Scientific recommendations for a Belgian Sepsis National Action Plan (Be-SNAP)

Version 1 30/05/2024


Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola
Universiteit Antwerpen
UZ GENT
UNIVERSITEIT GENT
UZ LEUVEN
jessa ZIEKENHUIS
Hôpital Erasme
ULB
Cliniques universitaires SAINT-LUC UCL BRUXELLES
SIZ
BELGIAN SOCIETY OF INTENSIVE CARE MEDICINE
DOMUS MEDICA
ALLES VOOR HUISARTSEN
GZA
ZAS
H.U.B
afiu
SEPSIBEL
Belgian Cancer Registry
CHR HAUTE SENNE
az Sint Blasius
BE·S·E·D·I·M
BELGIAN SOCIETY OF EMERGENCY AND DISASTER MEDICINE
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CHU de Liège
CHU UCL NAMUR
Dinant · Godinne · Sainte-Elisabeth
GHdC
BAPCOC
Belgian Antibiotic Policy Coordination Commission
UCLouvain BRUXELLES
sciensano
Volksgezondheid Veiligheid van de Voedselketen Leefmilieu
Vlaanderen is zorgzaam en gezond samenleven
vivalis.brussels Voel je goed, leef beter
VUB
zorgnet ICURO
AZ Voorkempen algemeen ziekenhuis emmaüs
azdelta
VVVS
BVIKM/SBIMC
zna
SIZ Nursing
EpiCURA mon hôpital
HAUTE ÉCOLE CONDORCET
azGlorieux
E17 ziekenhuis netwerk
REVARTE revalidatie ziekenhuis
AZ JAN PALFIJN GENT
inkendaal
netwerk verpleegkunde
ULB UNIVERSITÉ LIBRE DE BRUXELLES
HOST IRIS
LIÈGE université
BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE SOCIÉTÉ BELGE DE PÉDIATRIE
TRIaz zorg van a tot z
VITAZ STERK IN ZORG
iris
UZA
KU LEUVEN
LUHTAR
curoz
helix ziekenhuizen
Belgian Society for GERONTOLOGY and GERIATRICS
ziekenhuis netwerk gent
HOST Hospital Outbreak Support Team TRIaz
curoz
VLAAMSE VERENIGING INTENSIEVE ZORGEN VERPLEEGKUNDIGEN
UCL Université catholique de Louvain
plexus Zorgnetwerk Oost-Vlaams-Brabant

KEY TOPICS BELGIAN SEPSIS NATIONAL ACTION PLAN		Working group chair
1	**Sepsis Awareness of Public & Healthcare providers:** - Astrid Brys - Cindy Verthé - Els Duval - Jan Verbakel - Jolien Van Bever - Stefan Morreel - Thomas Snoeij	**Erika Vlieghe** **Ilse Malfait**
2	**Antibiotic stewardship – Infection prevention:** - An Merchie - Ann Caluwaerts - Cécile Meex - Emilie Bogaerts - Emilie Coppens - Ernestina Repetto - Greet Van Kersschaever - Hanna Masson - Heidi Theeten - Hilde Jansens - Jan Verbakel - Jo Demunck - Monia Chermais - Nathalie Layios - Pieter Depuydt - Reinoud Cartuyvels - Thomas Snoeij - Tom De Vos - Veerle Cossey	**Erika Vlieghe**
3	**Early Recognition & response:** - Astrid Brys - Cornelia Genbrugge - Emilie Bogaerts - Erika Vlieghe - Filip Haegdorens - Inge Matthijs - Jef Willems - Marc Cortens - Yanick De Wilde	**Ken Dewitte**

4	**Early Adequate Treatment:** - Alexia Verroken - Cornelia Genbrugge - Harlinde Peperstraete - Jef Willems - Johan Gillebeert - Josephine Declaye - Maya Hites - Reinoud Cartuyvels - Xavier Wittebole	**Patrick Van de Voorde**
5	**Early Rehabilitation – Long Term Care:** - Caroline Redant - Cheryl E. Hickmann O. - Cindy Verthé - Emilie Boussemaere - Ilse Malfait - Lina Van Brabander - Nathalie Vaes - Philippe Beutels - Sophie Martin - Wim Schrauwen - Ariane Willems	**Harlinde Peperstraete**
6	**Advance Care Planning – Ethical decision making:** - Alexandra Coulon - Astrid Brys - Katrin Gillis - Patrick Druwé - Patrick Lacor - Peter Pype	**Patrick Van de Voorde**
7	**Research & Surveillance:** - Boudewijn Catry - Daniel De Backer - Greet Van Kersschaever - Marc Van Nuffelen - Petra Schelstraete - Philippe Beutels - Stefan Morreel - Stefan Teughels	**Jan De Waele**

Coordination and redaction

Erika Vlieghe
Annelies Mondelaers

Disclaimer

This document is a first version, awaiting revision from external experts. A revised version based on their feedback will be submitted by the end of June 2024.

Acknowledgements

We would like to thank:
-all participants in the working groups and the chairs for their motivation and intense work, despite many other responsibilities
-our colleagues and relatives for their patience during many hours of work at this plan
-minister Frank Vandenbroucke for offering the community of health care workers and patients the opportunity to collaborate in this new plan
-FOD Volksgezondheid and BD for their support

The Be-SNAP working group
30/5/2024

In collaboration with

Table 1. Overview of the professional actors and societies involved in the Be-SNAP working group.

Participating societies	
BESEDIM	Belgian Society of Emergency & Disaster Medicine
SIZ	Belgian Society of Intensive Care Medicine
SIZ Nursing	SIZ Nursing French-speaking Association of Intensive Care Nurses
BVIKM	Belgian Society of Infectiology and Clinical Microbiology
SBIMC	Société Belge d'Infectiologie et de Microbiologie Clinique
Be-Pics	Belgian Pediatric Intensive Care Society
BVK	Belgian Society of Pediatrics
BSGG	Belgian Society of Gerontology and Geriatrics
Domus Medica	Flemish scientific society for General Practitioners
Sepsibel	Belgian Sepsis Survivors
VVVS	Scientific Societies of Emergency Nurses
AFIU	L'Association Francophone des Infirmiers d'Urgence
VVIZV	Flemish Scientific Society of Intensive Care Nurses
NVKVV	Netwerk Verpleegkunde
VVNP	Flemish Society for Neuropsychology
BSNR	Belgian Society for Neurorehabilitation
RBSPRM	Royal Belgian Society of Physical and Rehabilitation Medicine
Universities and research centres	
Ugent	University of Gent
UAntwerpen	University of Antwerp
KU Leuven	Catholique University of leuven
UCLouvain	Université catholique de Louvain
ULB	Université libre de Bruxelles (ULB)
Uliège	University of Liège
VUB	Vrije Universiteit Brussel
HEPH-Condorcet	Haute Ecole Provinciale de Hainaut-Condorcet
Public health actors	
Sciensano	
BAPCOC	Belgian Antibiotic Policy Coordination Commission
HOST	Hospital Outbreak Support Team
Federaal Platform voor ziekenhuishygiëne	
FPS Health	Federal Public Service Public Health, Food Chain Safety and Environment
Departement Zorg	
Vivalis	
CKB	Commissie voor Klinische Biologie, Microbiology working group
BCR	Belgian Cancer Registry

Hospital networks and other health care actors	
Plexus	
Helix	
ZAS	Ziekenhuis aan de Stroom
VITAZ	
CHU/UCL Namur	Centre Hospitalier Universitaire UCL Namur
IRIS	Brussels hospital network
TRIaz	
E17	
CUROZ	
Wit-gele Kruis	Wit-Gele Kruis Vlaanderen
Zorgnet -ICURO	Flemish Umbrella organization of general hospitals and care facilities
ZNG	Ziekenhuis Netwerk Gent

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LIST OF ABBREVIATIONS

ACP	Advance care planning
ACT	Acceptance and Commitment Therapy
ADL	activities of daily living
AHRQ	Agency for Healthcare Research and Quality
AI	Artificial Intelligence
AMR/AMS	Antimicrobial Resistance/ Antimicrobial Stewardship
AMU	Antimicrobial Use
AMT	antibiotic management teams
APG	Antibiotic policy groups
APIC	Association for Professionals in Infection Control and Epidemiology
ASP	Antimicrobial Stewardship Programs
AVIQ	l'Agence pour une Vie de Qualité.
BAPCOC	Belgian Antibiotic Policy Coordination Commission
BeNAP	Belgian National Action Plan
BSI	Bloodstream Infections
BSQ	Body Sensations Questionnaire
CAUTI	Catheter-associated urinary tract infection
CDSS	Clinical decision support systems
CDI	*Clostridioides difficile* infection
CIP	Critical Illness Prediction
CKD	chronic kidney disease
CLC-IC	Checklist for cognitive consequences after ICU admission
CLABSI	central line associated bloodstream infection
COPD	chronic obstructive pulmonary disease
CPM	continuous passive motion
CRP	C-reactive protein
CRA	Coordinerend en Raadgevend arts
CSS	Superior Health Council
DNAR	do-not-attempt-resuscitation (DNAR)
EBP	Evidence-Based Practice
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EEA	European Economic Area
EHR	Electronic Health Records
EMDR	Eye Movement Desensitization and Reprocessing
EMR	Electronic Medical Record
EMS	Emergency Medical Services
ERC	European Resuscitation Council
ESA	European Sepsis Alliance
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESICM	European Society of Intensive Care Medicine
EWS	Early Warning Score
FEES	flexible endoscopic evaluation of swallowing

FES	Functional Electrical Stimulation
FSS	Fatigue Severity Scale
FSS	family support structure
GAD	Generalized Anxiety Disorder scale
GBD	Global Burden of Disease study
GLOSS	Global Maternal Sepsis Study
GP	General practitioner
HABSI	health care-associated bloodstream infection
HADS	Hospital Anxiety and Depression Scale
HALT	Healthcare-associated infections and Antimicrobial use in Long-Term care facilities
HAP	hospital-acquired pneumonia
H(C)AI	health (care)-associated infection
HCP	Healthcare Professional/provider
HGR	Hoge Gezondheidsraad
HICPAC	Healthcare Infection Control Practices Advisory Committee
HOST	Hospital Outbreak Support Team
HRQL	health-related quality of life
IDSA	Infectious Disease Society of America
ICU	Intensive Care Unit
IPC	Infection Prevention and Control
IQR	Interquartile range
IRIS	Infection Risk Scan
JPI-AMR	Joint Programming Initiative on Antimicrobial Resistance
KCE	Belgian Health Care Knowledge Centre
LMIC	Low-Middle Income Countries
LOS	Length of Stay
LqSOFA	Lactate-enhanced-qSOFA
MAP	Mean Arterial blood Pressure
MDRGN	multidrug-resistant Gram-negative pathogens
MDRO	MultiDrug Resistant Organisms
MET	Medical Emergency Teams
MFO	Medical Pharmaceutical Consultation
MICA	Monitoring Intensive Care Activities
ML	machine learning
MMSE	Mini-Mental State Examination
MRSA	Methicillin-resistant Staphylococcus aureus
MUST	Malnutrition Universal Screening Tool
NEMS	neuromuscular electrical stimulation
NEOKISSBE	National Surveillance of Infections in Neonatology Units
NEWS	National Early Warning Score
NH	nursing home
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NIHDI	National Institute for Health and Disability Insurance
NIPDS	Nurse Intuition Patient Deterioration Score
OECD	Organization for Economic Cooperation and Development

OPAT	Outpatiënt Parenteral Antimicrobial Therapy
OST	outbreak support teams
PAT	Pediatric Assessment Triangle
PCPSTD DSM-5	Primary Care Post Traumatic Stress Disorder screen based on the Diagnostic and Statistical Manual-5
PCT	procalcitonin
PD	patient-days
PDMS	Patient Data Management Systems
PEWS	Pediatric Early Warning Score
PICS	Post-Intensive Care Syndrome
PICU	Pediatric Intensive Care Unit
PIDACS-IPC	Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control
PIDS	Pediatric Infectious Diseases Society
PIT	Paramedical Intervention Team
PICS	post-Intensive Care Syndrome
POCT	Point-of-care testing
PPS	Point Prevalence Survey
PROM	Passive Range of Motion
PSP	Pancreatic Stone Protein
PSS	post-sepsis syndrome
PSQI	Pittsburg Sleep Quality Index
QALY	Quality Adjusted Life Years
QI	Quality Improvement
QoL	Quality of Life
qSOFA	Quick Sepsis-Related Organ Failure Assessment
RCTs	randomized-controlled trials
RIZIV/INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité
RRT	Rapid Response Teams
SBAR	Situation Background Assessment and Recommendation
SCCM	Society of Critical Care Medicine
SDoH	Social determinants of health
SHEA	Society for Healthcare Epidemiology of America
SHC	Superior Health Council
SIRS	systemic inflammatory response syndrome
SNAP	Sepsis National Action Plan
SNAQ	Short Nutritional Assessment Questionnaire
SOFA	Sequential Organ Failure Assessment
SOP	standard operating procedures
SOT	solid organ transplantation
SSC	Surviving Sepsis Campaign
SSIs	surgical-site infections
TDM	therapeutic drug monitoring
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
VRE	vancomycin resistant enteroccoci
WHA	World Health Assembly
WHO	World Health Organization

EXECUTIVE SUMMARY

Sepsis is a life-threatening medical condition that occurs when the body's response to an infection causes intense inflammation, leading to dysfunction and failure of vital organs and functions, such as the kidneys, liver, heart, the brain or the blood clotting system. Sepsis and septic shock are associated with high mortality and substantial, long lasting morbidity. Depending on the location and population studied, about 10–30% of patients with sepsis die from the condition, with hospital mortality for septic shock approaching 40–60%.

A wide variety of microorganisms may trigger sepsis, including bacteria, fungi, viruses, and parasites, depending on the region and setting where the infection occurs: at home ('community-acquired'), during or shortly after a stay in the hospital or in a long term care facility ('health care associated').
Sepsis can present in many settings and in a wide variety of patients, and is easily missed in its early stages. There is no single laboratory or imaging test to unequivocally confirm the diagnosis of sepsis, which is made based on a combination of clinical findings and laboratory tests (i.e. suspicion of infection plus signs of organ failure). Cultures of blood and other body samples are used to determine the causal pathogen and guide antimicrobial treatment.

Sepsis can occur to anyone, but certain groups have particular risk: the very young and very old, pregnant women, persons with severe underlying co-morbidity and/or immune deficiency, persons who were recently admitted in hospital and/or have indwelling devices (e.g. vascular or urinary catheters), persons who survived earlier sepsis episodes, persons with severe underlying mental health, persons with limited education and/or precarious living circumstances (e.g. homeless, living in poverty, prisoners,…).

Global estimates mention yearly about 50 million cases of sepsis, leading to at least 11 million deaths, of which the majority occurs in low and middle income settings. However, also Europe and other high income settings have an increasing sepsis burden in its ageing and increasingly vulnerable population and the emergence of antimicrobial resistance. There are very few surveillance data on sepsis and on its impact available for Belgium. According to estimates based on the 2017 Global Burden of Diseases study and other literature, there are about 40,952 sepsis cases every year in Belgium (95% CI 31,938 - 54,451), equal to an estimated incidence of 358/100,000 population (279-477/100,000 population), leading to 7,675 (95% CI 6,421-9,089) premature deaths per year, and associated to an annual loss of 38106 QALYs (47% of which through premature mortality), and an annual cost between €277 million and €4.3 billion, depending on the method used.

In 2017, sepsis has been declared a priority for global health by the World Health Assembly (WHA). The WHA resolution on sepsis (WHA70.7) urges the member states to take action in developing and implementing national strategies to improve prevention, diagnosis and management of sepsis. Until date, there is no national sepsis plan nor coordinated action on the prevention and mitigation of the sepsis burden. Upon request of minister Frank Vandenbroucke, a multidisciplinary working group was set up in December 2023, with the mandate to deliver a scientific report within 4-6 months, that should be the fundament of a future national sepsis plan. The working group was created with representatives of various scientific professional organizations (including emergency medicine, primary care, nursing, infectious diseases and microbiology, intensive care, gerontology, pediatrics, rehabilitation,…), public health actors (e.g. Sciensano, regional and federal public health staff), sepsis researchers and representatives of the sepsis survivors patient organizations.

Seven main themes were identified as the major fields requiring interventions to reduce the incidence and impact of sepsis in Belgium:

1. Awareness and knowledge
2. Prevention of sepsis and safeguarding effectiveness of antimicrobials (IPC and AMS)
3. Early warning systems
4. Early adequate treatment
5. Care trajectory for sepsis survivors
6. Strengthen advanced care planning
7. Research agenda and surveillance

Each working group searched and summarized the available literature (with focus on systematic review), and formulated recommendations, which were discussed in two plenary sessions. For the final set of recommendations, an additional assessment of feasibility, cost and other implementation characteristics was carried out, with particular attention for the interface and synergism with already existing activities, plans and regulations (e.g. NAP-AMR, advanced care planning,…). The first version of this document (Version 30052024) will be delivered to minister Vandenbroucke on 31/05/2024, awaiting the feedback of external reviewers.

The Be-SNAP working group recommends the following:

Chapter 1. Awareness and knowledge

1. A National Sepsis Focal Point or Steering Group should be created, responsible for coordinating and following up of the implementation of interventions related to sepsis awareness and management (i.e. a National Sepsis Plan or Program). The focal point or Steering Group should include public health officers, scientific experts, (para)medical professionals, representatives of patient advocacy groups (example from Australia: https://www.safetyandquality.gov.au/our-work/national-sepsis-program)

2. A National Sepsis Foundation should be created to increase awareness of sepsis among the public, at-risk patient groups and healthcare professionals (HCP). It should serve as a hub for educational materials, advocacy and support of survivors. This could evolve for instance from the actual Sepsibel organization. The foundation should have an easily accessible website (e.g. Sepsisnet.nl; https://www.australiansepsisnetwork.net.au/, to serve as a centralized hub for information, resources, and support.

3. A general awareness campaign should be developed, with general messages for the general public and sufficient attention to reach persons with limited education levels and/or infrequent health information-seeking behavior.

    a. The concept 'sepsis' should be branded (use the word, in particular for highly vulnerable groups) in messages. Storytelling (survivors' testimonials) could support awareness messages.

    b. World Sepsis Day (September 13th) could be used as a focal point for raising public awareness through events, campaigns, and educational activities.

    c. Joint messaging initiatives linking sepsis awareness with antimicrobial stewardship should be foreseen to avoid redundant/conflicting messages.

4. Tailored awareness and educational interventions should be created directed towards higher-risk patient groups, such as oncological patients, immunosuppressed patients, children and their caregivers in collaboration with relevant other societal actors (e.g. other patient groups, associations,…)

5. Education on recognition and early management of sepsis for all relevant HCPs should be designed and implemented. This includes medical doctors, nurses, home care nurses, nursing aids in nursing homes, pharmacists, dentists… The specific roles and tasks for each group need to be defined.

    a. Training on sepsis should be part of the undergraduate and postgraduate education of these professional groups.

    b. For HCPs working in long-term care facilities, sepsis awareness training should be made mandatory.

    c. Training modules should be differentiated for the different HCPs groups, including pediatricians, pediatric care providers (nurseries, Kind & Gezin), geriatricians, home care nurses and chronic care providers.

    d. Training on sepsis for all HCPs working with children should be strengthened via:

        i. a clear set of learning objectives of pediatric sepsis into medical and nursing curricula,

        ii. a national consensus on guidelines for pediatric sepsis, readily available online,

        iii. reinforcing knowledge of pediatric sepsis as a mandatory part of the continuous professional development for nurses and doctors through accredited (simulation)training sessions, online learning platforms, interdisciplinary discussions or case reviews

        iv. development of transfer criteria to escalation of care (to regional PICU/NICU)

    e. Professional sepsis training should integrate sepsis recognition tools and early warning scores (see Chapter 3), as well as antimicrobial stewardship. For pre-hospital settings, telephone-triage tools should be explored.

Chapter 2. Prevention of sepsis and safeguarding effectiveness of antimicrobials (IPC and AMS)

2.1. Prevention of sepsis in the community

1. Strengthen/ensure access to (chronic) healthcare for all, with specific attention to the most vulnerable (medically and socio-economically). In particular, strengthen access and linkage to chronic care, including affordable wound care and dental care. The use of telemonitoring/remote patient monitoring may be further explored in this context.

2. Invest in health and vaccination literacy, in particular for most vulnerable populations, with emphasis on infection prevention (including food safety).

3. Combine education on sepsis awareness with prudent use of antibiotics and AMS. Several actors can bring this combined message (medical doctors, nurses, pharmacists, patient advocates,...)

4. Strengthen (catch up) vaccination programs for children and programs for adults with indications for additional vaccinations (65+, medically vulnerable, pregnant). This includes improved/easier registration and reduced cost of adult vaccination for at risk groups.

5. Develop specific guidelines and training on safe home care for patients with indwelling catheters (IPC training for home care nurses, interface with LTCF and HOST/ Outpatient Parenteral Antimicrobial Therapy (OPAT)-projects)

2.2. Prevention of sepsis in the acute care (hospitals)

1. A multimodal strategy for the prevention of health care associated blood stream infection should be implemented in all Belgian hospitals. This includes: (1) Build it: availability of the appropriate infrastructure means and supplies to enable IPC good practices. (2) Teach it: education and training of health care workers and key players. (3) Check it: monitoring infrastructures, practices, processes, outcomes and providing data feedback. (4) Sell it: reminders in the workplace/ communications. (5) Live it: culture change within the establishment or the strengthening of a safety climate.

2. Antibiotic policy groups (APG)/antibiotic management teams (AMT) have been assigned the responsibility of promoting AMS in acute care hospitals. Strengthening and providing sufficient financial support to APGs are essential to guarantee the effective execution of these responsibilities at the local level (including stewardship intervention and advice intra and transmural). This includes genuine

remuneration for bedside stewardship activities and multidisciplinary discussions on complex resistance cases

3. National antibiotic guidelines should serve as a robust foundation for the formulation of institution-specific protocols for managing antibiotic use in cases of sepsis. It is strongly advised to offer support mechanisms facilitating routine revisions and expansions of these guidelines.

4. Microbiology laboratories generate essential information for the adequate treatment of patients. Hospital laboratories should set up quality processes to further improve the quality of sampling, analyzing and early reporting for critically ill patients.

2.3. Prevention of sepsis in long term care facilities (LTCF)

1. Build/implement and follow up the presence of essential core components for IPC and AMS in LTCF. This includes the availability of specific guidelines, sufficient educated staff, availability of personal protective materials, surveillance of HAI/sepsis in LTCF and monitoring/audit and feedback on specific interventions, organized in care bundles and multimodal strategies
2. Define specific objectives and quality indicators for AMS and IPC in LTCF, as well as multimodal strategies to implement them. Priority should be given to concrete interventions.
3. Develop and teach a (postgraduate) education package for coordinating and advising clinicians in LTCF ('CRA') and for nurses working in LTCF
4. Give additional support (administrative and logistic) to nurses working in LTCF enabling them to focus on clinical work, advanced ward management, and coordinating care activities closely with CRA's.
5. Strengthen the role of the CRAs, allowing them more autonomy and responsibility for IPC and AMS-related tasks. Tele-advice with clinical infectiologists or microbiologists could be considered
6. Support should be foreseen for surveillance/registration of HAI / AMR / AMC in LTCF
7. More research on the effectiveness, implementation and (psychosocial) impact of specific IPC and AMS interventions is needed.

Chapter 3. Early warning systems

1. In LTCF: the paucity of literature and robust studies show that much still needs to be done to reduce sepsis-related morbidity and mortality in LTCF residents. This includes developing and validating an effective sepsis screening tool applicable in the LTCF setting.

2. In Primary Care settings: sepsis screening tools and (pediatric) early warning screening tools may provide practical and effective means for sepsis screening in primary care settings. Their use should be part of a broader sepsis strategy which includes education, triage tools and readily available expert advice and requires further research.

3. Pre-hospital teams: we recommend using a screening tool for prehospital teams to communicate the vital status of patients with possible sepsis. Further research is needed to validate the effectiveness of point-of-care testing in the prehospital setting.

4. In Hospitals: To enhance early detection and management of sepsis in the emergency department (ED), an early warning system such as the National Early Warning Score (NEWS) with point-of-care lactate testing is recommended. This approach combines NEWS's high sensitivity and specificity for sepsis and septic shock with lactate levels' prognostic value, facilitating timely and effective sepsis care.

    a. All adult patients admitted to an acute hospital ward should be observed regularly and systematically throughout their hospital stay with a minimal observation frequency of one observation per 12 hours.

    b. An Early Warning Score (preferably NEWS) should be used to estimate the acuity level in every hospitalized patient. All observations should be done, or at least verified, by experienced bedside nurses or medical doctors with a minimal level of education and training. Hospitals ought to exercise caution when assigning nurse assistants or students the responsibility of conducting patient observations since this is associated with patient deaths (32, 33). The Nurse Intuition Patient Deterioration Score (NIPDS) is a validated instrument that displays strong predictive capabilities for adverse events and can be used by nurses to translate 'clinical worry' into an objective score (34). A combination of NEWS with NIPDS (with thresholds of both scores ≥ 5), as a trigger criterion for rapid response, seems to provide the largest Net Benefit in hospitals (35).

    c. We recommend targeted education for non-ICU hospital clinicians on early clinical deterioration recognition, emphasizing specific actions like seeking help, following protocols, and performing

crucial tasks. However, to achieve meaningful clinical benefits, this education needs integration into a structured RRS with audits and feedback.

d. We advocate for the widespread implementation of RRT or Medical Emergency Teams (MET) across hospitals for patients outside the ICU. This approach should encompass clearly defined criteria for activating assistance from a designated response team. The implementation of RRTs, that can be nurse-led, physician-led, or mixed, is associated with a decrease in both mortality and non-ICU cardiac arrest rates. Hospitals should receive incentives to implement Rapid Response Teams (RRTs) since these can provide proactive, reactive, and supportive care to general wards, in addition to offering educational support. Advanced nursing profiles such as nurse practitioners with critical care expertise could take part in these teams.

e. Finally, hospitals should implement safe nursing staffing levels for acute care settings.

5. In ICU's: an early warning system that includes sepsis screening and alerting should be implemented in ICU wards. The deployment of AI in the ICU should focus on facilitating AI development and addressing ethical concerns.

6. For children: we recommend using PEWS as a triage and screening tool for sepsis among pediatric patients. Other assessment tools, such as the PAT, high-risk criteria or specific tools, such as the Phoenix Sepsis Score, can be combined with PEWS as part of a broader sepsis screening and diagnosis sepsis strategy. Family and caregiver-activated rapid response should be part of a broader strategy. Research should focus on validating current tools and developing and implementing machine learning-based screening tools.

7. For geriatric patients: while waiting for a validated geriatric EWS, we recommend using currently available EWS for sepsis detection, as with the general population. In addition, education in geriatric syndromes of healthcare providers involved with older patients may improve the correct interpretation of currently available EWS in older patients.

8. More research is needed to evaluate cost-effectiveness of machine learning and remote patient monitoring in patients at risk for sepsis.

Chapter 4. Early adequate treatment

1. At the 'Basic' level, large scale education of all relevant healthcare providers in early recognition and 'basic' treatment modalities. This education should be included in the general training for any (para)medical degree, as well as in on-site life-long learning. Systems should guarantee this 'basic' training and also provide their healthcare providers with tools and SOP to allow for 'timely' alarming of 'advanced' care providers and providing appropriate early 'basic' sepsis treatment (e.g. antibiotic guidelines, isolation practices, culture sampling and processing…). They should also guarantee sufficient staffing and resources to do so. Specific procedures should be in place for specific populations and circumstances such as young children, the elderly, or those institutionalized or immune-depressed... Systems should develop specific implementation strategies to create awareness, knowledge and skills and thus improve care at the 'basic' level within their organization.

2. Systems should also guarantee the 24/7 availability of specifically trained 'advanced' care teams that can provide early 'advanced' interventions at the bedside outside of the (P)ICU environment. SOPs should be in place to clarify indications and communication pathways for 'basic' providers to contact these 'advanced' teams. The minimum qualifications for such teams should be defined by law.

3. ICU (and PICU) should have specific -where possible, evidence-based- procedures in place to care for the critical sepsis patient. Specific patient populations -such as children or neonates, or those with refractory shock, needing organ support or extracorporeal membrane oxygenation- demand early referral to a dedicated highly specialized (P)ICU and each (P)ICU should have plans and collaboration agreements to allow for this.

4. The public health authorities should follow up on these requirements but also provide sufficient financial support to allow systems to implement these (in terms of staffing and resource use). Improving the care provided to sepsis patients is likely to be cost-effective when it subsequently has a positive impact on mortality and/or on ICU length of stay or long-term morbidity, or more specifically on the appropriateness of testing or antibiotic use. To do so, the government could specifically subsidize the implementation of 'advanced (rapid) response teams' within any healthcare environment; subsidize efforts to improve antibiotic stewardship and provide free access to national antibiotic guidelines; identify and subsidize the role of tertiary care (P)ICU in referral pathways for specific subpopulations, such as children, including the necessary highly- specialized emergency transport. All of this could be done as part of an overall 'Care Program ('Zorgprogramma/ Programme des soins') Sepsis' that covers

the whole spectrum of care and defines the locoregional requirements for this; the above mentioned requirements could be translated into a set of quality indicators.

Chapter 5. Care trajectory for sepsis survivors

I. Develop a multidisciplinary rehabilitation pathway for sepsis patients that encompasses the psychological, neurological and physical domains.

1. **Early and Individualized Rehabilitation Goals:**

   Within the first four days after admission due to sepsis, the goals of physical rehabilitation should be established in the physical domain. Physical rehabilitation is recommended once the patient is hemodynamically stable and starts with passive mobilization. Within the first seven days of this admission, a first evaluation of the emotional, psychological and cognitive condition should take place. If the patient is not responsive or lucid, heteroanamnesis of closest relatives will be needed to elucidate relevant antecedents in these domains. As soon as the patient's health condition permits, screening and further assessment in the physical, psychological, psychiatric, and neuropsychological domains are necessary to refine and further individualize the rehabilitation goals.

2. **Clear Communication and Care Pathway – use the word sepsis and PSS.**

   - From the first consultation with the patient and/or his relatives, the term sepsis should be named and explained. An introduction to Post-Sepsis Syndrome (PSS) should be provided next, to clarify the rehabilitation pathway, highlighting how the multidisciplinary team can offer support individually tailored to the patient’s needs.
   - Information (brochure ‘life after sepsis’) on long-term outcomes should be provided early in the patient treatment and rehabilitation process.

3. **Seamless Transition and Follow-Up:**

   A thorough handover from third- or second-line care to first-line care should take place. In addition, in the first months after hospital discharge, a strict monthly follow-up with re-evaluation is needed, with adjustments made to the rehabilitation plan as new PSS symptoms arise. In this handover, the status of the patient's remaining residual organ dysfunctions, rehabilitation trajectory, physical and

(neuro)psychological -emotional and neurocognitive- status should be discussed. The possible options for gradually resuming pre-sepsis daily life, work or school, and broader social participation are certainly outlined here as well.

For the reimbursement of the costs of care of patients post sepsis ("long sepsis" or PSS care trajectory) after discharge from the hospital or rehabilitation setting, we recommend to mirror the reimbursement model of the RIZIV agreement for long-COVID-19

4. **Patient and Family-Centric Approach:**

Emphasizing the interaction between the patient and their close relatives is key throughout the recovery process. Recognizing and addressing the unique needs and emotional responses of both the patient and their loved ones to the sepsis experience or PSS is crucial for holistic care.

II. Education about PSS

1. Educating primary care providers and the environment, including general practitioners, home nurses, physiotherapists, speech therapists and outpatient psychologists, about the PSS is very important to provide adequate support to sepsis survivors and their close network (immediate environment).
2. Develop information (brochure 'life after sepsis', …) and education materials on long-term outcomes after sepsis to educate patients, their environment and healthcare workers.

III. Peer support:

- Encouraging interactions with fellow sepsis survivors will ensure that the patients' and their loved ones' sense of loneliness can diminish. Fellow sufferers' conversations are invaluable for processing the emotional impact of the sepsis journey.
- We recommend that the national sepsis body endorse and invest in the Belgian sepsis support group. Linking the Belgian support group to the Belgian national sepsis body will allow healthcare workers or GPs to connect patients to appropriate support quickly.

Chapter 6. Ethical considerations and advanced care planning

1. Targeted education about critical illness (such as sepsis, cardiac arrest…) and outcomes of specific subgroups (older and/or frail patients, high-risk groups…), as well as about the importance of advance care planning, about goals of care and the notion of a 'palliative care' emergency should be an integral part of all professional training of physicians, nurses and other involved care providers.

2. A large-scale communication to all citizens about the importance of ACP, whether as part of a broader information campaign on sepsis is needed (whereby the already existing communication materials (www.mijnoudedag.be) can be used and promoted.

3. Better support for both GP's and relevant organ specialists in taking up the responsibility to assure proper ACP, at least for all patients with a high-risk profile for critical illness and/or those incapacitated. In residential care facilities and nursing homes the coordinating physician, as well as other members of the medical team can help to identify these patients (which should be part of the measured quality indicators for that facility). To support the GP (and relevant organ specialists) in this task several strategies should be considered, probably in parallel:

    a. Financial incentives to compensate for the time and effort invested. Currently, the possibility of reimbursement is linked to the identification of a palliative status while ACP is also relevant to consider far earlier. Moreover, ACP might need to be discussed at regular intervals, and thus needs more than a one-time reimbursement.

    b. The introduction (and reimbursement) of advanced nurse practitioners that, among others, can specifically support the GP (and/or organ specialists) in the process of identification, communication, and necessary follow-up as part of a qualitative ACP.

    c. Access to a locoregional ethical board, its composition defined by law, that has a supportive and advisory role in cases that are either complex or generating conflict or moral distress. It is important that the members of such an ethical advisory board have advanced practice-relevant expertise.

4. The availability 24/7 of existing advance directives, resulting from ACP, for all relevant healthcare providers via electronic way. A uniform framework to report such advance directives, as well as a standard timeframe for their validity should be developed.

5. The development of 'hospital at home' programs at the locoregional level, in support of the GP, to offer medical assessment, treatment, and follow-up at home for patients who no longer want hospitalization -or for whom hospitalization is mostly harmful- yet would still benefit from for instance short-term intravenous antibiotics or oxygen therapy.

Chapter 7. Research agenda and surveillance

Recommendations for surveillance

1. To minimize uncertainties and facilitate validation, following items should be developed:
    - a standardized case **definition** (numerator) using the Sepsis-3 definitions for all surveillance strategies in adults and the Phoenix Sepsis criteria in children
    - the **targeted patient population** (denominator)
    - an **indicator** of nationwide sepsis occurrence
2. To develop a **Belgian sepsis registry**. This implies establishing a centralized registry dedicated to tracking all sepsis cases, including those with septic shock, to collect detailed patient data across all healthcare settings. This registry would fill existing gaps by providing specific sepsis-related data.
3. **To streamline data collection.** This involves simplifying data collection methods to reduce the burden on healthcare providers by integrating an automatic data capture within electronic health records (EHR) and PDMS. Ideally, existing collection tools (e.g. MICA, …) should be used or integrated to reduce the administrative burden and improve responsiveness.
4. To develop **real-time analysis and reporting** to provide immediate insights into trends, allowing for timely interventions and resource allocation.
5. **To integrate detailed data collection** on sepsis and its management (e.g. need for surgery, mechanical ventilation, vasopressor support, renal replacement therapy or ExtraCorporeal Membrane Oxygenation (ECMO) **in the ongoing PPS** and other surveillance studies in the field of infectious diseases.

Recommendations for research

1. **To establish a Belgian sepsis research coordination and prioritization center** in order to streamline efforts, facilitate collaboration, and disseminate findings effectively.

2. **To establish a dedicated sepsis research funding scheme** by advocating for sepsis to be identified as a standalone category in funding programs to ensure dedicated resources are available.

3. **To promote inter-hospital research networks** through encouraging partnerships among hospitals to share data, resources, and expertise.

4. **To enhance international collaboration** as sepsis is similar in western European countries. This can be done by strengthening the interaction between international research bodies and funding agencies, similar to the Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR) program for antimicrobial resistance.

5. To include all **innovative aspects** of sepsis care as potential topics for research, including but not limited to the use of wearables, post sepsis syndrome recommendations and follow-up, among others.

INTRODUCTION

1. What is sepsis?

Definition and causes

Sepsis is a life-threatening medical condition that occurs when the body's response to an infection causes intense inflammation, leading to dysfunction or even failure of vital organs and functions, such as the kidneys, liver, heart, the brain or the blood clotting system. In the most severe cases, sepsis is accompanied by very low blood pressure, requiring specific medication (vasopressors), this is called septic shock. Sepsis thus occurs when the immune system overreacts to an infection and triggers a cascade of harmful inflammatory responses throughout the body (1-3). Sepsis and septic shock are associated with high mortality and substantial, long lasting morbidity. Depending on the location and population studied, about 25–30% of patients with sepsis die from the condition, with hospital mortality for septic shock approaching 40–60% (4).

A wide variety of microorganisms may trigger sepsis, including bacteria, fungi, viruses, and parasites, depending on the region and setting where the infection occurs: at home ('**community-acquired'**), during or shortly after a stay in the hospital or in a long term care facility ('**health care associated'**). Causes of community-acquired sepsis include severe skin and soft tissue infections (typically caused by skin bacteria *Staphylococcus aureus* and group *A streptococci*), urinary tract and abdominal infections (typically caused by gut bacteria *Escherichia coli*), respiratory tract infections (typically caused by *Streptococcus pneumoniae*) and to a lesser extent dental infections. Bacterial meningitis is a rare but life threatening condition and may typically be caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis* and more rarely the foodborne *Listeria monocytogenes* and other pathogens. Health care associated infections (HCAI) may be caused by a wide range of pathogens, often more resistant to antimicrobials and thus more difficult to treat.

Next to bacterial pathogens, severe viral infections (such as COVID-19, or influenza) can present with sepsis (5). In returning travelers, severe malaria can also complicate with sepsis and multiple organ failure. Finally, certain non-infectious conditions such as severe trauma, burns or pancreatitis may also trigger a systemic inflammatory response akin to that occurring in sepsis. Over the past 50 years, the knowledge base of the mechanisms, diagnosis and management of sepsis has grown substantially (6).

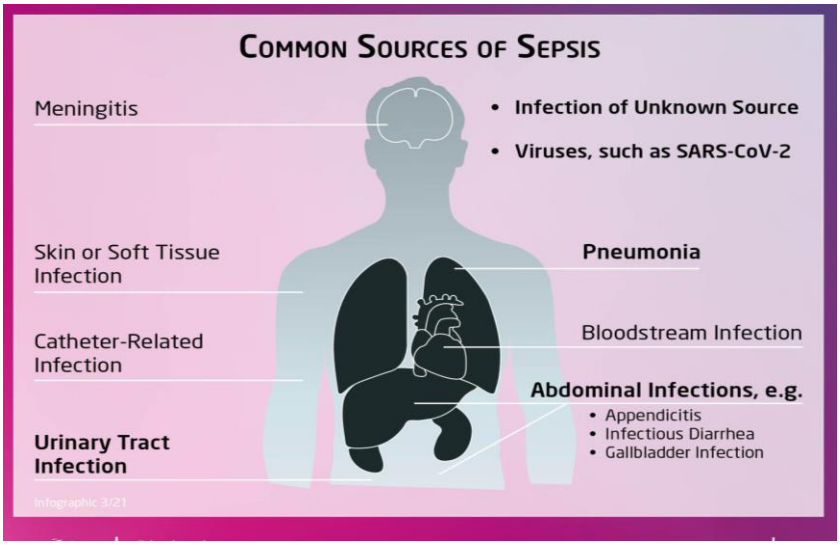

Figure 1. Common sources of sepsis (7)

Recognition and diagnosis of sepsis

Sepsis thus presents as the clinical deterioration of common and often preventable infections. Its early signs (e.g. fever, increased heart rate, difficulty breathing, increasing weakness, drowsiness or confusion) may not always be perceived nor understood as 'alarming' by the patient, caretakers and health care workers; sepsis is therefore frequently misdiagnosed or not recognized as potentially severe in its early stages. For example, a reconstruction of the health care seeking trajectory of 263 patients admitted with sepsis in a Dutch intensive care unit (ICU) revealed that 48.3% of these patients had contacts with their general practitioner (GP) in the days prior to their admission. Of those, only 64% were referred immediately, and the GP had not suspected an infection in 43% of the patients. In this group, the in-hospital mortality rate was significantly higher compared with patients with suspected infections (41.9% vs 17.6%) (8). Also, the clinical condition of certain patients with minor infections may deteriorate quite rapidly, hence the need to maintain a low threshold for clinical re-assessment and awareness among patients on the possibility of sepsis, and how to respond.

There is no single laboratory or imaging test to unequivocally confirm the diagnosis of sepsis, which is made based on a combination of clinical findings and laboratory tests. To avoid confusion and help standardize the approach to sepsis, researchers and health care workers have tried for decades to identify an easy-to-use set of criteria to accurately identify patients with sepsis. The currently applied definition is the set of the so-called 'Sepsis-3 criteria', introduced by the Third International Consensus Definitions for Sepsis and Septic Shock in 2016 (3).

The key criteria for diagnosing sepsis according to Sepsis-3 are:

1. Suspicion of infection, based on clinical signs and symptoms, along with laboratory or imaging findings that suggest an infectious process.
2. Indication of organ failure as noted by the 'Sequential Organ Failure Assessment (SOFA) Score', a score used to assess organ dysfunction and severity of illness. It evaluates six different organ systems (respiratory, blood clotting system, liver, cardiovascular, central nervous system, and renal) based on various clinical parameters. An acute increase of SOFA score of 2 points or more is indicative of organ dysfunction associated with sepsis (3).

Taken together, the presence of (1) suspected infection and (2) an increase in the SOFA score by 2 points or more identifies patients with sepsis, and is associated with an in-hospital mortality greater than 10%.

Septic shock should be defined 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. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%.

In about 20-50% of sepsis patients, the disease-causing bacteria or other micro-organisms can be found in cultures of blood, and serve as a proof of invasive infection (9). This is called **'blood stream infection (BSI)' or 'bacteremia',** and can be used as an (imperfect) proxy of sepsis e.g. in epidemiological studies. Bacteremia remains an imperfect proxy to sepsis, as it describes only the presence of pathogenic bacteria in the blood, rather than the clinical status of inflammation and organ dysfunction by which sepsis is defined. Nevertheless, there is a substantial overlap between the two groups, and bacteremia is more easily diagnosed in an unequivocal manner. For in depth discussion on blood cultures we refer to Chapter 2 and 4.

Treatment of sepsis and septic shock involves prompt administration of antibiotics to target the underlying infection (and sometimes additional interventions to achieve source control), intravenous fluids and vasopressors (in case of septic shock) to maintain blood pressure, and medication to support organ function, often along intensive medical care with mechanical ventilation and other life-support measures. Antimicrobials are typically started 'empirically '(i.e. based on a guideline, before information from bacterial cultures is available) and subsequently adjusted when more information has come available ('targeted treatment'). However, emerging antimicrobial resistance (AMR) can lead to a mismatch between the empirically chosen antimicrobial and the difficult-to-treat micro-organism, causing treatment failure and possible eventually patient death. Therefore, adequate sepsis care is closely related to the availability of accurate treatment guidelines and effective antimicrobials, and prevention of further emergence of AMR. Source control includes drainage of abscesses, removal of dead tissue, infected catheters and other materials,...

Early recognition and early adequate treatment of sepsis are crucial to improve outcomes. In 2002 the Surviving Sepsis Campaign (SSC) was set up as a joint initiative of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), and committed to reducing mortality and morbidity from sepsis and septic shock worldwide. The SSC is led by multidisciplinary international experts committed to improving time to recognition and treatment of sepsis and septic shock, which are leading causes of death worldwide. SCCM is also committed to improving outcomes for sepsis survivors, especially those with post-sepsis syndrome (10-13).

