



# WHITE PAPER ON RAPID DIAGNOSTIC TECHNOLOGIES TO TACKLE ANTIMICROBIAL RESISTANCE



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# EXECUTIVE SUMMARY

The excessive and inappropriate use of antibiotics and poor infection control practices have progressively turned antimicrobial resistance (AMR) into a massive threat for humankind. The misuse of antibiotics is eroding their efficacy and highly resistant bacteria - especially those resistant to lastline antibiotics - are rapidly emerging and spreading across the globe. At the same time, the pipeline of new antibiotics is almost dry. If the current trend is not altered, 300 million people worldwide are expected to prematurely die because of drug resistance over the next 35 years. There is the need for a coherent, comprehensive and integrated approach at all levels of government, involving different actors and sectors, i.e. human and veterinary medicine, agriculture, finance, environment and consumers.

This Policy White Paper aims to be an informative tool for policy makers and healthcare stakeholders to understand and raise awareness on the potential of rapid diagnostic innovations to support the global fight against antimicrobial resistance. Innovative, well-designed and well-adapted to patients' needs, rapid diagnostic tools can limit unnecessary use of antimicrobials by eliminating inappropriate prescriptions, tailoring treatment for bacterial infections, preventing the reproduction of infections and curbing the spread of infectious outbreaks.



*The excessive and inappropriate use of antibiotics and poor infection control practices have progressively turned antimicrobial resistance (AMR) into a massive threat for humankind*

Antimicrobial resistance - defined as the ability of a microorganism to resist the action of one or more antimicrobial agents - is a public health emergency. Resistant bacteria know no borders. Once a person is infected, antibiotic-resistant bacteria spread to others and a high antibiotic consumption in a population (hospital setting or community) strongly favours such a spread.

Rapid diagnostic technologies – as part of a multi-level and coherent AMR action plan - have the potential to limit antibiotic abuse. Implementing the use of rapid diagnostic technologies, inside and outside a hospital setting, will give a scientific tool to healthcare professionals in order to understand if a patient is affected by a bacterial or viral infection, analyse the kind of bacteria which causes infection, to screen if these bacteria are resistant or susceptible to treatment with antibiotics, and finally, to identify the best antibiotic to treat the infection.

What are the reasons limiting the uptake of rapid diagnostic technologies? A mix of social, economic and political elements have limited the advancement and uptake of rapid diagnostic technologies. Among others, there is a mismatch between the cost and benefits of rapid diagnostics in our healthcare systems.

Fostering the use of diagnostic technologies can help the whole society to protect better antibiotic conservation and slower development of resistance over time. Unfortunately, diagnostic technologies are currently seen as a non-critical cost for healthcare system institutions in the short term.

Looking forward, rapid diagnostic technologies have the potential to dramatically reduce the misuse of antibiotics by creating a situation whereby antimicrobials are prescribed based on diagnosis, in conjunction with presentation and clinical experience. Therefore, we call upon the European Commission and ECDC to:

- 1 • PROMOTE THE USE OF RAPID DIAGNOSTIC TECHNOLOGIES IN SCREENING PROGRAMME GUIDELINES FOR DRUG-RESISTANT BACTERIA.
- 2 • SET UP A EUROPEAN MONITORING PROGRAMME CAPABLE OF TRACKING IMPLEMENTATION AND THE USE OF RAPID DIAGNOSTIC TOOLS AND OUTCOMES IN EUROPEAN HEALTHCARE SYSTEMS.
- 3 • CHAMPION IN THEIR AWARENESS-RAISING CAMPAIGNS THE CRITICAL ROLE OF THE USE OF RAPID DIAGNOSTIC TECHNOLOGIES IN TACKLING ANTIMICROBIAL RESISTANCE.
- 4 • DEVELOP PUBLIC HEALTH MESSAGES TO PROMOTE A CHANGE IN PATIENT BEHAVIOUR TOWARDS ANTIBIOTIC MISUSE.
- 5 • ENCOURAGE THE UPTAKE OF RAPID DIAGNOSTICS IN PREVENTING ANTIMICROBIAL RESISTANCE BY CREATING A RAPID DIAGNOSTIC MARKET STIMULUS IN EUROPE, FUNDING TARGETED RESEARCH FOR INNOVATIVE RAPID TECHNOLOGIES.
- 6 • PROMOTE ALTERNATIVE REIMBURSEMENT SYSTEMS TO FACILITATE THE UPTAKE OF INNOVATIVE TECHNOLOGIES IN NATIONAL HEALTHCARE SYSTEMS.
- 7 • IMPLEMENT ONE HORIZON SCANNING TOOLS TO FACILITATE THE DEVELOPMENT OF CLINICAL EVIDENCE FOR RAPID DIAGNOSTICS.
- 8 • TAKE THE LEAD IN ADVOCATING EVIDENCE-BASED BEST PRACTICE MODELS FOR RAPID DIAGNOSTIC TOOLS.

# INTRODUCTION

## WHY A POLICY WHITE PAPER?

The introduction of the first antibiotic in the 1940s marks a true turning point in human history. For the first time, deadly infectious diseases, such as pneumonia and bloodstream infections became manageable, health problems and new horizons for modern medicine were defined. The marketing of other antibiotics soon followed and, as a result of their initial success, bacterial infections were considered to be permanently defeated. However, the misuse of antibiotics worldwide is reducing their efficacy. At the same time, the pipeline of new antibiotics is almost dry. Nowadays, patients are facing a new health threat in which no working treatments are available for their disease. Due to

the complexity of the problem, its cross-border dimension and the high economic burden, the impact of antimicrobial resistance has become a global public health concern that affects the whole society and requires urgent and coordinated intersectoral action<sup>1</sup>.

Antimicrobial resistance will affect everybody regardless of where they live, their health, economic circumstances, lifestyle or behaviour. It will affect sectors beyond human health, such as animal health, agriculture, food security and economic development<sup>2</sup>.

