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Diagnostic des sepsis : état des lieux et perspectives cliniques

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Déclaration d'intérêt

- Financial:
  - since 1995 I have received multiple grants from French ministry of health, French ministry of higher education, research and innovation, various European research programs, from charity entities - french national programme d'investissement d'avenir: anr rhu 004
  - Past 5 years: received honorarium to contribute to advisory board on corticosteroids for sepsis (Pfizer), biomarkers for sepsis (Baxter, Biomerieux, Volition, Sphingotec), vaccines (Janssen), drugs (viatris)
- Academic :
  - I contribute to SSC 2008/2012/2016 updates
  - I co-chair the Task Force of CIRCI/corticosteroids in the ICU guidelines, since 2008
  - Corticosteroids for acute inflammation is the main topic of research of my group since 1991

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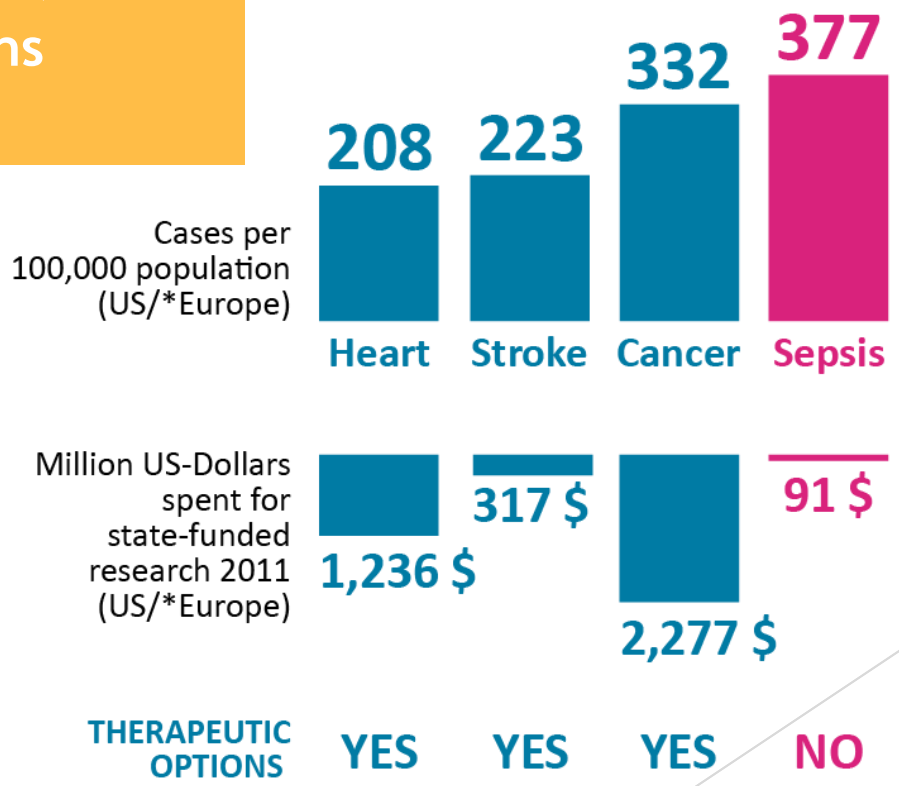
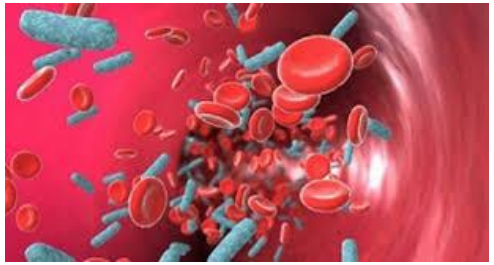
Definition

Sepsis priorité de santé publique mondiale
Fardeau socio-économique

50M cas, Fr:350/100,000
11M décès, Fr: 80,000
42% enfant <5 ans
50% séquelles



Sepsis – changing concepts over the 20th century



1892/1914
bacteremia
„blood poisoning“
(W. Osler, H. Schottmüller)

1992
SIRS /systemic
Inflammation (R. Bone)

2016
Organ dysfunction
(M. Singer)

Characteristics:

- Pre-antibiotic era
- Lack of ‚intensive care‘

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TABLE I.—CASE-MORTALITY RATE

TREATED CASES

Age in years—	8–19	20–29	30–39	40–49	50–59	60 and over.	Total.
Cases ..	31	20	18	13	13	5	100
Deaths ..	1	0	1	2	3	1	8

CONTROL CASES

Cases ..	25	19	24	22	6	4	100
Deaths ..	1	5	5	9	4	3	27

65% relative risk reduction compared to placebo

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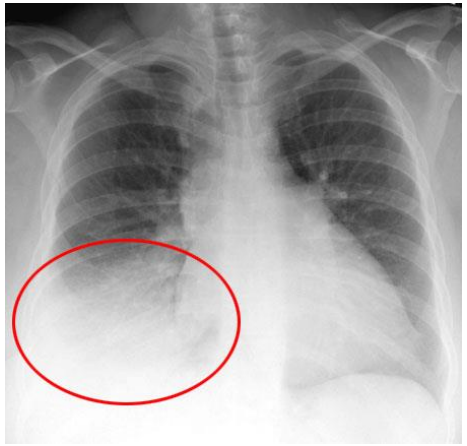

Infection

SOFA>2

LACTATE >2
VASOPRESSOR

- ***Sepsis***: Life-threatening organ dysfunction caused by dysregulated host response to infection
- ***Septic Shock***: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality

Singer JAMA. 2016

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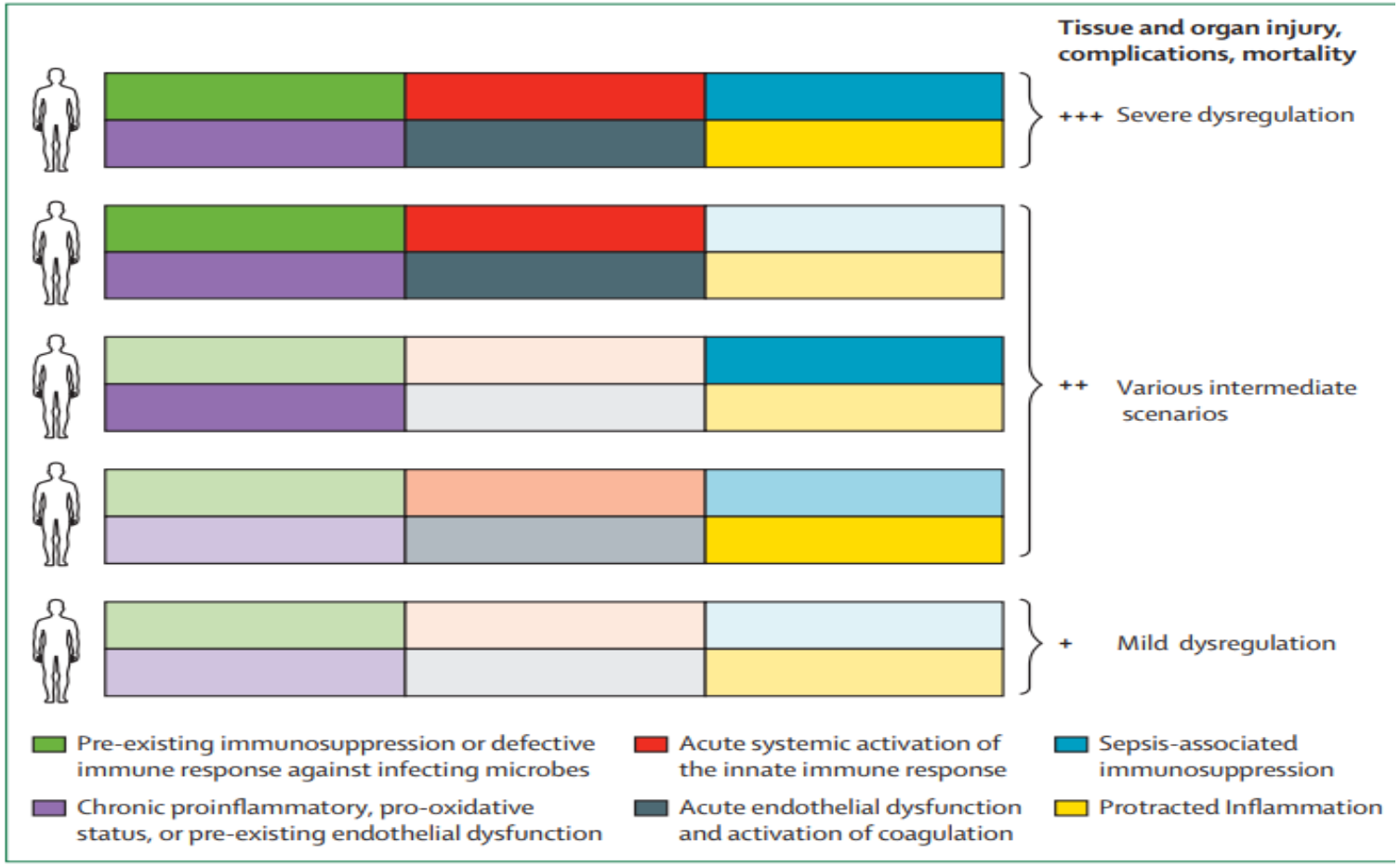

Figure 2: **Potential immunological phenotypes in sepsis**
Patients with sepsis can present with different features of immunological dysfunction and related endothelial and coagulation disturbances. These multisystem derangements can coexist, present with different magnitudes over the disease course, and are linked to varying degrees of organ failure. Accurate longitudinal profiling of the type and dimension of these features can guide appropriate interventions, not only with immunomodulatory drugs, but also with therapeutics targeting specific elements of the endothelial or coagulation derangements.

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Epidemiology

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Sepsis worldwide in 2017

48.9 million	11 million	20%
cases of sepsis	sepsis-related deaths	of all global deaths

Age-specific burden

Sepsis incidence in 2017 and children

Sepsis incidence was biphasic; it peaked in early childhood and again in elderly adults.

41.5% (20.3 million) of incident sepsis cases

26.4% (2.9 million) deaths related to sepsis

children younger than 5 years

Mortality due to severe neonatal infections

24% **of neonatal deaths are caused by severe neonatal infections (including sepsis)**

Geographical-specific burden

Sepsis regional and economic disparities

85.0% of sepsis cases and 84.8% of sepsis related deaths occurred in countries with low, low-middle, or middle sociodemographic indices, particularly in sub-Saharan Africa and South-East Asia.

WHO 2020, Rudd Lancet 2020

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Hospital-acquired sepsis cases

1 in 4 cases	**of sepsis were acquired in the hospital**

Patients with hospital-acquired sepsis had a longer length of stay and high AMR rates, which can significantly impact on patient outcomes.

AMR: antimicrobial resistance.

Sepsis in intensive care units (ICUs)

24.4%	**of cases of sepsis with organ dysfunction were acquired during ICU stay**
48.7%	**had a hospital origin**

WHO 2020, Rudd Lancet 2020

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Sepsis and mortality

24.4%	mortality of patients with HA-sepsis
52.3%	mortality among ICU-treated patients with HA-sepsis
2x to 3x	higher median length of stay of patients with HA-sepsis compared to community-acquired sepsis
Up to one third	of HA-sepsis cases were caused by drug-resistant bacteria

HA-sepsis: health care-associated sepsis. ICU: intensive care unit.

