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Diagnostic tools for bacterial infections in travellers: current and future options

Sophie BARON^{1,2}, Carole ELDIN^{2,3}, Frédérique GOURIET^{1,2}, Grégory DUBOURG^{1,2#}

1. Aix Marseille Université, IRD, Assistance Publique Hôpitaux de Marseille (APHM),
Microbes, Evolution, Phylogeny and Infection (MEPHI), Marseille, France
2. IHU Méditerranée Infection, Marseille, France
3. Aix Marseille Univ, IRD, AP-HM, SSA, Vecteurs, Infections Tropicales et
Méditerranéennes (VITROME), IHU-Méditerranée Infection, Marseille, France

#To whom correspondence should be addressed.

Dr Grégory DUBOURG

IHU Méditerranée Infection
19-21 boulevard Jean Moulin
13385 Marseille cedex 5
France
Tel: +33 (0)4 91 32 43 75
Fax: +33 (0)4 91 38 77 72

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ABSTRACT

International travel has increased dramatically over the past 50 years, and travel destinations have diversified. Although physicians are more familiar with the panel of aetiological agents responsible for illnesses of returning travellers, thanks to regular epidemiological studies, the spectrum of pathogens potentially encountered in various travel destinations is nevertheless increasing. In addition, the wide array of approaches currently available and addressed in this paper could render the procedures for microbiological analyses increasingly complex. As the time to result is crucial to adequately manage patients, modern approaches have been developed to shorten diagnosis delays. The syndromic approach, which consists of simultaneously testing a wide panel of microorganisms, substantially increases the diagnostic yield with significant time savings, particularly when coupled with point-of-care laboratories. The tools commonly used for this purpose are immunochromatographic tests, mainly targeting bacterial antigens, and multiplex real-time PCR. The emergence of next-generation sequencing technologies, which enable random amplification of genetic material of any microbe present in a clinical specimen, provides further exciting perspectives in the diagnosis of infectious diseases.

Keywords: infectious diseases; travellers; bacteria; diagnosis; PCR; NGS; Point-of-Care

Introduction

Over the past 50 years, international travel has dramatically increased, and more than one billion travellers were recorded worldwide in 2012 (1). It is expected that this number will reach 1.8 billion in 2030 (2). Currently, Europe has the highest number of international arrivals and remains the preferred destination of travellers (3). There is, however, a growing interest in travelling to other continents, such as Asia, the Americas, and Africa (2). Indeed, the spectrum of pathogens potentially encountered in these areas, which include tropical and low-income countries, differs considerably from those usually diagnosed in the tourists' countries of origin. Physicians are therefore more aware of the panel of aetiological agents responsible for illnesses of returning travellers according to the visited areas thanks to epidemiological studies regularly conducted (4–7). The procedures for microbiological analyses for diagnosis can, however, be complex. Indeed, a wide array of methods are currently available for this purpose; the performances of these methods are heterogeneous and can even differ depending on the aetiological agent.

Herein, we propose to review the different techniques commonly used to identify bacterial pathogens from clinical specimens underlining their weaknesses and strengths. We then detail, according to specific syndromes, the appropriate specimens for sampling and accurate methods to diagnose the specific pathogens involved. We finally provide the prospects and perspectives concerning the techniques of tomorrow, especially next-generation sequencing (NGS) approaches.

Tools for the diagnosis of bacterial infections: general considerations

Direct Diagnosis

Microscopic observation

The main advantages of microscopic observation are fast results and cost-effectiveness, rendering the technique suitable for low-budget laboratories, in particular in low-income

countries despite the laborious process. When this method is combined with Gram staining, a sensitivity of 10^5 CFU/mL(8) can be reached, which has been demonstrated to be useful in the diagnosis of urinary tract infections, pneumonia, and bacteremia (9). Combined with Ziehl Neelsen or auramine staining, direct examination adds real value for detecting mycobacteria, such as tuberculosis or leprae, as their definite diagnosis can take up to several weeks. Finally, relapsing fever could be diagnosed from blood by Giemsa staining or various microscopic approaches (10,11).

Culture

As culture is a sensitive, cost-effective and open approach, its application is essential to diagnose bacterial infections. The majority of agents can be easily grown on agar plates (i.e., axenic culture) within 2 days, while culture of enteric pathogens can require 5 days. Culture of *Legionella* spp. or *Mycobacterium tuberculosis* require specific culture approaches and thus have to be specifically mentioned. Finally, culture of facultative- or obligate-intracellular bacteria (i.e., *Bartonella* spp., *Coxiella burnetii*, *Rickettsia* spp., *Chlamydia* spp., *Borrelia* spp.) is not usually a first-line diagnostic test, as cell culture methods are labour intensive and some require a biosafety level-3 (BSL-3) laboratory due to high infectivity. For an extensive review concerning the culture of fastidious microbes, see (12).

Identification of grown colonies is currently widely performed using matrix assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF MS). This method has been used for the past decade and relies on the recognition of protein profiles compared to a database that can be regularly updated (13). The method is reliable, cost-effective, fast (i.e., few minutes) and versatile, up to the point that it is successfully used to identify bacteria directly from clinical specimens, arthropod vectors or for the vector themselves. When identification fails, molecular approaches are commonly used to achieve

final identification (see below). Alternatively, biochemical profiles are commonly used to identify grown bacterial species (14).