At the sixty-eight World Health Assembly held in May 2015, the World Health Assembly endorsed a global action plan to tackle antimicrobial resistance including the following strategic objectives aimed: (1) to improve awareness and understanding of antimicrobial resistance through effective communication, education and training; (2) to strengthen knowledge through surveillance and research; (3) to reduce the incidence of infection through effective sanitations, hygiene and infection prevention measures; (4) to optimize

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1 Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance – June 2016

2 <http://www.who.int/antimicrobial-resistance/global-action-plan/en/>

the use of antimicrobial medicines in human and animal health; and (5) to develop the economic case for sustainable investment that takes account of the needs of all countries and increase investment in new medicines, diagnostic tools, vaccines and other interventions<sup>3</sup>.

Diagnostic technologies can limit the unnecessary use of antimicrobials by eliminating inappropriate prescriptions for infections which are caused by viruses – for which an antibiotic can do nothing.

As stated in the Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance of June 2016, *a coherent, comprehensive and integrated approach at global, regional and national levels, in a “One Health” approach and beyond is needed, involving different actors and sectors such as human and veterinary medicine, agriculture, finance, environment and consumers.*<sup>4</sup> Despite the fact that rapid diagnostic technologies represent a critical tool to tackle antimicrobial resistance, their uptake and implementation in national healthcare systems remain low. Therefore, this policy White Paper aims to encourage a new approach to the use of diagnostic technologies through several policy interventions.

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# THE PUBLIC HEALTH ISSUE OF ANTIMICROBIAL RESISTANCE

## DEFINITION OF ANTIMICROBIAL RESISTANCE

Antimicrobials, such as antibiotics, are substances used to kill micro-organisms or to stop them from growing and multiplying, and they are commonly used in both human and veterinary medicine to treat a wide variety of infectious diseases<sup>5</sup>. Antimicrobial resistance is the ability of a microorganism to resist the action of one or more antimicrobial agents<sup>6</sup>.

While some bacteria are naturally resistant to certain antibiotics (intrinsic or inherent resistance), others, normally susceptible to antibiotics, become resistant as a result of genetic changes (acquired resistance). Such resistant bacteria survive in the presence of an antibiotic and continue to multiply causing prolonged illness, disability, and death<sup>7</sup>.

Additionally, within the body of a human being, the genes coding for antibiotic resistance in one species of bacteria can easily spread to other bacterial species through an exchange of genetic material. In the continuous fight for “ecological space”, all resistant bacteria are selected as the antibiotic kills the still-susceptible bacteria around them.

## ANTIMICROBIAL RESISTANCE AS A GLOBAL THREAT

Infections caused by antibiotic-resistant bacteria may require more care as well as alternative and more expensive antibiotics, which also may have more severe side effects. Treatment of antibiotic-resistant bacteria may also require intravenous antibiotics administered in hospitals instead of oral antibiotics that could be taken by patients at home. Once a person is infected, antibiotic-resistant bacteria can spread to another person and a high antibiotic consumption in a population (hospital or community) strongly favours such a spread<sup>8</sup>.

5 EFSA – AMR Topic <https://www.efsa.europa.eu/en/topics/topic/antimicrobial-resistance>

6 ECDC Report 2015, *Antimicrobial resistance surveillance in Europe* <http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf>

7 Infections such as urinary tract infection, pneumonia, skin infection, diarrhoea, bloodstream infection - See more at <http://ecdc.europa.eu/en/eaad/antibiotics-get-informed/factsheets/Pages/general-public.aspx>

8 ECDC – Factsheets for professionals - [http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/factsheet-for-health-professionals/Pages/factsheet\\_experts.aspx](http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/factsheet-for-health-professionals/Pages/factsheet_experts.aspx)

The latest data published by ECDC shows the emergence and rapid global spread of highly resistant bacteria, especially those resistant to last-line antibiotics. Carbapenems and colistin are considered 'last-line' antibiotics because they are the only antibiotics that still work when treating infections with bacteria that are resistant to all other antibiotics. Without antibiotics, we would return to the "pre-antibiotic era", when organ transplants, chemotherapy, intensive care and other medical procedures would no longer be possible. Bacterial diseases would spread and could no longer be treated, causing death. In the EU, infections resulting from these select, multidrug-resistant bacteria lead to extra healthcare costs and productivity losses of at least €1.5 billion each year. If the current trend is not altered, 300 million people worldwide are expected to die prematurely because of drug resistance over the next 35 years.

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The spread of these highly resistant bacteria is at very different stages in European countries, and an alarming increase of carbapenemase-producing Enterobacteriaceae (CPE) has been reported from several EU Member States. Since there are only a few remaining treatment options for patients infected by CPE, this highly resistant bacteria represents a serious threat to healthcare delivery and patient safety. It also results in higher healthcare costs, prolonged hospital stays, treatment failures and sometimes death. Specific infection control measures combined with a prudent use of antibiotics, are key to controlling the spread of CPE in European hospitals. Failing this, Europe may rapidly face hospital outbreaks of extensively drug-resistant (XDR), or even pandrug-resistant (PDR), Enterobacteriaceae<sup>9</sup>.

## ANTIBIOTIC CONSUMPTION IN EUROPE

Abuse of antibiotics is one of the most significant drivers for multidrug-resistant bacteria. Patients receiving antibiotics are more likely to be colonised with multidrug-resistant bacteria and are thus at greater risk of developing subsequent infections with these bacteria than patients who do not receive antibiotics.

Antibiotic consumption widely varies between EU/EEA countries. In the countries with the highest consumption, people consume 3.4 times more antibiotics

<sup>9</sup> ECDC - Update on the spread of carbapenemase-producing Enterobacteriaceae in Europe - Summary of the May 2015 expert assessment

compared to countries with the lowest consumption. In the hospital sector, consumption of antibiotics for systemic use keeps increasing as well as the trends of their consumption in the community<sup>10</sup>.