WHO 2020, Rudd Lancet 2020

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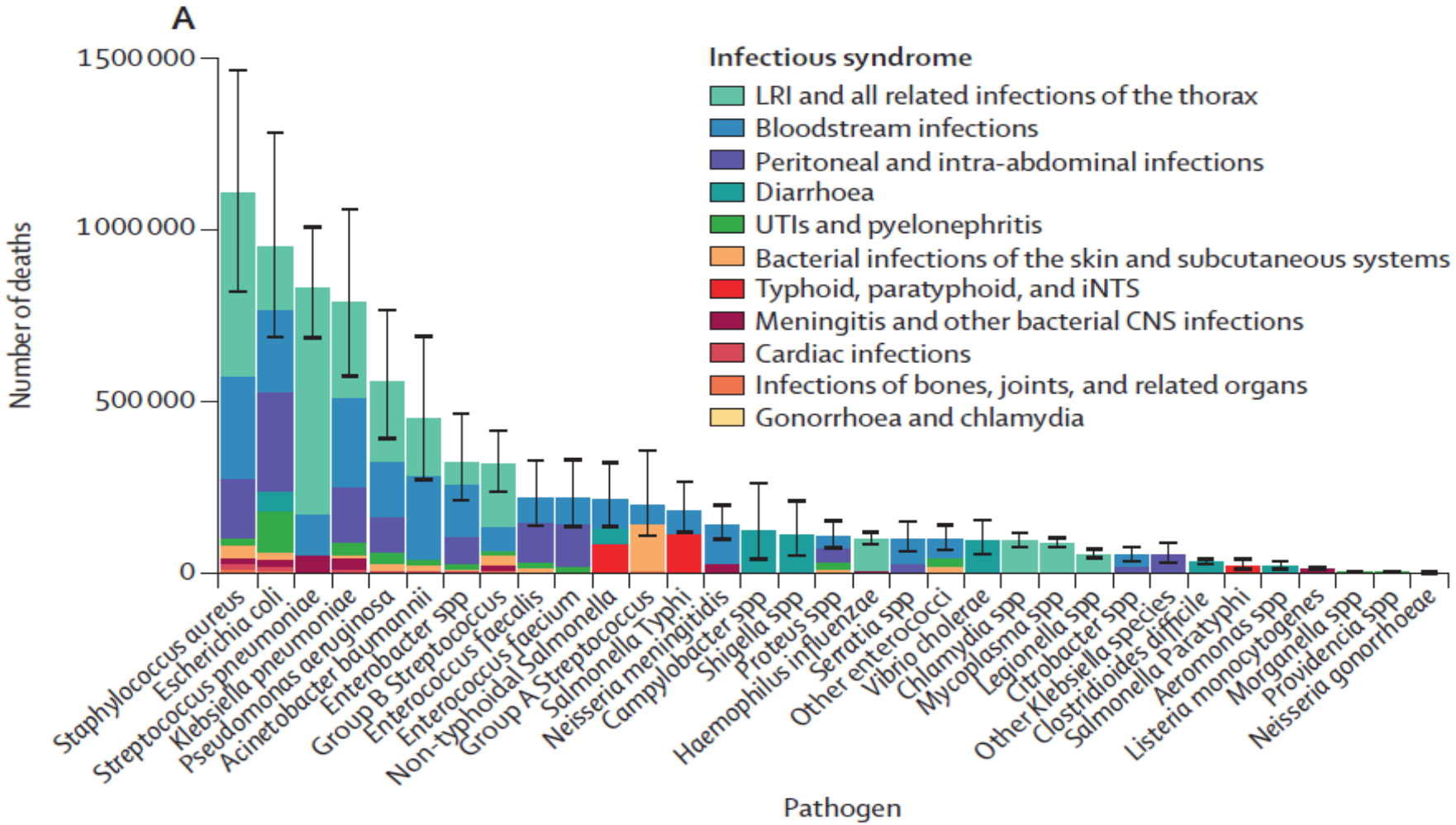

GBD 2019 AMR Coll - Lancet 2022

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Focus on France

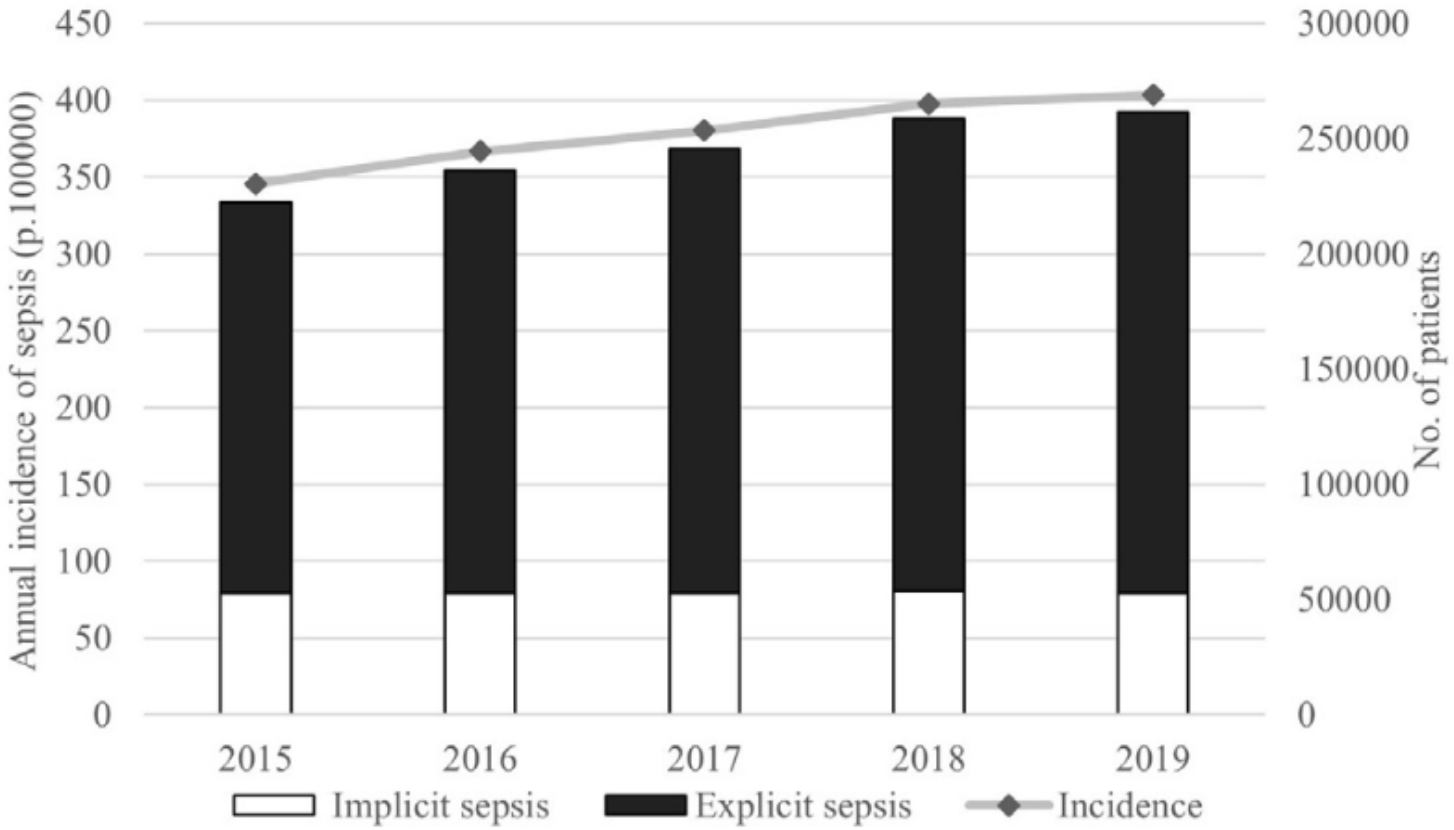

Figure 1 Sepsis incidence per 100 000 inhabitants and number of cases between 2015 and 2019 in metropolitan France.

Pandolfi BMJ Open 2022

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Table 3 Characteristics of hospital stays with sepsis, France 2015–2019

Variables	2015 (n=222 232)	2016 (n=236 314)	2017 (n=245 780)	2018 (n=258 608)	2019 (n=261 499)
Admission source, n (%)					
Home	194 616 (87.6)	202 500 (85.7)	210 221 (85.5)	221 543 (85.7)	223 879 (85.6)
Acute care*	22 651 (10.2)	28 743 (12.2)	30 312 (12.3)	31 483 (12.2)	32 093 (12.3)
Long-term care†	4965 (2.2)	5071 (2.2)	5247 (2.1)	5582 (2.2)	5527 (2.1)
Length of stay (days), n (%)					
<7	53 135 (23.9)	58 561 (24.8)	61 192 (24.9)	68 677 (24.6)	69 367 (24.9)
7–14	65 184 (29.3)	70 842 (30.0)	75 365 (30.7)	89 195 (32.0)	89 297 (32.0)
15–30	62 373 (28.1)	65 549 (27.7)	67 988 (27.7)	78 123 (28.0)	77 442 (27.8)
>30	41 540 (18.7)	41 362 (17.5)	41 235 (16.8)	43 187 (15.4)	42 771 (15.3)
Length of stay, median (P10–P90)	13 (3–43)	13 (3–41)	13 (3–41)	13 (3–40)	12 (3–39)
Septic shock‡, n (%)					
Yes	50 145 (22.6)	49 948 (21.1)	51 964 (21.1)	53 635 (20.7)	54 145 (20.7)
No	172 087 (77.4)	186 366 (78.9)	193 816 (78.9)	204 973 (79.3)	207 354 (79.3)
ICU admission§, n (%)					
Yes	130 587 (58.8)	134 181 (56.8)	137 025 (55.8)	142 001 (54.9)	141 685 (54.2)
No	91 645 (41.2)	102 133 (43.2)	108 755 (44.3)	116 607 (45.1)	119 814 (45.8)
Hospital discharge, n (%)					
Home	106 133 (47.8)	113 812 (48.2)	119 069 (48.5)	127 894 (49.5)	130 250 (49.8)
Acute care*	25 992 (11.7)	29 436 (12.5)	30 904 (12.6)	31 329 (12.1)	30 784 (11.8)
Long-term care†	33 035 (14.9)	34 958 (14.8)	36 198 (14.7)	38 010 (14.7)	38 891 (14.9)
Death	57 072 (25.7)	58 108 (24.6)	59 609 (24.3)	61 375 (23.7)	61 574 (23.6)

*Acute care unit in medicine, surgery or obstetrics or psychiatry unit.
†Follow-up and rehabilitation care unit, long-term care unit or home care.
‡10th revision of the International Classification of Diseases (ICD-10) codes R57.2 and R57.8 as the primary diagnosis, related diagnosis or significant associated diagnosis.
§Including implicit sepsis for which ICU admission is part of the selection criteria.
ICU, intensive care unit.

