Four diagnostic strategies for better-targeted antibiotic use

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Executive summary

In July 2015, the Wellcome Trust organised an interdisciplinary workshop to examine the potential use of diagnostic tools to guide antibiotic use in a range of common clinical scenarios (see Appendix 1 for list of workshop participants). Rapid diagnostics are thought to have a vital role to play in the battle against drug-resistant infections. They have the potential to guide more rational use of antibiotics, by distinguishing between viral and bacterial infections, and by identifying specific pathogens and their antibiotic resistance characteristics. Patients gain from more rapid use of effective antibiotics and society gains from less indiscriminate use of antibiotics, a major factor driving the emergence and spread of resistance.

Despite this promise, diagnostics have had less impact on antibiotic prescribing than might have been expected. A potential explanation explored at this workshop is that the general call for better diagnostics has lacked the specificity needed to deliver improvements in care or antibiotic stewardship. Enhancing clinician decision-making in different clinical situations calls for different types of information, delivered amid varying demands for speed and accuracy. The conflation of all tools that can provide such information into the single term 'diagnostic' may have slowed progress.

To generate greater clarity, the workshop considered in detail the information needs of clinicians facing a range of common clinical scenarios. The scenarios varied in the severity of infection, the potential consequences of an incorrect diagnosis, timescales in which diagnostic information is required, and clinical setting.

The workshop uncovered considerable previously unexplored complexity in the use of diagnostics in each clinical scenario. Hence, while the development and use of diagnostics is typically framed as a technological challenge, this overlooks the fundamental importance of (1) the specific clinical and health system context in which diagnostics are being used and (2) human factors such as physician behaviour and patient attitudes. These factors have a profound impact on the kind of information required from diagnostics and how it would be used.

Consequently, the use of diagnostic tools is better considered in the context of **diagnostic strategies** – broader approaches to characterise infection, guide treatment and minimise unnecessary use of antibiotics, tailored to the specifics of the patient, their symptoms, healthcare system, behaviours and social setting. The precise specifications of a diagnostic tool will then depend on the role it is envisaged to play within a broader diagnostic strategy.

Through discussions at the workshop, a typology of four specific diagnostic strategies were identified, each associated with distinct treatment and stewardship goals. Within each diagnostic strategy, diagnostic tools would have distinct and clearly defined roles:

- **Avoiding unnecessary antibiotic use**: A diagnostic test could support a physician's decision not to use antibiotics, for example by ruling out bacterial infection or conforming viral infection, or by distinguishing infection from colonisation. Providing support for 'not treating' requires consideration of the views of prescribers, patients and families, as well as a recognition that using a diagnostic not to treat might increase costs in one budget silo while decreasing costs in another. Development of suitable tools is complicated by the frequency of asymptomatic carriage of potentially pathogenic organisms.
- **Optimising patient treatment and antibiotic use**: Diagnostic tools could be used to identify specific pathogens and to more precisely characterise antibiotic susceptibility in serious infection, guiding targeted antibiotic escalation or de-escalation. Physicians must consider the risk to the patient of over-treatment or under-treatment, but will tend to favour over-treatment to minimise the likelihood of serious clinical outcomes; some may be reluctant to de-escalate even with relevant diagnostic information.
- **Identifying high-risk patients**: Identifying the presence of a pathogenic organism may not necessarily be clinically significant. Hence there is a complementary need for tools to identify host biomarkers indicative of infection and biomarkers prognostic for likely poor (or positive) outcomes.
- **Improving drug development**: Tools to support recruitment of appropriate patients into clinical trials, to predict at early stage which patients are more likely to have a positive culture, would improve trial efficiency. These tools could be the same as those used in patient care, or they might need distinct performance characteristics.

Importantly, this 'typology' approach provides a novel conceptual framework with the potential to accelerate future diagnostic development. It provides a foundation for defining more precise specifications for the tools needed to support distinct diagnostic strategies, and for identifying barriers to their development. These typologies have been arrived at through discussions focused on developed healthcare systems. It is possible the diagnostics strategies can be applied across different, diverse health systems, but the actual role and impact of diagnostics in low resource settings and LMIC geographies requires further exploration to determine the global utility of these diagnostics strategies.

The current emphasis on targeted treatment and development of new narrow-spectrum antibiotics highlights the importance of diagnostic tools in antibiotic development. However, the detailed dissection of the clinical scenarios suggests that there will be a continuing need in some diagnostic and treatment strategies for broad-spectrum agents, which should remain a priority for antibiotic development.

The workshop identified a range of factors critical to the use of the diagnostic strategies and the development of associated diagnostic tools and therapeutics:

- The importance of the host response in identifying infection and predicting prognosis was repeatedly stressed. More fundamental studies are required to identify appropriate host biomarkers to support the development of host-directed diagnostic tests.
- The use of diagnostic tests will remain highly sensitive to physician behaviour and patient attitudes and expectations. Prescribing practices currently vary markedly between countries, reflecting strong cultural influences on physician decision-making. A deeper understanding of psychosocial factors affecting physician behaviour and patient attitudes is required, to support educational or other initiatives to promote best practice, and to identify how diagnostic tools could best be utilised.
- The outcome of infection is fundamentally dependent on interactions between pathogen and host. Additional basic research is required on host–pathogen interactions and the human microbiome in health and disease.
- Current regulatory and reimbursement paradigms are not conducive to the development and implementation of diagnostic tests. Greater coordination and re-engineering of regulatory and reimbursement paradigms are required to align interests and remove disincentives.

"We want to commend you for the workshop which we believe has advanced the field through successful integration of key stakeholder perspectives. The exploration of the details around diagnostic needs, cultural differences, patient pressures and clinical benefit for select bacterial infections was unprecedented in its completeness and depth. This exploration of the details resulted in the creation of a set of four Typologies (or Operational Strategies) that provide a useful framework for future work."

Feedback from opinion leaders

Introduction

Antimicrobial resistance has emerged as one of the greatest health threats of the 21st century. The possibility has been raised of a 'post-antibiotic era' of untreatable infections, with many routine medical procedures rendered unsafe due to the risk of infection. Already, an estimated 25 000 people in Europe die from a multidrug-resistant (MDR) bacterial infection every year[1], with similar numbers affected in the USA[2]. In Europe, MDR infections are estimated to result in extra healthcare costs and productivity losses of at least €1.5bn[1].

The world has belatedly woken up to this growing threat. Bodies such as the WHO and the EU have published action plans to address drug-resistant infections. In the UK, the Chief Medical Officer has done much to raise the issue on the political agenda, making it the theme of the 2011 Chief Medical Officer Annual Report[3] and ensuring that it is a recognised national security risk. In June 2015, antibiotic resistance was an agenda item at the G7 summit in Germany. There is a growing global political momentum to tackle the urgent challenge of antimicrobial resistance.

Addressing antimicrobial resistance will require enhanced efforts to develop new agents – a focus of initiatives such as the UK's Review on AMR[4], the EU IMI and the US's BARDA. But there is an equally urgent need for better use of existing agents, to delay the development of resistance. This places great importance on antibiotic stewardship – minimising the unnecessary use of antibiotics and promoting use of the most appropriate (targeted) antibiotic to treat an infection. Optimal therapy for an individual therefore successfully treats a patient's specific infection and minimises collateral damage both to the patient (avoiding adverse effects or harm to commensal bacteria) and to society more generally (reducing the risk of resistance) (Figure 1).
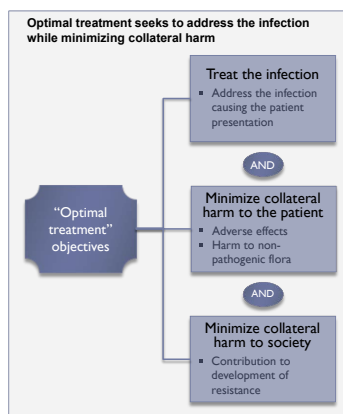

Figure 1: The objectives of optimal treatment of infections.

The emergence and spread of drug-resistant infections, and development of new antibiotics to treat them, reflects a complex set of interactions (Figure 2). Within this landscape, rapid diagnostics (and integrated use of diagnostics and therapeutics) have the potential to have a major impact on both the emergence of drug-resistant infections and the development of new targeted antibiotics (Figure 2).

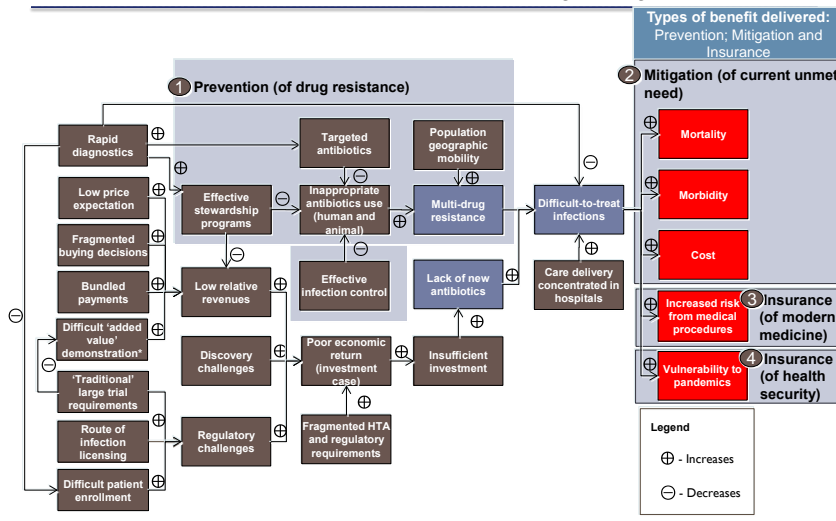[1] ECDC/EMEA. *The Bacterial Challenge: Time to react* (ECDC/EMEA Joint Technical Report); 2009. [http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?ID=199&List=4f55ad51%2D4aed%2D4d32%2Db960%2Daf70113dbb90]

