Forecast diagnostics for antimicrobial resistance (AMR)

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Context

When asked to make forecasts related to the AMR diagnostics of the future (15 to 20 years hence), we were faced with the dilemma of balancing accuracy with strong speculation. The development of novel diagnostic technologies is driven by progress in basic science, which is by nature unpredictable. It is therefore essential to note that this piece is highly speculative and largely reflects our opinion which is influenced by our knowledge of technologies which are currently under development, or recent progress in basic science which has come to our attention. There is also a strong emphasis on point-of-care tests for primary care or public health applications which is our area of interest and expertise.

The crux of the diagnostic problem facing clinicians when managing patients suffering from an infection is to safely distinguish between viral and bacterial illness, and the subsequent identification of drug resistance in bacterial infections. A more nuanced diagnostic issue facing doctors is the timely discrimination of self-limiting bacterial infections from those that require or would benefit from treatment. The latter is not necessarily an issue that will be readily addressed by new diagnostic technologies.

Type of test technology

Here we outline a number of testing methods which are largely in their infancy in terms of development and evidence generation of clinical impact. These methods may well form the basis of AMR-relevant diagnostic tests going forward.

Molecular technologies

To our knowledge, there are a considerable number of molecular-based diagnostic tests under development or in use which are relevant to AMR. These tests are able to identify microorganisms present in the milieu of a sample from their genetic material and have the capacity to provide information on known mechanisms of drug resistance.

Molecular tests are highly sensitive, and are currently unable to distinguish symptomatic from asymptomatic carriage of potentially pathogenic organisms during illness. Positive tests without additional information or sound judgement would have the potential to increase antibiotic prescribing where bacteria are identified. Molecular tests have a weakness in that they detect the presence of genes or mutations which can confer resistance to antimicrobials; this may not always result in phenotypic resistance. The identification of resistance markers in the absence of phenotypic resistance information would present prescribing quandaries to clinicians. Molecular diagnostics

must also keep pace with evolving mechanisms of resistance. Gram negative bacteria in particular are less favourable targets for molecular detection as resistance can be encoded by many different genes resulting in multiple resistance mechanisms. Molecular diagnostics could excel under circumstances where accurate pathogen identification and surveillance are important, particularly with pathogens of considerable public health significance such as drug-resistant malaria or multidrug resistant *Mycobacterium tuberculosis*.

Phenotypic resistance tests

A number of companies are developing point-of-care and lab-based methods for the detection of phenotypic drug resistance. Tests which detect phenotypic resistance to antimicrobials could have considerable utility as these tests aim to identify drug resistance irrespective of genotype. Generally, such tests still take the form of classical agar plates spiked with antibiotics on which samples are cultured in the microbiology lab. A more user friendly example would be the Flexicult system of zoned agar plates which have been developed for the detection of urinary tract infections and antibiotic susceptibility. Flexicult can be cultured at the point-of-care, however this approach requires an overnight incubation before plates can be interpreted so may have minimal impact on prescribing.

Pathogen identification associated with existing phenotypic tests is often quite subjective and operator dependent, and thus not best suited to the point-of-care, particularly in the primary care environment or in the field. More rapid phenotypic tests (around 10 minutes) are under development, and may be sufficiently quick to guide prescription in general practice. In specific populations, where patients are on long-term or frequent antibiotic treatment (e.g. cystic fibrosis, acne, COPD), resistance testing is more important than pathogen identification, and phenotypic AMR tests may be the most appropriate diagnostic for these patient groups.

Future perspectives: molecular and phenotypic tests

In circumstances where identification of the pathogen is important together with information related to antibiotic resistance, a test or platform that combines molecular and phenotyping technologies together with phenotypic information obtained by clinical examination of the patient may address the shortfalls of the two testing methods in isolation. Given progress in the development of both molecular and phenotypic tests, it is feasible that platforms which combine both approaches may be developed in the future.

Complex test panels

Many companies are exploring the utility of multiplex tests in which several assays are combined, testing for multiple organisms. For example, respiratory panels testing for 15 respiratory viruses including influenza A and B, rhinovirus and RSV. The utility of these assays will depend on the clinician's willingness to withhold antibiotics after a positive identification of a viral infection, i.e. excluding the possibility of bacterial co-infection.