2. Who is at risk to acquire sepsis?

Sepsis can develop in anyone, but certain factors increase the risk of developing this serious condition. Based on the available global and European epidemiological data, the following risk factors for sepsis and at risk patient groups have been identified, either based on medical vulnerability, or within a socio-economical vulnerability:

1. Male gender (14-16). Men experience a higher incidence and worse outcome as compared to women, even after correction for confounding factors , probably due to lifestyle and hormonal determinants.
2. Extremes of age: although sepsis occurs in all age groups, both the youngest and oldest are amongst the most severe at risk with the highest morbidity and mortality, i.e. young infants (in particular premature babies, but also neonates up to 3 months of age have increased sepsis risk) and older individuals due to immunosenescence and comorbidities (15)
3. Pregnancy: given the alterations in anatomy and immune status, particularly due to urinary tract infections or perinatal infections of the birth canal (17).
4. Chronic conditions such as diabetes, kidney disease, liver disease, lung disease, and active or past history of cancer (18, 19), due to impairment of the immune system and decreased organ resilience (15, 16, 20). In several studies, these groups were found to have limited knowledge on the preventive importance of vaccination and a low ability to recognize sepsis as a medical emergency (21).
5. Decreased immune status, either congenital or acquired e.g. (ill-controlled) HIV/AIDS, chemotherapy, long-term steroid use, or organ transplantation, due to increased susceptibility to infections and/or impaired immune response.
6. Alcoholism or substance abuse, through impairment of the immune system, and delayed health care seeking behavior or access to care. More in general, people with mental health problems have increased vulnerability (15).
7. Current or recent hospitalization: patients who have recently undergone surgery (16), received medical interventions (such as catheters or breathing tubes), or have been hospitalized for other reasons are at

increased risk of acquiring healthcare-associated infections (HCAI) that can progress to sepsis, in particular in presence of indwelling medical devices e.g. urinary catheters, intravenous lines, or ventilation tubes can serve as entry points for bacteria, increasing the risk of infection and subsequent sepsis.

8. Previous sepsis episodes: survivors of sepsis have been found to have an increased risk of developing recurrent episodes due to long-term effects on the immune system and organ function. A systematic review and meta-analysis on rehospitalization in adult sepsis survivors confirmed that rehospitalization is common, with one in five occurrences within 30 days of discharge following an index sepsis admission. Risk factors include age, comorbidities, prior hospitalization, site of infection at admission, and socioeconomic status. These predictors have also been identified as risk factors for long-term mortality (22).
9. Persons with limited education levels and living in socio-economically challenging situations (15, 20). The impact of low socioeconomic status on sepsis risk could be attributed to various factors, such as limited access to healthcare, unhealthy lifestyles, and low adherence to treatment for comorbidities. Limited evidence exists regarding the impact of race/ethnicity on sepsis-related mortality (23, 24).

It is important for healthcare providers to identify individuals who may be at increased risk of developing sepsis and to implement preventive measures when possible (see Chapter 2). Early recognition and treatment of infections in high-risk individuals can help prevent progression to sepsis and improve outcomes (Chapter 3-4). In addition to these known risk factors, more insights are to be expected on the genetic factors contributing to higher susceptibility for sepsis and sepsis related mortality.

Sepsis in children

Worldwide, almost 3 millions of children annually die related to sepsis. Fatality rates vary from 19% in developed countries to up to 32% in developing countries (25, 26). Its incidence is increasing, mainly due to higher survival of very low birthweight, infants and children with chronic conditions, and a higher incidence of multi-resistant bacteria (27, 28). Children surviving sepsis often suffer lifelong morbidity and psychological sequelae. Pediatric sepsis differs from adult sepsis in various ways, starting already with a different definition[1]. Sepsis should be suspected in children with infection and any alteration in vital signs, which can be challenging. This is related to the high prevalence of common febrile infections, poor specificity of discriminating features, and the capacity of children to compensate until shock is in an advanced stage. Suspicion of sepsis must even be higher in specific

[1] Since 2024 a new definition has emerged based on the 'Phoenix sepsis score': a score ≥ 2 in children with suspected infection defines sepsis, and sepsis with 1 or more cardiovascular points defines septic shock (29, addendum 1). Although the score seems very effective in in-hospital settings, it is far less so pre-hospital since it is complex and includes laboratory tests.

risk groups within the pediatric population. Neonates < 3 months (subtle clinical signs), children with comorbidities (often suffering hospital acquired infections), institutionalized children with special needs, children with indwelling devices, immunocompromised children (chemotherapy, immune deficiencies) or children after a recent hospitalization are at increased risk of septic events (30). In each of these groups, sepsis is characterized by different clinical presentations, microbiology and therapeutic approaches. Mortality of sepsis in children often occurs early, within 24 to 48 hrs, making it extremely time critical: every hour without restoration of the circulation, leads to a two-fold increase in mortality.

3. The burden of sepsis

The burden of sepsis can be considered as the combination of: (1) the incidence in a given population and (2) the clinical outcome, in terms of mortality and morbidity (sequelae). The outcome of sepsis is influenced by various factors, including the severity of the infection, the promptness of treatment, the overall health of the individual, and any underlying medical condition (see Figure 2) (adapted from 31).

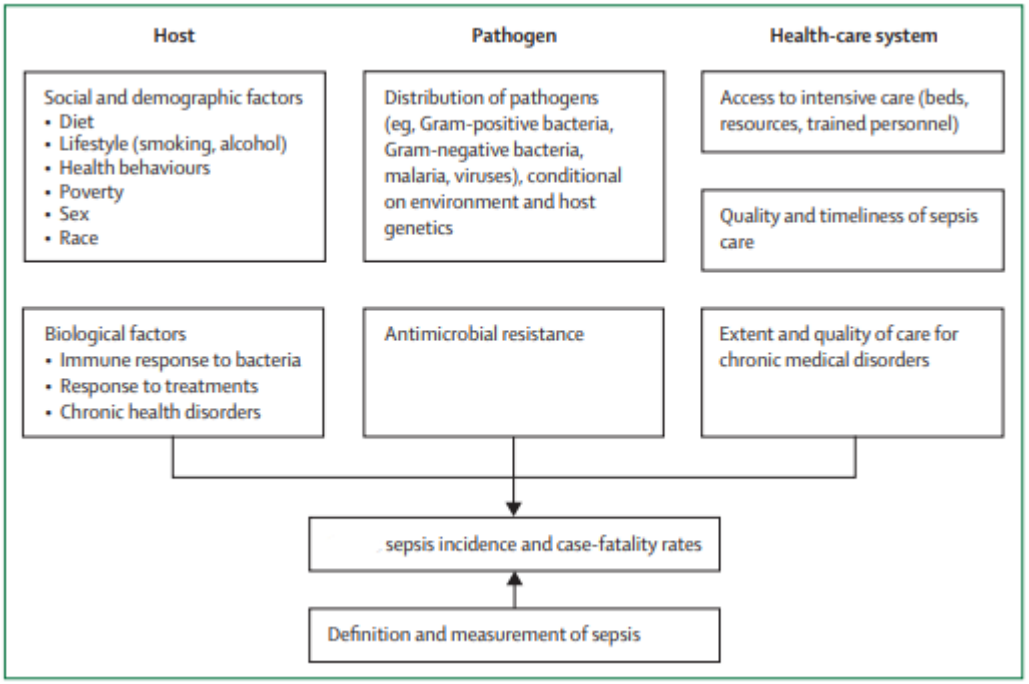

Figure 2 Factors determining the incidence and case-fatality rate of sepsis (adapted from Octavia Peck-Palmer and Cohen et al, Lancet Infect Dis 2015 (31).

Detailed epidemiological data on sepsis are limited, as sepsis, given its nature as a clinical diagnosis, is not systematically registered in a standardized manner in most countries. The Global Burden of Diseases Study (32)

estimated that about 49 million cases occur every year worldwide, causing 11 million deaths, with the large majority (about 85%) occurring in low and middle income settings. Globally, 20 percent of all deaths are likely caused by sepsis.

A systematic review based on 51 studies, mostly from high income countries, estimated a pooled incidence of 189 hospital-treated adult sepsis cases per 100 000 person-years with a mortality of 26.7% (33). For the European region, the hospital-treated sepsis incidence was 289/100.000 person years, with a mortality of 22.1% and up to 42.7% for ICU-treated sepsis.

Mortality due to sepsis occurs in two phases: about one third of deaths in sepsis patients occur early (e.g. within the first days of admission) (34), related to the primary disease course, while the other two thirds occur during the stay in ICU, related to nosocomial complications or intractable organ failure. Even after discharge, mortality rates are increased in the months and years following the sepsis episode. For those who survive, sequelae of sepsis include transient or long lasting organ dysfunction (e.g. renal failure), necrosis of peripheral body parts (e.g. limbs, nose,…) requiring amputation, longstanding neurocognitive impairment and mental health disorders as well as increased risk for new sepsis episodes. **Post-discharge sepsis complications** are associated with further worsening of the already impaired health status. In addition, surviving sepsis may be associated with a long-term, excess hazard of late cardiovascular events which may persist for at least 5 years following hospital discharge (35,36). This is explained more in depth in Chapter 5.

A German population-based cohort study of 116,507 survivors of hospital-treated sepsis identified from insurance providers revealed that in the first year post-sepsis, 48.9% of survivors had one or more adverse outcomes, including new dependency on chronic care (31.9%), dialysis (2.8%) or respiratory support (1.6%), and death (30.7%). Pre-existing comorbidities and age were risk factors. In particular hospital-acquired and multi-resistant infections were associated with increased risk of chronic care dependency, dialysis, and 12-month mortality risk (37, 38). Taken together, as summarized in a World Health Organization (WHO) report (39): about 1/3 patients with sepsis die within the first year, 1 out of six experience significant morbidity, and 4 of 10 are readmitted within ninety days.

In Europe, with its aging population, sepsis incidence is substantial and increasing, with variability across European countries due to differences in healthcare infrastructure, population demographics, and reporting practices. Each year in Europe, more than 3.4 million individuals develop sepsis. 700,000 do not survive, and an additional one-third of survivors die during the following year (6).

In the UK, sepsis is estimated to affect around 250,000 people annually, with approximately 44,000 deaths attributed to the condition each year. The incidence of sepsis has been steadily increasing in recent years, partly due to improved recognition and reporting. In a large German study (2013), 280,000 persons were diagnosed with sepsis per year, of whom 70 000 died (40). In France, in the period 2010-2015, 700.000 patients with sepsis

and 500.000+ with septic shock were notified (41). A Spanish study (42) showed an annual increase of 4.9% of septic shock among hospitalized patients (2003-2016), whereas the associated mortality decreased annually by 1.4%, probably reflecting the effect of improved and earlier sepsis care. A multicenter point-prevalence study in Dutch hospitals (2004) (43) indicated that annually between 9,726 and 20,632 sepsis patients were admitted to their ICU's, whereas the more recent Global Burden of Disease study (2017) estimates that 58,707 (46,160–77,794) patients in the Netherlands are affected by sepsis annually, admitted to either ICU or general ward (44). In spite of being estimates, these figures give us a good impression of the extent of the problem and its impact. Given the difficulty to obtain solid data on sepsis cases, the more easily retrievable cases with **blood stream infection (bacteremia) are often used as proxy**. A Finnish study (45) on bloodstream infections (BSI) from national registries between 2004-2018 described an annual incidence increase from 150 to 309 cases/100,000, with a most sharp increase among persons >80 years of age and male. The 1-month case-fatality was about 13%. Over the study period, a clear increase of community-acquired BSI and of multidrug resistant infections was noted. Swedish studies between 2000-2013 (46) and 2006-2019 (47) confirmed the observations of a significant increase in the incidence of community-acquired BSI in mostly male, and persons older than 80 years.

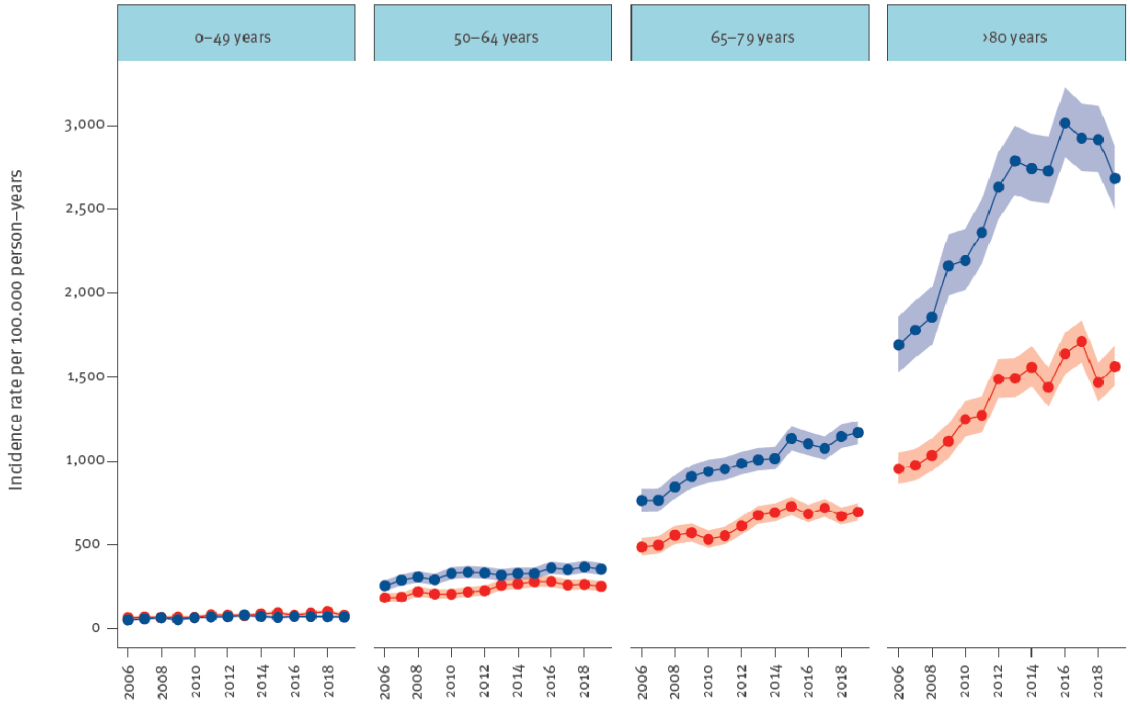

Figure 3. This graph represents the incidence of BSI by age, sex (blue = male, red = female) and year in southern Sweden, 2006-2019 (n = 54498). (adapted from Ljunquist Eurosurveillance 2022) (47).

Epidemiologic data on sepsis or even BSI in Belgium are unfortunately very scarce, and comprehensive, systematic surveillance data on sepsis are lacking. A monocentric, prospective cohort study between 2019-2020 described 1690 episodes of suspected sepsis at an emergency department (ED) in Hasselt, with an average age of 70 y (55-80), 57,8% male. The majority of these patients were moderately ill with median SOFA scores of 2, requiring admission to ICU in 7.8%; 5.3% died in hospital (48). A simple extrapolation of these 1700 patients with sepsis suspicion for one (large) hospital per year to the Belgian scale of 103 hospitals would already exceed the estimate for Belgium described in the Global Burden of Diseases study of 40,952 (31,938 - 54,451) yearly sepsis cases (44).

The only formal surveillance data that can be used as a (partial) proxy for sepsis in Belgium are on healthcare-associated bloodstream infections (HABSI). In their 2023 report, Sciensano described a gradually increasing incidence of HABSI, of 7.8/10,000 hospitalization days in 2013 to 9.2 in 2022, with even higher values during the early pandemic years 2020-2021. There was a large variability by region and type of hospitals; *E. coli* and *Staphylococci* were the underlying microorganisms causing the infections (49). Forty–three percent of hospital-wide HABSI cases and even 66% of ICU-BSI cases were linked to an invasive device, whether directly (central and other catheters) or indirectly (urinary catheter, endotracheal tube). Of these, exposure to central vascular catheters remained the most frequently reported origin of HABSI cases both hospital-wide (26% of HABSI) and ICU-only (39% of ICU-BSI). The authors, therefore, recommended a strong focus on the prevention of this type of HABSI.

The above-mentioned data, however limited, underscore the widespread impact of sepsis across Europe and highlight the urgent need for improved sepsis recognition, standardized management protocols, and public health interventions aimed at reducing the incidence and improving outcomes associated with this life-threatening condition. Efforts such as the Surviving Sepsis Campaign and other international collaborations play a critical role in addressing the challenges posed by sepsis in Europe and globally.

4. Health economic aspects of sepsis.

Sepsis imposes a significant burden, through relatively common severe to extremely severe and fatal episodes, as well as post-acute increased susceptibility to re-occurrences of severe disease and comorbidities, including life-changing permanent sequelae in survivors, reduced quality of life (QoL) during both the acute and post-acute stages, and premature mortality. These consequences undoubtedly bring about large healthcare and non-healthcare, direct and indirect costs incurred by patients, public and private health care providers and insurers, as well as society as a whole. In this section, we describe different aspects of this burden that are relevant to the situation in Belgium.

The following cost categories are often distinguished in health economic research, and some general aspects are mentioned below in relation to sepsis, most notably the wide-ranging impacts of sepsis on various providers and payers, and the presence of important spillover costs and effects, which are typically difficult to account for in any health economic impact estimation and therefore often left unvalued.

Different cost categories:

Direct health care costs

- Treatment costs directly related to medical consumption (consultations, medication, diagnostic tests, surgery, etc.) for diagnosis, treatment and medical follow-up (e.g. physiotherapy, regular check-ups, prosthetics and other devices) of **patients**.
- Most of these costs are borne by a public third payer (National Institute for sickness and invalidity (RIZIV/INAMI), social security), depending on the socio-economic background of patients, a significant part (on average in Belgium in the order of 25%) is borne by a private third payer (e.g. private insurance against hospital supplements), and/or by the patients themselves ("out of pocket payments").
- Family/friends spillover costs exist: informal direct health care is likely provided by family and friends of patients, which presents opportunity costs for which financial compensation may not be provided.

Direct non-healthcare costs

- Non-healthcare costs directly caused by the disease (and its consequences). Examples include costs for adapted education, transportation, housing, …
- These costs are borne by both the private (patient, private insurer) and the public sector (e.g. Vlaams Agentschap voor Personen met een Handicap).

- Family/friends spillover costs often exist without financial compensation: informal help, e.g. transportation, creating adapted living conditions at home.

Indirect costs

- Lost labor productivity.
- Lost/diminished education-related productivity.
- Family/friends spillover costs exist: family members may incur labor interruptions or may need to make permanent modifications to their participation in the workforce.

Intangible costs:

- Costs of pain and suffering:These are assumed to be captured by Quality-Adjusted Life-Year (QALY) estimation.
- Family spillover costs exist: measurable QALY impact on family members expected, especially through dimensions of anxiety/depression/worry.

A look at the international literature

First, considering only hospital costs, we list a recent review of the literature and a recent hospital cost analysis in France that was not included in that review.

Hospital-related costs of sepsis around the world: A systematic review exploring the economic burden of sepsis by van den Berg et al (50).

Van den Berg et al. conducted a systematic review to explore the hospital-related costs of sepsis worldwide published in the period January 2010 and January 2022. They identified 18 studies reporting mean hospital costs per patient ranging from €1101 to €91,951. The median (IQR) of these costs were €36,191 (€17,158 - €53,349). The review highlighted considerable variation in sepsis treatment costs among different countries (7 studies pertained to the USA, 6 to Europe, none to Belgium). Factors associated with higher costs included disease severity, older age, surgical indications, and specific infection sites. The costs for patients admitted to general wards were higher than those admitted to the ICU, due to longer stays and greater prevalence of sepsis on general wards.

Sepsis and septic shock in France: incidences, outcomes and costs of care by Dupuis et al (51).

Dupuis et al. conducted a retrospective cohort study of the French hospital administrative database to analyze patients hospitalized for sepsis and septic shock in France from 2010 to 2015. They examined trends in clinical characteristics, costs, and outcomes over this period. From 2010 to 2015, the incidence of sepsis and septic shock increased, respectively, from 206 to 243 and from 135 to 171 cases per 100,000 population. Case fatality remained at 34% for sepsis, but decreased from 46 to 44% for septic shock. Median hospital stay costs were substantial, with patients with septic shock incurring higher costs compared to those with sepsis. **Median hospital stay costs amounted to €11,400 (IQR: 5036; 24,364) for patients with sepsis and €16,439 (IQR: 7339; 29,360) for patients with septic shock.**

After adjustment for case-mix and illness severity, the risk of death was stable for sepsis (0.08% [− 0.04; 0.20] per year), but decreased for sepsis patients admitted to the ICU and for cases of septic shock (− 0.33%[− 0.40;− 0.27] per year).

The study highlighted the common occurrence, high fatality rates, and significant costs associated with sepsis and septic shock in France, emphasizing the importance of continued improvements in care to mitigate the burden of these conditions.

In addition to descriptive cost analyses, showing the between-country and even between-hospital variation in costs, we can observe for other diseases as well, an important question is the impact interventions may have on these costs. On this topic too, two studies present highly relevant information.

The Value of Quality Improvement Interventions for Blood Stream Infections Related to Central Catheters: A Systematic Review of Economic Evaluations by Nuckols et al (52).

Nuckols et al. conducted a systematic review of economic evaluations to assess the value of Quality Improvement (QI) interventions for BSI related to central catheters. They identified 15 eligible evaluations using data from 113 hospitals, which collectively demonstrated a 57% decline in infections and net savings of $1.85 million per hospital over three years. The interventions, predominantly involving practices recommended by the Agency for Healthcare Research and Quality (AHRQ), were associated with improved clinical outcomes and lower costs. Larger investments in prevention programs were associated with greater effectiveness and net savings. The study highlighted the importance of investing in QI interventions to prevent healthcare-associated infections (HAIs), despite potential financial burdens on hospitals.

A state-wide implementation of a whole-of-hospital sepsis pathway with a mortality based cost-effectiveness analysis from a healthcare sector perspective by Brusco et al (53).

Brusco et al. conducted a translational research study to evaluate the cost-effectiveness of a state-wide implementation of a sepsis pathway in Victoria, Australia, and report the implementation costs over 12-months. The study implemented a nurse-led sepsis pathway, "Think sepsis. Act fast" across 10 public health services (54). The pathway included early warning and severity criteria, with interventions initiated within 60 minutes of sepsis recognition (including oxygen administration; blood cultures (x2); venous blood lactate; fluid resuscitation; intravenous antibiotics, and increased monitoring). Implementation of the pathway resulted in a significant reduction in mortality and hospital costs. Mortality decreased from 11.4% to 5.8%, accompanied by a reduction in length of stay and cost per patient. At baseline and intervention the average length of stay was 9.1 (SD 10.3) and 6.2 (SD 7.9) days, and cost was $AUD22,107 (SD $26,937) and $14,203 (SD $17,611) per patient, with a significant 2.9 day reduction in length of stay (-2.9; 95%CI -3.7 to -2.2, p<0.01) and $7,904 reduction in cost (-$7,904; 95%CI -$9,707 to -$6,100, p<0.01). At an implementation cost of $1,845,230, the sepsis pathway was found to lead to reduced costs and mortality. This implies it is a dominant strategy, as it saves health care costs while at the same time saving lives, and is therefore a policy that would need to be implemented by any rational decision maker with an intent on saving lives and reducing costs.

All the above studies have in common that they focus on health care cost estimates, and in particular those associated with hospital admission. They show from this narrow perspective that interventions to tackle sepsis management early, save healthcare costs at the same time as gaining health (i.e. for policy making, these interventions exhibit dominance to be implemented instead of current practice). However, to better understand how heavily sepsis victims are affected, and how that translates on impacts exceeding hospital care and the health care sector, the following recent study for the Netherlands is also of major interest.

Societal costs of sepsis in the Netherlands by Luijks et al (55).

Luijks et al. conducted a model-based study using multiple data sources to estimate the costs of sepsis in the Netherlands. The authors aimed to estimate the direct health care and indirect economic costs associated with sepsis in the Netherlands. A central highly influential estimate they needed was that of the incidence of sepsis, which they assumed to be 341/100,000 population, based on the Global Burden of Disease (GBD) Study (56). Luijks et al estimated the annual QALY loss due to **sepsis mortality at 157 QALYs per 100,000 population** (based on Netherlands year 2017 death statistics), and due to morbidity and sequelae among **sepsis survivors at 177 QALYs per 100,000 population** (based on previous Dutch (57) and German (38) studies). The Netherlands mortality estimates cited in the Luijks et al article match exactly those of the GBD study (56) for the Netherlands

(9400 deaths). In Luijks et al. it is subsequently assumed that the average QALY loss per death (presumably based on the age profile of deaths) is 2.86 QALYs (using the same discount rate for effects as per the Belgium guidelines (58) i.e. 1.5%).

Note that the GBD study, on which Luijks et al. rely heavily, in turn used databases from 10 countries, including only 2 Western European countries (Austria and Italy), to extrapolate the incidence of sepsis and sepsis mortality to all the countries in the world. Using the Belgium population size in the same way as Luijks et al. did for the Netherlands, the corresponding GBD derived **incidence of sepsis for Belgium (40,952 (95% CI 31,938 - 54,451) cases in 2017**) is 358/100,000 population with a lower 95% confidence limit of 279 and an upper 95% confidence limit of 477/100,000 population, whereas the GBD derived **mortality of sepsis in Belgium (7,675 (95% CI 6,421-9,089) premature deaths per year)** implies an **average case-fatality ratio of 18.74%.**

The indirect economic burden, including lost labor productivity and increased healthcare expenditure, ranged from **€416.1 million to €3.1 billion per year (i.e. €24 to €180 per capita)**. Overall, using an equation proposed by De Wit et al (59) to convert QALY losses into work days lost (based on a regression of QALY losses and associated work days lost in a sub-sample of the Netherlands Mental Health Survey and Incidence Study (Nemesis-2 study), which was restricted to the Dutch workforce (60) and thence through the proportion of lost work days to total work days into monetary losses per year (using standard gross average labor costs and unemployment rates), the combined disease and indirect economic burdens Luijks et al. estimated ranged from **€3.8 billion to €6.5 billion per year (i.e. €221 to €378 per capita)**.

Conceptually, the latter estimates may suffer from double counting of part of the productivity losses, as the loss in labor productivity is valued through an assumed reduction in productivity (through working days) of 20.9% based in turn on an overall 0.15 decrease in QoL at 14 months post-sepsis to arrive at the indirect cost estimate ranging between €0.4 and €3.1 billion per year, while for the total indirect cost plus disease cost burden estimate the separately estimated QALY losses are also converted in monetary values using associated lost work days and the resulting values are then added to the initial estimates of lost labor productivity. The ranges show the difference in approach between the friction and human capital methods, which is somewhat in line with the Belgian guidelines (although these conceded that friction periods are not available for Belgium).

At the same time, this study underestimates the burden in several other aspects, like the family spillover effects, which are ignored for any level of costs (direct, indirect) and effects (QALYs). Similarly, costs falling outside the overall labor productivity losses expressed through lost working days in sepsis patients (such as costs and productivity losses as a consequence of modified education) are also ignored. That is, the value of lost productive time to unemployed/retired sepsis patients, as well as the value of lost time of any person indirectly affected as a family member or friend of a patient is ignored. We note that several key original data and

assumptions are not sourced from the Netherlands, and some also date back from some time ago. In particular prospective hospital-based and community-based cohort studies would be valuable to improve our insights on the health and economic impact of sepsis.

Despite these limitations, this study is important as it indicates clearly the health burden and societal costs of sepsis are likely to greatly exceed the direct health care costs of sepsis, and amount to substantial sums.

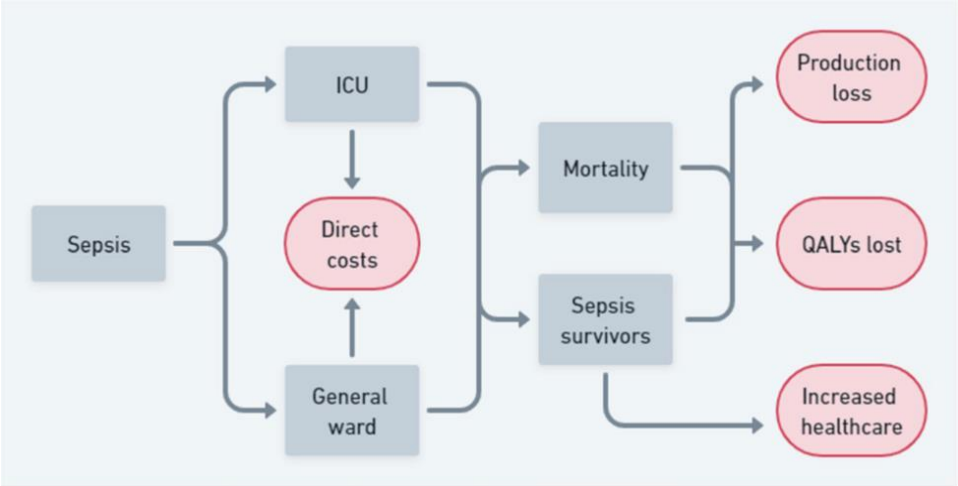

Figure 4. Cost of sepsis (55).

While there appear to be no Belgium-specific studies, we make simple extrapolations based on the literature in the next section.

The GBD-study estimated the **incidence of sepsis for Belgium at 40,952 (95% CI 31,938 - 54,451) cases in 2017** (or 358/100,000 population with a lower 95% confidence limit of 279 and an upper 95% confidence limit of 477/100,000 population), and the GBD derived **mortality of sepsis in Belgium of 7,675 (95% CI 6,421-9,089) premature deaths per year** implies an **average case-fatality ratio of 18.74%.**

If we transpose specific estimates for the Netherlands to **Belgium, we could infer an annual loss of 38106 QALYs** (47% of which through premature mortality), and an annual cost **between €277 million and €4.3 billion**, depending on the method used. By any measure, these are large amounts, illustrating the high severity, frequency and economic burden of sepsis. Most importantly, there is no reason to doubt that a combined plan to manage sepsis, akin to the "*Think sepsis. Act fast*"-plan in Victoria (AUS) can also be a dominant strategy for Belgium, even if only health care costs are considered. This initiative showed an impressive 6 fold return on investment in health care costs alone. When applied to the Belgian context, the annual implementation costs of this plan is difficult to estimate, given it translates in about €1.3 million for an implementation across 32 Victorian ED and urgent care centers. This is not a Victoria state-wide implementation, so it cannot be estimated

on a per-capita basis. It would therefore be relevant to estimate the costs for a similar plan for Belgium (or part of Belgium). We refer also to Chapter 5 (on the impact and management of post-sepsis sequelae) and Chapter 6 (on ethical considerations, given many of the sepsis deaths occur in the most vulnerable and frail).

Required data for a Belgium-specific estimate

For better understanding of the genuine scale and impact of sepsis in Belgium, ideally the following data should be made available:

- Age-specific incidence of sepsis
- Age-specific hospital admissions for sepsis, distinguishing general ward from ICU
- Age-specific Length of Stay (LOS) in general and ICU ward
- Age-specific case-fatality ratio
- Proportion of cases with long term sequelae
- Quality of Life (QoL) impact across the spectrum of severity, including for long-term sequelae in patients and their caregivers
- Direct healthcare and non-healthcare costs per episode (distinguishing hospital admissions, follow-up periods)
- Absenteeism and presenteeism associated with sepsis from work and school in patients and their caregivers

In Chapter 7, the realities, needs and opportunities on sepsis registration and research will be further discussed. For additional documentation on this chapter, we refer also to Appendix 2 (Key source of data for Global Burden of Disease (GBD) study-Additional tables on health economic aspects).

5. Why a National Sepsis Plan?

In 2017 sepsis was declared as a priority for global health by the World Health Assembly (WHA) at the WHO (61). The WHA resolution on sepsis (WHA70.7) urges the member states to take action in developing and implementing national strategies to improve prevention, diagnosis and management of sepsis. These actions require coordinated efforts by healthcare providers, consumers, survivors, administrators, researchers and governments across a broad healthcare landscape (62).

Seven years after this resolution, the following sixteen countries have prioritized sepsis in their national health policies, strategies and/or sepsis-related initiatives as of August 2023: Austria, Canada, England, France, Ireland, Italy, Saudi Arabia, Scotland, Spain, Sudan, Sweden, Switzerland, Turkey, Thailand, USA and Wales (63, 64). Figure 5 displays the state of sepsis plan development within Europe. Until date, Belgium still has no coordinated plan to tackle sepsis, despite several earlier initiatives, including a proposed resolution for a national sepsis plan by Mr. Robby De Caluwé and Ms. Nathalie Muylle (65) in 2021, an open letter from the patient association Sepsibel vzw and nine professional societies in 2022 (66) and an interpellation concerning this open letter in 2023 in ‘de Commissie voor Gezondheid en Gelijke Kansen’ (67; p. 68-69). Unfortunately, an overarching, multidisciplinary, multi-stakeholder approach has been lacking until date, to prevent or mitigate the burden in the estimated yearly 40.000+ sepsis cases in our country.

The experience from other countries or regions, such as Australia, United Kingdom, and the United States consistently demonstrates that coordinated programs in collaboration with governments, professionals and patient-advocacy groups can save lives, improve the outcomes for sepsis survivors, and are cost saving for the healthcare system (54, 68, 69). A national action plan has the aim to provide a structured framework for implementation and follow-up, ensuring synergy with other existing programs.

The key pillars of different sepsis quality improvement programs are similar when comparing countries who have successfully implemented sepsis campaigns (see Appendix 3 table 'Sepsis plans of other countries'). They include actions regarding:

1. Awareness and education of the public and healthcare professionals
2. Infection prevention and antimicrobial stewardship
3. Standards and pathways for early recognition and rapid response

4. Standards and pathways for early treatment
5. Advanced Care Planning
6. Post sepsis care and rehabilitation
7. Surveillance and research

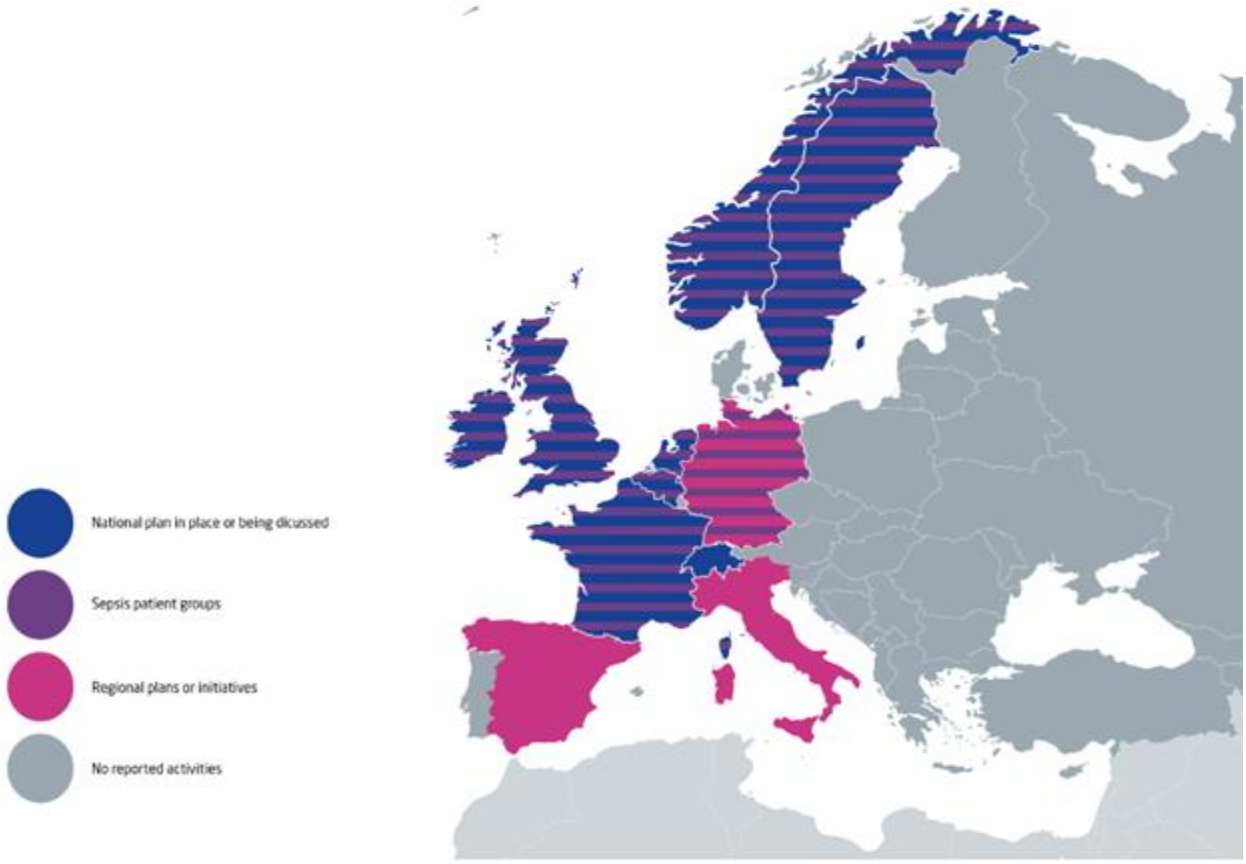

Figure 5. Status of national sepsis plans in Europe (70).

6. A Belgian National Sepsis Action Plan 'Be-SNAP': methodology

As mentioned above, in 2017 the World Health Assembly (resolution 70.7) urged member states to acknowledge the importance of sepsis as a healthcare problem and to implement practices focused on early detection and appropriate treatment within their national healthcare system. A first proposal about a national sepsis action plan was submitted in 2021 to the Belgian Chamber of Representatives, driven by several sepsis experts, scientific organizations, and patient groups. While this first proposal was still immature and not supported by all relevant actors, it reinforced the need for a federal action plan.

In 2023 a second initiative was taken, bringing all relevant actors together in a core working group with the aim to truly develop a Belgian Sepsis National Action Plan (Be-SNAP) (see table 1). As a result of the strong advocacy of both patient groups (Sepsibel) and local experts, this initiative subsequently was given an official mandate by the Belgian Minister of Health.

The core writing group met for the first time in November 2023. At this meeting, they defined the scope of the plan and the trajectory towards. To do so, the writing group identified Sepsis 3 as the way to define sepsis in adults (71). They acknowledged the lack of clear and unequivocal definition for children, awaiting at that moment the publication of the Phoenix Sepsis Score (29). In addition, plans from different other countries were identified and evaluated (see Appendix 3 table 'sepsis plans of other countries').

To further elaborate on the plan the core writing group identified sepsis as a public health problem within the Belgian healthcare system. They recognized many similarities with other sudden health problems that can result in serious harm and cost (such as injury or sudden cardiac arrest). Describing such healthcare problems in all its dimensions demands a broad and public health orientated conceptual framework. The Haddon matrix allows for this, thus aiding in the identification and consideration, beyond mere causality or chronology, of the means available for reducing the undesirable mortality and morbidity related to sepsis (72-74). The Haddon Matrix considers three main categories of factors (Personal Attributes, Vector or Agent Attributes and Environmental Attributes) and this across three different phases (pre- to post-event).

Each member of the core writing group, in consultation with the groups they represented, wrote out a full Haddon Matrix for the problem of sepsis and these matrixes were then combined into one (Figure 6).

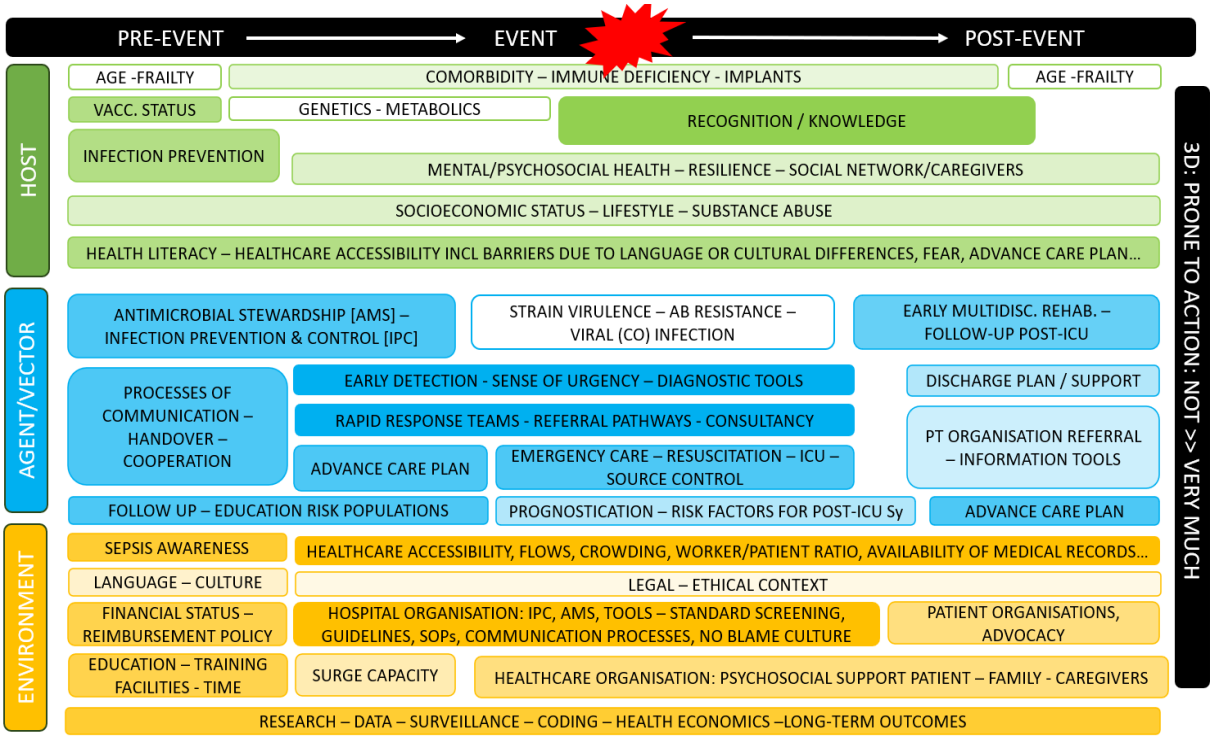

Figure 6. Haddon Matrix for sepsis as a public health problem.

In a second meeting the core group identified within the combined matrix (Figure 6) seven recurring priority topics that required further exploration in view of subsequent recommendations to policy makers and other relevant actors.

KEY TOPICS BELGIAN SEPSIS NATIONAL ACTION PLAN		**Working group chair**
1	Sepsis Awareness of Public & Healthcare providers	EV, IM
2	Antibiotic stewardship – Infection prevention	EV
3	Early Recognition & response	KDW
4	Early Adequate Treatment	PVDV
5	Early Rehabilitation – Long Term Care	HP
6	Advance Care Planning – Ethical decision making	PVDV
7	Research & Surveillance	JDW

For each of these seven topics, an enlarged working group was created with members of the core writing group, content experts, as well as representatives of different relevant groups and/or societies (see Table 1. Overview of the professional actors and societies involved in the Be-SNAP working group p5-6). The working groups had the task to explore existing literature and provide evidence of the key issue's impact on important outcome measures, as well as about strategies of implementation (how to reach the goal identified), considering the type of intervention (from a public health perspective) and its respective priority. A Haddon Matrix in itself does not provide prioritization nor strategy and for that there is need for a more general public health approach and a third dimension evaluating for each possible intervention also the cost-effectiveness, acceptability, feasibility, and equity (75-77). Finally, as a result of their literature evaluation and consensus discussions, the working groups proposed recommendations and provided insights and arguments to support. These proposals were subsequently discussed with all working groups during a one-day conclave. As a last step, the draft plan was reviewed by a reading panel of not previously involved national and international experts in infectious diseases, sepsis, public health and/or healthcare organization.

