Driving laboratory standardisation of bacterial culture and antimicrobial susceptibility testing in veterinary clinical microbiology in Europe and beyond

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Abstract

Globally, antimicrobial resistance is one of the most important public health challenges in which the clinical microbiology laboratory plays a critical role by providing guidance for antimicrobial treatment. Despite the recognition of its importance, there is still a real need for standardized training of clinical microbiologists and harmonisation of diagnostic procedures. This is particularly true for veterinary clinical microbiology where additional challenges exist when microbiologists are trying to fulfil a professional role very similar to their colleagues working in human microbiology laboratories. The specific points that need addressing to improve the outputs of veterinary microbiology laboratories discussed here include 1) harmonisation of methodologies used by veterinary laboratories for antimicrobial susceptibility testing (AST); 2) specific guidelines for interpretation and reporting of AST results for animal pathogens; 3) guidelines for detection of antimicrobial resistance mechanisms in animal isolates; 4) standardisation of diagnostic procedures for animal clinical specimens and 5) the need to train more veterinary clinical microbiology specialists. However, there is now a plan to address these issues led by the European Network for Optimisation of Veterinary Antimicrobial Treatment (ENOVAT) which is bringing together experts in veterinary microbiology, pharmacology, epidemiology and antimicrobial stewardship from Europe and wider afield. ENOVAT is aiming to work with project partners towards standardisation and harmonisation of laboratory methodologies and optimisation of veterinary antimicrobial treatment. Ultimately, the project may provide a mechanism for standardisation and harmonisation of veterinary clinical microbiology methodologies, which could then be used as a template for implementation at a wider international level.

Journal of Clinical Microbiology

Introduction

Antimicrobial resistance (AMR) is a global multifactorial issue, which endangers the ability to treat bacterial infections and hinders the implementation of important medical advances (i.e. complex surgeries, chemotherapy) in both human and veterinary medicine. The emergence of AMR has highlighted the key role that clinical microbiology laboratories play in driving antimicrobial stewardship and appropriate antimicrobial use (1).

Underuse or suboptimal use of microbiological culture and antimicrobial susceptibility testing (AST) and overreliance on empirical antimicrobial therapy can exacerbate AMR in both human and veterinary settings; therefore, in order to overcome these obstacles a closer partnership between diagnostic laboratories and clinicians is required for successful antimicrobial stewardship (1, 2). In addition, there have been calls for standardized training of clinical microbiologists, and a better understanding of the professional identity of clinical microbiologists in line with the recognition received by other specialities (3, 4). If calls for a greater professional recognition are warranted in human clinical microbiology where the field is already seen as an integral element of antimicrobial stewardship, a similar need exists for both closer laboratory-clinic collaboration and improved recognition of the role of clinical microbiologists in veterinary settings. To facilitate these needs, standardized training of veterinary clinical microbiologists, a better recognition of the clinical microbiologist's role in patient care and harmonization of professional standards is needed in veterinary clinical microbiology. In addition, several major challenges exist for veterinary microbiology laboratories, which we discuss here.

Harmonizing methodologies of antimicrobial susceptibility testing (AST) in veterinary laboratories.

Journal of Clinical Microbiology

Although international antimicrobial susceptibility testing (AST) standards for microbiology laboratories exist and are largely applicable to veterinary settings (https://www.iso.org/standard/70464.html), their implementation is dependent on local factors. Furthermore, currently there is no worldwide consensus for usage of a common methodology in veterinary laboratories. When performing culture and AST, veterinary laboratories generally follow methodologies developed for processing human clinical isolates. In that regard, laboratories adhere to either the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the American Clinical and Laboratory Standards Institute (CLSI) guidelines or, less commonly, guidelines issued by various national committees. This approach serves the immediate needs of clinicians and the data can be useful for detecting shifts in local antimicrobial susceptibility patterns. However, the use of multiple standards is a major limitation when comparing susceptibility data between laboratories or countries, thereby compromising global AMR surveillance in animal pathogens. Hence, early detection of emergent resistant pathogens or meaningful comparison of resistance rates within or between countries is hampered, as shown in a study comparing antimicrobial susceptibility data in canine urinary tract infections isolates from across Europe (5). Similarly, human studies have shown that the usefulness of AMR surveillance is often jeopardised by variability in laboratory procedures or non-compliance with international reporting standards (6). In addition, the quality management guidance provided by CLSI for monitoring antimicrobial resistance trends using cumulative susceptibility data provided by human epidemiologic studies (7) also needs to be followed in veterinary surveillance programmes.

