Microbiology Laboratories Work to Monitor the Spread of Infectious Diseases in Hospitals

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***Abstract*:** The current study aimed to examine microbiology laboratories that monitor the spread of Infectious Diseases in hospitals , to demonstrate their importance and role in early diagnosis and their relationship to early therapeutic intervention. The qualitative approach was used, and the effectiveness of this examination in reducing the spread of Infectious Diseases in hospitals was monitored.

Keywords: Microbiology Laboratories - Infectious Diseases - Hospitals

INTRODUCTION:

Accurate reporting of bacterial and fungal Infectious Diseases in hospitals (IDs) relies on the ability of traditional microbiological selective agars and media to inhibit the growth of co-colonizing flora or environmental organisms, thereby allowing the proliferation of the clinical pathogen under investigation.

The emergence of antimicrobial resistance (AMR) now threatens the ability to detect pathogens using traditional selective microbiological media, without a radical rethink and reformulation of many of these selective agars. This commentary wishes to highlight these issues among the infectious disease community and to start a discussion between the microbiology and Infectious Diseases in hospitals communities to ensure a continuum of accurate reporting from microbiology, supporting our ID colleagues.

AMR has now emerged as a global threat to public health, with the recent UK Review on Antimicrobial Resistance – Tackling Drug-Resistant Infections Globally forecasting that by 2050, there will be 10 million deaths per year due to AMR-related infections, compared with the current estimated 700 000 deaths per year [1]. Several other reports from organizations including the World Health Organization (WHO) report equally concerning estimations [2]. As a result, such reports carry several strategic objectives, including:

- to improve awareness and understanding of antimicrobial resistance
- to strengthen surveillance and research
- to reduce the incidence of infection
- to optimize the use of antimicrobial medicines
- to ensure sustainable investment in countering antimicrobial resistance.

With this growing burden of antibiotic resistance, there are obvious consequences for service clinical microbiology laboratories, including (a) the need to adopt rapid (molecular) diagnostic systems for antibiotic resistance detection, (b) an increase in specimen numbers and (c) the need to perform more complicated laboratory synergy antibiotic susceptibility testing, to inform physicians as to the what is the best (and worst) combination of antibiotics to prescribe in dual and triple combinations, so required to overcome the burden of such resistance.

One aspect of AMR, which so far has not been discussed or strategic plans put in place, is the problem of breakthrough AMR organisms growing on traditional laboratory selective agar and the consequences of this for routine microbiology testing. While molecular testing has made a significant impact on other areas of the biomedical sciences, including virology, tissue typing and cellular pathology, its impact has been slow in clinical microbiology, mainly due to the availability of, as yet, largely effective selective media, including mainly broths and agars, which remain the workhorse of the clinical microbiology laboratory. However, there is trouble ahead.

Many of these traditional agars have been formulated to be either diagnostic or selective, or both. An example of the last one would be Baird–Parker agar [3], which is a selective/diagnostic agar for Staphylococcus aureus. This agar relies on the presence of glycine, lithium and tellurite to add the selectivity, discouraging non-staphylococcal organisms from growing, while producing the least hurdle to the growth of S. aureus. Diagnostic ability is given by the addition of egg yolk emulsion, which allows the lipase production of S. aureus to produce opaque haloes around presumptive colonies. This activity, along with reduction of tellurite to give grey-black shiny colonies, makes Baird–Parker an example of an excellent selective/diagnostic agar.