Literature exploration was done by rapid review, primarily including systematic reviews or guidelines and/or pivotal clinical studies -published after 01/01/2000- as far as there is a link between the key identified topic and any important outcome and excluding studies that are non-human, non-English, LMIC environments, and/or letters or commentaries/opinions (78).

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Chapter 1. AWARENESS AND KNOWLEDGE ON SEPSIS

As mentioned in the Introduction, sepsis was declared as a priority for global health by the World Health Assembly (WHA) at the WHO in 2017, urging member states to take action in developing multidisciplinary strategies on sepsis (1). In this context, awareness and knowledge among both the general public and healthcare professionals are primordial factors in the prevention, early recognition, and clinical management of this life-threatening condition.

Awareness refers to the ability to recognize the phenomenon, to know that it exists and how and when to recognize it. Knowledge goes beyond mere awareness, involving understanding and proficiency through study, experience, or instruction. Unlike awareness, knowledge implies a deeper level of understanding. Awareness can be seen as the first step towards acquiring knowledge, as it lays the groundwork for further exploration and learning. Awareness is typically raised through broadly disseminated campaigns with easy-to-remember messages for a large audience. On the downside, campaigns may lack nuance and hold a risk for unintended consequences (e.g. fear, confusion) when not well prepared or embedded in a broader policy (2). Beyond awareness, the acquisition of new knowledge is a more lengthy, structured and nuanced process, which also feeds into the professional intuition that healthcare workers develop during their education and day-to-day working experience ('OK/not OK-feeling'). Also (chronic) patients and their caregivers (e.g. parents) may develop a strong intuition to judge a medical situation as 'OK' or 'not OK'.

Awareness can lay the base for knowledge which feeds into intuition together with working experience. As explained more in depth in Chapter 3, knowledge and intuition can then be further supported by early warning systems (EWS).

1.1 Awareness of sepsis in high-income settings, with a focus on high-risk patient groups

Sepsis, despite being a largely preventable cause of death worldwide, remains inadequately recognized by many, leading to persistent knowledge gaps among patients and their relatives, the general public and healthcare professionals (HCPs). Several studies indicate that insufficient knowledge of sepsis symptoms and underestimation of its severity can lead to delayed medical care, and subsequent mortality (3). Prehospital delays are a significant risk factor for mortality associated with community-acquired (bloodstream) infections, with sepsis being a critical complication (4).

1.1.1. General public

Fiest et al. conducted an exhaustive systematic review in 2022 and identified 80 studies that reported on awareness and knowledge of sepsis among patients, the public, or healthcare professionals (nurses, physicians, emergency medical technicians) (5). The review underscored that public knowledge of sepsis remains generally low, although there are indications of gradual improvement over time and considerable variations in public and HCP knowledge on sepsis among different countries. The proportion of patients/public who had heard of the term sepsis ranged from 2% (Japan) to 88.6% (Germany). The proportions of patients/public who correctly identified the definition of sepsis ranged from 4.2% (Singapore) to 92% (Sweden). It is important to note that no data were obtained for Belgium.

In a survey of the German older population, Eitze et al. reported overall certain awareness of sepsis among this high-risk group, however, the understanding of its risk factors, symptoms, and prevention methods was low (3). Such knowledge gaps were also described in two recent representative survey studies conducted in Canada and the Netherlands (6,7). Sepsis knowledge appeared to be higher among participants who are older, female, and highly-educated participants and who reported more extensive health information-seeking behavior (6,8). In addition, results from a cross-sectional survey in Germany showed that the ability to recognize sepsis as an emergency was higher among younger participants, participants without chronic diseases, and participants with higher health literacy, but it was not significantly associated with sepsis knowledge (8). Lack of awareness and knowledge of sepsis in the general public is also a particular problem encountered by sepsis survivors and their specific post-sepsis problems (see Chapter 5).

1.1.2. Parents and caregivers

Pediatric sepsis starts most commonly in the community and the decision and timing of parents in seeking medical care for children contributes significantly to sepsis-related outcomes of children. As sepsis progresses faster in children, the impact of lack of awareness is larger as compared to adults. Up to 33% of deaths in sepsis could be attributed to parental delay (9).

Poor outcomes in pediatric sepsis do not seem to be related to the limitation of resources but to the delays in the recognition and early treatment of sepsis (10). There are considerable knowledge gaps in parental awareness and knowledge of sepsis, particularly recognition. A large study amongst > 3000 Australian parents showed that 61% of them knew the term sepsis and realized it was a life-threatening condition but only 28% thought they could recognize sepsis in their child. Less than half of the respondents

correctly identified signs and symptoms suggestive of sepsis. The authors suggested addressing these knowledge gaps in parental education to enhance healthcare-seeking behavior and communication between parents and healthcare providers, promoting early sepsis diagnosis and treatment (11). Better information sharing is observed between health care professionals and parents of children with hemato-oncological problems. What worries parents is mostly fever and the risk of meningitis (12).

Nevertheless, parents seem to be experts in recognizing "something is wrong" with their child. Root cause analyses after fatal sepsis often report multiple presentations to hospitals and parents' concern that "this disease is different". This suggests that parents may have sensed the potential severity of the disease prior to the recognition of sepsis by clinicians (moaning, crying or behaving differently) (13). The potential value of including parental assessment in discriminating children with mild infections from sepsis has received little attention. A systematic Belgian review showed that a combination of parental concern and a clinician instinct that something was different had a high predictive value of a serious bacterial infection (14). Since then, many studies listed the degree of parental concern as a strong red flag (15-20).

1.2 Awareness and knowledge of sepsis among healthcare workers in high-income settings

Health care professionals (HCPs) generally have a better knowledge of sepsis than patients or the general public. HCPs working in hospitals (e.g. nurses and physicians) demonstrate better awareness of sepsis than their colleagues working in prehospital settings. While HCPs recognize sepsis as a leading cause of mortality and rank its lethality higher than other well-known diseases, they may underestimate its actual mortality rate (5).

1.2.1. Prehospital setting

Data on sepsis awareness among first-line HCPs are limited. A Dutch study on the management of sepsis in out-of-hours primary care in the Netherlands reconstructed the acute care-seeking trajectory of 263 patients who were admitted in ICU with sepsis (21). They concluded that GP cooperatives are crucial in the prehospital management and recognition of sepsis. However, GPs' clinical detection of sepsis in primary care proves to be complicated. More than one-third of the patients eventually admitted with sepsis and initially assessed by GPs were not referred to a hospital. In almost half of the patients the GP had not suspected an infection. The highest mortality rates were observed in those patients in whom GPs had not suspected an infection. The authors suggested that efforts to improve identification and management of sepsis in the primary care setting should not be limited to patients with obvious signs of infection, but also include acutely ill patients without a clear diagnosis. A second Dutch study revealed

that in prehospital and emergency department medical records, sepsis and a sense of urgency are documented in one out of five patients. In only 1 out of 20 patients, sepsis or a sense of urgency is documented by all involved professionals. Poor medical documentation may cause harm, due to delayed diagnosis or treatment, therefore awareness should be raised among HCP on the importance of their medical documentation (22). Mulders et al. (2021) conducted a cross-sectional survey to evaluate the use of sepsis-related diagnostic criteria in primary care. GPs seem to mostly use intuition to diagnose sepsis and are often not familiar with more formal criteria for presumed or suspected sepsis used in hospital settings, although their clinical reasoning was mostly concordant with the quick Sequential Organ Failure Assessment (qSOFA) score. The authors advocate to train GPs in the use of available screening or early warning tools to improve sepsis recognition in primary care (23). At the moment, there is no formal use of an EWS among primary care physicians in Belgium to objectivate or support their gut intuition.

Evidence on sepsis knowledge of other (paramedical) first line HCP is hardly existent, in spite of their crucial frontline position close to the patient. Home nurses, for instance, play an increasingly important role in our aging society. They are very approachable, low-threshold caregivers, and persons of trust for many chronically ill or frail persons. From this position, the home care nurse is ideally placed to detect changes in the patient's health condition, to signal and to refer where needed[2]. This position close to the patients underscores the importance of intuition and solid education on sepsis of home care nurses. Providing education and support to nurses, including tools and guidelines, may enable them to recognize deterioration in a patient's health condition and detect potentially life-threatening situations early. This includes taking swift and appropriate actions, such as contacting the GP or immediately referring to the emergency department in urgent situations. Of note, a pilot project among home care nurses is ongoing, in which intuition is objectivated using the ABCDE-method, with positive initial findings (24).

A survey-based cross-sectional study was performed among nurses (n=619) and physicians (n=348) of all adult departments of the Lausanne University Hospital and paramedics (n=149) transporting patients to the hospital (Switzerland). The authors identified a deficit of sepsis awareness and knowledge reflecting a lack of sepsis-specific continuing education requiring immediate corrective measures (25).

Also community pharmacists are low threshold frontline health care professionals. They play a key role in raising awareness and knowledge among the general public (including patients and caregivers) on various health topics during their daily work, including infectious diseases and rational use of antimicrobials. They

[2] Expert opinion of leading persons within a large home care nursing organization in Flanders (Wit-Gele Kruis van Vlaanderen)

can also identify high risk patients among their clients (such as diabetes patients, cancer patients). Data from the study by Eitze et al. (2018), who evaluated determinants of sepsis knowledge among the older population (n=701) in Germany, indicated that the only significant source of sepsis information for their respondents were pharmacists (3). This suggests that dedicated training of pharmacists on the recognition of sepsis and its risk factors can be important too. In hospitals, pharmacist involvement in sepsis response has been associated with a reduced time to antibiotic administration for hospitalized patients with sepsis or septic shock (26).

1.2.2. Hospital setting

In a systematic review on sepsis assessment and management in critically ill adults, Rababa et al. found that nurses' levels of knowledge to sepsis assessment varied greatly among different countries and could be attributed to variations in educational level and work environment (i.e., ICU vs. non-ICU) (27). A study among Canadian emergency department registered nurses highlighted the need of educational programs and coaching approaches to maximize their decision-making skills of early assessment and appropriate intervention for persons with sepsis (28).

A recent survey (2022) evaluating the knowledge of and adherence to sepsis guidelines among HCPs (working in hospitals) in six European countries (UK, France, Spain, Sweden, Denmark, and Norway revealed that adherence to sepsis bundles (i.e. a set of clinical practice guidelines) falls well below the standard of care. Barriers highlighted were high patient caseload and staff shortages (29). On maternal sepsis, more evidence is available from research worldwide. A survey on maternal sepsis awareness among healthcare providers (i.e. nurses, midwives, physicians, and residents) showed that 92% were familiar with the term, but only 15% accurately defined it and 43% identified initial management correctly (30). This highlights a clear need for resources and support to boost confidence in sepsis identification and management, crucial for improving awareness of maternal sepsis. In 2017, an awareness campaign set to accompany the Global Maternal Sepsis Study (GLOSS) was implemented in 53 low-, middle-, and high-income countries across the world (31).

Until now, limited evidence exists about the current state of sepsis awareness and early recognition in Belgium among HCPs. A multidisciplinary cross-sectional survey in 73 countries was recently conducted to explore sepsis care in acute care hospitals in Europe and worldwide. Preliminary data revealed significant room for improvement in various aspects of sepsis management, including early recognition,

implementation of sepsis protocols, availability of microbiological services, antibiotic stewardship, and quality improvement programs Figure 1) (32, preprint).

	Early recognition								Standard of care						Microbiological laboratory service		Quality improvement			
	Sepsis screening by standardised criteria						Medical emergency teams		Sepsis bundles and/or specific protocols or pathways)						Around the clock: BC incubation, pathogen ID, notification		Quality improvement programs		Mortality recroding	
	EDs		Wards		ICUs				EDs		Wards		ICUs							
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
Northern Europe																				
Finland	4/16	25	7/15	47	4/10	40	17/17	100	5/16	31	4/15	27	9/15	60	1/17	6	2/16	13	5/16	31
Ireland	8/8	100	10/10	100	3/6	50	7/15	47	8/9	89	11/11	100	4/7	57	3/15	20	10/12	83	12/12	100
Norway	5/6	83	5/6	83	1/4	25	5/5	100	6/6	100	5/6	83	1/4	25	0/6	0	4/5	80	1/6	17
Sweden	29/35	83	19/35	54	13/21	62	24/36	67	29/36	81	15/35	43	20/28	71	1/37	3	14/34	41	14/36	39
United Kingdom	18/19	95	13/14	93	5/9	56	22/23	96	17/19	89	14/14	100	7/11	64	4/23	17	8/13	62	11/15	73
Eastern Europe																				
Czechia	9/32	28	9/40	23	20/38	53	17/40	43	8/31	26	6/39	15	21/39	54	2/41	5	6/37	16	11/39	28
Poland	9/30	30	15/42	36	28/34	82	10/55	18	13/31	42	20/42	48	39/45	87	3/55	5	17/44	39	18/46	39
Romania	8/17	47	22/33	67	27/34	79	18/36	50	9/16	56	23/33	70	24/31	77	1/37	3	13/33	39	17/35	49
Russian Federation	8/17	47	29/60	48	34/58	59	20/66	30	12/18	67	25/59	42	35/59	59	0/68	0	23/57	40	41/59	69
Southern Europe																				
Croatia	2/13	15	2/17	12	6/15	40	3/20	15	2/14	14	3/16	19	10/19	53	1/22	5	2/20	10	8/20	40
Greece	4/12	33	6/12	50	11/14	79	8/17	47	6/13	46	7/13	54	9/12	75	4/17	24	2/11	18	9/15	60
Italy	32/52	62	28/49	57	35/46	76	45/62	73	35/54	65	28/48	58	35/46	76	7/63	11	14/48	29	23/53	43
Portugal	9/15	60	6/15	40	6/11	55	15/17	88	10/15	67	5/15	33	12/17	71	1/17	6	4/17	24	8/17	47
Serbia	2/7	29	2/9	22	2/7	29	3/9	33	0/7	0	1/9	11	2/7	29	0/9	0	1/9	11	4/9	44
Spain	36/53	68	30/49	61	30/41	73	30/55	55	37/52	71	32/49	65	38/49	78	9/55	16	24/52	46	22/53	42
Western Europe																				
Belgium	7/19	37	10/21	48	6/17	35	6/24	25	6/21	29	0/19	0	9/20	45	5/24	21	5/22	23	5/22	23
France	7/22	32	4/24	17	7/18	39	9/27	33	6/20	30	7/24	29	11/22	50	3/28	11	3/24	13	10/26	38
Germany	127/211	60	86/201	43	152/205	74	5/246	51	130/201	65	80/192	42	60/213	75	38/246	15	43/214	20	76/224	34
Netherlands	23/27	85	21/24	88	17/17	100	27/27	100	25/27	93	16/22	73	21/21	100	3/28	11	9/22	41	12/27	44
Switzerland	5/6	83	1/8	13	5/6	83	5/7	71	5/6	83	5/8	63	7/8	88	0/8	0	1/7	14	2/8	25
Other countries*																				
India	27/46	59	23/44	52	35/45	78	31/50	62	27/46	59	20/43	47	35/45	78	5/50	10	21/43	49	24/45	53
Mexico	2/5	40	3/4	75	5/5	100	3/5	60	2/5	40	3/4	75	5/5	100	0/5	0	2/5	40	5/5	100
Türkiye	21/51	41	30/63	48	35/52	67	37/70	53	21/52	40	26/63	41	36/53	68	2/75	3	21/52	40	38/71	54

*Countries with less than five included hospitals are not displayed.

Figure 1.1. Early recognition, standard of sepsis care, microbiological laboratory service and quality improvement for sepsis by country. Colored values present the proportions of hospitals having the element in place, with a range from red representing low rates to green representing high rates (32).

1.2.3. HCPs and pediatric sepsis

Sepsis awareness in pediatric patients is challenging: the burden of benign (viral) infections in children pre-hospital is very high and the incidence of sepsis low. In a prospective study in about 4000 Belgian children presenting with acute illness in primary care, only 31 (<1%) turned out to have a severe infection of whom 9 (0.22%) were diagnosed with sepsis. Parental concern and the assessment by the physician that “something was wrong” had a high sensitivity (78 and 89% respectively) and even higher specificity (95 and 97% respectively) (33). Normal ranges of vital signs are age dependent and not all HCPs are familiar with them, especially if they care for both adults and children (9, 13). Children also have a strong compensatory reserve, which makes recognition even more difficult. However, mortality of pediatric sepsis often occurs in these early stages (24-48hrs) making it very time critical: every hour without restoration of a normal blood pressure leads to a two-fold increase in mortality (9). This uncertainty inevitably leads to unnecessary use of antibiotics and hospitalization. Knowledge of pediatric sepsis seems

to be poor among HCPs, specifically in pre-hospital settings (9, 15, 34, 35). Several authors found that parental concern was the strongest factor in strengthening a clinician's intuition that the child was severely ill. (36-38). Parental concerns were found to be at times the only clues to severe disease .

1.3. Evidence on interventions to improve sepsis awareness and knowledge

1.3.1. General public

Over the past 3 decades, there has been a gradual increase in patient and public awareness of sepsis over time, due to the activities of the Survival Sepsis Campaign, including the creation of new sepsis definitions and the inception of World Sepsis Day in 2012 by the Global Sepsis Alliance. Additionally, various organizations and resources (such as the Global Sepsis Alliance, World Health Organization, U.S. Centers for Disease Control and Prevention, and The U.K. Sepsis Trust) have been established to further increase sepsis awareness (5), as highlighted in Figure 1.2. We refer to the Introduction and Appendix 3 for an overview of various initiatives launched by several countries worldwide.

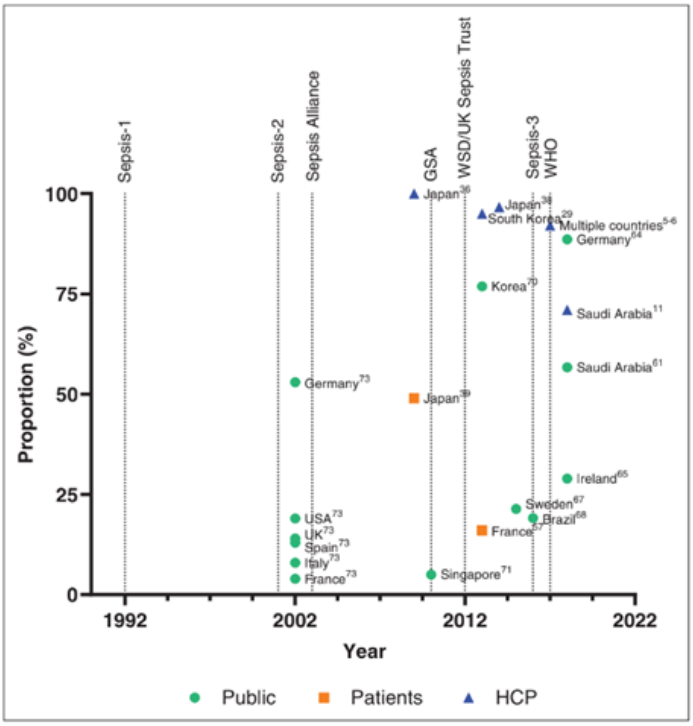

Figure 1.2. Patient, public and healthcare professional awareness of sepsis over time and in relation to changing international consensus-based sepsis definitions (5).

Given the sepsis mantra '*time is of the essence'*, large-scale interventions to improve sepsis awareness have been implemented in several countries, e.g. the UK, Australia, and Sweden, with the final aim to improve patient outcomes by reducing prehospital delays (7, 39, 40). Increased levels of sepsis awareness and knowledge have been observed in these countries. However there is no solid evidence to which extent this has led to lower sepsis mortality and incidence so far. Mass media health promotion campaigns for other major health problems (such as for stroke or myocardial infarction) have indeed gained increasing public awareness of signs/symptoms, which, in turn, was eventually associated with a reduction in both the number of patients who presented late to the hospital and who died. (3, 5, 39, 41-43). More research is needed on the impact that sepsis awareness campaigns have on public healthcare-seeking behavior, and/or on the performance of primary health care regarding sepsis diagnosis.

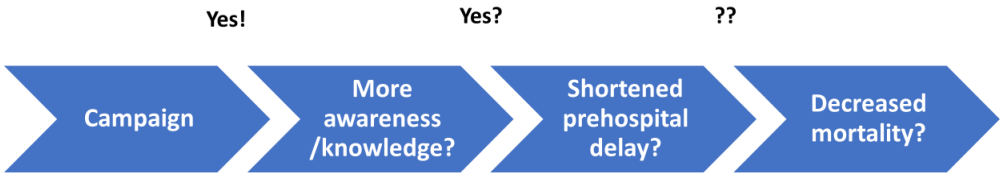

Figure 1.3. Uncertainties on the different outcomes of campaigns.

However, this uncertainty does not preclude the organization of broad awareness campaigns for sepsis, taking the following considerations into account:

- The awareness campaign should not be a one-off, standalone activity but rather be embedded in a broad (multimodal) strategy with a number of concrete and targeted activities over a longer period (a National Sepsis Plan). A National Focal Point or Steering Committee should follow up on the timely implementation and impact of the Plan. Mass media campaigns may need to be carefully thought over and well planned, in synergism (or at least not in contradiction) with pre-existing other campaigns, e.g. antimicrobial stewardship (AMS) or advanced care planning. Awareness campaigns may need to be connected to concrete educational initiatives, e.g. the UK course 'sepsis in primary care' (44). A similar course could be developed in Belgium based on these and other materials (45).
- The campaign's impact, direct and indirect effects, need to be monitored/researched and expectations need to be managed. For instance, incidences may transiently increase due to altered healthcare seeking behavior and pattern recognition, leading to a seemingly increased (or rather: more accurate) incidence.

- The campaign should combine generic aspects for all and targeted messages for high-risk populations. The generic messages should target the general public, and be understandable for everyone and in different languages, with special attention to difficult-to-reach groups in society. In addition, an awareness campaign targeted at patients at high risk of sepsis, such as oncological patients, immunosuppressed patients, at-risk children and their parents should be designed and started. Such a general awareness campaign should give sufficient attention for persons with lower education levels and infrequent health information seeking behavior.
- A broad campaign may have indirect advantages: understanding the realities of post-sepsis patients, generating public visibility, attracting financing and collecting more accurate data…. Many studies of incidence and mortality are based on registrations of diagnosis, and they are probably underestimating sepsis' burden of disease. Accurate data are essential and might, together with a general awareness of sepsis, improve its weight in political considerations to prioritize health interventions and support research or promote other actors for fundraising. The need to address this is obvious when looking at the disproportion in mortality and research funding (39). (see also Chapter 7). The awareness campaign should be grounded in locally relevant data.

Which tools/means should be used to improve awareness?

- Mass media and social media are the primary sources of sepsis information for the public. It is crucial to evaluate the quality of this content using tools like the Patient Education Materials Assessment Tool or Health-on-the-Net criteria, focusing on factors like understandability, actionability, and readability (5). An example of a printable qualitative patient education tool is the Centers for Disease Control and Prevention's Sepsis Fact Sheet (46).
- A newly founded 'Sepsis Foundation' with a dedicated and easily retrievable webpage (including its logo) could be created as a hub and community for sharing communications and educational materials.
- Personal storytelling, including high-profile sepsis-related stories, like celebrity deaths or healthcare errors, often prompts the public to seek sepsis-related information, providing an opportunity to embed awareness messages within such stories (5, 42). In the UK, sepsis awareness was promoted through a documentary in collaboration with Ireland's national TV, targeted social media posts, banners listing sepsis signs/symptoms, and links to the "What is Sepsis?" video from the Global Sepsis Alliance (47).

- Using World Sepsis Day (September 13d) as a frame for a temporary boost in knowledge and attention (48).
- Finally, health communications about sepsis in the media must balance messages about the importance of early treatment with antibiotics with information about the risks of overuse (49).

1.3.2. Parental education on pediatric sepsis

Because any delay in therapy significantly increases mortality in children, education should focus on improving healthcare-seeking behavior and communication between parents and healthcare providers. Structured parental education on early recognition of severe infections became standard practice, particularly for immunocompromised children (50, 51). While the setting of fever and neutropenia provides clearer guidelines than the more vague concept of sepsis, these parents are empowered to raise concerns and, as such, play a vital role in advocating for their child's care. Notably, in areas with limited resources, maternal education reduced infection-related mortality in childhood, likely due to improved preventive measures and quicker disease identification (52).

To address gaps in parental awareness, national sepsis plans can implement targeted campaigns focusing on recognizing signs and symptoms in children (e.g., the Sepsis Assessment and Management tool in the UK, sam-sepsis-leaflet.pdf (gpsurgery.net) or even address the children themselves (mandatory education of children on sepsis in NY (53). The National Institute for Health and Care Excellence (NICE) recommends a cautious approach, with clear red flags (54). In Flanders, the department 'Opgroeien' developed a flowchart for parents and day care centers, showing red flags when addressing a child with fever (55). Although sepsis is not explicitly mentioned, parents are encouraged to seek medical attention if one of the red flags is present. Any system used to identify pediatric sepsis must balance sensitivity with the risk of overtreatment, given the low prevalence of sepsis compared to non-septic febrile infections. (11, 13).

Parental understanding of sepsis´ life-threatening nature may be influenced by common beliefs ("fever" is dangerous), leading to requests for antibiotics (56). Doctors may feel the need to prescribe antibiotics when parental concerns are present (57). Despite potential challenges, a rather 'paternalistic' approach assuming healthcare professionals and PEWS perform superiorly to parents may fall short, especially considering the sometimes low pediatric experience of HCPs at initial presentation and the constraints of busy periods (58, 59). Further studies are required to assess the benefit of targeted sepsis education for parents, weighing against the risk of excessive healthcare resource consumption and unnecessary

treatment for mild infections (13). Ultimately informed decisions by HCPs are essential, with parents as key partners in safety netting through home observation and prompt representation for reassessment when necessary in case the child is sent home. Innovative initiatives that were implemented during COVID to offer continuous telemonitoring might be explored to raise acceptance and feasibility of safe home monitoring.

1.3.3. Healthcare providers

The systematic review by Rababa et al. (2022) gives us a broad overview of the different interventions to improve sepsis management among nurses, including educational sessions, simulations, screening or decision support tools, and intervention protocols. Results indicated the three most common facilitators of sepsis assessment and management: the presence of standard sepsis management protocols, professional training and staff development, and positive enforcement of successful stories of sepsis treatment. The study highlighted the significant role of education programs in improving nurses' knowledge, attitudes and practices related to sepsis (27). Another recent systematic review corroborated these findings by conducting a thorough assessment of sepsis education among HCPs and students. They recommended integrating active learning strategies into sepsis education interventions, as this approach holds promise for enhancing long-term outcomes among learners. Moreover, they highlighted the synergistic effects of sepsis education alongside a protocol-based sepsis care bundle, yielding more significant enhancements in care processes and patient outcomes (60). Education initiatives should prioritize infection prevention messaging, utilize broad media strategies, and use primary healthcare providers for disseminating evidence-based information (6).

For home care nurses, the continued emphasis on clinical reasoning in continuous education was underscored, for example, through internal training sessions for HCPs. Additionally, the use of a communication model (such as the SBAR method) was highlighted to provide HCPs with a framework for reporting in a structured, rapid, and appropriate manner to, for example, the GP or other healthcare providers. Educational materials could be provided by the Sepsis Foundation in collaboration with public health authorities, so that all healthcare providers have access to the same materials. The content of education and training for HCPs needs to be clearly defined, covering topics such as symptoms and risk factors of sepsis, clinical reasoning, effective communication, and referral possibilities.

In 2023, a state-wide 'Sepsis Pathway' initiative was implemented in 23 Australian hospitals and economically evaluated. The clinical pathway, along with an implementation toolkit, aimed to support

nurse initiation and utilize early warning criteria in combination with severity indicators. The study found that this initiative can save lives and reduce health service costs per admission (61).

Data indicates that implementing sepsis protocols and screening tools based on the Surviving Sepsis Campaign (SSC) guidelines improves early identification and management of sepsis, enhancing nurses' adherence to SSC guidelines. Decision support tools have also shown effectiveness (27, 62).

Early warning scores (EWS) improve predictability of clinical deterioration in hospital settings but are less suitable for prehospital use (63). This topic is discussed in depth in Chapter 3. There has been a lack of diagnostic models for sepsis management in primary care. Loots et al. (2022) developed and validated a sepsis prediction model for adult patients in primary care, comparable to the National Early Warning Score (NEWS) used in hospitals. This model showed superiority over systemic inflammatory response syndrome (SIRS) and qSOFA scores (64). Implementation of screening tools in emergency departments has led to a 17% reduction in in-hospital mortality in the Netherlands (21). Machine learning models provide an alternative to traditional scoring systems for predicting sepsis onset. A systematic review found that these models accurately predict sepsis onset ahead of time but study heterogeneity limits pooled performance assessment (65).

A recent qualitative study examined the impact of a cross-disciplinary quality improvement project on Nurses' and Physicians' Experiences regarding early identification and treatment of sepsis patients at a Norwegian hospital. The intervention, spanning medical, surgical, and gynecological wards, involved tool development, training sessions for nurses, information sessions for physicians, and clinical pathway development. Results showed increased sepsis awareness and collaboration between nurses and physicians, with professionals relying more on objective measurements. Continuous repetition and education for new colleagues were identified as essential factors for the sustainability of the intervention. Overall, the study highlights the importance of standardized protocols and training for early detection and management of sepsis in healthcare settings (66).

In the past, several interventions (UK and Australia) were launched that provide sepsis awareness training for pharmacists and pharmacy support staff in order to raise awareness of the condition, educate patients so that they learn to recognize it in future and seek help early for themselves or someone they know; and identify at-risk patients (67, 68). In 2017, the Department of Health (UK) recommended including sepsis training in mandatory first aid and resuscitation training for pharmacists and care home staff.

1.3.4. Interventions among HCPs working in long-term care facilities (LTCFs)

There is limited evidence available regarding interventions to enhance sepsis awareness among HCPs working in LTCFs. Mihaljevic et al. (2016) conducted a study describing the outcomes of interprofessional sepsis simulation training implemented in 19 long-term care facilities (LTCFs) in the USA. This training focused on urinary and respiratory sepsis to promote early recognition of sepsis symptoms and improve communication among interdisciplinary teams regarding sepsis symptoms. They concluded that establishing protocols and standardizing communication increases the probability of successful communication among interdisciplinary teams and decreases medical errors. Simulations proved to be a valuable educational methodology for implementing sepsis education and reinforcing interdisciplinary communication in the LTCFs (69). It fosters long-term knowledge retention and critical skill acquisition in a safe environment, adaptable to various educational strategies, from traditional teaching to gamification and multimodal training (70, 71).

A quality improvement project was conducted in 9 hospitals and 200 nursing homes in Texas (US). The aim was to improve sepsis identification and treatment by nursing staff through a multi-intervention strategy in hospitals (2015-2017) and a train-the-trainer (nurse leaders) strategy in nursing homes (2017-2019). The outcomes of the project supported the use of comprehensive nursing staff education on sepsis identification and treatment. They observed a decrease in sepsis mortality rate following the hospital intervention and an improvement in sepsis knowledge and awareness among nurse leaders in nursing homes (72). A very recent pre/post implementation design study (US) evaluated the implementation of a standardized sepsis pathway in skilled nursing facilities (SNF). The pathway incorporated a sepsis screening tool and a sepsis bundle. Implementation of the pathway involved educating nurses and certified nursing assistants. Implementing a modified SNF sepsis pathway resulted in accelerated identification of sepsis and improved clinical outcomes (73).

1.3.5. Interventions among HCP focused on pediatric sepsis

Enhancing awareness and knowledge of pediatric sepsis among HCPs dealing with children is crucial for timely diagnosis and intervention. There are many ways to achieve this, starting with increased efforts to incorporate pediatric sepsis into medical and nursing curricula (see below). Education on pediatric sepsis can only be achieved with simple diagnostic criteria. However, unfortunately neither an easy-to-use definition for pediatric sepsis nor a pediatric sepsis screening tool is available (10, 58, 59). Physiologic criteria and early warning/electronic health record-based trigger tools improve recognition and yield high

sensitivity but poor specificity. Although promising, neither PEWS (pediatric early warning score, addendum 3) nor POPS (pediatric observation priority score, addendum 4) turned out to be specific in diagnosing pediatric sepsis (35). Many sepsis screening tools include parental or HCP concern in combination with other signs, symptoms or scores (38, addendum 2-3). The development of an evidence-based pediatric early warning system that takes into consideration a variety of healthcare contexts, including family as well as clinician concern such as the ESCALATION system, might be worth looking at for Belgium (74, addendum 5).

Sepsis bundles for treatment in pediatrics do exist, but less than 60% of children with sepsis are currently treated according to existing guidelines (9). To overcome these barriers, written (national) guidelines should easily be available (e.g., via national societies such as the Belgian Academy of Pediatrics), with online learning platforms that HCPs can access at their convenience, including a 24/7 available advice line (e.g. integrated in hospital on call systems) . These platforms can offer interactive case studies, webinars, quizzes, and resources to reinforce learning. Multidisciplinary collaboration can be enhanced via simulation-based training (with or without virtual reality augmentation), allowing HCPs to practice their skills in a safe environment, improve their ability to manage sepsis and work as a team effectively. One of the barriers in sepsis treatment is access: training for intra-osseous access or ultrasound guidance might be a solution. Interdisciplinary discussions and case reviews (morbidity/mortality) can help improve understanding and standardize practices related to sepsis management. Targeted training for nurses is important since they play a pivotal role in early recognition (5, 9, 13, 15, 74-76).

Other solutions to enhance recognition could be the use of artificial intelligence or alert systems on triage/medical charts, the availability of charts with vitals for age ranges, the use of escalation systems, visual aids, posters, brochures and mobile applications (Pedi Help) to assist HCPs in the early recognition, and the development of artificial intelligence (e.g., Innocens, an AI software to empower clinicians to detect sepsis in the NICU (77, https://innocens.be/#/) Being part of the continuous professional development of both nurses and doctors, pediatric sepsis training should have regular repetition and reminders to solidify awareness and knowledge. Quality improvement initiatives could be helpful in institutions (audits, feedback mechanisms, and performance metrics) to track improvements over time.

An example of a successful educational initiative was launched in 2020 in a child hospital in the USA (Buffalo, NY), targeting previously identified barriers to pediatric sepsis recognition and treatment. They concluded that a multidisciplinary curriculum balancing active education—through brief, targeted

simulation—and general awareness—through electronic resources and a poster campaign—can improve sepsis-related knowledge, attitude, and behavior among pediatric practitioners (78).

1.4. Reality check on sepsis information and education in Belgium

Systematically retrievable information on the positioning and weight of sepsis in the training curricula of medical and paramedical schools in Belgium is unavailable. We gathered the following information:

1.4.1. Medical doctors

Most medical schools have started organizing dedicated classes or packages on sepsis in the undergraduate curriculum, although learning content and methodologies may differ substantially between universities (the focus may be rather on pathophysiology than on prevention or care bundles). CanMeds includes sepsis as a separate topic/learning objective, next to infectious diseases and AMR.

During GP training, a lot of emphasis is given to intuition ('OK/not OK'-feeling) within clinical reasoning. Sepsis may receive additional attention in specialist training of acute specialties, but a lot depends on the specialty, and there are no minimum requirements/formal learning objectives.

1.4.2. Nurses

Training in infectious diseases is very limited in Bachelor of nursing and typically very much applied (e.g. embedded in classes on wound care, vaccination, catheter related sepsis). In many schools, there is no particular focus on sepsis; there is only a limited focus on basic microbiology. In the third year, critical care and septic shock are discussed; some of these courses are elective only. In contrast, the Master of Nursing courses do include dedicated lectures on sepsis.
Nurses do receive information about pediatric sepsis and recognition of the severely ill child (+/—3-4 hrs.), and if they follow postgraduate training, they receive an additional 5 hours on the same topics.

Recommendations

1. A National Sepsis Focal Point or Steering Group should be created, responsible for coordinating and following up of the implementation of interventions related to sepsis awareness and management (i.e. a National Sepsis Plan or Program).
    a. The focal point or Steering Group should include public health officers, scientific experts, (para)medical professionals, representatives of patient advocacy groups (example from Australia: https://www.safetyandquality.gov.au/our-work/national-sepsis-program)
2. A National Sepsis Foundation should be created to increase awareness of sepsis among the public, at-risk patient groups and healthcare professionals (HCP). It should serve as a hub for educational materials, advocacy and support of survivors. This could evolve for instance from the actual Sepsibel organization (79).
    a. The foundation should have an easily accessible website (e.g. Sepsisnet.nl (80); https://www.australiansepsisnetwork.net.au/, to serve as a centralized hub for information, resources, and support.
3. A general awareness campaign should be developed, with general messages for the general public and sufficient attention to reach persons with limited education levels and/or infrequent health information-seeking behavior.
    a. The concept 'sepsis' should be branded (use the word, in particular for highly vulnerable groups) in messages. Storytelling (survivors' testimonials) could support awareness messages.
    b. World Sepsis Day (September 13th) could be used as a focal point for raising public awareness through events, campaigns, and educational activities.
    c. Joint messaging initiatives linking sepsis awareness with antimicrobial stewardship should be foreseen to avoid redundant/conflicting messages.
4. Tailored awareness and educational interventions should be created directed towards higher-risk patient groups, such as oncological patients, immunosuppressed patients, children and their caregivers in collaboration with relevant other societal actors (e.g. other patient groups, associations,…)
5. Education on recognition and early management of sepsis for all relevant HCPs should be designed and implemented. This includes medical doctors, nurses, home care nurses, nursing aids

in nursing homes, pharmacists, dentists… The specific roles and tasks for each group need to be defined.

a. Training on sepsis should be part of the undergraduate and postgraduate education of these professional groups. For HCPs working in long-term care facilities, sepsis awareness training should be made mandatory.
b. Training modules should be differentiated for the different HCPs groups, including pediatricians, pediatric care providers (nurseries, Kind & Gezin), geriatricians, home care nurses and chronic care providers.
c. Training on sepsis for all HCPs working with children should be strengthened via:
    i. a clear set of learning objectives of pediatric sepsis into medical and nursing curricula,
    ii. a national consensus on guidelines for pediatric sepsis, readily available online,
    iii. reinforcing knowledge of pediatric sepsis as a mandatory part of the continuous professional development for nurses and doctors through accredited (simulation)training sessions, online learning platforms, interdisciplinary discussions or case reviews,
    iv. development of transfer criteria to escalation of care (to regional PICU/NICU)
d. Professional sepsis training should integrate sepsis recognition tools and early warning scores (see Chapter 3), as well as antimicrobial stewardship. For pre-hospital settings, telephone-triage tools should be explored (81).

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Chapter 2. PREVENTION OF SEPSIS AND SAFEGUARDING TREATMENT OPTIONS (IPC & AMR)

When focusing on the prevention of sepsis, it is important to distinguish the different settings where sepsis may occur, as each setting comes with different challenges and possibilities:
(1) the community (i.e. at home), (2) the acute health care setting (i.e. during or shortly after a hospitalization, characterized by a high number of invasive procedures and high patient turnover, but already existing infection prevention and control (IPC) activities and expertise), and (3) the chronic care setting (i.e. while residing in a long term care facility (LTCF), representing the home setting for large numbers of vulnerable persons in settings with less IPC expertise and activities).

2.1. Prevention of sepsis in the community, while safeguarding the effectiveness of antibiotics

'Community-acquired sepsis' is, by definition, sepsis complicating an infection or disease occurring at home, in contrast with 'health care associated' sepsis, presenting during or shortly after a stay in the hospital or in a LTCF. Obviously, with the tendency towards more transmural and sophisticated medical care at home or in day-centers, the demarcation line between these two groups has become somewhat blurred. Nevertheless, the distinction remains clinically relevant, as the risks, underlying causes and affected population are markedly different and require another approach.
As described in the Introduction, there is a broad variety of micro-organisms and clinical syndromes potentially leading to community-acquired sepsis, each associated with different treatment challenges and/or opportunities for prevention. Community-acquired sepsis can occur at all ages and can affect otherwise healthy persons but high risk populations have been identified in epidemiological studies, as summarized in Table 2.1: patients at the extremes of age (very young or old patients), pregnant women, people with underlying chronic health conditions (e.g. diabetes, chronic cardiac failure, dialysis,...), people with immune depression, sepsis survivors, socio-economically vulnerable (including homeless, prisoners, persons with severe addictions and/or severe mental health problems). In addition, there is a growing number of chronic patients with indwelling devices (such as vascular or urinary catheters) following the increasing tendency for transmural and home care.
Given the heterogeneity of causes and at risk populations, the prevention of community-acquired sepsis includes a broad set of actions, including:
(1) ensuring sufficient access to health care and other social determinants of infectious diseases, in particular for the medical and socio-economical high-risk groups

(2) improving health and vaccination literacy of the general public and health care workers, to enable early recognition and health seeking behavior

(3) strengthening/enabling vaccination programs for children and at risk adults

(4) offering adequate and timely management of less severe infections with prudent use of antibiotics

Community-acquired sepsis	
Common infection sources	**Risk groups***
skin and soft tissue infections e.g. wounds, skin abcesses	extremes of age (young children, elderly)
urinary tract infections	pregnant women
respiratory tract infections e.g. pneumonia, COVID-19	persons with underlying chronic conditions e.g. diabetes, cancer
meningitis	persons with underlying immunedepression e.g. HIV, setroids, cancer treatment,...
intra-abdominal infections e.g. appendicitis, bowel perforation	persons who recently survived earlier sepsis episodes
dental infections	persons who were recently admitted in hospital and/or have indwelling device e.g. vascular or urinary catheters
	persons with addictions and other serious mental health problems
	persons with limited education and/or difficult living contexts e.g. living in poverty, homeless, prisoners,...
	** in all risk groups (except pregnant women), men appear to have a higher risk to develop sepsis*

Table 2.1. Common sources and at risk populations for community-acquired sepsis

2.1.1 Social determinants of health and access to health care in relation to sepsis

Social determinants of health (SDoH) are the conditions in which people are born, grow, live, work, which can impact their health outcomes. While sepsis itself is primarily triggered by infections, the social determinants of health can influence a person's susceptibility to infections, access to healthcare, and overall health status, which in turn may affect their risk of developing sepsis.

Key SDoH with relevance for the acquisition of infection and subsequent sepsis include: socioeconomic status, access to healthcare services, housing and living conditions (including quality of drinking water and indoor air, crowding, sanitation, homelessness,…), administrative status, food safety, education level, occupational exposure, social networking and social status (including gender, age, ethnic group, marital status,…). Obviously, many of these determinants are interlinked; interventions on one determinant may yield indirect impact through other SDoH.

In most European countries, including Belgium, huge steps have been made forward over the past century in reducing poverty and improving living conditions, which has led, together with vaccination programs and the availability of antimicrobials, to a significant decline of life-threatening community-acquired infectious diseases (e.g. tuberculosis, meningitis). However, the increase of non-communicable health problems (such as obesity, cancer or diabetes) and the overall aging of our population generated new, rapidly growing vulnerable groups. Of note, at the beginning of 2023, there were about 2.3 million people aged 65 years or more in Belgium. This age group now makes up nearly 20% of the population, and the Belgian Federal Planning Bureau expects this share to exceed 25% by 2050 (1).

Other societal phenomena, such as the increase of single parent families and migration contribute to socio-economical vulnerability. In many cases, medical and socio-economical vulnerability are mutually reinforcing each other. At European level, the relationship between social determinants of health, health inequalities and infectious diseases has been described in depth by the European Centres for Disease Control (2); a more recent report by the European Health Observatory (3), describing persisting inequalities for homeless and specific ethnic groups e.g. Roma. Also in Belgium, persons from lower socio-economical groups have markedly lower contact with health care services, in particular dental care (4).

