



WHO Sepsis Technical Expert Meeting

16–17 January 2018

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Contents

Abbreviations	3
Background	4
Welcome and introductions	5
Meeting overview: background, objectives and expected outcomes.....	5
WHO’s work on sepsis.....	6
Discussion.....	9
Overview of WHO’s work on sepsis: open discussion	10
Epidemiology and burden of sepsis	10
Maternal sepsis	10
Neonatal sepsis	11
Diagnosis	11
Clinical management.....	11
Antimicrobial resistance	12
WHO’s SAVE LIVES: Clean Your Hands campaign	12
5 May 2018 – Focus on preventing sepsis in health care	12
Overview of international sepsis activities and situation	13
Key aspects of epidemiology, prevention, diagnosis and clinical management of maternal sepsis	13
Key aspects of epidemiology, prevention, diagnosis and clinical management of paediatric sepsis.....	13
Overview of sepsis in low- and middle-income countries	14
Overview of the work of the Global Sepsis Alliance	14
Overview of the Surviving Sepsis Campaign	15
Overview of the work of the Centers for Disease Control and Prevention	15
Overview of the United Kingdom Surviving Sepsis Campaign	16
Overview of international sepsis activities and situation: open discussion	17
Summary of key points of discussion.....	19
Reporting back from working groups	20
Group 1: Epidemiology and the burden of sepsis.....	20
Group 2: Prevention of sepsis.....	21
Group 3: Diagnosis and clinical management.....	22
Group 4: Awareness-raising and advocacy	23
Priorities for action at country and international levels	25
Roles, responsibilities and collaboration to disseminate the resolution and implement the plans	26
Summary of the meeting and review of next steps.....	28
Closing.....	28
Appendix 1. Agenda	29
Appendix 2. List of participants	33

Abbreviations

AMR	Antimicrobial resistance
GARPEC	Global Antimicrobial Resistance, Prescribing and Efficacy among Neonates and Children
GBS	Group B streptococcus
GLASS	Global AMR Surveillance System
GLOSS	Global Maternal Sepsis Study
HAI	Health care-associated infection
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
IPC	Infection prevention and control
LMICs	Low- and middle-income countries
MEWS	Modified Early Warning Score
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NEWS	National Early Warning Score
qSOFA	quick Sepsis Related Organ Failure Assessment
SDG	Sustainable Development Goals
SEPSIS-3	Definitions for Sepsis and Septic Shock
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
TB	Tuberculosis
UHC	Universal Health Coverage
UK	The United Kingdom
US CDC	United States Centers for Disease Control and Prevention
USA	United States of America
WASH	Clean water, hygiene and sanitation
WHA	World Health Assembly
WHO	World Health Organization

Background

Although a precise estimate of the global epidemiological burden of sepsis is difficult to ascertain, some scientific publications have reported that it affects more than 30 million people worldwide every year, potentially leading to 6 million deaths. Global rates of sepsis are thought to be growing rapidly, particularly in low- and middle-income countries (LMICs). At the Seventieth World Health Assembly in May 2017, Member States of the World Health Organization (WHO) adopted a resolution (WHA70.7) on improving the prevention, diagnosis and treatment of sepsis.

The resolution requested WHO to develop guidance for the prevention and management of sepsis, to produce a report on the epidemiology and burden of sepsis, and to support countries to obtain the necessary infrastructure, laboratory capacity, strategies and tools to address sepsis. The Organization is also expected to work with partners to improve access to quality, safe, efficacious and affordable treatments for sepsis and tools for infection prevention and control (IPC), including immunization, particularly in developing countries.

Several WHO departments work on aspects of prevention, diagnosis and treatment of infections leading to sepsis, including research, both in the community and health care settings. A technical group (the Sepsis Coordination Group) coordinated by WHO's Service Delivery and Safety department was established to support and implement the resolution. Actions are being undertaken to make this group the most inclusive possible of all groups who can play a role in advancing the sepsis agenda at both the headquarters and regional levels. As of January 2018, the group included the following WHO departments: Service Delivery and Safety; Antimicrobial Resistance; Essential Medicines and Health Products; Immunization, Vaccines and Biologicals; Infectious Hazard Management; Information, Evidence and Research; Innovation Access and Use; Maternal, Newborn, Child and Adolescent Health; Public Health, Environmental and Social Determinants of Health; and Reproductive Health and Research.

WHO convened the Sepsis Technical Expert Meeting, inviting experts, stakeholders and professionals from around the world, including from countries that had already progressed in the development and implementation of prevention, diagnosis and treatment of sepsis. The overall objective of the meeting was to identify priorities and make plans to move the global agenda on sepsis forward in accordance with the resolution.

The meeting aimed to share an overview of current major initiatives on sepsis worldwide, to present WHO activities and plans, to discuss global needs and priorities for action, to gather input on the critical role of WHO and key areas of work, and to explore areas for collaboration between WHO and other key players with the common goal of furthering global efforts on sepsis.

Welcome and introductions

Ed Kelley, Marc Sprenger

Participants were welcomed to the meeting on behalf of WHO's Director-General. They were informed that WHO is undergoing a transformation process due to the efforts of the new Director-General and the Organization's leadership. This is very promising but decisions were still being developed regarding priorities and reorganization of the work, including that for sepsis. The next session of the WHO Executive Board in May 2018 would discuss WHO's global programme for the next 2 years. The results of the Sepsis Technical Experts Meeting would therefore feed into this discussion on the future global programme.

There are many challenges related to sepsis across countries. It is therefore important to understand what capacity each country has and how difficult issues such as antimicrobial resistance (AMR) should be dealt with. While there is an urgent need for new antibiotics, these alone are unlikely to overcome sepsis and AMR. The need for better diagnosis and infection control is paramount.

Meeting overview: background, objectives and expected outcomes

Benedetta Allegranzi

Participants were reminded of Resolution WHA70.7 on "Improving the prevention, diagnosis and clinical management of sepsis" (Appendix 1), adopted by the Seventieth World Health Assembly in May 2017. In addition, the report to the Health Assembly by the Secretariat is included in Appendix 2. The resolution, in which WHO is requested to provide support for countries, provides a political platform on which to base actions for the future.

In this regard, World Health Assembly resolution WHA70.7 makes a number of recommendations specifically to countries, such as: including prevention, diagnosis and treatment of sepsis in national health systems strengthening; reinforcing existing strategies or developing new ones; promoting comprehensive antimicrobial stewardship; implementing standard and optimal care and strengthening medical countermeasures; taking steps to diagnose and manage sepsis in health emergencies; increasing public awareness of sepsis; training all health professionals in IPC and patient safety; promoting research; using the International Classification of Diseases (ICD) to establish the prevalence and profile of sepsis and AMR; and supporting World Sepsis Day on 13 September each year.

The resolution calls on WHO to support country efforts and to provide guidance on normative approaches to sepsis, with a focus on the burden of disease. Timely diagnosis and management should be integrated into institutional health systems, and it is stressed that collaboration with many stakeholders is a major mandate for WHO. The complete list of recommendations can be seen in the full text of the resolution in Appendix 1.

The Sepsis Technical Experts Meeting was asked to look at four main aspects relating to sepsis, namely: 1) epidemiology and the global burden, 2) prevention, 3) diagnosis and 4) clinical management, including AMR.

While bearing in mind these four aspects, participants were asked to focus on the following main areas of activity for providing their advice and recommendations:

- Awareness-raising activities

- Reports
- Policies
- Evidence-based guidelines
- Implementation strategies
- Education and training activities
- Research
- Networking, and coordinating partners' actions.

It was agreed that the problem of sepsis must be considered at different levels – the global, national and health facility levels. Participants were urged to identify issues which are especially important in low- and middle-income countries (LMICs).

A number of questions would need to be answered. For instance: What is the evidence? What is the most important? In addition: Where are gaps? What are the priorities? What do people expect from WHO? Guidance needs to apply to all situations, regardless of the level of resources. WHO has been asked by the Director-General to work across programmes in multidisciplinary teams in order to obtain better results.

The agenda of the meeting was then summarized and was accepted by participants. A copy of the agenda can be found in Appendix 3.

Meeting participants introduced themselves around the room. Appendix 4 contains the full list of participants.

The presentations made at the meeting are available in pdf at www.who.int/servicedeliverysafety/areas/sepsis_meeting2018/en/index.html.

