

Improving the prevention, diagnosis and clinical management of sepsis

Report by the Secretariat

1. Sepsis arises when the body's response to infection injures its own tissues and organs. It can lead to septic shock, multiple organ failure and death, if not recognized early and managed promptly. It is a major cause of maternal and neonatal morbidity and mortality in low- and middle-income countries and affects millions of hospitalized patients in high-income countries, where rates of sepsis are climbing rapidly. The present report summarizes the problem of sepsis as a key issue for global health, describes the Secretariat's actions to address it and briefly outlines priority actions for the future.
2. An international consensus has recently recommended that sepsis should be defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone".¹ Both definitions are accompanied by clinical criteria to translate them into practice to support diagnosis and clinical management during patient care.
3. The occurrence and frequency of sepsis are determined by a complex interplay of many host, pathogen and health system response factors. Several chronic diseases, such as chronic obstructive pulmonary disease, cancer, cirrhosis, AIDS and other immunodeficiency disorders, are associated with an increased risk of sepsis. Demographic and social factors, such as diet and lifestyle (for example, use of tobacco and alcohol), poverty, sex and race, also influence the occurrence of sepsis. Access to health care systems, in particular intensive care, as well as the timeliness and quality of care, are also associated with the occurrence of sepsis and its fatality rate.
4. Most types of microorganisms can cause sepsis, including bacteria, fungi, viruses and parasites, such as those that cause malaria. Bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp. and *Neisseria meningitidis* are the most common etiological pathogens. Manifestations of sepsis and septic shock can be the fatal frequent pathway of infections with seasonal influenza viruses, dengue viruses and highly transmissible pathogens of public health concern such as avian and swine influenza viruses, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and most recently, Ebola and yellow fever viruses.

¹ Singer M et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-10. doi: 10.1001/jama.2016.0287.

5. It is impossible to estimate precisely the global epidemiological burden of sepsis. According to crude incidence estimates extrapolated from data gathered in the United States of America, there could be 15–19 million cases of sepsis every year worldwide. Further data report up to 31 and 24 million cases of sepsis and septic shock respectively globally, with clinical conditions resulting in sepsis accounting for about 6 million deaths. In the United States of America, more than 1.1 million patients were hospitalized with sepsis in 2008, corresponding to an incidence of 32.7/10 000 patients, a 70% increase compared with that in 2000. Between 2004 and 2009 the sepsis case fatality rate in the United States of America ranged from 14.7% to 29.9%. The financial burden due to sepsis has been calculated to be more than US\$ 24 billion, representing 6.2% of total hospital costs in 2013. Studies in Europe and Canada have estimated the daily costs of hospital care of a septic patient to be between €710 and €1033 in 2000 (equivalent to about US\$ 645 and US\$ 939, respectively). These estimates were based exclusively on data from high-income countries; the epidemiological burden of sepsis is likely to be much higher in low- and middle-income countries.

6. In the community, sepsis often presents as the clinical deterioration of common and preventable infections such as those of the respiratory, gastrointestinal and urinary tract, or of wounds and skin. Sepsis is frequently under-diagnosed at an early stage when it is still potentially reversible. Early diagnosis and timely and appropriate clinical management of sepsis is crucial to increase the likelihood of survival. Appropriate treatment of sepsis requires not only treatment of the underlying infection, but in parallel requires life-saving medical interventions such as fluid resuscitation or vital organ support. Even in viral epidemics such as Ebola virus disease or avian influenza A(H5N1), substantial improvement of case fatality rates was achieved by providing timely and appropriate patient care (resulting in a reduction of case fatality rates from 80–90% to 40% for Ebola virus disease in 2014–2015 and from 60% to 30% for influenza A(H5N1) in a WHO pooled analysis of data collected between 2004 and 2011).