However, the selective component(s) of many traditional agar formulations, particularly those employed to detect food-borne bacterial pathogens, commonly employed in service microbiology laboratories, have remained relatively unchanged since their first description, potentially dating back several decades, when issues of AMR in contaminating background were not as prevalent as they are today. Personally through our work, we are commonly witnessing this increased AMR burden of breakthrough contaminants in two areas of microbiology, namely in the traditional culture of Mycobacterium tuberculosis [4] and in the culture of fungi from the sputum of patients with cystic fibrosis (CF) [5], for which we have developed diagnostic strategies to circumvent such issues through the development of new more selective agars [[6], [7], [8], [9]]. Several other media may be at risk of breakthrough contaminants due to increased antibiotic resistance emergence, including Campylobacter – Blood free Selective Agar, Sabouraud Dextrose Agar, Middlebrook 7H10 Agar and Pseudomonas CFC Agar. This problem will be particularly marked where the organisms of interest are slow growing (e.g. Mycobacterium tuberculosis, filamentous fungi) and are mixed with a population(s) of antibiotic-resistant organisms, including Pseudomonas aeruginosa, extended spectrum β-lactamase (ESBL) producers and carbapenemase-producing organisms.

The consequence for the service microbiology laboratory of not being able to effectively isolate target bacterial pathogens using traditional selective media from mixed populations of more resistant commensal or background flora are fourfold, including the following.

- 1.

  Lower isolation rate, due to overgrowth/outcompeting from AMR contaminants.

- 2.

  Longer turnaround times, due to increased workload in dismissing AMR contaminants.

- 3.

  Increased workload—more isolates requiring identification workup, which may be offset through the use of rapid technologies, including MALDI-TOF.

- 4.

  Increased resources in terms of laboratory staff time and consumables.

With the continued growing burden of AMR organisms, service microbiology laboratories may need to re-evaluate the effectiveness of traditional selective media formulations, employing 'old' antibiotics, as selective agents. Commercial media manufacturers and suppliers will also need to consider performing additional studies to identify and stratify those agars which are at greatest risk from breakthrough with highly resistant contaminants and where necessary, control such contaminants with medium reformulation with newer and more effective antibiotics, thereby preserving the usefulness of traditional selective techniques. The reformulation of existing media will not be without its limitations too. Using highly selective and restrictive agar may introduce other limitations and may even reduce sensitivity. This limitation may apply to samples taken from patients under antibiotic treatment and potentially lower the detection rate of fastidious organisms due to unforeseeable synergistic effect of antibiotics and inhibitors in the media.

One possible solution to avoid the reformulation of existing media would be to embrace molecular methods more comprehensively, where culture and the problems thereof, can be largely avoided. Although the implementation of molecular testing methods can be considered 'slow' in the microbiology

compared with other areas (e.g. clinical virology), molecular methods are now widely used for rapid antimicrobial susceptibility testing (AST), where PCR-based detection of AMR (and species) from positive blood cultures has been achieved. Another application would be TB diagnostics, where molecular testing (despite limitations) is gaining more and more relevance in the management of TB patients in terms of rapid AST and detection of resistance to first-line agents. These advancements have a significant impact on microbiological diagnostic and reporting/therapy management. Therefore, clinical laboratories could effectively audit their reliance on cultural methods, where such AMR problems may present and thus consider alternative (non-cultural) methods, in an attempt to avoid such scenarios. Inevitably, there will be scenarios where avoidance of a requirement for culture will be unavoidable, thus requiring the need to use traditional culture media. However, while the uptake of new molecular methods may be adopted more smoothly in clinical laboratories, there may be problems in public health, food and water laboratories. This may be largely due to the legislative framework that such laboratories operate in, where the most of their testing standard operating procedures are enshrined in legislation, which is pegged to traditional cultural methods. Therefore any revision of these away from a traditional cultural basis to a molecular platform requires additional effort to update existing legislation to allow molecular data to be included.

Such discussions are now important as they highlight the impact of the growing burden of AMR on traditional microbiology laboratory isolation and the need to reformulate selective media, which risk becoming largely redundant due to increasing poor selectivity. In addition to the well-documented effects of AMR, colleagues in IDs need to be aware of the more subtle but nevertheless important consequences of AMR to traditional selective microbiology and what this may mean for ID reporting.