[2] CDC. *Antibiotic Resistance Threats in the United States, 2013*; 2013. [http://www.cdc.gov/drugresistance/threat-report-2013/]

[3] Department of Health. *Annual Report of the Chief Medical Officer 2011: Volume 2*; 2013. [https://www.gov.uk/government/publications/chief-medical-officer-annual-report-volume-2]

[4] Review on Antimicrobial Resistance. *Antimicrobial Resistance: Tackling a crisis for the future health and wealth of nations*; 2014. [http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf]
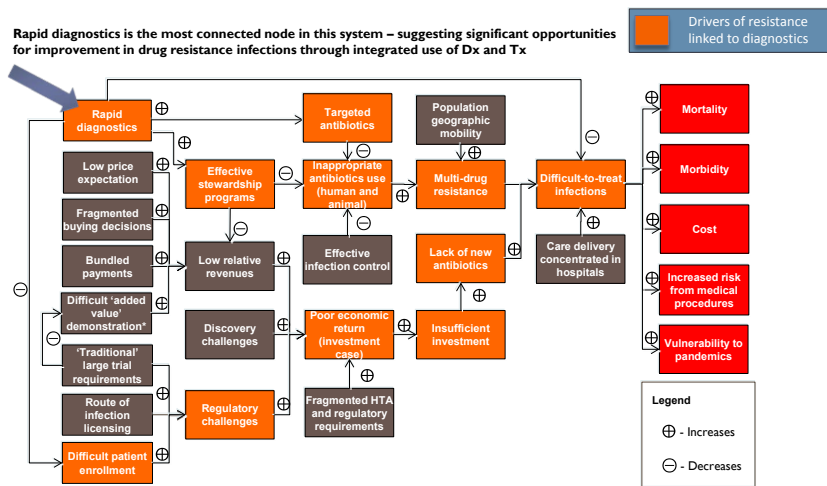
Drug resistant infections are the result of a complex set of
interactions, with effective interventions delivering a range of benefits

Types of benefit delivered:
Prevention; Mitigation and
Insurance

① Prevention (of drug resistance)

② Mitigation (of current unmet need)

Rapid diagnostics
Low price expectation
Fragmented buying decisions
Bundled payments
Difficult 'added value' demonstration*
'Traditional' large trial requirements
Route of infection licensing
Difficult patient enrollment

Targeted antibiotics
Population geographic mobility
Effective stewardship programs
Inappropriate antibiotics use (human and animal)
Multi-drug resistance
Difficult-to-treat infections
Low relative revenues
Effective infection control
Lack of new antibiotics
Care delivery concentrated in hospitals
Discovery challenges
Poor economic return (investment case)
Insufficient investment
Regulatory challenges
Fragmented HTA and regulatory requirements

Mortality
Morbidity
Cost

③ Increased risk from medical procedures — Insurance (of modern medicine)
④ Vulnerability to pandemics — Insurance (of health security)

Legend
⊕ - Increases
⊖ - Decreases

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Enhanced integration of diagnostics and therapeutics would have
cascading effects through the system

Rapid diagnostics is the most connected node in this system – suggesting significant opportunities
for improvement in drug resistance infections through integrated use of Dx and Tx

Drivers of resistance linked to diagnostics

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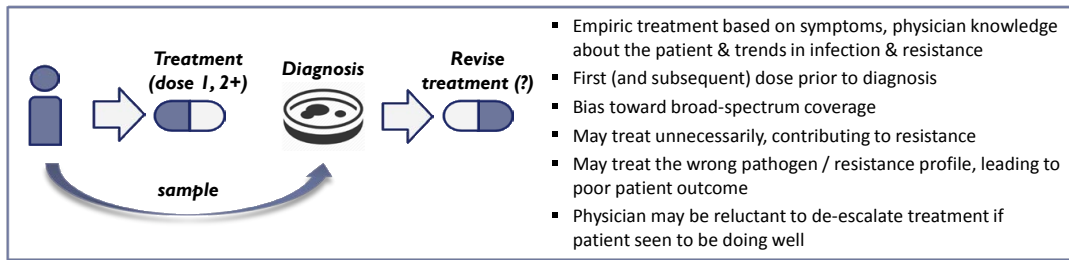From: Tapestry Networks; used with permission

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Figure 2: Upper: Drug-resistant infections are the result of a complex set of interactions, with effective interventions delivering a range of benefits. Lower: Enhanced integration of diagnostics and therapeutics would have cascading effects through this system

More specifically, diagnostics could be used to distinguish between bacterial and viral infections, to support targeted use of narrow-spectrum antibiotics, and to guide choice of antibiotic in drug-resistant infections. Diagnostics also have a potentially important role in antibiotic development, to identify patients with infections targeted by new narrow-spectrum antibiotics. Diagnostics can support both enhanced patient treatment and antibiotic stewardship (Figure 3).
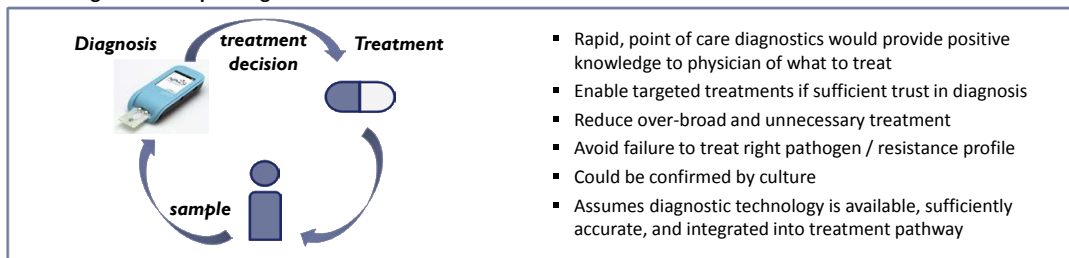
Speeding up the availability and uptake of diagnostic results would yield both treatment and stewardship benefits

At present, empiric treatment relies on initial physician judgment

- Empiric treatment based on symptoms, physician knowledge about the patient & trends in infection & resistance
- First (and subsequent) dose prior to diagnosis
- Bias toward broad-spectrum coverage
- May treat unnecessarily, contributing to resistance
- May treat the wrong pathogen / resistance profile, leading to poor patient outcome
- Physician may be reluctant to de-escalate treatment if patient seen to be doing well

The integration of rapid diagnostics into treatment decisions would have several benefits

- Rapid, point of care diagnostics would provide positive knowledge to physician of what to treat
- Enable targeted treatments if sufficient trust in diagnosis
- Reduce over-broad and unnecessary treatment
- Avoid failure to treat right pathogen / resistance profile
- Could be confirmed by culture
- Assumes diagnostic technology is available, sufficiently accurate, and integrated into treatment pathway

Figure 3: Speeding up the availability and uptake of diagnostic results would yield both treatment and stewardship benefits.

While the potential importance of diagnostics is widely recognised, progress in development and implementation of diagnostic tools in clinical practice has been slow. Although there are technological challenges, molecular-based and miniaturisation technologies are advancing rapidly, suggesting that multiple new opportunities could be exploited for patient benefit.

> "In most cases antibiotics are being prescribed in the community, it is complete guesswork."
>
> **Clinician**

Sotiris Zafeiris

One possible reason why the pace of implementation has been slower than anticipated is because diagnostic tool development has not fully considered the complexities of clinical practice. Fundamentally, diagnostic tools provide information to aid physician decision-making, and several important factors influence the value of that information to physicians:
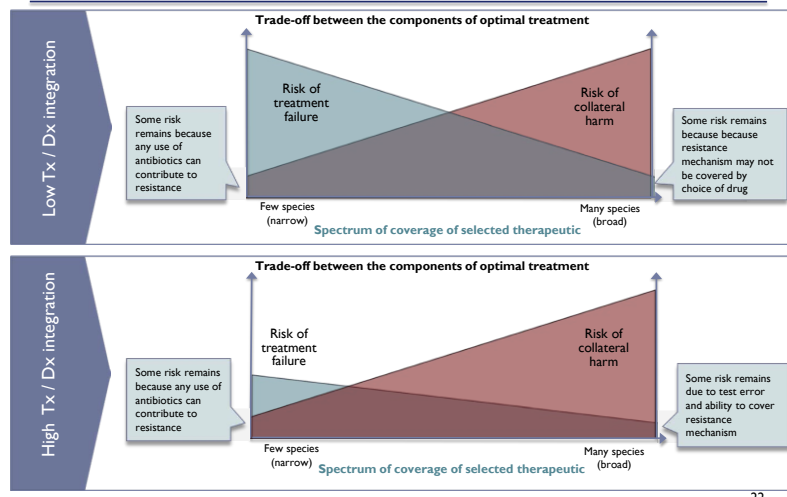
- Importantly, the **type of information** required by a physician will differ considerably between different clinical situations – from the simple presence of a pathogen to specific information about antibiotic resistance.
- The specific **time window** in which diagnostic information is required will also vary across different clinical scenarios.
- The necessary **sensitivity and specificity** of diagnostic tools may also vary significantly.
- Practicalities of **sample collection** may need to be considered.
- How new diagnostic information compares with that obtainable by traditional methods and **existing 'gold standards'** such as culture also needs to be borne in mind.
- The **health system context** in which the diagnosis is being made – primary care, secondary care, and critical care – is also important to consider.
- Finally, a physician must also interpret specific diagnostic results in the context of the wider **patient symptomology**.

