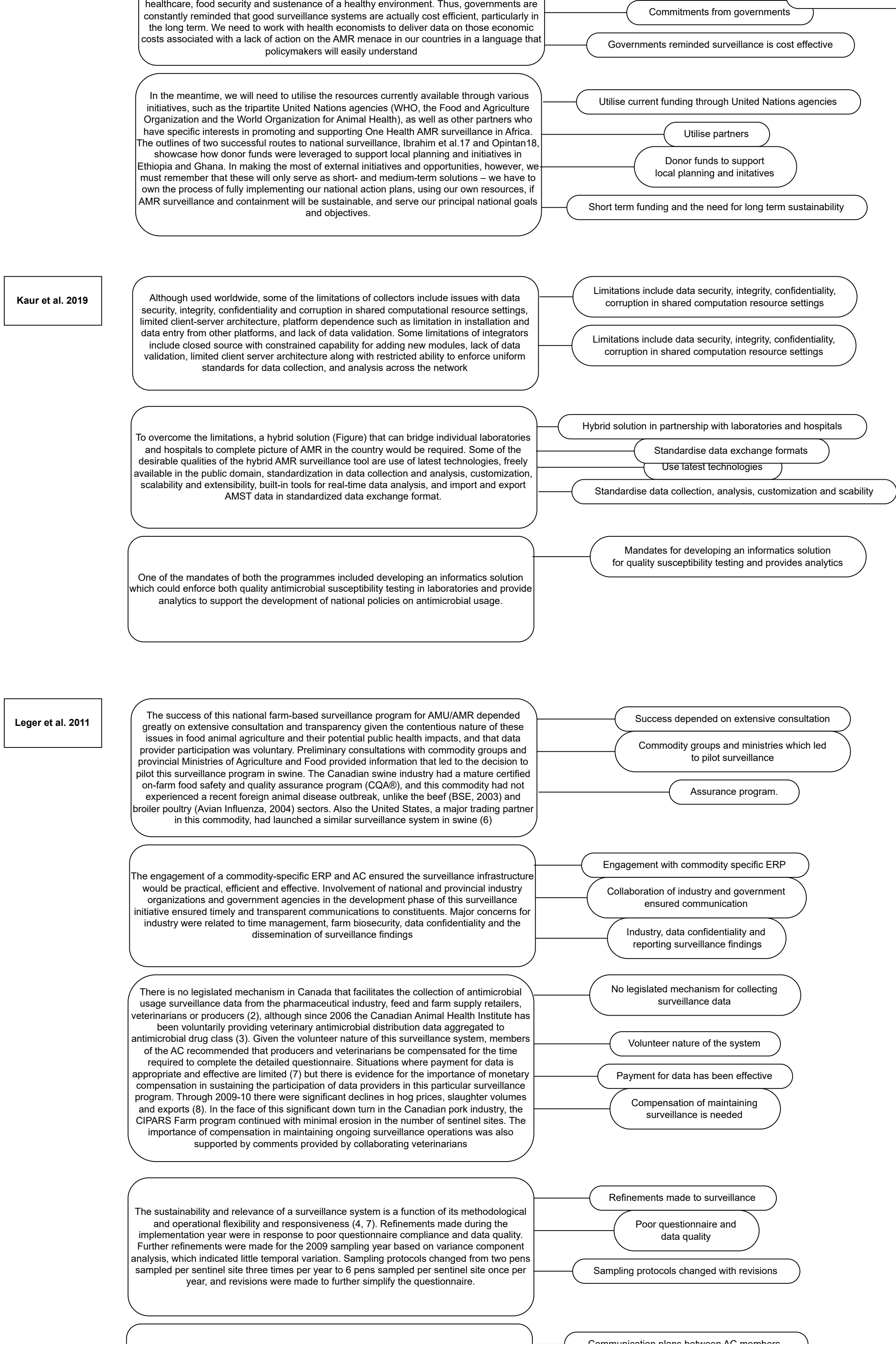




Lim et al. 2021