Transparency declaration:

Clinical microbiology has changed considerably over the past decade with the advent of new mass spectrometric methods. The success of whole-cell MALDI-TOF mass spectrometry for rapid pathogen identification has markedly improved diagnostic analysis while effecting real cost savings. Currently, new approaches based on tandem mass spectrometry are emerging for identifying pathogens without the need for time-consuming culture steps. Such deep approaches are expected to, once again, revolutionize pathogen diagnostics. Nonetheless, the successes made in microbiological typing should not overshadow the opportunities that exist within the entire breadth of the potential application space! In my opinion, this special issue of *Clinical Mass Spectrometry* on "Microbiology and clinical diseases" is the perfect arena to begin exploration of these opportunities. Ideally, the reader will evaluate the strengths presented, realize the challenges and opportunities, and develop appreciation and strategies for future development; such is the progression of scientific advancement.

In this special issue, we present publications that reflect the multi-faceted nature of applications of mass spectrometry in the clinical microbiology laboratory.

Firmly established as the reference method for bacterial identification in routine practice, MALDI-TOF is now being extended towards identifying specific antibiotic resistance markers. *Cordovana et al.* [1] successfully explore such application on a set of common bacterial pathogens. *Grenga et al.* [2] review the most recent methodologies for pathogen proteotyping by mass spectrometry.

Of note, tandem mass spectrometry-based proteotyping allows microorganism identification at an unprecedented specificity, even in complex samples, and, thus, should address the current method limits of whole-cell MALDI-TOF. Furthermore, such insightful proteotyping could provide additional phenotypic information, such as antibiotic resistance, on the pathogens present in the sample. Application of this proteomic approach for the analysis of human gut microbiota has been flourishing. *Ngom et al.* [3] review the potential of gut metaproteomics with a specific emphasis on combining other omics approaches, such as metagenomics and culturomics, to improve the reach of this area of research. There is little doubt that novel insights regarding human microbiota will be obtained. From this new knowledge, innovative diagnostic approaches will likely follow close behind.

Multitudes of bacterial strains have acquired a high degree of resistance against antibiotics and only a few new antibiotic substances have been developed in recent years. It has become clear that the clinical prescription and outcome of antibiotic use must be optimized. Along this line, *Zander et al.* [4] propose an interesting viewpoint on the role of mass spectrometry in antibiotic stewardship. Of primary interest is improved monitoring to not only optimize treatment outcomes, but also reduce toxicity and the risk of emergence of acquired drug resistance. *Kuhlin et al.* [5] offer an interesting analysis of therapeutic drug monitoring in the context of tuberculosis, a worldwide infectious disease caused by *Mycobacterium tuberculosis*. In their review, the authors outline the pertinence of liquid chromatography coupled to tandem mass spectrometry for multiplex assays using low-volume human fluid samples. In this vein, *Pautova et al.* [6] deliver a new methodology for capturing microbial metabolites from blood serum prior to detection using mass spectrometry. Finally, *Bregy et al.* [7] show how metabolites from the headspace of saliva detected by mass spectrometry may help to diagnose and monitor periodontal diseases.

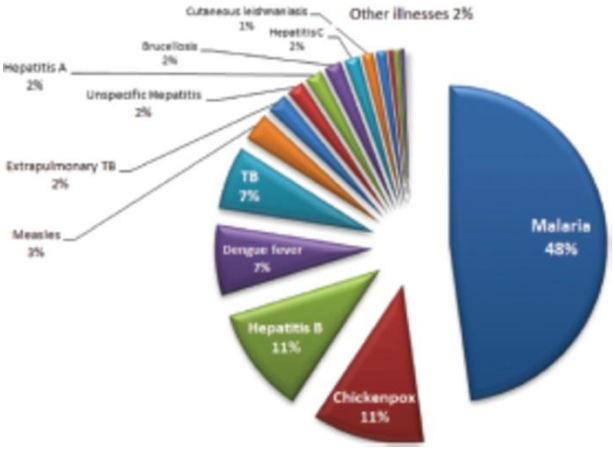

Figure 1

- The proportions of cumulative frequencies of notifiable diseases in Jazan region between 2006-2021. TB: tuberculosis