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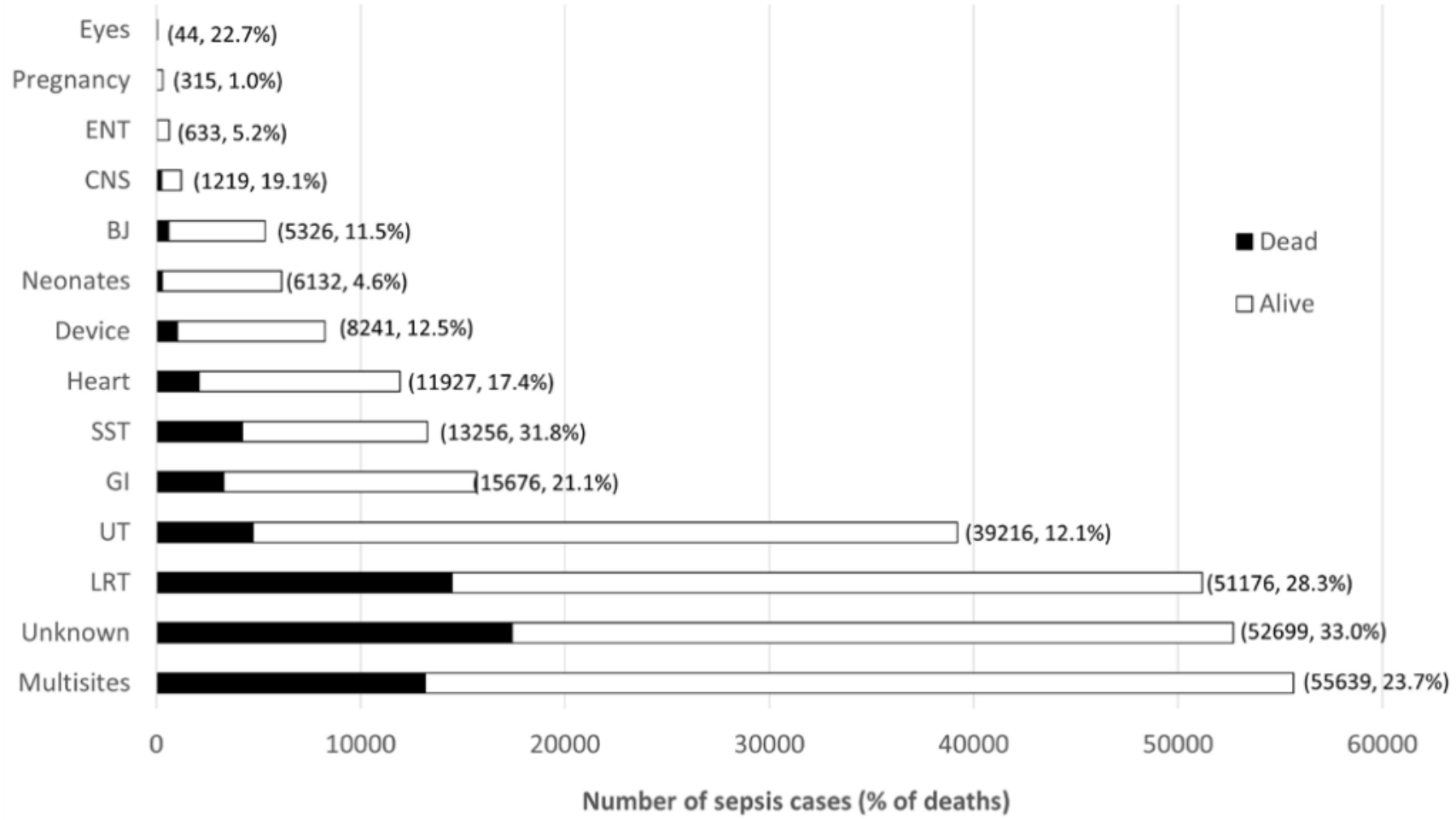

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Mid and long-term consequences

Sepsis survivors

One third	One sixth	40%
die within one year	experience significant morbidity, such as functional limitations	are re-hospitalized within 90 days of discharge

WHO 2020, Rudd Lancet 2020

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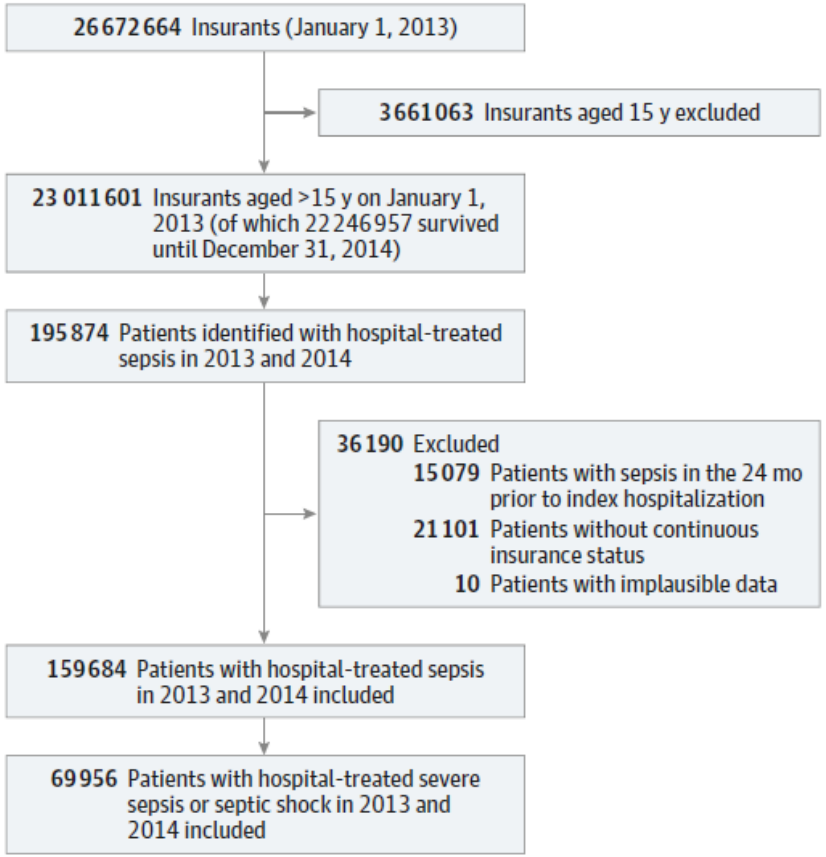
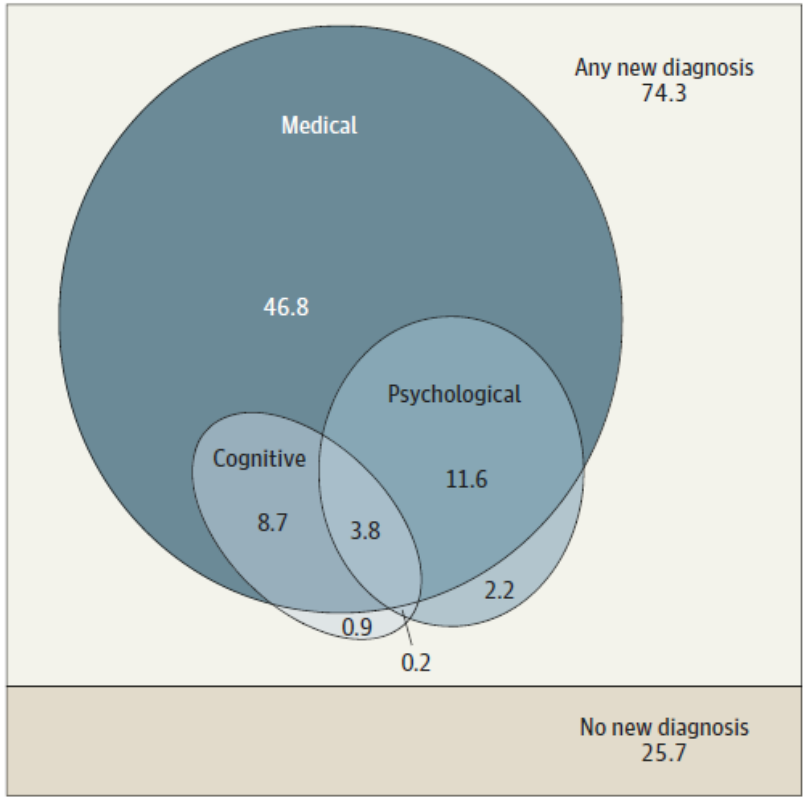
A Flow of cohort



B Postsepsis morbidity by domains and co-occurrence



Percentage of survivors of hospital-treated sepsis in 2013 and 2014 (n = 116 507). New diagnoses 12-mo postsepsis.

Fleischmann-Struzek, Jama NWO 2021

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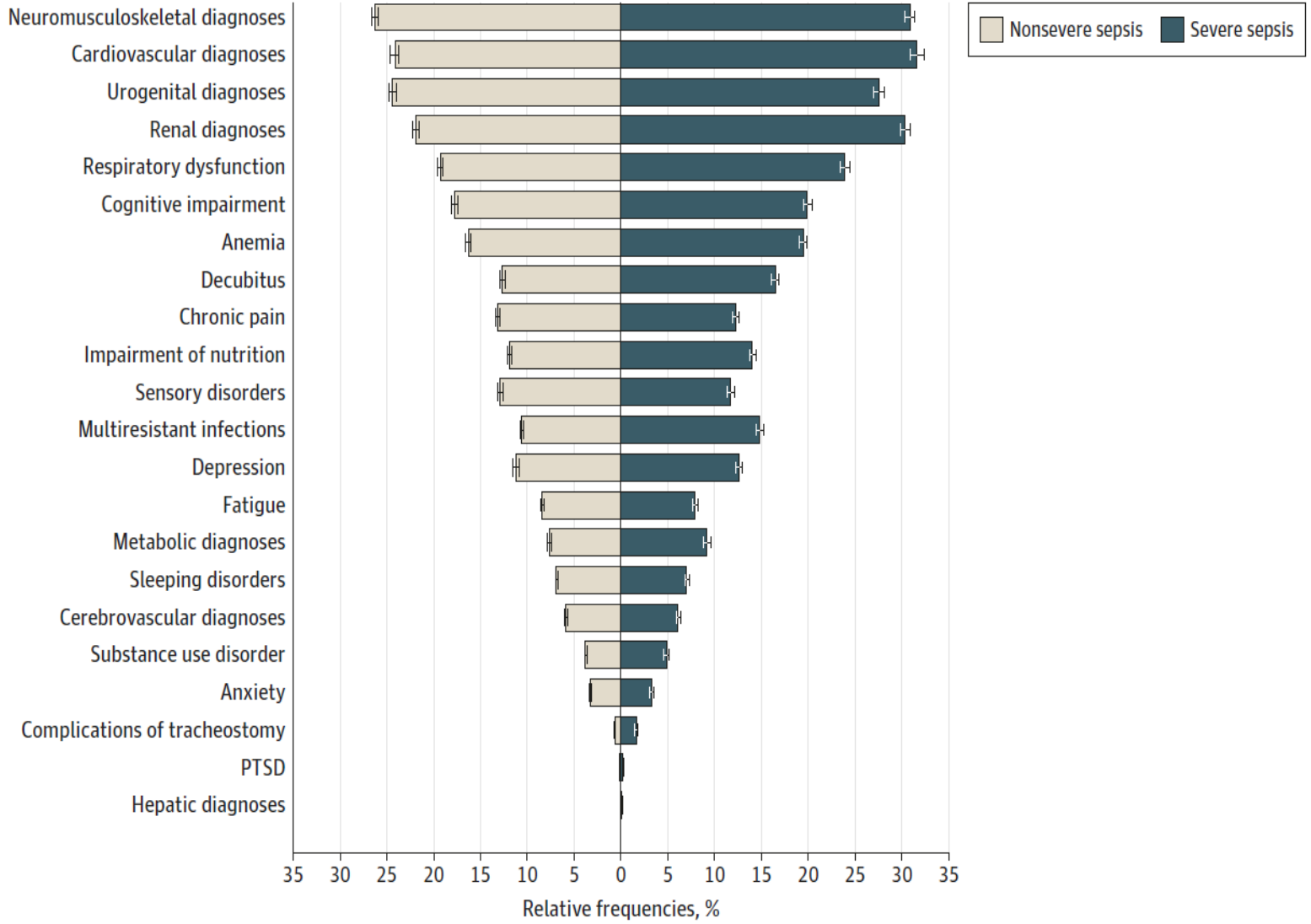
A New diagnoses among survivors of nonsevere vs severe sepsis