All Internet links in the footnotes were active as of 8 April 2018.

WHO's work on sepsis

Ed Kelley

WHO's work in this area is based on the Sustainable Development Goals (SDGs) and particularly SDG3 with its health targets. The key goal for the Organization is universal health coverage (UHC) which has a close link with the prevention of sepsis. How WHO balances its activities globally depends on the countries because initiative should be taken first of all at country level. WHO has a long list of activities related to sepsis, with important activities in maternal and newborn health, vaccines, water and sanitation and other programmes.

Sepsis is a very relevant cause of maternal mortality and death in neonates and children under 5 years of age. Consequently, combating sepsis will clearly contribute to the achievement of SDG targets 3.1 and 3.2. For these two SDG targets, maternal, neonatal and under-5 mortality rates are the indicators. Sepsis is clearly measured among the causes leading to these mortalities. It can also be the clinical condition that ultimately leads to death in patients affected by HIV, TB, malaria and other infectious diseases that are included in target 3.3, but it is not usually recorded among the causes of deaths in these patients and thus

is not captured as part of the indicators for SDG target 3.3. Less directly, sepsis is relevant to other health targets in SDG 3. For instance, prevention and/or appropriate diagnosis and management of sepsis are linked to adequate vaccine coverage, quality UHC, capacity to comply with the International Health Regulations, preparedness, and water and sanitation services. The challenge, however, is how to achieve universal prevention, diagnosis and management of sepsis.

Globally, 7% of mortality in children under 5 years and 15% in neonates was related to sepsis and meningitis in 2016. However, better data are needed to better understand the epidemiology of sepsis. For this reason, WHO is leading a periodic prevalence study on maternal and early newborn sepsis in the context of the Global Maternal and Neonatal Sepsis Initiative.

A new definition of maternal sepsis was issued in 2016, namely: “Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion or post-partum”. A WHO statement on maternal sepsis issued in 2017 highlights that sepsis is “a leading cause of maternal deaths”, representing about 11% of maternal deaths.¹ Sepsis can also be due to health care-associated infections (HAIs); hundreds of millions of patients acquire such an infection every year. For instance, up to 30% of patients are affected by HAIs in intensive care units. The frequency of HAIs is at least 2–3 times higher in LMICs. Data show that infections cause 4–56% of all neonatal mortality in LMICs, and 20% of women in Africa acquire surgical site infection after caesarean section.

The WHO’s IPC global unit coordinates IPC work through the three levels of WHO² with the main goal being to strengthen national and international IPC capacity and support implementation of safe practices at the point of care.

Functions of the IPC unit include:

1. Leadership, connecting and coordinating
2. Campaigns and advocacy
3. Technical guidance and implementation
4. Capacity building
5. Measuring and learning.

Technical areas of the IPC unit’s work are:

1. IPC programmes
2. IPC to combat AMR
3. Hand hygiene in health care
4. Injection safety
5. Surveillance and the burden of HAIs
6. Prevention of infections associated with invasive procedures (e.g. surgery and catheters)
7. Prevention of sepsis.

Group B streptococcus (GBS) is a leading etiological agent of neonatal sepsis and of neonatal meningitis with substantial maternal morbidity/mortality during pregnancy and postpartum. Vaccination against GBS is a priority for preventing neonatal meningitis and neonatal sepsis. In particular, the WHO Product Development for Vaccines Advisory Committee identified the development of GBS vaccines suitable for maternal immunization in pregnancy and use in LMIC as a priority.

¹ www.who.int/reproductivehealth/publications/maternal_perinatal_health/maternalsepsis-statement/en

² www.who.int/infection-prevention/en/

AMR is one of the factors accelerating infection to sepsis clinical conditions as a result of suboptimal or lack of response to antibiotic treatment. In May 2015, the Sixty-eighth World Health Assembly endorsed a global action plan to tackle antimicrobial resistance which included five strategic objectives:

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents; and
- 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.

WHO global efforts to tackle AMR are discussed at high political levels, such as at the World Health Assembly in 2015 and at the United Nations General Assembly in 2016. WHO has ongoing collaboration with the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health). One of the key needs is better AMR surveillance. Over the last few years, WHO and other stakeholders established a Global AMR Surveillance System (GLASS) coordinating national AMR data collection for priority pathogen-antibacterial combinations. The first GLASS report was published in January 2018.³

Other critical actions to combat AMR are being taken by the WHO Department of Essential Medicines and Health Products which developed key documents supporting the appropriate use of antibiotics such as:

- WHO Model Lists of Essential Medicines for adults and children^{4,5} including antimicrobial treatment;
- Critically Important Antimicrobials for Human Medicine;⁶
- WHO guidelines on use of medically important antimicrobials in food-producing animals;⁷
- Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.⁸

WHO campaigns, such as the World Antibiotic Awareness Week, and communication on raising of awareness are very important. WHO provides technical guidance on management of neonatal sepsis, such as that on early recognition of possible serious bacterial infections in neonates and young infants and management at lower-level facilities when referral to hospital is not possible.⁹ In 2017 WHO with many key players and international stakeholders launched the Global Maternal and Neonatal Sepsis Initiative to accelerate the reduction of preventable maternal and newborn deaths due to sepsis. In this context, the Global maternal Sepsis Study (GLOSS) and Awareness Campaign were launched with the participation of 53 countries to assess the burden and management of maternal and neonatal sepsis around the world.¹⁰

³<http://apps.who.int/iris/bitstream/10665/259744/1/9789241513449-eng.pdf>

⁴http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf

⁵http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017_FINAL_amendedAug2017.pdf

⁶<http://www.who.int/foodsafety/publications/antimicrobials-fifth/en/>

⁷<http://apps.who.int/iris/bitstream/handle/10665/258970/9789241550130-eng.pdf>

⁸<http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/>

⁹http://www.who.int/maternal_child_adolescent/documents/bacterial-infection-infants/en/

¹⁰ <http://srhr.org/sepsis/>

The Health Emergencies Programme Infectious Hazard Management team focuses not only on infections due to dangerous pathogens, but also on care of critically ill patients, including sepsis, septic shock and multi-organ failure. They publish a lot of training material¹¹ and guidelines¹² on critical care and clinical management aspects of severe infections, including sepsis.

As it appears from this overview, WHO leads a number of programmes that focus on sepsis. Furthermore, as a result of the World Health Assembly resolution, the Organization has strengthened networking and coordination, including with regional offices, and has progressed plans for the development of evidence-based guidelines and standards, implementation strategies (especially in LMICs) and further research. A mechanism for better coordination between the different WHO programmes working on sepsis has been put in place, and the Organization is seeking partners to raise awareness of the importance of sepsis.

A new WHO webpage has been launched on “Improving the prevention, diagnosis and clinical management of sepsis”.¹³

Discussion

Participants raised concerns about the need to find out the magnitude of the sepsis problem outside of hospitals. Most current knowledge is based on hospital statistics. There was also discussion on the need to record cases of sepsis through the International Classification of Diseases (ICD). It was noted that the new ICD-11 provides the possibility of coding AMR, and this could also be extended to include sepsis.

A number of participants drew attention to the lack of clarity of criteria and definitions, especially in developing countries. A new global consensus exists in relation to the Third International Consensus Definitions for Sepsis and Septic Shock (known as SEPSIS-3), but it is nevertheless difficult to see how the criteria of the Sequential (sepsis-related) Organ Failure Assessment (SOFA) can be applied in LMICs. In addition, it was stated that sepsis is more difficult to diagnose in countries that have seasonal infectious diseases such as malaria and dengue. AMR cannot be tackled without a clear definition of sepsis. At the same time, countries are trying to reduce the use of antibiotics for some conditions.

The 2017 Kampala Declaration to Improve Care for Sepsis and Severely Ill Patients in Africa indicates that sepsis is the most important preventable cause of death on that continent, resulting in over 2 million estimated deaths per year in Africa.¹⁴ Therefore the decision as to which definitions to use for clinical diagnosis for LMIC settings is urgent. In some high-income countries, sepsis diagnosis has improved at the point of clinical care. It is therefore essential to provide tools to help clinicians in LMICs to decide whether a patient has infection and sepsis.

It was stressed that recognition of the problem is the first step to dealing with it. WHO should make full use of materials that have already been developed, and there should be more information on the WHO website so it can be seen by health care workers and the general public. A lot of new information is available, particularly in relation to SEPSIS-3, and older documents and guidelines should be urgently updated.