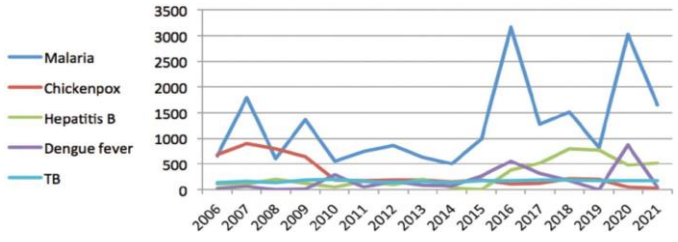

Figure 2

- Yearly number of cases of most frequently reported infectious diseases in Jazan, Saudi Arabia between 2006 and 2021. TB: tuberculosis

MICROBIOLOGY LABORATORY: TOWARDS A NEW SCENARIO?

In the last decade, new organizational models for microbiology laboratories have emerged, due to drastic changes in healthcare systems and the emergence of microbial threats in infectious diseases. The former have been deeply analysed [11] and are related to changes in patient demographics, technical developments and changes in the workforce. In addition, the objective of healthcare cost containment has had a drastic influence on this situation [12, 13]. As a result, most microbiology laboratories have changed their organizational structures or may be required to do so in the near future. Externalisation of the microbiology assistance in central laboratories belonging to the private sector has been accomplished in some countries [14]. Also, consolidation is an attractive way for microbiology laboratory survival [14]. In some cases, routine microbiology processes such as serology or urine screening are concentrated in a core laboratory, which can provide a rapid-response at a low cost.

Most of these core laboratories have emerged from biochemistry and haematology laboratories, due to the necessity of incorporating automatable processes in a rapid-response and cost-effective structure. Redundant instruments capable of multiple analyses are eliminated, and those remaining are concentrated in a core laboratory. Nowadays, core laboratories, including microbiology and immunology processes, have a horizontal organizational model (Fig. 1). Theoretically, with this organization, microbiology processes are under the supervision of senior clinical microbiologists. An inherent advantage is that non-repetitive microbiology techniques can be developed in specific microbiology laboratories. This may consolidate microbiology laboratories.

They can improve techniques in the field, including molecular techniques, implementing traditional microbiology-based techniques, and restoring the consultation role of the clinical microbiologist [13]. This has led to the active participation of microbiologists in nosocomial infection management. In some European countries, microbiologists are considered essential for the control of nosocomial infections. Microbiology surveillance studies, educational interventions, recommendations for the control of nosocomial infection, audits and feedback initiatives are developed with the active participation of the microbiologist.