Fleischmann-Struzek, Jama NWO 2021

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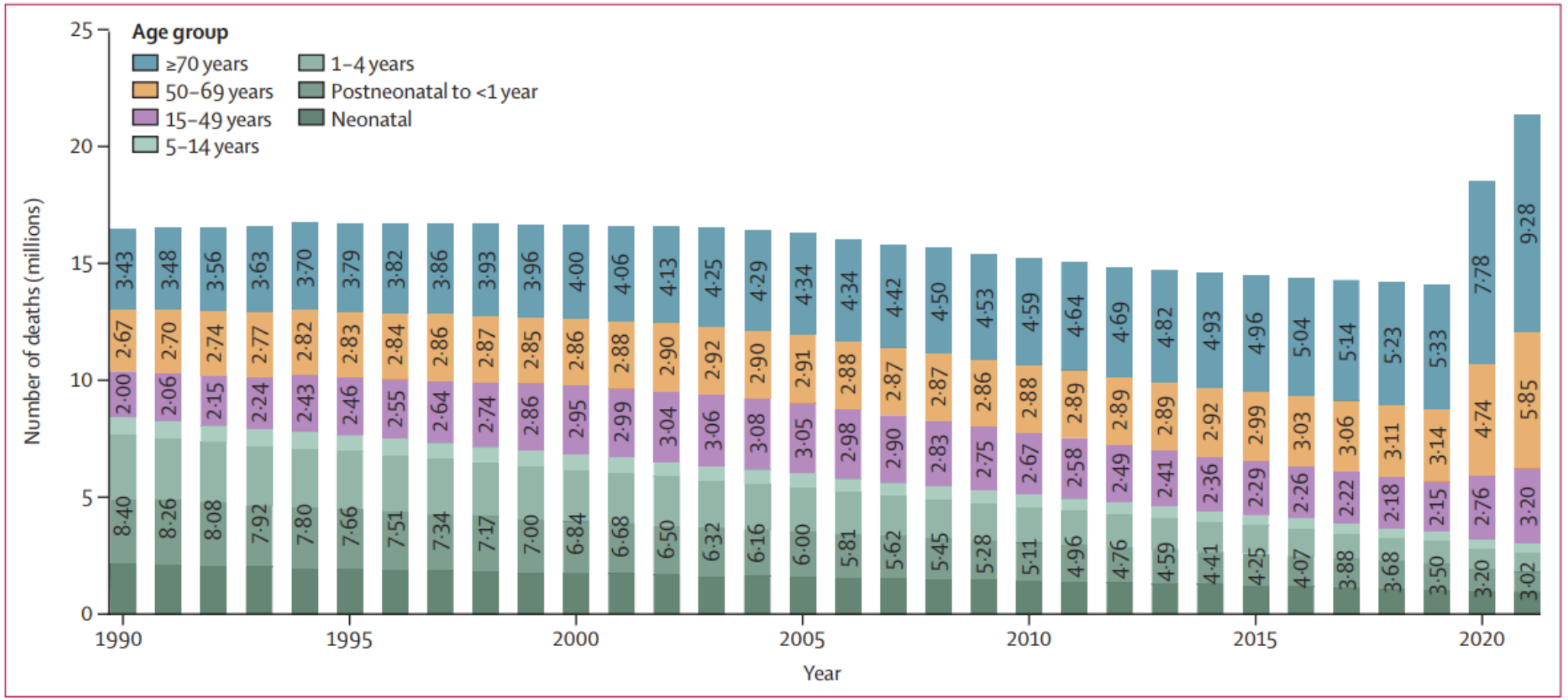

Figure 1: **Global time trend of sepsis, by age, 1990–2021**

Bar labels represent the number of sepsis deaths in a given year for people aged 0–14 years, 15–49 years, 50–69 years, and ≥70 years. Values for the age group of 0–14 years represent the sum of sepsis deaths among neonates, postneonates to <1 year, 1–4 years, and 5–14 years.

GBD 2021 AMR Coll, Lancet 2024

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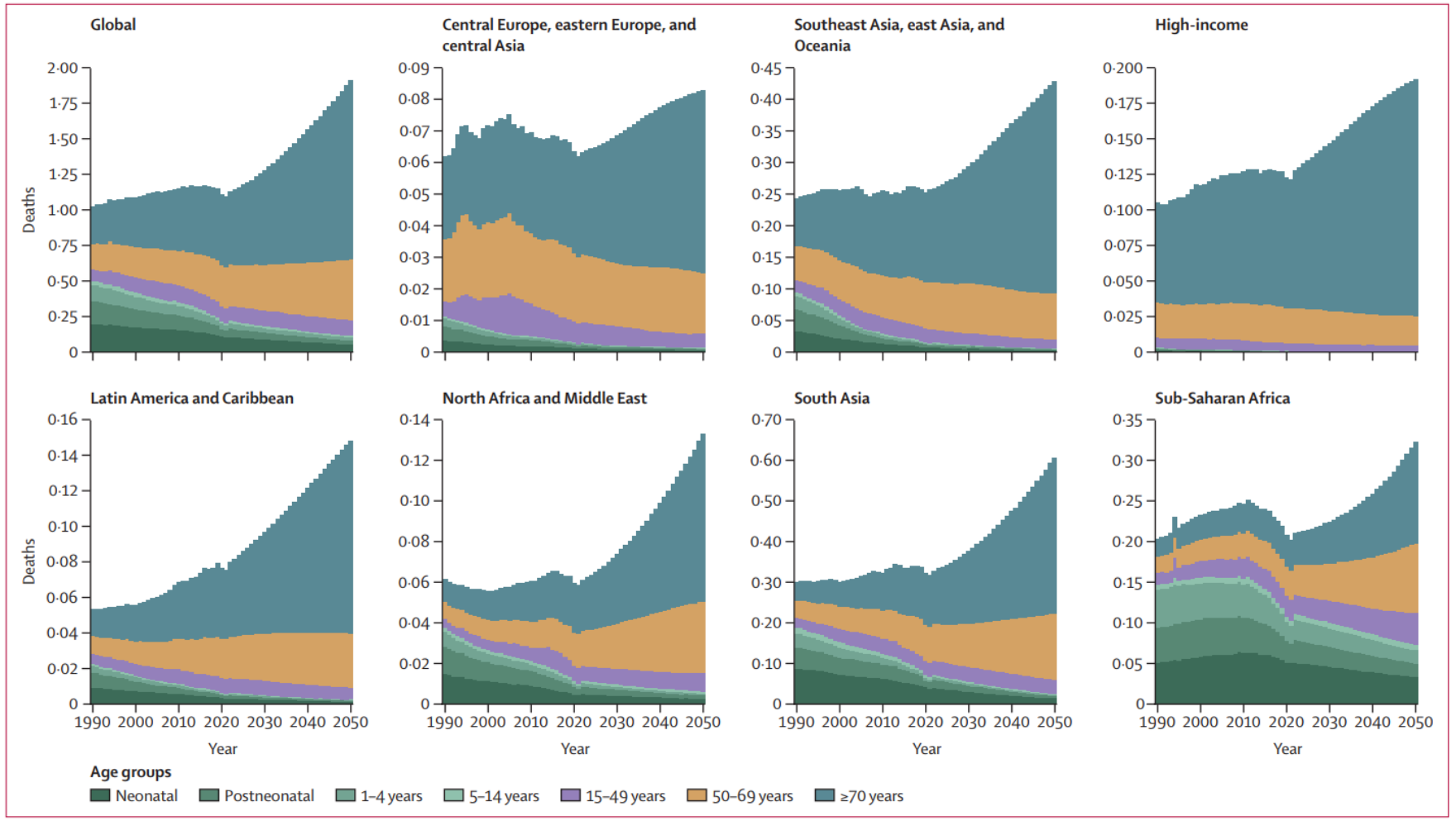

Figure 7: **Deaths attributable to AMR by age group and location in the reference scenario, 2022–2050 Units are in millions.**

GBD 2021 AMR Coll, Lancet 2024

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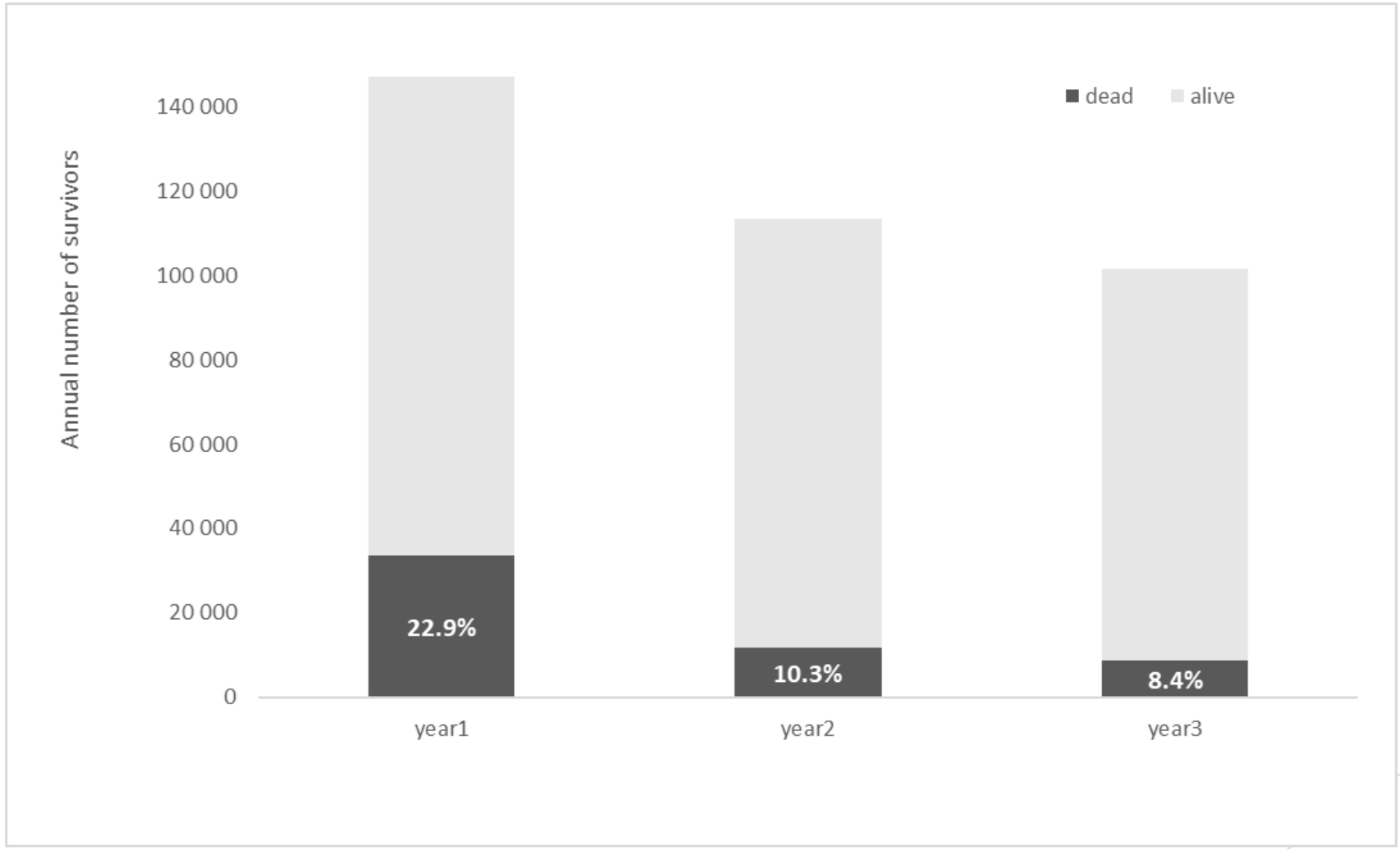