Additionally, a big concern lies in the increased consumption of carbapenems, a last-line group of antibiotics in six EU countries<sup>11</sup>. Carbapenems and polymyxins are antibiotic groups used for treating serious infections caused by multidrug-resistant gram-negative bacteria. In addition, penicillins combined with beta-lactamase inhibitors (e.g. piperacillin/tazobactam) represents another group of antibiotics to treat infections caused by extended-spectrum-beta-lactamase (ESBL) producing gram-negative bacteria.

“ Abuse of antibiotics is one of the most significant drivers for multidrug-resistant bacteria

Carbapenems are a last-line group of antibiotics and are mainly used in hospitals for the treatment of patients with confirmed or suspected infections involving a multidrug-resistant bacterium. Use of a carbapenem antibiotic is a risk-factor for subsequent infection with a carbapenem-resistant bacterium such as carbapenem-resistant Enterobacteriaceae (CRE, often through production of a carbapenemase enzyme), carbapenem-resistant *Acinetobacter baumannii* or carbapenem-resistant *Pseudomonas aeruginosa*. Carbapenem-resistant bacteria are highly drug-resistant and only a few antibiotic groups such as polymyxins are available for the treatment of patients infected with such bacteria.

In 2015, a joint report from ECDC, the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) showed a strong association between carbapenem consumption and the percentage of carbapenem-resistant invasive *Klebsiella pneumoniae*. In 2015, the consumption of carbapenems was 0.05 DDD per 1 000 inhabitants and per day. Assuming that the average duration of treatment is 10 days, this corresponds to more than one million carbapenem prescriptions issued in the EU/EEA each year.

10 ECDC - Summary of the latest data on antibiotic consumption in the European Union, ESAC-Net surveillance data - November 2016, <http://ecdc.europa.eu/en/eaad/antibiotics-get-informed/antibiotics-resistance-consumption/Documents/antibiotics-ESAC-Net%20Summary%202016.pdf>

11 [http://ecdc.europa.eu/en/eaad/antibiotics-news/\\_layouts/forms/News\\_DispForm.aspx?ID=28&List=f08f5a04-7f92-41cf-b4ef-d54289bc1a88&Source=http%3A%2F%2Fecdc%2Eeuropa%2Eeu%2Fen%2Fead%2Fantibiotics%2Dnews%2FPages%2Fnews%2Easpx#sthash.ASIfwOt3.dpuf](http://ecdc.europa.eu/en/eaad/antibiotics-news/_layouts/forms/News_DispForm.aspx?ID=28&List=f08f5a04-7f92-41cf-b4ef-d54289bc1a88&Source=http%3A%2F%2Fecdc%2Eeuropa%2Eeu%2Fen%2Fead%2Fantibiotics%2Dnews%2FPages%2Fnews%2Easpx#sthash.ASIfwOt3.dpuf)

# TACKLING AMR THROUGH RAPID DIAGNOSTIC TECHNOLOGIES

Given the rapid EU-wide spread of antimicrobial resistance and the limited pipeline of new antimicrobials, cost-effective interventions able to protect public health and contain healthcare costs are urgently needed. Rapid diagnostic technologies play a major role in the clinical care of patients with infectious diseases, by including detection and discovery of new pathogens, determining appropriate therapy, monitoring response to therapy and assessing prognosis and disease surveillance. In a broad sense, they cover accurate, simple to use, low cost, easy to interpret technologies able to provide testing results stable under extreme conditions, with little or no processing in a very short period of time (1-2 hours). These innovative technologies include both “point of care” (for doctor) and “walk away” tests (home tests) which are able to give a fast response to the four questions:

- Is the patient affected by a bacterial or viral infection?
- What kind of bacteria is causing the infection?
- Are the bacteria causing the infection resistant or susceptible?
- What is the best antibiotic to fight against the infection?

It is now possible with rapid diagnostics testing to determine the specific aetiology of a patient’s infectious disease in the hospital, clinic, office, remote village, or even at home. These technologies identify individual pathogens in a wide variety of specimen-types including blood, urine, tissue, mucosal swabs, cerebrospinal fluid, respiratory secretions, and stool samples. Innovative automation would help to report more accurate results, more quickly. For instance Point of Care (POC) testing have demonstrated that it is possible for sample collection and testing to be done in remote settings, away from the standard hospital and laboratory healthcare settings. If the tests are simple enough, collection and testing can be conducted by minimally trained personnel without extensive technical skills, or even at home by the patient. POC testing may also be of value in the determination of whether a higher level of care (e.g., outpatient to inpatient) is indicated. Rapid diagnostic technology has the potential to create a situation where antimicrobials are prescribed on the basis of a diagnosis, not simply based on presentation and clinical experience. It brings several advantages for hospitals, patients and healthcare systems by:

## REDUCING UNNECESSARY PRESCRIPTION

The vast majority of antibiotic prescriptions are made outside the hospital setting, by doctors. When doctors decide whether to prescribe an antibiotic, they usually use the so-called 'empirical' diagnosis: they will use their greatest expertise, intuition and professional judgement to prescribe the best treatment to alleviate patients' illness. In our healthcare systems, decisions to prescribe antibiotics are rarely based on confirmed diagnosis. Effective and rapid diagnostic tools are needed for guiding the optimal use of antibiotics in human and animal medicine, and such tools should be easily integrated into clinical, pharmaceutical and veterinary practices. Evidence-based prescribing and dispensing should be the standard of care<sup>12</sup>.

A study conducted in the United States - looking at adult patients visiting the doctor to treat respiratory problems - found that more than two-thirds of courses of antibiotics were likely to have been inappropriately prescribed for conditions that were not infections at all, or infections caused by viruses – for which an antibiotic would do nothing. That amounts to 27 million courses of antibiotics wasted a year in just one set of indications in the United States alone<sup>13</sup>.

Implementing rapid diagnostic technologies, particularly at the point of care, would assist clinicians in determining whether a patient requires antimicrobials without delaying the start of treatment. Being able to differentiate between bacterial diseases and those caused by other pathogens at the point of care would be a significant advance in clinical medicine and work well within the scope of current available technologies. Aside from providing patients with a clear diagnosis with unprecedented speed, this would prevent over-prescription of antimicrobials and reduce the selective pressures that drive up resistance against these vital drugs<sup>14</sup>.