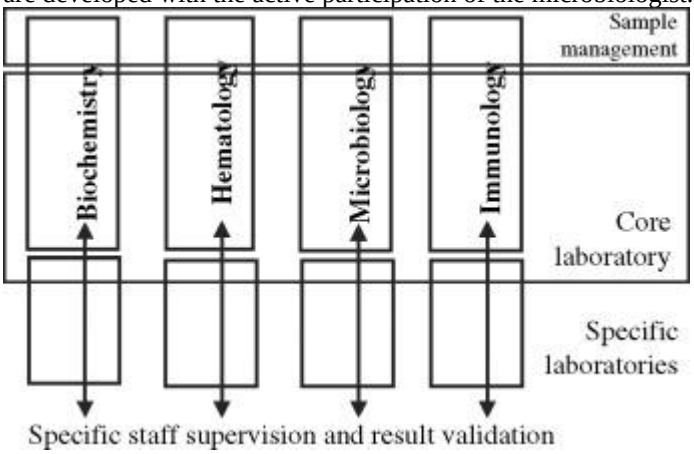

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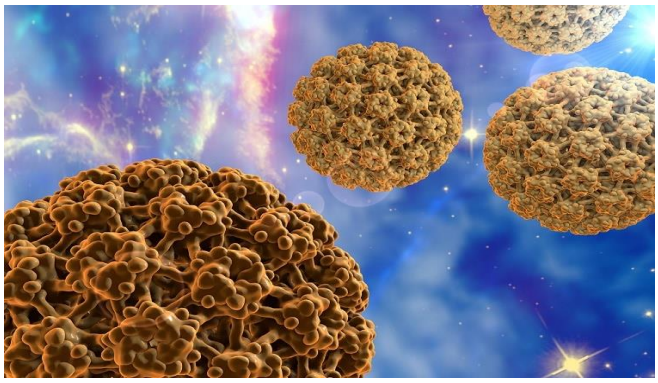
Fig. 1. Core laboratory structure with a horizontal model organization. Automation systems, technologies, management of patient samples. Quality control protocols are common but supervision of the results is performed by different staff.

It is worth noting that organizational models of microbiology laboratories may drastically affect infectious disease surveillance. The emergence of West Nile viruses in the USA has shown the need for the maintenance and revitalisation of microbiology laboratories [14]. The experience gained with emerging viral infections, including Ebola and influenza A viruses, and particularly with SARS, has revealed that microbiology laboratories might act as sentinels of emerging infectious disease threats [16].

Rapid alert to outbreak situations may be accelerated with microbiology laboratories integrated into national and supra-national global surveillance programmes. Open cooperation with international networks has been essential for the design of control strategies. In addition, the application of new molecular diagnostic techniques and the involvement of basic research microbiology laboratories have been effective in resolving new microbiological threats (e.g., the SARS experience).

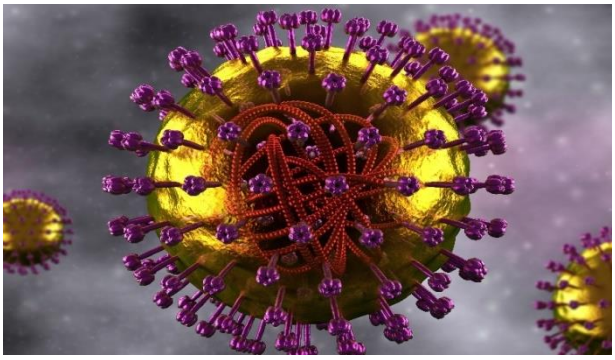


HPV (Human Papillomavirus)

Human papillomavirus (HPV) is the most common sexually transmitted infection in the US that can cause certain cancers and genital warts.

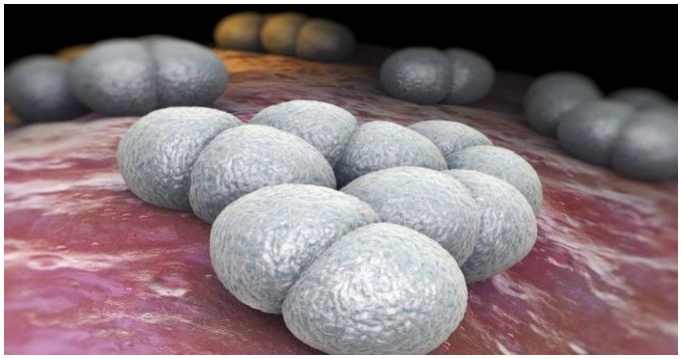
Japanese Encephalitis

Japanese encephalitis (JE) is a potentially severe disease caused by a virus spread by infected mosquitos in Asia and the western Pacific.



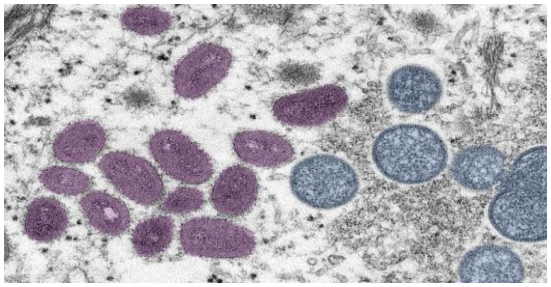
Measles

Measles is a highly contagious respiratory disease that can result in severe, sometimes permanent, complications including pneumonia, seizures, brain damage, and even death.