> *"I think there's recognition that the development of diagnostics should begin with the clinical niche rather than technological innovation, beginning with the problem to be solved, which is often predicting benefits from antibiotics rather than determining etiology."*
>
> *Clinician*

Further complexity arises from the need of a physician to consider not just immediate treatment and clinical outcomes but also the longer-term consequences to society more broadly of antibiotic use and the development of resistance. These factors are often in tension: use of broad-spectrum agents lowers the risk of treatment failure, but at the expense of an undesirable outcome to society – an enhance risk of resistance. Integrated use of diagnostics and therapeutics can potentially shift this risk profile, encouraging more socially desirable outcomes while maintaining effective treatment for patients (Figure 4).
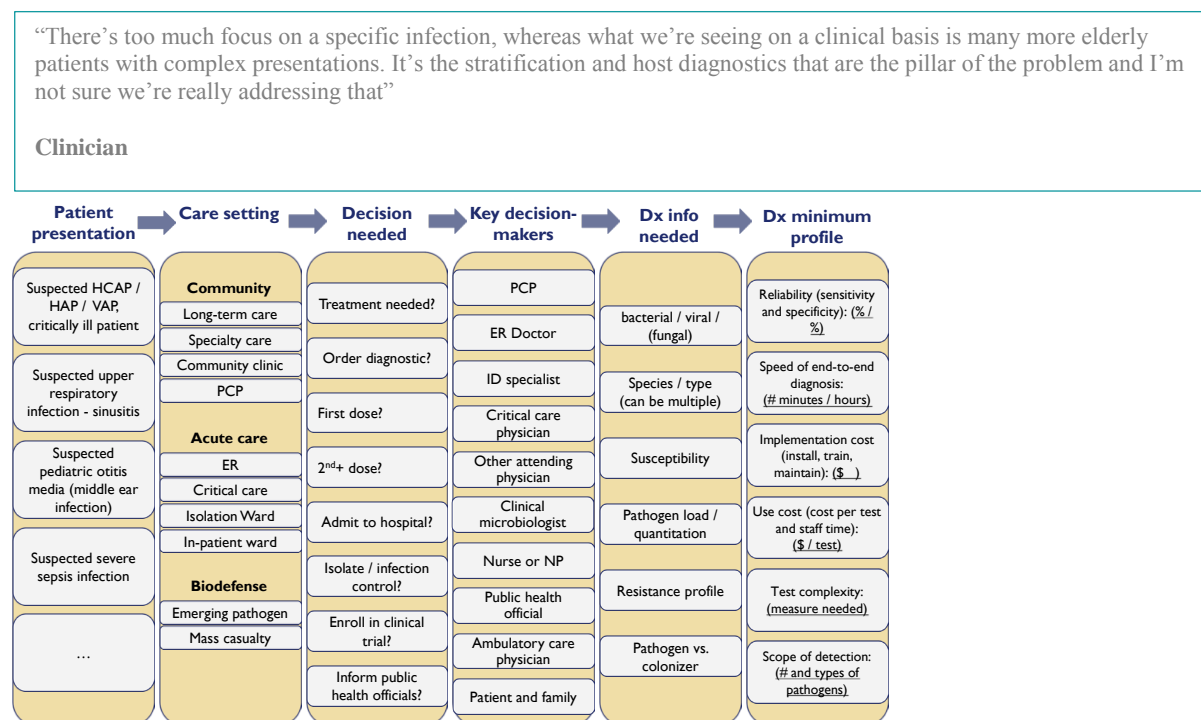

Figure 4: Without effective and timely diagnostic tools, the components of optimal treatment are in tension with one another. Integrated use of therapeutics and diagnostics can reduce this tension.

While conceptually simple, diagnostic tool use in reality may therefore be deceptively complex. One possible reason for the slow uptake of diagnostics could reflect too great a focus on the technological challenges of identifying specific pathogens and insufficient consideration of the practical issues surrounding diagnostic use in routine clinical practice. In particular, grouping all possible uses of diagnostic tools under a single heading of 'diagnostic' may have held back progress by preventing a focus on the specific and distinct needs of different clinical scenarios.

A more productive approach may be to adopt a patient-centric approach, to consider the scenario a clinician faces, what specific information a physician needs, and at what point in time, when faced with a particular type of patient in a specific healthcare setting. Greater clarity of these issues could underpin a more 'needs-driven' approach to the development of specific types of diagnostic device.

These ideas provided the foundation for the workshop, which brought together representatives from all relevant stakeholder communities – diagnostic developers, antibiotic developers, senior clinicians, and representatives of regulatory bodies and funding agencies. It was 'technology-agnostic', on the assumption that technological solutions would be available to meet defined needs.

Notably, it adopted a patient-centric viewpoint, focusing on the patient journey through healthcare systems. By focusing on a range of common clinical scenarios, the meeting embraced the complexity of clinical decision-making and recognised the heterogeneity of likely diagnostic use. This contextualised view of specific clinical scenarios (Figure 5) provided a mechanism to identify clinicians' needs more specifically and hence the desired performance characteristics of diagnostics.

> "There's too much focus on a specific infection, whereas what we're seeing on a clinical basis is many more elderly patients with complex presentations. It's the stratification and host diagnostics that are the pillar of the problem and I'm not sure we're really addressing that"
>
> **Clinician**

Figure 5: Diagnostic use can be considered in the context of patient journeys, focusing attention on who needs diagnostic information, of what kind, for what purpose and in which clinical setting.

The meeting identified general principles and commonalities across scenarios, with the aim of developing a 'typology' to guide the development of diagnostic tools with better-defined roles in patient care and in the development of new antibiotics.

As well as patient care and antibiotic stewardship, the workshop also considered the potential contribution of diagnostics to clinical trial recruitment. Rapid identification of suitable patients is of great importance to narrow-spectrum antibiotic development (and to development of broader-spectrum agents active against rare infections) (Figure 6).

The difficulty (time, cost, complexity) of a clinical trial is greater the less common the condition being studied, and the more targeted the treatment under evaluation.

The lower the prevalence (e.g., of resistant Pseudomonas), the more patients need to be enrolled to get the needed number of 'hits' – those proven by culture to have the studied pathogen
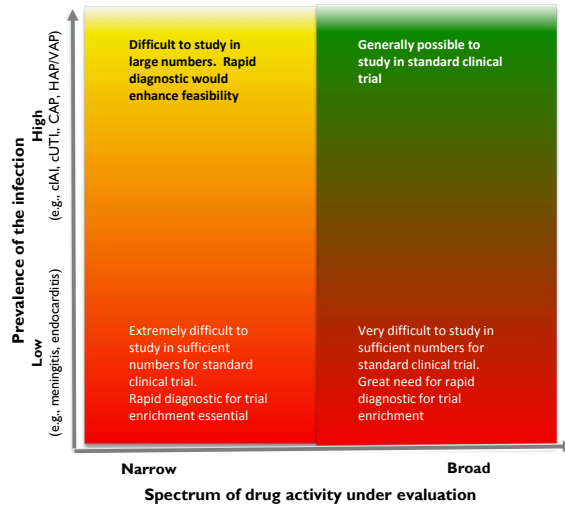
Figure 6: Diagnostics can support recruitment into trials of narrow-spectrum agents and of therapeutics for low-prevalence conditions.

Clinical scenarios

Detailed discussions focused on three clinical scenarios with contrasting clinical settings, typical patient characteristics, physician information needs, and potential roles for diagnostics (Table 1). Discussions covered how diagnostics could improve patient outcomes, the role they could play in new therapy development, and their potential contributions to enhanced antibiotic stewardship. Summaries of the specific scenarios considered are provided in Appendix 2.

The possible use of diagnostics in two further important and contrasting clinical situations – sepsis and otitis media – were also briefly discussed.

Table 1: Clinical scenarios discussed at the workshop

	Mild upper respiratory illness – sinusitis	HAP/VAP	Complicated UTI
Care setting	Community care setting	Acute care	Emergency Department/A&E
Treatment context	Patient not seriously ill: sinusitis almost always clears without treatment However, patients often seek some treatment and antibiotics historically overprescribed	Active therapy must not be delayed - mortality increases with each hour of delay HCAP, HAP, and VAP caused by wide variety of (mostly) bacterial pathogens, may be polymicrobial. Frequency of MDR pathogens varies by institution – link treatment to local surveillance data	Active therapy can be briefly delayed, though some risk of sepsis or other complications depending on severity cUTI often caused by *E. coli,* though other bacterial pathogens common Frequency of MDR pathogens varies by institution and patient treatment history
Treatment opportunity	Overriding need for reliable and rapid Dx confirming presence or absence of a bacterial infection Needs to be simple, inexpensive test, appropriate for range of care environments and limited cost to install	1st treatment: usually made based on available clinical data. Diagnostic development funding should favour new biomarker research, practical implementation and speed. 2nd treatment: Multiplexed tests needed as multiple types of resistance and pathogens. Focus on test reliability to inform change of therapy.	1st treatment: Not always clear when to treat empirically or await Dx results (cUTI higher likelihood of more resistant bacteria) 2nd treatment: Change to more targeted based on the specific infecting organism and susceptibility as determined by urine culture
Therapeutic development opportunity	Limited interest in enrolling patients into clinical trial	High possibility to enrich patients with microbiological data – but study drug should either be initial therapy or started within 24h to avoid trial exclusion	Possibility to enrich in MDR ABx programs – but study drug should either be initial therapy or started within 24h to avoid trial exclusion
Stewardship opportunity	High volume use of ABx; significant stewardship opportunity if rDx can rule out bacterial	More targeted (or even pathogen-specific) treatments will delay resistance	Avoid potential collateral damage through more targeted treatments

Sepsis

Systemic infection or sepsis is extremely serious. Each year, severe sepsis affects more than a million people in the USA, up to half of whom may die. It can be caused by a wide range of pathogens, although bacterial infections are the most common causes. Because of the severity of infection, and the speed at which infection can progress, treatment of suspected sepsis is generally begun immediately. Culture results are used to confirm bacterial infection and guide subsequent antibiotic regimes.