Molecular approaches

Molecular approaches rely on the detection of nucleic acids belonging to bacteria. An amplification step is required to render the DNA detectable through polymerase chain reaction (PCR). The universal approach (i.e., targeting the 16S rRNA gene) has gradually been replaced by a specific approach in which a region present exclusively in the pathogen of interest is targeted. This approach is currently the most widely performed as it displays a high analytical sensitivity (15), can be applied in polymicrobial specimens (i.e., stools, sputum) and offers a very short time to result (i.e., from 1 hour to several hours). Molecular methods are particularly useful for detecting bacteria for which culture approaches are too long or fastidious (i.e., Mycobacteria, intracellular bacteria) or when antibiotic therapy has been already administered.

Antigen detection

To reduce the time to diagnose infections, a wide array of tests have been developed that detect bacterial antigens based on an antigen-antibody reaction. These tests usually require a minimal hands-on time with a time to result that does not exceed 30 min and are very easy to interpret; therefore, they are commonly performed in point-of-care laboratories (POCLs) (16) in particular in low income countries (17). These tests display, however, lower sensitivity than the gold standard methods but take advantage of their high specificity.

Serological testing

Detection of antibodies from patient sera is particularly useful when direct diagnosis of bacteria is difficult, mainly intracellular bacteria. Serology could, however, lack sensitivity, and it requires the collection of paired samples to highlight serological conversion.

Principle of the syndromic approach to diagnose infectious diseases

While empirical therapy could fail, rapid pathogen identification enables the adequate management of patients suffering infectious diseases. The syndromic approach, which consists of simultaneously testing a large panel of microorganisms, represents a significant time saving strategy. Originally, syndrome- and disease-based diagnostic kits were designed for this purpose by optimizing the number of specimens to be sampled (18–20). The abovementioned kit consists of empty vials with pre-filled prescription forms. This strategy i) ensures that all the relevant pathogens will be tested according to each syndrome, ii) avoids resampling or retesting and iii) more importantly, reduces time to result by including rapid tests in particular in point-of-care laboratories (POCLs). Notably, our laboratory has designed a specific kit for the diagnosis of traveller's fever (unpublished data), and syndromic approaches are currently used to diagnose traveller's diarrhoea (21). (22). We propose to review in the following paragraphs the current methods to identify aetiological bacterial agents according to each syndrome.

Diarrhoea

Traveller's diarrhoea is the most common health problem of international travellers, representing 20-60% depending on the destination (1,23,24). The infectious aetiology of diarrhoea may be unknown in 40-50% of cases.

Bacterial traveller's diarrhoea is mainly represented by *Campylobacter*, *Escherichia coli*, *Salmonella*, *Shigella*, and *Aeromonas* spp. (21). Emerging enteropathogens, such as *Arcobacter* spp. (25), *Laribacter* spp. (26) and enterotoxigenic *Bacteroides fragilis* (27) were newly described in travel-related gastroenteritis. *Tropheryma whipplei* was recently suggested as a potential cause of diarrhoea in travellers (28). Indeed, treating travellers with antibiotics is not unusual, and the involvement of *Clostridium difficile* (29) or *Klebsiella oxytoca* might not be rare (30). The presumption of *V. cholerae* diarrhoea (i.e., return from endemic area, rice-

water diarrhoea) should be mentioned because its research is not usually performed in the laboratory because it requires specific culture media.

Rectal swabs could be used, but they are generally less sensitive than fresh stool for culture (30) and must be sampled during the acute phase of the disease. Gram staining is not useful with the exception of campylobacteriosis (30). Routine faecal specimens are inoculated on agar plates using a battery of chromogenic or selective medium, and suspicious colonies are subjected to MALDI-TOF MS analysis. The latter, however, is unable to accurately distinguish *Salmonella* serotypes or to distinguish *Shigella* spp. from *E. coli* (31), thus requiring additional tests such as latex agglutinations or biochemical testing. Serogrouping and serotyping using antibodies is also required for *Vibrio cholerae* isolates (32). As culture is usually long, antigen detection tests enable the early diagnosis of diarrhoeal aetiological agents, such as toxigenic *C. difficile* (33), *Campylobacter* spp. (34), *Vibrio cholerae* (35,36) or the detection of shigatoxin production (30). Regarding *T. whipplei*, classic Whipple's disease could be considered the cause of arthralgia and diarrhoea in Caucasian men, for whom positive PCR in stool and saliva are highly predictive. However, due to the significant faecal carriage of this bacterium, the definite diagnosis is established by histological examination of small bowel biopsies. PCR on urine specimens represents a promising alternative to increase the specificity of molecular methods.