Homelessness is probably the most extreme social determinant jeopardizing health, and a growing problem in several EU member states, despite the Lissabon declaration to end homelessness by 2030 - which was also signed by Belgium in 2021 (5). Recent counting studies, which are by definition underestimates, mention at least 19.547 homeless persons in Flanders and at least 7134 in Brussels (2023). Among them, about a quarter are children. About 10% of the homeless are more than 60 years old, and a quarter is more than 50 years old (6,7). Between 2008-2022, the number of homeless in Brussels quadrupled, but also in more rural areas in Flanders and Wallonia homelessness increased.

Infection	Health endpoint	Social determinants and site of study	Ref
Campylobacter	Intestinal disease	Pakistani community at greater risk of infection than White community in England.	[22]
Clostridium botulinum	Progessive bulbar palsy, diplopia, dysarthria, and a positive electromyography (EMG) test	Injecting heroin drug users at risk, Dublin, Ireland.	[23]
Common childhood pathogens	Infectious/parasitic diseases	High infection rates found in children in a lower socioeconomic area in Romania (Moldova)	[24]
Cytomegalovirus (CMV)	infectious mononucleosis, with fever, and mild hepatitis; congenital abnormalities	Low socioeconomic status and social environment risk factor for CMV seroprevalence and congenital CMV infection in Helsinki, Finland.	[25]
Bacillus anthracis	Inflammation or abscesses related to sites of heroin injection; death	Outbreak among (predominantly) people who inject drugs in Scotland	[26]
Drug-related infections and co-infections	Number of major health consequences	Marginalised (Roma or homeless) people who inject drugs suffer risks from injecting and sexual behavior risks, as well as from poor hygienic living and injecting conditions in Budapest, Hungary	[27]
Flaviviridae (Arbovirus) transmitted by ticks	Tick-borne encephalitis (TBE)	Socio-economic factors influence transmission of TBE in Central and Eastern European countries.	[28]
Herpes simplex virus type 1 (HSV1) and 2 (HSV2)	Significant morbidity, and HSV2 is considered a risk factor for HIV transmission	HSV1 seroprevalence increase with age among people of Turkish and Moroccan origin, men who have sex with men, and individuals with low educational level in Amsterdam, Netherlands.	[29]
Neisseria meningitidis (meningococcus)	Meningococcal disease	Parental smoking and unfavorable socioeconomic circumstances among children in the Czech Republic.	[30]
Rubella	Terminations and congenital rubella syndrome (CRS)	Low socioeconomic status associated with low rubella seropositivity in Dogankent Health Center, in Turkey.	[31]
Hepatitis A	Acute infectious disease of the liver	Outbreak in Lomnička, a village in the eastern part of Slovakia among the Roma population associated with low socio-economic conditions.	[32]
Hepatitis B	Malignant and non-malignant liver disease	Immigrant women in Greece significant higher prevalence.	[33]
Influenza	Vaccine coverage	Lower vaccine uptake in socio-economically deprived populations in Britain.	[34]
Methicillin-resistant Staphylococcus aureus (MRSA)	Postoperative infection	Patients from the most deprived areas at higher infection risk than those from the least deprived areas in England.	[35]
Neisseria meningitidis	Meningitis	Association with area deprivation of socio-economic environment in England.	[36]
Sexually transmitted diseases (STI)	STI	High-risk sexual behavior among immigrant groups in Amsterdam.	[37]
Toxoplasmosis	Encephalitis and congenital malformations	Migrants in Northern Italy not correctly monitored for toxoplasmosis during pregnancy, which precludes timely application of preventive measures.	[38]
Puumala virus (PUUV)	Nephropathia epidemica, a mild form of hemorrhagic fever with renal syndrome (HFRS)	PUUV infection risk higher among low-income populations in remote forest areas, where level of urbanization is low in Belgium.	[39]

Table 2.2. Illustration of a broad range of infectious diseases in Europe the link with SDoH (2).

As shown in a recent systematic review of 20 studies (8), there is a growing body of evidence to suggest that several SDoH also impact the incidence of sepsis, in particular socio economic status, gender, old age, and frailty. The authors' conclusions were limited by the heterogeneity of the studies and definitions used, urging the need for future standardized definitions and collection of SDoH data. In a US-based study, persons living in households with lower incomes had significantly higher mortality rates from sepsis as compared to higher income group (9). A rapid systematic review based on 50 studies (mainly from the US and UK) found clear correlations between sepsis morbidity and mortality and the presence of factors associated with health inequalities (10).

The recent experience with the COVID-19 pandemic has confirmed several of these insights. A systematic review of 52 studies with focus on the US revealed that African American/Black and Hispanic populations experienced disproportionately higher rates of SARS-CoV-2 infection and COVID-19-related mortality but similar rates of case fatality. The authors postulated that differences in health care access and exposure risk may be driving higher infection and mortality rates (11).

A systematic review from the UK, including 41 studies showed that people living in crowded settings had a higher risk of COVID-19 infection compared to rough sleepers and the general population. The homeless population had higher rates of hospitalization and mortality than the general population, lower vaccination rates, and suffered negative mental health impacts (12). Beyond case studies, relevant data for Belgium are not available as detailed demographic data are not collected within surveillance studies. Likewise, in a systematic review on drivers of vaccine-uptake among difficult-to-reach communities in Europe, influential factors included health service accessibility, language and vaccine literacy, and the authors listed a set of suggested community-based interventions (13). Also in Belgium, a lower COVID-19 vaccine uptake was found among young individuals, men, migrants, single parents, one-person households and disadvantaged socioeconomic groups (with lower levels of income and education, unemployed) (14). More research on effective interventions on how to reach these population groups and link them to care is needed; pilot experiences with community health care workers could be of help to bridge issues of trust and access to health care (15).

Finally, the aging population and increase of home care for patients with devices and catheters at home comes with particular challenges in the organization of safe care, including the need for training of the staff, timely and adequate communication with hospitals, sufficient time of all included health care workers (16). These patient groups are also vulnerable for colonization with Methicillin-resistant Staphylococcus aureus (MRSA) and other multi drug resistant organisms (MDRO), for which decolonization and follow up programs need to be foreseen.

2.1.2 Improving health and vaccination literacy of the general public and health care workers, to enable early recognition and health seeking behavior (17,18)

Health literacy refers to the ability of individuals to access, understand, evaluate, and use health information to make informed decisions about their health and healthcare. It involves not only the capacity to comprehend health-related information but also the skills to navigate healthcare systems and effectively communicate with healthcare providers. One third of the Belgian population aged 15 years and

over (33%) has a low level of health literacy, meaning they do not have sufficient skills to make decisions about their health (19). Low levels of health literacy are more prevalent among women (35%) than men (32%), and in Brussels and Wallonia (38% and 36%, resp.) than in Flanders (29%). Data on the levels of specific knowledge or awareness of sepsis in Belgium are not available. People in poor health, older people, and lower educated people have a lower level of health literacy; in other words, people who have higher needs for healthcare and health promotion, are those who benefit the least from such interventions. For the improvement of health literacy in Belgium, a dedicated plan has been proposed by Belgian Health Care Knowledge Centre (KCE) in their 2019 report, with activities extending far beyond the problem of sepsis. However, strengthening general health literacy can help to improve linkage to vaccination programs, acute and chronic care, while targeted interventions to increase awareness and knowledge on sepsis can help to improve early recognition of signals and health care seeking behavior. For details, we refer to Chapter 1 'Awareness and education'.

2.1.3 Strengthening/enabling vaccination programs for children and at risk adults

Over the past decades, vaccination of children and adults, especially the medically vulnerable adults, has proven very effective in reducing mortality and morbidity of a wide range of vaccine-preventable diseases. Within the context of sepsis prevention, the most directly relevant vaccines are those for *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* but also for the influenza virus and SARS-CoV2, as these vaccines have proven effectiveness in reducing the burden of acute, life-threatening pneumonia and/or meningitis potentially complicating in sepsis and death, and even in reducing the burden of antimicrobial resistance. These vaccines have therefore been included in Belgian recommendation vaccination schedules as follows (20-23).

		Streptococcus pneumoniae	*Haemophilus influenzae*	*Neisseria meningitidis*	influenzavirus and SARS-COV2
Children (0-17 y)		PCV13 included in basic schedule	included in basic schedule	ACWY included in basic schedule	only for severely immunodepressed
Adults (≥ 18 y)	pregnant women				recommended by SHC
	persons residing in LTCF				recommended by SHC
	persons with BMI ≥ 40				recommended by SHC
	persons with asplenism	PCV20 + PPV23 + repeat PPV23 1 x/5y	recommended by SHC	recommended by SHC	recommended by SHC
	18-64 y old, immunedeficiency	PCV20 + PPV23 + repeat PPV23 1 x/5y		recommended by SHC	recommended by SHC
	18-64 y old, with severe comorbidity	PCV20 + PPV23 + repeat PPV23			recommended by SHC
	≥ 65 y old	PCV20 +/- PPV23 (ages 65-85)			recommended by SHC
	household contacts of persons with severe immunedefinciency (cocoon)				recommended by SHC
	health care workers				recommended by SHC

Table 2.3. Overview of recommendations on 'sepsis-related' vaccines (based on recommendations of the Superior Health Council (SHC) (24).

For children, the majority of these vaccines are systematically offered in the routine vaccine programs ('basic and 'catch up' vaccination schedules), which has led to very high coverage rates in Belgium (25,26). Vaccination for adults is organized in a very different way: vaccines are not systematically offered/administerd/registered in high risk persons, and are often costly (with the exception of vaccines for influenza and SARS-CoV2). Beyond costs, other hurdles for vaccination include lack of awareness of their own high risk status and need for being vaccinated, lack of information and confidence in the required vaccines. Finally, vaccinations may be offered both by general practitioners and a wide range of treating specialists, leading to underregistration.

Data on coverage rates of the aforementioned vaccines for high-risk populations are scarce, but those available suggest insufficient take up, due to a combination of lack of knowledge and confidence as well as logistic and financial hurdles in both patients and health care workers.

The most recent 'Vaccinatiegraadstudie'(2020) (27), a periodic assessment of vaccination coverage for target vaccinations and target groups in Flanders, includes data in young children 18-24 months, adolescents, pregnant women, health care workers (for influenza) and childcare staff (for pertussis and influenza). Among 381 pregnant women, only 62.3% was vaccinated for influenza – albeit an improvement as compared to < 50% in earlier measurements. A recent systematic review (n = 32 articles) on the

willingness to be vaccinated during pregnancy revealed that vaccine hesitancy in pregnant and lactating women remains an important issue (28). However, knowledge and vaccine confidence among health care workers is very important in this context: in 46% of the unvaccinated pregnant women in Flanders, the vaccine was either not offered or recommended by the health care worker responsible for antenatal follow up (27).

A survey from the Intermutualistic Agency showed that in 2021, only 57.3% of persons of age ≥65 y old and living at home was vaccinated for influenza (29), far below the WHO target of 75%. There is a higher coverage rate in Flanders (64.7%) than in Wallonia (49.1%) and Brussels (46.3%), and large differences exist between provinces and age groups, as shown in Figure 2.1 (30)

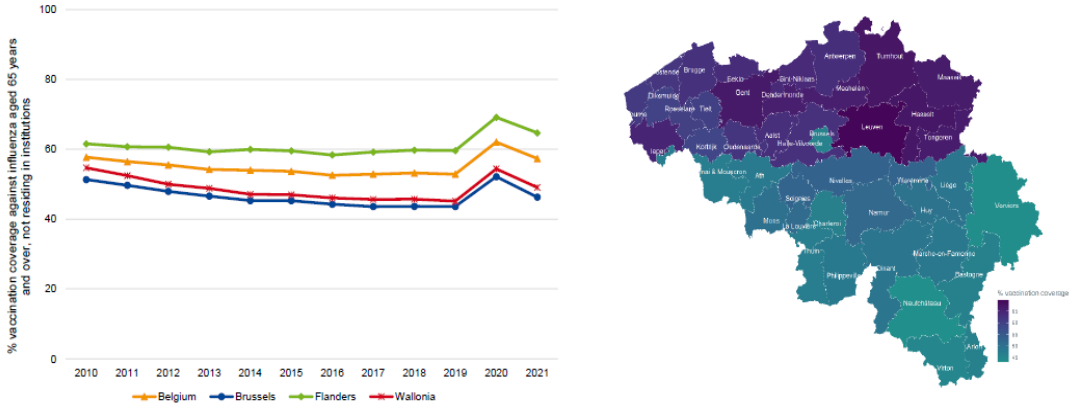

Figure 2.1. Coverage of vaccination against influenza in people aged 65 years and over, by region (2010-2021) and by district (2021) (30).

In a monocentric study on vaccination coverages in different patient groups with severe comorbidities (i.e. patients with diabetes mellitus type 1 (n = 173) and type 2 (n = 177), chronic kidney disease (CKD) (n = 138), heart failure (n = 200), chronic obstructive pulmonary disease (COPD) (n = 187), HIV (n = 201) or solid organ transplantation (SOT) (n = 201)), less than 10% of these patients had received all recommended vaccines; in particular, only 44% was vaccinated against influenza, 32% against pneumococcal disease. Reasons for non-vaccination were concerns about effectiveness, necessity and side effects of influenza vaccines, and not being aware of the recommendation for pneumococcal disease. The authors advocate systematic vaccination registration and frequent communication about vaccination, also by treating healthcare-workers (31).

Data on pneumococcal vaccination among adult target groups in Flanders were published also from repeated cross-sectional surveys in the first line health care INTEGO database (32). The authors concluded that pneumococcal vaccine coverage is slowly increasing in Flanders, but with less than one-fourth of the target population vaccinated, there is still much room for improvement. Adults with poor socioeconomic status had lower odds of primary vaccination and schedule adherence, demonstrating the need for a publicly funded program in Belgium to ensure equitable access. A study in four European countries including Belgium showed that an increasing number of GP visits was strongly associated with a higher prevalence of pneumococcal vaccination in high risk adults, underlining the important role of the GP in the provision of recommended vaccinations (33).

In conclusion, higher vaccination coverages for high risk populations are needed, through different interventions, including eliminating hurdles of cost and logistics (e.g. through co-administration (34)), improving registration, linking patients to primary care and improving vaccine literacy and confidence among patients and their health care workers.

Of note, the Flanders region has issued strategic targets for 2030 for adults, with focus on the improvement of coverage for specific vaccines in target populations. This would include for influenza the ambition to reach a 90% coverage in pregnant women (and preferably also their household contacts), a 80% coverage in healthy persons ≥65 y old and a 90% coverage for health care workers. For adult pneumococcal vaccination in healthy persons ≥65 y old, coverage rates should be at least 50%. In addition, there are also plans to improve coverage rates among difficult to reach patient groups and for those with underlying diseases (35).

2.1.4 Adequate management of less severe infections with prudent use of antibiotics (antimicrobial stewardship) (36)

Prevention of sepsis as the most severe complication of an infectious disease includes also early and adequate management of less severe presentations of infectious diseases, including urinary and respiratory tract infections, as well as adequate wound and dental care. However, certain infections, notably those affecting the respiratory or urinary tract, are mostly self-limiting and may not necessitate antibiotic treatment. Conversely, the rise of antimicrobial resistance (AMR) poses a challenge to effective antibiotic therapy for infections requiring such treatment. Thus, a balance must be struck between raising sepsis awareness and providing timely treatment on one hand, and avoiding antibiotic overuse, which exacerbates AMR, on the other.

One of the primary contributors to AMR is the indiscriminate use of antibiotics in human medicine (37,38). AMR is an important and growing problem and will have a lasting impact on our medical care in the coming decades. In ambulatory care, general practitioners are responsible for the majority of antibiotic prescriptions (39). Despite respiratory infections typically being self-limiting, general practitioners in Belgium frequently prescribe antibiotics (40). Targeted interventions aimed at improving appropriate antibiotic use are essential in combating antibiotic resistance in primary care. However, despite considerable efforts to reduce inappropriate antibiotic prescribing in Belgium, desired targets have yet to be achieved.

Antimicrobial stewardship (AMS) involves a broad range of actions aimed at promoting responsible use of antimicrobial agents across different levels, encompassing individual practices to global initiatives, and considering human and animal health as well as environmental factors (41). Formally defined by a consensus statement from the Infectious Diseases Society of America (IDSA 2007 and 2012) (5bis), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS), AMS focuses on coordinated interventions to enhance and evaluate the appropriate utilization of antimicrobial agents, which includes selecting the optimal drug regimen, determining dosing, duration of therapy, and route of administration. Examples of AMS actions include decision-support tools, audit and feedback mechanisms, educational programs including communication skills training, rapid diagnostic testing, delayed prescribing, fixed pack dispensing, and public awareness campaigns.

In 2019, a KCE report was published by the Federal Public Service Health, Food Chain Safety and Environment (FOD VVVL – SPF SPSCAE) on behalf of the Belgian Antibiotic Policy Coordination Committee (BAPCOC), addressing four key research questions (36): 1) Assess initiatives undertaken since BAPCOC's

establishment in 1999 for prudent antibiotic prescribing and combating antibacterial resistance in human and veterinary sectors, and evaluate their impact on reducing AMR; 2) Examine the current state of antibiotic use in Belgium; 3) Identify the primary drivers influencing current antibiotic usage patterns and 4) Propose strategies to enhance the prudent use of antibiotics in Belgium. The concept of 'prudent antibiotic use' as put forward in this report largely complies with the concept of 'antibiotic stewardship', in that it both stresses the importance of optimal use of antibiotics in case of infection, as well the need to limit, where possible, the use of antibiotics to curb the emergence and spread of antibiotic resistance. In the report, 16 recommendations were provided in order to promote prudent antibiotic use in both human and veterinary sectors. Six of these recommendations may apply to AMS in the face of sepsis: strengthen AMS in acute care hospitals, roll out local AMS teams in the ambulatory sector, develop AMS in nursing homes, improve the professional education on prudent antibiotic prescription and use/develop and implement interventions targeting psychological, social and institutional determinants of behavioral change, improve the compliance with evidence-based prescription guidelines, perform a health technology assessment on point-of-care testing for the diagnosis of infectious diseases in the Belgian ambulatory care.

AMS guidelines for acute care hospitals will be discussed separately. As for ambulatory care, while numerous interventions have been developed, launched, and evaluated over the past decade in Belgium and other European countries, many remain inadequately implemented or evaluated within the Belgian context (42). In addition, these interventions can be found scattered in a variety of formats and through different platforms. Therefore, there is a clear need to implement and evaluate interventions that improve antibiotic prescribing, to group them within a unified platform and to identify the barriers and facilitators to their implementation in Belgian primary care. Moreover, given the diversity in general practitioners' needs and practice contexts, a tailored approach addressing the determinants of antibiotic prescribing behavior is crucial, as what proves effective in one setting may not necessarily translate to another (43,44). It is important to realize that merely focusing on content knowledge is not very effective in bringing about behavioral change in antibiotic prescribing; neither is the principle that a one-model approach would work for every doctor and every practice tenable. 'Local champions' can play a pioneering and exemplary role here. Local champions are GPs who have access to a local network of other GPs (and possibly specialists such as clinical infectiologists or microbiologists) and can play a leadership and example role within the project. As 'local champions', they demonstrate the importance of this issue to the wider group of GPs and are convinced of the need for change. Their knowledge of the context and practical organization can help

design and use interventions that have already shown to be effective in improving antibiotic prescribing behavior (45,46).

Furthermore, diagnostic stewardship has emerged as a crucial aspect of antimicrobial stewardship, particularly in primary care settings. Diagnostic stewardship aims to optimize the diagnostic process to ensure accurate identification of bacterial infections, thereby facilitating targeted antibiotic therapy while minimizing unnecessary antibiotic use.

1. Clinical Assessment:
○ Emphasizing the importance of thorough clinical assessment, including history-taking and clinical examination, to identify signs and symptoms suggestive of bacterial infections.
○ Encouraging healthcare providers to consider differential diagnoses and utilize clinical decision support tools to guide antibiotic prescribing decisions.
2. Point-of-Care Testing (POCT):
○ Integration of rapid diagnostic tests, such as C-reactive protein (CRP) and procalcitonin, into primary care settings to aid in the differentiation between bacterial and viral infections.
○ Use of POCT CRP to support clinical decision-making and reduce unnecessary antibiotic prescriptions for (likely) viral infections (50).
○ Integration can include establishing patient-friendly reimbursement criteria for those requiring these tests.
3. Communication and patient education:
○ Effective communication with patients regarding the rationale behind diagnostic testing and antibiotic prescribing decisions.
○ Providing patient education on the risks of antibiotic overuse, antibiotic resistance, and the importance of completing prescribed antibiotic courses as directed.
4. Implementation of clinical guidelines:
○ Adoption and adherence to evidence-based clinical guidelines for the management of common infectious diseases in primary care.
○ Regular review and updating of guidelines to reflect current evidence and local antimicrobial resistance patterns.
5. Antimicrobial Stewardship Programs (ASP):
○ Integration of diagnostic stewardship principles into existing ASPs in primary care settings.
○ Collaboration between healthcare providers, microbiologists, pharmacists, and other stakeholders to promote judicious antibiotic use through diagnostic optimization.

Table 2.4. Key components of diagnostic stewardship in primary care (47-49).

Effective implementation of diagnostic stewardship strategies requires a multidisciplinary approach and ongoing education and support to optimize clinical practice in primary care settings.

Patients also need appropriate self-care advice and the necessary safety-netting advice when not prescribing antibiotics (51). Support materials (e.g. checklists, self-triage) as well as online advice can help GPs or other healthcare providers communicate with patients in a patient-centered way and increase patients' self-care capacity.

Feedback through quality indicators and realtime through peer support or expert advice can serve as a measure of (in)appropriate prescribing and encourage GPs to improve their prescribing behavior (52-54). It allows focusing on the specific challenges in each practice, setting targets for improvement and monitoring the effects of interventions. By providing this through the electronic health record (EHR), up-to-date feedback can be provided.

Within primary care, many interventions have been developed and researched to improve the quality of antibiotic prescribing, such as the BAPCOC antibiotic guide (55), e-learnings GRACE intro and TRACE (56), and the supporting patient leaflet associated with it, the medical-pharmaceutical consultation safe antibiotics (57), the BAbAR leaflet (58) (based on TARGET material (59)).

Available training materials:

- E-learning BCFI: Antibiotics in respiratory tract infections: https://auditorium.flowsparks.com/?startactivity=BAPCOCINF
- https://overlegorganen.gezondheid.belgie.be/sites/default/files/content/steekkaart_indicaties.pdf
- https://overlegorganen.gezondheid.belgie.be/sites/default/files/content/steekkaart_eerste_uitgifte_informatie.pdf
- E-learnings BAPCOC (FPS Public Health): Safe reduction in antibiotics (TRACE & GRACE INTRO): https://www.health.belgium.be/nl/e-services/e-learning
- Knowledge of existence of relevant guidelines: BAPCOC antibiotics guide: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/belgische_gids_bapcoc_nl_2021_a4_2.pdf

- Knowledge of existing consultation modalities such as the Medical Pharmaceutical Consultation (MFO) antibiotics; (https://www.medischfarmaceutischoverleg.be/antibiotica), in which GPs and pharmacists work together around safe antibiotic use
- 'Hospital Outbreak Support Teams' (HOST), pilot project of the FPS Public Health (https://overlegorganen.gezondheid.belgie.be/nl/pilootproject-hospital-outbreak-support-teams-host) One of the aims of the HOST teams is to strengthen the 'Antimicrobial Stewardship' (AMS) teams whereby hospital expertise is made available to both residential facilities and other healthcare providers.

Taken together, the preventive needs of a national sepsis plan and the already existing efforts to reduce AMR and to improve linkage to health care and vaccination are closely interconnected and should reinforce each other, rather than causing confusion or competition between programs. We are in favor of a clear alignment of awareness and educational messages of SNAP and existing public health goals of AMR and vaccination, and of jointly following up the progress in the goals for these programs. Similar recommendations have been made in sepsis plans in e.g. Switzerland and the UK.

Recommendations:

1. Strengthen/ensure access to (chronic) healthcare for all, with specific attention to the most vulnerable (medically and socio-economically). In particular, strengthen access and linkage to chronic care, including affordable wound care and dental care. The use of telemonitoring/remote patient monitoring may be further explored in this context.
2. Invest in health and vaccination literacy, in particular for most vulnerable populations, with emphasis on infection prevention (including food safety).
3. Combine education on sepsis awareness with prudent use of antibiotics and AMS. Several actors can bring this combined message (medical doctors, nurses, pharmacists, patient advocates,...)
4. Strengthen (catch up) vaccination programs for children and programs for adults with indications for additional vaccinations (65+, medically vulnerable, pregnant). This includes improved/easier registration and reduced cost of adult vaccination for at risk groups.
5. Develop specific guidelines and training on safe home care for patients with indwelling catheters (IPC training for home care nurses, interface with LTCF and HOST/ Outpatient Parenteral Antimicrobial Therapy (OPAT)-projects)

2.2 Prevention of sepsis and antimicrobial stewardship in the acute care (hospital) setting

As mentioned above, the acute care setting is characterized by a high turn-over of patients, undergoing a diagnostic or therapeutic interventions jeopardizing the patient's skin and mucosal integrity (e.g. through blood sampling, placement of catheters and other foreign body materials, surgical interventions,...) and being exposed to pathogens in the hospital environment and on health care workers hands or materials.

Healthcare associated infections (HAIs) have been defined as infections that manifest during a patient's hospitalization but were not yet present or in the incubation stage upon the patient's admission to the hospital (60). Health care-associated sepsis can thus be defined as sepsis resulting from HAI; in a subset of patients the causal pathogen can be found in blood cultures (HA-BSI).

2.2.1 Main risk factors for health care-associated sepsis in acute care setting

The most recent systematic review and meta-analysis on risk factors for HAI included 65 studies (61). Intrinsic (patient) risk factors relate to host susceptibility, determined by the acute conditions of the individual at the time of admission, together with chronic diseases and comorbidities. These factors are associated with age, immune status, comorbidities (mainly diabetes, COPD and neurologic diseases), and the acute pathological condition(s) requiring healthcare. Preventable risk factors in this category are (lack of) vaccination, personal hygiene/lifestyle and substance (ab)use (see part 2.1 on Prevention of community-acquired sepsis).

Extrinsic risk factors refer to the treatment and the acquisition of pathogenic microorganisms. Acquisition of pathogenic micro-organisms can occur through 1) endogenous sources following previous colonization and dysbiosis (e.g. following antibiotic use) 2) exogenous sources in the hospital environment for example water, contaminated surfaces in the healthcare environment and 3) contact transmission from healthcare workers, primarily through their hands.

Extrinsic risk factors are related to the duration and type of hospitalization (e.g. ICU), invasive procedures (e.g. invasive mechanical ventilation, central venous catheter placement, surgery), exposure to antibiotics and other drugs such as corticosteroids.

Infection risk associated with these factors can be reduced through the application of evidence-based infection control practices; there is a notable correlation between the type or source of HAI and the presence of specific risk factors (e.g. pneumonia and presence of endotracheal and nasogastric tubes, urinary tract infection and presence of urinary tract catheter). The duration of exposure to these risk

factors, particularly the presence of invasive devices, and overall healthcare exposure, constitutes an overarching, and potentially modifiable risk factor.

Focus on hospital-associated bloodstream infection (HABSI)

HABSI is defined as a laboratory-confirmed bloodstream infection occurring ≥2 days after admission at the hospital. For Belgium, the 2022 results of Sciensano's National Surveillance of Bloodstream Infections report (NSIH-SEP) describe a HABSI cumulative incidence of 5.4 patients with HABSI per 1,000 hospitalizations, and a HABSI incidence density of 9.2 episodes per 10,000 patient-days (pd). Incidence of central line-associated bloodstream infection (CLABSI) in 2022 was 2.4 episodes per 10,000 pd. Generally, hospital-wide incidences of HABSI show decreasing trends since 2020, however, their 2022 results remain higher as compared to pre-COVID19 levels (2019 and before). Forty–three percent of hospital-wide HABSI cases and even 66% of ICU-BSI cases were linked to an invasive device whether directly (central and other catheters) or indirectly (urinary catheter, endotracheal tube). As shown in Figure 2.2, exposure to central vascular catheter remains the most frequently reported origin of HABSI cases both hospital-wide (26% of HABSI) as well as ICU-only (39% of ICU-BSI). In 2022, the most commonly micro-organisms isolated from hospital-wide HABSI cases were *E. coli*, *S. aureus*, and *S. epidermidis*, the latter is also the most commonly isolated from hospital-wide CLABSI cases (62).

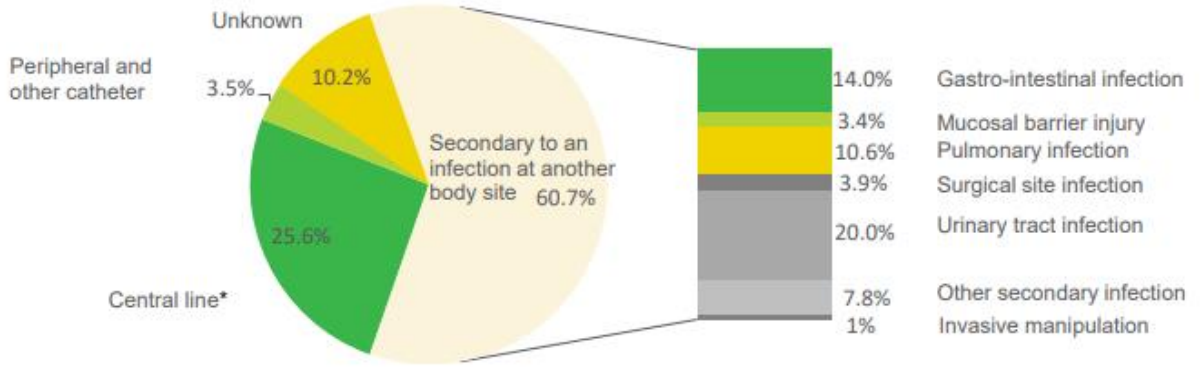

*Figure 2.2: Sources of hospital-associated bloodstream infections, Belgium 2022 (*Includes 'confirmed', 'probable' and 'possible' central line-associated bloodstream infection) (62).*

2.2.2. Infection prevention and control (IPC)-interventions to reduce health care-associated sepsis in acute care setting.

Interventions to prevent HAIs

Interventions aimed at reducing healthcare-associated sepsis essentially relate to modifiable, extrinsic risk factors of HAI and the acquisition of pathogenic micro-organisms, and primarily focus on decreasing the incidence of major types of preventable HAIs: central-line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), surgical-site infections (SSIs), *Clostridioides* and hospital-acquired pneumonia (mainly ventilator-associated pneumonia) (HAP/VAP). The evidence supporting interventions to reduce these HAIs, obtained through systematic literature reviews with formal grading of the evidence, was initially published in 2008 and revised in 2014 and 2022 by organizations such as the CDC, Healthcare Infection Control Practices Advisory Committee (HICPAC), Society for Healthcare Epidemiology of America (SHEA), the Infectious Disease Society of America (IDSA), and the Association for Professionals in Infection Control and Epidemiology (APIC). These revisions resulted in comprehensive guidelines with a level of evidence rating and a grade of recommendation for each infection prevention measure (63-72).

The latest version of the above mentioned guideline also provides information on approaches to performance measurement, conceptual models and frameworks, and implementation models (73). While the document, particularly in terms of process measurement and implementation, is derived from the U.S. healthcare system, the evidence base for the individual recommendations is universal. However, for practical measurement and implementation, adaptation to the Belgian healthcare organization is necessary.

A specific method of implementing evidence-based preventive measures involves the development and introduction of so-called intervention bundles. These bundles have been designed for the prevention of CLABSIs, CAUTIs, and HAP/VAP. In a recent systematic review and meta-analysis covering 114 studies published between 2005 and 2016, it was estimated that multifaceted interventions, usually in the form of care bundles, have the potential to consistently reduce HAI rates by 35-55%. However, it is important to note that the risk of bias was considered high, given that most studies were before-after studies, that the limited number of controlled before-after studies and randomized-controlled trials (RCTs) were unblinded, and that publication bias was observed for studies on CAUTI and SSIs (74). Several good examples of national campaigns to promote prevention of CLABSI have been published (75).

Interventions to prevent the transmission of specific pathogens

Guidelines for the prevention of MRSA infection and transmission in acute care hospitals are provided by SHEA/IDSA/APIC; among the 11 essential practices recommended, three were rated with a moderate quality of evidence: these practices include hand hygiene, contact precautions for MRSA carriers, and the cleaning and disinfection of equipment and the environment. Additionally, there are five recommendations concerning active surveillance testing, with high evidence supporting one and moderate evidence supporting four. Screening of healthcare workers has low evidence according to one recommendation. Furthermore, nine recommendations pertain to MRSA decolonization, with two having high evidence and seven having moderate evidence. There is also one recommendation advocating for the universal use of gowns and gloves, supported by high evidence. It is however important to note that the majority of these recommendations are particularly relevant in settings with high MRSA endemicity (69). Also the Belgian Superior Health Council has made guidelines for the containment of different types of multi drug resistant organisms (MDROs) (76).

Numerous national and regional guidelines are available for controlling the transmission of Vancomycin-Resistant Enterococci (VRE). While there are variations in the advice for screening for VRE, most guidelines designate high-risk patients based on units of admission (such as burn units or hematology/oncology wards) and underlying illnesses (like hematological malignancy, bone marrow and solid organ transplantation, and hemodialysis). Across all guidelines, hygiene management and contact precautions are consistently emphasized as essential components of prevention strategies (77-81).

WHO evaluated the evidence from 19 studies and mentioned in the above mentioned 2016 guidance document on core components that bed occupancy exceeding the standard capacity of the facility is associated with the increased risk of HAI in acute care facilities, in addition to inadequate health care worker staffing levels. MRSA transmission and infection seemed to be associated with bed occupancy in six studies and the nurse-to-patient ratio in seven studies. Three studies reported that increases in nurse-to-patient ratios resulted in reduced HAI, while inadequate adherence to hand hygiene protocols was associated with low staffing levels in one study and with high workload in another (72). Similar results were reported by a scoping review, comparing rates of VRE infection in Germany and the Netherlands, who identified the following modifiable risk factors for VRE transmission: high bed occupancy rates with a lack of available single rooms and an inadequate nurse-to-patient ratio, lower rates of screening (limited to high-risk wards such as hematology wards), a lack of formal contact isolation and a higher use of broad-spectrum cephalosporins (82). As an example of these guidelines, the Provincial Infectious Diseases

Advisory Committee on Infection Prevention and Control (PIDACS-IPC), a multidisciplinary scientific advisory body providing evidence-based advice to Public Health Ontario, Canada, offered evidence-based guidance for preventing VRE infection in 2012, and this guidance was updated in 2019. Based on systematic reviews of the literature, PIDACS-IPC recommended that all acute care and chronic care hospitals, as well as long-term care homes, conduct risk-factor-based screening upon admission and implement contact precautions for VRE. High-risk patients were defined as those with previous colonization or infection with VRE, those who had been hospitalized in the past 12 months, those with recent exposure to a healthcare facility experiencing a VRE outbreak, those who received healthcare in another country, and those with recent exposure to broad-spectrum cephalosporins. It is important to note that this recommendation was made in the context of a significant increase in VRE prevalence (81). In contrast, contact precautions have been challenged by a systematic review of 17 studies: The authors noted no significant differences in MRSA infection rates before and after the cessation of contact precautions. Additionally, there was an inverse ratio observed for VRE infection and the discontinuation of contact precautions. These findings align with a previous systematic review that similarly demonstrated no increased rate of MRSA and VRE infections following the discontinuation of contact precautions (83,84). Further research in this field is needed.

In addition to these guidelines, the WHO systematic review of hand hygiene studies found that studies with achievement of significant improvement in hand hygiene and/or increased use of alcohol-based hand rub were associated with significant reductions in MRSA and VRE colonization and infections (SR of 39 studies (17 before-after, 2 RCTS, 12 temporal association studies, 4 mathematical models) (85).

ESCMID has issued guidelines for preventing the transmission of multidrug-resistant Gram-negative pathogens (MDRGN), utilizing a GRADE approach for assessing the quality of evidence and strength of recommendation, following a systematic review. The guidelines distinguish between epidemic and endemic settings. The implementation of hand hygiene programs has received a strong recommendation for both epidemic and endemic settings and for all types of MDRGN. Additionally, the WHO has developed guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities (86). For epidemic settings involving all types of MDRGN, strong recommendations include contact precautions, alert codes to identify colonized patients, single-room placement, staff cohortation, screening upon admission followed by contact precautions, and intensive environmental cleaning with monitoring of cleaning performance. In endemic settings, a strong recommendation is given for contact precautions for patients known to be colonized by

all types of MDRGN, as well as for alerting, followed by pre-emptive contact precautions and screening for patients known to be colonized by MDR *Acinetobacter* spp.

AMS programs (see 2.2.3) have received a strong recommendation for both epidemic and endemic settings to reduce the spread of extended-spectrum beta-lactamase Enterobacterales (87). In addition to these guidelines, the above mentioned WHO systematic review (85) on hand hygiene demonstrated significant reductions in colonization and infection caused by MDRGN in studies that achieved marked improvement in hand hygiene and/or increased the use of alcohol-based hand rub (SR of 39 studies) (17 before-after, 2 RCTS, 12 temporal association studies, 4 mathematical models). They clearly emphasized the association of multidrug resistant organisms and clinical outcomes of adult patients with sepsis in the ICU. The high prevalence of MDRO organisms has a role in the patients' mortality.

Nosocomial fungal infections, especially invasive candidiasis and aspergillosis primarily impact critically ill and severely immunocompromised patients. Additionally, *Candida auris*, an emerging pathogen, poses a significant threat due to its high intrinsic antifungal resistance and considerable potential for nosocomial spread. Implementation of recommended infection control strategies can prevent catheter-related candidemia (see above for prevention of CLABSI) and minimize exposure of severely immunocompromised patients to airborne *Aspergillus* spores within the hospital environment. In select patient populations at high risk for invasive fungal infections, antifungal prophylaxis should be considered during the periods of intense immunosuppression. Newer nonculture-based methods have the potential to improve the early identification and detection of *C. auris* (but are not reimbursed actually), followed by vigilant infection control measures to prevent its dissemination in healthcare environments (88).

Summary of key aspects and core components of IPC

The following interventions are considered as the key aspects in the context of sepsis prevention in the acute health care settings (72):

1. Standard precautions:
    - Hand hygiene
    - Hygiene in the direct patient environment:
        - Cleaning (and disinfection if applicable) of the direct patient care environment
        - Cleaning (and disinfection if applicable) of patient care equipment
        - Correct use of waterpoints in the direct patient care environment (sinks)
    - Use of personal protective equipment
    - Sterilization and decontamination of medical devices

2. Transmission based precautions when indicated:
    - Adequate screening practices
    - Apply transmission based precautions when indicated (contact, droplet, air)

3. Care bundles to prevent specific HAI:
    - central-line-associated bloodstream infections (CLABSIs),
    - catheter-associated urinary tract infections (CAUTIs)
    - surgical-site infections (SSIs),
    - hospital-acquired pneumonia (mainly ventilator-associated pneumonia) (HAP/VAP)

In 2016, WHO published guidelines on core components to implement infection prevention and control (IPC) programs at the national and acute health care facility level. These guidelines provide evidence-based recommendations on the core components of infection prevention and control (IPC) programmes that are required to be in place at the national and acute facility level to prevent HAI and to combat antimicrobial resistance (AMR) through IPC good practices (72). These guidelines cover:

(1) IPC programmes

(2) IPC guidelines

(3) IPC education and training

(4) Surveillance

(5) Multimodal strategies

(6) Monitoring/audit of IPC practices and feedback

(7) Workload, staffing and bed occupancy (acute healthcare facilities only)

(8) Built environment, materials and equipment at the facility level (acute healthcare facilities only).

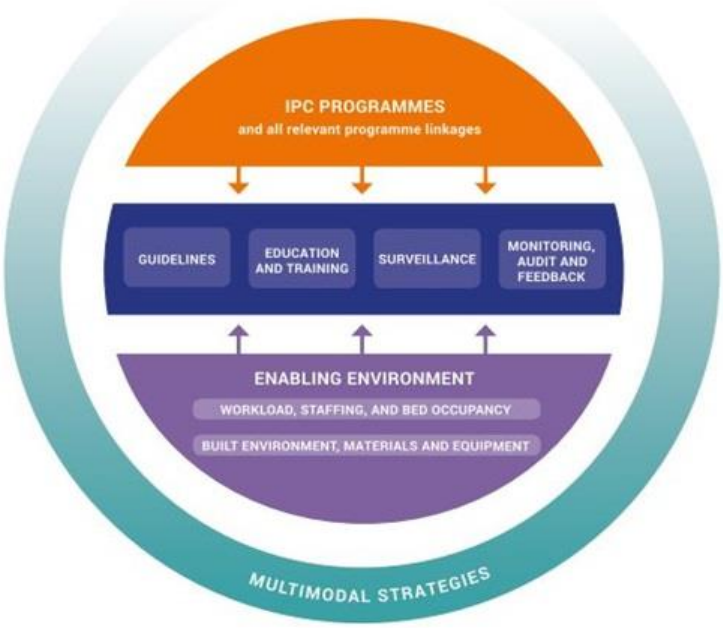

Figure 2.3: The core components of Infection Prevention and Control (IPC) (72).

Multimodal strategies refer to a combination of elements or components implemented in an integrated way with the aim of improving an outcome and changing behavior. It includes tools, such as bundles and checklists. The five most common components include:

(1) system change (availability of the appropriate infrastructure and supplies to enable infection prevention and control good practices)

(2) education and training of health care workers and key players

(3) monitoring infrastructures, practices, processes, outcomes and providing data feedback

(4) reminders in the workplace/ communications

(5) culture change within the establishment or the strengthening of a safety climate.

By focusing on these key aspects and core components, healthcare facilities can significantly reduce the risk of sepsis, ultimately saving lives and reducing healthcare costs.

2.2.3. Belgian reality check: available and required guidelines and tools on IPC in Belgium

Guidelines currently available:

- Recommendations for hand hygiene during medical care (revised 2018) (HGR 9344)
- Recommendations for prevention, control, and management of patients colonized with MDROs in healthcare facilities. Brussels: HGR; 2019. Advisory No. 9277. Update November 30, 2022 (89)
- Recommendations for prevention and control of bloodstream infections related to intravascular catheters (HGR advice No. 9553): ongoing - finalization expected by end of 2024.
- Recommendations for prevention, control, and management of urinary tract infections during medical care (July 2017, revised version May 2019)
- Recommendations for control of postoperative infections in the operating room (May 2013) (HGR 8573, revision 2024-2025)
- Recommendations for control and prevention of *Clostridium difficile* infections in healthcare facilities (July 2017, revised version May 2019)

Guidelines and tools missing, or in the pipeline:

- Guideline on CLABSI prevention (expected 2024)
- Guideline on HAP/VAP prevention
- Guideline for *C.auris* (in draft)
- TOOLKIT with teaching and sensitization material
- Monitoring tool to monitor and give feedback on the compliance to care bundles
- Surveillance tool for CAUTI and VAP/HAP
- Clinical decision support systems (CDSS). These systems can simplify access to necessary decision-making data, provide timely reminders and cues during patient interactions, aid in diagnosing and ordering, and alert clinicians to emerging patterns in patient data and inform on the use of invasive devices.
- Hospital Information System to access aggregated data on ward level for the use of invasive device (to calculate the denominator in surveillance)

Recommendations

WHO recommends that national IPC programmes should coordinate and facilitate the implementation of IPC activities through multimodal strategies on a nationwide or sub-national level.