> "If I make a mistake in managing sepsis, it's a mistake I may get to bury: I may not get a second chance."
>
> **Clinician**

Sepsis presents a major diagnostic challenge to clinicians, as many symptoms are shared with other conditions, speed is of the essence, and the risks associated with misdiagnosis are high. Hence physicians are likely to prescribe antibiotics before confirmation of an infection, and the main role for a diagnostic is in tailoring therapy after initial empirical treatment.

Discussions emphasised the current difficulties of identifying cases of sepsis in the absence of a diagnostic test. The first signs of possible sepsis are typically when an ICU patient begins to deteriorate, but other conditions (such as some autoimmune disorders and adverse drug reactions) can generate similar symptoms. When sepsis is suspected, a key clinical challenge is to identify the source of infection and to administer the appropriate antibiotic.

Depending on the state of the patient, the window of opportunity for initiating treatment is small – at most a few hours. The cost of being wrong is high – inappropriate treatment is associated with higher mortality. Hence initial treatment is empirical, begun before culture results are available. Culture results can be used to support escalation strategies – adding antibiotics if patients are not responding to initially prescribed drugs – or de-escalation strategies, with drugs discontinued if they are unlikely to be effective against identified organisms or drug-resistant strains.

If clinicians suspect an infection is present, even negative culture results may not lead them to discontinue antibiotic use (a single blood sample, for example, may by chance not contain invasive bacteria and may therefore test negative). Similarly, clinicians may in practice be reluctant to de-escalate treatment in light of culture results, if a patient appears to be responding to initial treatment. Due to the severity of the condition and the potentially lethal consequences of a wrong decision, clinicians typically err on the side of caution and over-treat.

> "If I've raised the possibility of sepsis, a diagnostic has to be enormously powerful to change my mind about that."
>
> **Clinician**

A further important point is that simply detecting an organism is not necessarily clinically meaningful. Many people harbour virulent micro-organisms while remaining healthy. Different people will be affected to a different degree by the same microbial challenge. It is therefore difficult to distinguish colonisation from infection, and infection from sepsis. What would be particularly useful to clinicians would be host-directed tests – e.g. gene expression profiles or metabolomic signatures or biomarkers – that identified patients at an early stage who were at risk of developing severe sepsis.

> "We all live in a sea of bacteria. Every one of us would be positive on a rapid test for E. coli and one-third us would be positive for Streptococcus pneumoniae. Merely detecting an organism is inadequate."
>
> **Clinician**

One analysis of deaths from sepsis found that more than half did not get appropriate treatment, as sepsis was not considered a possible cause until too late in disease progression. Monitoring for signs of sepsis is currently low-tech, with frontline staff such as nurses often raising the alarm as patients deteriorate. An analysis of health data from some five million US patients suggests that just three clinical signs – altered level of consciousness, increased respiratory rate and lowered rate – can help to identify those at enhanced risk of death. Use of such signs could provide a way to identify at-risk patients who could then be assessed with more sophisticated tests.

Otitis media

At the other end of the clinical spectrum, a typical case of otitis media would be a child taken to general practice with earache. In around 95% of cases, the condition is caused by a virus, is benign and will self-resolve. Even the relatively rare cases of bacterial infection often spontaneously resolve. More problematic outcomes – such as infection of nearby bone (clinically challenging but not life-threatening) or progression to meningitis (clinically much more serious) – are rare (around 1 in 100 untreated cases for the former, 1 in 300–500 cases for the latter).

The time course of infection is relatively slow, so urgency is low; treatment can be delayed to see how the condition progresses without major risk to the patient. Clinical examination of the eardrum can give some indication of whether an infection is bacterial or viral. Ideally a diagnostic test would indicate whether an infection was viral or bacterial, without the need for specialist ENT skills. For those cases identified as bacterial, it would also be helpful to distinguish infections that were likely to turn serious. Currently there are no known host biomarkers that could identify such at-risk patients.

Unnecessary antibiotic use is common in otitis media. Physicians may come under pressure to prescribe, particularly if parents have made sacrifices to attend a practice or have faced long waits to see a physician and do not want to feel that their time has been wasted. They naturally want to feel that their child has been assessed appropriately and their discomfort taken seriously. Delayed prescribing has been used with varying degrees of success: some parents insist on receiving something immediately, and others go to alternative providers to secure a prescription.

> *We've tried a delayed prescribing approach. That's met with varying degrees of success. Some really want us to give a medicine straight away, others will be happy, others will just move on somewhere else."*
>
> *UK clinician*

Workshop participants discussed whether there was a need for a diagnostic in this scenario, and what function it might perform. Doctors can be reasonably sure in advance that the infection is likely to be viral. Alongside clinical assessment, a test with high negative predictive value could provide reassurance to a physician and support communication with patients about whether antibiotics are appropriate. Conversations with patients could also emphasise not only the societal benefits of not taking antibiotics but also the individual downsides of antibiotic use, such as the possibility of adverse reactions.

Physicians need to feel supported should complications develop, and a diagnostic test could provide reassurance that they followed good clinical practice, made an accurate clinical assessment, and were justified in not prescribing antibiotics. They may also feel a need to give patients 'something', and a diagnostic result may be a satisfactory alternative to an antibiotic prescription from a parent's perspective.

> *"Things are going to go wrong. The ability to say 'well, I looked really carefully' is actually helpful."*
>
> *Clinician*

A key issue highlighted by the case of otitis media is that clinical outcome is the only measure ever assessed – there is no way to capture the potentially negative societal impact of treatment, as a risk to balance against possible patient benefits. Mechanisms of antibiotic stewardship (such as clinical guidelines) are intended to address this issue but provide no simple metric to capture the value of diagnostic tools that influence physician behaviour.

Mild upper respiratory tract infection (sinusitis)

Sinusitis, inflammation of the sinuses, is generally associated with colds and in the vast majority of cases it is linked to viral infection. It is extremely common, with around one in eight adults affected each year. It is typically diagnosed by physical examination, with symptoms including facial congestion and pain and nasal blockage. Long-term persistence of symptoms is indicative of a bacterial cause. Over-use of antibiotics is a major concern – in the USA, sinusitis is responsible for one in five antibiotic prescriptions. Adverse reactions to antibiotics prescribed for sinusitis are also a common cause of emergency room visits.
Consultations for sinusitis typically take place in primary care. Only around 2% of cases are likely to be bacterial in origin, the gold standard for diagnosis being recovery of bacteria in high density from the cavity of a paranasal sinus. However, results may be hard to interpret, as bacteria identified may not necessarily be harmful.

Symptoms typically clear naturally within two to three weeks, and clinical guidelines generally recommend judicious use of antibiotics. However, in the USA, antibiotics are prescribed in more than 80% of patient visits for sinusitis, often to provide mental comfort to patients. A 'wait-and-see' antibiotic prescription is sometimes given to patients, who can obtain antibiotics if their infection fails to clear up.

Discussions emphasised the importance of sinusitis to a primary physician's workload. Some 10% of people are likely to experience the condition each year in the UK, and GPs are likely to see at least one case a week. Although patients often use sinusitis to describe cold-related facial pain, technically it refers to inflammation of the sinuses, and formal diagnosis reflects a range of signs and symptoms such as unilateral facial pain, high temperature and a cold lasting at least 10 days.

Sinusitis usually self-resolves. However, patients may pressure GPs into prescribing antibiotics, particularly if they have been given them during past episodes and attribute their recovery to antibiotics. Although serious complications can occur, they are extremely rare in developed countries and essentially impossible to predict. There is little or no evidence that early antibiotic treatment prevents serious complications.

Hence there is usually very little need to prescribe antibiotics for sinusitis. As patients may be expecting to be prescribed antibiotics, effective communication between physician and patient is crucial to generate a shared understanding of appropriate treatment. As well as emphasising the very low likelihood that the infection is bacterial, and discussing other possible causes, physicians can discuss the pros and cons of antibiotic use – to patients as well as society, including the risks of adverse reactions and of developing a resistant infection – as well as other treatment options to ameliorate symptoms.

Arguably, therefore, a diagnostic that distinguished bacterial and viral infections would not be of great clinical usefulness. Moreover, most bacterial infections resolve without the need for antibiotics. More useful diagnostic information would be provided by a test that could predict outcome or clinical benefits of treatment rather than aetiology, as long as it provided more information than clinical assessment and was quick, easy to use and cost-effective.

> *"I would want a diagnostic in this area that predicted outcome or benefit from antibiotics rather than aetiology and I would like that diagnostic to be shown to be better than clinical assessment – what is the added value of the diagnostic?"*
>
> *Clinician*

On the other hand, it was pointed out that patients want to feel that they have been listened to and assessed appropriately. As part of a strategy to reduce antibiotic use, a diagnostic test result could provide patents with tangible evidence that they had been taken seriously. However, it would also be important to ensure that patients did not feel as if they had been 'processed', with machines deciding treatment.

> *"Patients want to be assessed properly and taken seriously, they want to be listened to and they want something that is going to help them. That doesn't have to be antibiotics if they feel they have been assessed properly. So perhaps a diagnostic could add to that sense they've been taken seriously."*
>
> *Clinician*

Many factors could be contributing to the continued high use of antibiotics to treat sinusitis. Prescribing habits differ markedly between countries, highlighting the importance of cultural factors (and local health systems) in shaping prescribing practice. Ingrained medical traditions may be being perpetuated in routine practice, and gaps in evidence on the effectiveness of alternatives (such as steam inhalation, decongestants or nasal steroids) could be limiting their use. Social science research is needed to develop a better understanding of factors affecting prescribing practices, including patient expectations.