Substantial improvements have recently been made to the multiplexing of molecular tests for which panels targeting the most important enteric bacterial pathogens directly from faecal samples have been designed (37). There are valuable tools for the identification of microbiologic agents from the stool of patients with traveller's diarrhoea (21), thus allowing early diagnosis (37) and detection of co-infections (38). Syndromic panels, such as Biofire's FilmArray Gastrointestinal (GI) Panel, allow the simultaneous identification of 22 different enteric pathogens, including bacteria parasites and viruses, directly from stool specimens in

less than 1 hour (39), and other multiplex molecular assays are available (37). Metagenomic sequencing has also been evaluated to identify gastro-intestinal pathogens. While agreement with multiplex PCR is often high (40), the ability of multiplex PCR to find pathogens among conventionally negative specimens could be valuable in second line diagnosis (41). Moreover, multiplex PCR enables the detection of virulence genes and emerging pathogens and provides an opportunity for typing bacteria such as *C. difficile* or *E. coli* (41). These tests are expensive and should be reserved for patients with severe clinical presentation or for difficult cases. In addition, positive results should be carefully interpreted according to symptoms and epidemiological data (age, season, country), as coinfections are frequently detected (42) and faecal carriage could lead to erroneous diagnosis.

Cutaneous infections

Skin or soft tissue infections after superficial wounds are the most frequent dermatologic disease in travellers returning from tropical areas (43). Pyogenic bacteria are recovered by standard culture followed by identification by MALDI-TOF MS from skin biopsies, blood samples or swabs, while detection of production of Pantone-Valentine leucocidin (PVL) by PCR in *S. aureus* isolates can be further performed (44).

Tick-borne diseases are frequently reported in returning travellers (45–47). Spotted fever group rickettsioses are strongly associated with arthropods (i.e., ticks or fleas, lice or mites) (48), and thus, the notion of bite revealed by the anamnesis is crucial to direct microbiological procedures. Because vectors are sometimes kept by the patient, their identification could help for the diagnosis, which could be performed by PCR or more recently by MALDI-TOF MS in record time without entomology expertise (49). The detection of pathogens in vectors as revealed by PCR or more recently by MALDI-TOF MS (50) should be interpreted with caution due to the high prevalence of several pathogens, notably in ticks (51,52). Definite diagnosis can be established from clinical specimens. Serology and targeted PCR on skin

biopsies or eschar swabs (53) represent the cornerstone of the diagnosis of rickettsiosis.

Diagnosis of cutaneous infections involving Mycobacteria relies on the direct examination of skin biopsies for identifying acid-fast staining bacilli and cultures (54). Molecular tests could be helpful in particular in the case of uncultured *Mycobacterium leprae*, for which assays are compatible with point of care testing (55), which could be used either in endemic areas or in countries of returning travellers as imported leprosy is not infrequent (56,57).

When travelling to temperate areas, localized Lyme disease (*Erythema migrans*) can be observed after a tick bite. The diagnosis is mainly based on clinical history and presentation, as the serology is usually negative at this stage. However, the diagnostic can be performed by a specific PCR targeting *Borrelia burgdorferi* on a cutaneous biopsy, for which performances are poorly known (10).

Respiratory infections

Respiratory infections account for approximately 10% of traveller's infections (43,58). They are one of the most common causes of hospitalization, especially among travellers (59,60), and mortality due to travels is evaluated at 1%. If viruses are main aetiological agents, the bacteria commonly found in community-acquired pneumonia can also be involved (43) (**Table 1**), while some more "exotic" bacteria are rarely encountered, such as *Burkholderia pseudomallei*, which can be encountered in Southern Asia in patients suffering from melioidosis (61).

Direct examination

Direct staining with fluorescent antibodies allows the detection of *Legionella* (62), while light microscopy or immunofluorescence microscopy can be used to detect *B. pseudomallei* but lacks sensitivity (61) (<50%). Indeed, direct examination is currently only relevant for the detection of *Mycobacterium tuberculosis* (MTB), for which Auramine O (more rapid) or

Ziehl-Neelsen (reference method) staining is used to rapidly identify a bacilliferous patient (63). This technique is specific but lacks sensitivity (50-60%) and requires repeated experiments on several samples. Its role in extra-pulmonary tuberculosis is limited because its sensitivity is lower than on pulmonary samples. However, direct examination is utilized if the laboratory does not have access to molecular tools (64,65). *Nocardia spp.* and other non-tuberculosis bacteria can be positively identified with direct examination, and a combination of direct examination with fluorescence in situ hybridization (FISH) using a specific probe was recently proposed to fasten the identification of MTB with enhanced specificity (66).

Culture

Sputum samples have been shown to be sufficient to recover the vast majority of easily cultivable bacteria responsible for respiratory infections by culture (67). As *Legionella* species require specific media for growing, the specific culture should be specified to the laboratory. Culture is still considered the gold standard because all the *Legionella spp.* can be detected, but it is fastidious and lacks sensitivity (62,68). Research for MTB must be specifically mentioned because this bacterium belongs to risk group 3 of pathogens and is therefore carried out in NSB3 laboratories. Culture is highly sensitive and specific but requires a long incubation period of up to 30 days (12), although recent advances have reduced the time required to obtain colonies (69). The development of colony imaging could improve the delay for solid culture (12,69). Blood culture is useful in cases of fever, particularly for invasive pneumococcal disease (IPD) (70); it is the gold standard for the recovery of *B. pseudomallei*, and other specimens, such as urine, rectal swabs could be sampled and repeated to increase the culture sensitivity (61).