Inspired by the framework of the WHO multimodal strategy, we propose the following action plan to target the reduction of HABSI in the Belgian hospitals as listed in Table 2.5:

Element of the multimodal strategy	Objective	Activities	Means and Cost	Responsible entities
'Build it'	IPC teams have access to updated **guidelines** on device-associated HABSI (CLA)BSI, (CA)-UTI, VAP-HAP, SSI in health care facilities	Update /develop the guidelines	Cfr HGR/CSS	HGR/CSS
		Recommendations for prevention and management of bloodstream infections related to intravascular catheters (HGR advice no. 9553): ongoing - finalization expected by end of 2024		
	IPC teams have access to updated **care bundles** on (CLA)BSI, (CA)-UTI, VAP-HAP, SSI in health care facilities	Update /develop the guidelines and bundles	Cfr HGR/CSS	HGR/CSS
	IPC teams have access to **national** (campaign) **material for the "teach it" and "sell it": TOOLKIT**	Develop new national sensitization material	National focal point IPC?	BAPCOC Support Team
		Develop new national training material: an escape game, serious computer game or translate international work (e.g. WHO),...	Costs to develop sensitization material (not to print): marketing specialist, ...	
		Update of the e-learning modules	Support to be clarified (FOD/SPF or RiZIV)	
	IPC teams have access to **materials locally produced** in the hospitals for **the "teach it"**	Create a digital platform to share material produced in the hospital	National focal point IPC?	BAPCOC Support Team
		Share locally produced teaching materials on the national digital platform		IPC Teams
		Create a process to validate the proposed material before publication on the digital platform		BAPCOC Support Team
	IPC teams have access to a national **monitoring tool** for the "check it" of the **care bundles** incl. handhygiene monitoring tool	Develop the (easy to use) tool	Structural financing for a monitoring tool (cfr Sciensano)	Sciensano
		Maintain the tool		
		Foresee an interface to have real time feedback of the results and the possibility to benchmark with peers (in the form of a dashboard)		
		The tool can be used on the smartphone and tablet with an application		
	IPC teams have access to a national **surveillance tool** for (CLA)BSI, (CA)-UTI, VAP-HAP, SSI for the "check it"	Develop the (easy to use) tool	Structural financing for a monitoring tool (cfr Sciensano)	Sciensano
		Maintain the tool		
		Foresee an interface to have real time feedback of the results and the possibility to benchmark with peers (in the form of a dashboard)		
		The tool can be used on the smartphone and tablet with an application		
		Surveillance of bloodstream infections in Belgian hospitals (Protocol 2019)		Sciensano + IPC expert working group
		https://www.sciensano.be/sites/default/files/bsi_surv_protocol_nl_april2019.pdf : under revision		
	IPC teams have access to a **Clinical decision support systems (CDSS).** These systems simplify access to necessary decision-making data, provide timely reminders and cues during patient interactions, aid in diagnosing and ordering, and alert clinicians to emerging patterns in patient data and informs on **the use of invasive devices.**			
	IPC teams have access to **aggregated data on ward level for the use of invasive device** (to calculate the denominator in surveillance): Hospital Information System			
	Health care worker **staffing levels** should be adequately assigned according to patient workload			

'Teach it'	Health care workers are trained on the prevention of (CLA)BSI, (CA)-UTI, VAP-HAP, SSI			IPC Teams in the hospitals + reference nurses
				HOST teams
				Universities and higher education institutions (cr Chapter 1)
				National campaign of CLABSI/CAUTI guideline in addition to HH campaigns
	Observers are trained to measure care bundle compliance	Train the observers before they perform observations		IPC Teams in the hospitals
	IPC professionals are trained to perform surveillance and give feedback on (CLA)BSI, (CA)-UTI, VAP-HAP, SSI			
'Check it'	All IPC teams perform **monitoring of care bundle compliance** and give feedback on the compliance with best practices care and highlights of good performance and areas for improvement	Make yearly national report & provide individual feedback and benchmarks to the hospitals		Sciensano
		All hospitals give internal feedback		IPC Teams, to be published together with surveillance data
	All IPC teams perform **surveillance of** (CLA)BSI, (CA)-UTI, VAP-HAP, SSI according to the local risk assessment and give feedback on the compliance with best practices care and highlights of good performance and areas for improvement	Make yearly national report & provide individual feedback and benchmarks to the hospitals (NSIH-SEP/BSI mandatory surveillance of bloodstream infections in Belgian Hospitals - yearly national report https://www.sciensano.be/sites/default/files/sciensano_national_bloodstream_infection_report_2023_1.pdf)		Sciensano (see also recommendations in Ch 7) fast feedback and reporting, data transfer of electronic patient data
'Sell it'	Health workers, patients and visitors are reminded about the importance of IPC measures in the hospital (hand hygiene, environmental cleaning, minimize the use of invasive devices, ...)	Reminders are continuously spread during the year		IPC Teams
	During the campaign week the IPC teams distribute targeted communications in the hospitals (To have/keep a national day/period of the year dedicated to the sensibilization of sepsis)	Present the yearly report and present the new tools during the week of the campaign		
'Live it'	Health workers and patients are nurtured and supported in a milieu that values IPC	Engage hospital management, head nurses, head cleaners, medical responsible as leaders/examples for IPC		IPC Teams
		Ensure that IPC activities are integrated in the strategic plan of the hospital		BAPCOC–P4P team
		Consider to incentivize IPC through P4P		

Table 2.5. Proposed action plan to reduce health care associated bloodstream infections (HABSI) in the Belgian hospitals.

2.2.4. Antimicrobial stewardship in the acute care setting

The adverse outcome of sepsis and the increasing challenge of antimicrobial resistance are inextricably linked. A micro-simulation model designed by the OECD (referred to in the KCE report 311 on antibiotic policy (2011) (42,90) has estimated that on average antimicrobial resistance causes per year around 33.000 deaths in the EU/EAA countries, of these around 533 occur in Belgium. Given that sepsis serves as a major mediator between infection and mortality, the association between sepsis and antimicrobial resistance is clear.

As discussed before, it becomes evident that any comprehensive program designed to improve outcomes in sepsis must incorporate antimicrobial stewardship (AMS). By integrating AMS into sepsis management protocols, it can be ensured that the choice, dosage, and duration of antibiotics are not only prompt but also tailored to the specific characteristics of the infection. This approach not only optimizes patient outcomes but also addresses the broader issue of antibiotic overuse and misuse, mitigating the risk of further inducing resistance. Recent Surviving Sepsis Campaign guidelines address these concerns, offering recommendations for starting antibiotics based on infection suspicion and patient clinical stability (86). In addition, empirical antibiotic administration should consider local epidemiological data and resistance profiles, with current guidelines serving as the foundation for schemes. National guidelines for antibiotic therapy in hospitals, as issued by the BVIKM/SBIMC (IGGI-guidelines) should serve as a basis for empirical schemes in Belgian hospitals (91). Similar to AMS in primary care, treatment guidelines are an essential backbone for the improvement of antimicrobial therapy. However, these guidelines require sufficient support for updating and making them easily accessible and userfriendly.

AMS guidelines usually provide three categories of recommendations for successful development and implementation of AMS programs (87). The first category includes recommendations on appropriate structural or system prerequisites that should be met when establishing an AMS program, e.g. the availability of a financially compensated multidisciplinary AMS team. The second category includes recommendations on appropriate use at the patient level, which constitute the objectives of the AMS teams/actors, e.g. choosing empirical antibiotic therapy according to national and (preferably) locally adapted guidelines. The third type encompasses recommendations on improvement strategies that AMS teams/actors have to perform at the professional or institutional level in order to guarantee that these objectives are met, e.g. monitoring and advice or education. The third category of recommendations consist of core strategies, including pre-authorization or restriction and prospective audit and feedback, as well as supportive interventions (some of which may pertain to structural of system characteristics).

The WHO has developed a practical guide on AMS for administrators and healthcare leaders intending to implement interventions in their healthcare settings (92). The guide focuses on ten interventions, including clinician education, patient and public education, institution-specific guidelines for managing common infections, cumulative antibiograms, prior authorization of restricted antimicrobials, de-labeling of spurious antibiotic allergies, prospective audit and feedback, self-directed antibiotic reassessment (antibiotic time-outs), dose optimization, and duration optimization. It is important to note that many of these interventions involve a combination of two or more types discussed earlier. The practical document does not provide a formal rating of strength or evidence base for the recommendations.

Antibiotic policy groups (APG) or antibiotic management teams (AMT) have been committed with the task of facilitating AMS in Belgian acute care hospitals by, inter alia, developing antibiotic formularies and locally adapted guidelines for empirical, directed and prophylactic antibiotic use, providing permanent education, measuring implementation of this formulary and guidelines, and measuring antibiotic consumption and antibiotic resistance (93-95). These AMTs are positioned as a subgroup within the Drugs and Therapeutics Committee of their institution. Their composition, mandate and tasks have been consolidated in the legislation on hospitals and an annual budget of 3.6 million Euros is divided among these hospitals according to the number of beds.

To examine the association between AMS and outcomes in sepsis, a scoping PubMed search was conducted using the search terms 'antibiotic stewardship' (title/abstract) and 'systematic review' (Publication type). A total of 102 publications were retrieved, and 14 were chosen for further review based on the abstract. Systematic reviews that did not provide information on individual patient outcomes were excluded, as were reviews that only included Asian studies, studies in low-to middle-income countries or studies prior to 2010, as well as systematic reviews that substantially duplicated others.

A systematic review of 26 studies on AMS interventions in hospitals aimed at reducing antibiotic consumption showed a notable decrease in antimicrobial usage, with no significant changes in overall mortality, mortality related to infections, or infection rates (96). Hospital length of stay decreased by 9% on average, with most studies employing multiple strategies. Another review focused on AMS interventions at the patient level, revealing significant benefits for patient clinical outcomes, adverse events, and costs for various interventions such as use of empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral therapy, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation for *S. aureus* bacteremia (97). Following guideline-based treatment and therapy de-escalation significantly impacted mortality. Additionally, non-significant

reductions in mortality were observed with interventions like switching from intravenous to oral therapy, therapeutic drug monitoring (TDM), employing restricted antibiotics, and bedside consultation. In this systematic review, no relevant studies on AMS in LTCFs were identified.

The IDSA and the SHEA have published guidelines featuring 27 recommendations for strategies aimed at achieving AMS goals at the patient level, five of which received strong endorsement with moderate-quality evidence (98): these include pre-authorization and prospective audit and feedback interventions, strategies to reduce the use of antibiotics associated with a high risk of *Clostridioides difficile* infection (CDI), implementation of aminoglycoside TDM, programs to increase oral antibiotic use and transition from IV to oral administration, and interventions to shorten antibiotic therapy duration. Patient outcome data were assessed for 8 recommendations: while most interventions showed neutral outcomes, improvements were noted for prospective audit and feedback (resulting in reduced incidence of CDI), development of local guidelines (leading to reduced mortality, length-of-stay, and antibiotic adverse events), infection-specific interventions for *S. aureus* and Gram-negative bacteremia (reducing mortality), TDM of aminoglycosides and vancomycin (reducing nephrotoxicity and mortality (for aminoglycosides only)), and IV-to-oral antibiotic switch (resulting in reduced length-of-stay).

In addition to these three comprehensive systematic reviews, a number of systematic reviews examined patient outcomes in relation to specific AMS interventions or programs (n=7), examined specific endpoints (CDI or infections/ colonization with multidrug antibiotic pathogens) (n=2), or examined patient outcomes in relation to AMS interventions in specific settings (pediatrics and nursing homes) (n=2).

Within a Cochrane systematic review addressing interventions to improve antibiotic prescribing in hospitalized patients, the authors identified, in a sub-analysis of five studies, that interventions that increased antibiotic guideline compliance for pneumonia were associated with improved survival (99).

A patient-level meta-analysis of interventional trials on procalcitonin (PCT)-guided antibiotic treatment in acute respiratory infections concluded that it led to reduced antibiotic use, fewer antibiotic side effects, and lower 30-day mortality (100). In a subsequent patient-level meta-analysis of interventional trials involving ICU and sepsis patients, lower mortality rates were observed with PCT guidance (101). An updated Cochrane database systematic review concluded that PCT guidance of the initiation and duration of antibiotic treatment led to reduced risks of mortality, lower antibiotic consumption, and antibiotic-related side effects (102). In the most recent meta-analysis on PCT-guided antibiotic therapy in patients with bacteremia, the use of PCT was associated with reduced antibiotic usage with no effect on mortality (103).

A systematic review on antibiotic de-escalation strategies in patients with BSI and pneumonia found that de-escalation was associated with reduced mortality in the unadjusted analysis of observational studies but not in the adjusted analysis of observational studies or in RCTs (104). Another systematic review of observational studies on antibiotic de-escalation in ICU patients with pneumonia found a significant impact on the duration of hospitalization but not on mortality (105).

A systematic review concluded that AMS programs, in particular audits and restrictive policies, significantly reduced the incidence of infections and colonization with antibiotic-resistant bacteria and CDI in hospitalized patients; in 30%, AMS programs were concurrently implemented with infection control measures, most frequently hand hygiene and patient screening (106). A different systematic review revealed that AMS programs led to a reduced incidence of CDI, with the most significant impact in geriatric populations and with restrictive antibiotic policies (107).

In a systematic review addressing AMS programs implemented in nursing homes, the authors identified a limited number of studies (n=14) of good to fair quality. These studies demonstrated a reduction in antibiotic use but did not show significant changes in mortality rates, rates of CDI, or hospitalizations (108).

A systematic review of AMS programs in pediatric settings within US hospitals identified a limited number of studies (n=17). These studies demonstrated reductions in antibiotic use but did not show any significant effect on patient outcomes (109).

In summary, numerous systematic reviews have investigated the influence of AMS interventions in hospital settings on individual patient outcomes, potentially mediated through sepsis. Generally, these interventions have demonstrated an overall reduction in antibiotic consumption without adverse effects on patients. Moreover, limited evidence suggests that specific AMS interventions are linked to improved outcomes, including reduced mortality and avoidance of superinfections. Examples of such interventions include PCT guidance in the treatment of acute respiratory infection or sepsis, measures to enhance guideline adherence in respiratory infection management, and TDM of aminoglycosides. Antibiotic restrictive measures have been associated with a lower incidence of colonization and infection with MDRO, as well as a decreased occurrence of CDI infections. Notably, evidence in the context of pediatrics and nursing homes is largely lacking.

2.2.5. The role of clinical microbiology in sepsis care and antimicrobial stewardship (110-118)

Information from microbiological samples and in particular from blood cultures are of high value to patients in a context of the sepsis, both to inform the most effective empirical treatment (based on the local epidemiology) as well as to guide the directed treatment (based on the patient's individual culture results).

Up to now blood cultures remain the gold standard in the laboratory diagnosis of bloodstream infection and sepsis (although cultures from other clinical samples can also yield relevant information). Prompt collection of blood cultures (before antibiotic administration) and rapid initiation of antibiotic treatment for patients who meet criteria are absolutely indispensable in sepsis management (we refer also to Chapter 4 for the acute management of the patient with sepsis). An essential point determining sensitivity of blood cultures is the blood volume. Furthermore, good sampling practices are necessary to limit blood culture contaminations and avoid single blood cultures. Particular attention to educate non-laboratory personnel involved in blood sampling on the variables that influence the sensitivity and specificity of blood cultures is essential to improve the diagnosis and management of bloodstream infections in septic patients.

In the microbiology laboratory, turnaround time to report complete and reliable identification and antibiotic susceptibility results of positive blood culture bottles can be significantly shortened using recently developed methods such as direct inoculation methods for MALDI-TOF MS identification and susceptibility testing and the use of rapid molecular diagnostic tests.

Laboratories need to organize their processes so that preliminary and final results of blood cultures can be communicated as soon as possible to the treating physician. This requires inoculation of positive blood culture within a few hours and daily (7/7) microbiological analysis activity supervised by trained and specialized medical staff (preferably a recognized medical microbiologist (level III)). The latter has the responsibility to identify laboratory results requiring prompt verbal reporting towards the treating physician, in addition to electronic transfer in the electronic patient record. Positive blood culture Gram stain results, identification of important pathogens and unexpected microorganism resistance profiles require an immediate active communication as studies have demonstrated a positive impact on the patient's outcome.

It is essential that every clinical laboratory stays up to date with innovative technologies aiming to improve sepsis diagnosis and management. Large-scale interventional clinical impact and cost effectiveness studies can be used to guide decision makers in view of future investments. In the short-term pipeline, research interest should go towards sepsis biomarkers (we refer to Chapter 4), bacteraemia diagnosis directly from

whole blood, rapid antimicrobial susceptibility testing from positive blood cultures and the potential of artificial intelligence.

Recommendations:

1. Antibiotic policy groups (APG)/antibiotic management teams (AMT) have been assigned the responsibility of promoting AMS in acute care hospitals. Strengthening and providing sufficient financial support to APGs are essential to guarantee the effective execution of these responsibilities at the local level (including stewardship intervention and advice intra and transmural). This includes genuine remuneration for bedside stewardship activities and multidisciplinary discussions on complex resistance cases
2. National antibiotic guidelines should serve as a robust foundation for the formulation of institution-specific protocols for managing antibiotic use in cases of sepsis. It is strongly advised to offer support mechanisms facilitating routine revisions and expansions of these guidelines.
3. Microbiology laboratories generate essential information for the adequate treatment of patients. Hospital laboratories should set up quality processes to further improve the quality of sampling, analyzing and early reporting for critically ill patients.

2.3. Prevention of sepsis in the chronic care setting

Long term care facilities (LTCF) include a variety of home-replacing settings for persons with specific care needs because of age, frailty and/or underlying physical or mental disease or disabilities, including nursing homes (NH's), institutions for persons with disabilities, rehabilitation centers, psychiatric hospitals. There is significant heterogeneity between LTCF, based on differences in residents and their specific risk factors and needs, the scope of the facility, the level of complexity in care offered, and the availability of specialized healthcare professionals.

LTCFs share similarities with hospitals (e.g. a large number of medically vulnerable persons living together, with numerous medical needs), but differ also markedly from acute care settings in several critical aspects:

- Home replacement: LTCFs act as substitutes for home environments, providing ongoing care and support for individuals who are unable to fully care for themselves at home due to aging, chronic illnesses, or disabilities. Unlike acute care hospitals, LTCFs focus on long-term care needs.
- Less medical interventions: LTCFs prioritize supportive care, assistance with activities of daily living (ADLs), management of chronic conditions, and variable degree of rehabilitation activities.
- Limited autonomy of patients: In LTCFs, patients often have long-term limited autonomy compared to acute care settings. This is due to the nature of long-term care, where residents may require assistance with daily activities and may have more structured routines and care plans.
- Staffing challenges: LTCFs often face challenges related to staffing. Staffing shortages, including challenges in education and availability of qualified personnel, can impact the quality of care provided in LTCFs.

Depending on the specific medical needs of the residents in LTCF, there is frequent transfer of patients from LTCFs to hospitals and back to LTCFs. Effective communication between LTCFs and hospitals, and vice versa, is a critical element for ensuring the quality of care. In Belgium, the coordination and quality insurance of care in LTCFs is a regional competency. In this context we refer also to Chapter 6 (on ethical considerations and advanced care planning).

2.3.1. Burden and main risk factors for health care-associated sepsis in LTCF

Since 2009, Sciensano has coordinated the 'HALT'-studies (Healthcare-associated infections and Antimicrobial use in Long-Term care facilities) at the service of and in close collaboration with the European Center for Disease Prevention and Control (ECDC). These point prevalence studies (PPS) aim to prevent healthcare infections and antimicrobial use in European chronic diseases to measure healthcare institutions using a standardized methodology. The HALT study has been organized three times at European level to date: HALT-1 in 2010, HALT-2 in 2013 and HALT-3 in 2016-2017. Belgium always participated in these studies with 107, 87 and 107 respectively 158 chronic care institutions, mainly nursing homes. This systematic participation makes it possible to monitor the prevalence of HAIs and antimicrobials over time.

In 2023, ECDC published the surveillance data of the HALT-3 report (2016-2017 data) (119). This report enables us to compare the data on risk factors, HAI distribution, IPC measures, and AMS status with other European countries and with the more recent findings of the HALT-2021 study carried out in Belgium (120). As shown in Table 2.6, the presence of HAI risk factors such as urinary catheters, vascular catheters, pressure sores, other wounds and recent surgery among residents of LTCF in Belgium was at the lower side within the European spectrum, and lower than the Netherlands and Germany, but higher than France.

	% residents with urinary catheter			% residents with vascular catheter			% residents with pressure sores			% resident with other wounds			% residents with recent surgery		
	mean	P25	P75	mean	P25	P75	mean	P25	P75	mean	P25	P75	mean	P25	P75
Belgium	3,1	1,2	4,7	0,3	0	0	3,5	1,2	5,1	9,4	5,8	13	1	0	1,6
Netherlands	6,3	2,9	9,5	0,1	0	0	6,1	2,3	7,8	10,3	5,7	13	3,7	1,4	3,4
France	1,6	0	2,5	3,4	0	4,5	-	-	-	-	-	-	0,8	0	1,3
Germany	8	4,5	11,8	0,3	0	0	4	2,1	5,8	7,5	4,2	10,8	1,3	0	2,1
EU	8,4	1,4	11,1	1,5	0	0	5,9	0	8,3	8,8	2,3	12,5	1,7	0	1,7

Table 2.6.: Distribution of risk factors for HAI in the included LTCFs, for a selection of countries studied on the HALT-3 survey (adapted from Table 8 in the HALT-3 survey) (119).

The most recent Belgian data on HAI in LTCF can be found in the Sciensano report on the above mentioned HALT-2021-study (121). The majority of the participating LTCFs were nursing care homes situated in the Flanders region.

Geïncludeerde instellingen	Aantal instellingen (n=35)	Aantal residenten (n= 3 151)
Per type		
Woonzorgcentra (WZC)	31 (88.6%)	2 607 (82.7%)
Psychiatrisch verzorgingstehuis (PVT)	2 (5.7%)	253 (8.0%)
Psychiatrisch ziekenhuis	1 (2.9%)	182 (5.8%)
Revalidatiecentrum	1 (2.9%)	109 (3.5%)
Per regio		
Vlaanderen	34 (97.1%)	3 042 (96.5%)
Wallonië	0 (0.0%)	0 (0.0%)
Brussel	1 (2.9%)	109 (3.5%)
Per statuut		
Privé	24 (68.6%)	2 212 (70.2%)
Publiek	11 (31.4%)	939 (29.8%)
Per grootte (aantal bedden)		
Kleine instelling (<80)	5 (14.3%)	232 (7.4%)
Middelgrote instelling (80-129)	15 (42.9%)	1 301 (41.3%)
Grote instelling (≥ 130)	15 (42.9%)	1 618 (51.3%)

Table 2.7: Characteristics of included chronic care facilities (121).

Of these 2,607 residents**,** 66.5% were older than 85 years and 26.6% of the residents were men. Interestingly, 4.3% of the patients present with a urinary catheter (3.1% in 2016-2017) and 9.9% (9.4% in 2016-2017) with wounds other than pressure wounds. (Table 2.8)

Kenmerken	WZC residenten (n= 2 607)
Demografische factoren	n (ruw %)
Leeftijd >85 jaar	1 733 (66.5)
Mannelijk geslacht	693 (26.6)
Risicofactoren	
Urinekatheter	113 (4.3)
Vasculaire katheter	11 (0.4)
Doorligwonde	68 (2.6)
Andere wonde	257 (9.9)
Chirurgische ingreep in voorbije 30 dagen	18 (0.7)
Zorgzwaarte indicatoren	
Gedesoriënteerd in tijd en/of ruimte	1 651 (63.3)
Verminderde mobiliteit (rolstoelgebruiker of bedlegerig)	916 (35.1)
Incontinentie (voor urine en/of stoelgang)	1 608 (61.7)

Table 2.8: Patient characteristics from 31 participating long term care facilities, HALT-2021, Belgium (121).

The HALT-4 study is still ongoing. The initial phase took place in November 2023 with almost exclusively participants from Flanders. Currently, Sciensano is conducting a second round of outreach to engage structures in the French-speaking region. Based on the 2021 report, the top 3 most reported HAI in Belgium are: urinary tract infections (30.1%), respiratory infections (26%) and skin infections (13.7%)/gastro-intestinal infections (13.7%)[3] (Figure 2.4). Together, they cover approximately 75% of the HAIs in LTCF.

These are all conditions with the known potential to evolve into sepsis, but these data are not recorded, as they occur outside hospitals and are hence not registered in the above mentioned Sciensano surveillance of healthcare-associated BSI (62). Patients with sepsis are likely to be transferred to acute hospitals, so data would need to be obtained from hospital records. The lack of compulsory registration of community-acquired sepsis in Belgium is an important challenge, as well as a lack of a mandatory HAI surveillance system specifically required for LTCFs. While nursing homes are required to maintain a minimum record of certain data, including the number of HAI infections, the structure for HAI surveillance in LTCFs is not standardized. Each LTCF is responsible for developing its own surveillance system for HAIs based on their specific needs and resources. This includes deciding which types of HAIs to monitor. LTCF are expected to participate in national surveillance programs such as HALT-4 or the Sciensano LTCF MDRO surveillance, however, participation is not mandatory nor rewarded/reimbursed. Rehabilitation hospitals usually comply with the recommendations of Sciensano's yearly surveillance program for HAIs, which helps to ensure consistent monitoring and reporting of infections in these settings. However, LTCFs have more flexibility in how they establish and implement their surveillance systems for HAIs, depending on their individual capacities and priorities.

Finally, a list of infections notifiable to the regional public health authorities exists (122), although this list does not specifically focus on sepsis or HAI.

[3] Gastrointestinal infections encompass diarrheal episodes (e.g., Norovirus, C. difficile, among others) or intra-abdominal infections (e.g., cholecystitis, cholangitis). In LTCFs, the occurrence of intra-abdominal infections is relatively rare since such cases typically require admission to an acute hospital setting. Norovirus outbreaks are epidemic and occur quite frequently in LTCFs. A significant portion of the reported 13.7% of infections can be attributed to norovirus.

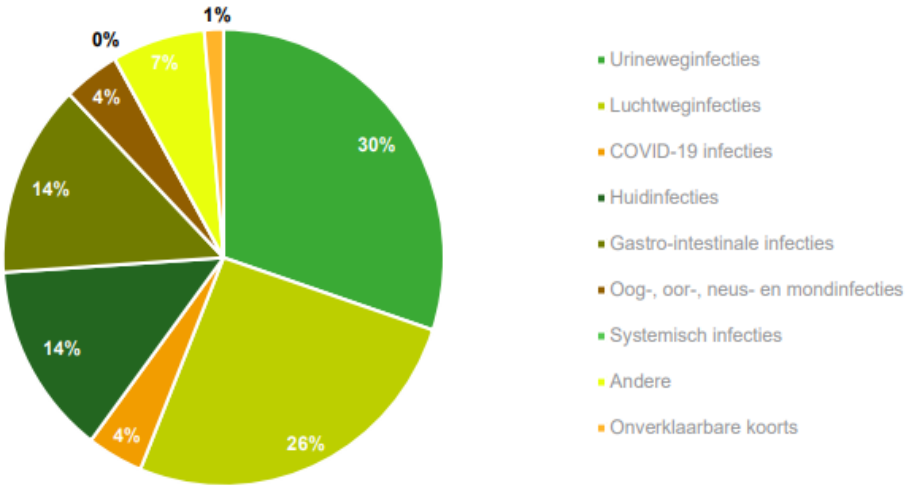

Figure 2.4: Healthcare-associated infections (n=73) in the 31 participating long term care facilities by type, HALT-2021, Belgium (121).

2.3.2. Evidence on IPC-interventions to reduce health care associated sepsis in the chronic care setting

Although HAIs may occur in acute and chronic care settings, the available evidence on specific IPC interventions to reduce HAI in LTCF, is limited in terms of quality and quantity so far. Of note, data on the influence of IPC measures on the QoL in long-term care institutions is sparse or even non-existent.

In a first systematic review (2017) encompassing 17 studies (of which 10 RCT) published between 2007-2016,it was observed that infection prevention programs incorporating a minimum of four core elements from the WHO multimodal strategy were effective in significantly reducing HAIs in nursing homes. Although no specific component emerged as singularly successful, and none of the programs integrated all eight core elements outlined by the WHO, the authors concluded that there is some evidence for the effectiveness of IPC interventions using education, monitoring, feedback and four or more elements of the WHO multi-modal strategy to control HAIs in LTCFs (123).

Another systematic review (2017) of 20 articles out of 5794 records, with focus on the prevention of urinary tract infections in LTCF, concluded that several practices, often implemented as bundles, such as enhancing hand hygiene, minimizing and improving catheter use, managing incontinence without catheters, and employing enhanced barrier precautions, appeared to reduce the incidence of UTIs or CAUTIs, in nursing home residents - although most studies were underpowered to reach statistical significance (124).

A more recent systematic review (2022) of 3877 studies, of which 19 were included (including 8 RCT) studied the effects of different IPC measures on a broad range of MDRO MRSA (n = 15), vancomycin-resistant enterococci (VRE) (n 4), *Clostridium difficile* (n = 2), and Gram-negative bacteria (n = 2). Overall, studies were heterogenous and low in quality. The authors did not find compelling evidence to support the effectiveness of IPC interventions on MRSA reduction, in particular for barrier precautions. The authors concluded that, in the absence of a clear benefit from interventions and the presence of evidence that various adverse outcomes linked with decolonization and barrier precautions, basic standard precaution (including hand hygiene, environmental cleaning, and staff education) which are low-cost and not menacing to residents should be the optimal approach in LTCFs. They concluded that 'LTCFs should consider a pragmatic approach to reinforce standard precautions as routine practice and implement barrier precautions and decolonization to outbreak responses only' (125).

Finally, a Swiss research group assessed 8676 publications (2017-2023), of which 74 met the inclusion criteria for systematic review: 34 (46%) in the non-outbreak setting and 40 (54%) in the outbreak setting (126). The most commonly studied interventions in the non-outbreak setting included the effect of hand hygiene (N = 10), oral hygiene (N = 6), antimicrobial stewardship (N = 4), vaccination of residents (N = 3), education (N = 2) as well as IPC bundles (N = 7). All but one study assessing hand hygiene interventions reported a reduction of infection rates. Further successful interventions were oral hygiene (N = 6) and vaccination of residents (N = 3). The findings are summarized in Figure 2.5. In outbreak settings, studies mostly focused on the effects of IPC bundles (N = 24) or mass testing (N = 11). In most of the studies evaluating an IPC bundle, containment of the outbreak was reported. Overall, only four articles (5.4%) were rated as high quality.

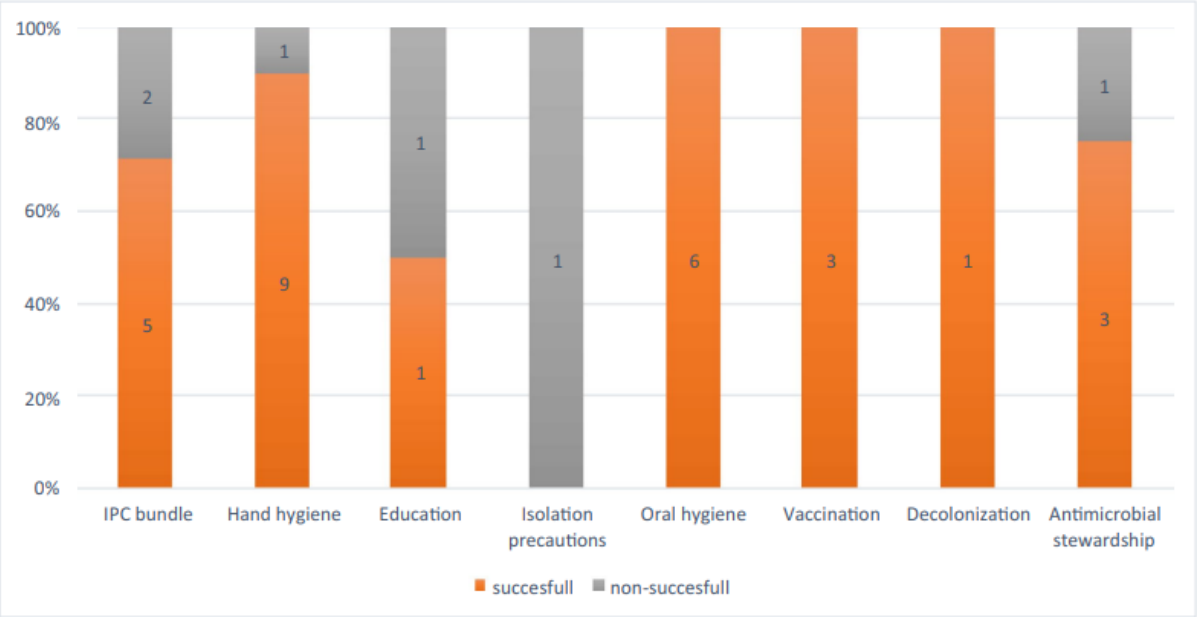

Figure 2.5. Overview of effective interventions to reduce HAI in LTCF (126).

With regards to vaccination, we refer to Chapter 2, part 2.1.3 on the importance of the preventive impact of vaccination for influenza, SARS-CoV2 for all persons residing in LTCF, and for invasive pneumococcal disease in residents with additional medical high risk, which contrasts with the actual coverage song these persons.

With regards to antimicrobial stewardship, we refer to parts 2.3.4 and 2.3.5 of this Chapter 2.

2.3.3. Belgian reality check on IPC in LTCF

In the effort to strengthen IPC in LTCFs, several initiatives have been launched in Belgium over the past years:

- In 2014, the report of a pilot project on the containment of HAIs in LTCF (2010-2014) was coordinated and published by the Belgian federal public health authority. The report contained recommendations on prevention, procedures, registration and monitoring, audit and evaluation, quality indicators, training, antimicrobial stewardship and transmural collaboration based on the experiences in this pilot project (127).
- Due to the 6th state reform, the chronic care settings have become a regional competence since 2014. The regional public health authorities have thus developed each their own policies (Zorginfecties | Zorg en Gezondheid (zorg-en-gezondheid.be)). Oral hygiene guidelines are

incorporated into the chapter within the working instrument on infection prevention policy for nursing homes (www.gezondemond.be).

- In all regions the OST (outbreak support teams dedicated to first line /LTCF) have started supporting IPC in LTCF. These are teams dedicated to enhance IPC in LTCF; there is one per province. They are leading projects, giving support for clusters or handling of infectious problems, producing guidelines and tools, and giving education and training in IPC. Since 2021, also the hospital outbreak support teams (HOST) have started collaborations with LTCF e.g. in helping to revise guidelines and tools, or giving support with surveillance or training.
- Every two years, a hand hygiene campaign for LTCFs is initiated. The most recent campaign took place in 2023 and was aligned with the focus from national hand hygiene campaign, specifically addressing the proper use of gloves (128).
- A Belgian surveillance tool, the Infection Risk Scan (IRIS), is available to measure the quality of infection control and antimicrobial use, and accompany the facility to implement specific improvement plans. The IRIS method was developed at Amphia Hospital (Breda, Netherlands), optimized within the I-4-1 Health project (Interreg, 2017-2019), and introduced within the HOST pilot project at the Plexus Hospitals in 2021. In 2022, the scan was conducted in several LTCFs (129).
- At the end of 2023, a UTI campaign for nursing homes In Flanders was initiated, aligning with the UTI consensus document tailored for nursing home settings, a collaborative effort involving various HOST teams (130). The campaign featured flowcharts, posters, and brochures aimed at raising awareness and improving management. The next steps include: the development of Cebam validated guidelines for the diagnosis and treatment of UTIs specifically in nursing homes, implementation of UTI campaign in collectivities (especially in LTCFs) based on the transmural HOST criteria for 2024; and expansion of the consensus document to encompass catheter-associated urinary tract infections (CAUTI) in nursing homes.
- For vaccinations, new strategic objectives for the period 2024-2030 have been drafted by Vlaams Department Zorg (see also Chapter 2) (131). One of these objectives is that by 2030, the vaccination coverage rate for influenza vaccination among healthcare workers should be 90%. Although recommendations are available and regularly updated by the Superior Health Council (CSS), the implementation phase at LTCFs is still ongoing and raises some important questions and issues, including:

- Responsibility: who is responsible for vaccinating residents, monitoring vaccination status, and recording information in a centralized register?
- Data availability: are vaccination coverage data (e.g. vaccine against COVID-19, influenza, pneumococcal disease, tetanus, respiratory syncytial virus) for each LTCF readily available and shared with local authorities?
- Follow-up: is there ongoing analysis and monitoring of vaccination indicators from year to year?
- Coordination: the role of the coordinating physician ("Coordinerend en Raadgevend arts" or "Médecins Coordinateur", CRA) in this process aligns with legal responsibilities and should be considered.

Despite several recent investments in IPC strategies in Belgium, clear needs remain and focused action is needed:

- For many situations, LTCF-specific IPC guidelines are not yet available in Belgium. It is common practice to translate and adapt acute hospital guidelines for use in LTCFs, although specific needs and realities may require dedicated guidelines (e.g. on urinary catheter placement and care, on parenteral nutrition, see Table 2.9)
- A formal surveillance for HAIs in LTCF, as well as a formal overall (multimodal) strategy has been lacking so far
- The COVID-19 crisis in the LTCF has revealed also painfully the lack of sufficiently trained health care workers and the availability of necessary personal protective materials of good quality.
- The role and training of the 'CRA' (coordinating clinician) should be clarified

WZC met	n/N (%)
IPC expertise	
Persoon met training in IPC	24/31 (77.4)
IPC comité	17/31 (54.8)
Toegang tot IPC expert	29/31 (93.6)
Beschikbaarheid van geschreven protocollen	
Dragerschap van MRSA en/of andere multiresistente kiemen	31/31 (100)
Handhygiëne	31/31 (100)
Verzorging van bewoners met:	
Urinekatheter	*19/30 (63.3)*
Vasculaire katheter	*8/30 (26.7)*
Parenterale voeding	*13/29 (44.8)*
Aanpak van lokale uitbraken van:	
Gastro-intestinale infecties	*23/30 (76.7)*
Respiratoire infecties	*22/30 (73.3)*
Surveillance van zorginfecties	7/30 (23.3)
Handhygiëne	
Routinematig gebruik van volgende producten:	
Handalcohol	*31/31 (100)*
Ontsmettingsdoekjes	*22/29 (75.9)*
Vloeibare zeep	*31/31 (100)*
Vaste zeep	*3/28 (10.7)*
Papieren wegwerkhanddoekjes	*31/31 (100)*
Verbod op lange nagels/nagellak/ringen/uurwerken	31/31 (100)
Handhygiëne vormingssessie	30/31 (96.8)
Arts(en)	*2/26 (7.7)*
Verpleegkundigen en/of verzorgend personeel	*30/30 (100)*
Paramedisch personeel	*30/30 (100)*
Logistiek personeel	*30/30 (100)*
Schoonmaakpersoneel	*30/30 (100)*
Administratief personeel	*22/30 (73.3)*

MRSA: Meticilline-resistente *Staphylococcus aureus*

Table 2.9. Available structure and resources for an infection prevention and control (IPC) policy in the 31 participating long term care facilities, HALT-2021, Belgium (121).

2.3.4. Antimicrobial stewardship in LTCF

Given their frailty, the lack of clear guidelines, surveillance and well-trained HCP in the field of HAIs, residents of LTCF are at increased risk of harm from inappropriate antibiotic use. Antimicrobial stewardship in LTCF involves changing the way prescribers, nurses and residents think in regards to the use of antibiotics. Approaching antimicrobial stewardship as an evidence-based quality improvement initiative promotes the judicious use of antibiotics to improve quality of care and support safety of LTC residents.

These harms, caused by inappropriate antibiotic use, include increased risk of adverse drug events, *Clostridioides difficile* infection (CDI) and infection with antimicrobial-resistant organisms (MDROs) (132). Infections with MDROs in LTCF-residents are also associated with more severe infection, hospitalization, increased risk of death and increased cost of care (133). LTC-residents present unique challenges to antimicrobial stewardship. Symptoms of infection may be atypical, cognitive impairment limits communication of symptoms, and risks for acquisition of resistant organisms are increased due to aging immune systems, complex comorbidities and frequent hospitalizations (108). Increased antibiotic use in LTCF has also been attributed to limited resources to diagnose infections, lower staff-to-resident ratios

and increased dependence on diagnostic tests, such as urinalyses or chest radiographs for suspected infections (134).

As described in parts 2.1.4 and 2.2.4 of this Chapter 2, in hospitals and first line health care settings, antimicrobial stewards have shown to promote the judicious use of antibiotics to optimize clinical outcomes, limit development of MDROs, and preserve the efficacy of antibiotics for future generations. Formal antimicrobial stewardship programs (ASPs) have been shown to be effective and safe in reducing unnecessary antimicrobial use by implementing "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents" (135). One of the local champions in a long term care facility to promote prudent antibiotic use and foster antimicrobial stewardship could be the local coordinating physician (CRA) As part of their mandatory training (i.e. 24 hours within 2 years of appointment at the LTFC), they are trained in infection control and antibiotic use in the LTFC (123-124). As this is one of the cornerstones of their training, awareness and training on sepsis management alongside appropriate antibiotic use should be prioritized as a large proportion of patients admitted to hospital with sepsis originate from the LTFC setting.

The US Centers for Disease Control and Prevention (CDC) have issued a guideline on 'Core Elements of Antibiotic Stewardship for Nursing Homes', including a checklist (132) and include:

leadership commitment (Demonstrate support and commitment to safe and appropriate antibiotic use in your facility)

- Accountability: 'identify physician, nursing and pharmacy leads responsible for promoting and overseeing antibiotic stewardship activities in your facility'
- Drug expertise: 'establish access to consultant pharmacists or other individuals with experience or training in antibiotic stewardship for your facility. For example, with HOST projects and their transmural axis, having access to expertise in pharmacology and infectious diseases.
- Action: 'implement at least one policy or practice to improve antibiotic use'. For example, there has been a recent focus on UTI through collaboration between regions, HOSTs, and facilities.
- Tracking: 'monitor at least one process measure of antibiotic use and at least one outcome from antibiotic use in your facility'
- Reporting: 'provide regular feedback on antibiotic use and resistance to prescribing clinicians, nursing staff and other relevant staff'

- Education: ‘provide resources to clinicians, nursing staff, residents and families about antibiotic resistance and opportunities for improving antibiotic us’

2.3.5. Belgian reality check on AMR in LTCF

The following initiatives and guidelines are available in Belgium regarding AMR/AMS:

- Two national expert working groups have been established (Belgian Antibiotic Policy Coordination Committee BAPCOC), i.e. the Hospital AMS and Primary care AMS working groups. Guidelines and activities for LTCF tend to fall in between those two groups and risk not to be given the specific attention they require. This has been highlighted by the HALT-3 study (121), which revealed needs of improving the availability of context adapted guidelines, availability of AMS training programs, audit and feedbacks, and antibiotic consumption monitoring (Table 2.10). A significant finding highlighting the urgent need for formal AMS programs in LTCF was that 42% of prescriptions were for prophylactic purposes, and in 41% of cases, there is no mention of the end date or revision of treatment (120).
- Likewise, the Belgian “One Health” national action plan on the fight against Antimicrobial Resistance (NAP-AMR) (2020-2024) A royal decree (28/03/2008) described the AMS objectives in acute (and chronic) hospitals, but not in nursing care homes (138). The requirement to have a LCTF formulary could be the entry point for starting AMS activities for LTCF.
- A national antibiotic treatment guideline exists for ambulatory care (Guide BAPCOC ambulatory 2022) and for hospitals (IGGI, by the Belgian Society for Infectiology and Clinical Microbiology) (91). For the organizational and access needs of the IGGI, we refer also to Chapter 4. In addition, adaptations are needed for rehabilitation hospitals and other LTCF.
- For the implementation of AMS in LTCF, the CRAs can be confronted with the prescription autonomy of colleagues. One potential strategy could be to officially empower their role, potentially through a royal decree, specifically focusing on AMS.