Another aspect of increasing complexity is the construction of tests that combine the three modalities of laboratory testing, i.e. chemistry assays, immune-assays and haematology assays. This would allow the user to test for antibodies and proteins such

as inflammatory markers, electrolytes and blood gases (including lactate), together with full blood counts simultaneously from one sample. Although increasing complexity has the advantage that more diagnostic information becomes available from a single specimen and with the necessity to handle only one test procedure, it also poses the problem of lack of flexibility and therefore may not always suit each situation. Too much diagnostic information may lead to overdiagnosis and subsequent treatment decisions. The challenge is to develop technology that allows multiple tests to be combined in a flexible manner.

Disposable tests

In contrast to more complex testing platforms, there is a case for single-use disposable tests similar to point-of-care hCG tests for pregnancies. These tests would be able to test for one or a small number of inflammatory markers or pathogenic antigens aimed directly at predicting the need for antibiotic prescribing in certain indications. Disposable tests are particularly appealing for primary care because they can be taken on house calls, do not require quality control/calibration schemes and are less prone to operator variability. The range of disposable tests applicable to AMR is currently limited and tend to focus on the detection of pathogen associated antigens (e.g. Strep A+B), so there is perhaps scope for more comprehensive coverage in the future.

Novel approaches

We are aware of entirely novel diagnostic methods being developed by basic scientists, which may well be deployable in the AMR diagnostics space. Evidence from the bench suggests that it should be feasible to package these methods as point-of-care tests which combine speed, accuracy, capacity to significantly multiplex, with the potential to glean genetic and biomarker information simultaneously from low sample volumes.

Specimens

Many diagnostic tests require samples which can be difficult to obtain with the requisite precision, or which lack patient acceptability. We postulate that sample volumes will be minimised where intrusive sampling is required (important for blood tests taken from the young or elderly), that sampling methods will reduce risk of sample contamination (particularly relevant when associated with highly accurate tests for microorganisms), and that sampling methods and / or devices will be sufficiently robust and simple to be used in the field (e.g. by primary care clinicians on house calls, by public health personnel, or by patients). Novel sample types could be intrinsically acceptable to patients, such as breath, sweat or epidermal secretions. Greater understanding of biomarker profiles and information carriage in sample types such as urine or saliva may see movement away from more intrusive and painful methods of sample collection.

Implementation features of future diagnostics

We highlight here some of the attributes that future AMR diagnostics may need in order to impact on clinical decision making and to be acceptable for implementation in the future.

Faster turnaround times

In primary care, the decision to prescribe antibiotics is fast with little need for re-consultation or review. Motivation to change patient flow around test turnaround time to improve antibiotic prescribing is practically non-existent, in contrast to for example the decision to urgently refer the patient to hospital which is much more time-consuming. Therefore new tests will have to fit into the existing patient flow, with consultation times in primary care typically less than 10 minutes as evidenced in a recent publication in The Lancet by our department.

Data interpretation

Tests will require features such as integrated algorithms which will help physicians to understand and interpret complex data and aid decision making. In particular, the integration of test information with clinical information that is obtained in the clinical assessment has great potential to increase accuracy and stratify patients with more precision.

Connectivity

Connectivity of diagnostic platforms to electronic medical records will be desirable, so that test results can be integrated into a patient's record without unduly burdening the attending clinician. Innovative methods for the transfer of information from disposable tests would be useful.

Independent of fixed power sources

For clinicians attending patients during house calls or for those operating in locations which lack reliable sources of power, the capacity for the diagnostic device to operate independently of a fixed power source will be essential.

Training

It would be beneficial if new tests are as simple and intuitive to operate as feasible, thus minimising training requirements for use and associated costs.

Requirements for maintenance and calibration

The best platforms will be stable, robust, and will require as little routine maintenance and calibration as possible so that associated costs and inconvenience to practices would be kept to a minimum.

Stability during transport

For public health clinicians working in the field or for general practitioners on house calls, stability during transport without requirements for complex recalibration would be essential.

Liability and financing

Importantly, health service system level structures will be required to both legally and financially support the implementation of new diagnostics for AMR, particularly at the level of point-of-care tests in primary care, where reimbursement structures for test costs is often complex and disadvantageous for the practice.

Outlook

Given the current speed of diagnostic tests through the development and evidence generation pipeline, it is likely that technologies which are currently in relative infancy will form the diagnostics base in 10 – 15 years hence, unless measures are taken to expedite this process.

About the authors

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