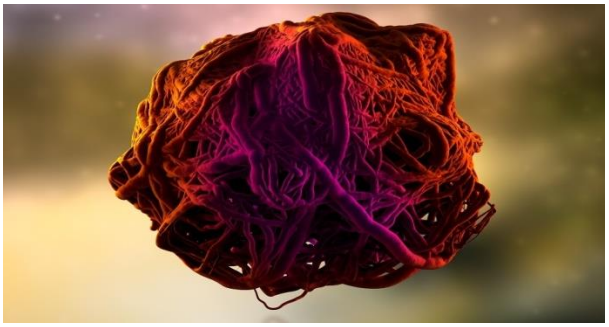
Meningococcal Disease

Meningococcal disease is a serious bacterial infection that most often leads to severe swelling of the tissues surrounding the brain and spinal cord (meningitis) or infection of the bloodstream.



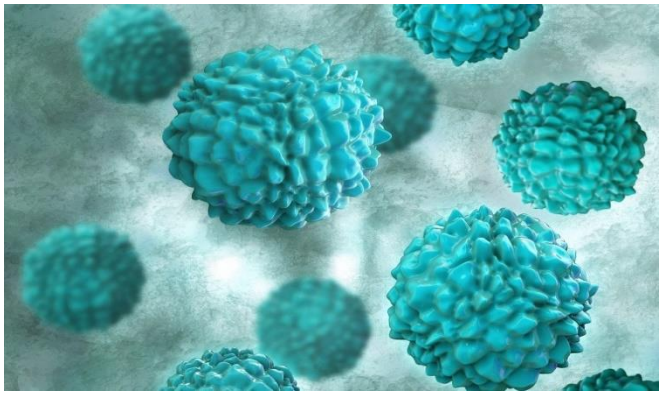
Mpox

Mpox is a rare disease that is caused by infection with mpox virus. It is spread through contact with the virus from an animal, human, or materials contaminated with the virus.



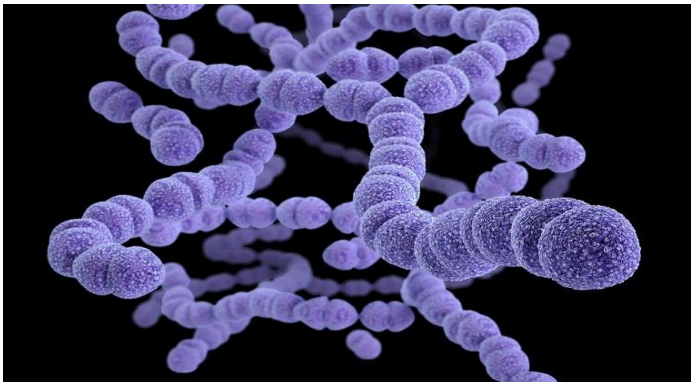
Mumps

Mumps is a contagious disease caused by a virus that spreads easily through coughing and sneezing.



Norovirus

Noroviruses are a group of related viruses that are highly contagious. Commonly referred to as "food poisoning" or a "stomach bug," noroviruses are the most common cause of gastroenteritis in the US.



Pneumococcal Disease

Pneumococcal disease is caused by common bacteria that can infect different parts of the body and is a leading cause of serious illness in people of all ages.

ALERT AND RESPONSE OF MICROBIOLOGY LABORATORIES IN INFECTIOUS DISEASE SURVEILLANCE PROGRAMMES :

The alert and response of microbiology laboratories in infectious disease surveillance programmes should be performed with the implementation of natural workflows in microbiology laboratories. Some of these processes can be developed in cooperation with research laboratories if this activity is not integrated in the same laboratory (Fig. 2). Natural workflow of microbiology laboratory includes: (1) specimen management, (2) specimen processing (methods), and (3) results and data flow.