Beschikbare middelen en praktijken	n/N (%)
Systeem voor toestemming voor voorschriften buiten het formularium	4/31 (12.9)
Antimicrobieel comité	1/31 (3.2)
Lokale resistentieprofielen beschikbaar in het WZC	1/31 (3.2)
Regelmatige jaarlijkse vorming m.b.t. goede voorschrijfpraktijken	2/31 (6.5)
Systeem dat herinnert aan het belang van microbiologische staalname	2/31 (6.5)
Feedback aan artsen over AM gebruik in de instelling	4/31 (12.9)
Advies van apotheker bij keuze van een AM buiten formularium	11/31 (35.5)
Beschikbare AM consumptiegegevens per AM klasse op jaarbasis	8/31 (25.8)
Geschreven richtlijnen over correct AM gebruik	4/31 (12.9)
Therapeutisch formularium met een specifieke lijst met AM	13/31 (41.9)
Surveillance	
Surveillance van antimicrobieel gebruik	8/31 (25.8)
Surveillance van resistentie kiemen	6/31 (19.4)
Beschikbaarheid van geschreven therapeutische richtlijnen	
Luchtweginfecties	10/24 (41.6)
Urineweginfecties	8/24 (33.3)
Wondinfecties	12/24 (50.0)

Table 2.10: Available resources and practices for an antimicrobial (AM) policy in the 31 participating residential care centers (WZC), HALT-2021, Belgium (121).

Recommendations for prevention of HAI and sepsis in LTCF

1. Build/implement and follow up the presence of essential core components for IPC and AMS in LTCF. This includes the availability of specific guidelines, sufficient educated staff, availability of personal protective materials, surveillance of HAI/sepsis in LTCF and monitoring/audit and feedback on specific interventions, organized in care bundles and multimodal strategies
2. Define specific objectives and quality indicators for AMS and IPC in LTCF, as well as multimodal strategies to implement them. Priority should be given to concrete interventions.
3. Develop and teach a (postgraduate) education package for coordinating and advising clinicians in LTCF ('CRA') and for nurses working in LTCF
4. Give additional support (administrative and logistic) to nurses working in LTCF enabling them to focus on clinical work, advanced ward management, and coordinating care activities closely with CRA's.
5. Strengthen the role of the CRAs, allowing them more autonomy and responsibility for IPC and AMS-related tasks. Tele-advice with clinical infectiologists or microbiologists could be considered
6. Support should be foreseen for surveillance/registration of HAI / AMR / AMC in LTCF
7. More research on the effectiveness, implementation and (psychosocial) impact of specific IPC and AMS interventions is needed.

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Chapter 3. EARLY RECOGNITION AND RAPID RESPONSE SYSTEMS

Analysis of medico-legal cases between 2011 and 2020 involving physicians from a Canadian national database repository showed that patients who had a delayed diagnosis of sepsis made multiple visits to outpatient care leading up to hospitalization and had a high mortality rate (40%). Deficient assessments, such as failing to consider sepsis or not reassessing the patient prior to discharge, contributed to the majority of cases.

Sepsis screening is a key part of sepsis quality improvement projects, and it has a proven effect on morbidity, mortality, and costs (1-3). In Belgium, currently, approximately only 40% of the ED perform structured protocolised sepsis screening in contrast to countries in northern Europe where up to 100% of hospitals perform screening in the ED. Above this, medical emergency teams that perform rapid response in case of possible sepsis cases are being used in up to 100% of hospital networks in northern Europe, while in Belgium, only about 25% have structured protocolised rapid response systems (4). Several studies have shown that sepsis screening in various settings (including home health care) positively impact costs for sepsis patients and significantly reduce ICU length of stay and total cost per case (5).

3.1 Recognition of sepsis in different settings

Long-term care facilities

Very little literature is available on sepsis screening or recognition in LTCFs. Qualitative studies investigating the recognition and initial management of sepsis in LTCFs are lacking. Several states may have developed protocols for identifying and managing sepsis in LTCFs in the US. However, no results of their impact on hospitalization or the outcomes of the residents have been published. An early detection tool for sepsis in LTCF residents, called '3-100s or 100-100-100 criteria', was developed by the Minnesota Hospital Association in order to reduce sepsis-related mortality (6). In patients with suspected infection, criteria of this 3-100s tool are met if two or more following are present: temperature > 100 °F (37.7°C), heart rate > 100 bpm, and systolic blood pressure < 100 mm Hg. However, this 3-100s sepsis screening tool was used in only one relatively small, retrospective, observational study evaluating the sensitivity and specificity of SIRS criteria, qSOFA, and 3-100s criteria to identify nursing home residents transferred to the hospital with an eventual diagnosis of sepsis (7). The study found a sensitivity of 79% and a specificity of 69% for the 3-100s early detection tool, suggesting this may be a useful screening tool for sepsis risk in LTCF residents (6,7).

Recommendation

The paucity of literature and robust studies show that much still needs to be done to reduce sepsis-related morbidity and mortality in LTCF residents. This includes developing and validating an effective sepsis screening tool applicable in the LTCF setting.

Primary Care

In out-of-hours primary care, recognition of sepsis is particularly challenging, with a high mortality rate among patients in whom the GP did not suspect an infection (8). Based on self-reported cases of possible serious infections, the factors most often indicated as important for the decision to refer patients to the hospital were: general appearance (94.1%), gut feeling (92.1%), history (92.0%), and physical examination (89.3%). Temperature (88.7%), heart rate (88.7%), and blood pressure (82.1%), were the most frequently measured vital signs. In general, GPs more likely referred patients in case of: altered mental status (98.7%), systolic blood pressure <100 mmHg (93.7%), unable to stand (89.3%), insufficient effect of previous antibiotic treatment (87.4%), and respiratory rate ≥22/minute (86.1%). The GPs' assessment of patients with possible serious infection is a complex process, in which besides checking vital signs, many other aspects of the consultation guide the decision to refer a patient to the hospital. These findings suggest that a significant number of (early) sepsis cases are being missed, highlighting the need for improved education, training, and protocol adherence among healthcare professionals. The diagnostic and prognostic value of assessing vital signs and symptoms.

Given resource constraints in a primary care setting, such as limited access to comprehensive laboratory testing, selecting an appropriate rapid and straightforward sepsis screening tool or strategy is paramount. The qSOFA and NEWS/PEWS, particularly, are favored for their simplicity, making them suitable for primary care settings (9). However, a recent scoping review of 23 studies by Oanesa et al (2024) failed to identify a well-performing EWS for detecting sepsis in the pre-hospital setting. The authors suggested to focus on combining standardized prehospital care with clinical judgment to provide timely interventions for unstable patients where infection is considered a likely etiology, in addition to improving sepsis education for prehospital clinicians. At most, EWS can be used as an adjunct to these efforts, but they should not be relied on alone for prehospital sepsis identification (10). GPs' gut feeling (intuition), and additional diagnostic tests with or without telephonic expert advice should be prospectively studied in the primary care setting.

These tools should be used alongside clinical judgment to identify and manage sepsis promptly (11). It is crucial to train primary care providers to recognize sepsis signs and symptoms and employ screening tools as part of a broader strategy, including patient/caregivers education and awareness of local epidemiology

(12). The choice of specific tools or combinations should consider the local context, available resources, and healthcare system structure.

Expert advice to discuss patient cases should be readily available to GPs as the exposure rate to sepsis is generally low. A working group of GPs suggested an 24/7 available specialist advice line comparable to other initiatives of readily available expert advice such as the Belgian Poison Centre.

A range of studies have explored the use of telephone triage in sepsis management. A telephone call from a specialist in Clinical Microbiology improves sepsis recognition and reduced antimicrobial consumption. Triage tools to improve sepsis management increase compliance with sepsis management guidelines and reduce time to treatment initiation in children. Emergency medical dispatchers and telephone nurses can appropriately direct resources and reduce non-urgent ambulance missions.

Recommendation:

In conclusion, sepsis screening tools and (pediatric) early warning screening tools provide practical and effective means for sepsis screening in primary care settings. Their use should be part of a broader sepsis strategy which includes triage tools and readily available expert advice.

Emergency medical services (ambulance and paramedic)

Many studies have explored the effectiveness of different sepsis screening strategies for emergency medical services (EMS) including paramedic and ambulance personnel in the prehospital setting (13). The Critical Illness Prediction (CIP), National Early Warning Score (NEWS), Quick Sepsis-Related Organ Failure Assessment (qSOFA) score and the Sepsis Alert Protocol Sepsis Alert Protocol, or the Pediatric Early Warning Score (PEWS) or Pediatric Observation Priority Score (POPS) were proven to be effective sepsis screening tools in both adults and children respectively (14, 15). However, validation studies are needed, as varied success of EMS providers in identifying sepsis has been noted (16).

Recommendation

We recommend using a screening tool for prehospital teams to communicate the vital status of patients with possible sepsis. Further research is needed to validate the effectiveness of point-of-care testing in the prehospital setting.

Emergency Department

Possible sepsis patients should be identified during triage and first rapid assessment in the ED. Currently, various triage tools are being used in Belgium, and few hospitals use formal sepsis screening in the ED compared to other European countries. Clinical screening tools should be combined with early bedside point-of-care lactate testing. Lactate measurement is part of the 1-hour bundle issued by the Surviving Sepsis Campaign. However, the performance requirements for cost-effective point-of-care sepsis tests must be further explored (17).

The Manchester Triage System (MTS), one of the most used triage systems, has shown high sensitivity and negative predictive value in predicting sepsis or septic shock in patients with fever. However, it has been found to have weaknesses in prioritizing emergency patients with septic illness, particularly in considering key symptoms and vital parameters (18). Despite these limitations, when used with the NEWS, the MTS may allow for earlier identification of patients at risk for severe sepsis and septic shock (19).

Of note, the Surviving Sepsis campaign advised not using the qSOFA criteria for sepsis screening in the ED. The highest sensitivity for sepsis diagnosis was observed for the NEWS at the cut-off equal to or greater than four (71.8 to 88.1%), along with high specificity (84.8 to 90.2%). NEWS also demonstrated high sensitivity (92.9%) and good predictive ability for predicting sepsis-related mortality and ICU admission. Moreover, NEWS is already a well-known tool among Belgian ED professionals. Overall, the level and evidence of quality were strong and high, respectively, for qSOFA, SIRS, and NEWS and limited-moderate and low-medium for Lactate-enhanced-qSOFA (LqSOFA) and MEWS.

Recommendation

To enhance early detection and management of sepsis in the emergency department (ED), an early warning system such as the National Early Warning Score (NEWS) with point-of-care lactate testing is recommended. This approach combines NEWS's high sensitivity and specificity for sepsis and septic shock with lactate levels' prognostic value, facilitating timely and effective sepsis care.

Hospital wards

Vital signs, observations, and scores should be collected in a standardized manner that allows clinicians to visualize deviating scores and trends in the data (20). Using a standardized electronic patient record linked with a bedside spot-check monitor can reduce workload, increase adoption, and reduce delays between measurement and registration (21). In addition to vital signs and NEWS, bedside nurses should use their ‘feeling of concern or worry’ as an escalation criterion (22).

The NEWS is a validated score that performs superiorly compared with several other Early Warning Scores for predicting patient deterioration and death within 24 hours after registration (23-25).

A person's risk of severe illness or death from sepsis may be high regardless of the NEWS score if any of the following clinical symptoms are present: mottled or ashen appearance, non-blanching petechial or purpuric rash, and cyanosis of the skin, lips, or tongue (26).

Continuous measurement of vital signs in patients through wearables or other smart devices is under investigation, yet it yields conflicting outcomes in clinical practice, influenced mainly by the current state of these technologies (27, 28).

There is a causal relationship between low Bachelor degree Nurse (BN) staffing and patient mortality from longitudinal studies underpinned by decades of research (29, 30). The implementation of Rapid Response Teams (RRS), which can be nurse-led, physician-led, or mixed, is associated with a decrease in both mortality and non-ICU cardiac arrest rates (31).

Recommendations

1. All adult patients admitted to an acute hospital ward should be observed regularly and systematically throughout their hospital stay with a minimal observation frequency of one observation per 12 hours.
2. An Early Warning Score (preferably NEWS) should be used to estimate the acuity level in every hospitalized patient. All observations should be done, or at least verified, by experienced bedside nurses or medical doctors with a minimal level of education and training. Hospitals ought to exercise caution when assigning nurse assistants or students the responsibility of conducting patient observations since this is associated with patient deaths (32, 33). The Nurse Intuition Patient Deterioration Score (NIPDS) is a validated instrument that displays strong predictive capabilities for adverse events and can be used by nurses to translate 'clinical worry' into an objective score (34). A combination of NEWS with NIPDS (with thresholds of both scores ≥ 5), as a trigger criterion for rapid response, seems to provide the largest Net Benefit in hospitals (35).
3. We recommend targeted education for non-ICU hospital clinicians on early clinical deterioration recognition, emphasizing specific actions like seeking help, following protocols, and performing crucial tasks (31). However, to achieve meaningful clinical benefits, this education needs integration into a structured RRS with audits and feedback.
4. We advocate for the widespread implementation of RRT or Medical Emergency Teams (MET) across hospitals for patients outside the ICU. This approach should encompass clearly defined

criteria for activating assistance from a designated response team. The implementation of RRTs, that can be nurse-led, physician-led, or mixed, is associated with a decrease in both mortality and non-ICU cardiac arrest rates (36, 37). Hospitals should receive incentives to implement Rapid Response Teams (RRTs) since these can provide proactive, reactive, and supportive care to general wards, in addition to offering educational support. Advanced nursing profiles such as nurse practitioners with critical care expertise could take part in these teams.

5. Finally, hospitals should implement safe nursing staffing levels for acute care settings.

Intensive care

A range of sepsis screening methods have been proposed in the ICU. Data integration systems combined with early warning scores (such as NEWS) and logistic regression models can serve as practical tools for early sepsis prediction (38-41). There is growing expertise and evidence for developing and implementing machine learning methods and artificial intelligence in the high data load environment of the ICU. Challenges in the ICU, such as the COVID-19 pandemic, have highlighted the potential of AI in areas like patient deterioration detection and work organization (42), but deployment is hindered because of ethical concerns. The integration of AI into the ICU4Covid project has shown promise in predicting mean arterial pressure values (43).

Recommendation

An early warning system that includes sepsis screening and alerting should be implemented in ICU wards. The deployment of AI in the ICU should focus on facilitating AI development and addressing ethical concerns.

3.2 Recognition of sepsis in specific populations

Pediatric population

Early detection of sepsis in pediatric patients can be challenging as they can present atypical or subtle clinical symptoms. Common presentations include poor feeding, lethargy, poor tone, irritability, and signs of upper airway infection. A screening tool should be used for all pediatric patients presenting signs of infection and abnormal heart rate for their age (44). For example the sepsis screening tool displayed in Figure 3.1 could be included in a recognition bundle to aid clinicians in evaluating children with possible sepsis and initiating appropriate care pathways and treatment (45).

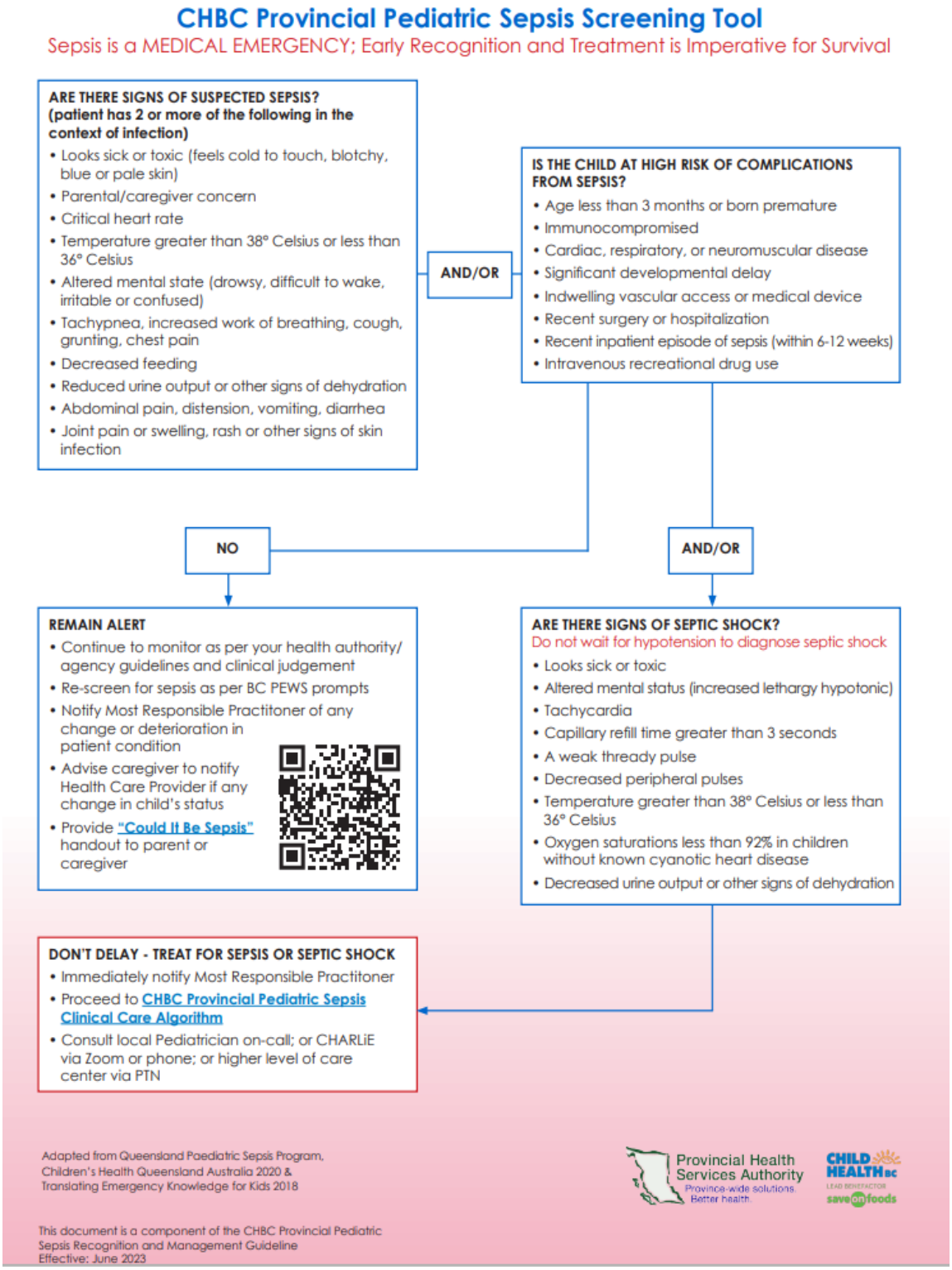

Figure 3.1. CHBC Provincial Pediatric Sepsis Screening Tool (40).

Several high-risk groups have been defined in pediatric patients. Children younger than three months are especially vulnerable and represent 70% of children diagnosed with sepsis. Immunosuppression or development delay are also high-risk conditions. The ERC guidelines 2021 indicate that proper assessment requires an integrative approach (clinical symptoms, history, biomarkers/imaging) and recommend using the Pediatric Assessment Triangle (PAT, see figure 3.2) or similar models (46, 47). They also state that Pediatric New Early Warning Score (PEWS) implementation should be part of an overall clinical response system. Although national PEWS has a smaller evidence base than NEWS for the adult population and is more complex to implement, this generic tool is already widespread and well known among healthcare professionals, making it a valuable choice for early detection in ED and primary care settings. Different versions of the PEWS, pediatric observation priority scores and locally developed scoring systems have been studied. Results suggest that PEWS is the most used and accurate scoring tool. However, a combination of an automated and nurse-driven screening tool could be the most effective approach. (48-52). In 2024, international consensus sepsis criteria for children using the Phoenix Sepsis Score were published (53). While this tool is effective in in-hospital settings, its pre-hospital and primary care performance is inconsistent (10). This score includes lactate and coagulation laboratory results that require resources and could delay early support. Comparable with the SOFA score for adults, its use in many settings (pre-hospital, ED triage, GP) could be limited by its complexity and implementation difficulties. However, its use could bring a gain in more specialized environments such as ICU. Several studies also highlight that parents/caregivers' concerns could be an indication of severity (44) and plead using it as a trigger (54) and promote family-activated rapid response (55).

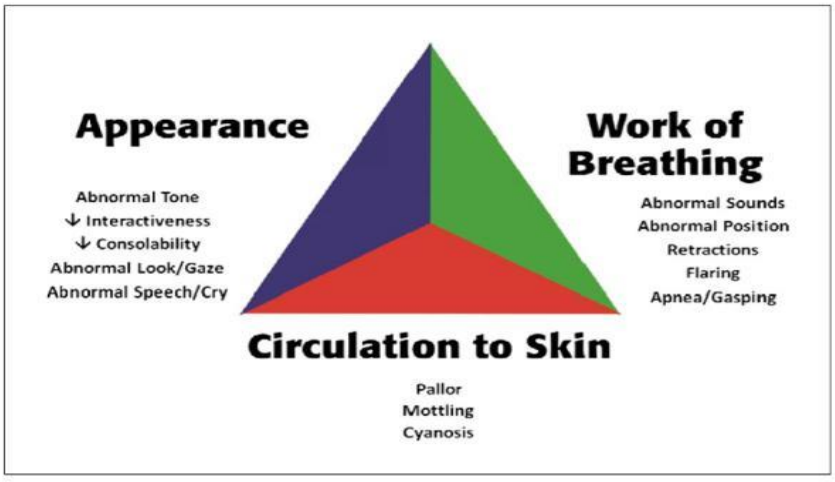

Figure 3.2.The Pediatric Assessment Triangle (47).

Recommendation

We recommend using PEWS as a triage and screening tool for sepsis among pediatric patients. Other assessment tools, such as the PAT, high-risk criteria or specific tools, such as the Phoenix Sepsis Score, can be combined with PEWS as part of a broader sepsis screening and diagnosis sepsis strategy. Family and caregiver-activated rapid response should be part of a broader strategy. Research should focus on validating current tools and developing and implementing machine learning-based screening tools.

Older patients

Given that older age is a significant risk factor for sepsis and that older patients often present themselves atypically, the implementation of EWS for sepsis is of utmost importance to detect sepsis, initiate treatment early and reduce sepsis-related morbidity and mortality. However, older patients' physiology differs from average adult patients. For instance, older patients usually have higher blood pressure because of arterial stiffness, a lower maximal heart rate, lower arterial oxygen due to a ventilation-perfusion mismatch, lower body temperature, etc. Moreover, a change in clinical and functional status may be the only sign of disease manifestation. Therefore, currently used EWS and their thresholds may be less sensitive to clinical deterioration in older patients. To our knowledge, no meta-analysis about EWS in older patients is available. Only one systematic review evaluating EWS in older patients (>= 65 years) hospitalized for sepsis, stroke or pneumonia has been published. The authors found a strong association between increasing EWS/MEWS and mortality and transfer to the ICU in older patients (56). However, a large observational prospective multi-center study in the Netherlands (n=2280 patients) that stratified patients with sepsis on the ED by age (<70 years vs >= 70 years) showed that disease severity scores, such as the qSOFA, the MEWS and NEWS were associated poorly with mortality in older patients compared to younger patients (57). They concluded that most commonly used disease severity scores are less useful for risk stratification of older ED sepsis patients. Similarly, a large, retrospective, single-centre observational study in Japan showed that prehospital NEWS/MEWS had a low utility as a predictor of admission or in-hospital mortality in older patients (>= 65 years) admitted for sepsis, among other diseases (58). A geriatric EWS, specifically for older patients considering different physiological thresholds for clinical deterioration and changes in functional status needs to be developed and validated.

Recommendation:

While waiting for a validated geriatric EWS, we recommend using currently available EWS for sepsis detection, as with the general population. In addition, education in geriatric syndromes of healthcare providers involved with older patients may improve the correct interpretation of currently available EWS in older patients.

3.3 Patient, family and care partner concerns as a formal part of detecting sepsis

Patient, family, and care partners of hospitalized patients can recognise subtle changes in the clinical status that could have been overseen by healthcare providers (59). Therefore, we recommend that patient, family, and care partners' concerns are formally integrated into hospital early warning systems as is more frequently the case internationally (60,61).

All patients, family, and care partners must have 24/7 direct access to a rapid response team (which can be a single person) that is able to provide a rapid review when called (62, 63).

3.4 Artificial intelligence (AI) and future design of sepsis screening tools

A range of studies have demonstrated the potential of machine learning (ML) in improving triage systems in emergency departments. ML methods, including real-time Electronic Medical Record (EMR) monitoring screening tools consistently predict important outcomes such as mortality, critical care, and hospitalization, outperforming traditional triage scales (64). ML and initial nursing assessment-based triage systems have been found to predict clinical outcomes more accurately than existing systems (65). Future research should focus on validation studies in order to be able to compare different machine learning based EWS (66) AI has the potential to improve ICU workflow, reduce documentation burden, and support clinical decisions (67).

3.5 Remote patient monitoring for sepsis

In the home health care setting, a sepsis-screening protocol has been effective in prompting early medical intervention and avoiding hospitalization (68). Remote patient monitoring has shown potential in detecting sepsis in home settings, with studies indicating its feasibility and acceptability (69).

Recommendation

More research is needed to evaluate cost-effectiveness of machine learning and remote patient monitoring in patients at risk for sepsis.

3.6 Considerations for implementation in Belgium

Simple and accurate sepsis screening tools can be implemented in current healthcare systems. Various European countries have proven that screening tool implementation is feasible and cost-effective.

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Chapter 4. EARLY ADEQUATE TREATMENT

Sepsis is a global healthcare problem that can lead to severe morbidity or mortality if not timely and appropriately treated. To describe factors that positively impact outcome we borrow two concepts well-known in the literature of sudden cardiac arrest.

First of all, the Utstein Formula for Survival describes the potential for survival as the product of medical science (knowledge and technology), educational efficiency (both healthcare providers and lay persons), and local implementation (within a specific community or healthcare system) (1). Final outcomes might decrease rapidly when lower than 100% is seen in any of the three given elements.

Second, the Chain of Survival identifies all necessary steps in the treatment of cardiac arrest (2). This chain is equally applicable to the problem of sepsis. A sequence of actions can be identified, that all need to be present and effective, to optimize outcomes. As with any chain, not only the parts themselves but also the 'transition' links between each are crucial.

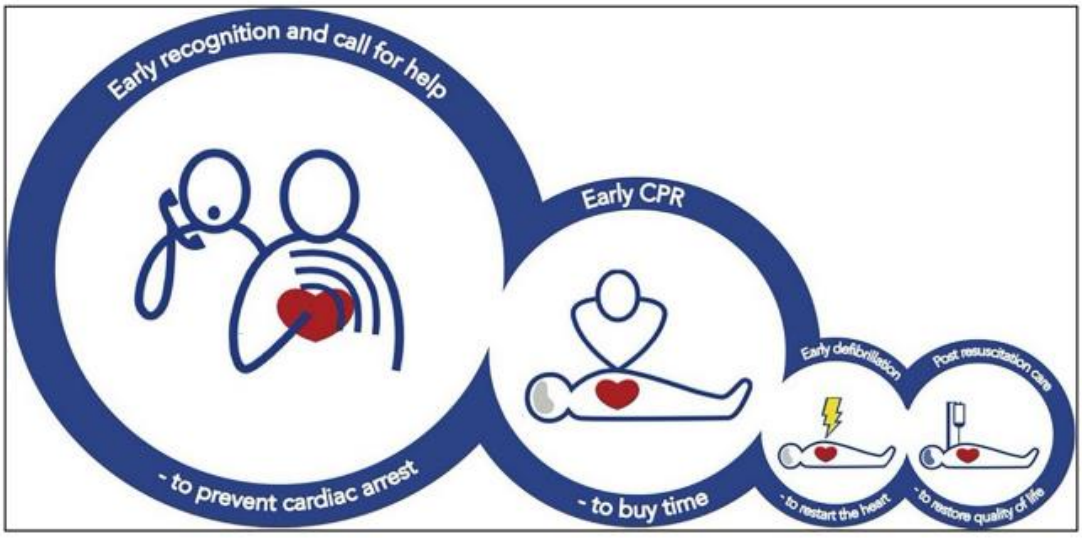

Figure 4.1: Chain of survival for out-of-hospital cardiac arrest (3).

For this SEPSIS CHAIN OF SURVIVAL, we recognize the following linked parts:

1. Early recognition and Access to Emergency Medical Care (further described in Chapter 3)
2. Early Basic support
3. Early Advanced support
4. Intensive Care (ICU) Treatment
5. Recovery Care (further described in Chapter 5)

Optimizing care in each of these steps should be based on scientific evidence, but equally focused on education and implementation strategies. Sepsis management guidelines of good quality exist and are regularly updated but, as the authors themselves emphasize, should never replace "the clinician's decision-making capability when presented with a unique patient's clinical variables" (4). Local healthcare systems should try and integrate these guidelines into their practice, considering that the evidence for each of the components is far less than that of the program in total (5-10). When implementing guidelines, systems should consider their local context and available resources, but guarantee equal care for everyone regardless of sociocultural background, ethnicity, or age as such. They should also be able to capture changes in evidence and update/revise their guidelines in a timely manner.

Existing guidelines emphasize the importance of early recognition (see Chapter 3) and emergency treatment. Very often clinical deterioration of a sepsis patient will occur in an environment where healthcare providers are not trained to provide advanced support. It is imperative -regardless of this being pre-hospital or for instance a hospital ward- for such 'basic' sepsis care providers to recognize, and timely alarm 'advanced' care providers as needed per local protocol (11-13). Healthcare systems should have protocols and standard operating procedures [SOP] about whom to contact and when, including specific guidance of the mode and content of communications. These protocols and SOP should be regularly evaluated for performance. Importantly, 'basic' sepsis care providers should be able to provide necessary early treatment in line with their expected level of knowledge and skills. This typically includes (4, 5, 13-16):

- early fluid resuscitation
- titrating oxygen to a saturation target of 94%
- taking blood for biochemistry (and specifically serum lactate)
- taking blood and other cultures (we refer to Chapter 2 on the role of microbiology)
- starting appropriate antibiotics in a timely way, according to local guidelines and depending on the setting in which these 'basic' care providers are working, along adequate source control where possible (e.g. drainage of abscess, removal of catheter,...)
- start accurate monitoring of urine output

Blood cultures remain the gold standard in the laboratory diagnosis of bloodstream infection and associated sepsis. Prompt collection of blood cultures (before antibiotic administration, and with rapid inoculation and other recent approaches to allow rapid and qualitative results) and rapid initiation of antibiotic treatment for patients who meet criteria are absolutely indispensable in sepsis management.

Good sampling practices for blood and other cultures are essential and systems should have clear written protocols about among other indications, necessary volume, contamination avoidance, timely communication of preliminary results of identification and susceptibility and/or presence of unexpected microorganism resistance profiles.
To support 'basic' providers, systems should have dedicated procedures in place and ensure easy access to these at all times. In addition, teams -especially those more likely to be confronted with a patient in sepsis- should be sufficiently staffed and have sufficient resources to address early sepsis (17).

Specific procedures might be in place for specific populations and circumstances such as young children, and specifically neonates, older individuals, or those institutionalized or immune-depressed (18). In these populations, sepsis is a frequent cause for mortality and morbidity, but the presentation might be far less unequivocal and differentiating sepsis from more benign infections is difficult (19-21). Clinical signs might be more subtle or less specific. Healthcare providers working with these populations should be specifically trained to recognize sepsis and start early treatment in them.

An important part of this 'basic' support is the prevention of infection transmission to other patients, bystanders and/or healthcare providers. Rapid identification of the need for transmission-based precautions (i.e. contact, droplet or airborne transmission prevention) should lead to reflex measures as per local protocol (see also Chapter 2). Healthcare providers should be trained to initiate such measures but also in transmission dynamics and the underlying rationale for certain isolation decisions. Systems should have comprehensive 'isolation' plans in place, that can be consulted at any time and are monitored for efficacy at regular intervals.

While certain 'basic' actions should be instituted at any moment by any trained healthcare provider, more 'advanced' treatments should be the remit of 'advanced care' teams (e.g. prehospital Paramedical Intervention Team (PIT) or MUG teams, or in-hospital Emergency Department (ED) or rapid response teams). These dedicated teams should be specifically trained and regularly retrained for this task, both for what concerns specific 'advanced' medical interventions and more broadly the 'team-based' approach to care (crew resource management) (18). They should be able to respond rapidly and support 'basic' care providers in a timely manner. Systems should have SOP in place to facilitate this. In addition to 'basic' interventions, advanced care teams should be able among others to provide advanced airway management, more extensive fluid resuscitation, early administration of vasoactive medications, advanced monitoring…. If not obvious or already done, they should institute further diagnostics to identify the focus and nature of the presumed underlying infection (to differentiate from non-infectious critical

illness) and the sepsis-associated metabolic disorders and/or organ failure. Early initiation of vasopressor support in patients with septic shock improves outcomes (4, 18, 22). If no central access is yet available, vasoactive medication should be given peripherally or intraosseous. Effectiveness of therapeutic interventions can be monitored in many ways but should at least include monitoring of the urine output, the mean arterial blood pressure [MAP] and of lactate clearance (23).

Biomarkers might be of help to support the diagnosis of sepsis as far as they have proven high diagnostic performance (sensitivity and specificity). Despite some papers highlighting the potential of procalcitonin to guide treatment or more recently of pancreatic stone protein (PSP), overall, there is insufficient evidence in literature to favor any specific biomarker and none of the more recent biomarkers has yet proven improved test performance compared to C-reactive protein (CRP) (4, 23-27). As more recent literature considering the potential associated cost and use of resources becomes available, the introduction of additional biomarkers should only be done if their cost-effectiveness is clearly proven (28). Finally, advanced care teams should have protocols and communication plans in place for timely referral of critical patients to intensive care (4).

Adequate patient-centered (pediatric) intensive care is one further important link in the chain of survival. The care provided in (P)ICU is to a certain extent also based on existing guidelines but for the most critical patients it goes far beyond, relying on the expertise of the teams involved and the available specific resources. (P)ICU teams are multidisciplinary, primarily consisting of (pediatric) intensivists and intensive care nurses, but at all times supported by all relevant medical subdisciplines (infectiology, cardiology, nephrology, surgery…), as well as physiotherapists, psychologists, and social support.

Early rehabilitation is important and the necessary staff to facilitate this should be available (see Chapter 5). Teams should have timely access to all diagnostic (imaging, microbiology, biochemistry…) and therapeutic (cardiorespiratory support, renal replacement therapy) resources when needed. Laboratories need to organize their processes so that preliminary and final results of blood cultures can be communicated as soon as possible to the treating physician, as studies have demonstrated a positive impact on the patient's outcome.

ICU (and pediatric ICU) should have specific -where possible, evidence-based- procedures in place to care for the critical sepsis patient. These procedures include at least antibiotic management (considering focus, resistance patterns, presumed causative agent, patient factors…), patient isolation, early source control, advanced organ support, family-centered care and early rehabilitation (3, 4, 29, 30). Specific patient

populations such as children or neonates, or those with refractory shock, needing organ support or extracorporeal membrane oxygenation, demand early referral to a dedicated highly specialized P/NICU and each P/NICU should have plans and collaboration agreements to allow for this (31, 32).

As indicated above, truly improving outcome demands not only a focus on science but equally on education and implementation strategies. Providing education on sepsis and (early) treatment has proven to be a crucial yet challenging step (33, 34). Interventions delivered via an active learning approach (simulation, game-based learning) seem to produce greater gains, especially if accompanied by dedicated sepsis care implementation strategies (35). Digital learning has taken flight in the last years and might be as effective as 'traditional' education in terms of behavior change, satisfaction, knowledge, and skill improvement (36). Local champions might be pivotal in such a change trajectory (37). Importantly, sepsis care is team-based and team approach, (interprofessional) communication and crew resource management should be an integral part of any training and subsequent implementation (18, 35). Within a team, each member has his task and should be trained to that extent. As such the training of the 'basic' provider will inherently differ from that of the 'advanced team' member. Decay of knowledge and skills within months or years of training is well-described and as part of an implementation strategy, procedures should be in place to facilitate life-long learning, rather than one-off initiatives (38, 39).

Currently there is no single optimal strategy described in the literature to implement early adequate sepsis care. If a new strategy is implemented, it should also focus on usability and usefulness, the experience of the user and the coherence with common objectives for nurses and physicians. It should highlight its ability to be time saving and to improve professional control and cross-professional collaboration (40, 41). It should equally include junior and senior staff to reduce heterogeneity in practice among physicians with various levels of experience. Combining educational programs and clinical decision support tools appears to be very effective (42, 43). For example, implementing a nurse-driven screening tool and management protocol to identify and initiate early treatment of patients with sepsis together with a computer-assisted screening algorithm that generates a sepsis alert for treating clinical healthcare providers and an automated suggested sepsis-specific order sets for initial workup and early therapy, increased compliance to the sepsis bundle from 28% at baseline to 71% (44). Overcrowding at the ED and at the ICU can have a negative impact on guideline adherence (41, 45). Realtime electronic surveillance might help in such situations, yet studies have failed to confirm this potential positive effect so far (46). Further identified barriers to guideline implementation are either patient-related (advanced age, comorbidity, cryptic

shock…) or organizational (clinician inexperience, lack of interprofessional collaboration, interhospital transfers, staff shortage, lack of meaningful real-time metrics…) (41, 47, 48).

Recommendations

1. At the 'Basic' level, large scale education of all relevant healthcare providers in early recognition and 'basic' treatment modalities. This education should be included in the general training for any (para)medical degree, as well as in on-site life-long learning. Systems should guarantee this 'basic' training and also provide their healthcare providers with tools and SOP to allow for 'timely' alarming of 'advanced' care providers and providing appropriate early 'basic' sepsis treatment (e.g. antibiotic guidelines, isolation practices, culture sampling and processing…). They should also guarantee sufficient staffing and resources to do so. Specific procedures should be in place for specific populations and circumstances such as young children, the elderly, or those institutionalized or immune-depressed... Systems should develop specific implementation strategies to create awareness, knowledge and skills and thus improve care at the 'basic' level within their organization.
2. Systems should also guarantee the 24/7 availability of specifically trained 'advanced' care teams that can provide early 'advanced' interventions at the bedside outside of the (P)ICU environment. SOPs should be in place to clarify indications and communication pathways for 'basic' providers to contact these 'advanced' teams. The minimum qualifications for such teams should be defined by law.
3. ICU (and PICU) should have specific -where possible, evidence-based- procedures in place to care for the critical sepsis patient. Specific patient populations -such as children or neonates, or those with refractory shock, needing organ support or extracorporeal membrane oxygenation- demand early referral to a dedicated highly specialized (P)ICU and each (P)ICU should have plans and collaboration agreements to allow for this.
4. The public health authorities should follow up on these requirements but also provide sufficient financial support to allow systems to implement these (in terms of staffing and resource use). Improving the care provided to sepsis patients is likely to be cost-effective when it subsequently has a positive impact on mortality and/or on ICU length of stay or long-term morbidity, or more specifically on the appropriateness of testing or antibiotic use. To do so, the government could specifically subsidize the implementation of 'advanced response teams' within any healthcare environment; subsidize efforts to improve antibiotic stewardship and provide free access to

national antibiotic guidelines; identify and subsidize the role of tertiary care (P)ICU in referral pathways for specific subpopulations, such as children, including the necessary highly- specialized emergency transport. All of this could be done as part of an **overall 'Care Program ('Zorgprogramma/ Programme des soins') Sepsis'** that covers the whole spectrum of care and defines the locoregional requirements for this; the above mentioned requirements could be translated into a set of quality indicators.

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Chapter 5. Post-sepsis care and rehabilitation

5.1 Burden and risk factors of post-sepsis sequelae (physical, mental, neurocognitive)

What are post-sepsis long term sequelae?

Persons hospitalized due to sepsis have an increased risk of readmission due to infection, cognitive impairment, mental and immunological problems, renal failure, and cardiovascular events compared to non-sepsis hospitalized persons, as well as a higher risk of reduced quality of life and death (1-5). Thus, in addition to the physical problems sepsis survivors face, they often suffer from cognitive and emotional disorders. It is important to pay sufficient attention to these, as they have a significant impact on quality of life and social participation, potentially precluding previously employed patients from returning to work after hospital discharge (6-10).

A. Physical impairment

Patients may encounter various physical challenges, ranging from new functional limitations, both peripheral muscle weakness and respiratory muscle weakness (11-13), to amputations and cachexia. Critical illness polyneuropathy and myopathy can manifest, alongside functional dependence and reduced endurance. The aftermath of sepsis often involves profound fatigue, affecting a significant percentage of survivors during the initial year following hospitalization (14). Additionally, dysphagia may arise as a complication (15, 16).

B. Cognitive impairment

Regarding neurocognitive impairments, dysfunctions were observed in the areas of attention and information processing, visuospatial or visuoperceptual, memory and executive functions. The following hypotheses have been raised to explain these phenomena: a reduced hippocampal volume, a breakdown of the blood-brain barrier with cerebral inflammation, septic encephalopathy, cerebral ischemia due to hypotension, hypoxia and microvascular occlusion due to disseminated intravascular coagulation (multiple) infarcts are reported (17-19).

C. Emotional impairment

Mental health and overall wellbeing may be affected, with depression impacting a notable portion of survivors (14). Anxiety and posttraumatic stress symptoms or syndrome are also prevalent (6, 20).

D. Physical impairment

Sepsis survivors are at significant risk for multi-organ and systemic sequelae. Furthermore, they may experience exacerbation of existing medical conditions, necessitating vigilant attention from caregivers such as general practitioners and physiotherapists. There is also an elevated risk of cerebrovascular and cardiovascular events post-sepsis (21, 22). Controlling chronic conditions like heart disease, diabetes, lung issues, and renal problems may pose difficulties in the aftermath of sepsis (23).

How many sepsis survivors have long-term sequelae?

50% to 75% of sepsis survivors develop at least one new medical, psychological, or cognitive diagnosis after hospital discharge. Only half of the sepsis survivors (both ICU and non-ICU) achieve complete or near-complete recovery within two years after hospital discharge. On the other hand, one in six patients experiences persistent impairments. One third develops a new nursing care dependency. Sepsis survivors are at risk for rehospitalization, recurrent infections and chronic illness and have a shorter life expectancy, and lower quality of life. Three out of ten will die during the first year after sepsis (4, 6, 24).

Duration of the sequelae

Sepsis patients have an increased risk of long-term consequences on the physical level but also on the psychological, emotional, and cognitive levels. Quality of life can decrease significantly in sepsis survivors and their caregivers ranging from six months up to ten years, in the worst case sequelae can persist for life. Health related QoL can remain impaired at ten years after ICU discharge compared with pre-admission values and an age reference population (6, 8, 25, 26). In worst case the sequelae last for the rest of life.

Risk factors of post-sepsis long term sequelae

The following risk factors are reported for developing critical illness weakness: older age, more specific older than 80 years, pre-existing comorbidity, prolonged duration of mechanical ventilation, the duration of sepsis and associated organ dysfunction, female gender, elevated blood glucose levels, prolonged immobility and deep sedation, administration of vasopressors, inadequate delivery or absorption of nutrients, renal failure, low levels of albumin in the blood, hyperosmolarity, hospital acquired infections and systemic inflammatory response syndrome (SIRS) (24, 27). The role of neuromuscular blockers and

steroids is uncertain (28). It seems important to limit parental nutrition in the first week of ICU admission as the catabolic state cannot be reversed by nutrition and enteral feeding should only be started after hemodynamic stabilization on a stepwise basis with a hypocaloric target in the acute phase. After the acute illness isocaloric feeding can be implemented. Of course, physical therapy will promote the beneficial effects of nutrition (29).

Diagnostics

There is a risk for cognitive deficits and emotional disorders in patients, as well as emotional disorders in family members to be diagnosed late, as the initial focus will be on organ failure and somatic complaints of the sepsis patient. First, ideally every sepsis patient should receive a brief screening in terms of cognition and mood. This screening can then inform whether further diagnosis and treatment in one or both domains is desirable or appropriate. If, for practical reasons, standard screening cannot be conducted, it is relevant that appropriate neuropsychological care is provided based on the informed patient's own perceived difficulties, and the symptoms noted by the treating team. For this reason, it is important that each patient and their close relatives receive psychoeducation about the possible symptoms and consequences post-sepsis, and the care that can be offered for them.