Most of the cultured microorganisms can be identified using MALDI-TOF MS. However, this could fail to discriminate some species closely related to Mycobacteria (71) or to distinguish

pneumococci from oral streptococci (72), thus requiring other methods (i.e., molecular tests or phenotypic reactions, respectively). In a similar fashion, *B. pseudomallei* can be confused with *Burkholderia thailandensis* (73,74). Molecular methods may therefore be necessary for final identification, for which the *groEL* gene has been suggested as more discriminating than the 16S gene.

Molecular tests

A wide array of PCR systems is available to detect bacterial pathogens from respiratory samples. Various PCRs targeting different genes have been developed to detect *Haemophilus influenzae* (75) or *Streptococcus pneumoniae* (76) from various respiratory specimens (77). However, a positive result must be interpreted with caution because these are commensals of upper airways. Several targets exist for pneumococcus, and the *lytA* and *psaA* genes were shown to be more specific than the pneumolysin gene (*plyN*) (70). Quantitative PCR could be used to predict invasive pneumococcal diseases in influenza patients (78).

Legionella PCR is highly sensitive (97%) and specific (>98%) in respiratory samples (79) and can also detect all the serotypes (80). Concerning MTB, only the Xpert MTB/RIF assay is sensitive enough to be recommended by the WHO. The Xpert MTB/RIF assay involves a closed PCR system that directly extracts and PCR-amplifies a sample or an isolate. This system allows the diagnosis and detection of rifampicin resistance in a few hours and requires little handling. Other specific PCR methods to detect resistance to anti-tuberculosis drugs have also been commercialized (71). Other systems have been designed to detect the DNA of intracellular bacteria, such as *Bordetella*, *Chlamydomphila* and *Chlamydia* species (81). Multiple systems for the diagnosis of melioidosis from clinical specimens exist, and the results can vary even if the T3SS gene cluster is targeted and seems to be the most interesting candidate. *T. whipplei* pneumonia is an emerging entity that could be diagnosed by PCR on

broncho-alveolar lavage specimens (82). Finally, as a part of the syndromic approach of the diagnosis of respiratory infections, multiplex PCR systems or DNA microarrays have been designed (83). Of these, particular attention is currently given to “sample to answer” systems that require very little handling. Extraction, DNA amplification and interpretation of the result is carried out in a closed system, with a time to result that does not exceed two hours and is compatible with POCLs (84).

Serological testing

Serological testing is gradually less employed to diagnose pulmonary bacterial infections, with the exception of *Coxiella burnetii*. For the latter, a risk factor analysis could be performed to identify patients with Q fever pneumonia (85). Serology is not useful for the diagnosis of Legionnaire’s disease or diseases involving intracellular bacteria but could be useful as a screening tool for epidemiological studies (62,86–88) while the diagnosis of melioidosis could be difficult to interpret, especially in endemic countries where the prevalence of positive infection can be high (61).

Rapid tests

Two reliable rapid urine tests are widely used to fasten the detection of pneumococcal antigens from urine (70) and have good sensitivity (77-88%) and specificity (67-100%); however, these tests remain positive several weeks after the infection treatment, cross-react with some closely related streptococci and are not specific enough to be used for children (76). It is recommended to combine this antigen detection tool with another method to confirm the diagnosis of pneumococcal disease. The detection of *Legionella* antigen in urine is rapid, sensitive (96%) and highly specific (>95%), but only serotype 1 of *L. pneumophila* can be detected, and this serotype persists after the onset of the disease (80). Rapid tests detecting several *Legionella* species (including *L. longbeachae*) or combined detection of *S.*

pneumoniae and *L. pneumophila* are also currently available with a high sensitivity (89). An immunochromatographic test has also been developed to detect antibodies against melioidosis that could be used for rapid screening despite modest sensitivity to the culture (90).

Next-Generation Sequencing

The increased number of *S. pneumoniae* genomes available has made it possible, through the analysis of its pan-genome, to design new and very specific PCR targets (91). For MTB, direct genome sequencing allows accurate identification and profiling of antibiotic resistance (92), but bioinformatics tools and the resistance mutation database need to be improved. More importantly, these molecular approaches enable the detection of pathogens in situ. Since respiratory specimens are frequently contaminated with resident flora, quantitative analysis could distinguish infection from colonization. A preliminary study showed that metagenomics can detect viruses but also relevant bacteria using the Illumina sequencing approach (93). Although the time to result of this method is incompatible with emergency diagnostics, several studies have succeeded in detecting the aetiological agent of respiratory infections such as *P. aeruginosa*, *S. aureus* or *H. influenzae* (94) using nanopore sequencing. Finally, a study reported that the use of NGS technology in the context of severe pneumonia is associated with a reduction in mortality (95).