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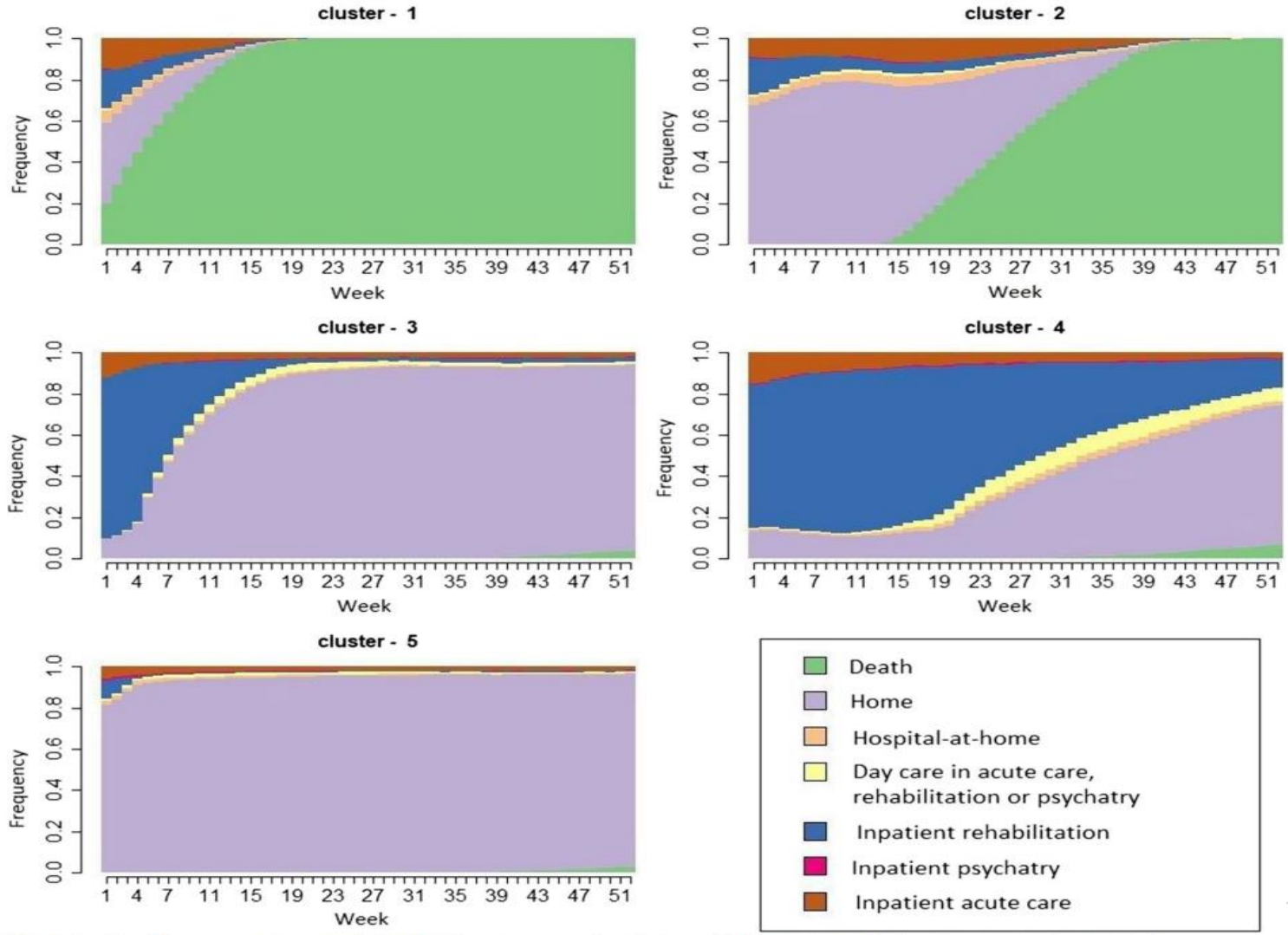

Fig. 2 Results of the state sequence analysis of the 1-year post-sepsis period: weekly distribution of the health states by cluster. This figure is composed of 5 chronograms for each of the 5 identified care trajectories (clusters). On the *x* axis, time is graduated from discharge after the index sepsis hospitalization (week 1) to 1-year post-discharge (week 52). The *y* axis corresponds to the proportion of patients (from 0 to 1) in each health state. Clusters determined by the state sequence analysis of the healthcare pathways of survivors: cluster 1 (early death), cluster 2 (late death), cluster 3 (short-term rehabilitation), cluster 4 (long-term rehabilitation), cluster 5 (home)

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	All survivors			
	1-year pre-sepsis 147013	1-year post sepsis 147013	2-year post sepsis 113415	3-year post sepsis 101730
	k€	K€	K€	
Ambulatory cost	1 333 502. 993	1 571 656.775	974 342.98	792 697.503
Community ambulatory visits				
Cost per patient (median. IQR)	3.240 [1.172 – 8.949]	3.912 [1.314 – 10.683]	3.034 [1.074 – 9.059]	2.803 [0.992 – 8.351]
Total cost	1 142 669.641	1 297 111.175	846 073.693	690 698.280
Hospital outpatient visits				
Cost per patient (median. IQR)	0.165 [0-0.711]	0.243 [0.026-0.802]	0.121 [0 – 0.443]	0.056 [0 – 0.334]
Total cost	190 833.352	274 545.600	128 269.287	101 999.223
Inpatient and day care hospital cost[a]	1 201 965.855	1 819 748.754	1 128 149.215	
Acute care				
Cost per patient (median. IQR)	6.696 [2.881 – 15.055]	8.169 [3.412 – 18.347]	6.005 [2.437 – 14.081]	5.524 [2.315 – 12.811]
Total cost	931 864.990	1 345 811.905	590 421.971	437 722.356
Total extra medication costs [b]	87 776.781	112 631.972	59 645.276	45 004.167
Rehabilitation				
Cost per patient (median. IQR)	7.816 [2.467 – 17.906]	8.127 [2.459-20.036]	11.044 [3.470 – 25.890]	11.886 [4.433 – 25.166]
Total cost	181 827.564	359 450.540	165 582.968	129 187.626
Total extra medication costs [b]	496.521	1 854.337	312 499	149 401

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Recommandations de bonnes pratiques - HAS

HAUTE AUTORITÉ DE SANTÉ

RECOMMANDER LES BONNES PRATIQUES

NOTE DE CADRAGE

Prise en charge du sepsis du nouveau-né, de l'enfant et de l'adulte : recommandations pour un parcours de soins intégré

Validée par le Collège le 16 février 2022

Date de la saisine : 11 juin 2019 **Demandeur** : Direction Générale de la Santé

Service(s) : SBP/URBP

Personne(s) chargée(s) du projet : E. Nouyrigat

Groupe de travail

Le coordonnateur de l'élaboration de la recommandation de bonne pratique est le Pr Djillali ANNANE (réanimateur, Garches), membre de la Société de réanimation de langue française (SRLF).

Le groupe de travail comprend une quinzaine de sociétés savantes dont les représentants travailleront dans différents **sous-groupes en fonction des 3 étapes du parcours de soins intégré : amont de l'urgence** (avant l'enclenchement du dispositif d'urgence), **pendant l'urgence** (phase aiguë), **aval de l'urgence** (période post-aiguë hospitalière et à domicile) :

- Collège national des généralistes enseignants (CNGE) : 3 membres
- Groupe de pathologies infectieuses pédiatriques (GPIP) : 1 membre
- Groupe francophone de réanimation et urgences pédiatriques (GFRUP) : 2 membres
- Société de pathologie infectieuse de langue française (SPILF) : 4 membres
- Société de réanimation de langue française (SRLF) : 5 membres
- Société française d'anesthésie réanimation (SFAR) : 2 membres
- Société française d'hygiène hospitalière (SF2H) : 2 membres
- Société française de gériatrie et gérontologie (SFGG) : 2 membres
- Société française de médecine d'urgence (SFMU) : 2 membres
- Société française de médecine physique et de réadaptation (SOFMER) : 5 membres
- Société française de microbiologie (SFM) : 3 membres
- Société française de mycologie médicale (SFMM) : 1 membre
- Société française de néonatologie (SFN) : 1 membre
- Société française de pédiatrie (SFP) : 1 membre
- Société française de santé publique (SFSP) : 1 membre
- France Sepsis Association (association d'usagers) : 1 membre

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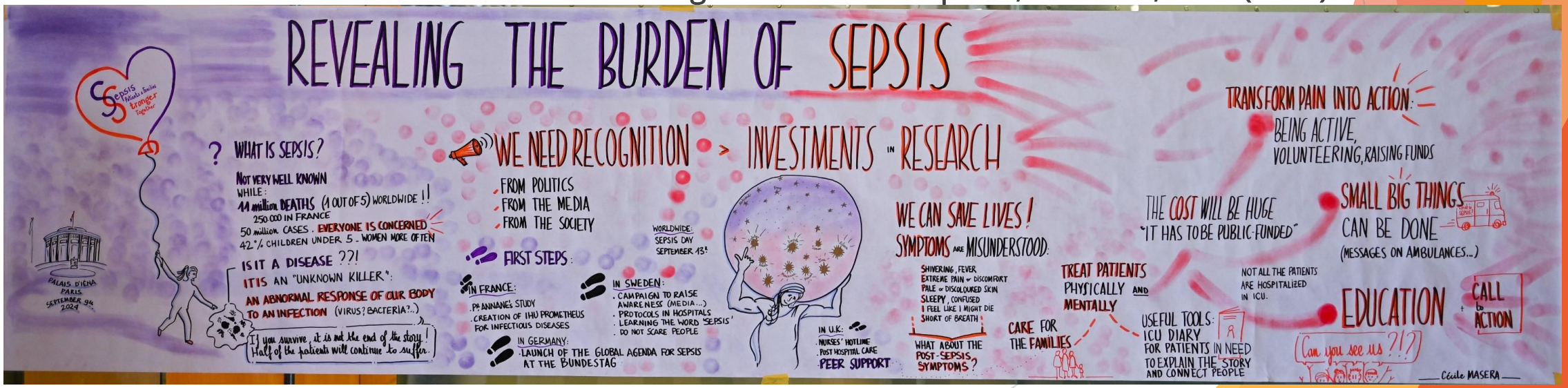
Sepsis survivors call for the development of a European sepsis plan

www.thelancet.com Published online October 3, 2024

Published Online
October 3, 2024
https://doi.org/10.1016/
S0140-6736(24)02078-6

« Revealing the burden of sepsis », 09/09/24, CESE (Paris)



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Launch of the 2030 Global Agenda for Sepsis, 10/09/24, German Bundestag (Berlin)

With:

- Stefan Schwartze, the Federal Government Commissioner for Patients
- Prof. Konrad Reinhart, Founding President of the GSA, and Dr. Mariam Jashi, CEO of the GSA
- Mr. Roland Göhde, Co-founder and CEO of the Virchow Foundation and CEO of the German Health Alliance
- Dr. Hans Henri P. Kluge, WHO Regional Director for Europe
- Prof. Dr. Axel R. Pries, President, World Health Summit
- Dr. Rudi Eggers, Director, Director Integrated Health Services, World Health Organization
- Prof. Djillali Annane, Dean, Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines
- Mariah McKimbrough, an artist and sepsis survivor (Sepsis Stiftung as its Art Director)

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1-hour Bundle

Surviving Sepsis Campaign Guidelines

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Step 1

- Recognizing sepsis

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2021 RECOMMENDATIONS ON
SCREENING FOR PATIENTS WITH SEPSIS AND SEPTIC SHOCK

Surviving Sepsis Campaign®

For hospitals and health systems, we **recommend** using a performance improvement programme for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment.

Screening

Standard operating procedures

We **recommend against** using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.

For adults suspected of having sepsis, we **suggest** measuring blood lactate.