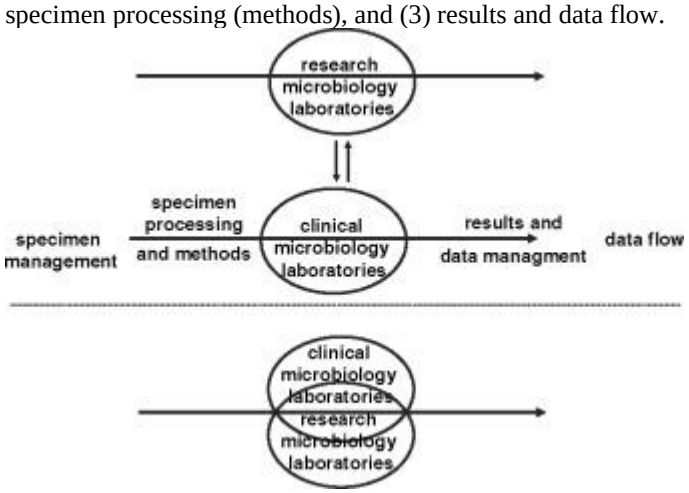


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Fig. 2. Work flow of microbiology laboratories, integration of research laboratories and processes that can be implemented for Infectious Diseases in hospitals surveillance in these laboratories.

Specimen Management:

Specimen management is essential for accurate work in the clinical laboratory. It has been recognised that appropriate collection and handling are essential for the diagnosis of Infectious Diseases in hospitals and also for infectious disease surveillance [17]. Specimen selection criteria, collection procedures, labelling, transport conditions and storage criteria should be established with the participation of the clinical microbiologist. All these processes should be performed under adequate biosafety conditions capable of protecting laboratory workers.

Nowadays, transport of biological material to different laboratories or from healthcare facilities to a laboratory is a common feature of healthcare systems. Moreover, in infectious disease surveillance networks, transportation of biological samples, including patients' material and viable microorganisms, to a central laboratory is a common practice. These materials should be adequately packed, not only to protect transport handlers, but also to prevent specimen deterioration and avoid the spread of infectious agents.

In addition, labelling should be performed according to national and international regulations. Although these processes are bureaucratic and time-consuming, microbiologists should be familiar with these procedures, particularly when samples are sent for processing in a central laboratory.

Specimen Processing and Methods:

Microbiology laboratories must implement rapid techniques, including immunoassay, microscopy and molecular testing [13]. New molecular methods have been developed during the last two decades and have recently been introduced in clinical laboratories as a consequence of automation and the development of techniques that are easier to perform. Clinical microbiologists should become familiar with molecular techniques and incorporate these in the normal microbiology routine. The introduction of rapid response in some laboratory areas has demonstrated clinical and economic benefits for healthcare systems, particularly in antimicrobial susceptibility testing and virology [18, 19].

Molecular techniques have had a direct impact on rapid response and infectious disease surveillance. They have been shown to be essential for the identification of emerging pathogens and for understanding their population structure. They are also useful for characterising virulence determinants and the genes participating in antimicrobial resistance. During outbreaks, they are essential tools for tracking the spread of microbial pathogens and for evaluation of intervention strategies [6, 20]. The results of a large number of researchers have shown the advantages of molecular techniques in infectious disease surveillance, including local studies and international networks, not only in the nosocomial setting but also in the community. Molecular techniques also have the advantage of being useful for researching genetic determinants without culturing organisms, thus allowing a more rapid laboratory response.