Meningitis

Meningeal syndrome in travellers returning from the sub-Saharan meningitis belt or after the Hajj pilgrimage is strongly associated with meningococcus. Basically, gram staining performed on cerebrospinal fluid (CSF) could provide a rapid response if the bacterial load is high, indicating characteristic gram-negative diplococci. More reliable rapid tests are

available, in particular as a part of POCLs. Antigen detection is simple and fast and makes it possible to distinguish serogroups; however, according to the studies, analytical performance may vary, particularly with regard to sensitivity (96). Real-time PCR is the most reliable tool to confirm or exclude meningococcal disease with a diagnosis time of a few hours, as it could be performed in POCLs (97). Targeting two genes is recommended (frequently *CRGA* and *CTRA* genes) because cross reactivity with other species exists (98). Standard culture could also be performed but is not compatible with emergency diagnosis. False negative could also occur as meningococcus is a fragile microbe (15). The same strategy is applicable to the diagnosis of pneumococcal meningitis. While specific antigen detection tests from CSF are available to detect *S. pneumoniae* (99), those commonly used for urine samples could also be used (100). Nevertheless, these antigenic tests remain less sensitive than real-time PCR. Real-time PCR could be multiplexed, such as in the BioFire FilmArray Meningitis/Encephalitis Panel, allowing the detection of 14 pathogens including 6 bacteria in approximately one hour (101), although some false-positive and false-negative results have been reported. Finally, NGS applied to CSF has shown promising results, such as the detection of uncultured *M. tuberculosis* or *Listeria monocytogenes*, indicating that these tools could be used in the second line if the first microbiological investigations are negative (102).

Febrile illness

Fever should in any case encourage blood cultures (BC) as they could help to quickly recover the usual bacterial agents responsible for invasive infections. Importantly, BC currently remains the most reliable approach to diagnosing typhoid fever. However, the identification could be challenging because MALDI-TOF MS does not distinguish serovars among *Salmonella* isolates, even if sophisticated approaches have been proposed for this purpose (103). The use of conventional PCR followed by sequencing nevertheless showed that BC may have under-diagnosed typhoid fever. (104). Despite the development of several molecular

tools to identify Typhi serovar directly from blood specimens (105,106), there is currently no simple marketed molecular test available. Antibody detection is an alternative, but Widal's performance is low (107), and several rapid diagnostic kits have been developed to quickly detect IgM antibodies. Some of these display fairly good analytical performances and could be used in POCLs (108).

In travellers returning from Southeast Asia, murine typhus caused by *R. typhi* (transmitted by rat fleas) and scrub typhus caused by *Orientia tsutsugamushi* (transmitted by mites) are frequent causes of fever (43). Since inoculation eschar is not constant, the diagnosis first relies on serology. Serum samples were analysed using the indirect immunofluorescence assay (IFA) against typhus group and *O. tsutsugamushi* antigens (109). In scrub typhus, when an eschar is present, real-time quantitative PCR (qPCR) specific for the periplasmic serine protease gene of *O. tsutsugamushi* can be performed (110) on a swab eschar sample.

The diagnosis of leptospirosis represents a conundrum for microbiologists as its culture requires laborious processing. Direct diagnosis currently relies on PCR detection, which can be performed on either blood, serum, urine or cerebrospinal fluid (CSF). Greater sensitivity has been suggested when molecular amplification is performed from serum (111), while DNA is detectable longer from urines (112). Housekeeping genes are usually targeted to detect all *Leptospira* species, while specific PCR allows species identification (113). The performance of PCR on blood and urines is highly variable and depends on the timing of the test (i.e., higher sensitivity in very early samples). The main advantage of molecular detection is that DNA is detectable during the early acute phase of infection. Alternatively, IgM antibodies can be detected in a few hours when ELISA assays are performed, for which a wide variety of kits are currently available. Interestingly, NGS performed on CSF has recently led to the diagnosis of a case of neuroleptospirosis (114).

Relapsing fevers caused by *Borrelia duttonii*, *Borrelia crocidurae*, *Borrelia recurrentis*, *Borrelia persica* and *Borrelia hispanica* are mainly observed in tropical and subtropical regions and are transmitted by soft ticks, or lice for *B. recurrentis* (10). These infections can lead to massive bacteraemia, so direct detection methods on blood samples are possible (10). The traditional method of detection is optical microscopy after Giemsa staining of blood smears or thick blood drops. Specific quantitative PCR is now available, allowing a better sensitivity of detection on blood samples (10). Specific serological tests for the causative agents of relapsing fever have been developed, but they can be negative during the first episodes of fever and are most used as a retrospective diagnostic tool.

Acute Q fever is a clinical entity seen in travellers infected by *C. burnetii* (48,115). Serological tests remain the easiest and most common method to detect the presence of IgM against Phase I and Phase II antigens(116), although cross reactions may occur. The PCR on serum in the acute phase could be valuable for diagnosis. Further tests are useful for the prevention of persistent endocarditis (i.e., aCL, TTE) or to diagnose acute Q fever endocarditis (117). Hot prospects currently concern the use of fluorescence in situ hybridization (FISH) to diagnose persistent infections (118).

MDR bacteria carriage

Multidrug resistant (MDR) bacteria carriage is a risk to be considered in any patient who has travelled to countries where the prevalence of resistance is high (119) (i.e., Asia and Northern Africa) (120). Hospitalization, the use of antibiotics during travel and gastro-intestinal disorders are associated with a higher carriage rate, while refugee patients could constitute a substantial reservoir of antibiotic resistance (121). There is no consensus, but the multidrug-resistant bacteria usually screened include methicillin-resistant *Staphylococcus aureus*, plasmid-mediated cephalosporin-resistant *Enterobacteriaceae*, vancomycin-resistant Enterococci, carbapenemase-producing *Acinetobacter baumannii* and *Enterobacteriaceae*.