Lack of specific guidelines for interpretation and reporting of AST results for animal pathogens

Although Veterinary Antimicrobial Susceptibility Testing subcommittees have been established within both the CLSI (-VAST) and EUCAST (VetCAST), there is still a shortage of animal-, infection- and pathogen-specific clinical breakpoints (CBPs) for antimicrobial drugs used in veterinary medicine. Both subcommittees are actively developing more clinical breakpoints for veterinary antimicrobial agents; however, this is a slow process due to the complexity of the tasks for various pathogen-antimicrobial combinations in different infections and animal hosts. In the meantime, the lack of specific interpretative criteria for animal pathogens represents a great difficulty for laboratory staff. Thus, developing best practice guidelines for interpreting and reporting AST results for animal pathogens for which CBPs are not yet available must be regarded as a priority for the veterinary profession.

Lack of guidelines for detection of AMR mechanisms in clinical companion animal isolates

AMR is widespread in companion and livestock animals (8, 9), and accurate detection and identification of resistant organisms is paramount for infection control and preventing zoonotic transmission. Although harmonisation of methods and interpretative criteria for monitoring AMR in zoonotic and commensal bacteria from healthy food-producing animals has been established through the EU-Commission Decision 2013/652/EU (https://www.eumonitor.eu/9353000/1/j9vvik7m1c3gyxp/vk0vn25n5e9o), AMR surveillance in companion animals, primarily cats, dogs and horses, has not been included. Veterinary laboratories, which actively perform AMR surveillance, often follow either the CLSI (10) or EUCAST procedures (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_170711.pdf) for specific detection of resistance mechanisms; however, these are not entirely applicable for veterinary clinical isolates. For instance, consensus on detection methods for methicillin-resistance in important

139 animal pathogens such as methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) or
140 *S. schleiferi* (MRSS), is still lacking (10, 11). In addition, detection of these and other
141 multidrug resistant (MDR) organisms emerging in companion animals [e.g. carbapenem-
142 resistant *Escherichia coli* and *Acinetobacter baumannii* (12, 13)] are often restricted to
143 specialised research laboratories, raising the question of whether many AMR issues remain
144 undetected. All of this points to a clear need for guidance for veterinary laboratories on
145 screening and reporting policies, including when to refer emerging multidrug resistant
146 (MDR) organisms to specialist laboratories.

147 ***Standardisation of diagnostic procedures for animal clinical specimens***

148 The absence of specific guidelines and methodologies for processing animal clinical
149 specimens for microbiology testing is a well-recognised and serious challenge to the
150 profession (14). Consequently, there is an urgent need for standardisation of the diagnostic
151 process from sample collection, processing, pathogen identification, selection of isolates for
152 AST and reporting, in veterinary laboratories across all veterinary services providers. Such a
153 lack of specific guidelines for common procedures in veterinary laboratories has multiple
154 implications that influence the appropriate diagnosis and clinical management of infections,
155 directly impacting on antimicrobial stewardship. Thus, AMR surveillance programs may
156 become ineffectual, therapeutic interventions inappropriate and significant zoonoses may go
157 undetected. A comprehensive set of recommended clinical microbiology procedures,
158 covering all stages of microbiological investigations, is necessary to ensure common
159 standards across microbiology laboratories processing veterinary specimens. These should
160 include guidelines for (i) clinical specimen collection and laboratory management specific to
161 the clinical condition/animal species, (ii) specimen-specific culture, (iii) organism isolation
162 and identification, (iv) selection of relevant bacterial pathogens for AST, and (v) the
163 interpretation and reporting of culture and susceptibility results. A widely available resource

for such protocols, similar to what is available for human microbiology laboratories in the UK [Standards for Microbiology Investigations (UK SMIs); https://www.gov.uk/guidance/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories] should be created through a similar consultation process involving all partners and organisations active in this field. Ideally, these laboratory procedures should be standardised at a European level and made available to all veterinary microbiology laboratories. In addition, a new framework for Microbiology Investigation Criteria for Reporting Objectively (MICRO) to ensure accurate and comparable microbiology laboratory results are produced among human laboratories, has been recently published and could be adopted by veterinary laboratories (15).

