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Review

Interdependence of diagnostics and epidemiology, a European perspective Position paper on the need for an intrinsic cooperation and data sharing

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ABSTRACT

For some well-known pathogens like influenza or RSV, diagnostic and epidemiological data is available and continuously complement each other. For most other pathogens however, data is not always available or severely delayed. Furthermore, clinical data is needed to assess the burden of disease, which will enhance awareness and help to gain knowledge on emerging pathogens. In this position paper, we discuss the interdependence of diagnostics and epidemiology from a European perspective. In 2004, the European Centre for Disease Prevention and Control (ECDC) was founded to coordinate European wide surveillance and control. At present however, the ECDC still relies on university hospitals, public health institutions and other diagnostic institutions. Close collaboration between all stakeholders across Europe is therefore complex, but necessary to optimize the system for the individual patient. From the diagnostic side, data on detected pathogens should be shared with relevant health institutions in real-time. From the public health side, collected information should be made accessible for diagnostic and clinical institutions in real-time. Subsequently, this information needs to be disseminated across relevant medical disciplines to reach its full potential.

1. Diagnostics as the source for clinical care and epidemiology

Every day, microbiological laboratories generate numerous diagnostic results. They provide crucial information regarding patient management (e.g. treatment, isolation measures), indicating that diagnostic laboratories have a strong connection with clinical care providers across all specialisms. This information also provides a continuous update on the prevalence of pathogens and the treatment options. It can be used to determine deviations and show trends, although often in a retrospective manner. For some well-known pathogens such as influenza or RSV, this information is more readily available, sometimes even in real-time and on publicly available websites [1]. For most pathogens however, this information is not available or delayed. For instance, the “Surveillance Atlas of Infectious Diseases” by the European Centre for Disease Control (ECDC) offers a tool to visualise the prevalence of various pathogens [2]. For measles, information is available on prevalence, number of deaths and even vaccine status within several months. For other pathogens (such as MRSA, MERS or hepatitis C), there is little to no data available on the prevalence over the recent years.

There are tools available which have the potential to be effective in tracking (emerging) pathogens. A recent paper by Edelstein et al. describes a set of principles to encourage the process of data sharing [3]. They discuss the importance of wider communication, good practice in terms of the quality of the data and its dissemination, from an epidemiologic perspective. Without communicating data, the true burden of disease may stay unknown and upsurges could be missed or reported late, when the information could be clinically not of any value anymore. While delays are sometimes inevitable, initiatives have shown that it is possible to publish the gathered data within a few weeks [4]. By combining diagnostic and clinical information in a more real-time manner, the severity of emerging threats (i.e. in outbreak settings) can be estimated in order to prepare and respond adequately. This should involve both local and national institutions.

2. Epidemiology as the source for clinical care and diagnostics

For clinical practice, it is challenging to continuously select the right sample, the right test, the right patient and the right time frame, particularly for emerging pathogens. These decisions rely on available diagnostic, clinical and epidemiological information to shape the case definition. Using this information to direct the most appropriate route

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for infection management, is the essence of diagnostic stewardship [5]. Routine diagnostic data could be gathered and shared in a more comprehensive and rapid way, resulting in more accurate and up-to-date epidemiologic data.

Importantly, dissemination of data between and within European countries is highly challenging due to financial and geographical variation, as well as differences in health policies. The ECDC has been established in 2005 to coordinate Europe-wide surveillance and control of communicable disease. However, several limitations regarding infectious disease surveillance have been reflected upon before, already in 2008 [6]. We share these concerns, adding that they are still relevant today. Without having centralized European reference laboratories, the ECDC relies on information provided by university hospitals and research institutions, which they also recognise in their long-term surveillance strategy 2014–2020 [7]. A recent example is the EV-D68 outbreak in 2014, reflecting a close collaboration within the European Society of Clinical Virology [8]. The informal but rapid type of collaboration and communication shown here, is particularly important when little is known about the prevalence, which also varies between countries. The low number of initial reported cases has led to an underestimation of the real burden of disease [9].

During outbreaks of persistent or well-known pathogens, like during the 2007 multi-country outbreak of *Salmonella typhimurium* DT104 in Denmark and the Netherlands, there were well established channels for international communication [10]. This ranged from local initiatives such as *Enter-net* and *Salm-gene* (databases comprised of lab results with epidemiological information and background levels), which were rapidly disseminated to all relevant parties [11] right through to formal communication such as the Early Warning and Response System (EWRS) of ECDC [12]. Networks across several clinical disciplines can take responsibility for the sharing of diagnostic and epidemiological information, although often based on individual initiatives.