## TAILORING TREATMENT FOR BACTERIAL INFECTIONS

An acutely ill patient cannot wait for days to get the right treatment. Empirical decision-making will often result in the use of broad-spectrum antibiotics and this is also a major driver of the AMR problem. Rapid diagnostic tools for bacterial infections, which allow doctors to identify the nature of an infection in hours, have the potential to transform the diagnosis and treatment process

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12 WHO Global Action Plan on AMR – 2015 [http://www.wpro.who.int/entity/drug\\_resistance/resources/global\\_action\\_plan\\_eng.pdf](http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf)

13 The review on antimicrobial resistance chaired by O'Neill – Rapid diagnostics : Stopping unnecessary use of antibiotics – October 2016

14 All-Party Parliamentary Group for Patient Safety – Time to Act: Inquiry into Hospital-Acquired Infections and Antimicrobial Resistance p.20

from an empirical to a precise method. They can help doctors identify the strain of bacterial infections and the antibiotics to which it is resistant or susceptible, allowing more precise prescribing of narrow spectrum antibiotics. This in turn reduces our dependence on broad-spectrum products, slowing the development of resistance and improving the treatment that patients receive<sup>15</sup>. Doctors would be able to prescribe antibiotics in response to the specific indications of a given infection by discerning between different types of bacteria, and even to determine which resistances and susceptibilities a bacterial sample has. The key is to prescribe the right drug to the right patient as soon as possible, by rapidly and reliably identifying the bacteria involved.

## IMPROVING INFECTION CONTROL AND LIMITING THE SPREAD

Earlier diagnosis of infection and colonization would ensure that patients receive effective treatment more rapidly and can be isolated if there is a clear danger of the infection spreading to other patients. This would:

- **Prevent infection “outbreaks”.** An infected patient can be rapidly isolated and infection control measures activated<sup>16</sup>.
- **Avoid wasting resources in unnecessary isolation.** Patients who might otherwise be identified empirically as being at high risk of carrying drug resistant infections - and thus subjected to precautionary isolation pending confirmatory diagnosis – could be quickly screened using a rapid diagnostic, so that unnecessary (and costly) isolation and expensive infection control measures more promptly stepped down<sup>17</sup>.
- **Shorten patient stays and free up beds.** The use of rapid diagnostics and bacteriology laboratory automation is associated with lower rates of progressive infection, improved patient outcomes, decreased mortality and short durations of hospitalization<sup>18</sup>. As a result of implementing new diagnostic technologies, the treatment of patients can be streamlined, with treatment regimens starting faster and the potential to discharge patients sooner, freeing up much-needed hospital beds<sup>19</sup>.

15 The review on antimicrobial resistance chaired by O’Neill – Rapid diagnostics : Stopping unnecessary use of antibiotics – October 2016

16 The review on antimicrobial resistance chaired by O’Neill – Rapid diagnostics : Stopping unnecessary use of antibiotics – October 2016

17 Wassenberg M, Kluytmans J, Erdkamp S, et al. Costs and benefits of rapid screening of Methicillin-Resistant Staphylococcus Aureus carriage in intensive care units.

18 Caliendo et al. (2013) Better Tests, Better Care: Improved Diagnostics for Infectious Diseases. *Improved Infectious Diseases Diagnostics* 57(3) S139-S170 DOI: 10.1093/cid/cit578

19 Woo et al. (1997) Cost-effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients. *Journal of Clinical Microbiology* 35(6) p. 1579–1581

- **The Research Report: Cost-Effectiveness of Policies to Limit Antimicrobial Resistance in Dutch Healthcare Organisations**<sup>20</sup> has shown that the cost-savings of using rapid diagnostic technologies are larger than the initial investments, even after just one month of running the pilot programme.

Lower respiratory tract infection (LRTI) is one of the most common reasons to consult primary care, accounting for 17 million consultations in the EU annually<sup>21</sup>. Acute bronchitis accounts for 80% of these LRTIs<sup>22</sup>. Even though evidence suggests that acute bronchitis benefits little or not at all from antimicrobials, general practitioners (GP) prescribe them to 80% of the patients<sup>23</sup>. Limiting antimicrobial use in the treatment of LRTI is therefore a priority in the prevention of antimicrobial resistance.

Through the combination of both diagnostic tools – which are able to differentiate between acute bronchitis and pneumonia – and communication skills training for general practitioners to manage patient expectations, there was a significant reduction in the number of antimicrobial prescriptions. The antimicrobial prescribing rate was 68% in the control group (usual care), compared to 23% for patients in the combined intervention group. The researchers claimed that antimicrobial prescriptions between 150,000 and 240,000 could be saved annually, assuming nationwide implementation in the Netherlands. As the use of antibacterial is relatively low in the Netherlands, cost savings could be higher in most other EU countries. Importantly, despite the substantial reduction in antimicrobial prescribing, patients’ recovery and satisfaction were similar in both study groups. The economic analysis showed that the cost-savings are larger

than the initial investments, even after just one month of running the programme. Patients in the intervention group required less additional diagnostics (e.g., chest X-ray and spirometry), used less antimicrobials, and visited the GP less often than control group patients (accounting for a cost-saving of €22). Given the lower intervention costs (€15 per patient) and the fact that the test can be performed in just three minutes, the feasibility and financial investments cannot act as deterrents for further implementation, when savings can be quantified at €7 per treated patient.