Although the points highlighted here are long-held goals, there is now a plan for action which is being led by the European Network for Optimisation of Veterinary Antimicrobial Treatment (ENOVAT). ENOVAT is an EU COST Action project bringing together experts in veterinary microbiology, pharmacology, epidemiology and antimicrobial stewardship throughout Europe and wider afield via collaborations with Near Neighbour Countries and International Partner Countries. Amongst other important objectives (https://enovat.eu/about/), ENOVAT is aiming to use online surveys to critically review the current methodologies and interpretive criteria used by veterinary microbiology diagnostic laboratories and identify gaps and challenges of microbiological diagnostic procedures. The survey outcome will provide an invaluable data source which can be used to draw a roadmap outlining how ENOVAT can work with project partners towards standardisation and harmonisation of veterinary microbiology methodologies.

The role of veterinary clinical microbiologists in the context of emerging molecular technologies

188 Similar to humans, animal infections are often caused by opportunistic pathogens residing in
189 the commensal bacterial population, making interpretation of culture results and pathogen
190 selection for AST challenging (16). Optimisation of this process requires the expertise of a
191 clinical microbiologist, ideally with a veterinary background to guide the laboratory technical
192 staff, to give advice at all analytical stages, and to facilitate the dialogue between the
193 laboratory and clinicians. Such dialogue is increasingly important due to the advent and
194 uptake of new laboratory diagnostic technologies. For example, matrix-assisted laser
195 desorption ionization–time of flight mass (MALDI-TOF) spectrometry is increasingly
196 adopted as the gold standard for bacterial and fungal identification in the veterinary
197 microbiology laboratories (17-19). MALDI-TOF has revolutionised clinical microbiology by
198 introducing an easy to perform, rapid, low-cost method of identification; however, veterinary
199 microbiologists need also to be aware of the new challenges arising as the low-cost of testing
200 per isolate can lead to more isolates being identified to species level compared to the pre-
201 MALDI-TOF era. To reduce the risks of "over identification", a very careful process of
202 "clinical microbiology reasoning" needs to be undertaken by the bench microbiologist to
203 ensure that only isolates which are clinically relevant are selected for AST (20, 21).
204 Although the occurrence of technical errors in laboratory testing is reduced by following
205 quality control programs, interpretation of culture results should integrate multiple clinical
206 and laboratory factors to identify and pursue clinically significant bacterial isolates. The
207 wealth of knowledge built up in human clinical microbiology studies shows that
208 underestimation of the value of this process can lead to testing and reporting of organisms not
209 associated with infection and hence contributing to inappropriate or ineffective antimicrobial
210 therapy (22).

211 Furthermore, new molecular tools aiming to improve diagnostic quality or speed up result
212 turnaround time, have emerged in clinical microbiology. These molecular diagnostic

technologies are designed to detect single or multiple pathogen(s) (bacterial, viral or fungal) associated with clinical syndromes. These molecular tools include point of care tests (POCTs), gene-based resistance detection platforms, single or multiplex PCR assays, immune-chromatographic tests, peptide nucleic acid fluorescent in situ hybridization (FISH) technologies, loop-mediated isothermal assays (LAMP), mass spectrometry and next-generation sequencing (21, 23). POCTs, also known as "rapid diagnostic tests" or "near patient tests", are used in both human and animal settings; these, are designed to be used outside the laboratory and to generate results under an hour allowing timely interventions. A recent study which has sought to identify POCTs currently available for diagnosing animal disease in developing countries, has found that many POCTs target a small number of key zoonotic animal diseases, while few exist for other important animal diseases (24). This study also highlighted that the lack of validation regulations for veterinary POCTs has allowed tests which have been improperly validated to enter the market, presenting challenges for customers and undermining their true potential on disease control (24). Multiplex PCR assays have the advantage of simultaneously detecting multiple bacterial, viral and/or fungal pathogens likely to be associated with a particular clinical syndrome (e.g., respiratory, gastrointestinal (GI), sepsis or central nervous system (CNS) infections); however, the disadvantage is that novel unsuspected pathogens may be missed (21). These multiplex detection platforms have gained a place in human and veterinary clinical practice as they support timely detection and clinical management decisions but have also introduced challenges in the clinical microbiology laboratory. These include evaluation of cost-value analysis, integration of molecular platforms in the laboratory workflow and the need for experienced specialists for results interpretation and monitoring results accuracy (21). Not last, these molecular advances include next generation sequencing (NGS) and bioinformatics, which are increasingly used for high resolution typing of pathogens or