7. Sepsis may also result from infections acquired in health care settings. These health care-associated infections are mainly caused by bacteria that are often resistant to antibiotics and therefore the clinical condition of the patient can rapidly deteriorate. Hundreds of millions of patients are estimated to be affected annually by health care-associated infections. In Europe, about 80 000 hospitalized patients are estimated to have at least one health care-associated infection on any given day. On average, health care-associated infections affect 7% and 15% of patients in high-income and low- and middle-income countries, respectively. In high-income countries, about 30% of patients in intensive-care units have at least one such infection. In low- and middle-income countries, the frequency of infection acquired in an intensive-care unit is at least two to three times higher than in high-income countries and device-associated infection densities are up to 13 times higher than in the United States of America. Hospital-born babies in low- and middle-income countries are at a higher risk of being affected by neonatal sepsis, with infection rates three to 20 times higher than in high-income countries.

8. In 2015, infectious diseases accounted for more than 50% of all deaths in neonates and children aged under 5 years, especially in southern Asia and sub-Saharan Africa. Among these, pneumonia (920 000 deaths/year), diarrhoea (526 000 deaths/year), neonatal sepsis (401 000 deaths/year) and malaria (306 000 deaths/year) were the most frequent causes of death. As almost all these fatal cases have signs and symptoms of sepsis or septic shock, more aggressive approaches to improving the management of sepsis with simple tools could have a major impact on child mortality globally. Between 1995 and 2005 in the United States of America, the incidence of severe sepsis in children increased from 0.56 to 0.89 cases per 1000 children, across all age groups. In the United States of America, the overall incidence of neonatal sepsis from 2005 to 2008 was 0.77 cases per 1000 live births, with the highest incidence in African American preterm babies (5.14 per 1000 live births). In southern Asia, sub-Saharan Africa and Latin America, there were an estimated 6.9 million episodes of

possible severe bacterial infection in neonates needing treatment in 2012, with overall mortality at about 10%, representing 670 000 deaths. Infections are the third direct leading cause of maternal mortality, causing about 11% (more than 30 000 deaths/year) of maternal deaths; in addition, sepsis is a contributing cause in many other maternal deaths every year. The burden of maternal deaths directly associated with infection is higher in low- and middle-income countries (10.7%), with the greatest burden in southern Asia (13.7%) and sub-Saharan Africa (10.3%), compared with high-income countries (4.7%). In Africa, up to 20% of women who have a caesarean section get a wound infection affecting their health and ability to take care of their baby.

9. Antimicrobial resistance is a major factor determining clinical unresponsiveness to treatment and rapid evolution to sepsis and septic shock. Approximately 214 000 neonatal deaths due to sepsis worldwide each year could be attributable to resistant pathogens. Sepsis patients with resistant pathogens have been found to have a higher risk of hospital mortality: in Europe, for example, *S. aureus*, including methicillin-resistant *S. aureus*, was found to be the most common causative organism among sepsis patients with positive cultures in intensive-care units. The estimated mortality rate associated with methicillin-resistant *S. aureus* is about 50% higher than that for patients affected by methicillin-susceptible *S. aureus*.

INTERNATIONAL CONTEXT – RECENT EFFORTS ON SEPSIS

10. Recognition of sepsis as a major cause of preventable morbidity and mortality globally has grown in recent years, due to efforts of a wide range of public and private actors. One such actor, the Global Sepsis Alliance, a non-profit organization, was launched in 2010 to understand and combat sepsis better. The main initiatives to date include the promotion of World Sepsis Day (on 13 September) and the World Sepsis Congress (the first congress was held in 2016).

11. In order to mitigate sepsis-associated mortality, the Surviving Sepsis Campaign developed guidelines that recommend administration of empirical antimicrobial therapy within 1 hour of recognition of severe sepsis or septic shock in adult and paediatric patients. Observational studies have demonstrated that adherence to these guidelines improves processes of care and survival in high-income countries. Implementation in low- and middle-income countries, however, is proving very challenging. A survey of 185 African hospitals conducted in 2009 showed that less than 1.5% of the hospitals surveyed implemented the guidelines.