ESICM
The Intensive Care Connection

Society of Critical Care Medicine
The Intensive Care Professionals

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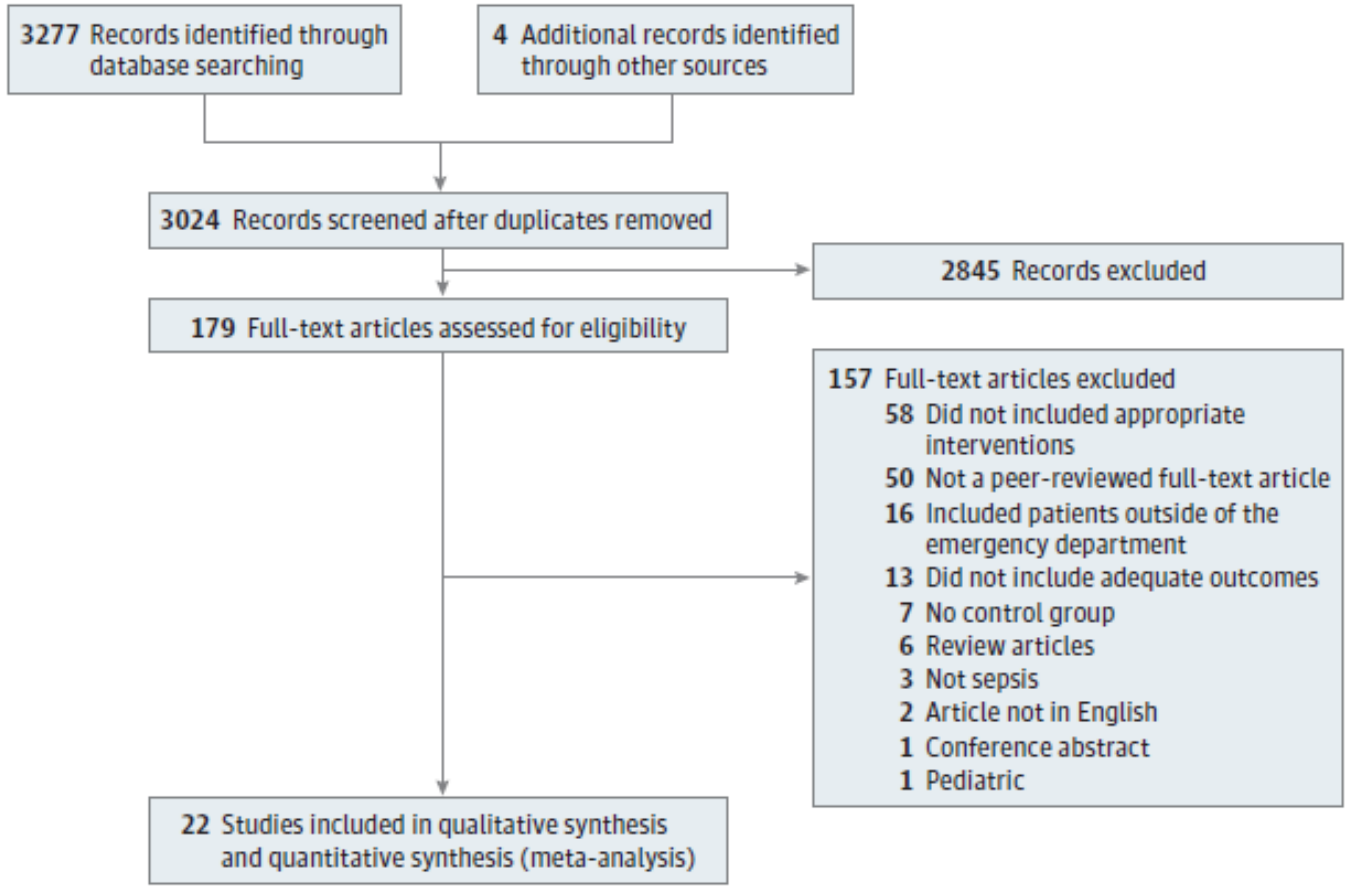
Figure 1. Flowchart of the Study Selection Process



Sepsis Alert Systems, Mortality, and Adherence in Emergency Department
A Systematic Review and Meta-Analysis – Kim et al, 2024

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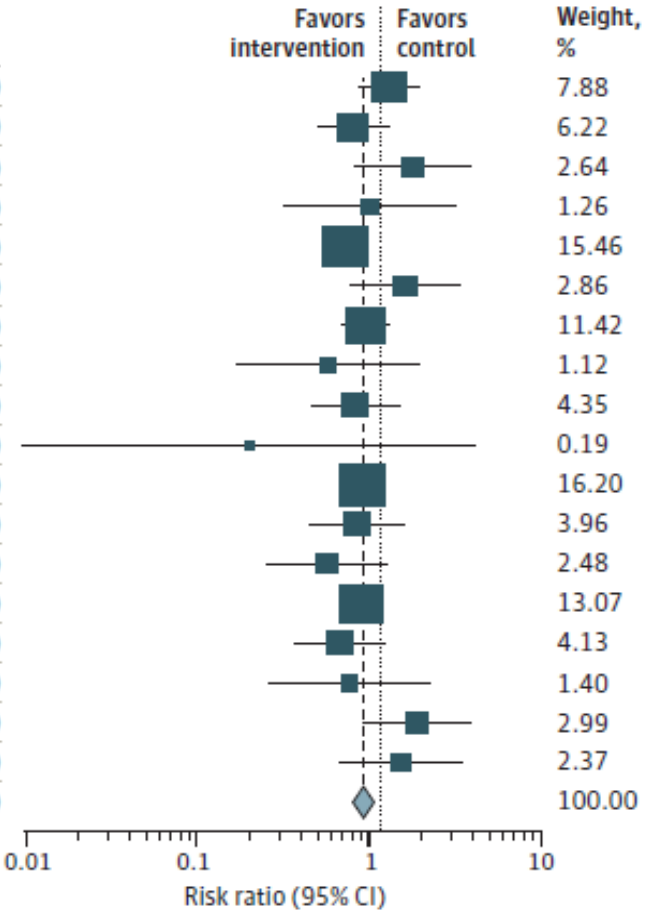
Figure 2. Association of Sepsis Alert Systems With Mortality of Patients in the Emergency Department

Study	Treatment, No./ Total No.	Control, No./ Total No.	Risk ratio (95% CI)	Weight, %
Berger et al,[20] 2010	52/908	46/890	1.11 (0.75-1.63)	7.88
Patocka et al,[21] 2014	26/170	40/185	0.71 (0.45-1.11)	6.22
Hayden et al,[22] 2016	18/130	10/108	1.50 (0.72-3.10)	2.64
Idrees et al,[23] 2016	5/45	7/55	0.87 (0.30-2.57)	1.26
Arabi et al,[25] 2017	60/195	208/436	0.64 (0.51-0.81)	15.46
Rosenqvist et al,[26] 2017	27/152	9/69	1.36 (0.68-2.74)	2.86
Austrian et al,[27] 2018	91/1306	71/838	0.82 (0.61-1.11)	11.42
McDonald et al,[28] 2018	4/270	10/346	0.51 (0.16-1.62)	1.12
Shah et al,[29] 2018	15/57	21/58	0.73 (0.42-1.26)	4.35
Borrelli et al,[30] 2019	0/20	5/43	0.19 (0.01-3.29)	0.19
Song et al,[32] 2019	93/315	118/316	0.79 (0.63-0.99)	16.20
Petit et al,[35] 2020	19/350	24/328	0.74 (0.41-1.33)	3.96
Threatt et al,[36] 2020	9/145	20/165	0.51 (0.24-1.09)	2.48
Rosenqvist et al,[37] 2020	85/533	90/443	0.78 (0.60-1.03)	13.07
Tarabichi et al,[38] 2022	17/285	31/313	0.60 (0.34-1.06)	4.13
Troncoso et al,[39] 2023	6/109	8/98	0.67 (0.24-1.88)	1.40
Schinkel et al,[40] 2023	19/133	12/132	1.57 (0.79-3.11)	2.99
Roman et al,[41] 2023	15/104	9/80	1.28 (0.59-2.78)	2.37
Overall, DL	561/5227	739/4903	0.81 (0.71-0.91)	100.00

(I^2 = 18.2%, P = .24)



Kim et al, 2024

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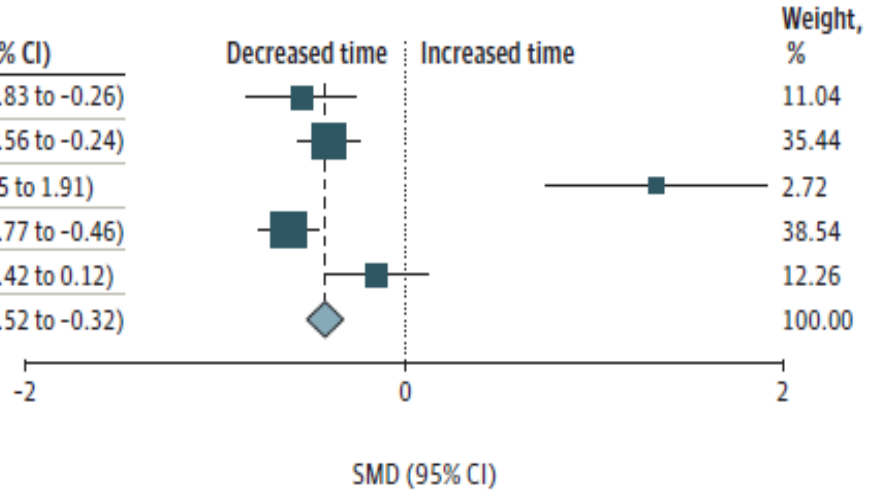
A Time to intravenous fluid administration

Study	Treatment Participants, No.	Treatment Time, mean (SD), min	Control Participants, No.	Control Time, mean (SD), min	SMD (95% CI)	Weight, %
Hayden et al,[22] 2016	120	51.40 (47.50)	80	81.90 (66.80)	-0.54 (-0.83 to -0.26)	11.04
McDonald et al,[28] 2018	270	90.70 (86.40)	346	131.00 (111.00)	-0.40 (-0.56 to -0.24)	35.44
Borrelli et al,[30] 2019	20	46.00 (32.96)	43	6.50 (28.15)	1.33 (0.75 to 1.91)	2.72
Petit et al,[35] 2020	350	38.00 (36.30)	328	134.00 (222.22)	-0.61 (-0.77 to -0.46)	38.54
Troncoso et al,[39] 2023	109	54.00 (50.40)	98	61.00 (41.40)	-0.15 (-0.42 to 0.12)	12.26
Overall	869		895		-0.42 (-0.52 to -0.32)	100.00

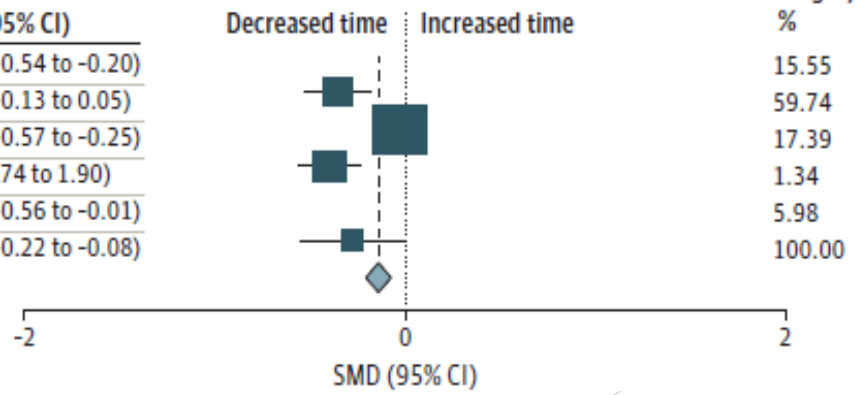
$I^2 = 91.2\%$; $P < .001$; Egger $P = .09$