Questions also frequently arise whether diagnostics should be performed for diseases without effective treatment options. In general, for respiratory diseases more attention is given to influenza and RSV, since both can be treated in an acute setting. However, the outcome of respiratory diagnostics is always informative, including results for pathogens that cannot be treated at this point in time, or results that are negative. Diagnostics are not only crucial for treatment, but also for clinical awareness, patient management, infection control, as well as epidemiological purposes e.g. to track trends and link specific clinical presentations to a specific pathogen, to make risk assessments. Furthermore, diagnostics could rule out pathogens, which helps to optimize therapy, for example ceasing antibiotic treatment if a viral pathogen is detected.

3. The current diagnostic network

Despite international efforts have been made to strengthen infectious disease surveillance in Europe for many decades, individual countries, as well as the responsible national and international institutions are still unable to optimally use and share microbiological data. The challenge is to organise a closer cooperation that invites stakeholders across clinical, diagnostic and (public health) epidemiology institutions to share information in a prospective and proactive manner. As long as there are no centralized European reference laboratories, local initiatives are important for diagnostic laboratories, to be beneficial for the individual patient. As with EV-D68, it takes effort to involve this large group of stakeholders. Nevertheless, rapid, translational communication and data sharing between patient care, diagnostic and public health institutions could be established. Many different networks exist within the healthcare system, and each stakeholder has its own perspective and responsibility (and interest), which is essential for determining patient outcome. Therefore, we have elaborated on the stakeholders and how data is communicated within these networks (Fig. 1). As mentioned before, there is a strong

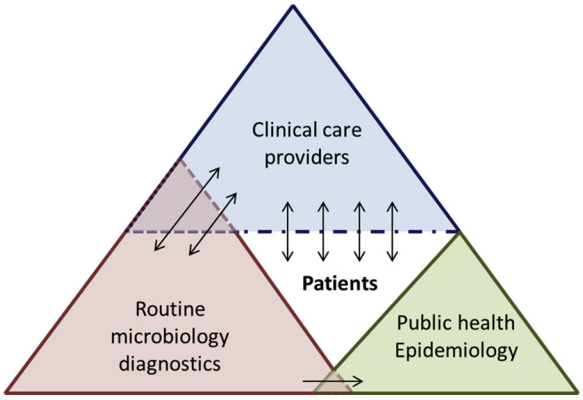

Fig. 1. Microbiology diagnostic network. Arrows representing the interactions between stakeholders including the direction. The more arrows the more interaction.

connection between diagnostic laboratories and clinical care providers, who are the direct link to the patients. The connection between diagnostic laboratories and public health institutions is present, but often only in one direction initially. Diagnostic information is used for epidemiological purposes, but in many cases this is not being used in real-time to directly assist patient care, particularly when regarding lesser known pathogens.

The patient remains the most important stakeholder. When a patient visits a clinical care provider, a rapid and accurate diagnosis is crucial for their recovery as well as for the impact on them and their family. Clinical care providers are their first and often only point of contact. Clinical laboratories are the link to the clinical care provider by developing and performing diagnostic tests: *Diagnostic Stewardship*. Results of routine diagnostics are used to guide treatment for the recovery of the patient: *Antimicrobial Stewardship*. In addition to this, diagnostics could also assist patient management to prevent further infections: *Infection Prevention Stewardship*. All together, they comprise the concept of *AID-stewardship*, as described before [5]. However, there is no real-time link to epidemiological data, specifically the feedback of epidemiological data into diagnostic practices in the case of an emerging pathogen. This should contain detailed knowledge on circulating pathogens, which allows health care providers to anticipate on the current situation by means of prevention strategies and diagnosis.

4. Perspectives based on current networks and initiatives

With this position paper, we envision a closer and stronger connection of information generated by clinical care providers (clinical data), clinical laboratories (diagnostic data) and public health institutes (epidemiological data). As shown in Fig. 1, the diagnostic parties are the link in this spectrum, and could therefore act as the designated stakeholder to take the lead and act proactively within this network. As clinical laboratories continuously generate diagnostic data, they could assess rather quickly whether an emerging pathogen is present, or if there are fluctuations in persistent pathogens such as changes in baseline prevalence, susceptibility or pathology. Subsequently, data can be shared with other stakeholders, for example university hospitals, regional diagnostic centres for infectious diseases and public health institutes on a weekly or biweekly basis, to create a feedback loop of information.

