

LETTER



Sepsis, a call for inclusion in the work plan of the European Center for Disease Prevention and Control

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Dear Editor,

Sepsis is a devastating condition resulting from our bodies' dysregulated immune system response to infections, which can lead to organ failure, death, or sometimes life-long disability. Common infections with bacterial, fungal and viral diseases or as a consequence of injury, can cause sepsis. In addition, emerging infectious diseases either directly cause sepsis or predispose to sepsis. In the case of coronavirus disease 2019 (COVID-19), 52% of hospitalized patients in the wards and 78% of hospitalized patients in an intensive care unit meet the Sepsis-3 definitions [1]. Sepsis affects all age groups, the highest incidence is seen at the extremes of age, neonates and young children [2], and the elderly.

Each year, sepsis affects close to 50 million people globally, of whom 11 million die and more than half suffer long-term consequences such as physical or mental disabilities.

In the European Union (EU), estimates extrapolated from a Swedish study of 2015 suggest that more than 3 million people suffer from sepsis each year resulting in

680,000 deaths [3]. The incidence of sepsis is only second to cancer (2,681,958 cases with 1,261,722 deaths) [4]. Across EU countries, stroke accounted for 375,000 deaths in 2017 [5]. In 2016, 542,700 were due to coronary diseases, including heart attacks [6]. Antimicrobial resistance (AMR) is another well-known health threat and priority for health authorities: each year more than 670,000 infections are due to bacteria resistant to antibiotics and approximately 33,000 people die as a direct consequence [7]. However, many studies indicate that the number of deaths due to sepsis as well as the burden of post-sepsis morbidity and resultant costs for health care systems are grossly underestimated, also due to a lack of accurate data collection.

Costs of sepsis and benefits of quality improvement initiatives

Sepsis is a huge burden for European health systems and society. It is estimated, for example, that the average cost of treatment for a single patient in France amounts to about € 16,000 [8], but severe sequelae can potentially raise costs to € 2,267,251 per patient in children with sepsis and amputations [9]. The cost of care in the intensive care unit (ICU) in Greece exceeds € 27,000 per patient [10]. The burden of sepsis persists through the years because of very frequent sequelae, which mimic those of long-COVID symptoms [11] so far observed. A recent study in Germany revealed that three out of four sepsis survivors have new physical, cognitive, or

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psychological diagnoses that require multidisciplinary healthcare support, and 32% become newly dependent on chronic nursing care. As a result, the direct costs for a 3-year follow-up for sepsis survivors amounts to € 6.8 billion per year in Germany alone [12]. The York Health Economics group estimated the grand total of sepsis to be as high as £7.4 billion across the United Kingdom with a direct cost of the National Health Service over £0.6 billion [13]. According to an analysis run in Sweden, sepsis quality improvement programs have enormous potential to be very cost effective, because the initial cost increase (e.g., new processes, new recruitment, and routine patient follow-up) will be offset by shorter hospital stay and reduced readmission frequency [14]. These estimates are supported from the evaluation of other sepsis programs in non-European high-income healthcare settings. Studies from Australia [15] and Canada [16] both underline the large burden of sepsis and the significant benefits from initial investments in quality improvement programs. In Australia, the Australian Commission of Safety and Quality in Healthcare recently defined standards for sepsis care [17], which form part of regulatory requirements for hospital accreditation. These figures are far higher than the cost of cancer reported to range between 37,000 and 42,000 USD for colon cancer resection and breast cancer treatment [18, 19].

Evidence must be met by political will in Europe

The staggering data of the burden of sepsis collide with the limited action undertaken so far by relevant authorities to tackle such an evident but underestimated global health threat.

In 2017, the World Health Assembly approved resolution 70.7, urging World Health Organization member states to prioritize sepsis in their national health systems. After almost 5 years, the uptake of the recommendations has been limited, although several countries have started implementing awareness and quality improvement measures across Europe, as highlighted in a recent report from the European Sepsis Alliance [20]. EU institutions can support member states to implement the resolution by introducing harmonized and systematic approaches to measure and monitor the burden of sepsis, facilitating the exchange of good practices and providing common guidelines on prevention and treatment.

In order to better understand the impact of what is the most preventable cause of death and disability in Europe, more accurate data collection on the incidence of sepsis is needed. In this context, the undersigning organizations believe that a greater role should be played by the European Centre for Disease Prevention and Control (ECDC) in coordinating member states' monitoring and data collection and in establishing a common minimum data set.

Such a data set should be applicable to neonatal, pediatric, and adult patients to capture the true burden across the life span. In this framework, the interoperability of existing national or regional datasets should be facilitated to better understand the epidemiology of sepsis and its links with antimicrobial resistance and COVID-19. Better understanding, improved monitoring, detection and treatment of sepsis across all age groups would bring invaluable benefits to European citizens, European health systems and the economy at large.