12. A *Lancet Infectious Diseases* Commission recently discussed the global burden of sepsis, its determinants, clinical management and most importantly a new roadmap for future research.¹

WHO'S RESPONSE TO SEPSIS

13. WHO's response to sepsis spans different Secretariat programmes and is part of the Organization's wider efforts to tackle the causes of global neonatal, paediatric and maternal mortality, to prevent health care-associated infections and epidemic-prone infections caused by highly transmissible pathogens, and to improve the clinical management of communicable diseases, including identification of the most effective treatment regimens to be included in the WHO Model List of

¹ Cohen J et al. Sepsis: a roadmap for future research. *Lancet Infect Dis.* 2015;15(5):581-614. doi: 10.1016/S1473-3099(15)70112-X.

Essential Medicines. Preventing and reducing harm from sepsis is relevant to achieving targets 3.1, 3.2, 3.3, 3.8, 3b, 3d of Goal 3 (Ensure healthy lives and promote well-being for all at all ages) and Goal 6 (Ensure availability and sustainable management of water and sanitation for all) of the 2030 Agenda for Sustainable Development,¹ the United Nations Global Strategy for Women's, Children's and Adolescents' Health, the WHO global action plan on antimicrobial resistance, implementation of the International Health Regulations (2005) and of the WHO framework on integrated, people-centred health services.

14. WHO and other key stakeholders are in the process of launching a global quality of care network for maternal, newborn and children's health to accelerate reduction of preventable maternal and neonatal deaths, which includes prevention, early detection and prompt management of sepsis, in particular through implementation of essential newborn care packages and care at home. This initiative aims to ensure that every pregnant woman and newborn receives good-quality care throughout pregnancy and childbirth and in the postnatal period too. WHO has also developed the following: guidelines for the early identification of possible severe bacterial infection in newborns and infants; comprehensive packages for the diagnosis and treatment of sepsis at the referral level of care facilities; and guidelines for management of possible serious bacterial infections in newborns and young infants when referral is not possible.

15. WHO has issued recommendations for the prevention and treatment of maternal peripartum infections. Furthermore, WHO has recently developed a new definition for maternal sepsis and, together with Jhpiego and other key partners, launched the global maternal and newborn sepsis initiative. This initiative proposes a new collaborative and innovative approach that combines research, service-delivery programming and advocacy to strengthen the response to maternal and newborn sepsis.

16. Regarding the prevention of sepsis in children and the reduction of its contribution to the global burden of child mortality, the following Health Assembly resolutions have been approved over the past few years: on working towards the reduction of perinatal and neonatal mortality (WHA64.13 (2011)); global vaccine action plan (WHA65.17 (2012)); and newborn health action plan (WHA67.10 (2014)).

17. Working with several key partners such as FAO, OIE and UNICEF, WHO developed the global action plan on antimicrobial resistance. Resolution WHA68.7 on this plan was approved by the Sixty-eighth World Health Assembly in 2015. All five principles of the global action plan are relevant to reducing the burden of sepsis worldwide, as they aim to increase awareness of the problem, strengthen surveillance capacity and data dissemination, prevent antimicrobial resistance through infection prevention and control, improve water quality and sanitation, and promote a more appropriate use of antibiotics, as well as research to develop new medicines to overcome the problem of antimicrobial resistance. WHO has developed various recommendations, guidance documents and tools, and launched several new initiatives to accomplish its mandate of combating antimicrobial resistance. All three levels of the Organization are working with Member States to implement the global action plan through national action plans and related activities.

18. The Secretariat provides support to countries in their efforts to develop or strengthen infection prevention and control programmes to reduce both the endemic and the epidemic burden of health care-associated infections. New evidence-based guidelines outlining the core components for effective

¹ See United Nations General Assembly resolution 70/1 (2015).

infection prevention and control programmes at national and health care facility levels were issued in November 2016 to provide support to capacity-building efforts in countries, including national action plans on antimicrobial resistance. In a global report, WHO and UNICEF recently highlighted major gaps in hygiene, sanitation and access to clean, reliable water in health care facilities and have pointed out priorities for action in a global action plan. WHO provides guidance, in several documents and tools, on standards for water, sanitation and hygiene and management of health care waste; relevant monitoring indicators in health care facilities have also been identified. WHO evidence-based guidelines and implementation strategies to improve hand hygiene practices in health care have been adopted by more than 19 000 health care facilities in 177 countries through WHO's global campaign, "Save Lives: clean your hands". Specific recommendations and procedures are also being developed to prevent sepsis associated with invasive procedures such as surgical interventions and use of invasive devices (for example, vascular catheters), as well as infections due to antibiotic-resistant bacteria.