D Time to lactate measurement

Study	Treatment Participants, No.	Treatment Time, mean (SD), min	Control Participants, No.	Control Time, mean (SD), min	SMD (95% CI)	Weight, %
Arabi et al,[25] 2017	195	150.00 (318.00)	436	558.00 (1326.00)	-0.37 (-0.54 to -0.20)	15.55
Austrian et al,[27] 2018	1306	230.40 (835.20)	838	273.60 (1353.60)	-0.04 (-0.13 to 0.05)	59.74
McDonald et al,[28] 2018	270	71.80 (53.70)	346	131.10 (187.90)	-0.41 (-0.57 to -0.25)	17.39
Borrelli et al,[30] 2019	20	46.00 (17.04)	43	15.00 (25.93)	1.32 (0.74 to 1.90)	1.34
Troncoso et al,[39] 2023	109	28.00 (20.70)	98	35.00 (28.10)	-0.29 (-0.56 to -0.01)	5.98
Overall	1900		1761		-0.15 (-0.22 to -0.08)	100.00

$I^2 = 91.6\%$; $P < .001$; Egger $P = .85$



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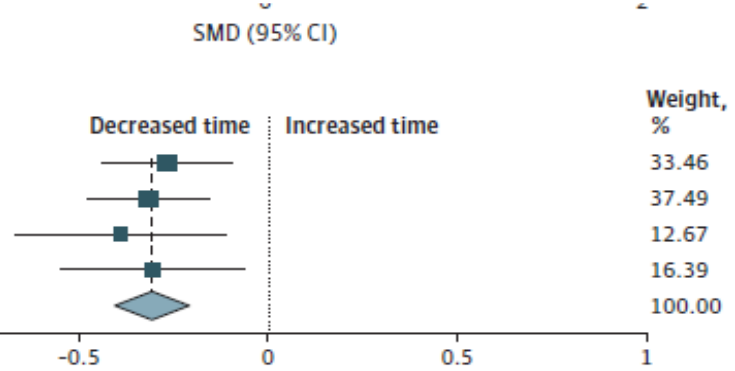
B Time to blood culture

Study	Treatment Participants, No.	Treatment Time, mean (SD), min	Control Participants, No.	Control Time, mean (SD), min	SMD (95% CI)	Weight, %
Arabi et al,[25] 2017	195	54.00 (84.00)	436	144.00 (402.00)	-0.27 (-0.44 to -0.10)	33.46
McDonald et al,[28] 2018	270	73.50 (56.20)	346	109.80 (146.20)	-0.31 (-0.47 to -0.15)	37.49
Troncoso et al,[29] 2023	109	28.00 (20.70)	98	38.00 (30.30)	-0.39 (-0.66 to -0.11)	12.67
Schinkel et al,[40] 2023	133	24.00 (29.63)	132	42.00 (78.52)	-0.30 (-0.55 to -0.06)	16.39
Overall	707		1012		-0.31 (-0.40 to -0.21)	100.00

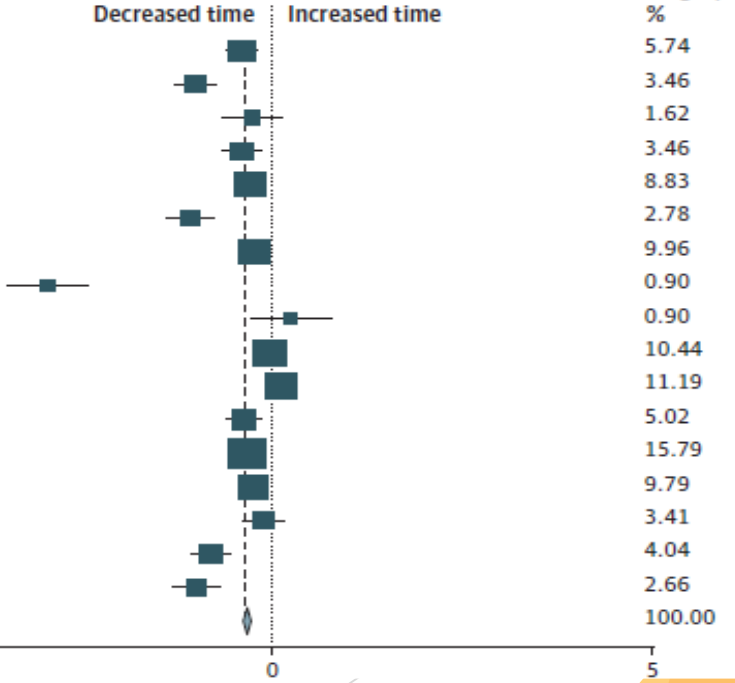
$I^2 = 0.0\%$; $P = .90$; Egger $P = .34$



C Time to antibiotic administration

Study	Treatment Participants, No.	Treatment Time, mean (SD), min	Control Participants, No.	Control Time, mean (SD), min	SMD (95% CI)	Weight, %
Patocka et al,[21] 2014	170	207.00 (150.00)	185	283.00 (213.00)	-0.41 (-0.62 to -0.20)	5.74
Hayden et al,[22] 2016	130	80.60 (38.80)	108	40 (74.30)	-1.02 (-1.29 to -0.75)	3.46
Idrees et al,[23] 2016	45	85.00 (66.67)	55	105.00 (77.78)	-0.27 (-0.67 to 0.12)	1.62
Narayanan et al,[24] 2016	103	29.00 (42.20)	111	61.50 (102.20)	-0.41 (-0.68 to -0.14)	3.46
Arabi et al,[25] 2017	195	180.00 (216.00)	436	288.00 (402.00)	-0.30 (-0.47 to -0.13)	8.83
Rosenqvist et al,[26] 2017	152	261.00 (257.00)	69	719.10 (649.30)	-1.09 (-1.39 to -0.79)	2.78
McDonald et al,[28] 2018	270	191.80 (303.90)	346	253.90 (193.60)	-0.25 (-0.41 to -0.09)	9.96
Shah et al,[29] 2018	57	61.50 (19.05)	58	154.50 (39.85)	-2.97 (-3.50 to -2.44)	0.90
Borrelli et al,[30] 2019	20	72.00 (38.89)	43	63.50 (35.56)	0.23 (-0.30 to 0.76)	0.90
Song et al,[32] 2019	315	121.00 (91.11)	316	125.00 (91.85)	-0.04 (-0.20 to 0.11)	10.44
Petit et al,[35] 2020	350	244.00 (167.41)	328	226.00 (160.00)	0.11 (-0.04 to 0.26)	11.19
Threatt et al,[36] 2020	145	84.00 (150.00)	165	185.00 (337.00)	-0.38 (-0.60 to -0.15)	5.02
Rosenqvist et al,[37] 2020	533	26.00 (13.33)	443	37.00 (45.93)	-0.34 (-0.47 to -0.21)	15.79
Tarabichi et al,[38] 2022	285	138.00 (146.67)	313	180.00 (173.33)	-0.26 (-0.42 to -0.10)	9.79
Troncoso et al,[39] 2023	109	94.00 (68.00)	98	103.00 (76.00)	-0.13 (-0.40 to 0.15)	3.41
Schinkel et al,[40] 2023	133	66.00 (62.04)	132	143.00 (117.78)	-0.82 (-1.07 to -0.57)	4.04
Roman et al,[41] 2023	104	38.00 (20.00)	80	91.00 (77.04)	-1.00 (-1.31 to -0.69)	2.66
Overall	3116		3286		-0.34 (-0.39 to -0.29)	100.00

$I^2 = 93.1\%$; $P < .001$; Egger $P = .01$



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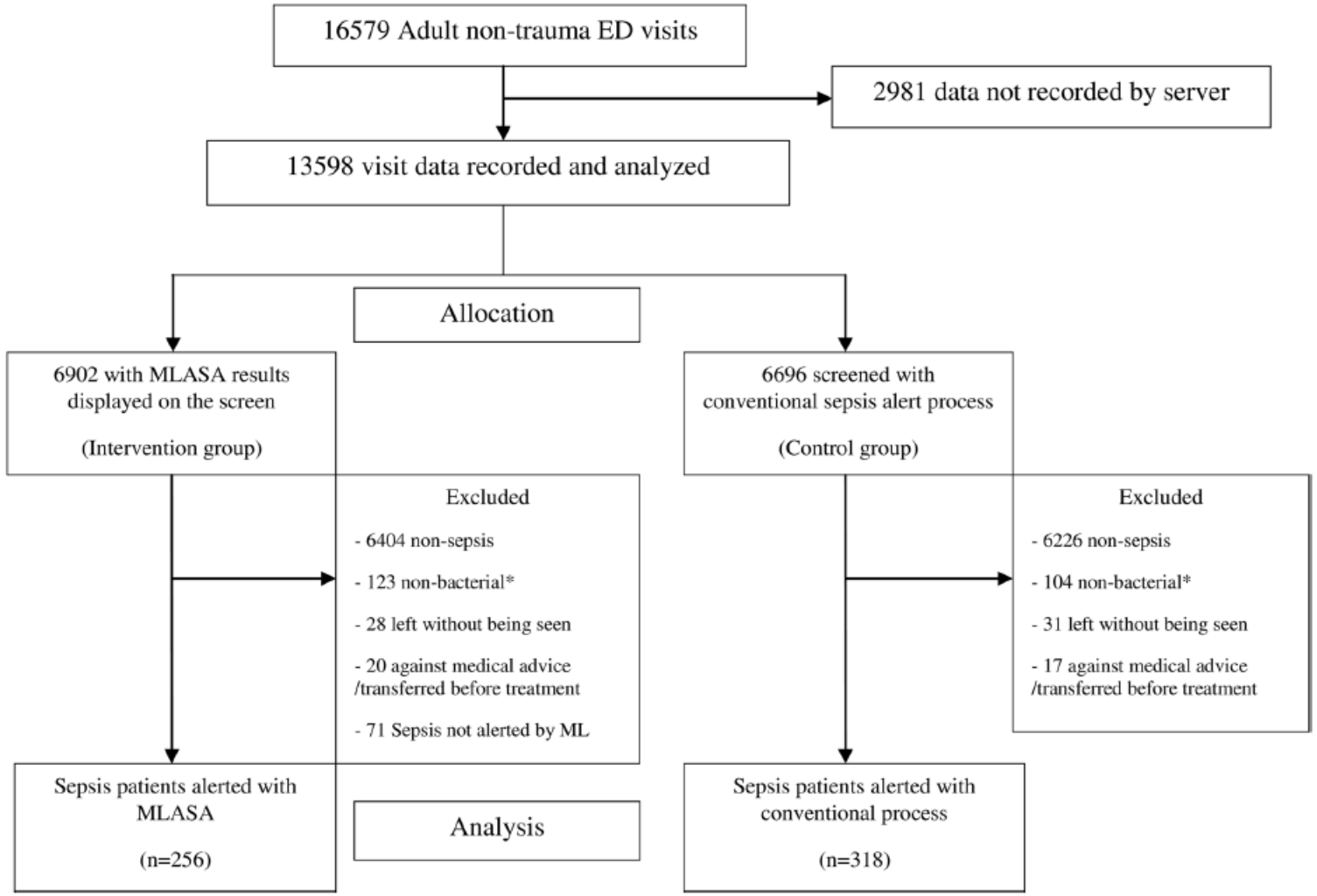

Fig. 1 The CONSORT diagram demonstrating patient flow. *Non-bacterial infections (e.g., coronavirus, influenza, tuberculosis) that do not require antibacterial treatment