¹¹ <https://openwho.org/courses/diphtheria-clinical-management>

¹² http://www.who.int/influenza/patient_care/DCM_Volume_1.pdf

¹³ <http://www.who.int/sepsis/en/>

¹⁴ <https://static1.squarespace.com/static/5a058c03ace864161674cef2/t/5a09a95cc83025174d36b96f/1510582621818/Kampala+Declaration.pdf>

Overview of WHO's work on sepsis: open discussion

Chair: Liz Tayler

Following Dr Kelley's presentation on WHO's work on sepsis, an open discussion was held on the key WHO areas of work, namely: prevention, diagnosis, AMR, epidemiology and burden of sepsis, maternal sepsis, and neonatal sepsis. Responsible WHO staff were in the room to answer questions and make additional remarks on these areas of work.

Epidemiology and burden of sepsis

Colin Mather

It is important to consider the significant burden of disease in addition to maternal and neonatal cases. A clear strategy on collection of sepsis data is needed since data are currently captured in health institutions, yet 60–80% of sepsis cases are community-acquired. How do we capture these data? Several concerns were raised, including the following:

- Use of an ICD classification to estimate sepsis epidemiology is a potential problem since sepsis is not an underlying cause of death.
- Sepsis is a second-level risk factor. Many deaths are attributed to deficiencies in the water supply and sanitation system.
- There is a lack of well-designed studies on the burden of surgical diseases related to sepsis.
- Estimates of global deaths from infectious diseases are missing or are old.
- Data should be well documented, showing what was collected, how and from which source. WHO must ensure that estimates of burden of disease are evidence-based.

Maternal sepsis

Mercedes Bonet Semenas

WHO is already working on maternal sepsis, especially in relation to awareness, definitions, prevention and management of maternal sepsis. One guideline on prevention and treatment of maternal peripartum infections exists. The GLOSS study¹⁵ will provide data on frequency of maternal sepsis and assessment of preventive practices and management. The WHO Department of Reproductive Health and Research is ready to share its experience in this area, particularly since some guidelines could be used as the basis for overall sepsis prevention.

¹⁵<http://srhr.org/sepsis/>

Neonatal sepsis

Ornella Lincetto

WHO works on tackling both maternal and neonatal sepsis, but currently has a specific programme for the latter. We can already observe measurable reductions in neonatal mortality. WHO considers sepsis as a good example of a cross-cutting approach.

It was pointed out that morbidity and mortality are very high during the first 6–12 months after treatment. The fact that many patients treated previously for sepsis are dying at home is under-recognized and under-reported. Indeed, it is still unclear why they die. Guidelines on prevention, early diagnosis and management of neonatal sepsis exist and are very clear, but unfortunately implementation in countries is limited due to various health system constraints, including poor prevention strategies, insufficient and late identification of cases at community and facility levels, limited availability of neonatal health services, and poor surveillance systems.

Diagnosis

Francis Moussy

It is essential to improve diagnosis of sepsis. WHO is advocating for new biomarkers of sepsis and early diagnosis is a priority for research and development. Improved sepsis diagnostics will help in combating AMR. However, it is up to those working on sepsis to help industry by specifying what is needed. There are many areas that need improvement, such as education and overall awareness about sepsis, how to use diagnostics, and how to prescribe medications.

In discussion, participants raised the following issues:

- If we have the right diagnosis we have more targeted treatment and less unnecessary treatment with antimalarials, antivirals and antibiotics.
- It is important to focus on health care workers skills; they should know how to diagnose sepsis and that it looks different in neonates and geriatric patients.
- In countries with high malaria prevalence it is important to recognize that not every fever is malaria. Antigen tests, polymerase chain reaction and other tests all have a cost. What kind of test is appropriate? Accurate diagnosis of tropical diseases is crucial.
- In the United Kingdom, sepsis diagnosis has improved at the clinical point of care. We should provide tools that will help them health care workers to decide whether the patient has an infection or sepsis. In the case of sepsis, time is life. However, critical care services in LMICs lack resources.
- Clinical vital signs are very important in diagnosis.

Clinical management

Janet Diaz

Different WHO teams are working on critical care, including care of adult sepsis and paediatric sepsis. Closer collaboration between the teams is now underway. However, in the past, for instance, management of adult sepsis was the responsibility of the Integrated Management of Adolescent and Adult Illness programme, which is part of the HIV team. Paediatric sepsis on the other hand was part of the Emergency

Triage Assessment and Treatment programme. The adult management guidelines were last updated in 2012, while the paediatric guidelines were updated in 2016.

It was agreed that a global clinical management guide on sepsis is needed. Nevertheless, publishing guidelines is only the first step; health workers need to be encouraged and trained to use them. The use of diagnostic tools and guides on how to deliver supportive care works only if health workers follow guidelines. Undergraduate medical students are an important target for sepsis training, and midwives should also receive education on sepsis as they have a very specific role in the prevention, recognition and management of sepsis in women and newborns that may be overlooked.

Antimicrobial resistance

Liz Tayler, Carmem Pessoa da Silva

The GLASS surveillance system is collecting data on eight pathogens. Blood is the most reported type of specimen, so it is likely that this will be linked with the work of the GLASS team. More than 50 countries are enrolled in GLASS and have nominated contact points who are responsible for sharing data with WHO. Efforts are also being made to work on the burden of disease for selected types of resistant pathogens, with a particular focus on bloodstream infections.

WHO's SAVE LIVES: Clean Your Hands campaign

Chair: Benedetta Allegranzi

5 May 2018 – Focus on preventing sepsis in health care

Didier Pittet

Hand hygiene, a core element of IPC, plays a critical role in preventing avoidable events such as sepsis. Each year on or around 5 May, WHO's SAVE LIVES: Clean Your Hands campaign aims to bring people together in support of hand hygiene improvement globally.

In 2018, the campaign focuses on supporting the prevention of sepsis in health care with the campaign slogan "It's in your hands – prevent sepsis in health care". WHO urges ministries of health, health facility leaders, IPC leaders, health workers and patient advocacy groups to take action on hand hygiene to prevent sepsis in health care.

WHO invites health facilities to join the global campaign to demonstrate ongoing commitment to hand hygiene and IPC.¹⁶ The hand hygiene campaign also enables WHO and governments to bring broader IPC messages to communities.

¹⁶ See: <http://www.who.int/infection-prevention/campaigns/clean-hands/register/en/>

Overview of international sepsis activities and situation

Chair: Denise Cardo

Key aspects of epidemiology, prevention, diagnosis and clinical management of maternal sepsis

Carlos Füchtner, Mercedes Bonet Semenas

WHO works closely with the International Federation of Gynecology and Obstetrics (FIGO). Around 10–11% of maternal deaths are due to sepsis. Although in some countries sepsis is third in the list of causes of maternal mortality, in high-income countries it is the leading cause.

Infection after caesarean section is an important element in the epidemiology of sepsis because caesarean section is the most common surgical procedure in the world. In Africa, 20% of caesarean sections lead to surgical site infections which may turn into sepsis, resulting in inability of the mother to take care of the newborn and death in some cases. Implementation strategies to minimize maternal sepsis are being developed.

Key aspects of epidemiology, prevention, diagnosis and clinical management of paediatric sepsis

Mike Sharland

The epidemiology of sepsis is better known in adults than in children, yet neonatal and child mortality due to sepsis is a major problem. There are an estimated 2.9 million deaths worldwide from sepsis every year (44% of them in children under 5 years of age) and one quarter of these are due to neonatal sepsis. The main pathogens of neonatal sepsis are gram-negative bacteria (*Klebsiella spp*, *Enterobacter spp*, *Acinetobacter spp*) and gram-positive bacteria (Methicillin-resistant *Staphylococcus aureus* [MRSA]). In neonatal intensive care units in LMICs a higher frequency of gram-negative bacteria is found, though in paediatric intensive care units the proportions of gram-negatives and gram-positives are similar. Additionally, blood culture rates vary between countries.

A 2016 project by GARPEC (Global Antibiotic Resistance, Prescribing, and Efficacy among Neonates and Children) looked at bloodstream infection mortality and found that *Streptococcus pneumoniae* remains one of the dominant pathogens in children, despite being easy to control with vaccination.