The specimen to be sampled includes a rectal swab for *Enterobacteriaceae* and *Enterococci*, while a nasal swab is usually performed to detect the presence of methicillin-resistant *S. aureus* (MRSA). A large number of selective chromogenic media for the detection of MDR bacteria have been developed, requiring growth time (i.e., 24-48 hours) with a good negative predictive value but a lower positive predictive value. Additional testing is required to confirm the presence of MDR bacteria, including identification, antibiotic susceptibility tests (ASTs) and minimum inhibitory concentration (MIC) determination by the gradient strip test or microdilution method. As conventional complementary techniques can delay response time, several rapid phenotypic tests have been designed to identify the resistance mechanism involved, such as ESBL, carbapenemase-producers and MRSA (122–125). Resistance genes coding for carbapenemases, methicillin-resistance or vancomycin-resistant genes could be targeted by real-time PCR, in particular in a multiplexed fashion with excellent analytical performances (126). Closed systems also exist, thereby enabling a time to result of one hour without prior extraction. Because the detection could be performed directly from clinical specimens, the time saved is particularly valuable for managing outbreaks of multi-resistant bacteria. These PCRs are, however, limited to what is currently known, while NGS technology allows deciphering the entire resistome of a bacterium by sequencing its whole genome. While Illumina technology (Illumina, USA) is limited for studying whole plasmids due to the presence of transposons, Nanopore technology (Oxford Nanopore, Oxford, UK) allows the sequencing of long DNA fragments, thereby enabling the reconstitution of an entire plasmid (127). The determination of the genetic environment and other resistance genes carried by the same plasmid enables real-time monitoring of outbreaks in a clinical setting by comparing the plasmids found in patients to understand the transmission of these genes. It also allows new variants to be identified that could be negative using the usual targeted PCR. However, this approach remains costly and requires further development.

Conclusions

While a wide array of technologies is currently available to diagnose infectious diseases, intense efforts are dedicated to shortening the time from sampling to result. Multiplexed molecular tests, rapid assays and integration in POCLs are the current directions for this purpose, while further developments are needed to routinely use NGS technologies.

BOX: Key messages and novel diagnostic approaches.

- The spectrum aetiological agents responsible for illnesses of returning travellers is increasing.
- The clinical examination remains crucial to adequately guide microbiological investigations.
- The syndromic approach that consists of systematically testing from the start a wide array of microorganisms increases the diagnosis yield.
- The routine microbiological examination remains essential for the first line diagnostics in particular in low-income countries.
- Point-of-care laboratories (POCLs) enable a significant time-saving for the diagnosis by using rapid tests
- Next-generation Sequencing (NGS) approaches are promising but are currently limited to the field of research and in specialized laboratories.

FIGURE AND TABLE LEGENDS

Figure 1. Overview of the syndromic approach for the diagnosis of infectious diseases, from the specimen to the laboratory. BC, blood cultures; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; FISH, fluorescence in situ hybridization; IIF, indirect immunofluorescence; NGS, next-generation sequencing technologies.

Table 1. Main aetiological agents responsible for each syndrome and key tests commonly used in routine laboratories for their detection. The tests are sorted (from the left to the right) in order of increasing time to result.

Table 2. Main aetiological agents responsible for each syndrome and modern key tests available for their detection. The tests are sorted (from the left to the right) in order of increasing time to result.

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Conflict of interest: none to declare.

1 **Table 1.**

Aetiological agent	Key tests	Remarks
Respiratory infections		
<i>Streptococcus pneumoniae</i>	Antigen detection (urine) Culture (sputum, blood culture)	
<i>Haemophilus influenzae</i>	Standard culture (sputum, blood culture)	
<i>Staphylococcus aureus</i>	Standard culture (sputum, blood culture)	
<i>Mycobacterium tuberculosis</i>	Direct examination / Ziehl Neelsen (sputum) Targeted culture (sputum)	Cultured should be carried out in BLS-3 laboratories
<i>Legionella pneumophila</i>	Antigen detection (urine) Targeted culture (sputum)	
<i>Burkholderia pseudomallei</i>	Standard culture (sputum, blood culture)	
<i>Bordetella pertussis</i>	Serological testing Targeted culture	poor performance of serological testing during acute phase, culture is laborious
<i>Chlamydia pneumoniae</i>	Serological testing	poor performance during acute phase
<i>Mycoplasma pneumoniae</i>	Serological testing	poor performance during acute phase
Cutaneous infections		
<i>Treponema pallidum</i>	Serological testing	Dark field microscopy is gradually less employed
Spotted fever group <i>Rickettsiae</i>	Serological testing	
<i>Staphylococcus aureus</i>	Standard culture (skin biopsy/swab)	
<i>Streptococcus pyogenes</i>	Standard culture (skin biopsy/swab)	
<i>Mycobacterium leprae</i>	Direct examination / Ziehl Neelsen (skin biopsy)	