Sepsis surveillance programs have the potential to save lives and improve patient outcomes. However, some barriers hamper their implementation, such as the lack of standardized definitions (implementing Sepsis-3 definition uniformly across different healthcare settings can still be challenging), data availability and quality, limited resources, and interdisciplinary collaboration. Effective management of sepsis is the result of collaboration between specialties.

We are aware of the difficulties in developing a surveillance definition for sepsis that is sensible and specific enough, and feasible. Since such a surveillance may require intense patient-based activities, exploring the development and validation of semiautomatic procedures would be helpful. Despite the fact that an etiological diagnosis cannot be achieved in a substantial proportion of patients with sepsis, including the causative microorganism (when available) in reporting and coding is a must. The European Sepsis Care Survey recently revealed one of the weaknesses of European health systems, which is the delay of microbiological services to deliver blood culture results. Improvement of microbiological diagnosis is crucial for sepsis treatment [21].

As for any health problem, the quality and interpretation of surveillance data must be adequate. In the case of sepsis, an overdiagnosis of sepsis cases may unintentionally promote the overuse of broad-spectrum antibiotics. To avoid this, adequate training of local staff and quality control for data collection, and balanced analysis of the results are critical. These challenges do not mean that an adequate surveillance for sepsis cannot be achieved. On the contrary, the recent advances in our understanding of sepsis and in technical developments provide a good opportunity to develop innovative surveillance methods to be applied.

Sepsis can and must be integrated in the extension of the ECDC mandate

European institutions have recently agreed on an extension of the ECDC mandate, following the demand for a coordinated response to communicable disease outbreaks, triggered by the pandemic. The revised mandate strengthens the powers of ECDC and increases the scope

of its work with the aim to support the European Commission and EU member states in epidemiological surveillance, preparedness and response planning to health threats, reporting and auditing. The analysis of the incidence of sepsis in 2020 showed that 1.6 million incident cases were reported in Central and Eastern Europe and 1.3 million incidence cases in Western Europe [22].

This desired improvement in the EU's response capacity to cross-border health threats is a much needed measure, as the pandemic has put lack of coordination and limitations in resources under the spotlight. However, it remains unclear why a major global and European health threat such as sepsis still falls outside the scope of ECDC's work. Notwithstanding the limitation in budget and resources compared to similar authorities in other regions of the world, the importance of sepsis and the intercorrelation with infectious diseases is not yet reflected in the work of the European body in charge of monitoring and surveilling their development, spread and burden. In fact, sepsis quality improvement programs are expected to be cost saving for the health care systems [23] and can leverage from the experience on successful ECDC programs on preventing nosocomial infections. The lack of focus and of specific resources is a common trait encountered in global advocacy for sepsis. In the vast majorities of cases, competent authorities lack specific departments or programs, with few exceptions such as the Centers for Disease Control and Prevention (CDC) in the United States (US). This shortcoming does not help to prevent sepsis from affecting around 50 million people every year.

To those policy makers who truly understand it, sepsis is today seen as a cross cutting healthcare problem, with touch points with a variety of other issues that are currently prioritized in the global healthcare agenda such as infection prevention and control (IPC), pandemic responsiveness, antimicrobial resistance, healthcare-acquired infections and patient safety. Placing sepsis as a core part of infection management strategies will provide opportunities to increase sepsis awareness on a variety of contexts thus reducing its burden on healthcare and rehabilitation systems. However, we are concerned that, unless prioritized by policy makers, it will not be afforded the focus, solutions and resources needed to tackle such a scourge.

With the revision of the ECDC mandate, the EU now has the opportunity to set new standards for sepsis care, through improved data collection and the development of European guidelines. Policy makers in Europe have realized the importance of preparedness and coordination to respond to future cross-border health threats across the continent. Any strategy aiming at tackling

communicable diseases cannot prescind from including sepsis prevention and treatment. In fact, management guidelines for COVID-19 have been directly developed from similar sepsis guidelines [24].

Sepsis should be considered by ECDC as one of those "special health issues" mentioned in the agreed text of its mandate, such as AMR and healthcare-associated infections (HAIs), because of its close interlink with these public health issues and with communicable diseases. AMR will hamper successful sepsis treatment. At the same time, effective quality improvement initiatives targeting recognition and treatment of sepsis need to go hand in hand with antimicrobial stewardship initiatives, and HAI prevention initiatives—in fact, these three priorities share substantial overlap which should be used to create synergisms. Early recognition and treatment would minimize the burden of HAIs, and sepsis surveillance would provide valuable data on the quality of care in Europe. It would also help assess, monitor and improve health systems' preparedness to respond to communicable disease outbreaks, treat them and assess clinical complications.

ECDC should also use its influence to include sepsis among the research priorities for EU-funded programs, and to include sepsis management in guidelines for the case management of communicable diseases. Finally, sepsis could act as an extremely valuable indicator for the capacity of health systems to diagnose, prevent and treat communicable diseases and their burden.

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