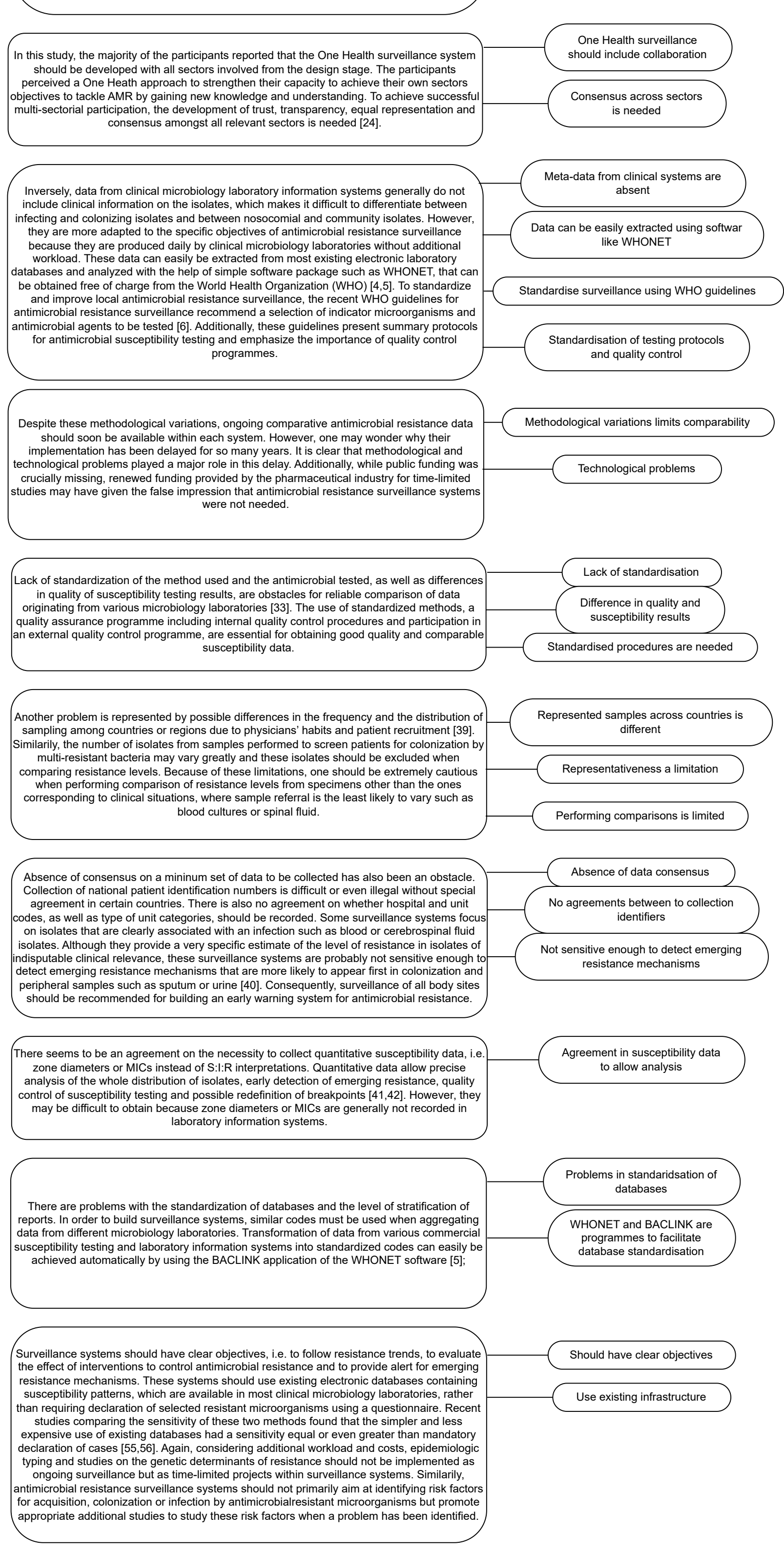
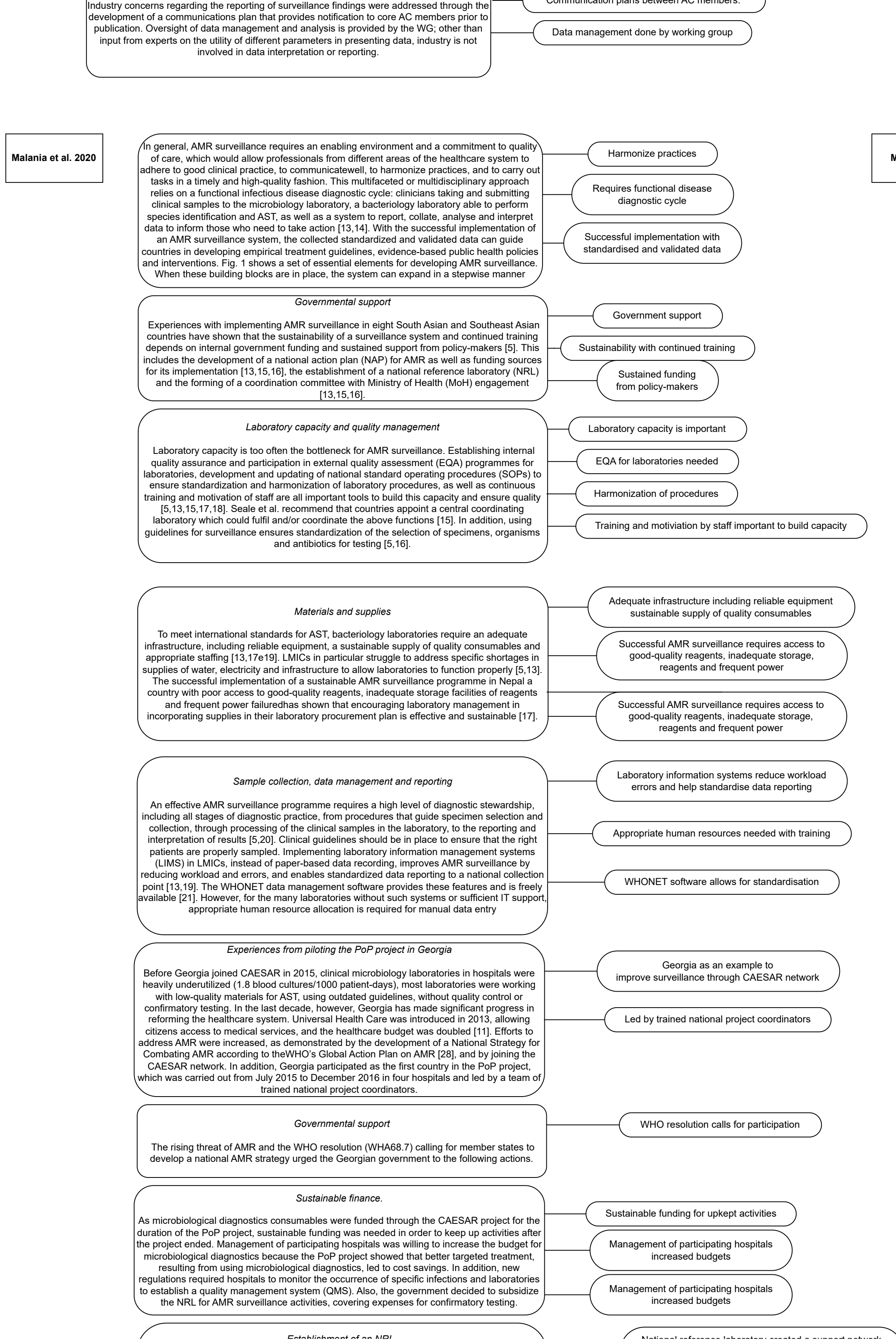