*The cost-savings are larger than the initial investments, even after just one month of running the programme.*

20 Celsus Academie voor Betaalbare zorg. Cost-effectiveness of policies to limit antimicrobial resistance in dutch healthcare organisations. Research report. January 2016 p 21

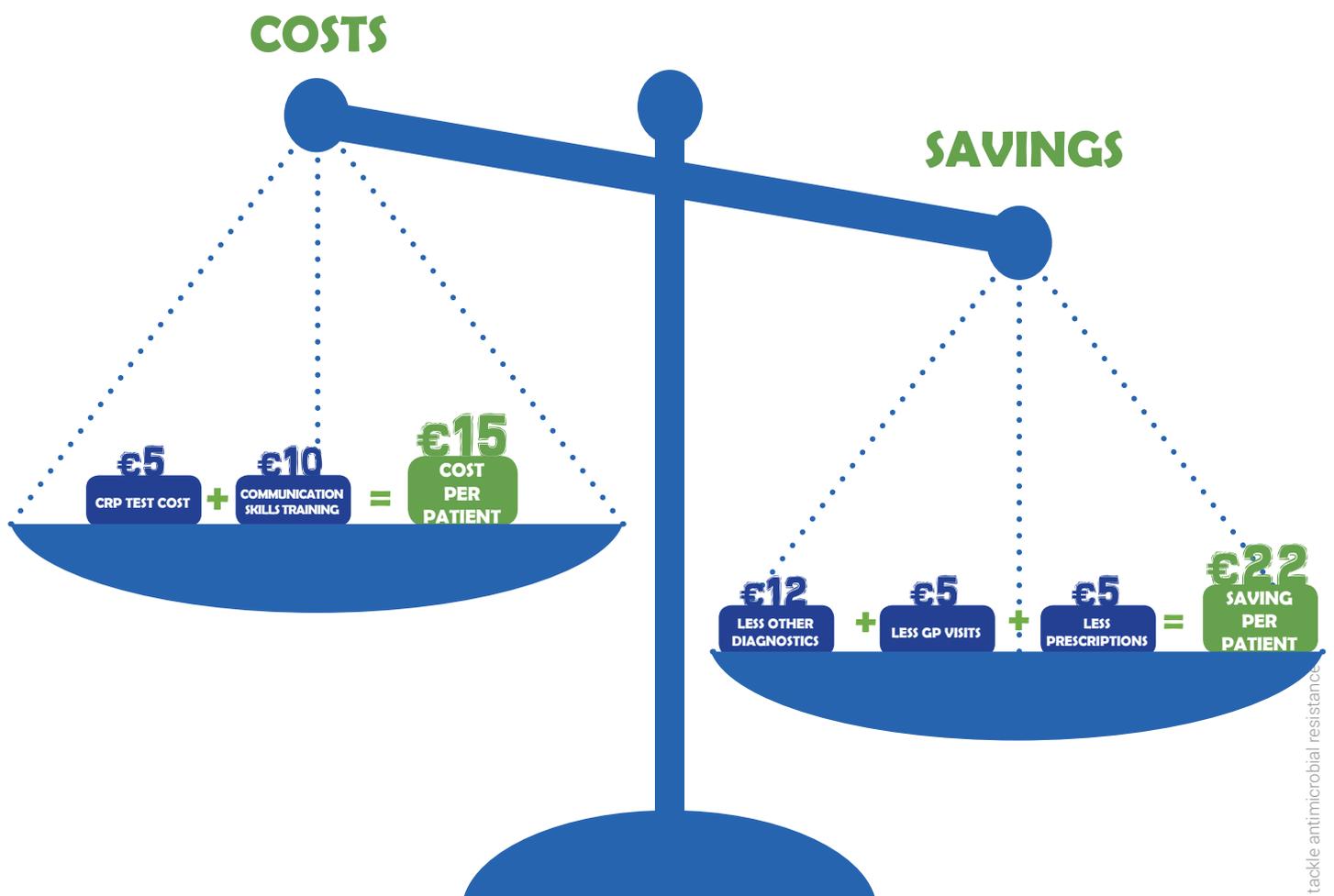
21 Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Ortqvist A, et al. Guidelines for the management of adult lower respiratory tract infections. The European Respiratory Journal. 2005;26(6):1138-1180.

22 Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991-1999. Annals of Internal Medicine. 2003;138(7):525-533.

23 Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. Journal of the American Medical Association. 1997;278(11):901-904.

The one-month follow-up period was too short to capture all potential health and economic benefits. Nevertheless, the short-term effects found on antimicrobial prescribing are considerable and may merit further EU-wide implementation, while taking into account variations within countries and healthcare systems<sup>24</sup>.

The effectiveness of fostering the use of Point of Care Test was studied in the Netherlands and four additional EU countries (United Kingdom, Poland, Spain, and Belgium). GPs across nations were trained online to interpret the tests adequately and to communicate these effectively. Although online training can be assumed to be less effective than face-to-face training, the study proved transferability between very different primary care settings<sup>25</sup>.



24 Celsus Academie voor Betaalbare zorg. Cost-effectiveness of policies to limit antimicrobial resistance in dutch healthcare organisations. Research report. January 2016 p 21

25 *Ibid.*

# LIMITATIONS OF THE IMPLEMENTATION OF RAPID DIAGNOSTIC TECHNOLOGIES

Several rapid diagnostic technologies currently available in the market are able to reduce the level of unnecessary antibiotic prescriptions. Despite their value, their development and uptake have been slow due to a complex mix of social, economic and political reasons:

## LOW AWARENESS

The clearest driving factor lies around the low awareness of the value that new diagnostic technologies can bring to both healthcare professionals and patients. Healthcare workers have a vital role in preserving the power of antimicrobial medicines. Inappropriate prescribing and dispensing can lead to their misuse and overuse if medical staff lack up-to-date information, cannot identify the type of infection, yield to patient pressure to prescribe antibiotics, or benefit financially from supplying the medicines. Patients should be aware that most colds and flu are caused by viruses against which antibiotics are not effective and how rapid tests are used and their role in determining whether or not antibiotics should be prescribed<sup>26</sup>.

## MISMATCH BETWEEN THE COST AND BENEFITS OF RAPID DIAGNOSTICS

This is the most important limitation for the uptake of rapid diagnostics. The use of diagnostics represents a classic example of “benefit for the society”. These benefits encompass superior antibiotic conservation and a slower development of resistance. Despite these values, diagnostic technologies are seen as a non-critical cost for healthcare institutions in the short term, and there is a general lack of investment and economic incentives to use innovation to tackle antimicrobial resistance. Because antibiotics are generally cheap and rapid diagnostic tools are considered to be a short-term expense, few doctors are incentivised to use them. In our healthcare systems, treating a “potential” bacterial infection with a broad-spectrum antibiotic is easier and cheaper than using a diagnostic technology which could help to save costs, reduce waste across healthcare levels, and preserve the usefulness of antibiotics for everyone over the long term.