To reach such a situation, there is one crucial condition needed: real time reporting and sharing of epidemiological information by (National and International) laboratories. These institutes should act together as a focus point for communicating their collected diagnostic information. Of course, the delay in the availability of information, as well as privacy concerns may complicate data sharing. It is also difficult to implement frequent reporting or to manage emerging outbreaks in a multi-country

setting, knowing that the diagnostic capacity is different and often difficult to perform in the European countries. Indeed, determining the exact burden of an emerging pathogen is particularly difficult; this can be due to low circulation generally in the community or to inadequate testing, fuelling a vicious cycle of low numbers found. Current (rapid) risk assessments still have a retrospective character, rather than prospective. This kind of communication does not reach clinical care providers, and will therefore not help the field move forward during rapid upsurges.

Epidemiological data should also be more easily accessible and manageable. A good and visual example is the HealthMap Initiative, developed by a group of researchers, epidemiologists, and software developers at the Boston Children's Hospital [13]. HealthMap monitors outbreaks and other public health threats by accumulating online informal health information. Visitors can immediately select a country to see the latest news in that region. The data can be as recent as 24 h and is accessible to everyone. The downside is that HealthMap depends on news sites to share the information first. Similar open access, custom web-based platforms are available as well, for instance nextrain.org [14]. It would be beneficial to have the diagnostic data available on a similar public database directly. A further example of an existing public database is MSIS, the Norwegian Surveillance System for Communicable Diseases. By law, clinicians must report from a list of nearly 70 notifiable diseases which then would be made publicly available online [15]. Furthermore, tools are available on the website to make your own tables and perform statistics, however it does note that there can be delays in reporting. EPIS (Epidemic Intelligence Information System) by the ECDC, offers an online platform for public health experts, nominated by EU Member States, to communicate and to determine the impact of current and emerging threats [16]. Additional platforms offered by the ECDC include EWRS and tESSY. However, this content is not accessible for all routine diagnostic parties, which delays the sharing of useful information. Furthermore, these databases only address diagnostic results and can be outdated, even for years. Ideally, some general clinical and epidemiological information should be included as well, to accurately estimate the severity of the threat. On the diagnostic side, even when only looking at respiratory viruses, many initiatives to share data do exist. For example, the RespVir network [17] based in Germany and TypeNed [18] in the Netherlands. In the United States, the CDC provides a clear view on recent influenza activity on both national and state level, which is publicly available [19]. Finally, also commercial partners of syndromic point-of-care systems are already implementing online databases, where diagnostic results are uploaded in real-time, e.g. www.syndromictrends.com or www.rsvalert.com [20,21]. These initiatives are good examples which show that it is possible to utilise data in an optimal manner.

5. The take home message

Driven by local initiatives, responsibility should be taken collectively to structurally create symbiosis between patient care, diagnostics and public health epidemiology. Interdisciplinary dissemination of relevant diagnostic, epidemiologic and clinical information should be used for epidemiological analysis in real time, which in turn can be used by diagnostic laboratories to be beneficial for the individual patient. Diagnostic laboratories should routinely share data to public health institutes in a timely manner, while these institutes should make that data available and accessible in real-time for the relevant diagnostic laboratories and clinical care providers. This system could be accessed to visualise trends and will be instrumental for preparedness and outbreak response.

Additionally, the available data should preferably be combined with clinical information, since this adds relevance to the diagnostic data. After all, a single detection with a unique clinical presentation can already have a significant impact.

In conclusion, all involved stakeholders share the responsibility to ensure that the available diagnostic, epidemiological and clinical information reaches its full potential. Translation, communication and interpretation between disciplines is essential in advancing healthcare. A prerequisite for this is that the responsible European institutions need to add more pathogens to their portfolio. By making use of the numerous advanced technologies (e.g. artificial intelligence, data mining, machine learning) that are currently available, we should be able to predict future trends and understand more about transmission routes and pathology, particularly in emerging pathogens. A strong European surveillance network should after all be beneficial for the most important stakeholder: the patient.

Author's contribution

All authors were involved in the discussions that lead to this manuscript. The first draft was made by MvG, HC and RP and all authors edited the manuscript while the discussions continued on the subject.

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