Journal of Clinical Microbiology

238 plasmids during hospital outbreaks, detection of genes associated with antimicrobial
239 resistance or pathogenicity, although they are more commonly undertaken as part of research
240 investigation (25). The role of whole genome sequencing (WGS) in predicting AST was
241 reviewed by Ellington M. J. et al., and concluded that currently, for most bacterial species
242 there is insufficient evidence to support the use of WGS-inferred AST to guide clinical
243 decision-making (26). Furthermore, direct pathogen detection in clinical specimens
244 (metagenomics NGS) via Nanopore MinION sequencing is gaining popularity due to the
245 advantages provided by its novel features (compact portable device providing real-time
246 sequencing and analysis) allowing easier integration in the microbiology laboratory workflow
247 (27). However, the transition of NGS from research to the clinical human and veterinary
248 clinical laboratory setting seems to be a distant prospect due to its complexity and the need
249 for expert input, especially bioinformatics knowledge required for interpretation of results, as
250 well as validation and quality assurance (28). The issue around availability and integration of
251 molecular diagnostics in the human and veterinary routine microbiology laboratory workflow
252 are even more profound in developing countries due to poor infrastructures, financial
253 inequities and lack of training. In addition, there is a lack of effective AMR surveillance
254 networks and diagnostic capacity in both human and animal populations in developing
255 countries, leading to an increase use of broad-spectrum antimicrobials by health professionals
256 (29).

257 As the technical advances continue to emerge in clinical microbiology, careful integration of
258 what is technically possible with what is clinically relevant, will require regular appropriate
259 training of staff to keep pace with the developments in the field (23, 27). This highlights the
260 importance of the veterinary clinical microbiology training and specialisation, which has a
261 longstanding history in America where the American College of Veterinary Microbiology
262 was formed in 1968 (https://www.acvm.us/about-acvm/). . In Europe, the formation of the

European College of Veterinary Microbiology (ECVM) became reality in 2016 (https://ebvs.eu/colleges/ECVM). In addition, the Study Group of Veterinary Microbiology (ESGVM), established within the European Society for Clinical Microbiology and Infectious Diseases, also promotes the need for training and specialisation in veterinary microbiology in Europe (https://www.escmid.org/research_projects/study_groups/study_groups_o_z/veterinary_microbiology/). Furthermore, the European Association for Veterinary Diagnosticians (EAVLD, https://www.eavld.org/eavld/) provides a platform for networking and communication among veterinary laboratories.

Ultimately, the increasing threat from AMR and zoonotic emerging infectious diseases is underlying the need to improve and integrate veterinary microbiology services with public health services worldwide, to provide the backbone of a global One Health approach. Ensuring that veterinary microbiology laboratory have the technical facilities and the expertise of veterinary microbiology specialists, provides the necessary infrastructure to change and adapt to new challenges such as the one represented by the SARS-Cov-2 pandemic. This major public health issue has created unprecedented pressure on the global health services and provided an opportunity for veterinary microbiology services to rise to the challenge and show their adaptability by joining the global effort of controlling the pandemic through PCR testing when it most needed it (30).

Summary

Within the ENOVAT project, we are developing united complementary approaches within the veterinary microbiology profession to help achieve the long-held goals of harmonisation of AST methods and standardisation of diagnostic procedures across veterinary microbiology laboratories in Europe and beyond. We are also lobbying for more training of clinical

287 veterinary microbiologists to enable the roll out of high quality diagnostic and treatment
288 protocols for animals. This would ensure the implementation of common strategies and a
289 level playing field across all laboratories, which will positively reduce the AMR burden and
290 ultimately improve animal and public health. The outcomes may well bring benefits to
291 veterinary diagnosticians worldwide.

292

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