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26 The review on antimicrobial resistance chaired by O'Neill – Rapid diagnostics: Stopping unnecessary use of antibiotics – October 2016

Budget silos are reported to be a major challenge for managers. Firstly, when a new clinical service or treatment is introduced, invariably the role that the laboratory might play in the innovation is not considered. Secondly - and by far the more challenging - is the fact that the benefit of using any test that has been demonstrated to be clinically effective does not accrue to the laboratory where the cost of the test was incurred. This may have important consequences for the introduction of tests related to antimicrobial resistance, as clinicians and clinical managers rarely understand the financial consequences of using diagnostic tests; e.g. in primary care the diagnostic test budget is often part of a block contract with secondary care<sup>27</sup>. Bringing technologies into care pathways will require an integrated approach that incentivises the appropriate uptake of innovative technology among them all<sup>28</sup>.

*Treating a “potential” bacterial infection with a broad-spectrum antibiotic is easier and cheaper than using a diagnostic technology which could help save costs and reduce waste across healthcare levels, and help preserve the usefulness of antibiotics for everyone over the long-term.*

Furthermore, existing reimbursement structures and healthcare management rules often disincentivise the uptake of new innovative technology which would minimize the risk of healthcare associated infections, reduce antibiotic misuse and slow the growth of antibiotic resistance. Diagnosis Related Groups (DRG) are a widely-used mechanism for reimbursement of public hospitals across Europe. As opposed to a fee-for-service reimbursement model that is based on volume of inputs (in this case, testing), under a DRG system hospitals are paid on the basis of the number and type of DRGs that they produce<sup>29</sup>. A number of negative incentives have been associated with the use of DRGs such as premature discharge of patients, “cream-skimming” of the more straightforward patient cases where possible and under-treatment of diagnostic tests in order to save on costs. The cost-reduction incentives associated with the use of DRGs as a reimbursement model may have particular implications, not just for the use of existing diagnostics but also for innovation and the uptake of new technology<sup>30</sup>.

27 Annette Plüddemann, Igho Onakpoya, Sian Harrison, Bethany Shinkins, Alice Tompson, Ruth Davis, Christopher P. Price and Carl Heneghan, Position Paper on Anti-Microbial Resistance Diagnostics, Oxford University, June 2015.

28 All-Party Parliamentary Group for Patient Safety – Time to Act: Inquiry into Hospital-Acquired Infections and Antimicrobial Resistance p.20

29 Payment levels in most cases tend to be based on average costs of a given group of providers, although they can be designed based on the costs of a group of the most efficient providers, or some other subset, such as grouped by facility size, depending on both the aims of the DRG reimbursement structure and ability to manage complexity in the design and management of the system.

30 Morel C, McClure L, Edwards S, Goodfellow V, Sandberg D, Mossialos E, Ensuring Innovation in Diagnostics for Bacterial Infection : Implications for Policy, World Health Organization European Observatory on Health Systems and Policies, 2015, chapter 10

## LIMITED CLINICAL EVIDENCE

While the amount of robust evidence supporting the use of rapid diagnostics to guide antibiotic treatment is limited, there are reasons to assume that much could be gained from encouraging the development of well-designed, fast and well-adapted diagnostic technologies at a patient's bed-side<sup>31</sup>.

“ *Comparing the effectiveness of diagnostic devices will require new models that incorporate an in-depth knowledge of how these diagnoses will be used to inform treatment decisions.*

The entry and the uptake of novel diagnostic technologies is linked to their ability to demonstrate their clinical value and their cost benefit. Unfortunately, diagnostic devices pose unique challenges to economic assessment, in particular to the formulation of informative cost–effectiveness models. Comparing the effectiveness of diagnostic devices will require new models that incorporate an in-depth knowledge of how these diagnoses will be used to take treatment decisions. Appropriate analysis must include a sufficiently long timeline to demonstrate the impact of more appropriate prescribing of antibiotics, while also incorporating both the societal benefits and the cost offsets accrued in that time<sup>32</sup>. Moreover, by the time this analysis is disseminated, the evidence base used for this will have evolved.

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31 The review on antimicrobial resistance chaired by O'Neill – Rapid diagnostics : Stopping unnecessary use of antibiotics – October 2016

32 Morel C, McClure L, Edwards S, Goodfellow V, Sandberg D, Mossialos E, Ensuring Innovation in Diagnostics for Bacterial Infection : Implications for Policy, World Health Organization European Observatory on Health Systems and Policies, 2015, chapter 10

# HOW TO ENCOURAGE A POLICY CHANGE ?

Rapid diagnostic technologies have the potential to dramatically reduce the misuse of antibiotics by creating a situation where antimicrobials are prescribed based on diagnosis, not simply on presentation and clinical experience. Therefore, we welcome the European Commission's intention to emphasise the critical role of research, development and innovation in the upcoming Action Plan and we encourage a new approach to the use of diagnostic technologies through several policy interventions:

## 1 WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO: PROMOTE THE USE OF RAPID DIAGNOSTIC TECHNOLOGIES IN SCREENING PROGRAMME GUIDELINES FOR DRUG RESISTANT BACTERIA

New techniques allowing rapid screening for bacterial infections should be implemented in healthcare systems to reduce the logistic and financial burdens associated with pre-emptive isolation and improve the quality of care for patients<sup>33</sup>. Active screening of 'at-risk' patients upon admission to a hospital is an effective method to detect whether patients are carrying highly resistant bacteria. This is crucial for the prevention of spread in hospitals, because when a patient is found to be a carrier of highly resistant bacteria, infection prevention measures can be immediately implemented. This can only be done in conjunction with timely reporting of positive results by the microbiological laboratory. This measure is especially relevant to EU Member States because there is an increased mobility of patients between countries for the receipt of healthcare<sup>34</sup>.