19. To provide relevant guidance on clinical management during outbreak responses, WHO developed the *IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of common illnesses with limited-resources* in 2011, which includes guidance on sepsis and severe respiratory infections. During the 2009 A(H1N1) influenza pandemic, previously drafted guidelines were rapidly adapted and disseminated for the management of severely ill patients in low- and middle-income countries. WHO has used the manual to train thousands of front-line health workers during outbreaks in affected, neighbouring and at-risk countries. During the 2013–2016 outbreak of Ebola virus disease in West Africa, WHO incorporated these WHO adult sepsis guidelines into guidance on management of patients (*Clinical management of patients with viral haemorrhagic fever: a pocket guide for front-line health workers. Interim emergency guidance for country adaptation*, first issued in March 2014, updated February 2016). Support for training on sepsis management tailored to settings with limited resources has also been provided through development of a learning programme, the WHO IMAI Quick Check+/Clinician's role in disease surveillance and response training curriculum (QC+). Complementing existing WHO guidance, this learning programme focuses on triage during emergencies, support for differential diagnosis and early detection of notifiable diseases, infection prevention and control and emergency management of severe conditions such as sepsis.

20. WHO will update the Model List of Essential Medicines in March 2017 and will review the information on antibiotics by reviewing treatment of 20 of the most prevalent and severe syndromes globally. A specific guidance document on neonatal sepsis will be included in the revised list in 2017 to provide support to countries in implementing evidence-based recommendations.

21. WHO and the Drugs for Neglected Diseases Initiative have collaborated in recent years to create the Global Antibiotic Research and Development Partnership, which aims to develop new antibiotic treatments for global health needs and promote sustainable and equitable access to them, including optimal conservation of antimicrobials. This not-for-profit partnership, together with several experts, has set up a project to develop a new first-line treatment for neonatal sepsis, as well as new antibiotics to be used against multidrug-resistant pathogens. The project designs and conducts studies in settings where levels of multidrug-resistance are high to determine the effectiveness and safety of new regimens, comparing them with existing therapies.

FUTURE PRIORITIES

22. The Secretariat has identified the following priorities for WHO and other stakeholders in addressing sepsis.

- (a) To work together to improve understanding of the epidemiological and financial burden of sepsis worldwide and its continuous monitoring through availability of reliable data according to standardized definitions.
- (b) To eliminate health systems factors that contribute to sepsis occurrence and inappropriate diagnosis and clinical management, and in particular, to prioritize strengthening of infection prevention and control programmes and implementation of infection prevention and control best practices at the point of care, particularly during labour, childbirth and postnatal care, and in intensive-care units and in the community.
- (c) To increase access to and use of available vaccines that prevent the most common infections that can lead to sepsis.
- (d) To prioritize actions that increase awareness of the clinical manifestations of sepsis among the public and community health care practitioners, to facilitate efforts related to the quality of care aimed at improving early diagnosis and appropriate clinical management.
- (e) To support the use of appropriate diagnostic tools, including laboratory quality control, and further research on sensitive and specific new biomarkers and microbiological tests for early identification of sepsis conditions and assessment of their severity.
- (f) To ensure that the basics of care – including availability of life-saving supplies required to treat sepsis and reduce its case fatality rate and rates of disability following sepsis – are reliably delivered as part of global efforts to achieve high-quality universal health coverage.
- (g) To increase access to management of neonatal and infant sepsis when referral is not possible.
- (h) To coordinate, support and undertake high-quality research to identify new medicines and treatments, for prevention and management of infections that most frequently lead to sepsis, in particular those caused by multidrug-resistant pathogens.

ACTION BY THE EXECUTIVE BOARD

23. The Board is invited to note the report and provide further guidance.

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