How can diagnostics be used to lower unnecessary use of antibiotics?

A low- and middle-income perspective

Introduction

Infections with antibiotic resistant bacteria cause hundreds of thousands of deaths every year. Access to diagnostic tools has been identified, among others by the World Health Organization (WHO), as one key factor to slow down resistance development (1).

However, the different potential gains of well-functioning diagnostics have not been thoroughly described, nor have the prerequisites for their successful implementation. Due to logistical and financial constraints, many diagnostic tools are currently only useful in high-resource settings. At the same time, a simulation study from 2006 showed that a universally available diagnostic test for identification of bacterial casuses of lower respiratory tract infections could have a huge impact on reducing unnecessary antibiotic use and child mortality in Africa, Asia and Latin America (2).

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"Ensure healthy lives and promote wellbeing for all at all ages"

Access to good diagnostics is an essential cornerstone of health-care, and is therefore also an important component for reaching universal health coverage (UHC). Achieving universal health coverage is one of the targets (3.8) of Sustainable Development Goal 3: "Ensure healthy lives and promote wellbeing for all at all ages"(3) and was also the subject of a high-level meeting held in the general assembly of the United Nations in September 2019. It is stated in paragraph 24 of the political declaration approved at the meeting that an additional billion people should be covered with essential health-services, including diagnostics, in 2023 (4).

The importance of diagnostics has also been highlighted in various other contexts lately. For example, the WHO released the second iteration of its model list of essential in vitro diagnostics in 2019 (5) and in 2016, the Foundation for Innovative New Diagnostics (FIND) initiated publication of an expert consensus article on how to use diagnostics to reduce overuse of antibiotics in resource-limited settings (6). The Longitude Prize is awarded to innovators of a diagnostic test for bacterial

infections, which facilitates correct use of antibiotics. Encouragingly, the evaluation criteria for the prize include that the test must be needed, accurate, affordable, rapid, easy-to-use, scalable and safe which is highly relevant from the perspective of low- and middle-income countries (7).

However, the question remains: Is it possible to develop a test with all essential characteristics, that also could be useful in all settings? In order to maximize the impact of diagnostics, stakeholders must indeed be aware of the need for tailored strategies that take differing needs of patients and health-care systems into account as new diagnostics are developed and introduced. Below, we discuss what functions diagnostic tools could have, and focus particularly on discussing how diagnostic tests could be used to lower unnecessary use of antibiotics.

Diagnostics could reduce antibiotic use in patients with mild to moderate disease

Improving antibiotic use in patients with mild to moderate disease could have large effects on decreasing the selection pressure on bacteria to develop antibiotic resistance. Development of new or improved diagnostic tools could surely facilitate proper antibiotic use, although it is important to remember there is much to be gained by simply ensuring global access to already existing technologies, particularly if combined with other preventive interventions that promote sustainable use of these life-saving medicines.

Upper respiratory tract infections (URTIs) are predominantly caused by viruses. Nevertheless, antibiotics are commonly prescribed to patients with such infections, resulting in a massive misuse of antibiotics and thereby accelerated development of resistance. Some studies have shown that in China, Korea and Thailand, over 80% of patients with URTIs are prescribed antibiotics (8). Corresponding figures from Ecuador was 37.5 % in one study and over 90% of these prescriptions were inappropriate (9). In France, 59% of children with URTIs admitted to an emergency room had already been prescribed antibiotics by a general practitioner. Roughly three quarters of the prescriptions were considered inappropriate, being unnecessary or of too wide spectrum (10).

There are existing biomarker tests that can aid in distinguishing bacterial infections from viral. For example, measurements of the concentration of C-reactive protein (CRP) in the blood are at times included in the clinical management of infected patients, although practices vary between countries. Meta-analyses on randomized controlled trials conducted in Europe and US have shown that point-of-care CRP testing of patients with respiratory tract infections decreases antibiotic prescription rates in general practice (11,12). The same effect has been demonstrated in Vietnam, suggesting usefulness also in low- and middle-income settings (13). However, concerns about cost-effectiveness of CRP testing was raised in another Vietnamese study, as a a consequence of limited adherence to test results (14). Hence, introduction of CRP tests into new settings should be accompanied by other preventive measures like educational interventions that target both prescribers and patients (14,15).

What is the role of diagnostics in patients with severe infections?