## 2 WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO: SET UP A EUROPEAN MONITORING PROGRAMME ABLE TO TRACK THE IMPLEMENTATION AND USE OF RAPID DIAGNOSTIC TOOLS AND OUTCOMES IN EUROPEAN HEALTHCARE SYSTEMS.

Current surveillance and monitoring programmes covering healthcare-associated infections' spread and antibiotic consumption have provided a clearer picture of the scale of the problem and of the challenges faced in tackling

<sup>33</sup> Celsus Academie voor Betaalbare zorg. Cost-effectiveness of policies to limit antimicrobial resistance in dutch healthcare organisations. Research report. January 2016

<sup>34</sup> ECDC – Policy Briefing: Last-line antibiotics are failing: options to address this urgent threat to patients and healthcare systems – November 2016

antimicrobial resistance. However, in order to encourage a transparent uptake on rapid diagnostic technologies in terms of cost, patient safety and efficiency, monitoring programmes should be in place to track the implementation and use of diagnostic tools in European healthcare systems.

3

### WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO:

- CHAMPION IN THEIR AWARENESS-RAISING CAMPAIGNS THE CRITICAL ROLE OF THE USE OF RAPID DIAGNOSTICS TECHNOLOGIES IN TACKLING AMR.
- DEVELOP PUBLIC HEALTH MESSAGES TO PROMOTE A CHANGE IN PATIENT BEHAVIOUR TOWARDS ANTIBIOTIC MISUSE.

The latest Eurobarometer shows that there is an issue of awareness when effectively tackling antimicrobial resistance. For instance, 57% of citizens are unaware that antibiotics are ineffective against viruses. This has obvious consequences for the use of antibiotics<sup>35</sup>. Despite the fact that antibiotics cannot treat the flu, a large share of respondents say it was what last prompted them to take antibiotics. The clearest driving factors for antibiotic misuse lies in the education of the public and staff, the training of medical professionals and structural changes to the healthcare system - to ensure that doctors are supported in withholding antimicrobials. It is critical to make antimicrobial resistance a core component of professional education, training, certification, continuing education and development in the human health and veterinary sectors and agricultural practices, to ensure the proper understanding and awareness of professionals. Diagnostic technologies have the potential to supplement and replace empirical prescribing, creating a situation in which antimicrobials are prescribed based on diagnosis and not on simply presentation<sup>36</sup>.

4

### WE CALL UPON THE EUROPEAN COMMISSION TO:

- ENCOURAGE THE UPTAKE OF RAPID DIAGNOSTICS IN PREVENTING AMR BY CREATING A RAPID DIAGNOSTIC MARKET STIMULUS IN EUROPE, FUNDING TARGETED RESEARCH FOR INNOVATIVE RAPID TECHNOLOGIES.
- PROMOTE ALTERNATIVE REIMBURSEMENT SYSTEMS FOR RAPID DIAGNOSTICS IN EU MEMBER STATES.

Improving diagnosis and treatment of bacterial infections should be considered a public good - to justify public intervention in this sector. There is also an economic rationale for public support for rapid diagnostics and innovative

35 Eurobarometer results on Antimicrobial Resistance awareness – April 2016

36 All- Party Parliamentary Group for Patient Safety – Time to Act: Inquiry into Hospital-Acquired Infections and Antimicrobial Resistance p.20

automation development and uptake. The cost–efficiency associated with the improved targeting of antibiotic treatment is changing. While most antibiotic therapies are currently available cheaply, in generic form this is likely to change. Higher-priced third-line antibiotics and new antibiotics (that we hope will come out of the pipeline in the coming years) will highlight the need to improve and speed up the identification of bacteria and rule out differential diagnoses to use such antibiotics only in specific cases<sup>37</sup>. It is critical to support model which would allow for spread and affordable use of rapid diagnostic technologies. A large number of potential improvements and multilevel coherent strategies need to be adopted to overcome the current mismatch between the costs and benefits of using innovative technologies:

### **Pulling incentives**

Creating a diagnostic market “stimulus” has the potential to incentivise the purchase and uptake of rapid diagnostics technology. Companies would sign up to the funding system and sell their products under certain conditions, such as at affordable prices. Every time a product was sold, a payment would be made from the assigned funding system, until it would be empty<sup>38</sup>.

This payment/refunding system would guarantee that firms would still require that their product is adopted and face competition from other products, to ensure that firms would be incentivised to devote resources to innovation. The greatest advantage of this system is that it allows multiple companies to come up with useful products, and lets health professionals decide which is the most effective. Companies then get rewarded based on the number of products they sell. This means that if there are two diagnostic devices and one is quicker or easier to use, whilst the other is more accurate, doctors can decide which one makes more sense for their specific circumstances and the needs of their patients, and the companies will be rewarded as they normally would in a market, with the exception that they gain an additional subsidy<sup>39</sup> to encourage the uptake.

### **Pushing incentives**

Given the urgent public health interests in tackling antimicrobial resistance, subsidies for targeted research and development should be available to those looking to create new rapid diagnostics. Push incentives should focus on removing barriers for the developer to invest in research and innovation as well as to support research with a high risk of failure which often dissuade the private sector from investing.

37 Morel C, McClure L, Edwards S, Goodfellow V, Sandberg D, Mossialos E, Ensuring Innovation in Diagnostics for Bacterial Infection : Implications for Policy, World Health Organization European Observatory on Health Systems and Policies, 2015, chapter 12

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Grants are provided to co-finance research, development and demonstration projects, and funding is allocated on the basis of calls for proposals and a highly competitive peer review process. Almost any type of organization, including academia, SMEs, civil society and corporations can apply for funding. Encouraging public–private partnerships can leverage the different types of expertise among the partners. Given the novel techniques and technologies being used, no one organization has all the necessary capabilities. The academic partners offer clinical expertise, samples, laboratory capabilities and knowledge of innovative technologies. SMEs offer knowledge of innovative approaches and bring a flexible attitude, while larger companies offer expertise in clinical development, regulatory affairs, communication, samples and laboratory capabilities<sup>40</sup>.