Mitchell et al. 2020





The R. Lugar Centre for Public Health Research at the National Centre for Disease Control and Public Health was appointed as NRL, as a prerequisite for the PoP project implementation. During the project, laboratories sent bacteria isolated from blood cultures to the NRL for confirmation of identification and AST results, which strengthened the role of the Lugar Fig. 1. Essential elements for developing AMR surveillance, supporting the infectious diseases diagnostic cycle [4,5,13,15e19,22e27], NAP, national action plan; NRL, national reference laboratory; EQA, external quality assessment; IQA, internal quality assurance; SOP, standard operating procedure; LIMS, laboratory information management system. Centre as reference laboratory, and created ample opportunity to engage and communicate with clinical laboratories participating in the project. As a result, the Lugar Centre has maintained its status as NRL, and has been providing technical and human resource support across the country. In addition, the NRL processes blood cultures for clinics in the state programme that do not have the in-house laboratory capacity to perform such tests.

National reference laboratory created a support network to communicate with other laboratories

To create national reference laboratory EQA, internal assurance, LIMS are needed

Support laboratory capacity for those who do not have it

Coordination at central level.

A national AMR expert committee was established after the PoP project ended, which provides coordination and oversight at the central level, and evaluates the implementation of the NAP.

Coordination at a central level with expert committee

Legislation for surveillance.

Several orders and decrees have been adopted since 2015 to promote AMR surveillance through accountability, and to regulate, among other things, QMS in laboratories and monitoring of infections in hospitals.