Severe infections, such as sepsis, require immediate attention since mortality increases significantly if appropriate treatment is delayed (16,17). Broad-spectrum antibiotic therapy is therefore standard procedure, since it maximizes the chances of successful outcomes. The negative aspects of such treatment, like the broad selection pressure imposed on a wide range of bacterial species to develop antibiotic resistance, is simply inferior to the risk of losing the patient. Hence, there are limitations to what practical effects new diagnostic tests could have on preventing unnecessary antibiotic use in this group of patients. Would a clinician ever be willing to trust a test result that proposes use of a narrow-spectrum antibiotic if the patient's life is at stake?

With that said, a rapid diagnostic test could facilitate de-escalation and thus shorten the time on initial broad-spectrum antibiotics. What more, a diagnostic test that rapidly could identify antibiotic resistance patterns of bacteria could play a crucial role for critically ill patients in settings with high levels of resistance to standard therapy. On this note, data from sub-Saharan Africa has shown that 68% of bacteria causing invasive infections in neonates are resistant to the beta-lactam antibiotics recommended for treatment by the World Health Organization (WHO) (18). A new, rapid diagnostic test could thus significantly improve patient outcomes in such a setting, given that the test would guide to the right diagnosis and antibiotic choice, with highest possible accuracy, already at the initiation of treatment.

Diagnostics could also give a snapshot of the resistance situation

Diagnostics could also be used for antibiotic resistance surveillance and patient screening. As these procedures are not directly linked to the treatment of an individual patient, the requirements of diagnostics are different. Common ground is the need to identify the infecting pathogen and susceptibility to a selected panel of antibiotics. Other aspects, such as how rapid the test is, often become less important. If the same methods and standards are used in both routine clinical diagnostics and surveillance, and if there is cross-talk or reporting between the systems, significant synergies can be achieved by sharing both costs and benefits between the systems.

Patient screening is useful in admission of patients that may potentially carry resistant bacteria. A screening method could be used to determine if a patient needs to be isolated from others due to carriage of a pathogen. In such situations, a decision needs to be made rapidly at admission and the patient isolated until the laboratory result is available. In such cases, a "quick-and-dirty" method could provide useful. In both surveillance and screening, hundreds or thousands of samples are collected and analysed on a regular basis. Even though each individual test may be cheap to perform, the accumulated cost is substantial.

Are diagnostics sufficient to change prescibing?

Many factors contribute to the overprescription of antibiotics: some are context-specific, others are universal. Aspects that may influence prescribing practices include time constraints at clinics, real and perceived expectations from patients,

whether or not a consultation fee has been paid, the patient load and diagnostic uncertainty (19). On the other hand, multiple interventions have proven to decrease antibiotic prescribing. These include educational campaigns focusing both on health-care professionals and patients, delayed prescriptions and diagnostic testing at point of care, including CRP testing (19). Since a large proportion of antibiotics are prescribed "just in case", research is needed on what effects a rapid diagnostic test for viral infections would have, given that the specificity is better than that of already existing methods. Could a positive confirmation of viral infections more clearly eliminate a perceived need for antibiotics? Could it reduce the tendency to prescribe antibiotics for reassurance?

Diagnostics need to be tailored to the need and resources of countries

In low- and middle-income countries (LMICs), the lack of both funds and human resources, as well as weak health care systems, currently place a serious constraint to the design and use of diagnostic tests. Where there is a lack of laboratory capacity, standards and sufficiently trained staff, high-tech tests are not feasible to implement or are simply too expensive. In addition, many LMICs have to grapple with matters such as irregular electrical supply for equipment, low budgets in health care systems and transportation cost, poor patient data management systems where test results may be delayed or lost, long travel distances and waiting times to see a physician, too short time for the consultation and high out of pocket expenditures on healthcare (20,21). Many health facilities are relatively remote in rural areas and often have weak, inefficient supply chain systems. Hence, a constant supply of materials needed for tests, or maintenance of equipment, could be a challenge. All of these hurdles need to be addressed and should be at the centre of thought as new diagnostic tests are developed and implemented. Encouringely, paragraph 76 in the political declaration on UHC calls to "ensure equitable access to affordable, safe, effective and quality existing and new antimicrobial medicines, vaccines and diagnostics…" (4). This must be the guiding principle in any endeavour to develop and use diagnostics - that both patient safety and sustainable use of antibiotics is ensured.

Conclusions

Diagnostic tests can play an important role in decreasing misuse of antibiotics and ensuring UHC. However, the usefulness and characteristics of diagnostics tests vary depending on both the medical conditions of patients and the health-care systems into which they are applied. Funding of research and development of new diagnostics should be directed toward methods that address LMIC needs and thus are possible to roll out even in resource-limited settings, like affordable and safe rapid diagnostic tests. Other key factors and considerations should not be neglected, including human resource, capacity, test results turn-around time, supply chain and transportation cost. Moreover, we believe that ensuring global access to existing technologies is fundamentally important and therefore urge governments to transform the political declaration on UHC, including paragraph 76 on antimicrobial resistance, into action.