<i>Borrelia burgdorferi sensu lato</i>	Serological testing (ELISA + western blot)	Dark field microscopy is gradually abandoned
Diarrhea		
<i>Aeromonas spp.</i>	Targeted culture (stool) and biochemical identification	
<i>Arcobacter spp.</i>		undistinguishable using biochemical identification
<i>Clostridium difficile</i>	Toxin detection (stool)	The toxin is targeted by immunochromatographic tests
<i>Campylobacter spp.</i>	Gram staining Targeted culture (stool) and biochemical identification	
<i>Escherichia coli (EHEC, ETEC)</i>	Targeted culture (stool) and biochemical identification	
<i>Laribacter spp.</i>		undistinguishable using biochemical identification
<i>Salmonella spp. (non-typhoid)</i>	Targeted culture (stool) and biochemical identification	
<i>Shigella spp.</i>	Targeted culture (stool) and biochemical identification	
<i>Tropheryma whipplei</i>	Microscopy following PAS and IHC staining (small bowel biopsies)	Microscopy confirms the diagnosis
Febrile illness		
<i>Typhoid fever</i>	Blood cultures Serological testing (Widal)	
<i>Rickettsia typhi, Orientia tsutsugamuchi</i>	Serological testing	
<i>Leptospira spp.</i>	Serological testing	
<i>Coxiella burnetii</i>	Serological testing	
<i>Brucella spp.</i>	Serological testing Targeted culture (blood cultures)	Cultured should be carried out in BLS-3 laboratories
Relapsing fever <i>Borrelia</i>	Microscopy (GIEMSA coloration) Quantitative Buffy Coat	
Meningitis		

<i>Streptococcus pneumoniae</i>	Microscopy (gram staining)	Standard culture (CSF, blood culture)	
<i>Neisseria meningitidis</i>	Microscopy (gram staining)	Standard culture (CSF, blood culture)	

BLS : Biosafety level; CSF : cerebrospinal fluid; FISH: Fluorescence in situ hybridization; PAS: Periodic acid-Schiff; POCLs: Point-of-Care Laboratories; PVL : Panton-Valentine Leucokidin

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16 **Table 2.**

Aetiological agent	Key tests		Remarks
Respiratory infections			
<i>Streptococcus pneumoniae</i>	Quantitative PCR (sputum)		Quantitative PCR could be used to assess risk of pneumonia during flu
<i>Haemophilus influenzae</i>	Quantitative PCR (sputum)		
<i>Staphylococcus aureus</i>	PCR (sputum)		Toxin detection (i.e. PVL) may be performed in case of necrotizing pneumonia
<i>Mycobacterium tuberculosis</i>	PCR (sputum)		Genexpert is approved by OMS, highly sensitive and detect rifampicin resistance
<i>Legionella pneumophila</i>	PCR (sputum)		
<i>Burkholderia pseudomallei</i>	PCR (sputum, blood)		Rapid serological tests exist
<i>Bordetella pertussis</i>	PCR (sputum)	Multiplexed PCR (sputum)	Other methods are gradually abandoned
<i>Chlamydomphila pneumoniae</i>	PCR (sputum)	Multiplexed PCR (sputum)	Other methods are gradually abandoned
<i>Mycoplasma pneumoniae</i>	PCR (sputum)	Multiplexed PCR (sputum)	Other methods are gradually abandoned
Cutaneous infections			
<i>Treponema pallidum</i>	PCR (skin biopsy)		Dark field microscopy is gradually less employed
Spotted fever group <i>Rickettsiae</i>	PCR (skin biopsy or eschar swab)		
<i>Staphylococcus aureus</i>	PCR (skin biopsy/swab)		
<i>Streptococcus pyogenes</i>	PCR (skin biopsy/swab)		
<i>Mycobacterium leprae</i>	PCR (skin biopsy)		

<i>Borrelia burgdorferi sensu lato</i>	PCR (skin biopsy)		Dark field microscopy is gradually abandoned
Diarrhea			
<i>Aeromonas spp.</i>	Multiplexed PCR (stool)	targeted culture (stool) and MALDI-TOF identification	
<i>Arcobacter spp.</i>	targeted culture (stool) and MALDI-TOF identification		
<i>Clostridium difficile</i>	PCR (stool)		Genes coding for toxin production are targeted by PCR assays
<i>Campylobacter spp.</i>	Multiplexed PCR (stool)	targeted culture (stool) and MALDI-TOF identification	
<i>Escherichia coli (EHEC, ETEC)</i>	Multiplexed PCR (stool)	targeted culture (stool) and MALDI-TOF identification	Shiga-toxin detection by immunochromatographic test (stool)
<i>Klebsiella oxytoca</i>	targeted culture (stool) and MALDI-TOF identification		
<i>Laribacter spp.</i>	targeted culture (stool) and MALDI-TOF identification		
<i>Salmonella spp. (non-typhoid)</i>	Multiplexed PCR (stool)	targeted culture (stool)	
<i>Shigella spp.</i>	Multiplexed PCR (stool)	targeted culture (stool) and MALDI-TOF identification	Difficult to distinguish from <i>E. coli</i> using MALDI-TOF
<i>Tropheryma whipplei</i>	PCR (stool, small bowel biopsies)		PCR is used as a screening tool while microscopy confirms the diagnosis
Febrile illness			
<i>Typhoid fever</i>	Rapid Serological tests		PCR may also be used
<i>Rickettsia typhi, Orientia tsutsugamuchi</i>	PCR on eschar swab if present (scrub typhus)		
<i>Leptospira spp.</i>	PCR (urine, blood, CSF)		