Several decrees have been adopted to promote AMR surveillance

Laboratory capacity and quality management

External and internal quality assurance, and accreditation. The NRL and the network laboratories have been enrolled in the CAESAR EQA programme since 2015. Furthermore, the NRL provides a quarterly national EQA programme for the country's laboratories, starting with 11 laboratories in 2016 and expanding to 25 laboratories in 2020. Results of this programme are used for feedback and education of the laboratories. In addition, the NRL currently mentors 17 laboratories to establish internal quality assurance programmes. Further quality control is ensured by confirmatory testing of exceptional phenotypes and unexpected results performed at the NRL, using phenotypic and genotypic methods. Since 2016 it is mandatory for laboratories to send to the NRL 'alert' organisms and organisms with unlikely AST results requiring confirmation. After the Lugar Centre initiated its function as NRL, it received ISO 15189 accreditation in 2017. In 2021e2022 the NRL will work to acquire accreditation as EQA provider (ISO17043).

Laboratory capacity and quality management through EQA, IQA, and accreditation

National reference laboratory provides EQA

Feedback to help educate laboratories

Standardization and harmonization of guidelines and standard operating procedures (SOPs).

The NAP requires all laboratories to use the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for AST. At the moment, approximately 60% of laboratories participating in the national network have adopted EUCAST guidelines, and the other 40% will switch in the near future. The PoP project's SOPs for blood sampling, sample processing and AST were shared within the national network and are now used by most of the hospitals and laboratories.

NAP requires all laboratories to use EUCAST for AST.

Training and knowledge.

Training of clinicians and laboratory staff was an important aspect of the PoP project. Initially, training was given by WHO experts and consultants, but during the project training and support was taken over by the NLR. After the project, the NRL continued to train new members of the network and organizes annual microbiology network meetings, data collection workshops, symposia and lectures. As a member of the CAESAR network, Georgia has access to annual training and support from WHO/Europe and ESCMID.

Training of clinicians is an important aspect

NRL continued training of members of the network

Materials & supplies

Sustainable supply of good-quality materials. To ensure timely receipt of supplies, the NRL aids laboratories with tender procedures. The NRL performs quality verification testing and provides laboratories with a list of reliable manufacturers. This way, the quality of consumables procured by laboratories is ensured. In addition, the national laboratory network frequently communicates with manufacturers and providers within Georgia, to prevent and address supply-chain issues. In case of severe disruption of the supply chain, hospitals have emergency funds to procure materials following other procedures

Materials need to be good quality

NRL verified consumables

Hospitals have emergency funds

Sample collection, data management and reporting

Access to laboratory information management systems. Enabling electronic data collection for laboratories using paperbased forms is one of the priorities for the national AMR committee. In 2019, a WHONET training was organized by the WHO for the national team and the network laboratories, but follow-up training is needed

Electronic data collection using paperbase

WHONET training implemented

Electronic data capturing and standardized and consistent data collection.

As a result of the PoP project, the same isolate record forms are used by all laboratories, or alternatively, AST results are entered in WHONET. The NRL developed a routine for standardized data collection from the network laboratories and enters the data into an electronic database to be exported to CAESAR. Postanalytical steps (e.g., data entry, feedback report) were standardized by the national AMR committee.

AST results entered into WHONET

NRL established a standardised data collection procedure

Opintan et al. 2015

Participating microbiology laboratories should use standardized methods, internal quality control procedures and participate in an external quality control programme. They should implement and adhere to a continuous quality improvement programme including the whole process from collection and analysis of specimens to the interpretation and validation of test results [39]. Although participation only of laboratories that satisfy external accreditation procedure has been advocated by some experts, it may not be feasible for the moment because of the small number of accredited laboratories.

Laboratories should use standardised methods

Adhere to quality assurance

In the current laboratory-based surveillance of AMR, data sets were received and processed from .70% of the 24 laboratories that participated in the training workshop. However, six laboratories did not submit any data during the surveillance period. Our preliminary investigations revealed some lapses within these hospitals, including breakdown culture facilities, clinicians not making request for culture, and some internal managerial issues. More than two-thirds of the data analyzed in the current surveillance were from the southern sector, with less than one-tenth from the northern sector. In 2003, a similar nationwide surveillance of AMR also received a relatively small number of isolates from the northern parts of Ghana.¹⁹ Such disparities may introduce some biases while interpreting the results to direct antibiotic policy in Ghana. Considerations such as the general lack of access to health care facilities in remote and rural parts in the northern parts of Ghana, economic and social reasons, and patronage of traditional medications (herbs) compared to orthodox medicine have to be factored into interpretation of surveillance data.⁴¹ The Korle-Bu Teaching Hospital alone submitted .50% of the total data sets. Generally, academic tertiary referral laboratories are known to be over-represented in national and multicenter surveillance systems.⁴² This overrepresentation of data introduces some biases in the overall AMR surveillance results. The Komfo Anokye Teaching Hospital did not submit enough data in the current surveillance compared to their output in the previous study.¹⁹