For paediatric bloodstream infections, there is a need for wider surveillance and a large database. The clinical signs of sepsis are specific in children. The results from the European point prevalence survey conducted in 2011–2012 showed that patterns of HAI differ in children and in adults. More than 17000 children were included in the survey, and it was found that sepsis is the one of the commonest HAI diagnoses in children. *Klebsiella spp* and *Escherichia spp* resistant to third generation cephalosporins are very important causes of HAI according to these data.

The choice of empirical antibiotics for suspected neonatal sepsis is complex. Ampicillin (or penicillin) and gentamicin are recommended as the first-line antibiotic treatment for at least 10 days for suspected neonatal sepsis (WHO 2017 guidelines). However, the GARPEC study showed a great variation in antibiotics prescribed for neonates and children with sepsis.

As an indication of the seriousness of sepsis as a cause of mortality, the Department of Health in the United Kingdom has announced its aim to reduce gram-negative bloodstream infections by 50% by 2021. Gram-negative bloodstream infections are believed to have contributed to some 5500 patient deaths within the United Kingdom's National Health Service in 2015.

Overview of sepsis in low- and middle-income countries

Flavia Machado

Data are available only from high-income countries where it is estimated that, out of 31.5 million sepsis cases, more than half are severe sepsis (19.4 million with 5.3 million deaths). Data from Brazil showed a sepsis mortality rate of around 50%, but interventions were begun to minimize this and mortality fell from 53.9% in 2005 to 38.5% in 2014. On a global level, the mortality rate shown in many studies is around 55%, and 60% in cases of septic shock. In some African countries there is even 100% mortality from sepsis.

As for resources, many countries lack sufficient clean water, soap and hand rub. Many doctors have never used blood lactate diagnostic tests, chiefly because they are not available, with the result that septic shock cannot be diagnosed using SEPSIS-3 definitions. In some countries the access to intensive care units is very limited. Many people have never heard of sepsis, so campaigns linked to World Sepsis Day are important. In Brazil, for instance, awareness of sepsis increased from 7% of the population to 14% after World Sepsis Day.

Many LMICs have a shortage of health care professionals. More medical staff are needed, and they need to understand how to deal with sepsis. Importantly, we must find a way to validate global guidelines. A recent study in Brazil found that 40% of mortality was in patients with sepsis but negative for quick Sepsis Related Organ Failure Assessment (qSOFA), which means that in Brazil qSOFA is not working (in screening for sepsis) as was expected.

Participants discussed the fact that criteria for sepsis diagnosis need to be re-discussed in the perspective of feasibility for LMICs. They also agreed that it is urgent to raise awareness and combat sepsis in LMICs.

Overview of the work of the Global Sepsis Alliance

Konrad Reinhart

The Global Sepsis Alliance is an alliance of more than 80 organizations in different parts of the world.¹⁷ The slogan of the alliance is to “Stop sepsis, save lives”. It was noted that a disease must be transformed politically before it can be transformed scientifically, and at present there is need for a lobby to argue for the prevention of sepsis. The Global Sepsis Alliance generates and collects data to convince people, including politicians, that there is a big gap in knowledge of sepsis at all levels. The alliance has had some success in mobilizing states, policy-makers and health authorities to endorse its aims.

The Global Burden of Disease report lists neonatal sepsis as the fourth cause of death in infants. In addition, data from Sweden show 687 cases of severe sepsis per 100 000 population. Mortality was 19.8% in two regions of Sweden in 2015. Only 15% of cases were correctly coded using the ICD, thus underestimating the magnitude of the problem. Extrapolated to the population of the European Union, this would mean

¹⁷ www.sepsis.org

3 427 521 sepsis cases and 678 649 deaths due to sepsis in Europe alone. United States data based on electronic medical records indicate that 5.9% of all admissions had sepsis, which means 1.67 million sepsis cases per year with 260 000 deaths only in the USA. Sepsis also has an economic impact since it is a major driver of increased medical costs.

Sepsis is a major cause of avoidable deaths in hospitals, yet sepsis management can be improved only if awareness of the problem is increased. Many people do not know what sepsis is. For instance, Germany has high numbers of intensive care beds but mortality due to sepsis is more than 40%. The problem is not low access to intensive care but the need to improve early recognition and treatment.

The goals of the Global Sepsis Alliance for 2018–2020 are:

- Have a Global Sepsis Action Plan.
- National cross-sectoral coalitions in at least 50% United Nations member states.
- At least 25% of countries with effective and funded national sepsis plans in place.
- Regional sepsis alliances in all continents where WHO has regional offices.
- Have World Sepsis Day mandated by the World Health Assembly.

It was announced that the European Sepsis Alliance would be launched on 20 March 2018.

Overview of the Surviving Sepsis Campaign

Massimo Antonelli

The Surviving Sepsis Campaign started its work in 2002 with its Barcelona declaration and the publication of its guidelines. The Surviving Sepsis Campaign has collaborative efforts with the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Educational initiatives continue at critical care conferences around the world. The Campaign is working to promote data collection in several regions; local campaigns are organized in local hospitals (with guidelines for implementation, behaviour change and data collection). It has been shown that care bundles (of interventions) may reduce mortality due to sepsis by 20%. The Surviving Sepsis Campaign stresses that sepsis and septic shock are medical emergencies and recommends that treatment and resuscitation should begin immediately. Participants agreed on the importance of collaboration since more and more individuals and organizations should work together to increase knowledge about sepsis and improve efforts to prevent it.

Overview of the work of the Centers for Disease Control and Prevention

Denise Cardo

In the past, the United States Centers for Disease Control and Prevention (US CDC) has focused on the main pathogens, possible risk factors and demographics of sepsis. More recently US CDC has been focusing on how to prevent death related to sepsis. The challenges are enormous: in spite of the abilities of microbiological laboratories, it is still not possible to identify more than 50% of the pathogens that cause sepsis. US CDC wishes to promote use of the correct antibiotics for sepsis that is recognized early, and to promote prevention of sepsis in communities (by vaccination) and in hospitals. Prevention of HAIs is an important element of sepsis prevention.

Some 80% of sepsis cases start in the community, usually in patients with a chronic disease, HIV or malnutrition and with some exposure to health care. US CDC estimated that there are 1.7 million sepsis

cases in the USA each year (based on electronic data on adults), and one third of these cases result in death. There is collaboration with partners who can help with targeted interventions. In particular, hospitals should have tools to track sepsis and should use electronic data sources much better.

It was stressed that sepsis is a medical emergency and that patients can be protected if action is taken quickly. Delayed recognition leads to delayed action which leads to a risk of death. “Get ahead of sepsis” is a US CDC infographic that was developed to increase sepsis awareness.¹⁸ US CDC’s core message for health care providers is: recognize sepsis, treat sepsis quickly, get cultures before antibiotic treatment, re-assess the antibiotic treatment after 24–48 hours.

Overview of the United Kingdom Surviving Sepsis Campaign

Ron Daniels

Awareness about sepsis is quite low in the United Kingdom because sepsis is often under-coded and under-reported. Health professionals worldwide use a variety of scoring systems to diagnose sepsis. Researchers in the United Kingdom showed that the National Early Warning Score (NEWS) works better than the SOFA score, so United Kingdom hospitals use NEWS which is based on six main physiological parameters – respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, and temperature. One of the biggest advantages of the NEWS score is its very good prediction of mortality:

- NEWS score 4+ mortality 20%
- NEWS score 6+ mortality 23%
- NEWS score 8+ mortality 29%.

Out of four scores – NEWS, Modified Early Warning Score (MEWS), qSOFA and Systemic Inflammatory Response Syndrome (SIRS) – the NEWS score is the best predictor of mortality, especially in combination with lactate level:

- NEWS score 4+ and lactate < 2 mortality 16%
- NEWS score 4+ and lactate 2-4 mortality 21%
- NEWS score 4+ and lactate >4 mortality 23%.

Table 1. Red flag criteria

RED FLAG CRITERIA
AVPU=V,P or U (if changed from normal)
Acute confusion
Respiratory rate ≥ 25 per minute
Needs of oxygen to keep SpO ₂ $\geq 92\%$ (88% in COPD)
Heart rate >130 per minute
Systolic B.P ≤ 90 mmHg (or drop > 40 from normal)
Snot passed urine in last 18 hours/UO<0.5ml/kg/hour
Non-blanching rash, mottled/ashen/cyanotic
Recent chemotherapy (last 6 weeks)

AVPU: alert, voice, pain, unresponsive; SpO₂: oxygen saturation; COPD: chronic obstructive pulmonary disease; B.P. : blood pressure; UO: urine output.