The recommended neuropsychological assessment for cognition (30), along with the brief screening instrument (MoCA), are shown in Table 5.1. If necessary, the neuropsychologist can add specific tests to the recommended list based on his or her own insights. To further supplement the diagnostics, the self-report list 'Checklist for cognitive consequences after ICU admission' (CLC-IC) (31, 32) and the 'Fatigue Severity Scale' (FSS) can be used (33, 34).

The brief screening for emotional disorders is based on two questions of the Generalized Anxiety Disorder scale (GAD-2) for anxiety and on two questions for depression by using the Whooley questions (35). This can be done as soon as the patient is cooperative. The recommended diagnostics for emotional disorders after ICU admission are the Hospital Anxiety and Depression Scale (HADS, 36), The Primary Care Post Traumatic Stress Disorder screen based on the Diagnostic and Statistical Manual-5 (PCPSTD DSM-5, 37), Body Sensations Questionnaire (BSQ, 38), Pittsburg Sleep Quality Index (PSQI, 39) and Quality of life testing can be done by the TNO-AZL Adult Quality of life questionnaire (30, 40-43).

Cognitive functions	Test
General screening	Montreal Cognitive Assessment (MoCA, www.mocatest.org)
Memory	Rey Auditory-Verbal Learning Test (AVLT)
Executive + Attention	Trail Making Test A-B (TMT) Stroop Test Digit Span WAIS Digit-symbol coding WAIS
Visuospatial	Judgement of Line Orientation (JLO)
Language	Boston Naming Task (BNT) Letter Fluency Category Fluency

Table 5.1. Recommended cognitive diagnostics (30).

The emotional well-being of close relatives also warrants significant attention. They frequently experience emotional disturbances and a diminished QoL due to the severe medical history and PICS affecting their loved one, this is called PICS-F. It is advisable to implement the same brief screening for anxiety and depression used for patients in the assessment of PICS-F. Additionally, if necessary or suggested, employing the more comprehensive diagnostic tools mentioned above is appropriate for close relatives as well (44).

Economic impact of the post-sepsis long term sequelae

Due to the high mortality rates within the first-year post-hospitalization, there is a significant loss of productivity within the community (45). Increased morbidity also contributes to lower employment rates, with nearly half of sepsis survivors who were previously employed remaining unemployed after recovering from an ICU-admitted sepsis episode (46-48). The reported decrease in Quality of Life underscores the ongoing need for assistance across both mental and physical domains as individuals strive to regain normalcy in their lives (8, 46, 49). Consequently, healthcare consumption remains elevated, with frequent unplanned rehospitalizations being reported (23, 50). It's noteworthy that 70% of the total costs associated with sepsis are indirect, and some authors argue that the indirect burden of sepsis could be four to seven times higher than that of chronic heart disease and stroke (51).

For detailed discussion, calculation and estimation of the cost of sepsis or sepsis survivors to society, we refer to the dedicated section on the burden of sepsis in the Introduction. The burden is very high and underscores the importance of prevention of sepsis and multidisciplinary rehabilitation interventions on short-term and after discharge from ICU and from hospital.

5.2 Effective interventions to improve the long-term outcome of sepsis survivors. How can discharge planning and transmural post-sepsis care be improved and more patient-friendly?

By implementing a multidisciplinary approach, injury in sepsis can be mitigated and improve outcomes. The cornerstone of treatment is the early administration of appropriate antibiotics, coupled with optimal supportive care. This includes titrated oxygen therapy, fluid resuscitation, and the timely administration of vasopressors to stabilize hemodynamics. Additionally, once hemodynamically stabilized, early nutritional support is crucial for patients with sepsis. Strategies aimed at improving mitochondrial function and enhancing immune function play a vital role in reducing sepsis-related injury (29). Furthermore, prioritizing the prevention of sepsis and its recurrence is essential. This involves implementing antibiotic stewardship programs to ensure judicious antibiotic use, promoting hand hygiene practices, encouraging vaccination against common pathogens, and creating awareness among the population about the signs and symptoms of sepsis (6).

5.2.1 Physical rehabilitation

In the initial ten days following admission to the ICU, there is a notable loss of muscle mass, amounting to approximately 30%. The Rectus femoris muscle is among the first affected. Engaging in early rehabilitation efforts yields positive outcomes, both in terms of preserving muscle mass and reducing ICU-related complications (52).

Early mobilization typically begins between the second and fifth day after ICU admission, with the pre-existing condition of the muscles playing a crucial role in the process (53). This proactive approach to rehabilitation can lead to various benefits, including shortened ICU stays, reduced incidence and duration of delirium, increased walking distance, and improved functional status upon discharge. Moreover, it can contribute to the normalization of blood pressure and enhance overall QoL, ultimately resulting in improved long-term survival rates up to three years post-sepsis without incurring additional healthcare costs (54).

Research indicates that early rehabilitation interventions also mitigate short-term weakness (55-58). Establishing rehabilitation goals within four days of ICU admission or prior to discharge is recommended, with input from patients and/or their caregivers (59). Furthermore, early initiation of physical therapy during the initial week of septic shock is deemed safe and effective in preserving muscle fiber cross-sectional area, leading to improved short-term physical outcomes and functionality (60-62).

Mobilization is defined as physical activity sufficient to elicit acute physiological effects that enhance ventilation, central and peripheral perfusion, circulation, muscle metabolism and alertness and are countermeasures for venous stasis and deep venous thrombosis (58). Mobilization can be initiated and combined with several therapeutic strategies. Passive mobilization (63), changing the position, passive to active cycling episodes (60, 62, 64), neuromuscular electrical stimulation (65-67), respiratory muscle training (68).

We propose a weekly bedside tour with the whole multidisciplinary team were individualized program is installed and if needed adapted. This program can combine therapies (60, 68). The implementation of multidisciplinary mobilization protocols is recommended to ensure safety and the systematic implementation of multiple interventions tailored to each level of activity (69, 70).

Passive and passive-to-active

Passive mobilization techniques involve the application of external force and are utilized for patients who are unconscious or lack the ability to mobilize actively. One basic method is manual mobilization of each limb, referred to as Passive Range of Motion (PROM), involving at least 10 repetitions of each full joint movement to maintain flexibility and prevent muscle shortening due to prolonged immobility. Motorized devices, such as continuous passive motion (CPM) devices and motorized pedal exercisers, allow for passive mobilization of isolated segments. CPM devices facilitate continuous passive motion, while motorized pedal exercisers, enable passive and/or active mobilization of both lower and upper limbs for bedridden or seated patients (62, 71). Studies have shown that very early passive and passive-to-active cycling exercises in mechanically ventilated patients are safe and do not significantly affect hemodynamic, respiratory, or metabolic variables, even in patients requiring vasoactive agents (60, 63).

Positioning

Transitioning from the supine to upright position can have notable effects on both axial and respiratory musculature, promoting arousal and cognitive activation. For patients who are non- or partially participating, achieving position changes can be facilitated by using motorized lifts to transfer them to a chair, adjusting the bed to a chair position, or employing a tilt table (72).

Passively positioning patients upright, whether seated or standing, can also help to open dependent lung zones by elevating the thorax, as observed in studies by Dellamonica (2013) (73). This upright posture has a beneficial impact on oxygenation, particularly when combined with passive or active mobilization techniques (74).

Physical exercise or active mobilization

Physical exercise, also known as active mobilization, involves activities that induce metabolic changes and require patient participation (75). This includes movements against gravity or resistance imposed by a therapist, as well as the use of motorized devices like cycle ergometers for resistance training (62).

Research supports the benefits of active mobilization over passive mobilization. It contributes to preserving muscle mass, strength, and functionality in critically ill patients, leading to shorter durations of mechanical ventilation and hospital stays (60-62, 76, 77).

Early mobilization within 48–72 hours of mechanical ventilation initiation is associated with improved clinical outcomes (78). Patients, especially those with sepsis, may benefit most from mobilization within 2–4 days of ICU admission (79). Longer mobilization durations, exceeding 40 minutes, positively impact functional outcomes at ICU discharge (80).

Electrostimulation

The difficulty in eliciting active efforts from patients in the early stages of critical illness has prompted the search for solutions aimed at mimicking muscle contraction or boosting minimal metabolic effects. Among these methods, the most common is neuromuscular electrical stimulation (NEMS). Its principle of operation relies on the activation of superficial muscles by external electrical currents (81). An association between its use and the prevention of muscle wasting or weakness has been demonstrated in different types of patient populations, including those in ICUs (82-84). Routsi et al (85) also showed that NMES could prevent ICU AW in critically ill patients. New cycle ergometers models allow for the combination of pedaling with screens that display interactive courses and/or adding Functional Electrical Stimulation (FES). The current state of knowledge does not allow for the identification of critical patients who would be most likely to benefit from this approach, although it appears that older patients are less likely to benefit from it. Electrostimulation should start as soon as possible since muscle fiber degradation and reduction proceed from day one in ICU (81). Monitoring creatine kinase during routine blood work is suggested to identify early side effects of EMS including rhabdomyolysis.

5.2.2 Occupational therapy

Occupational therapy in the ICU is vital for the recovery of critically ill patients within the multidisciplinary team. It takes a holistic approach, enhancing patients' strength, cognition, and functional independence in activities of daily living (ADLs) and mobility. This leads to reduced incidence and duration of delirium, decreased time on mechanical ventilation, shorter hospital stays, and cost savings (86, 87).

Tasks include functional activities like active upper limb exercises, ADL training, and transfer training to maintain mobility and prevent complications like nerve injury and contractures (88). Occupational therapists also manage environmental controls, communication skills, and basic adaptations such as using adapted cutlery and ergonomic measures.

Cognitive training focuses on assessment and intervention to improve functions like orientation, memory, attention, and problem-solving skills. This therapy reduces delirium duration and incidence in non-ventilated patients, enhancing functionality at discharge.

Incorporating video games and virtual reality into therapy enables endurance, balance, and coordination training for conscious patients, including those on mechanical ventilation. These interventions are feasible and safe, offering adaptable scenarios to encourage mobility and cognition, potentially reducing anxiety, and improving respiratory dynamics (89, 90).

Music interventions decrease heart rate and blood pressure, due to lower sympathetic drive. It activates areas of the brain involved with memory, cognitive function and emotion (91).

Occupational therapists also provide crucial support and communication with the patient's family.

5.2.3 Screening for dysphagia

Systematic screening for dysphagia is recommended in all sepsis patients. Being mechanically ventilated or experiencing severe critical illness are two major risk factors for dysphagia (92). The relevant presence of ICU acquired weakness will affect the swallowing apparatus. Also contributing is the presence of reduced consciousness, that can further increase the risk for aspiration and may delay therapeutic measures for dysphagia (93-94).

The diagnosis of dysphagia can be made using non-instrumental tests and instrumental tests (92, 94). A non-instrumental test provides a comprehensive swallow evaluation conducted by a trained speech pathologist to diagnose swallowing impairments and safely facilitate the transition to oral intake (95). The

instrumental test, flexible endoscopic evaluation of swallowing (FEES) may be regarded as the gold standard of dysphagia assessment in the critically ill. (FEES can be performed at the ICU bed using a small flexible endoscope passing through a nostril into the epipharynx so that the oro-/ hypopharynx and the glottic area can be visualized.) Using a multicolor dye technique, testing of different food consistencies can be performed (92). It provides detailed diagnostic information and guides swallowing management. In addition, dysphagia was associated with longer hospitalization, more discharges to a nursing home, and increased need for placement of a feeding tube. Evidence for dysphagia treatment, especially in dysphagia-positive ICU patients, is limited. Generally, three major therapeutic pillars for dysphagia treatment are considered: dietary texture modifications, postural changes/compensatory maneuvers, and interventions aiming to improve swallowing function (92).

Dysphagia should be routinely screened in sepsis patients in the ICU. In sepsis-survivors speech language therapy incorporated in a swallowing rehabilitation program must be implemented to restore dysphagia and by this the nutritional status, moreover, improving the comfort of the patient and the QoL.

5.2.4 Psychological and neuropsychological care post-sepsis

In the scientific literature, the (neuro)psychological disorders (neurocognitive and emotional) post sepsis came to attention relatively recently. Moreover, they have not always been thoroughly investigated. In the remainder of this paragraph, recommendations will be made to identify such disorders. We will discuss cognitive disorders on the one hand, and emotional disorders on the other.

Since sepsis is one of the leading causes of admission to an ICU, the PSS following hospitalization in ICU is an example of Post-Intensive Care Syndrome (PICS), and more recent scientific literature has appeared on PICS following the COVID-19 crisis (Post-COVID-19 Syndrome after admission to IC is also an example of PICS), we describe the neuropsychological care (both cognitive and emotional) for sepsis patients based on guidelines and best clinical practice in PICS (40).

The PICS model (42) broadly summarizes patient characteristics, in addition to focusing on the close relatives. It provides good guidance to systematize the treatment pillars, see Figure 5.1 for an adapted version.

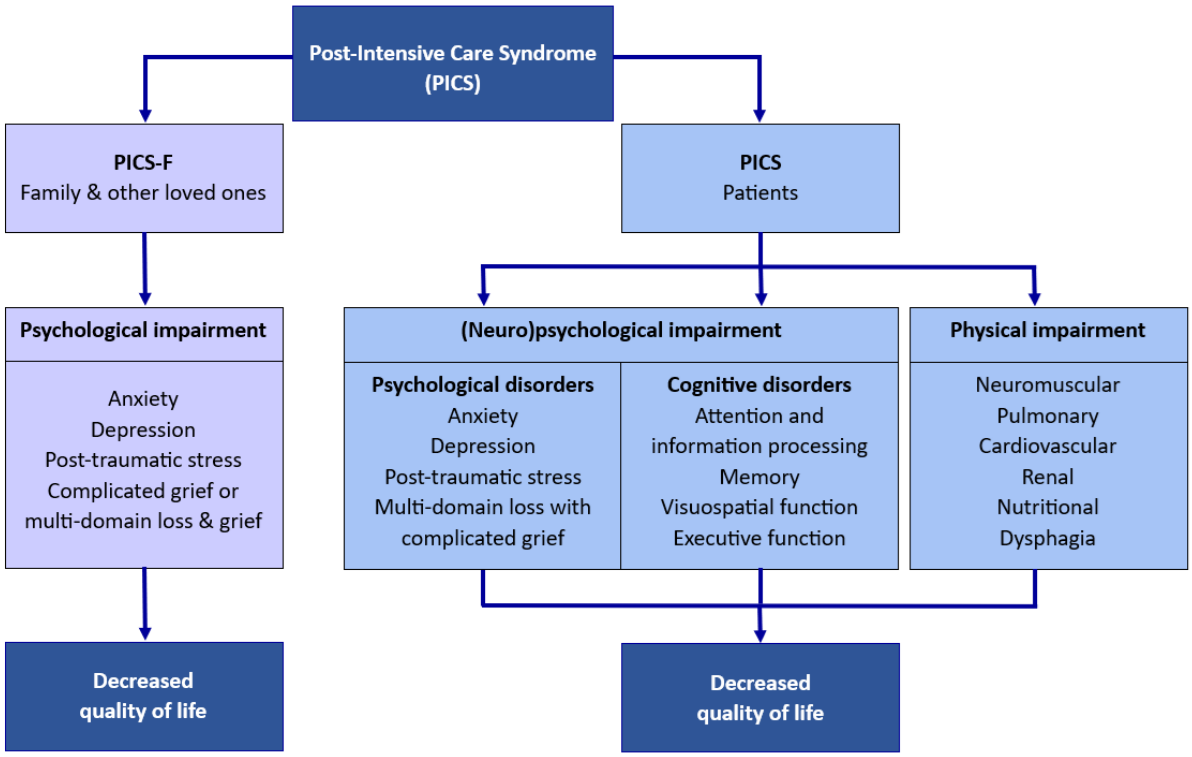

Figure 5.1. The PICS model (adapted from Randall, 2016, in Burdick et al.) (42).

In addition to medical care coordination and follow-up of multi-organ and systemic consequences post sepsis, interdisciplinary patient-centered rehabilitation fits with the PICS model, initiated as soon as the patient's health status allows. To the pillar of physical rehabilitation, the cognitive and emotional pillars of neuropsychological rehabilitation are added, as cognitive and emotional disorders contribute to reduced quality of life and are often limiting recovery (40, 96-98).

The treatment components result from the findings of the neuropsychological examination and can contain the following care:

- Information & psycho-education based on the neuropsychological examination and about PICS
- Interdisciplinary integration of and systematic build-up in cognitive rehabilitation
- Individually tailored training of strategies for coping with or compensating for cognitive difficulties
- Involvement of close relatives for explanation and recommendations on neuropsychological functioning
- Coaching in terms of energy balance, sleep, coping with experienced difficulties such as sensory sensitivity and mental fatigue

Emotional disorders in patients

The treatment components of psychological/psychotherapeutic care for emotional distress (40, 41, 99, 100) are individually tailored based on the patient's needs and clinical judgment and guided by the results of the questionnaires and include the following:

- Psycho-education on Post-Intensive Care Syndrome (PICS)
- Focusing on resources, resilience, coping skills
- Clarifying specific symptoms, vulnerabilities, reassurance on emotions and characteristics
- Interventions to increase self-efficacy and confidence in own abilities
- Training in mindfulness and/or relaxation techniques
- Counseling for the adjustment process, grief and loss experiences
- Integrating fragmentary and severe experiences, e.g. while using the diary about the IC stay (involvement of family, especially in case of memory loss)
- Eye Movement Desensitization and Reprocessing (EMDR), Acceptance and Commitment Therapy (ACT), body-oriented and/or cognitive-behavioral approaches for the integration process, for PTSD, anxiety/tension and/or depression

Emotional disorders in close relatives

Because a significant number of close relatives struggle with emotional disturbances following the admission of their loved one to ICU, it is relevant that the care process is taking them into account (40, 42, 100). It is helpful to inform and involve the relatives as much as possible. Next, keeping a diary is helpful, this can be done by the patient's network, the medical team, hospital psychologist,...). It can be shared with their loved one later on. Psycho-education, psychosocial information and support are important as well. Provide, for the first time, information about Post-Sepsis Syndrome (PSS)/PICS-F at discharge from Intensive Care to install awareness and recognition of symptoms. This can be done by a brochure.

The emphasis is on emotional support and psychoeducation. There is also a need for psychological and psychiatric assessment to identify certain vulnerabilities (lack of a network, previous addiction problems,...). These vulnerabilities (and, conversely, strengths) are important elements both in the acute phase and in the longer term.

The brief screening for anxiety and depression, as used in patients, is also recommended in PICS-F. When needed or indicated, the more extensive diagnostic tools listed above in diagnostics of emotional disorders in patients, and the psychological and psychotherapeutic interventions described for the patients with emotional disturbances, are suitable for the close relatives too.

5.2.5 Post-sepsis discharge planning and support

Given the broad spectrum of possible post-sepsis impairments, the high risk of rehospitalization and the life-changing impact of sepsis on survivors and caregivers, both have an obvious need for structured aftercare and support.

There is a paucity of studies evaluating current levels of patient education or ancillary services provided for sepsis survivors. Nevertheless, an international survey suggests a need for improved management after hospital discharge. The study emphasizes the overall low satisfaction rate of survivors and the need for healthcare practitioners and their hospitals to strengthen support to them (Figure 5.2).

This need for better sepsis support is confirmed in a recent German cohort study of adult ICU-treated sepsis survivors and their caregivers. In this study three core categories were defined of unmet needs (a) sepsis knowledge, (b) in-patient rehabilitation after hospital discharge, and (c) aftercare and structural support frameworks (101). Current thinking suggests that endpoints like mortality or rehospitalization may be unavoidable or undesirable for seriously ill patients with declining health. Instead, focusing on comfort and function-oriented outcomes may be more relevant (102).

Given the absence of a Belgian post-sepsis policy management, the absence of post-sepsis discharge planning and leaflets describing the issues of sepsis survivorship and the cries for help from sepsis survivors addressed to the Belgian patient association Sepsibel vzw after the Pano documentary, we can assume that the need for structured sepsis aftercare and support is also present among Belgian sepsis survivors.

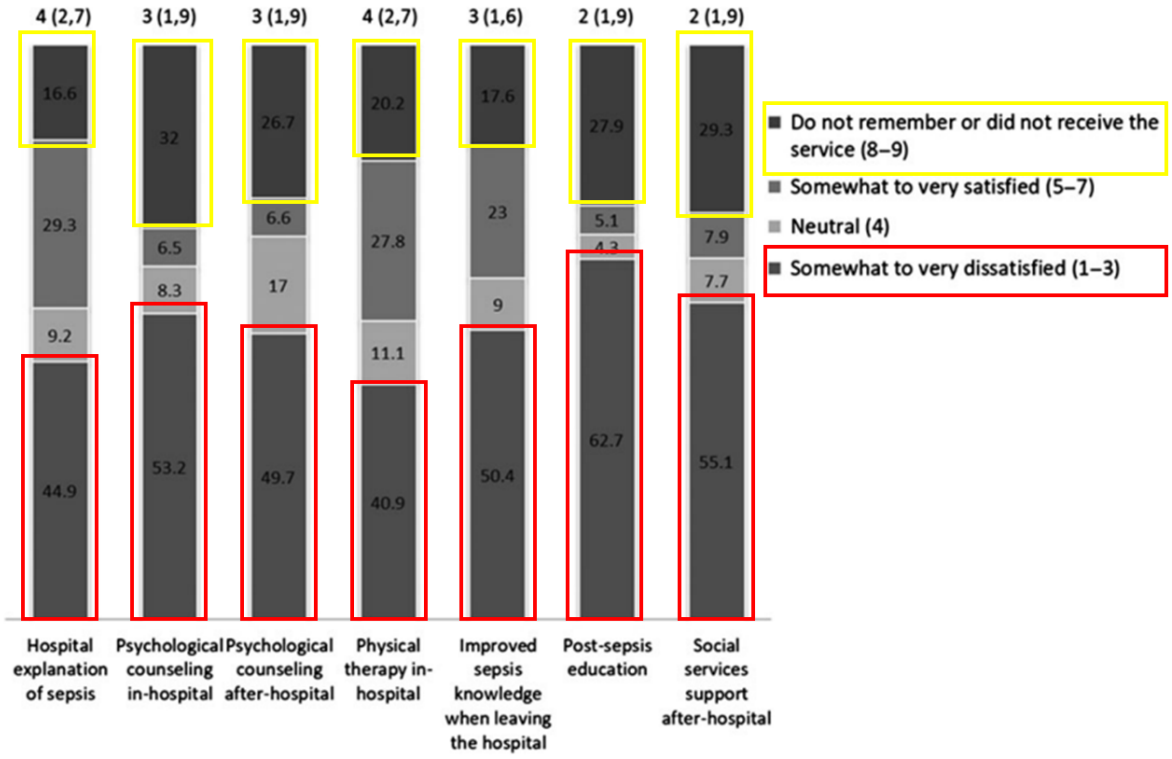

Figure 5.2. Survivor satisfaction with hospital services (10).

Personalized, patient-centered approach

There is limited clinical trial evidence to guide management of patients after hospitalization for sepsis. Despite the lack of high-quality evidence, several expert panels suggest that rehabilitation with physical, occupational, and speech therapy benefits patients who develop new weakness following sepsis. This recommendation is supported by an observational study involving 30 000 sepsis survivors that found that referral to rehabilitation within 90 days was associated with lower risk of 10-year mortality compared with propensity-matched controls (103).

Given the large interindividual differences in clinical presentation and outcomes among patients with an infection and sepsis, a one-size-fits-all approach is unlikely to benefit every patient. Research around tools helping to predict the needs after sepsis is necessary. Those tools, such as endotype stratification, could help to detect patients at higher risk for long-term sepsis outcomes (104-106). Until those tools become available, it seems most appropriate to invite all patients with sepsis in hospital, either being admitted to the ward or ICU, to a post-sepsis outpatient clinic to be seen by a consultant in general/internal medicine, geriatrics (in case of frail or older persons), general practitioner of family doctor.

Screening medical condition	Assess patients' risk of common and potentially preventable causes of hospital readmission (infection, congestive heart failure exacerbation, acute renal failure, chronic obstructive pulmonary disease exacerbation, and aspiration pneumonitis) and tailor medical care to anticipate and prevent these problems
Medications	All current medications, potential side effects and interactions. Critically review (contra-)indications, assess cardiovascular risk and adjust medication where necessary, while taking frailty and polypharmacy into account as trigger to deprescribe.
Functional assessment	Mobility, activities of daily living, rehabilitation needs and ability for improvement (eg, consider physiotherapy or referral to rehabilitation physician).
Psychological and Cognitive Evaluation	Depression, anxiety, PTSD, cognitive impairment (eg, MoCA or MMSE), delirium during hospitalization (risk factor for future delirium), mental health support and requirement (eg, consider referral to(neuro) psychologist).
Nutritional Assessment	Current nutritional status (eg, MUST, SNAQ), dietary advice or interventions (eg, hand out information, refer to online documentation or refer to dietician).
Lifestyle and Social Assessment	Smoking, alcohol and illicit drug use, physical activity, social support network, return to work planning.
Self-management Education of sepsis Support groups	Patients and caregivers should be educated about sepsis including common sequelae and informed of peer support resources.
Referrals	Because of the heterogeneity of potential problems after sepsis, clinicians may consider early referrals to multiple subspecialists and ancillary services. Clinicians should avoid overly complex treatment plans and should consider starting with 1 or 2 referrals to address the most significant symptoms, then place additional referrals over time.
Establishing Goals of Care	Given the high rates of death, disability, and health care use after sepsis, it is important to discuss goals of care and consider whether a palliative focus is appropriate, in particular for patients with declining health prior to sepsis.

Table 5.2 Elements of Post-Sepsis Outpatient Follow-Up by a Clinician (adapted from (6)).

Return to work after critical illness

Returning to work after critical illness is a difficult process with significant implications for patients' quality of life. Failing to resume work under the same conditions or needing to change jobs can lead to (financial) stress, depressive symptoms, and has broader economic consequences. Only 40%-60% of patients can return to work, not necessarily in the same working regimen. Age, gender, comorbidities, level of education, severity of condition, prior major life events are co-determinants in the likelihood of returning to work. Physical ability and cognitive functioning impact work resumption, albeit at different stages of recovery. Early rehabilitation is crucial. It should address both neuropsychological/cognitive impairments and physical limitations. Evaluating the work situation promptly is useful to identify the necessary skills. A multidisciplinary rehabilitation program is useful to promote return to work. A multidisciplinary team may include doctors, ICU nurses, occupational therapists, physiotherapists, neuropsychologists and social workers. It is crucial to establish a post-discharge care pathway to ensure follow-up and identify any persistent issues or needs and to promote return to work (46, 107-111).

5.3 Post sepsis trajectory of specific patients groups

5.3.1 Older persons

People over 65 are 13 times more likely to develop sepsis. A holistic approach is essential (we refer also to Chapter 6 on Advanced care Planning), taking into account frailty, comorbidities, patient values, and the limited applicability of available evidence and guidelines. There is an increased demand for ICU for old intensive care patients (80 plus) over the last years. Determining the health status 14 days prior to hospital admission is essential to assess the patient recovery capacity. The clinical Frailty scale, cognitive decline and sarcopenia are required to make the decision. Shared decision making (with involvement of the patient and his family) should start long before ICU admission. (52, 112) The geriatrician plays an important role in this process. Importantly, the patient's expectations and understanding of the scope of ICU support should be explored. The uncertainty about survival in ICU is at its peak for old patients with marked geriatric features. The 6 months survival for elderly following ICU ranges from 30- 40%. Mortality stays higher in the years following ICU. PICS occurred in 45% elderly with highest prevalence of depression, anxiety, frailty, and posttraumatic stress disorder. Nutritional support, early mobilization and education can improve the functional outcome and quality of life (113, 114). Early rehabilitation exercises were found to be beneficial to the recovery of autonomic blood pressure in elderly patients with septic shock and shortened the time of norepinephrine use and ICU stay (52).

5.3.2 Pediatric sepsis patients

5.3.2.1 Burden and risk factors of pediatric post-sepsis sequelae

Sepsis and septic shock have been identified as one of the leading causes of childhood mortality. As seen in critically ill children overall, mortality has been greatly reduced in pediatric sepsis over time, but it is well established that many pediatric survivors will experience long-term disabilities, higher readmission rates, and overall poorer health status (115). Until the past decade, little was known about pediatric post-sepsis sequelae and morbidity. In recent years clinicians and researchers have made great efforts to fill this knowledge and research gap. Those works have put in light the long-term effects on physical, psychosocial, educational, and family functioning of pediatric sepsis.

Recent prospective data reported that up to 28% of children surviving sepsis developed a new disability by the time of hospital discharge (116) and that this population also seem at higher risk for readmission (117, 118), with recent data reporting a readmission rate at 30 days of more than 15% in children surviving severe sepsis (118).

Among sepsis survivors of an American prospective cohort, 35% demonstrated significant health-related quality of life (HRQL, including four domains: physical, emotional, social, and school functioning) deterioration compared to baseline persisting for at least 1 year following hospitalization (119). Risk factors included severity and duration of organ dysfunction, adverse neurologic events during PICU admission (120) and changes in functional status compared to baseline (121).

Although most families seem to have resilient trajectories after septic shock, a subset of families can demonstrate persistently elevated distress and family dysfunction (121). This suggests a need for family-based psychosocial screening after pediatric septic shock to identify and support families at-risk (122).

Finally, neurophysiological and academic difficulties have also been described after sepsis. Retrospective data showed that pediatric septic shock survivors' cognitive function was significantly lower than the norm population with young age as risk factor (123). Although admission to the PICU is reported to be associated with deficits in neuropsychological performance and educational difficulties, more severe difficulties are noted following meningoencephalitis and septic illness (124, 125).

Yet not all children receiving treatment for sepsis require an ICU admission. To date, follow-up studies have only focused on PICU cohorts. A study designed to provide a comprehensive understanding of the long-term outcomes associated with pediatric sepsis survivorship in children treated in a non-PICU

environment is presently enrolling patients and will soon help understanding physical, cognitive, emotional and social outcomes in this specific population (126).

5.3.2.2. Effective interventions are to improve long-term outcome of pediatric sepsis survivors

Although long-term sequelae of pediatric sepsis are increasingly reported in the literature, presently, there is a lack of known effective interventions that improve these outcomes in the pediatric population. Since the concept of post intensive care syndrome (PICS), a group of cognitive, physical and mental health impairments that commonly occur in patients after intensive care unit discharge, is well-recognized in children, bundled care plans and support programs are proposed to improve patient recovery (127-129). In children following sepsis, two papers describe innovative post-sepsis follow-up and support programs. The first one describes the implementation of a follow-up program for pediatric sepsis survivors in the PICU of the Children's Hospital of Philadelphia. The Pediatric Sepsis Survivorship Program was led by a nurse coordinator who met with families to educate about sepsis and offer post-discharge follow-up. For selected patients, the nurse coordinator administered a telephone-based health assessment 2–3 months after discharge to screen for new needs and refer concerns to appropriate health care professionals. Although inspiring, such programs remain challenging in maintaining contact with families after hospital discharge and in generalizability to other healthcare systems as based on institutional resources and pre-existing outpatient programs (130).

The second one, The Queensland Paediatric Sepsis Program, is a family support structure (FSS) providing support to the child and family from acute phase of sepsis, to discharge and long-term recovery. This program has two goals: (1) creating psychological support through linkage with networks, peer mentor program, and direct contact with social work and (2) education about sepsis and post-sepsis support through online videos, websites, webinars, media, and public awareness campaigns. The FSS is delivered by a multidisciplinary team acting with clinicians local to the child (131).

Numerous studies have found that children have cognitive, physical, and psychiatric deficits after a PICU stay called the post intensive care syndrome. The effects of the full ICU liberation bundle in children have not been published, but in adults, bundle implementation resulted in significant improvement in survival, mechanical ventilation use, coma, delirium, restraint-free care, ICU readmissions, and post-ICU discharge disposition (132). The ICU liberation bundle is feasible in children and may ameliorate the effects of a PICU stay. Further studies are needed to characterize the benefits of the ICU liberation bundle in children, and how to continually improve follow-up programs and completion of follow-up (133-135). Parents, families,

and close relatives can also develop impairments. Beyond the psychological impairments, physical and socioeconomic threads can also affect quality of life and should be considered in post critical illness rehabilitation and outpatient programs (136). One obvious distinction to adult patients is the wide range of different developmental stages of children and the even closer relationship between patient and family. Therefore, efforts should be pursued to focus liberation bundles, rehabilitation and outpatients' programs on adjusting them for the entire pediatric age group. But also, on strengthening families' decision-making power, understanding parents as a resource for their child and involving them early in the care of their children (135, 136).

5.4. Milestones in the recovery of a sepsis survivor

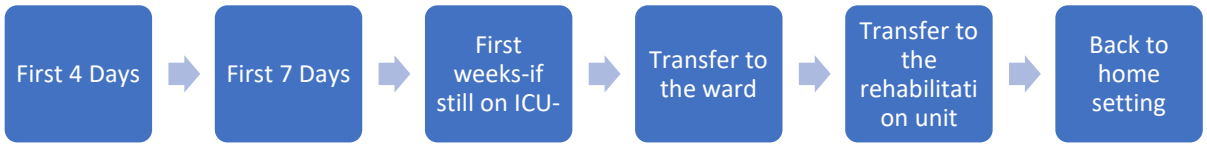

Figure 5.3. Milestones during recovery of a sepsis survivor.

First 4 days	● discuss rehabilitation goals within 4 days of arrival in intensive care or before discharge to a general ward. If this cannot be done with the patient, it can be done with his/her family and his/her carers.
First 7 days	● a first evaluation of the emotional, psychological and cognitive condition should take place. If the patient is not responsive or lucid, heteroanamnesis of closest relatives will be needed to elucidate relevant antecedents in these domains. ● provide psychosocial support of the patient as soon as he is awake and adequate ● provide emotional support of the patient's network ● encourage involvement of the patient's network such as extended visiting hours, writing in a diary by the patient's network, or the medical team, or the hospital psychologist,... ● provide first information about Post-Sepsis Syndrome (PSS)/PICS-F at discharge from Intensive Care, create awareness of and recognition of symptoms of PSS. ● the emphasis is on emotional support and psychoeducation. There is also a need for psychological and psychiatric assessment to identify certain vulnerabilities (lack of a network, previous addiction problems,...). These vulnerabilities (and, conversely, strengths) are important elements both in the acute phase and in the longer term.
First weeks -if still on ICU	● Mobilization plan needs to be individualized towards active mobilization and standing ● Dysphagia treatment ● Tracheal cannula care ● Psychotherapy or continuing psycho-emotional support ● Brief neuropsychological screening and cognitive training may start if possible.

Transfer to the ward	○ Patients are informed upon discharge to a general ward, about their specific problems and needs (physical, psychosocial, emotional, neurocognitive, communication and sensory) ○ On transfer, a formal handover is done with the staff of the general ward, where the rehabilitation goals are also discussed. A handover is best done in a structured way. It contains the following elements of the multidisciplinary team: ▪ summary of stay intensive care ▪ further follow-up examinations and tapering plan of medication ▪ psycho-therapy ▪ psycho-social support, family support ▪ neuropsychological assessment and support ▪ dietary support ▪ rehabilitation plan ▪ occupational therapy and cognitive trainings ▪ specific communication and language needs ▪ dysphagia treatment and tracheal cannula care if needed ▪ specific limb care or amputation care ▪ attention to initial symptoms of PSS or PICS and if needed start-up of extra specific therapy ▪ do not focus on physical recovery solely ▪ talk about 'normal life' and going back to it, skills needed to return to work or school remain long-term goals
Transfer to rehabilitation unit	● On transfer, a formal handover is done with the staff of the general ward and the rehabilitation unit, where the rehabilitation goals are discussed. A handover is best done in a structured way. It contains the following elements of the multidisciplinary team: ○ summary of stay in the hospital ○ further follow-up examinations and tapering plan of medication ○ psycho-therapy ○ psycho-social support, family support ○ neuropsychological reassessment and rehabilitation

	○ dietary support ○ rehabilitation plan ○ occupational therapy and cognitive training ○ specific communication and language needs ○ dysphagia treatment and tracheal cannula care if needed ○ specific limb care or amputation care ○ attention to initial symptoms of PSS or PICS and if needed start up of extra specific therapy ○ do not focus on physical recovery solely ○ talk about 'normal life' and going back to it, skills needed to return to work or school remain long-term goals.
Back to home-setting	● a formal handover is done with the staff of the rehabilitation unit and the general practitioner, home-physiotherapist and psychologist, and other caregivers are needed. The rehabilitation goals are discussed. A handover is best done in a structured way. It contains the following elements of the multidisciplinary team: ○ Physical and cognitive problems at the time of discharge and what to expect back at home ○ Impact of cognitive status on daily life functioning and options for neuropsychological care ○ Psychological and emotional impact and recovery (e.g. depressed mood, anxiety, nightmares, ...) ○ Information on medication and possibly specific nutrition ○ Information on restarting driving, work resumption, restarting school, home support, support for family
Follow-up appointment at 2-3 months after discharge.	● Regular check-ins are essential for monitoring progress and addressing any emerging needs. ● Ensure that patients have the option to self-refer for additional support or reassessment at any time.

Recommendations

These recommendations aim to improve the quality of life of sepsis survivors and their relatives, by ensuring that their complex needs are met in intensive care units, nursing wards, rehabilitation settings and after hospitalization.

I. Develop a multidisciplinary rehabilitation pathway for sepsis patients that encompasses the psychological, neurological and physical domains.

1. **Early and Individualized Rehabilitation Goals:**

   Within the first four days after admission due to sepsis, the goals of physical rehabilitation should be established in the physical domain. Physical rehabilitation is recommended once the patient is hemodynamically stable and starts with passive mobilization. Within the first seven days of this admission, a first evaluation of the emotional, psychological and cognitive condition should take place (see the PICS-model, Figure 5.1.). If the patient is not responsive or lucid, heteroanamnesis of closest relatives will be needed to elucidate relevant antecedents in these domains. As soon as the patient's health condition permits, screening and further assessment in the physical, psychological, psychiatric, and neuropsychological domains are necessary to refine and further individualize the rehabilitation goals.

2. **Clear Communication and Care Pathway – use the word sepsis and PSS.**
   - From the first consultation with the patient and/or his relatives, the term sepsis should be named and explained. An introduction to Post-Sepsis Syndrome (PSS) should be provided next, to clarify the rehabilitation pathway, highlighting how the multidisciplinary team can offer support individually tailored to the patient's needs.
   - Information (brochure 'life after sepsis') on long-term outcomes should be provided early in the patient treatment and rehabilitation process.

3. **Seamless Transition and Follow-Up:**

   A thorough handover from third- or second-line care to first-line care should take place. In addition, in the first months after hospital discharge, a strict monthly follow-up with re-evaluation is needed, with adjustments made to the rehabilitation plan as new PSS symptoms arise. In this handover, the status of the patient's remaining residual organ dysfunctions, rehabilitation trajectory, physical and (neuro)psychological -emotional and neurocognitive- status should be discussed. The possible options for gradually resuming pre-sepsis daily life, work or school, and broader social participation are certainly outlined here as well.

For the reimbursement of the costs of care of patients post sepsis ("long sepsis" or PSS) after discharge from the hospital or rehabilitation setting, we recommend to mirror the reimbursement model of the RIZIV agreement for long-COVID-19, please see https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/ziekten/long-covid-19-tegemoetkoming-in-de-kosten-van-zorg-bij-aanhoudende-covid-19-symptomen#wat-betaalt-een--patient-bij-een-zorgtraject-longcovid. Moreover, in the recent meeting of the corresponding Transverse Working Group Long-COVID (22/05/2024), it was repeated that this care approach could be extended to a larger patient population, including post-infectious diseases, PICS,…, providing that a literature study is done and that a guideline is proposed based on the available evidence.

4. **Patient and Family-Centric Approach:**

   Emphasizing the interaction between the patient and their close relatives is key throughout the recovery process. Recognizing and addressing the unique needs and emotional responses of both the patient and their loved ones to the sepsis experience or PSS is crucial for holistic care.

II. Education about PSS

1. Educating primary care providers and the environment, including general practitioners, home nurses, physiotherapists, speech therapists and outpatient psychologists, about the PSS is very important to provide adequate support to sepsis survivors and their close network (immediate environment).
2. Develop information (brochure 'life after sepsis', …) and education materials on long-term outcomes after sepsis to educate patients, their environment and healthcare workers.

III. Peer support:

1. Encouraging interactions with fellow sepsis survivors will ensure that the patients' and their loved ones' sense of loneliness can diminish. Fellow sufferers' conversations are invaluable for processing the emotional impact of the sepsis journey.
2. We recommend that the national sepsis body endorse and invest in the Belgian sepsis support group. Linking the Belgian support group to the Belgian national sepsis body will allow healthcare workers or GPs to connect patients to appropriate support quickly.

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Chapter 6. ETHICAL CONSIDERATIONS IN THE CARE FOR PATIENTS WITH SEPSIS.

As described in the Introduction and in Chapter 5, sepsis is responsible for many deaths and in those surviving, might generate significant long-term morbidity and associated economical cost (1, 2). Timely adequate prevention, recognition and treatment can improve outcomes. A Sepsis National Action Plan identifies strategies to do so. However, for all potential benefits, such a plan inherently also incorporates risks. It can increase resource use and negatively impact efforts to decrease and optimize antimicrobial use. It can create unrealistic expectations of outcomes and feed therapeutic tenacity. Stories of young sepsis victims might help in creating awareness and improving policies. Most patients with infection, however, do not develop sepsis and recover after a few days of illness. Data from the UK (2015) show that of those admitted to hospital for infection in emergency -themselves already a fraction of the total number of people with infection- only 2.5% are admitted to ICU and only 0.8% die. The majority of non-survivors are either very young or are frail, with major comorbidities, immunocompromised and/or approaching the end of life. These deaths are often not solely attributable to sepsis nor preventable through timely and effective health care (3). The same reality is seen in most high-income countries (1, 2, 4-7).

The number of very old (80+) within society is growing rapidly. Delivering emergency care to this population is in many ways complex, yet even at high age early aggressive treatment might improve outcomes (2, 8). Importantly, chronologic age itself should not be used to predict outcomes or limit treatment efforts. Although very old age is often combined with frailty, this is not always the case in either direction (9). Frailty is a known risk factor to develop sepsis and for those patients having sepsis, it is associated with more ventilator days, longer ICU length of stay and higher mortality. Survivors are confronted with further functional decline, prolonged morbidity and risk of nursing home admission or hospital readmission (2, 5, 10-15). There is a significantly higher cost per survivor for frail patients (2, 14). Such higher cost, regardless of outcome, might also occur in case of non-ICU admission (16). Even after correction for treatment limitations (in as much as 34.4% of patients), frailty remained an independent risk factor for mortality in the large multinational observational VIP2 study on older patients in ICU (17). Still 35.7% of survivors were recognized as frail.

The majority of older patients indicate that, for them, quality of life takes precedence over quantity of life, that independence in terms of physical and mental functioning is crucial to maintain dignity and quality of life, and that there is a willingness to talk about end of life and be part of the decision-making process (18, 19). Furthermore, when people over 80 are properly informed about the impact and

consequences of invasive procedures and treatment, such as invasive mechanical ventilation in the ICU, a significant proportion of them appear rather reluctant to accept life-sustaining treatments. Quality of life is a determining factor hereto (20). Patients over 80 are, however, rarely asked for their opinion when it comes to a transfer to ICU (21). This entails the risk of over- or undertreatment. Treatment limitation decisions are often based on information collected in the first 48-72 hours of ICU care as individual patient's values and preferences are not always clear upon admission. In this, there is a clear risk for a self-fulfilling prophecy (10, 17, 22-24). Several studies show that the existence of for instance a do-not-attempt-resuscitation (DNAR) order, even if only for resuscitation, is in itself associated with decreased survival regardless of disease severity or comorbidities (25-29). While DNAR orders are not synonymous for 'do not treat', they may thus unintentionally limit aggressive treatment for e.g. severe sepsis patients, especially in older adults.