Investigations revealed lapses in hospital for microbiological services

Internal management issues

2/3 of data from one locality

One facility sent more than 50% of all samples

Over-representativeness

Some proposals have suggested that AMR surveillance systems should be coordinated by PHRLs.⁴³ In the case of Ghana, perhaps PHRLs are not yet ready to spearhead AMR surveillance activities. The mandate, direction, and functions of PHRLs in Ghana must be critically aligned to address the global public health threat of AMR. Grundmann et al suggested that global AMR surveillance systems must have separate functions including reference work, quality assessment, and the actual surveillance.⁴³ In Ghana, the NPHRL may play a vital role in future laboratory-based surveillance, by participating in quality assessments. In the present study, faith-based and district hospitals also submitted data. Since these hospitals contribute greatly to the health needs of Ghana, they should be included in future national AMR surveillance programs. In general, the current study did not observe disparities in susceptibility results compared to the results of the previous study in Ghana.¹

Coordination of system through reference laboratory

Laboratories are not ready to lead surveillance

Mandates must be critically aligned

Quality assessment by reference laboratories

Perovic and Schultsz 2016

AMR surveillance relies on diagnostic laboratories; in sub-Saharan Africa, the need for laboratory improvement is evident, with some countries in need of laboratory system built from the ground up. This prevalent lack of laboratory resources and the subsequent difficulty of obtaining accurate results on antimicrobial susceptibility testing is an important challenge to address when proposing a stepwise approach

Surveillance requires diagnostic capacity of laboratories

Lack of resources leading to inaccurate results

In Africa, the development and improvement of laboratory capacity, including standardised testing, external quality assessment programmes, procurement, and timely and cost effective reports, should eventually lead to the establishment of an integrated and coordinated surveillance system for AMR in the region, which will strengthen knowledge about AMR through surveillance and research. This surveillance should increase understanding of the implications of AMR and its epidemiology and allow for monitoring the effectiveness of guidelines and policy implementation. In addition, it would permit research and development of new diagnostics and novel technologies, optimisation of treatment, and other interventions as well as build human resource capacity as a secondary objective. Collaboration within a team of human and animal experts in AMR surveillance would allow for a One Health approach. This requires the establishment of coordinated surveillance in animals, the ability to control and regulate antibiotics use in animals, and the identification of alternative options for growth promoters in agriculture.

Development and improvement of laboratory capacity needed

External quality assessment

Procurement

Effective data reporting

One Health approach

There are several approaches toward surveillance of AMR, including population-, sentinel- and laboratory-based surveillance. The general perception is that laboratorybased surveillance is currently the most efficient method of surveillance of AMR, which is what the WHO and GHSA advocate.^{1,4,5} However, laboratory-based surveillance is often biased, because of the potential barriers to and selection processes for submission of clinical specimens to laboratories for culture and susceptibility testing, particularly in resourceconstrained settings.² This bias may result in laboratory based surveillance data being skewed toward a higher prevalence of AMR.

Different approaches to surveillance

Population, sentinel, and laboratory

Laboratory based may be most efficient

Laboratory surveillance may also be biased

For laboratory-based surveillance to yield comprehensive data, a functional infectious disease diagnostic cycle is required. This cycle includes clinicians submitting samples for culture and susceptibility testing, a bacteriology laboratory that can generate quality culture and susceptibility test results, and a reporting system that includes not only the clinician requesting the test, but also a laboratory information system (LIS) that can inform the surveillance programme, which may be steered by a central body (Figure 1). In addition, for laboratory surveillance programmes that are technically carried out by national public health laboratories, a crucial element of the cycle is the rapid and complete transfer of all required materials, isolates and/or data from peripheral laboratories to the national site, and back reporting of results to ensure continuous engagement of laboratories and clinicians.