¹⁸https://www.cdc.gov/sepsis/pdfs/HCP_infographic_protect-your-patients-from-sepsis_508.pdf.

Red flag criteria (table 1) were developed to recognize sepsis as early as possible and to start clinical management. If red flags are 5+, mortality is at 23%; if there is no red flag it is 13%. If at least one of the red flag criteria is present, sepsis is to be suspected and clinical management should be started (Table 1).

A lot of communication activities were organized around the theme “Just ask: could it be sepsis?” to promote early recognition of sepsis in communities. The messages were placed on ambulances and family doctors’ cars, and even in movies. “When sepsis strikes, awareness is the best defence” was a message placed at football stadiums. The United Kingdom’s National Institute for Health and Care Excellence produced guidelines on sepsis in 2016.¹⁹

Overview of international sepsis activities and situation: open discussion

Chair: Mike Sharland

The following concerns and proposals were raised during by the technical experts in the discussion of the previous presentations during this session:

Awareness, campaigns

- Campaigns are mostly carried out by professional societies but not by governments. Quite often the Ministry of Health is involved (as in Germany, Spain, Sudan, Uganda, United Kingdom and other countries) and its participation is very important.
- Patients die because they arrive too late at the intensive care unit. Sepsis work should also be conducted outside intensive care units.
- Sepsis messages should be broadcast on television and in newspapers.
- Some information is missing even in high-income countries. The population groups are very different (e.g. ageing populations, malnourished, immunosuppressed, residents of long-term care facilities, newborn babies and postpartum women).

Education, training

- Reaching consensus on training content takes a long time. The training tools may need to be modified, particularly in LMICs.
- Specific briefings on sepsis should be prepared for policy-makers, as many of them are not familiar with the topic.
- Medical educational programmes need to be adjusted; nursing schools should include recognition of sepsis in their programmes.
- In the education of health care workers, invitation of foreign experts to congresses is helpful.
- Consensus is needed within professional organizations. Infectious disease physicians within the same professional group have many discussions but reaching agreement is often difficult. It is critical to agree at local level when to implement sepsis programmes.
- Close collaboration with staff of intensive care services is important. They start with broad-spectrum antibiotics while those working on antibiotic stewardship are more restrictive.

Communication

- More coordination and synergies should be established between programmes such as AMR and sepsis in order to raise awareness, especially at the political level.
- Global communication is also very important. If everything we do at national and institutional levels works, WHO should give its support and endorse the activities. When the United Kingdom’s

¹⁹<https://www.nice.org.uk/guidance/ng51>.

National Health Service officially endorsed sepsis work, it became easier for hospitals to take up the recommendations.

- Coalition is important.
- There is a big gap between the Ministry of Health and front-line workers. Clinicians and medical workers often do not know the guidelines. Staff do the work, but guidelines often do not reach them.

Guidelines

- Guidelines are needed for training and for quality improvement.
- Use the best guidelines from other countries. The United Kingdom's new sepsis manual is now completed.²⁰

Global action plan

- A global action plan will make an important difference, especially for LMICs.
- A global action plan would also be very helpful in providing templates for national action plans for LMICs.

Involvement

- For the future, it is absolutely necessary to involve national policy-makers. It becomes easier because of the World Health Assembly's resolution on sepsis. We need to establish national coordination based on the evidence we create.
- We should create relationships between different entities. Presidents of national societies are important drivers of action. Both national societies and their local branches are very important.
- Personal connections are important too – especially for reaching professionals. Most of the Sepsis Surviving Campaign's work did not come through government involvement. Regional and local connections are very helpful.

Early diagnosis

- Early diagnosis is very important. Patients die when they arrive too late in intensive care.
- Global clinical management guidelines are needed.

Antibiotic stewardship

- Restrictive use of antibiotics should be considered.
- Local data on the most common pathogens of sepsis and their resistance should be made available.

Implementation

- Adapting guidelines into usable material and implementation tools is very helpful for front-line staff.
- In some countries guidelines are not disseminated because of lack of resources for copying and distribution.

Surveillance, data

- ICD codes should be used more appropriately for coding of sepsis as an underlying cause of death.
- Sufficient laboratory capacity, together with surveillance of AMR and HAIs, is essential for early diagnosis and appropriate antibiotic treatment.

WHO's role

- WHO should endorse the technical experts' activities on sepsis.
- WHO should consider whether sepsis is a public health emergency. It appears to be a public health emergency at the global level.

²⁰https://sepsistrust.org/wp-content/uploads/2018/02/Sepsis_Manual_2017_final_v7-red.pdf.

Summary of key points of discussion

Benedetta Allegranzi

In preparation for working group discussions, the key points of the earlier discussion were summarized. The technical experts noted that:

- Training on sepsis should be included in health worker education on emergency treatments.
- Many activities are ongoing and it is necessary to avoid duplication. A solution should be found to try to unify some of the current approaches.
- The goal of the working groups is to define priorities and decide who is leading each specific activity.
- Data are collected according to agreed definitions. However, it seems that not all definitions are acceptable to everyone.
- Sepsis is a cross-cutting topic that requires serious attention. The intensive care community is leading this topic, but others should become involved. Connections and synergies between different initiatives and disciplines are important.
- Sepsis is related to UHC and to efforts to deal with AMR. Sepsis is also potentially linked to emergency response. WHO and the United Nations have agendas on (and potentially funds for) each of these topics. The language used and the approaches taken are important for getting things done.
- While there is a need for tailored approaches in LMICs, as well as in some high-income countries, it must be remembered that we all aim for the same goal.
- When referring to a global action plan on sepsis, what do we really mean? Any plan on sepsis should be integrated with other plans. Otherwise, there is a risk of overwhelming countries with plans.

Participants in the meeting were assigned to one of four working groups (each with its own facilitator and rapporteur) for more focused discussion on four key subject areas, namely:

1. Epidemiology and the burden of sepsis
2. Prevention
3. Diagnosis/clinical management
4. Awareness-raising/campaigns.

The purpose of the working groups was to discuss current progress, to identify gaps to be filled and to propose actions needed for each area.

Reporting back from working groups

Ornella Lincetto

The rapporteurs and chairs of the four working groups presented summaries of the discussions in their groups.

Group 1: Epidemiology and the burden of sepsis

Rapporteur: Mike Sharland

Current situation

There are very limited data, especially from LMICs. Overall, not enough data exist on the burden of sepsis. On the basis of where (in the community or in hospital) symptoms occur, all sepsis cases might be classified as follows:

- community-acquired and community-presenting;
- community-acquired and hospital-presenting;
- hospital-acquired and hospital-presenting; or
- hospital-acquired and community-presenting.

Data are needed on the relationship between sepsis and other infection diagnoses. Additionally, the roles of SOFA and other sepsis scores need further clarity. Long-term follow-up is required to determine the overall impact of disease. Disease-specific sepsis outcomes (e.g. diarrhoea) need further evaluation. Definition is needed of the proportion of adverse outcomes that can be modified by specific interventions.

Gaps and challenges

In terms of clinical case definitions, positive predictive value or negative predictive value of specific signs are not yet clear. The major gap is the difficulty to apply current sepsis case definitions, especially in LMIC settings when the main tests are not available. In addition, diagnosis of organ dysfunction is complex when laboratory facilities are very limited. There is much less information on maternal and neonatal sepsis than on sepsis in children and adults. The surveillance case definition differs from the clinical definition and is less clear. ICD-11 data collection remains part of the picture.

Actions needed

The current sepsis burden in LMIC settings is unclear; there is a need to collect prospective clinical-based surveillance data on sepsis, initially focused on hospitals. We can use and build on existing structures such as the GLASS platform, the point prevalence survey etc. The key for success could be harmonization of data collections, using existing programmes to harmonize methodology. It is also crucial to highlight the importance of collecting blood culture specimens when sepsis is diagnosed.