Overall, there was considerable debate about whether a diagnostic tool was needed in this scenario, or would be used if it were available. At least two distinct types of tool could be envisaged: a 'rule out' test, distinguishing between viral and bacterial infections and supporting a decision not to prescribe antibiotics; and an 'outcome' test, focused on host responses, to identify patients at risk of developing serious complications.

Although not overwhelmingly seen as a priority, a rule out test could help reduce uncertainty about aetiology, provide input into dialogue with patients, reassure patients they have been assessed appropriately, and provide reassurance to physicians. Given the currently high levels of antibiotic usage, even an incremental reduction in antibiotic use would be socially beneficial. Nevertheless, practical challenges such as how to obtain samples would also need to be considered.

No suitable host-directed test yet exists to identify at-risk patients. Existing host response tests such as C-reactive protein (CRP) are not sufficiently sensitive or specific to provide clinically useful information.

Any tests would need to undergo rigorous clinical trials, ideally assessing clinical outcomes. A general issue in diagnostic development is that regulation focuses primarily on technical performance – sensitivity and specificity – so there is little incentive to generate data on clinical outcomes, the most useful information for clinicians. Furthermore, health economic analyses face the challenge of assessing the social benefit of using diagnostic tools to reduce antibiotic usage, so the full value of a diagnostic tool is hard to quantify. Rule out tests would also pose challenges to regulatory systems, which are not set up to assess such uses – a test with low predictive value, for example might be judged poor from a regulatory perspective while still being clinically useful.

Although rule out tests might initially be developed for primary practice settings, ultimately there could be a case for using them in community sites such as pharmacies or even developing them for the home or workplace. Such uses could promote greater health self-management, be more convenient for patients, and reduce physicians' workloads.

Surveillance data might also provide useful information to physicians, identifying organisms known to be in circulation locally. As well as guiding GP decision-making, this information could also aid communication with patients.

> *"GPs don't have graphic tools to help visualise uncertainty for patients. I think we need to get graphic designers involved."*
>
> *Academic*

In summary

- It is debatable whether a diagnostic is truly needed in sinusitis assessment.
- However, a rule out test could support efforts to minimise unnecessary antibiotic usage.
- In particular, test results could support dialogue with patients and promote behaviour change reducing antibiotic usage.
- More speculatively, tests to identify patients at risks of severe complications would be desirable.
- Current reimbursement practices could be a significant obstacle to rule out test use.

"My wife's a primary care paediatrician. She tries her best not to give antibiotics. She was scolded by her boss because these folks come, they want antibiotics, if you don't give them, they get annoyed and go to another practice."

US clinician

Hospital-acquired and ventilator-acquired pneumonia

Hospital-acquired pneumonia (HAP) is generally defined as pneumonia occurring 48 hours or more after patient admission or associated with a previous hospital stay. Ventilator-acquired pneumonia (VAP) is HAP affecting patients receiving mechanical ventilation.

Mortality rates for HAP are high, typically around 62% crude mortality, although patients often have other morbidities. HAP occurs in around 5–10 cases per 1000 hospital admissions, although it is ten times more common in mechanically ventilated patients. HAP generally accounts for one in four ICU infections and half of all antibiotics prescribed.

HAP and VAP are usually bacterial in origin, often Gram-negative organisms such as *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae* or *Acinetobacter* spp. Predominant organisms vary from hospital to hospital (and even in different locations within hospitals). MDR organisms are a growing challenge in most centres.

The challenge for physicians is not just to determine whether a patient has an infection (several other conditions produce similar symptoms) but also which specific organism is present (including its antibiotic sensitivity). Culture results are generally available within one to two days, but due to the rapid progression of pneumonia, treatment is generally initiated within a few hours. Culture results (and clinical assessment) can then be used to refine treatment – patients receiving therapies appropriate for their specific infections generally achieve better outcomes.

Discussions highlighted several similarities with sepsis, particularly the difficulty of identifying infection. Coughs are common in ICUs and could reflect lung injury after surgery or transfusion or other causes rather than infection. In practice, any sign of deterioration will cause a physician to initiate empirical antibiotic treatment, in advance of culture results.

Reimbursement practices can also have a significant influence on reported prevalence. In the USA, reimbursement is not now available for VAP, leading to a dramatic fall in its diagnosis (but no corresponding decline in antibiotic use to treat it). An unfortunate consequence of this change has been to make VAP much harder to study.

Although HAP and VAP are generally treated in much the same way, clinical assessment of VAP is made significantly easier by the ease in which samples can be collected from intubated patients.

There is generally significant urgency to begin treatment. After initial empirical treatment, cultures are used to identify specific pathogens causing infections and their susceptibility profiles, to guide subsequent treatment regimes. Escalation or de-escalation strategies can be adopted. In the USA, it is increasingly common to use back-up drugs such as colistin as first-line treatment, on the assumption that infections stand a high chance of being drug-resistant. The UK may make more use of escalation strategies, although practices vary widely. Diagnostic information has an obvious role to play in escalation strategies but, as in sepsis, de-escalation may in practice be less straightforward – physicians may be reluctant to modify treatments that appear to be working.

> *"A diagnostic that could be used for de-escalation sounds good but you'd be looking for a change in prescribing habits from something that may appear to be working so there's a lot of behavioural resistance to that."*
>
> *Clinician*

There is a strong case for rapid diagnostics to identify the specifics of infections so tailored antibiotic therapies can be initiated as rapidly as possible. However, the presence of a pathogen is not necessarily indicative of a harmful infection, so assessment of host responses to confirm infection would also be useful (one possibility being studied in a research setting is use of fibre optics to directly observe activated neutrophils in the lungs).

In the longer term, full genome sequencing of pathogens from clinical samples could provide comprehensive information on the organisms present and their resistance genes, with the potential to guide treatment decisions. Within a few years, it is likely that such information would be available in clinically meaningful timeframes – within 48 hours. However, there are concerns that the genotypic correlates of resistance may not necessarily translate directly to phenotypic correlates, and may not therefore be predictive of clinical outcomes. Clinicians are currently more comfortable with the information on resistance provided by culture (although it was also acknowledged that even supposedly gold standard culture results do not always correspond with clinical outcomes).

> *"The fundamental need is not the species: We don't need to know how to name it, we need to know how to kill it."*
>
> *Clinician*

Diagnostic development may also need to be mindful of therapeutic strategies targeting virulence. Rather than eradicating particular bacteria, these aim to prevent them from harming a host. In such cases, it might again be important to distinguish between colonisation and infection, or between pathogenic and non-pathogenic variants of the same bacterium.

HAP and VAP: Clinical trials

HAP and VAP also illustrate how diagnostic tools can be used to support enrolment in clinical trials. Importantly, however, the specification for a diagnostic in this context need not necessarily be the same as that for a tool guiding clinical decision-making.

HAP and VAP represent areas of significant unmet clinical need, and there is considerable pharmaceutical company interest in developing new agents. HAP and VAP provide a rare opportunity to test drugs developed for Gram-negative organisms. Gathering data on their effectiveness in these conditions can provide a foundation for further work in other infections. Recruitment is challenging, however. Many patients are likely to be excluded (for example because they are unlikely to survive). Patients also have to be caught at just the right moment – ideally within 24 hours, either before they have been given any antibiotics or in advance of the start of a second day's course to avoid confounding evidence gathered in a trial.

The main focus is on narrow-spectrum antibiotics, particularly those suitable for drug-resistant organisms. Key information therefore includes the infecting species and its drug resistance profile. Time is also critical – ideally, this information should be available before the first dose of antibiotics is given.

Trials would be considerably easier to run if specific organisms or strains could be rapidly detected, so possibly suitable patients for enrolment could be identified. Whether the same test would also be suitable to guide patient treatment in addition to support clinical trial enrolment remains open to debate. In particular, a rapid (less than one hour) test would be most useful for clinical trial enrolment, but this speed might not be necessary for clinical tools, as empirical therapy would still probably be initiated even if a rapid test were available.

Given the importance of identifying target organisms, diagnostic tools are likely to be integral to narrow-spectrum antibiotic development. However, there was some concern that diagnostic tools were still seen as an add-on and insufficiently integrated into antibiotic development by pharmaceutical companies. In addition, current regulatory pathways may not provide enough incentives to test diagnostic tools and therapies together, exacerbating the disconnect between diagnostic tool and therapy development.

Current reimbursement models also put diagnostic developers at a disadvantage, with little connection made between reimbursement rewards and the medical value provided by diagnostics, in terms of the initial savings on antibiotic use or longer-term social value of reduced resistance.

In summary:

- There is a clear role for diagnostics to identify and characterise HAP/VAP infections, to support choice of antibiotic therapy.
- Diagnostic information is likely to be used to refine initial empirical therapy; it could support escalation or de-escalation strategies (although use in the latter is likely to be more problematic)
- Host-directed tools to identify infection would also be valuable in initial clinical assessments.
- Diagnostics are important in the development of targeted antibiotics, particularly against Gram-negative organisms; the required performance characteristics of diagnostic tools for clinical trial recruitment may not necessarily be the same as those needed for patient assessment.

Complicated urinary tract infection

Urinary tract infections (UTIs) are extremely common, and account for a high proportion of nosocomial infections. Complicated urinary tract infections (cUTIs) are associated with additional morbidities or other factors (such as the presence of a catheter). The likelihood of treatment failure and development of antibiotic resistance is higher in cUTIs.

Most UTIs are caused by *E. coli*, although a wider range of organisms are seen in cUTIs. The number of cUTI cases caused by MDR Gram-negative bacteria is on the rise. Failure to treat a cUTI effectively can have serious consequences, potentially leading to septic shock and even death.