Results and data Management:

Most of the infectious disease surveillance networks have based their strategies on the management of results generated by microbiology laboratories [21, 22, 23]. The different experiences at local and international levels have increased the efficiency of this process. The clinical laboratory should ensure sufficient internal data management resources and a substantial database storage capacity, as well as adequately developed computing equipment and protocols. Internal microbiology software should permit the automatic alert of unusual results, and detection of increased trends and accumulation of cases. These systems must be flexible and accessible to other computing systems in order that microbiology data can be integrated in regional, national and international databases. Again, experience in this area is based on resistance surveillance with the active participation of microbiologists.

ROLE OF THE MICROBIOLOGIST AND CLINICAL MICROBIOLOGY LABORATORIES IN PASSIVE, ACTIVE AND VIRTUAL SURVEILLANCE:

Surveillance programmes have made apparent the importance of microbiology laboratories for public health action in Infectious Diseases in hospitals [24]. The strategies of traditional systems (passive surveillance), which have been used on national and international levels, were based on detecting problems through the systematic routine analysis of all microbiological data. These systems are time-consuming and do not require personnel trained in Infectious Diseases in hospitals or infection control. Alert is commonly performed with a paper-based system and requires a prolonged period of time for response.

The alternative to passive surveillance is the active surveillance system, which targets infectious disease problems and thresholds that have been previously established. Trained professionals, including clinical microbiologists and epidemiologists, actively participate in surveillance, and information is more rapidly processed. Recently, there has been an increase in international use of sentinel laboratories to improve upon traditional systems [23]; unreported infectious disease problems have been detected, and additional information obtained by global surveillance networks has been provided.

Active surveillance systems are now augmented by the inclusion of new computing technologies and the use of mathematical models. This novel strategy, also called 'virtual surveillance', is one of the most attractive options to optimise available laboratory information and can be developed with the active participation of specifically trained clinical microbiologists to provide real-time information. Nowadays, virtual surveillance should be the goal for early detection of unusual patterns of microbial pathogens and healthcare-associated infections [25].

Recent experience has demonstrated the advantages of surveillance systems that employ electronic laboratory-based reporting systems. They are frequently promoted to improve data quality and efficiency of collection, but they are essential for outbreak detection. In this sense, the availability of internet access permits rapid feedback and even interactive interventions for the exchange of interpretation and action plans. In the Pennsylvania experience, which covered a large population area [20], several laboratories implemented their computing systems and connected them to the regional healthcare electronic information system. Automatic reporting was found to be more effective than the conventional system, reducing the time needed for a paper-based report (median, 5 days), to a median of 1 day for an electronic report. Similar systems have now been developed in some European countries [22].

Features include the use of a flexible algorithm for daily analysis of data and presentation of signals on the internet for interpretation by health professionals. These systems are designed to complement, but not replace, conventional methods, as they receive reports from sources other than laboratories (e.g., clinician-based surveillance of notifiable diseases). Electronic/laboratory-based surveillance will allow early implementation of response and control strategies. Moreover, electronic reporting is highly sensitive and specific, with a low rate of false-positive and false-negative results.

ADVANTAGES OF MICROBIOLOGY LABORATORY PARTICIPATION IN INFECTIOUS DISEASE SURVEILLANCE:

The participation of routine microbiology laboratories in surveillance has clear advantages for infectious disease surveillance. Technical methodologies and reporting of results can lead to better analysis, and all the information can be centralised, particularly when laboratory computing systems are connected to regional, national and supra-national systems. Automatic 'expert systems' can thus be developed to augment the analysis of surveillance data, and automatic alerts can be centralised for response strategies. Microbiology laboratories and microbiology resources may also facilitate temporal and spatial analysis of surveillance data, which would ensure the complete collection of notifiable diseases, as well as the detection of changing patterns.

CONCLUSION:

In conclusion, infectious disease surveillance requires the active participation of microbiology laboratories, in which new methodologies and robust information technologies should be implemented in order to guarantee early detection of outbreaks. Early response strategies should be designed with the cooperation of microbiology laboratories, in which the efforts of clinical and research microbiologists should be coordinated.

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