In contrast, functional decline does not necessarily lead to self-perceived poor quality of life and likewise unwillingness to receive life-sustaining therapy (12, 18, 30). While many people in tempore non suspecto would identify a significant decline in physical functioning and/or a loss of independence as unacceptable, this may be far less clear once actual intensive care need occurs. Patients may hold on to life and will then often value other determinants of health-related quality of life more than functioning as such. This knowledge is important when guiding shared-decision making on ICU admission and life-sustaining treatments, taking into account that, even for frail patients, reliable risk prediction of long-term outcomes is sometimes difficult (8, 13, 15, 23 ,24, 30, 31). Moreover, acutely occurring frailty might still be a dynamic condition and while it often worsens over time, it also can improve and/or be treated (9).

Sepsis is a major healthcare problem, with a huge associated economic cost, primarily affecting those already frail and/or with severe comorbidity. As indicated above, there is a clear potential for harm associated with therapeutic tenacity. Considering the current ethical principles that guide our practice (autonomy, beneficence, nonmaleficence and justice), it is essential that an a priori discussion about goals of care should take place with the patient, his relatives and healthcare providers, at least in all with an increased risk for a bad outcome (Belgian Law Patient rights). Too often this only happens at the very end (if ever). Somogyi-Zalud described the 'dying' experiences of patients (and family) with acute respiratory failure or multiple organ failure and sepsis in five US teaching hospitals (n=2956) (32). Patients who died during hospitalization (43.8%) had significant functional impairment and reduced quality of life even before hospitalization. They preferred less aggressive treatment, but less aggressive care was explicitly considered only when death was imminent. Surrogates indicated that one out of four patients died with

severe pain and one out of three with severe confusion. Families of 42% of the patients who died reported one or more substantial concomitant burdens (emotional, economical…).

Advance care planning (ACP) based on shared decision-making might improve such reality (31, 33). It is important to understand that ACP in many ways differs from installing a DNAR order (34, 35). Most DNAR orders are decided during hospitalization for severe conditions and this most often in the first 24-48h of admission (36). Reasons for such orders are multifactorial but not always unequivocal (37). While it might include a specific DNAR order, ACP has and needs to have a much broader focus. It allows individuals to clearly define their goals and preferences for future care (in case of serious illness), to thoroughly discuss these with family and HCP, and to record and review these preferences as appropriate (31). Such goals go far beyond the question about 'resuscitation or not', and might include for instance whether hospitalization, certain invasive techniques or even antibiotics would still be considered appropriate in certain conditions. ACP is ideally done before the actual deterioration occurs, hence the term 'advance', although revision of the set goals might be considered at any moment.

Decisions about goals of care should primarily be based on the informed choices of the patient and their norms and values (31). Providing proper and unbiased information considering the often uncertain prognosis of severe illness, the unclear cost-effectiveness of certain treatment options and the provider's own values and preferences is difficult (2). The decision-making capacity of the patient should be assessed as part of this process (e.g. Aid to capacity evaluation ACE tool), as well as the role and mandate of possible surrogate decision makers (8, 38, 39). The local legal, organizational, religious, and cultural context should be considered when defining treatment goals (40). Importantly, this does not mean that healthcare providers are obliged to provide a treatment that is either futile, disproportional, not cost-effective or in conflict with their own norms and values (Belgian law patient rights). The latter is even more an issue if resource demands significantly exceed resource availability (such as during a pandemic). Healthcare teams should then carefully assess each patient's likelihood of good long-term outcome and expected resource use to optimize allocation of resources. They should, however, never use blanket criteria (e.g. age thresholds) to determine the eligibility of an individual patient to receive treatment (31).

Despite national guidance in many countries, the actual number of patients with available advance directives and/or defined care goals is limited, even in those with a high risk of adverse outcomes (8, 41-46). For instance, in Flemish residential care centers, where the oldest and most vulnerable patients reside, 40% did not have an ACP in 2022; notwithstanding the fact that 'end of life care' is a core quality indicator on which residential care centers are assessed for their accreditation (47). Official data about

community dwelling older patients are lacking. In patients without ACP, healthcare providers can only start with all necessary care and try to obtain clarity about patient baseline status and perceived quality of life, expected outcomes and survival potential, based on illness severity, treatment response and burden (2, 39). Evidence that further (intensive) care would not be consistent with the patient's values and preferences, or in their best interests should lead to limitations in (life-sustaining) therapy (31, 33).

Predefined goals of care might aim for life-sustaining care regardless of consequences or rather focus on avoiding functional decline or only aiming for comfort, even if that could mean a shorter lifespan. Limiting life-sustaining treatment is not synonymous with stopping medical care. For many patients palliative care might be appropriate as part of their ACP. Palliative care focuses on the relief of suffering, based on a holistic approach (biopsychosocial), but not necessarily limits any further treatment of for instance co-morbidities (2). It is important to understand the complexities and ethical principles associated with these patients when they have an acute medical problem (such as sepsis) (33). It is not because people are in palliative care that they would not call upon emergency services, nor that they would not deserve treatment under certain conditions. Half of the older patients visit an ED in the last month of their life and many of them have unmet palliative care needs. (40, 48). Many such patients also would not want or have a high risk of additional harm from hospitalization but would still profit from short-term therapies such as intravenous antibiotics or oxygen if these could be provided in their own environment (49-52). As in any other patient, it is the task of the healthcare providers involved to evaluate as soon as possible in how far treatments align with an advance directive, with predefined care goals or if unavailable, with the balance between benefit and harm for the individual patient. Although many healthcare providers feel uncomfortable with withdrawing a therapy started in an emergency when that therapy turns out to be not/no longer in the patient's best interest, this in fact might be the more valid option from an ethical perspective, especially if in a comfortable and controlled manner. Healthcare providers should be very much aware of potential barriers to appropriate palliative care and try to improve on them. For instance, patients and families might disagree among themselves or struggle with the either-or nature of their previous commitment and second-guess decisions made once actual life-threatening problems arise. Fear and panic might influence their decision-making capacity and/or opinions about treatment goals. Healthcare providers might have difficulty estimating their patient's decision-making capacity and equally be confused about 'palliative' goals in an emergency setting. They often have only incomplete understanding of the patient's medical status or values and preferences and might not have access to existing advance directives. At the same time, they are obliged to make decisions about life-sustaining treatments that are sometimes time-critical.

ACP is not only relevant for sepsis but should be an integral part of the care we provide to all those at increased risk of severe illness and/or physical deterioration. All healthcare providers should work together to achieve this. The overall coordinating role generally lies with the patient's general practitioner (GP) -or for some children, their pediatrician. However, identifying those who will likely benefit from ACP and overcoming a reluctance to address this complex issue in tempore non suspecto is a team effort. More specifically, for patients with severe chronic conditions, there is a crucial central role for the treating specialist team to take up this responsibility. Educational and practical tools have been developed and made available nationwide for patients, GP's and all other relevant healthcare providers (53), and since 1/11/2022 nomenclature has been introduced for GPs discussing ACP with palliative patients (54). Considering the characteristics of ACP-related discussions (time intensive, iterative, sometimes involving other disciplines (e.g. pediatrics), and ideally starting prior to the palliative phase), there is a need to update and adjust this regulation.

If such incentives allow for widespread ad-hoc availability of advance directives in all appropriate cases, then this would clearly be cost-effective and improve the overall care provided. In case of ethical conflicts or confusion during ACP conversations or if, at some point, there are actual discussions or disagreements between the treating team and surrogate decision makers (or sometimes even the patient), an ethical committee might have an advisory or mediating role. GP's, non-hospital care facilities and nursing homes should have access to an ethical advisory board at locoregional level. This board should be defined by law and support the GP and treating team with decisions regarding appropriate care in complex cases.

ACP starts with the patient and their family. Although there is a clear responsibility for all healthcare providers, the number of high-risk patients with a proper advance directive would clearly be higher if all patients were made aware of its importance and implications. To inform all citizens about this concept, ACP should be an integral part of any large-scale communication about critical illness and specifically sepsis. Finally, to prevent miscommunication or ambiguity and avoid delay in appropriate care, it is important that a patient's advance directives becomes available and accessible at any moment 24/7 for all involved healthcare providers (both ED, in- and out-of-hospital), via for instance an electronic platform, the patient's e-healthbox, passport or other.

Recommendations

1. Targeted education about critical illness and outcomes of specific subgroups as well as about the importance of ACP, about goals of care and the notion of a 'palliative care' emergency should be an integral part of all professional training of physicians, nurses and other involved care providers.
2. A large-scale communication to all citizens about the importance of ACP, whether as part of a broader information campaign on sepsis is needed (whereby the already existing communication materials (53) can be used and promoted).
3. Better support for both GP's and relevant organ specialists in taking up the responsibility to assure proper ACP, at least for all patients with a high-risk profile for critical illness and/or those incapacitated. In residential care facilities and nursing homes the coordinating physician, as well as other members of the medical team can help to identify these patients (which should be part of the measured quality indicators for that facility). To support the GP (and relevant organ specialists) in this task several strategies should be considered, probably in parallel:
    a. Financial incentives to compensate for the time and effort invested. Currently, the possibility of reimbursement is linked to the identification of a palliative status while ACP is also relevant to consider far earlier. Moreover, ACP might need to be discussed at regular intervals, and thus needs more than a one-time reimbursement.
    b. The introduction (and reimbursement) of advanced nurse practitioners that, among others, can specifically support the GP (and/or organ specialists) in the process of identification, communication, and necessary follow-up as part of a qualitative ACP.
    c. Access to a locoregional ethical board, its composition defined by law, that has a supportive and advisory role in cases that are either complex or generating conflict or moral distress. It is important that the members of such an ethical advisory board have advanced practice-relevant expertise.
4. The availability 24/7 of existing advance directives, resulting from ACP, for all relevant HCPs via electronic way. A uniform framework to report such advance directives, as well as a standard timeframe for their validity should be developed.
5. The development of 'hospital at home' programs at the locoregional level, in support of the GP, to offer medical assessment, treatment, and follow-up at home for patients who no longer want hospitalization -or for whom hospitalization is mostly harmful- yet would still benefit from for instance short-term intravenous antibiotics or oxygen therapy.

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Chapter 7. SURVEILLANCE AND RESEARCH

7.1. Sepsis surveillance

As mentioned in the Introduction, our understanding of sepsis patients in Belgium is markedly incomplete. Current national surveillance efforts primarily concentrate on HCAI such as CLABSI, as well as other hospital-acquired infections. The surveillance systems in place, such as the National Surveillance of Healthcare-Associated Bloodstream Infections (HABSI) are organized by Sciensano (1). This is a mandatory annual surveillance regulated by Royal Decree. Others include the National Surveillance of Infections in Neonatology Units (NEOKISSBE) (2), extending laboratory-documented case definition of BSI towards clinical BSI. In addition, the PPS of HAI and antimicrobial use (ECDC HAI PPS) provides a comprehensive EU-wide perspective on HAI and BSI using standardized case definitions, capturing data from about 30-40% of Belgian general hospitals every five years, which includes acute hospitals and care homes (3).

However, these surveillance systems have significant limitations. They do not collect specific data on sepsis and septic shock as defined in the Sepsis-3 definitions, and often sepsis refers to clinical picture of infection – with or without confirmed microbiology. Additionally, there is a problematic delay in the reporting of this information.

The Monitoring Intensive Care Activities (MICA) project (4), which gathers data directly from Patient Data Management Systems (PDMS) in (P)ICUs in selected hospitals, could potentially serve as a valuable resource for sepsis data, especially considering that a significant proportion of sepsis patients are admitted to ICUs at some point. The future of the MICA project is currently under discussion with RIZIV/INAMI.

Further complicating matters, the reliability of sepsis data coding, such as ICD9 and ICD10, is questionable, adding another layer of complexity to the accurate tracking and analysis of sepsis within the country.

To address these issues and improve our understanding of the epidemiology and management of sepsis, a collaborative effort to refine data collection and reporting mechanisms is urgently needed. This will require updating and expanding the scope of existing registries, considering the integration of new data sources, and ensuring timely reporting to capture the most accurate and current state of sepsis epidemiology in Belgium.

Objectives

The objectives of this sepsis surveillance should include (1) monitoring the evolution of sepsis and septic shock prevalence and incidence, and thereby assessing the impact of the SNAP, (2) estimating the burden of disease caused by sepsis/septic shock and (3) assessing the implementation of the different components of the SNAP in the community and first line health care, hospitals and LTCFs.

Recommendations for surveillance

Therefore, we recommend:

1. To minimize uncertainties and facilitate validation, following items should be developed:
    - a standardized case **definition** (numerator) using the Sepsis-3 definitions for all surveillance strategies in adults and the Phoenix Sepsis criteria in children
    - the **targeted patient population** (denominator)
    - an **indicator** of nationwide sepsis occurrence
2. To develop a **Belgian sepsis registry**. This implies establishing a centralized registry dedicated to tracking all sepsis cases, including those with septic shock, to collect detailed patient data across all healthcare settings. This registry would fill existing gaps by providing specific sepsis-related data.
3. **To streamline data collection.** This involves simplifying data collection methods to reduce the burden on healthcare providers by integrating an automatic data capture within electronic health records (EHR) and PDMS. Ideally, existing collection tools (e.g. MICA, …) should be used or integrated to reduce the administrative burden and improve responsiveness.
4. To develop **real-time analysis and reporting** to provide immediate insights into trends, allowing for timely interventions and resource allocation.
5. **To integrate detailed data collection** on sepsis and its management (e.g. need for surgery, mechanical ventilation, vasopressor support, renal replacement therapy or ExtraCorporeal Membrane Oxygenation (ECMO) **in the ongoing PPS** and other surveillance studies in the field of infectious diseases.

7.2. Sepsis research

Research setting in Belgium & beyond

Research is an indispensable part in the ongoing effort to advance the quality of care for sepsis patients in Belgium. The COVID-19 pandemic has unequivocally demonstrated the critical role that research plays in addressing complex health challenges. Sepsis remains an area with abundant research questions and opportunities for investigation.

Belgium has established itself as a hub of sepsis research, with several prominent researchers contributing to the knowledge in this field. Since the initiation of the campaign, there was always at least one Belgian representative in the expert panel of the renowned Surviving Sepsis Campaign Guidelines. Research activities in our country range from academic research to industry-initiated studies. The Belgian healthcare system not only facilitates but actively encourages research, with patients typically well-informed and willing to engage in clinical studies. This readiness to participate is strengthened by the high-quality support provided by clinical trial units and dedicated study teams.

There is funding available for sepsis research, including grants that focus on international collaboration. However, a notable challenge is the categorization of sepsis within funding schemes. Sepsis research often finds itself competing for attention and funding resources in broader categories such as basic research and immunology, rather than being recognized as an individual topic.

Despite the extensive research activity, there is little - if any - coordination and collaboration across hospitals and institutions. The potential for progress in understanding and treating sepsis is hindered by the different efforts that would benefit greatly from a more harmonized approach.

Recommendations for research

Therefore, we recommend:

1. **To establish a Belgian sepsis research coordination and prioritization center** in order to streamline efforts, facilitate collaboration, and disseminate findings effectively.
2. **To establish a dedicated sepsis research funding scheme** by advocating for sepsis to be identified as a standalone category in funding programs to ensure dedicated resources are available.
3. **To promote inter-hospital research networks** through encouraging partnerships among hospitals to share data, resources, and expertise.
4. **To enhance international collaboration** as sepsis is similar in western European countries. This can be done by strengthening the interaction between international research bodies and funding

agencies, similar to the Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR) program for antimicrobial resistance.

5. To include all **innovative aspects** of sepsis care as potential topics for research, including but not limited to the use of wearables, post sepsis syndrome recommendations and follow-up, among others.

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4. https://www.micaprogram.be/nl/

List of Appendices

Appendix I: List of recommendations

Workgroup	Recommnr	Recommendations	Further clarification	Additional considerations for implementation	Main actors
1. General coordination, awareness and knowledge					
1. General coordination, awareness and knowledge	**1.1**	General coordination and organisation with the creation of a **National Sepsis Focal Point or Steering Group** (1) and a **National Sepsis Foundation** (2).	(1) Responsible for coordinating and follow-up of all plans and initiatives related to sepsis awareness and management. It should include public health officers, scientific experts, (para)medical professionals, representatives of patient advocacy groups.		(1) Should be interfederal, funded structure, to be defined by RMG/IMC. It could be BAPCOC-like structure. (2) Private initiative with mixed (public and private) funding. Could be NGO/vzw/asbl, e.g.building further from already existing Sepsibel.
	1.2	A **general awareness campaign** should be designed and started. General messages for general public with sufficient attention for persons with lower education levels and infrequent health information seeking behavior. Tailored interventions should be created directed towards **higher risk patient groups**, such as oncological patients and immunosuppressed patients.	(1) The concept 'sepsis' should be branded in messages. (2) World Sepsis Day (September 13th) could be used as a focal point for raising public awareness. (3) Joint messaging initiatives linking sepsis awareness with antimicrobial stewardship (AMS). (4) targeted campaigns focusing on recognizing signs and symptoms in children.	(1) Storytelling (survivors' testimonials) could be used to support awareness messages	National Sepsis Focal point and (1, 2, 3) Foundation, (1,2) communication services of regional and federal public health administrations. (3) BAPCOC, NAP-AMR actors, (4)First line health care, pediatric professional societies, Opgroeien/ONE

	1.3	**Education packages** for all relevant healthcare professionals (HCPs) should be designed and implemented with specific focus on: sepsis awareness, early recognition, early management of sepsis, basic treatment modalities, prudent use of antibiotics, the importance of advanced care planning, and post-sepsis syndrome.	(1)Primary care: combine early warning for sepsis with AMS in awareness campaigns and educational material (expert advice); (2) Long term care facilities (LTCFs): sepsis awareness training should be incentivised by uptake in mandatory training programmes for HCPs in LTCFs; (3) Child health: enhancing awareness and knowledge of pediatric sepsis among all HCPs working with children via: clear set learning objectives of pediatric sepsis into medical and nursing curricula; a national consensus on guidelines for pediatric sepsis, easily available online; reinforcing knowledge of pediatric sepsis as mandatory part of the continuous professional development for nurses and doctors through accredited (simulation)training sessions, online learning platforms, interdisciplinary discussions or case reviews; development of transfer criteria to escalation of care (to regional PICU/NICU)	*Specific roles for each group of HCPs (MDs, nurses, home nurses, pharmacists,...) need to be defined.*Training on sepsis should be part of undergraduate and postgraduate education, and should integrate the use of sepsis recognition tools and early warning scores (see WG 3),*Tailored training modules should be provided for different HCPs groups, including pediatricians, pediatric care providers (nurseries, Kind & Gezin), geriatricians, home care nurses, and chronic care providers.	Universities and other higher education centres, in collaboration with National Sepsis Foundation. (1) Professional societies for first line health care, BAPCOC, public health authorities. (2) Quality control systems for nursing homes and other LTCFs. (3) Professional societies for pediatrics and first line health care.
2. Prevention of sepsis and safeguarding treatment options: Infection Prevention Control (IPC) and antimicrobial resistance (AMR)					
2. Prevention of sepsis and safeguarding treatment options (IPC and AMR)	**2.1**	**Prevent sepsis and safeguard antibiotics' effectiveness in the community.**	(1) strenghten access to (chronic) health care for all, with specific attention to most vulnerable (medically and socio-economically). (2) invest in health and vaccination literacy, (3) strenghten vaccination programs for children and adults with indications for additional vaccinations (65+, medically vulnerable, pregnant). (4) develop specific guidelines and training for on safe home care for patients with	(1) In particular, strengthen access and linkage to chronic care, including affordable wound care and dental care. (2) In particular for most vulnerable populations, with emphasis on infection prevention (including food safety). (3) This includes improved registration and reduced	(1) First line health zones, regional public health administrations, patient advocacy groups, mutualities. (2) National sepsis foundation in collaboration with communication services of regional public health actors, CLB/ONE, Instituut gezond leven, Gezondheid en wetenschap,…

			indwelling catheters (IPC training for home care nurses, interface with LTCF and HOST/OPAT-projects)	cost of adult vaccination for at risk groups.	
	2.2	**Set up a national multimodal strategy to prevent Healthcare Associated Sepsis in hospitals.**	(1) Build it: availability of the appropriate infrastructure means and supplies to enable IPC good practices. (2) Teach it: education and training of health care workers and key players. (3) Check it: monitoring infrastructures, practices, processes, outcomes and providing data feedback. (4) Sell it: reminders in the workplace/ communications. (5) Live it: culture change within the establishment or the strengthening of a safety climate.	(5) Engage hospital management, head nurses, head cleaners, medical responsiblse as leaders. Ensure that IPC activities are integrated in the strategic plan of the hospital. Consider to incentivize IPC through P4P.	(1) BAPCOC, Superior health council, Sciensano, hospitals, IPC teams in hospitals, hospital management. Regional and federal authorities, professional nursing associations (2)Universities and higher education institutions, IPC teams in hospitals. (3) hospitals, IPC-teams in hospitals, HOST, Sciensano. (4) hospitals, IPC-teams in hospitals, HOST, BAPCOC.
	2.3	**Strengthen already existing antimicrobial stewardship (AMS) activities in hospitals.**	(1) Strengthening and providing sufficient financial support to already existing antibiotic policy groups in hospitals are essential to guarantee the effective execution of these responsibilities at the local level (including the creation of nomenclature for stewardship activities by clinical infectiologists). (2) Ensure and support the availability of regularly updated, free of charge antimicrobial treatment guidelines for hospitals.	In addition to the (limited) available funding, formal staffing standards for AMS similar to those for IPC should be considered	(1) Federal public health administration/BAPCOC, RIZIV-INAMI. (2) Federal public health administration/BAPCOC
	2.4	**Build and strengthen IP and AMS in LCTFs (with particular focus on nursing homes).**	(1) Define specific objectives and quality indicators for AMS and infection prevention in LTCF, as well as multimodal strategies to implement them. (2) Postgraduate education package for coordinating and advising clinicians in LTCF ('CRA') and for nurses working in LTCF should be revised or made. (3) Nurses in LTCFs need strong support (from administration and	(1) Locally relevant IPC-guidelines for LTCF should be made and implemented. A specific AMS strategy for LTCF should be developed (formularium, audit en feedback, based on insights from behavioral sciences). (2) Inclusion of package on IPC, AMS, sepsis recognition	(1) Regional public health administration/OST, HOST, BAPCOC. (2) universities and higher education centres, professional societies, regional public health administrations. (3) regional public health administration, nursing professional organisations. (6) regional and federal public health actors, in collaboration with first line health care, CRA's, HOST/OST

			logistics) to focus on clinical work, advanced ward management, and coordinating care activities closely with CRA's. (4) AMS & IPC core components for LTCF should be implemented and followed up. (5) Priority should be given to concrete interventions. (6) Support should be foreseen for surveillance/registration of HAI / AMR / AMC in LTCF	and advanced care planning. Adapted educational packages on IPC and sepsis awareness should be made for nursing aids and other (para)medical professionals in LTCF. (4) leadership commitment, accountability,drug expertise, action,tracking, reporting, and education. (5) Hand hygiene, oral hygiene, guidelines for UTI and decreased use of urethral catheters (continence management), improve vaccination coverage (influenza, COVID, pneumococcal) for residents and staff, and transfer policy and culture of advanced care planning.	
3. Early warning, early diagnosis					
3. Early warning, early diagnosis	**3.1**	**Stimulate the use of context-specific, effective early warning screening tools, integrated in a broader Rapid Response Strategy.**	(1) Primary care settings: EWS should be part of a broader sepsis strategy. (2) LTCFs: effective sepsis screening tool should be developed and applied. (3) Pre-hospital teams: a validated EWS should be used to communicate the vital status of patients with possible sepsis. Further research is needed to validate the effectiveness of point-of-care (POC) testing in the prehospital setting. (4) Emergency departement: validated early warning scores with POC testing for early detection. (5) Hospital wards: minimum observation frequency of once every 12 hours for all adult patients admitted to an acute	(2) Clear communication with hospital teams is essential (both on early warning score and on possible advanced care planning). (4,5) The National Early Warning Score (NEWS) 1 or 2 currently is considered as the most appropriate early warning score for Belgium. However, we support the development and validation of a geriatric EWS, as the NEWS is less accurate in geriatric patients.(6) to	all involved professional societies, federal public health

			hospital wards. (6) standardized electronic patient record that is linked with a bedside spot-check monitor. (7) targeted education for non-ICU hospital clinicians and nurses on early clinical deterioration recognition.	reduce workload, increase adoption and reduce delays between measurement and registration	
	3.2	**Implement Rapid Response Teams (RRTs) in hospitals.**	(1) Widespread implementation of RRTs or Medical Emergency Teams (MET), across hospitals for patients outside the Intensive Care Unit (ICU). (2) Hospitals should receive incentives to implement RRTs.	RRTS can provide proactive, reactive, and supportive care to general wards, in addition to offering educational support.	
	3.3	**Support the development of screening tools for children.**	A sepsis screening tool should be included in a recognition bundle to aid clinicians in evaluating children with possible sepsis and initiating appropriate care pathways and treatment. The use of Pediatric Early Warning Score (PEWS) as a triage and screening tool for paediatric sepsis is recommended.		
4. Early effective treatment					
4. Early effective treatment	**4.1**	Hospitals should guarantee **the 24/7 availability of specifically trained 'advanced' care teams.**	These advanced care teams (RRTs) can provide early 'advanced' interventions at the bedside outside of the ICU environment. SOP's should be in place to clarify indications and communication pathways for basis providers to contact these advanced teams. The minimum performance requirements for such teams should be defined by law.		Health care structures, federal public health administration

	4.2	ICU should have specific, **(as much as possible) evidence-based- procedures in place to care for the critical sepsis patient.**	Specific patient populations (e.g. children, those with refractory shock or severe organ failure, needing organ support or even extracorporeal membrane oxygenation) might demand early referral to a dedicated highly specialized ICU and each ICU should have plans and collaboration agreements to allow for this.		Health care structures with help of scientific and professional societies and National Sepsis Focal point
	4.3	The government should **follow up** on these requirements but also **provide sufficient financial support to allow systems to implement** these (in terms of staffing and resource use).	Improving the care provided to sepsis patients is likely to be cost-effective when it subsequently has a positive impact on mortality and/or on ICU length of stay or long-term morbidity, or more specifically on the appropriateness of testing or antibiotic use.	The government could specifically subsidize the implementation of 'advanced response teams' within any healthcare setting; strengthen support for AMS interventions and provide free access to national antibiotic guidelines; identify and subsidize the role of tertiary care ICU in referral pathways for specific subpopulations and/or for patients with refractory shock, including the necessary highly-specialised emergency transport.	Federal public health administration
5. Post sepsis trajectory					
5. Post sepsis trajectory	**5.1**	Develop a **multidisciplinary rehabilitation care pathway** for sepsis patients that encompasses the psychological, neurological and	(1) Apply early and individualised Rehabilitation Goals. (2) Clear Communication and Care Pathway – use the words 'sepsis' and 'Post sepsis syndromes'. (3) Seamless Transition and Follow-Up. (4) Patient and family-centric approach: emphasizing the interaction between the patient and		Hospitals, professional societies for intensive care, and rehabilitation, first line actors, RIZIV/INAMI. (1) Health care professionals at ICUs and rehabilitation services (medical, nursing, physiotherapy/ergotherapy, psychology, social services,…)

		physical domains, with clear transition into home setting.	their close relatives is key throughout the recovery process.		
	5.2	**Facilitate peer support.**	(1) Encouraging interactions with fellow sepsis survivors (Fellow sufferers' contact and peer support). (2) The Belgian national sepsis foundation should endorse and invest in the Belgian sepsis support group.	(1) This will ensure that the patients' and their loved ones' sense of loneliness can diminish. Fellow sufferers' conversations are invaluable for processing the emotional impact of the sepsis journey. (These peers' conversations are extremely valuable in processing the trauma that is this sepsis journey). (2) Linking the Belgian support group to the Belgian national sepsis body will allow healthcare workers or general practitioners (GPs) to connect patients to appropriate support quickly.	
6. Advanced care planning (ACP)					
6. Advanced care planning	**6.1**	**Targeted professional education** of physicians, nurses, nurse aids and other involved care providers.	Education about critical illness (such as sepsis, cardiac arrest…), outcomes of specific subgroups (older and/or frail patients, high-risk groups…), the importance of advance care planning, goals of care and the notion of a 'palliative care' emergency. This education should be an explicit part of the professional training of the coordinating GP in nursing homes (CRA), and should be included as quality indicator for nursing homes.		Universities, nursing schools, professional societies for nurses, GP's and relevant specialities (e.g. oncologists, hematologists, geriatricians, nephrologists, pneumologists, neurologists,…)

	6.2	A large-scale **communication to all citizens about the importance of ACP,** not only as part of sepsis plan but more in general for all chronically ill, elderly and/or frail persons			Public administration campaign, in collaboration with the involved professional societies, patients groups (e.g. Vlaams Patienten Platform/LUSS), other relevant organisations (e.g. Ouderenraad), mutualities,… The website https://mijnoudedag.be/ exists already, but might require renewed attention.
	6.3	**Supporting and stimulating GP's in taking up the responsibility to assure proper ACP**, at least for all patients with a high-risk profile for critical illness and/or the frail.	In residential care facilities and nursing homes the coordinating physician (CRA), as well as other members of the medical team, can help to identify these patients (which should be part of the measured quality indicators for that facility). To support the doctor in this task several strategies should be considered, probably in parallel: (1) different financial incentives, (2) the introduction (and reimbursement) of advanced nurse practitioners for primary care, (3) access to a locoregional ethical board.		Specific reimbursement is foreseen for GP's, although also other relevant medical specialists could be involved in the discussion on ACP (e.g. pediatrician, neurologist, oncologist, pneumologist, nephrologist,…)
	6.4	The **24/7 availability of the conclusions of the ACP in existing clear advance directives**, for all relevant healthcare providers **via electronic way**.	The directive needs to be as explicit as possible on the type of care the person would wish for (standardized content).		IT solutions within public health services
	6.5	The further development of transmural **'hospital at home' programs** at the locoregional level, in support of the GP.	These programs offer medical assessment, treatment, and follow-up at home for patients who no longer want hospitalization -or for whom hospitalization is mostly harmful- yet would still benefit from for instance		Hospitals, first line zones, nursing homes

			short-term intravenous antibiotics or oxygen therapy.		
7. Surveillance and research					
7. Surveillance and research	**7.1**	A **centralized Belgian sepsis registry** should be developed to track all or at least a representative groups of sepsis cases occuring in Belgium, including those with septic shock, to collect detailed patient data across all healthcare settings. This registry would fill existing gaps by providing specific sepsis-related data.	(1) For sepsis registration, the following should be defined: a standardized case definition (applying the Sepsis-3 defintions), the targeted patient population, an indicator of sepsis occurrence. (2) Data collection should be streamlined. (3) Development of real-time analysis and reporting to provide accurate insights into trends, allowing for timely interventions and resource allocation. (4) Clear definition of pediatric sepsis should be made to facilitate data registration. For this, the phoenix sepsis criteria can be used.	(1) This is a first step in order to minimise uncertainties and facilitate validation. For the case definition the Sepsis-3 definitions should be used for all surveillance strategies. (2) Simplifying data collection methods to reduce the burden on HCPs by integrating of automatic data capture within electronic health records (EHR) and patient data management systems (PDMS).	Sciensano, as an extension of already existing data collections (e.g. health care assocated bloodstream infection). Data should be added to the national health data (https://www.gezondbelgie.be/nl/gezondheidstoestand) (1,2,3) Sciensano together with the National sepsis focal point/steering group.
	7.2	**Integrate detailed data collection** on sepsis and its management in the ongoing point prevalence study (PPS) and other monitoring/surveillance studies in the field of infectious diseases.	Data on sepsis in Belgium should be collected, focusing on epidemiology, demographics and outcome of community- and healthcare-associated sepsis but also on gaps in knowledge and awareness in target groups.	These data are essential: to serve as a base for designing and following up interventions and multidisciplinary research projects; and to inform and support targeted public awareness campaigns; Such data should be added to the national health data (https://www.gezondbelgie.be/nl/gezondheidstoestand) and could be used to support national quality improvement initiatives. (Point 1.1.3)	Hospitals in collaboration with Sciensano. Sciensano, as an extension of already existing data collections (e.g. healthcare-associated bloodstream infection). Data should be added to the national health data (https://www.gezondbelgie.be/nl/gezondheidstoestand)

	7.3	**Establish a Belgian sepsis research coordination and prioritisation centre** in order to streamline efforts, facilitate collaboration, and disseminate findings effectively.	(1) A national sepsis research day may be organized at regular basis. (2) Establish a dedicated sepsis research funding scheme by advocating for sepsis to be identified as a standalone category in funding programs to ensure dedicated resources are available. Include the public (3) Promote inter-hospital research networks through encouraging partnerships among hospitals to share data, resources, and expertise.	(2) Research funding should encourage a broad range of relevant topics including socio-epidemiological context, early warning and diagnostics, pathofysiology, therapeutic trials, outcome and public health impact.	KCE, Belspo, FWO, FNRS
	7.4	**Enhance international collaboration** as sepsis is similar in western European countries.	This can be done by strengthening the interaction between international research bodies and funding agencies.		FWO/FNRS and other funding agencies
	7.5	**More research is needed to evaluate cost-effectiveness of remote patient monitoring and home health care in patients at risk for sepsis.**			

Appendix 2: Key source of data for Global Burden of Disease (GBD) study

(Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; published online Jan 16. http://dx.doi.org/10.1016/S0140-6736(19)32989-7.) (56)

Data sources for modelling sepsis incidence

Country	Data source	Location-years	Number of locations	Years	ICD classification	Individual records	Hospitalisations with sepsis
Austria	Austria Hospital Inpatient Discharges	14	1	2001–2014	ICD9, ICD10	37,632,608	357,772
Brazil	Brazil Hospital Information System	52	26	2015–2016	ICD10	21,792,143	602,753
Canada	Canada Discharge Abstract Database	16	1	1994–2009	ICD9, ICD10	2,390,381	22,312
Chile	Chile Hospital Discharge Information System	11	1	2001–2004, 2006–2012	ICD10	16,355,550	208,088
Georgia	Georgia Hospital Data	1	1	2014	ICD10	398,822	3,797
Italy	Italy – Hospital Inpatient Discharges	12	1	2005–2016	ICD9	110,811,752	2,002,710
Mexico	Mexico Automated Hospital Discharge System	160	32	2003, 2005, 2007–2009	ICD10	9,549,237	389,761
New Zealand	New Zealand National Minimum Dataset	32	2	2000–2015	ICD9, ICD10	8,159,218	256,072
Philippines	Philippines Health Insurance Corporation Claims	2	1	2013–2014	ICD10	7,742,328	329,417
United States	National Hospital Discharge Survey	31	1	1980–2010	ICD9	7,730,286	315,079
United States	States Inpatient Databases	78	13	2003–2008	ICD9	86,661,803	4,185,230

All data sources represent national population-level data, with no restrictions as to age, sex, or cause of death. We included all population-level sources of individual-level hospital admission or discharge data with multiple diagnoses available within the GBD database, with no ad-hoc exclusions. Data from Brazil, the United States, New Zealand, and Mexico were extracted at the subnational level

Abbreviations: ICD=International Classification of Diseases.

GBD estimated sepsis-related incidence by location for all ages, both sexes, and all underlying causes, 1990 and 2017

Location	All underlying causes			Underlying infection			Underlying non-communicable disease			Underlying injury		
	Incident sepsis cases (95% UI), 2017	Percentage change in sepsis ASIR (95% UI), 1990-2017	Sepsis ASIR per 100,000 population (95% UI), 2017	Incident sepsis cases (95% UI), 2017	Percentage change in sepsis ASIR (95% UI), 1990-2017	Sepsis ASIR per 100,000 population (95% UI), 2017	Incident sepsis cases (95% UI), 2017	Percentage change in sepsis ASIR (95% UI), 1990-2017	Sepsis ASIR per 100,000 population (95% UI), 2017	Incident sepsis cases (95% UI), 2017	Percentage change in sepsis ASIR (95% UI), 1990-2017	Sepsis ASIR per 100,000 population (95% UI), 2017
Western Europe	1,310,922 (1,069,548 - 1,682,660)	-25.3 (-44.6 - -2.6)	167.8 (137.5 - 210.2)	682,920 (466,754 - 1,030,675)	-7.8 (-44.7 - 42.1)	89.3 (62.8 - 128.5)	586,357 (471,753 - 745,327)	-34.9 (-54.5 - -9.5)	71.7 (56.6 - 90.3)	41,645 (27,548 - 62,125)	-54.5 (-75.3 - -26.2)	6.8 (4.7 - 9.8)
Belgium	40,952 (31,938 - 54,451)	-13.2 (-38.3 - 14.9)	195.1 (153.8 - 253.7)	24,762 (16,023 - 37,055)	27.8 (-30.1 - 108.9)	116.1 (77.8 - 173.8)	14,687 (11,744 - 19,003)	-38.7 (-58.2 - -15.7)	69.5 (55.7 - 87.6)	1,504 (992 - 2,266)	-44.1 (-70.1 - -5.5)	9.5 (6.4 - 14.0)
France	176,908 (146,143 - 221,269)	-34.0 (-50.9 - -9.2)	154.5 (125.3 - 202.3)	87,728 (60,866 - 129,591)	-25.5 (-56.1 - 24.2)	81.8 (55.6 - 128.0)	80,706 (64,637 - 102,294)	-36.4 (-53.7 - -14.3)	64.0 (51.3 - 79.9)	8,474 (5,510 - 12,769)	-57.4 (-76.6 - -30.1)	8.7 (5.9 - 12.8)
Germany	278,978 (223,434 - 361,735)	-22.2 (-43.5 - 5.4)	175.9 (139.2 - 224.7)	136,622 (90,890 - 205,699)	-6.4 (-47.7 - 49.2)	87.4 (59.7 - 134.2)	133,680 (106,173 - 168,518)	-29.4 (-51.4 - -1.7)	81.4 (63.2 - 105.3)	8,676 (5,550 - 13,531)	-49.8 (-74.5 - -18.5)	7.0 (4.6 - 10.3)
Luxembourg	1,362 (1,084 - 1,779)	-30.1 (-48.9 - -6.5)	156.3 (125.8 - 202.7)	665 (441 - 1,008)	-10.6 (-48.9 - 48.3)	79.6 (52.5 - 122.0)	639 (505 - 825)	-39.6 (-56.4 - -16.9)	68.8 (54.5 - 87.3)	59 (38 - 90)	-56.1 (-77.3 - -28.5)	7.9 (5.2 - 11.7)
Netherlands	58,707 (46,160 - 77,794)	-7.1 (-35.4 - 31.9)	215.3 (163.5 - 289.8)	35,208 (23,315 - 53,354)	22.1 (-32.7 - 112.3)	135.2 (86.6 - 206.7)	21,970 (17,525 - 28,479)	-31.0 (-52.7 - -3.7)	74.0 (58.2 - 94.5)	1,529 (957 - 2,555)	-41.9 (-68.8 - -0.0)	6.1 (4.1 - 9.5)
United Kingdom	245,783 (191,983 - 330,996)	-2.2 (-32.3 - 36.1)	216.2 (173.2 - 280.5)	148,548 (96,687 - 227,079)	22.3 (-34.9 - 105.2)	124.4 (83.3 - 184.5)	92,125 (73,299 - 117,720)	-18.5 (-44.4 - 16.6)	86.0 (66.1 - 114.0)	5,109 (3,327 - 7,674)	-43.4 (-68.1 - -10.4)	5.8 (3.9 - 8.5)

GBD estimated sepsis-related mortality by location for all ages, both sexes, and all underlying causes, 1990 and 2017.

Location	All underlying causes			Underlying infection			Underlying non-communicable disease			Underlying injury		
	Percentage change in sepsis ASMR (95% UI), 1990-2017	Sepsis ASMR per 100,000 population (95% UI), 2017	Sepsis-related deaths (95% UI), 2017	Percentage change in sepsis ASMR (95% UI), 1990–2017	Sepsis ASMR per 100,000 population (95% UI), 2017	Sepsis-related deaths (95% UI), 2017	Percentage change in sepsis ASMR (95% UI), 1990–2017	Sepsis ASMR per 100,000 population (95% UI), 2017	Sepsis-related deaths (95% UI), 2017	Percentage change in sepsis ASMR (95% UI), 1990–2017	Sepsis ASMR per 100,000 population (95% UI), 2017	Sepsis-related deaths (95% UI), 2017
Belgium	-39.8 (-50.9 - -26.8)	29.6 (25.0 - 34.6)	7,675 (6,421 - 9,089)	-12.3 (-41.4 - 28.6)	13.9 (10.0 - 18.2)	3,791 (2,686 - 5,020)	-52.1 (-61.5 - -40.9)	15.6 (13.6 - 18.1)	3,889 (3,360 - 4,551)	-56.0 (-71.1 - -36.0)	1.2 (0.9 - 1.6)	254 (179 - 358)
Netherlands	-38.2 (-49.3 - -25.8)	26.8 (23.1 - 31.1)	9,400 (8,073 - 10,984)	-18.2 (-43.7 - 14.6)	12.0 (8.9 - 15.5)	4,305 (3,162 - 5,593)	-47.6 (-57.6 - -34.8)	14.8 (12.8 - 17.2)	5,116 (4,379 - 5,983)	-49.5 (-68.9 - -21.4)	0.8 (0.5 - 1.1)	248 (163 - 380)

Appendix 3: Overview of sepsis plans of other countries												
Country	Sepsis prioritized in national health policies, strategies and/or sepsis-related initiatives	Sepsis-plan	Funding by government	Foundation	Webpage foundation	Patient organisation	Participation World Sepsis day	Awareness Campaigns	Guidelines early recognition (EWS) and treatment	Sepsis Pathway	Registration	Research
Australia	**x**	**x**	**x**	**x**	https://www.australiansepsisnetwork.net.au/		**x**	**x**	**x**	**x**	**x**	**x**
Belgium						https://www.sepsibel.be/						**x**
Canada	**x**		**x**	**x**	https://www.canadiansepsisfoundation.ca/		**x**	**x**	**x**	**x**	**x**	**x**
France	**x**	**x**	**x**	**x**		https://www.francesepsisassociation.com/	**x**	**x**	**x**	**x**	**x**	**x**
Germany	**x**		**x**	**x**	https://sepsis-stiftung.de/		**x**	**x**	**x**	**x**	**x**	**x**
Italy	**x**	**Regional plans**					**x**		**x**			**x**
the Netherlands			**x**	**x**	https://www.sepsisnet.nl	https://www.sepsis-en-daarna.nl/		**In development**	**x**		**Only in ICU**	**x**

Norway			**x**	**x**	https://sepsisfonden.se/	**https://www.lhl.no/lokallag/interessegrupper/lhl-sepsis-og-meningitt/**			**x**			**x**
Spain	**x**	**Regional plan (Cataluña)**	**x**	**x**	https://www.fundacioncodigosepsis.org/	**https://sepsisinfo.es/**	**x**		**x**			
Sweden	**x**	**x**	**x**	**x**	https://sepsisfonden.se/	https://sepsisforeningen.se/		**x**	**x**	**x**	**x**	**x**
Switzerland	**x**	**x**	**x**					**x**	**x**	**x**	**x**	**x**
UK	**x**	**x**	**x**	**x**	https://sepsistrust.org/ https://www.sepsisfoundation.ie/		**x**	**x**	**x**	**x**	**x**	**x**
USA	**x**	**Several states**	**x**	**x**	https://www.sepsis.org/	**https://www.endsepsis.org/**	**x**	**x**	**x**	**x**	**x**	**x**