The diagnostic challenge for physicians varies according to the severity of a UTI. Uncomplicated cases do not generally lead to serious symptoms and often self-resolve; several empirical treatment options are available. Identifying a cUTI may be more difficult, particularly in older people, and physicians need to weigh up the pros and cons of prompt treatment versus waiting for the results of culture tests and the possible adverse effects of antibiotic treatment on host microflora and increased risk of resistance.

Discussions highlighted the great variation in UTI presentations. In A&E/emergency rooms, a typical patient is likely to be elderly, often from a care home environment, with a range of undifferentiated symptoms – confusion, fever, incontinence – who may have experienced a fall. UTIs are one possible explanation, but a whole range of other conditions could generate similar symptoms. By definition, any UTI in a patient over 65 would be classified as complicated.

By a process of elimination, an A&E doctor seeks to identify if a patient has an infection, its likely source and whether it is local or systemic. The urinary tract is an obvious place to start the search. Samples are easy to obtain, although often of low quality due to contamination. A urinary dipstick is available but provides limited diagnostic information: a negative result is useful in ruling out a UTI but a positive result is not a reliable guide to infection – it may reflect contamination and cannot distinguish between bacteriuria and true infection.

> *"The biggest challenges are dividing patients into whether they need an antibiotic or not when they don't have classic symptoms, and dividing patients into the ones who are progressing towards sepsis and determining what antibiotic to give them."*
>
> *Clinician*

The timeframe for action is variable, depending on the state of the patient. In the UK, Government waiting time targets impose a four-hour deadline on physician decision-making in A&E.

The key decisions for a clinician are whether to give antibiotics and whether to admit a patient to hospital. For the former, any test that could distinguish asymptomatic bacteriuria from infection would be valuable – some 60% of patients from care homes, for example, will have bacteriuria so deliver a positive dipstick test. This could be based on host biomarkers of an inflammatory response in the lower urinary tract. Hospitalisation is likely to be required when infection spreads more widely, so tests of a systemic host response would be most useful. (Diagnostic test results would of course always be considered alongside other clinical information.)

Although there is evidence of relatively high levels of antibiotic resistance in cultured samples, in A&E at least treatment failure appears to be fairly rare. This may be because treated cases did not actually have an infection, the infection self-resolved, or antibiotics retained enough effectiveness to affect clinical outcomes. There may also be significant differences across UTIs – cUTI cases, for example, have often been previously treated with antibiotics and resistance levels would thus be expected to be higher. More basic research is needed to understand the relationship between *in vitro* assessments of resistance and *in vivo* resistance and clinical outcomes.

In this scenario, therefore, over-treatment is common (as in the otitis media and sinusitis situations) but also a greater risk of serious consequences if infections are not treated effectively.

Hence, the argument for a diagnostic to identify bacterial infection is strong. The main challenge would be to distinguish true infection from colonisation. When infection was confirmed, identifying which specific organisms were present and which antibiotics they were resistant to would also be a priority.

Potentially, therefore, clinical assessments might require multiple diagnostic tools performing different roles. It would be important to consider how these would be used within the context of the decision trees used by clinicians to assess patients and select management strategies. UTIs are highly diverse – for simple UTIs, the diagnostic information required by clinicians are likely to vary significantly across different presentations.

Tests designed to minimise antibiotic use might again raise reimbursement issues. For example, it may be cheaper to prescribe an antibiotic than to use a diagnostic to test whether that antibiotic was actually needed (further evidence of the challenges of quantifying the value of diagnostics). It might be possible to adapt reimbursement pathways to promote pro-social practices – for example, reimbursement for an antibiotic could be made contingent on the use of a diagnostic confirming infection.

Innovative approaches may also be needed to encourage more effective use of existing agents. Although the current focus is on tests to detect resistance, identifying susceptible infections could also be useful, enabling antibiotics partially compromised by resistance to be used safely. Despite the strong public health benefit, there are currently few incentives for diagnostic manufacturers to develop such tests.

Thought also needs to be given to the thresholds used to define UTIs and how they might vary between different groups of patients (such as children, adults and older people). A better understanding is needed of the link between bacteria levels, symptoms and recovery. With contamination a major issue, more thought also needs to be given to sample collection.

While a range of possible diagnostic tools could be envisaged, each with a distinct role to perform, they would need to be considered in the context of healthcare setting, physician behaviour, and communication with patients. Again, the potential for 'rule out' tests ultimately to be used in a range of healthcare or community settings could be considered.

- UTIs are a diverse range of conditions in which diagnostics could perform a range of roles.
- Even within cUTIs, distinct diagnostics might be needed to support different aspects of patient assessment.
- In cUTIs, there is a clear need for tools to rule out bacterial infection and to distinguish colonisation (bacteriuria) from infection.
- When infections have been confirmed, tests to identify specific infections and drug resistance would be useful to guide choice of treatment.
- Tests to identify high-risk patients developing systemic infection could also make a valuable contribution to physician decision-making.

Emergent themes

A typology of diagnostic strategies

Detailed discussion of each clinical scenario, in the context of patient journeys through health systems, identified considerable complexity. Physician decision-making is highly nuanced and subject to multiple influences, including a patient's symptomology, healthcare settings and reimbursement practices, and social and cultural context. Diagnostic tests can provide information to reduce uncertainty in physician decision-making, but the exact information required, and how it would be used, will be highly dependent on these contextual factors.

Further detailed examination of specific clinical scenarios is therefore likely to be necessary to understand clinicians' needs and to define the desired specifications of suitable diagnostic tools. Nevertheless, a key insight to emerge from the workshop was the identification of commonalities across different clinical scenarios. Four distinct diagnostic strategies were identified, in which diagnostic tools could provide information to inform clinical decision-making as one aspect of a more complex 'ecosystem' (Table 2).

Importantly, diagnostic devices are only one element of each diagnostic strategy and might not even be the most important element of a particular strategy – in some cases, tools to support behavioural change (especially in the face of uncertainty and time pressures) might be more important than any laboratory test. Nevertheless, a key feature of this typology is that it provides greater clarity on the 'job to be done' by a diagnostic in different settings.

Table 2: Diagnostic typologies identified at the workshop

	Avoid unnecessary treatment	**Optimise patient treatment and antibiotic use**	**Identify high-risk patients**	**Improve drug development**
Diagnostic role	Diagnostic to support not treating	Diagnostic to select treatment (escalate/de-escalate)	Tool to predict host response	Tool to support clinical trial recruitment
Diagnostic example	• Confirm viral/bacterial aetiology • Distinguish infection from colonisation	• Pathogen identification • Susceptibility • Resistance markers	• Prognostic biomarkers (host response) • Multifactorial risk assessment tools	• Clinical trial enrichment tool
Use case	• Reduce unnecessary prescribing • Confirm/rule out bacterial infection	• Match treatment to pathogen and susceptibility	• Rule in treatment where would not treat pathogen alone •Predict treatment outcome	• Identify patients who would be appropriate candidates for a clinical trial
Benefit	• Avoid collateral harm to patient • Avoid harm to society • Assurance of clinician	• Improve treatment outcomes • Reduce collateral harm • Avoid using newer drugs when older drugs work	• Prevent bad mistakes (e.g. low-probability outcomes) • Triage for treatment	• Improve feasibility and reduce cost of antibiotic development

Avoiding unnecessary treatment: One suggested use of diagnostic tests is to identify cases of bacterial infection where antibiotic use is appropriate ('rule in' tests). However, in practice, over-treatment is far more common than under-treatment, undermining a key principle of antibiotic stewardship. A more effective diagnostic strategy may be to focus on ruling out bacterial infections, to support a decision not to treat with antibiotics.

In many cases, as exemplified by sinusitis and otitis media, the likelihood of a bacterial infection is already known to be low, and clinical examination can provide some indication of whether a bacterial infection is present. Diagnostic test results may therefore have marginal clinical utility in terms of reducing physician uncertainty about the cause of infection. However, they may have greater value in physician–patient communication and in helping patients understand why they have not been given an antibiotic prescription. They may also provide reassurance to physicians who are concerned about the potential negative consequences – clinical and professional – of not identifying a bacterial infection that goes on to have a serious impact on a patient's health.

There is therefore considerable scope to consider how diagnostic tools could support this novel diagnostic strategy. Their use would need to be considered in the wider context of the behavioural and social factors that influence patient expectations and physician prescribing behaviour, physician education, as well as health system mechanisms that drive physician behaviour. Enhanced dialogue with patients may be an important opportunity to improve antibiotic stewardship, with more emphasis placed not just on the societal risks posed by excessive antibiotic use but also the personal harm from adverse reactions or increased risk of future drug-resistant infections. There is also scope to consider how the presentation of test results, and effective information design, could be used to support patient dialogue.

Optimising patient treatment and antibiotic use: There are strong clinical arguments to target antibiotic use to a patient's specific infection. Targeted treatments avoid collateral damage to host microflora, and with drug-resistant infections increasingly common, identifying which antibiotics are likely to be effective is critical to successful treatment.

Across a range of conditions, diagnostics therefore have a potentially crucial role to play in identifying specific organisms and their antibiotic resistance profile. This use can support both escalation and de-escalation strategies, although again the significance of behavioural factors in de-escalation should not be underestimated – a physician may be reluctant to cease antibiotic treatment even when diagnostic information is available.

With emerging technologies, tools to support this diagnostic strategy are increasingly available. Key to their success will be the extent to which they can provide the precise information required by physicians in clinically relevant timeframes, can be integrated into clinical work practices, and can be demonstrated to deliver improved patient outcomes cost-effectively.

Identifying high-risk patients: A recurrent theme across multiple clinical scenarios was the importance of identifying infection in syndromically treated patients and in distinguishing infection and colonisation. Simply identifying a potentially pathogenic organism in a patient may not provide certainty that it is responsible for a patient's condition. Healthy people may carry pathogenic bacteria without suffering adverse consequences, while detection of bacteria in patients does not necessarily mean they are responsible for symptoms.