WHO's role

WHO should:

- have a convening role to develop consensus on surveillance definitions for sepsis at all ages, taking into account the availability of laboratory facilities;
- conduct a matrix evaluation of current sources of data in LMIC settings, including landscape analysis from Member States;
- identify existing data sources that could assist future modelling;
- provide assistance with technical methods for the design and conduct of further data collection on clinical prospective surveillance;
- delineate the roles and responsibilities of various sepsis-related WHO programmes for collecting, collating and reporting data.

Group 2: Prevention of sepsis

Rapporteur: Mpoki Ulisibysya

Current situation

Sepsis is the most severe form of infection. Consequently, prevention of infection prevents sepsis, as does prevention of the evolution of infection into sepsis. The pillars of sepsis prevention in the community are access to clean water, hygiene and sanitation (WASH), nutrition, vaccines (more vaccines for more pathogens, with adequate coverage), antibiotic stewardship and breastfeeding. Preventing sepsis in hospitals leads to an increase in patient safety. In hospitals, measures such as WASH, IPC implementation, evidence-based interventions, antimicrobial stewardship and quality data have very important roles. Progress in prevention so far includes:

- increased awareness, but not to the level at which it should be;
- behaviour change (this is the most difficult, but practice is the key);
- practice/interventions.

Gaps and challenges

Major gaps include:

- access to vaccines, WASH, equipment, infrastructure for IPC, and the right antibiotics;
- lack of connections between the different agendas, such as AMR, WASH, UHC, Global Health Security Agenda;
- lack of adequate knowledge (no data means no knowledge);
- lack of quality data;
- failure to optimize sepsis prevention in emergencies (as in a silo approach to emergencies, except natural disasters);
- optimization of antibiotic use (re-assessment and de-escalation);
- lack of connection, knowledge and surveillance (e.g. peripartum, neonatal and surgical site infections are causes of sepsis, especially in low-income countries);
- lack of funds for the sepsis agenda.

Actions needed

- Political commitment, as well as policies, budget lines for WASH and IPC, and behaviour change in the entire community. Very few persons said they came from countries with political commitment to WASH and IPC. This shows the importance not only of the health ministry but also of ministries dealing with water, environment, finance and planning.
- The improvement of quality bacteriology (diagnostics) and data in specific patient groups – especially patients at high risk, such as patients with malnutrition, diabetes, chronic kidney disease or immunodeficiency.
- Evidence-based guidelines with specific target groups (policy-makers, health care workers, administrators). A cross-cutting document of guiding principles, ranging from prevention to clinical diagnosis and management, could link various stakeholders.
- A strategy of implementation that includes tools for advocacy and communication about the importance of sepsis, how infection evolves into sepsis, and how prevention of infection eventually prevents sepsis.

Participants pointed out that an important guidance principle to be considered by all stakeholders is the “prevention of infection prevents sepsis” and early detection concept (access to a health care facility with proper clinical and laboratory capacity). This should be described in guidelines and documents.

Antimicrobial stewardship is important at community level, and yet initial timely antibiotic treatment is often not accessible, especially in remote locations. De-escalation of antibiotic treatment must be considered in antimicrobial stewardship activities.

Group 3: Diagnosis and clinical management

Rapporteur: Janet Diaz

Diagnosis: screening tools that are time-sensitive and context-specific

Several aspects of diagnosis were discussed, including how to suspect infection (using vital signs), which available scores are the best (NEWS, SIRS), and how to identify the source pathogen (by clinical parameters, breathing, SpO₂, mental status, skin mottling and other warning signs). The process of diagnosis also needs to find out if there is organ dysfunction. Other elements include laboratory diagnostic testing (point-of-care testing, C-reactive protein, procalcitonin and arterial blood gases which are very helpful for diagnosis). We should also stress the importance of laboratory-testing in LMICs. Research is needed for a prospective screening strategy based on clinical parameters, innovative rapid diagnostic tests, technology and devices, biomarkers and point-of-care testing.

Management strategies

- To keep patients safe, better pre-hospital and in-hospital treatment strategies are needed. Some good documents already exist for maternal sepsis but their content and use need to be expanded. We should review other guidelines that are available.
- Syndromic approaches such as fluid therapy and vasopressors are useful (but how much, how often, etc.).
- Quality improvement strategies show the importance of protocol use, especially in emergency departments. Nevertheless, despite the importance of protocols for haemodynamic monitoring, it is difficult to apply the guidelines if there is no laboratory.
- Supportive care plays an important role in the clinical management of sepsis patients. The conditions needed include safe ventilation practices, renal replacement therapy and blood transfusion.
- There are good examples of online training by openWHO,²¹ with training tools from the British Society for Antimicrobial Chemotherapy massive open online courses.²²

Gaps and challenges

- There is no doubt of the need for evidence-based guidance. We should not invent something new but should build on existing best practices (for instance, the Surviving Sepsis Campaign and the ESCMID consensus papers use the WHO peer review approach).
- Data availability from LMIC is limited.
- Specific problems concern neonatology, paediatrics and specific adult groups. The added value of WHO would be to focus outside of the intensive care unit. We should be very clear that minimum requirements should apply to all levels of resources – low, middle and high.
- Microbiological diagnostics are crucial for the diagnosis of sepsis. As soon the capacities exist, data should be collected, networked and reported. All data on most common pathogens and their resistance to antibiotics that are collected to improve individual treatment should also be used for regional, national and international sepsis control.

²¹ See: <https://openwho.org/>.

²² See: British Society for Antimicrobial Chemotherapy at <http://www.bsac.org.uk/massive-open-online-course-on-antimicrobial-stewardship/>.

- Different levels of help could be provided in the intensive care unit during an emergency or in outbreak circumstances.
- Sepsis is about identifying patients and treating them early. Pre-critical care is essential; the basic elements of health care should be in place and health services improved.
- It is important to re-assess the initial antibiotic therapy based on microbiological results and patient clinical conditions. De-escalation of antimicrobial therapy, particularly when broad-spectrum regimens were empirically established, should be considered after 48–72 hours. This important approach aims to reduce the emergence of AMR but it is not yet consistently followed.

Group 4: Awareness-raising and advocacy

Rapporteur: Charles Gomersall

There is already a lot of experience and we should focus on two main targets: health care workers and the general population (Table 2)

Table 2. Available resources

	PUBLIC	HEALTH CARE WORKER	STUDENT
High-income countries	UK Sepsis Campaign Sepsis Alliance Global Sepsis Alliance US CDC Other national campaigns	Surviving Sepsis Campaign UK Sepsis US CDC	BASIC ^a collaboration
LMIC	? National campaigns	BASIC collaboration Society of Critical Care Medicine/European Society of Intensive Care Medicine	BASIC ^a collaboration

^a BASIC collaboration is an informal grouping of Intensive Care specialists with an interest in the development and dissemination of teaching material.

Among the general public, awareness-raising is a process in stages. However, we must define exactly what we want to achieve. The level of knowledge differs from “heard of it” to “chase the doctors to do right thing”.

It was recognized that a **Toolbox** of strategies for running sepsis campaigns would be very useful, including:

- different materials and strategies;
- an indication of when it might be useful and the target population;
- evidence of usefulness;
- if possible, measurement of effectiveness.

Considerations for choosing campaign materials

- They are tested.
- They have no adverse consequences.
- They are acceptable to health specialists.
- There is evidence of benefit.
- There is no evidence of pushback.

Health specialists should generally be taught about sepsis before the public. Different cultures and different settings need different tools and different campaigns. We recommend not to reinvent the wheel but to adjust/check how it works in specific settings.

WHO's role

- Make tackling sepsis important to governments and commercial entities. As soon as WHO says it is important, this helps to open doors.
- Map available resources.
- Encourage funding of behavioural research.

Although some languages do not have a term equivalent to sepsis, we must go ahead with global action. We have to achieve the same level and standard of campaign with sepsis as with hand hygiene. If WHO supports a campaign, it will be much easier to implement it in many countries. Endorsement by WHO, of World Sepsis Day for instance, would be helpful. It could be useful to develop a visual global brand for the campaign. Information could be disseminated with the help of the communication department, risk communication and others. World Sepsis Day presents an important opportunity to strengthen communication on aspects of sepsis prevention and to raise awareness.

Priorities for action at country and international levels

Chair: Mike Sharland

This session aimed at summarizing the most important points emerged in the working groups discussion and identifying priorities for action at the country and international levels. Following discussion, meeting participants agreed on 16 priorities which are listed in Table 3 according to the main areas for activity highlighted in the World Health Assembly resolution on sepsis.