### **Alternative reimbursement models for rapid diagnostic technologies**

It is possible to build in explicit mechanisms within a DRG system to capture the product's value and encourage the uptake of a particular drug or device that is seen as desirable on a system-wide basis. This can be done through the creation of new DRG codes that reflect the costs and utilization of new technology. In many European countries, the uptake of particularly innovative technology may be reimbursed outside of the DRG system (at least in some circumstances), in acknowledgement of the barriers to uptake which the DRG system may otherwise present.

New financial incentive structures intended to encourage hospitals to minimize healthcare associated infections could build serious momentum to bring new innovative rapid diagnostic devices to the market. Bringing these technologies into care pathways will require an integrated approach that incentivises the appropriate uptake of innovative technology among all<sup>41</sup>.

## **WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO:**

5

- **IMPLEMENT ONE-HORIZON SCANNING TOOL TO FACILITATE THE DEVELOPMENT OF CLINICAL EVIDENCE FOR RAPID DIAGNOSTICS.**
- **TAKE THE LEAD IN ADVOCATING EVIDENCE-BASED BEST-PRACTICE MODELS FOR RAPID DIAGNOSTIC TOOLS.**

In order for health systems to adopt new technologies, clinical value and cost benefits must be demonstrated. The best way to do this is through large controlled trials to prove clinical effectiveness and cost benefit studies to demonstrate economic value to regulators and healthcare providers. It would seem logical to have an ongoing horizon-scanning service solely dedicated to clinic trials on

40 Morel C, McClure L, Edwards S, Goodfellow V, Sandberg D, Mossialos E, Ensuring Innovation in Diagnostics for Bacterial Infection : Implications for Policy, World Health Organization European Observatory on Health Systems and Policies, 2015, chapter 12

41 Morel C, McClure L, Edwards S, Goodfellow V, Sandberg D, Mossialos E, Ensuring Innovation in Diagnostics for Bacterial Infection : Implications for Policy, World Health Organization European Observatory on Health Systems and Policies, 2015, chapter 12

antimicrobial resistance and emerging diagnostic technologies. The aims of a horizon-scanning would be to identify:

- New diagnostic technologies with the most potential in primary and secondary care and prioritise those with the greatest health impact;
- Rapid evidence reports;
- Field studies of new point-of-care tests<sup>42</sup>.

This horizon-scanning tool can hugely reduce the cost of testing a diagnostic. If diagnostic test becomes a common practice, there can be one standard process that new tests can be dropped into, rather than creating one for every test. This can include things like having a template contract and price for doing the trial, which will again reduce the trial time and cost to each trial. Finally, since it will be so much easier to set up test sites and have the diagnostics tested, patients could be more efficiently tested. Reducing the time and cost of trials should not only improve uptake, but will also hopefully improve the diagnostics itself. If reliable information is on both a product's accuracy and sensitivity is quickly fed back to diagnostic companies, they will be able to effortlessly tweak their products and re-test them under the current system<sup>43</sup>.

<b>CURRENT LIMITATIONS</b>	<b>CALL FOR ACTIONS</b>
<b>LOW AWARENESS</b>	<p><b>WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO: PROMOTE THE USE OF RAPID DIAGNOSTIC TECHNOLOGIES IN SCREENING PROGRAMME GUIDELINES FOR DRUG RESISTANT BACTERIA</b></p> <p><b>WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO: SET UP A EUROPEAN MONITORING PROGRAMME ABLE TO TRACK THE IMPLEMENTATION AND USE OF RAPID DIAGNOSTIC TOOLS AND OUTCOMES IN EUROPEAN HEALTHCARE SYSTEMS.</b></p> <p><b>WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO:</b></p> <ul style="list-style-type: none"> <li>• CHAMPION IN THEIR AWARENESS-RAISING CAMPAIGNS THE CRITICAL ROLE OF THE USE OF RAPID DIAGNOSTICS TECHNOLOGIES IN TACKLING AMR.</li> <li>• DEVELOP PUBLIC HEALTH MESSAGES TO PROMOTE A CHANGE IN PATIENT BEHAVIOUR TOWARDS ANTIBIOTIC MISUSE.</li> </ul>
<b>MISMATCH BETWEEN THE COST AND BENEFITS OF RAPID DIAGNOSTICS</b>	<p><b>WE CALL UPON THE EUROPEAN COMMISSION TO:</b></p> <ul style="list-style-type: none"> <li>• ENCOURAGE THE UPTAKE OF RAPID DIAGNOSTICS IN PREVENTING AMR BY CREATING A RAPID DIAGNOSTIC MARKET STIMULUS IN EUROPE, FUNDING TARGETED RESEARCH FOR INNOVATIVE RAPID TECHNOLOGIES.</li> <li>• PROMOTE ALTERNATIVE REIMBURSEMENT SYSTEMS FOR RAPID DIAGNOSTICS IN EU MEMBER STATES.</li> </ul>
<b>LIMITED CLINICAL EVIDENCE</b>	<p><b>WE CALL UPON THE EUROPEAN COMMISSION AND ECDC TO:</b></p> <ul style="list-style-type: none"> <li>• IMPLEMENT ONE-HORIZON SCANNING TOOL TO FACILITATE THE DEVELOPMENT OF CLINICAL EVIDENCE FOR RAPID DIAGNOSTICS.</li> <li>• TAKE THE LEAD IN ADVOCATING EVIDENCE-BASED BEST-PRACTICE MODELS FOR RAPID DIAGNOSTIC TOOLS.</li> </ul>

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## ABOUT HEALTH FIRST EUROPE

Health First Europe was established in 2004 as a non-profit, non-commercial alliance of patients, healthcare workers, academics, and healthcare experts and the medical technology industry.

We aim to ensure patient access to modern, innovative and reliable medical technology is regarded as a vital investment in the future of Europe.

We call for truly patient centred healthcare and believe that every European should benefit from the best medical treatments available.



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