Hence there is also a strong clinical need for indicators of infection, to reliably identify local or systemic infection. As well as identifying 'true' infections, such tests could be used to identify patients at risk of rare severe outcomes and those progressing to more disseminated infection. Markers such as CRP are not currently sensitive enough to provide clinically actionable information. More research is needed to identify potentially useful biomarkers in different conditions and to evaluate their clinical utility.

Improving drug development: Recruitment into clinical trials has been identified as an important obstacle to the development of new antibiotics. In particular, development of new narrow-spectrum antibiotics requires identification of relevant target organisms. Recruitment into trials has to be undertaken within the context of routine patient care, which impose key constraints, such as the need for rapid empirical treatment of serious infections.

The specification of diagnostics to support enrolment into clinical trials may therefore be different from those for routine clinical use; speed and precision are likely to be less crucial factors. Nevertheless, it may be possible to design diagnostics to support both uses.

More generally, there are strong arguments that the development of diagnostics and narrow-spectrum therapeutics should be more closely integrated, with greater coordination between diagnostic developers and pharmaceutical companies and a greater focus on combined use by regulators and bodies responsible for health technology assessment.

Applying the typology

This diagnostic typology provides an important foundation for future work. The term 'diagnostic' has been used to describe tools with a range of possible functions, and distinguishing more specific roles that they can perform can support more focused discussions and accelerate future progress. In particular, an agreed diagnostic typology will enable the precise specifications of diagnostic tools to be defined, in the context of specific patient presentations. It will also help to generate a shared understanding of how they would be used as part of wider patient-management strategies, and identify obstacles to their development, reimbursement and uptake into care pathways.

In terms of the application of the typology to the clinical scenarios discussed at the meeting, it is clear that a 'many-to-many' relationship exists between the two – each diagnostic strategy could be applied to multiple scenarios, and each scenario could exploit more than one diagnostic strategy (Table 3).

Table 3: Potential use of diagnostics in clinical scenarios discussed at the workshop

	Sepsis	Sinusitis	HAP/VAP	cUTI
Purpose	• Aid in treatment selection	• Aid in preventing unnecessary treatment • Support behaviour change by patient and clinician	• Rule in/rule out pneumonia • Guide escalation/ de-escalation • Support targeted therapeutic use • Support therapeutic development for Gram-negative organisms	• Distinguishing bacterial/non-bacterial infections • Distinguishing colonisation and infection • Support treatment selection • Avoid needless step-up of treatment
Urgency and cost of being wrong	• High urgency • High mortality without appropriate treatment	• Low urgency • Manageable	• Medium to high urgency • Significant mortality risk	• Moderate urgency • Must identify patient at sepsis risk
Benefits	• Reduce mortality	• Reduce massive over-prescribing, with benefits to: - patients - society	• Improve outcomes by reducing time to appropriate therapy •Reduce hospital stay	• Reduce antibiotic over-use • Avoid last-line antibiotic use • Treat effectively
Challenge	• Complexity of sepsis makes linking to outcomes difficult	• Complex determinants of behaviour • Perception of major risk from non-treatment	• Getting samples in HAP • Getting sufficient certainty for targeted treatments • Clinical trial enrolment	• Introduction of diagnostic where not used before • Requires new reimbursement approach

After the meeting, the draft typology was endorsed by the Diagnostics Action Team (DAT), an informal US-based group including individuals from academia, diagnostic companies, pharmaceutical companies, payor groups, and the National Institute of Allergy and Infectious Diseases/National Institutes of Health, and the Food and Drug Administration. The group was created to identify hurdles and facilitate development of rapid diagnostic tests for bacterial infections that would transform the way antibiotics are prescribed and studied.

Following a meeting to discuss the implications of the workshop, the DAT proposed two priority areas for further work. The first was more basic biomedical research on host biomarkers, particularly in upper respiratory tract infection and sepsis. In addition, a host biomarker differentiating colonisation and infection could have a huge impact on treatment of elderly patients with bacteriuria, and also facilitate clinical trials in UTI infections.

The DAT also recommended a greater emphasis on behavioural/social science. Data to support prescribers' strategies to treat or not to treat with antibiotics, or to escalate or de-escalate therapy, would have real value in ensuring both that patients who need antibiotics are treated and also that antibiotics are not used when not needed.

> *"Recommendation: Win 3-4 battles before trying to win hundreds of battles. Narrow the wish list to 3-4 items that could make a major dent and marshal all stakeholders in this direction."*
>
> ***Feedback from pharma representative***

Enablers/obstacles

Workshop discussions identified a range of factors likely to affect the development and use of diagnostic tools within these diagnostic strategies. These enablers and obstacles provide potential targets for further work to accelerate the development and implementation of diagnostics and of targeted antibiotics.

Host responses/patient physiology: A recurrent theme was the importance of patients' physiological responses as indicators of infection or poor outcomes, revealing a complementary need for tools based on host biomarkers in addition to diagnostics that detect or characterise disease-causing organisms. This class of tools could support a range of diagnostic strategies. Further research is required to identify and validate potential biomarkers of local or systemic infection, and to assess how such host-directed tools could generate clinically actionable information.

> *"The crying need identified at the meeting was for rapid distinction between viral and bacterial infection of simply between bacterial infection vs colonization. Here, it is my view that more basic research is required to identify putative biomarkers."*
>
> ***Feedback from opinion leader***

Health system context: Health system and care setting context emerged as powerful influences on the use of diagnostics tests, and are important considerations for diagnostic development. Diagnostic developers need to consider how tools would integrate into everyday clinical practice in specific care settings. Conversely, manipulating health system processes may provide ways to embed diagnostic use and rationalise antibiotic use, for example by linking reimbursement mechanisms to use of diagnostics, or by monitoring of individual physician's antibiotic prescribing.

> *"The much discussed reluctance of clinicians to modify their "gold standard" of culture (dubbed the 'culture culture') is a huge barrier. It is a symptom of tremendous risk aversion when it comes to care of patients, and in many ways that's understandable. Any diagnostic test that suggests they shouldn't do something that might help, even in just a few rare cases, is swimming against a very strong current."*
>
> ***Feedback from academic***

Sociocultural influences: Physician behaviour and physician–patient interactions, and attendant social and cultural factors, were identified as key influences on antibiotic prescribing, particularly in primary care settings. A greater understanding of the factors affecting patient attitudes (see Box 2) and physician behaviour is required, including international comparisons, calling for more inter-disciplinary research and insight from social research.

> *"Culture (in the conventional senses) is the probable explanation for the four-fold difference in prescribing rates across European countries. That points to an opportunity to make substantial inroads into usage by changing doctor-patient behaviour. That would be no small task of course, but it is a researchable topic and one with an obvious potential to make a substantial difference."*
>
> ***Feedback from academic***

Diagnostic development landscape: Several features of the current diagnostic development landscape present obstacles to the development of tools required to support particular diagnostic strategies. Diagnostic and therapeutic development remains insufficiently well integrated. Closer relationships are needed between diagnostic developers and pharmaceutical companies. How regulatory agencies assess diagnostics is also problematic, and regulatory approvals and health technology assessments need to place more emphasis on the combined use of diagnostics and therapeutics and clinical outcomes.

Central to these issues are the difficulties in assessing the medical and societal value of diagnostics, including that associated with delayed development of resistance. Implementation of diagnostics can also be held back by silo budgeting, if the additional costs of new laboratory tests are considered in isolation of cost savings or medical benefits achieved in other parts of a health system. More holistic (e.g. hospital-wide) approaches to budgeting can overcome these obstacles (although capturing social value remains hard).

> *"You look at the holistic health system, and say spending more money in microbiology will save pharmacy costs, and save me diagnostic costs and if I can get that patient out of the hospital three days earlier I can put another patient in that bed. You've gone from a cost avoidance model to a revenue model."*
>
> *Diagnostic developer*

Greater clarity on the kinds of diagnostics required to achieve public health benefits through enhanced antibiotic stewardship could support a thorough review of the diagnostic development landscape, and identification of mechanisms to remove obstacles and promote the development of socially desirable diagnostic tools.

Box 2: Antibiotic resistance – the public perspective

Focus groups have revealed new insight into how the general public perceives antimicrobial resistance, with potentially important consequences for public communication.

The workshop heard a brief summary of research commissioned by the Wellcome Trust to gain a better understanding of the public's perceptions of antibiotic resistance and likely responsiveness to different kinds of messages. The research was based on focus groups and observation of individuals in discussion with friends and acquaintances.

One of the most striking findings was that the understanding of 'antibiotic resistance' was very low, and often associated with the body itself becoming resistant to antibiotics. This contributed to a sense that antibiotic resistance was 'somebody else's problem'. It is therefore likely to be more helpful to talk about 'drug-resistant infections' or 'antibiotic-resistant germs' rather than 'antibiotic resistance' when addressing general audiences.

The work also suggested that focusing on statistical aspects of antibiotic resistance did little to engage people with the scale of the problem. A more effective approach was to talk about common medical conditions and the risk to routine medical procedures, and in particular to use images of relevant organisms.

A summary of the project's findings can be downloaded at www.wellcome.ac.uk/About-us/Policy/Spotlight-isswes/Antimicrobial-resistance

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Wider issues

The workshop also touched upon a range of longer-term issues of importance to diagnostic and therapeutic development.

Drug-resistant infections in the developing world: Although antibiotic resistance is a major issue in low- and middle-income countries, considering diagnostic use in such settings was beyond the scope of the meeting. Nevertheless, the key theme of the workshop – that diagnostic development should be rooted in the specificities of clinical scenarios and patient journeys – provides a framework that could be applied in resource-constrained countries.