Table 3. Priorities for action

AREAS FOR ACTIVITY	PRIORITIES
Policies	<ul style="list-style-type: none"> Global Action Plan on sepsis, including linkages with other action plans (e.g. antimicrobial resistance)
Awareness/public health campaigns	<ul style="list-style-type: none"> Global awareness campaign (whole-of-society approach) with targeted outcomes Development of a campaign toolbox (allowing for local adaptation and synergies with other campaigns), including prevention of infection
Reports	<ul style="list-style-type: none"> Situation report on current sepsis data and activities from all Member States and WHO departments
Guidelines	<ul style="list-style-type: none"> Consensus document on surveillance and clinical case definitions and scores (tiered approach) Guiding principles document on the pathway to sepsis prevention Development of guidance on the clinical management (including diagnosis and treatment) of sepsis for different resource levels
Implementation tools	<ul style="list-style-type: none"> Template for sepsis National Action Plan Development of toolkit of care bundles, adapted to different resource settings – including recognition, diagnosis (both clinical and laboratory), management and outcomes
Education/training	<ul style="list-style-type: none"> Educational campaign and capacity-building on prevention of infection Core competency framework on sepsis for health care workers (curricula and in-service training)
Research	<ul style="list-style-type: none"> Observational clinical cohort studies (include validation of consensus case definitions) to guide optimal clinical diagnosis, management and policy Economic impact of sepsis and underlying causes (to support prioritization) Optimal diagnostics including laboratory tests, for low- and middle-income countries Methods for evaluating effectiveness of campaigns (including in low-resource settings)
Other	<ul style="list-style-type: none"> Sepsis portal (international sharing platform)

Roles, responsibilities and collaboration to disseminate the resolution and implement the plans

Chairs: Konrad Reinhart, Paul Rogers

The chairs pointed out the importance of collaboration and synergy in action. The objective of this session was to start to define roles and responsibilities for participant organizations and key players, to discuss opportunities for collaboration, and to propose actionable plans for implementation.

Regarding the priorities identified, roles and responsibilities of WHO, Member States and stakeholders were suggested (Table 4).

Table 4. Roles and responsibilities to achieve the identified priorities

PRIORITIES	WHO	MEMBER STATES	OTHER STAKEHOLDERS
Global Action Plan	- Co-development (L)	- Co-development (L) - Support development process (S)	(S)
Global awareness campaign	- Leading role (L)	- Adaptation (S)	- Formulation of consortium including WHO
Campaign toolbox	- Co-sign as co-product (S)		- Global Sepsis Alliance to lead (L)
Situation report on sepsis	- Coordination group/ Technical working group to be established (L)	- Provide existing data/activities (S)	- Provide existing data/activities and contribute/co-lead the technical working group (S)
Consensus document on sepsis definitions	- Leads technical working group (L)		- Various professional groups to participate (S)
Guiding principles document on aspects of sepsis prevention	- Leading role (L)		- Global IPC network (S)
Guidance on clinical management	- Leads technical working group (L)		- Various professional groups to participate (S)
Template for sepsis National Action Plan	- Leading role (L)	- National Action Plan to be implemented in the context of the Global Action Plan (S)	- Global Sepsis Alliance to coordinate with other countries and provide input (L, S)
Toolkit of care bundles	- Potential joint product (S)	- Provide critical input particularly from LMIC	- Various professional groups(L) - Surviving sepsis campaign, campaigns, patient advocacy
Educational campaign and capacity-building	- Coordinates information exchange (S) - Reviews and shares products (S) - Harmonization of products - Translation	- Mandate sepsis education	- Chinese University of Hong Kong to share and distribute activities - Various professional groups to participate (S) - Links with other types of activities, across different stakeholders

PRIORITIES	WHO	MEMBER STATES	OTHER STAKEHOLDERS
Core competency framework on sepsis for health care workers	- Leading role (L)	- Mandate sepsis education	- Various professional groups (S)
Research: Observational studies for consensus case definitions	- Highlights this research gap and advocates for research on it - Possible participation in joint research proposal (S)	Member States to participate	- Sepsis research alliance in Africa under development - Global Sepsis Alliance, European Society of Intensive Care Medicine to help coordinate research - US CDC to share ongoing activities - Latin American Sepsis Institute to share its study Any stakeholder, particularly academic and research institutions, to take the lead
Research: Economic impact of sepsis	- Highlights this research gap and advocates for research on it - Possible participation in joint research proposal (S)	Member States to participate	Any stakeholder, particularly academic and research institutions, to take the lead
Research: Laboratory diagnostics for LMIC	- Highlights this research gap and advocates for research on it - Possible participation in joint research proposal (S)	Member States to participate	Any stakeholder, particularly academic and research institutions, to take the lead
Research: Evaluation of campaign effectiveness	- Highlights this research gap and advocates for research on it - Potential area for WHO to lead		Stakeholders to collaborate
Sepsis portal	- Potential area for WHO to lead		Any stakeholder, particularly international networks/organizations could take the lead

L: leading role; S: support; IPC: Infection prevention and control; LMIC: Low- and middle-income countries.

Summary of the meeting and review of next steps

Ed Kelley, Benedetta Allegranzi

The World Health Assembly resolution WHA70.7 makes sepsis an important part of our future work. The meeting heard overviews of WHO's activities from at least 10 WHO units and departments that are working on different aspects of sepsis surveillance, prevention, diagnosis and clinical management. Participants discussed what WHO does and what other organizations are doing. The meeting focused specifically on the situation in LMICs, looking at the current situation and the major gaps, and participants agreed the directions for future action. The meeting defined the priorities for the next 5 years and identified who would be the key players in each area; this is an invaluable asset for WHO to make meaningful plans and concretely fit sepsis in the future technical agenda.

The development of a Global Action Plan was considered a high priority for which WHO will consider the feasibility and timeline. The preparation of a toolkit for a global sepsis campaign would be very helpful, including as a model for national campaigns. It was agreed that better definitions of sepsis need to be developed. The difficulties in data collection were recognized and it was agreed that definitions must be harmonized to make them applicable in LMICs. A global guideline on the clinical management of sepsis is needed. There are inconsistencies in current guidelines, and difficulties are encountered in applying them globally. Specific toolkits for applying guidelines in different contexts would be very helpful. More educational activities are needed for both the general public and health care workers. The meeting identified the areas for research in a number of domains – observational studies to reach consensus on definitions and to validate them, to assess the economic impact of sepsis, and studies to find the most cost-effective interventions to prevent sepsis. Research is needed to identify new diagnostics, to assess the effectiveness of campaigns, and to examine a range of other concerns relating to sepsis. It was agreed to share these roles and responsibilities, and WHO was ready to accept the responsibilities that it was given.

Participants welcomed the fact that the World Health Assembly resolution made it possible to take steps forward together.

Closing

Dr Naoko Yamamoto (WHO Assistant Director General, [Universal Health Coverage and Health Systems](#)) thanked all participants for their active contributions to this WHO technical experts meeting on sepsis. She shared her personal experience as a medical doctor dealing with sepsis and septic shock. Sepsis can be seen as “a mirror of the quality of health care” as the rate of sepsis is a very good indicator of health systems. She described the meeting as a major step by WHO to link with partners to identify priorities and make plans to move the global agenda on sepsis forward in accordance with the World Health Assembly resolution.

WHO will strive to work closely with all the technical experts, Member States and other key stakeholders to create cohesion and build momentum in the battle to tackle sepsis.

Appendix 1. Agenda



WHO Sepsis Technical Expert Meeting

16–17 January, 2018

Place: Best Western Chavannes-de-Bogis Hotel, Chavannes-de-Bogis, Switzerland

Agenda

Background:

Sepsis is estimated to affect more than 30 million patients every year worldwide and global rates of sepsis are thought to be growing rapidly. At the Seventieth World Health Assembly, Member States adopted a resolution on improving the prevention, diagnosis and treatment of sepsis.

According to the resolution, WHO is requested to develop guidance for the prevention and management of sepsis, to produce a report on the epidemiology and burden of sepsis, and to support countries to get the necessary infrastructure, laboratory capacity, strategies and tools to address sepsis. The Organization is also expected to work with partners to improve access to quality, safe, efficacious and affordable treatments for sepsis and tools for infection prevention and control (IPC), including immunization, particularly in developing countries.