Comprehensive data through clinicians submitting samples and quality microbiological testing

Need for laboratory information system (LIS)

Ensure continuous engagement of laboratories and clinicians

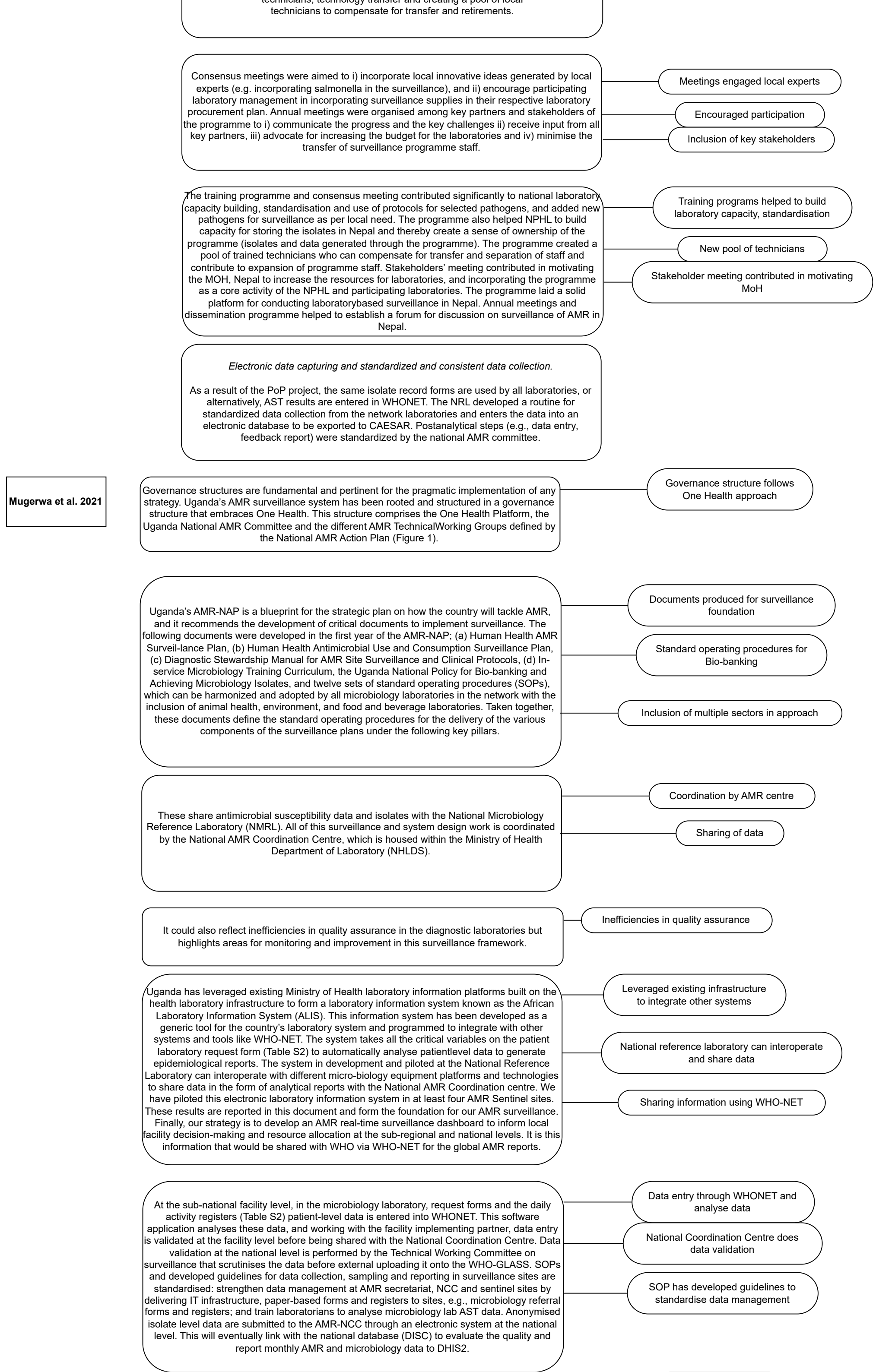
Malla et al. 2014

A total of 10 training workshops and five consensus meetings among participating laboratories were organised during 1999 to 2003, and from 2004 to 2012 annual refresher training was organised among participating laboratories. Training workshops mainly focused on improving the skill of local technicians, technology transfer and creating a pool of local

Training workshops helped train local technicians

For a national laboratory-based surveillance programme to be successful, government commitment to support the surveillance programme for AMR at the country level is essential

Government commitment is crucial for AMR surveillance programmes



Mugerwa et al. 2021