Pathogen sequencing: The workshop focused on current clinical needs and near-term product development. With the rapid growth in whole genome sequencing, and a growing understanding of the genetic basis of resistance, there is potential for disruptive game-changing technologies to transform clinical diagnostic practices. Encouraging further interdisciplinary contact could be used to explore practical application of these technologies in clinical settings. Genotype–phenotype correlations – the extent to which genetically identified resistance markers reflect antibiotic sensitivity and clinical outcomes – is an issue of particular importance.

Surveillance: As well as patient-specific tools, enhanced routine surveillance could be an additional source of data, providing clinicians with more information about the types of organisms currently in circulation locally and patterns of antibiotic resistance. Surveillance information could support both clinical decision-making and communication with patients.

Broad-spectrum antibiotics: There is currently a strong focus on the development of targeted, narrow-spectrum antibiotics, to minimise collateral damage to the host microflora. However, treatment strategies indicate a continuing need for new broad-spectrum as well as narrow-spectrum antibiotics. Diagnostic strategies will help to preserve the effectiveness of both types of medicines.

Appendix

(1) Workshop participants

Health system leaders
Sarah Byron, NICE
Dame Sally Davies, UK Department of Health
Sarah Garner, NICE
Sumathi Nambiar, FDA
Gahda Zoubiane, Medical Research Council

Patient advocates
Koen Block, European AIDS Treatment Group
Brendan Gilligan, European Heart and Lung Transplant Federation
Margaret Walker, European Liver Patients Association

Antibiotic innovators
James Anderson, GSK
Barry Eisenstein, Merck/MSD
Barbara Klughammer, Roche
Stephan Laage-Witt, Roche
Marc Lemonnier, Antabio
Linda Miller, GSK
Kenny Simmen, Janssen, Infectious Disease
Aurelio Otero, Merck/MSD
John Rex, AstraZeneca

Diagnostic innovators
Daniel Alderstein, Atlas Genetics
Tobi Karchmer, BD
Oliver Liesenfeld, Roche Molecular Diagnostics
Mark Miller, bioMérieux
Fred Tenover, Cepheid
Marcel van Kasteel, Philips
Lena Wahled, HemoCue AB
John Wisson, Alere

Clinicians and key opinion leaders
Emilio Bouza, Hospital Gregorio Maranon, University of Madrid
Chris Butler, University of Oxford
Tim Coats, University of Leicester
Ross Coppel, Monash University
Gregory Daniel, Brookings Institution
Nick Day, Wellcome-Mahidol-Oxford Tropical Medicine Research Unit
Vance Fowler, Duke University Medical Center
William Hall, Review on Antimicrobial Resistance
Pieter Moons, University of Antwerp
Julian Parkhill, Wellcome Trust Sanger Institute
Céline Pulcini, ESCMID
Mike Sharland, St George's University of London
David Shlaes, independent consultant
Carolyn Shore, Pew Charitable Trusts
Mervyn Singer, University College London
Estee Torok, University of Cambridge
Mark Wilcox, the Leeds Teaching Hospitals NHS Trust
Mark Woolhouse, University of Edinburgh

Wellcome Trust
Stephen Caddick
Michael Ferguson
Mark Henderson
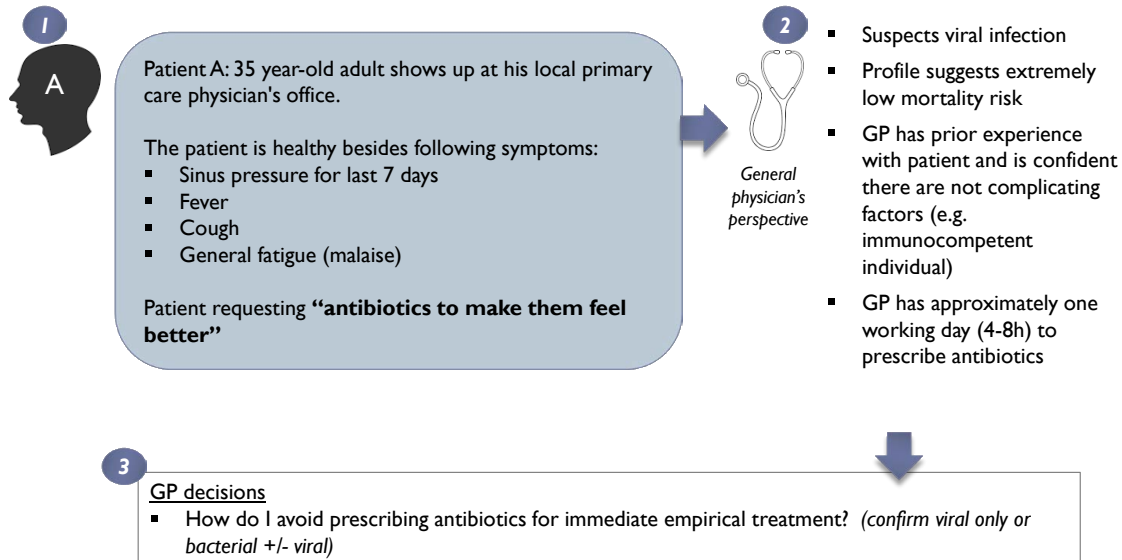Tim Jinks
Nancy Lee
Richard Seabrook
Keith Spencer
Mike Turner

Workshop facilitators
Matt Diver, Galen/Atlantica
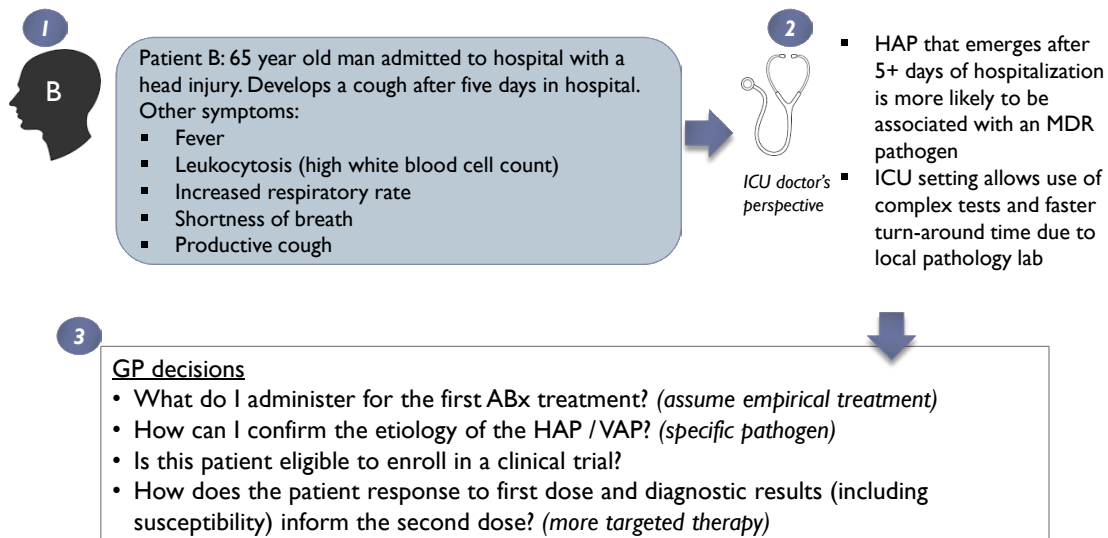Nicholas Gertler, Galen/Atlantica

(2) Summaries of clinical scenarios

Sinusitis | What decisions does a doctor need to make?

1

A

Patient A: 35 year-old adult shows up at his local primary care physician's office.

The patient is healthy besides following symptoms:
- Sinus pressure for last 7 days
- Fever
- Cough
- General fatigue (malaise)

Patient requesting **"antibiotics to make them feel better"**

2

General physician's perspective

- Suspects viral infection
- Profile suggests extremely low mortality risk
- GP has prior experience with patient and is confident there are not complicating factors (e.g. immunocompetent individual)
- GP has approximately one working day (4-8h) to prescribe antibiotics

3

GP decisions
- How do I avoid prescribing antibiotics for immediate empirical treatment? *(confirm viral only or bacterial +/- viral)*

HAP / VAP | What decisions does a doctor need to make?

1

B

Patient B: 65 year old man admitted to hospital with a head injury. Develops a cough after five days in hospital. Other symptoms:
- Fever
- Leukocytosis (high white blood cell count)
- Increased respiratory rate
- Shortness of breath
- Productive cough

2

ICU doctor's perspective

- HAP that emerges after 5+ days of hospitalization is more likely to be associated with an MDR pathogen
- ICU setting allows use of complex tests and faster turn-around time due to local pathology lab

3

GP decisions
- What do I administer for the first ABx treatment? *(assume empirical treatment)*
- How can I confirm the etiology of the HAP / VAP? *(specific pathogen)*
- Is this patient eligible to enroll in a clinical trial?
- How does the patient response to first dose and diagnostic results (including susceptibility) inform the second dose? *(more targeted therapy)*

What decisions must an ED doctor make?

1

C

Patient B: 80-year-old woman is referred to the ED from her nursing home. Patient had antibiotics use within last ~8 weeks to treat bacterial pneumonia, but unclear of specific prescription. Patient complains of classic UTI symptoms:
- Dysuria
- Urgency
- Frequency

ED doctor's perspective

2
- ED work in fast-paced environment – often spend 5-10 minutes per patient.
- Must balance risks of providing suboptimal ABx treatment with need to expedite discharge of patients to make space
- ED doctor will often lack relationship or detailed clinical context on a patient
- Turnaround time is critical for tests in ED – ideally result in <1 hour

3

ED doctor decisions
- Should this patient be admitted to the hospital? What specific care setting?
- Should I treat empirically, or await results from a diagnostic test to target treatment?
- What specific tests should I order?

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