Several WHO departments work on aspects of prevention, diagnosis and treatment of infections leading to sepsis including research, both in the community and the health care settings. A technical group coordinated by the Service Delivery and Safety department (“Sepsis Coordination Group”) has been established to support and implement the resolution. Actions to make this group the most inclusive possible of all groups who can play a role in advancing the sepsis agenda both at the HQ and regional levels are being undertaken; the group currently includes the following departments: *Service Delivery and Safety; Antimicrobial Resistance; Essential Medicines and Health Products; Immunization, Vaccines and Biologicals; Infectious Hazard Management; Information, Evidence and Research; Innovation Access and Use; Maternal, Newborn, Child and Adolescent Health; Public Health, Environmental and Social Determinants of Health; and Reproductive Health and Research.*

At this crucial time following the resolution adopted by Member States, WHO convenes the Sepsis Technical Expert Meeting inviting experts, stakeholders and representatives from countries that have already progressed in the development and implementation of prevention, diagnosis and treatment of sepsis. The overall objective of the meeting is to identify priorities and make plans to move forward the global agenda on sepsis according to the resolution.

Objectives:

The main objectives of the meeting are as follows:

- To share an overview of major initiatives ongoing worldwide on sepsis
- To present current WHO activities and plans
- To discuss global needs and priorities for action
- To gather input on the critical role of WHO and key areas of work
- To explore collaborations between WHO and other key players with the common goal of progressing the sepsis agenda

Day 1: Tuesday, 16 January 2018

8:45–9:30 Session I (*chair: Ed Kelley*)

Welcome and round of introductions

Ed Kelley and Marc Sprenger

Meeting overview: background, objectives and expected outcomes

Benedetta Allegranzi

9:30–10:30 Session II

Overview of WHO work on sepsis (*chair: Liz Tayler*)

Overall presentation of WHO work (*Ed Kelley*)

followed by

Open discussion of the following key areas of work (10 min each):

- Epidemiology and burden of sepsis – attended by *Colin Mathers*
- Maternal sepsis – attended by *Mercedes Bonet*
- Neonatal sepsis – attended by *Ornella Lincetto*

10:30–10:50 Coffee/tea break

10:50–11:30 Session II

Overview of WHO work on sepsis (cont.)

Open discussion of the following key areas of work (10 min each):

- Prevention – attended by *Benedetta Allegranzi & Philipp Lambach*
- Diagnosis – attended by *Francis Moussy*
- Clinical management – attended by *Janet Diaz*
- Antimicrobial resistance – attended by *Liz Tayler & Carmem Pessoa Da Silva*

Final discussion

11:30–12:00 Session III

The WHO SAVE LIVES Clean Your Hands campaign (*chair: Benedetta Allegranzi*)

5 May 2018 – Focus on preventing sepsis in health care

Didier Pittet

12:00–13:00 Lunch

13:00–14:30 Session IV

Overview of international sepsis activities and situation (*chair: Denise Cardo*)

Presentations (12 min each) by:

- Carlos Füchtner: key aspects of epidemiology, prevention, diagnosis and clinical management of maternal sepsis
- Mike Sharland: key aspects of epidemiology, prevention, diagnosis and clinical management of paediatric sepsis
- Flavia Machado: overview of sepsis in low- and middle-income countries
- Konrad Reinhart: overview of the work of the Global Sepsis Alliance
- Massimo Antonelli: overview of the Sepsis Surviving Campaign

- Denise Cardo: overview of the work of CDC
- Ron Daniels: overview of the United Kingdom Sepsis Surviving Campaign

14:30–14:45 Coffee/tea break

14:45–15:30 Session IV

Overview of international sepsis activities and situation (continued)

Open discussion and additional contributions

15:30–18:00 Session V

Mapping out global work on sepsis and identification of gaps and actions needed

- Presentation of objectives and methodology (*Hiroki Saito*)
- Four working groups (with facilitators and rapporteurs for each group), for each to discuss the following key subject areas:
 1. Epidemiology and burden of sepsis (facilitators: Simon Finfer & Carmem Pessoa)
 2. Prevention (facilitators: Alison Holmes & Benedetta Allegranzi)
 3. Diagnosis/clinical management (facilitators: Flavia Machado & Janet Diaz)
 4. Awareness raising/Campaign (facilitator: Ron Daniels & Mercedes Bonet)

Purpose: Further discuss the current progress, gaps to be filled and actions needed for each area.

19:00–21:00 Dinner (hosted by WHO)

Day 2: Wednesday, 17 January

8:30–8:45 Session VI

Recap Day 1 and Plan for Day 2

Benedetta Allegranzi

8:45–10:30 Session VII

Reporting back from working groups (*chair: Ornella Lincetto*)

10:30–10:45 Coffee/tea break

10:45–12:45 Session VIII

Priorities and plans for action at country and international level (*chair: Ed Kelley; facilitator Benedetta Allegranzi*)

Based on the findings shared from Sessions I to VIII, with focus on epidemiology, prevention, diagnosis, clinical management, and on specific patient populations, discuss the following actions (and beyond) *at country and international levels*:

- Awareness raising/campaigning actions
- Reports

- Policies and evidence-based guidelines
- Implementation strategies and tools
- Education and training activities
- Research
- Networking, coordinating partners' actions

12:45–13:45 Lunch

13:45–15:15 Session IX

Roles, responsibilities and collaborations to disseminate the resolution and implement the plans (*chair: Konrad Reinhart; facilitator: Paul Rogers*)

Define roles and responsibilities for participant organizations and key players, and opportunities for collaboration, and discuss actionable plans to be implemented

15:15–15:30 Coffee/tea break

15:30–16:30 Session X

Summary of the meeting and review of next steps

Ed Kelley

Closing remarks

Naoko Yamamoto

Appendix 2. List of participants



WHO Sepsis Technical Expert Meeting, 16–17 January 2018, Geneva, Switzerland

List of Participants

African Region

Shevin JACOB

African Sepsis Alliance
Uganda

Halima Salisu KABARA

National Association of Nurse Intensivists of
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Kathryn MAITLAND

Imperial College
Kenya

Mpoki ULISUBISYA

Society of Anaesthesiologists of Tanzania
Tanzania

Region of the Americas

Denise CARDO

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Laura EVANS

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United States of America

Carl FLATLEY

Sepsis Alliance
United States of America

Carlos FÜCHTNER

International Federation of Gynecology
and Obstetrics
Bolivia

Niranjan KISSOON

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Flavia MACHADO

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United States of America

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Raghib MANZOOR

Bangladesh Society of Critical Care Medicine
Bangladesh

Erwin PRADIAN

Indonesian Society of Intensive Care Medicine
Indonesia

Amin PRAVIN

Indian Society of Critical Care Medicine
India

European Region

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China

WHO

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Maternal, Newborn, Child and Adolescent
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Benedetta ALLEGRANZI
Infection Prevention and Control Global Unit

Rajiv BAHL
Maternal, Newborn, Child and Adolescent
Health

Peter BEYER
Essential Medicines and Health Products

Mercedes BONET SEMENAS
Reproductive Health and Research

Vanessa BRIZUELA
Reproductive Health and Research

Ana Paula COUTINHO
WHO Regional Office for Europe

Nino DAYANGHIRANG
WHO Regional Office for Africa

Jerome DELAUZUN
Infection Prevention and Control Global Unit

Janet DIAZ
Infectious Hazard Management

Theresa DIAZ
Maternal, Newborn, Child and Adolescent Health

Sergey EREMIN
Antimicrobial Resistance

Ahmet GULMEZOGLU
Reproductive Health and Research

Robert JAKOB
Information, Evidence and Research

Edward KELLEY
Service Delivery and Safety

Philipp LAMBACH
Immunization, Vaccines and Biologicals

Ornella LINCETTO
Maternal, Newborn, Child and Adolescent Health

Nicola MAGRINI
Essential Medicines and Health Products

Colin MATHERS
Information, Evidence and Research

Margaret MONTGOMERY
Water, Sanitation and Hygiene

Allisyn MORAN
Maternal, Newborn, Child and Adolescent Health

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Essential Medicines and Health Products

Dhamari NAIDOO
Infectious Hazard Management

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Innovation Access and Use

Astrid WESTER
Public Health, Environmental and Social Determinants of Health

Naoko YAMAMOTO
Health Systems and Innovation

Observers

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