References

1. World Health Assembly S session. Governing body matters: Key issues arising out of the Sixty-eighth World Health Assembly and the 136th and 137th sessions of the WHO Executive Board. 2015 Aug 23;

2. Lim Y-W, Steinhoff M, Girosi F, Holtzman D, Campbell H, Boer R, et al. Reducing the global burden of acute lower respiratory infections in children: the contribution of new diagnostics. Nature. 2006 Nov 23;444 Suppl 1:9–18.

3. United Nations. Goal 3: Ensure healthy lives and promote well-being for all at all ages [Internet]. United Nations Sustainable Development. [cited 2019 Dec 10]. Available from: https://www.un.org/sustainabledevelopment/health/

4. United Nations, Heads of State and Governments and representatives of States and Governments. Political Declaration of the High-level Meeting on Universal Health Coverage "Universal health coverage: moving together to build a healthier world" [Internet]. [cited 2019 Dec 11]. Available from: https://undocs.org/en/A/RES/74/2

5. World Health Organization. Second WHO model list of essential in vitro diagnostics [Internet]. 2019 [cited 2019 Dec 6]. Available from: https://www.who.int/medical_devices/publications/Second_WHO_Model_List_of_Essential_In_Vitro_Diagnostics/en/

6. Dittrich S, Tadesse BT, Moussy F, Chua A, Zorzet A, Tängdén T, et al. Target Product Profile for a Diagnostic Assay to Differentiate between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus. Yansouni C, editor. PLOS ONE. 2016 Aug 25;11(8):e0161721.

7. Prize rules | Longitude Prize [Internet]. [cited 2019 Dec 6]. Available from: https://longitudeprize.org/applying/prize-rules

8. Teng C. Antibiotic prescribing for upper respiratory tract infections in the Asia-Pacific region: A brief review. Malays Fam Physician Off J Acad Fam Physicians Malays. 2014 Aug 31;9(2):18–25.

9. Sánchez Choez X, Armijos Acurio ML, Jimbo Sotomayor RE. Appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in ambulatory health care centers in Ecuador. BMC Pharmacol Toxicol. 2018 27;19(1):46.

10. Marc C, Vrignaud B, Levieux K, Robine A, Gras-Le Guen C, Launay E. Inappropriate prescription of antibiotics in pediatric practice: Analysis of the prescriptions in primary care. J Child Health Care Prof Work Child Hosp Community. 2016 Apr 18;

11. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract. 2013 Nov;63(616):e787–94.

12. Aabenhus R, Jensen J-US, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014 Nov 6;(11):CD010130.

13. Do NTT, Ta NTD, Tran NTH, Than HM, Vu BTN, Hoang LB, et al. Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial. Lancet Glob Health. 2016 Aug 3;4(9):e633–41.

14. Lubell Y, Do NTT, Nguyen KV, Ta NTD, Tran NTH, Than HM, et al. C-reactive protein point of care testing in the management of acute respiratory infections in the Vietnamese primary healthcare setting – a cost benefit analysis. Antimicrob Resist Infect Control [Internet]. 2018 Oct 4 [cited 2019 Oct 11];7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6172744/

15. Aabenhus R, Jensen J-US. Biomarker-guided antibiotic use in primary care in resource-constrained environments. Lancet Glob Health. 2016 Sep 1;4(9):e586–7.

16. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017 Jun 8;376(23):2235–44.

17. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589–96.

18. Okomo U, Akpalu ENK, Doare KL, Roca A, Cousens S, Jarde A, et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: a systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. Lancet Infect Dis [Internet]. 2019 Sep 12 [cited 2019 Oct 11];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30414-1/abstract

19. O'Connor R, O'Doherty J, O'Regan A, Dunne C. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. Ir J Med Sci. 2018;187(4):969–86.

20. Kumari Indira KS, Chandy SJ, Jeyaseelan L, Kumar R, Suresh S. Antimicrobial prescription patterns for common acute infections in some rural & urban health facilities of India. Indian J Med Res. 2008;128(2):165–71.

21. Chandy SJ, Mathai E, Thomas K, Faruqui AA, Holloway K, Lundborg CS. Antibiotic use and resistance: perceptions and ethical challenges among doctors, pharmacists and the public in Vellore, South India. Indian J Med Ethics. 2013 Jan;(1).