<i>Coxiella burnetii</i>	PCR (serum, blood or other specimen if persistent infection)	FISH may be used for persistent infections
<i>Brucella spp.</i>	PCR (lymph node, blood)	
Relapsing fever <i>Borreliae</i>	PCR (blood)	
Meningitis		
<i>Streptococcus pneumoniae</i>	PCR (CSF)	
<i>Neisseria meningitidis</i>	PCR (CSF)	Serotyping may be performed by PCR

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Aetiological agent	Key tests		
Respiratory infections			
<i>Streptococcus pneumoniae</i>	Antigen detection (urine)	Quantitative PCR (sputum)	Culture (sputum, blood culture)
<i>Haemophilus influenzae</i>	Quantitative PCR (sputum)	Standard culture (sputum, blood culture)	

<i>Staphylococcus aureus</i>	PCR (sputum)	Standard culture (sputum, blood culture)	
<i>Mycobacterium tuberculosis</i>	PCR (sputum)	Direct examination / Ziehl Neelsen (sputum)	Targeted culture (sputum)
<i>Legionella pneumophila</i>	Antigen detection (urine)	PCR (sputum)	Targeted culture (sputum)
<i>Burkholderia pseudomallei</i>	PCR (sputum, blood)	Standard culture (sputum, blood culture)	
<i>Bordetella pertussis</i>	PCR (sputum)		
<i>Chlamydia pneumoniae</i>	PCR (sputum)		
<i>Mycoplasma pneumoniae</i>	PCR (sputum)		
Cutaneous infections			
<i>Treponema pallidum</i>	PCR (skin biopsy)	Serological testing	
<i>Rickettsia spp.</i>	PCR (skin biopsy)	Serological testing	
<i>Staphylococcus aureus</i>	PCR (skin biopsy/swab)	Standard culture (skin biopsy/swab)	
<i>Streptococcus pyogenes</i>	PCR (skin biopsy/swab)	Standard culture (skin biopsy/swab)	
<i>Mycobacterium leprae</i>	PCR (skin biopsy)	Direct examination / Ziehl Neelsen (skin biopsy)	
<i>Borrelia burgdorferi</i>	PCR (skin biopsy)	Serological testing with western blot	
Diarrhea			
<i>Aeromonas spp.</i>	Multiplexed PCR (stool)	targeted culture (stool)	
<i>Arcobacter spp.</i>	targeted culture (stool)		
<i>Clostridium difficile</i>	antigen detection (stool)	PCR (stool)	
<i>Campylobacter spp.</i>	Gram staining	Multiplexed PCR (stool)	targeted culture (stool)
<i>Escherichia coli (EHEC, ETEC)</i>	Multiplexed PCR (stool)	targeted culture (stool)	
<i>Klebsiella oxytoca</i>	targeted culture (stool)		
<i>Laribacter spp.</i>	targeted culture (stool)		
<i>Salmonella spp. (non-typhoid)</i>	Multiplexed PCR (stool)	targeted culture (stool)	
<i>Shigella spp.</i>	Multiplexed PCR (stool)	targeted culture (stool)	
<i>Tropheryma whipplei</i>	PCR (stool, small bowel biopsies)	Microscopy following PAS and IHC staining (small bowel biopsies)	

Febrile illness			
<i>Typhoid fever</i>	Blood cultures		
<i>Rickettsia typhi, Orientia tsutsugamuchi</i>	Serological testing	PCR if eschar (scrub typhus)	
<i>Leptospira spp.</i>	PCR (urine, blood, CSF)	Serological testing	
<i>Coxiella burnetii</i>	Serological testing	PCR (serum, blood or other specimen if persistent infection)	
<i>Brucella spp.</i>	PCR (lymh node, blood)	Targeted culture (blood cultures)	Serological testing
<i>Borrelia spp.</i>	Microscopy (GIEMSA coloration)	PCR (blood)	Serological testing
Meningitis			
<i>Streptococcus pneumoniae</i>	PCR (CSF)	Microscopy (gram staining)	standard culture (CSF, blood culture)
<i>Neisseiria meningitidis</i>	PCR (CSF)	Microscopy (gram staining)	standard culture (CSF, blood culture)

BLS : Biosafety level; CSF : cerebrospinal fluid; FISH: Fluorescence in situ hybridization; PAS: Periodic acid-Schiff; POCLs: Point-of-Care Laboratories; PVL : Panton-Val

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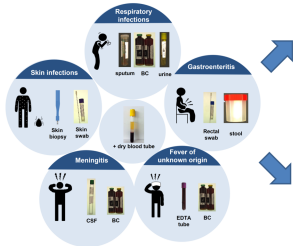
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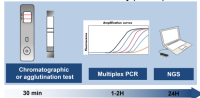
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Syndrome-based sampling



Point-of-care laboratory (POCLs)



Core laboratory