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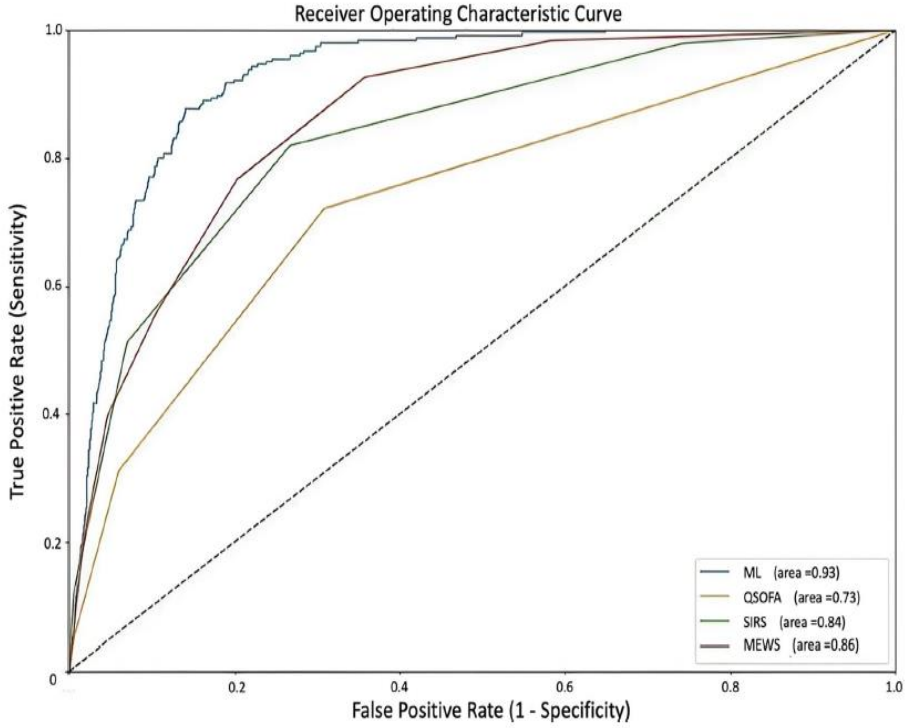

Fig. 2 Receiver operating characteristic curves (ROCs) and AUROCs of sepsis recognition among the tests

Table 4 The diagnostic parameters of sepsis recognition among the tests

Tests	Sensitivity	Specificity	PPV	NPV	AUROC	*P*
MLASA	79.69 (76.37–82.73)	88.24 (87.67–88.79)	25.23 (24.10–26.40)	98.87 (98.68–99.03)	0.93 (0.92–0.94)	Ref
qSOFA	31.15 (25.39–37.37)	93.99 (93.28–94.64)	20.82 (17.46–24.63)	96.41 (96.11–96.70)	0.73 (0.71–0.76)	< 0.001
MEWS	55.74 (49.26–62.07)	89.49 (88.59–90.35)	21.22 (18.99–23.63)	97.55 (97.19–97.87)	0.86 (0.84–0.89)	< 0.001
SIRS	81.91 (71.99–86.58)	73.27 (71.99–74.52)	13.47 (12.62–14.37)	98.77 (98.39–99.05)	0.84 (0.82–0.85)	< 0.001

P values were calculated to compare the AUROC of MLASA (used as a reference) among that of the other sepsis scoring systems

MLASA machine learning-assisted sepsis alert, *qSOFA* quick sepsis related organ failure score, *MEWS* Modified Early Warning Score, *SIRS* systemic inflammatory response syndrome criteria, *PPV* positive predictive value, *NPV* positive predictive value, *AUROC* area under receiver operating characteristic curve

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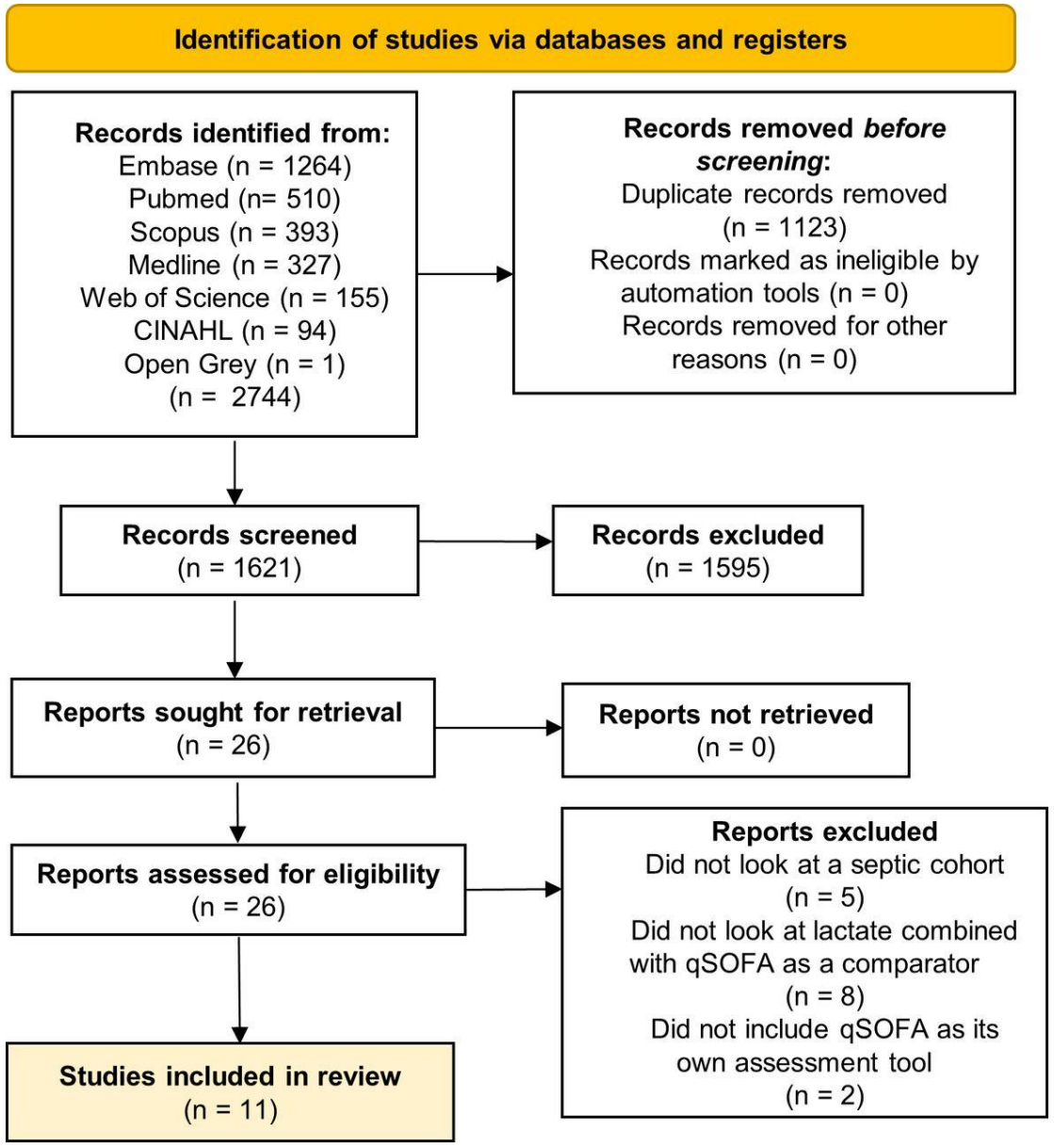

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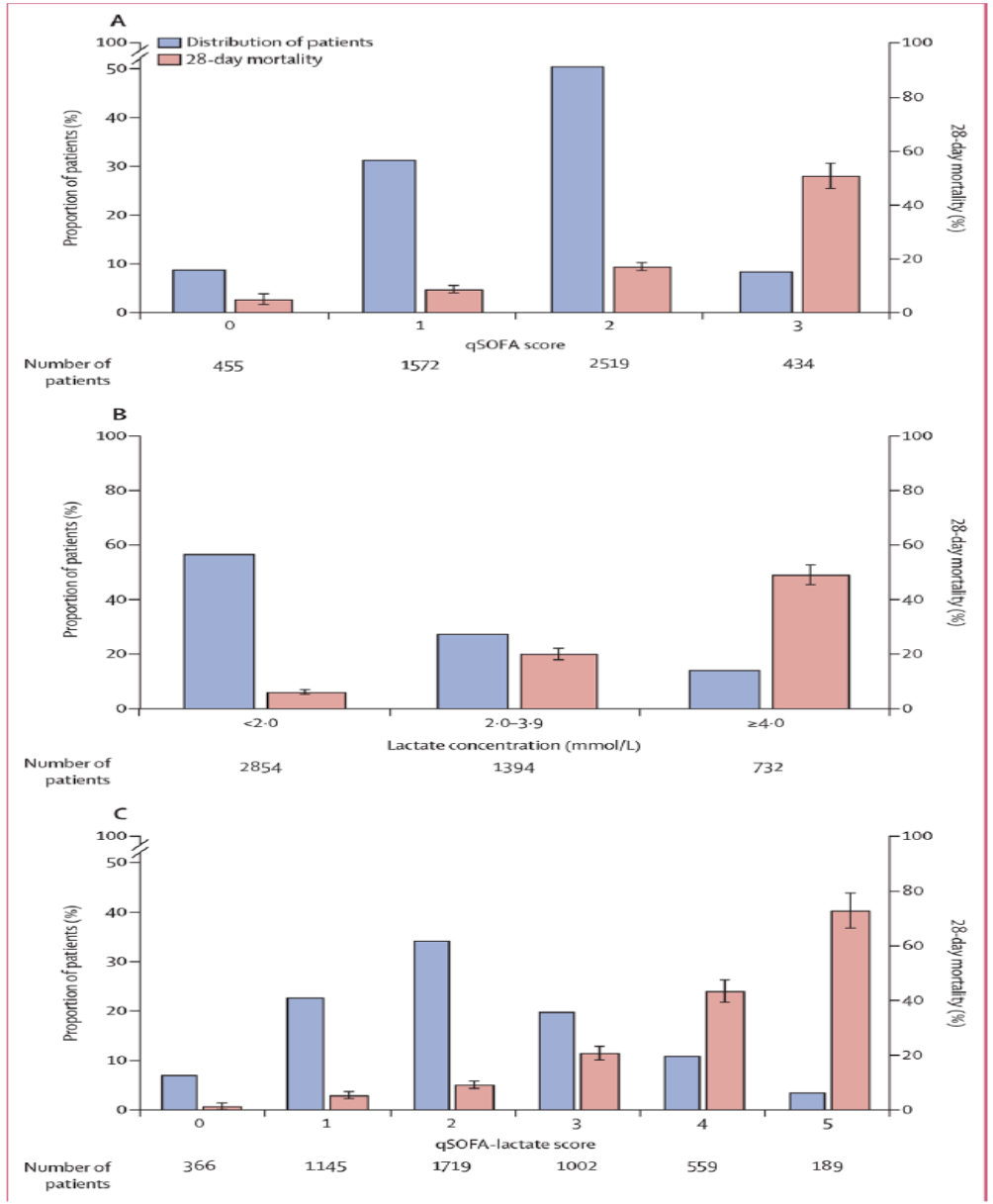

Figure 2: Distribution of patients and 28-day mortality by qSOFA score, lactate concentration, and qSOFA-lactate score in the derivation cohort

Bars show distribution of patients (blue bars) and 28-day mortality (red bars) by qSOFA score (A), lactate concentration (B), or qSOFA-lactate score (C). Error bars show 95% CIs for 28-day mortality. qSOFA=quick Sequential Organ Failure Assessment.

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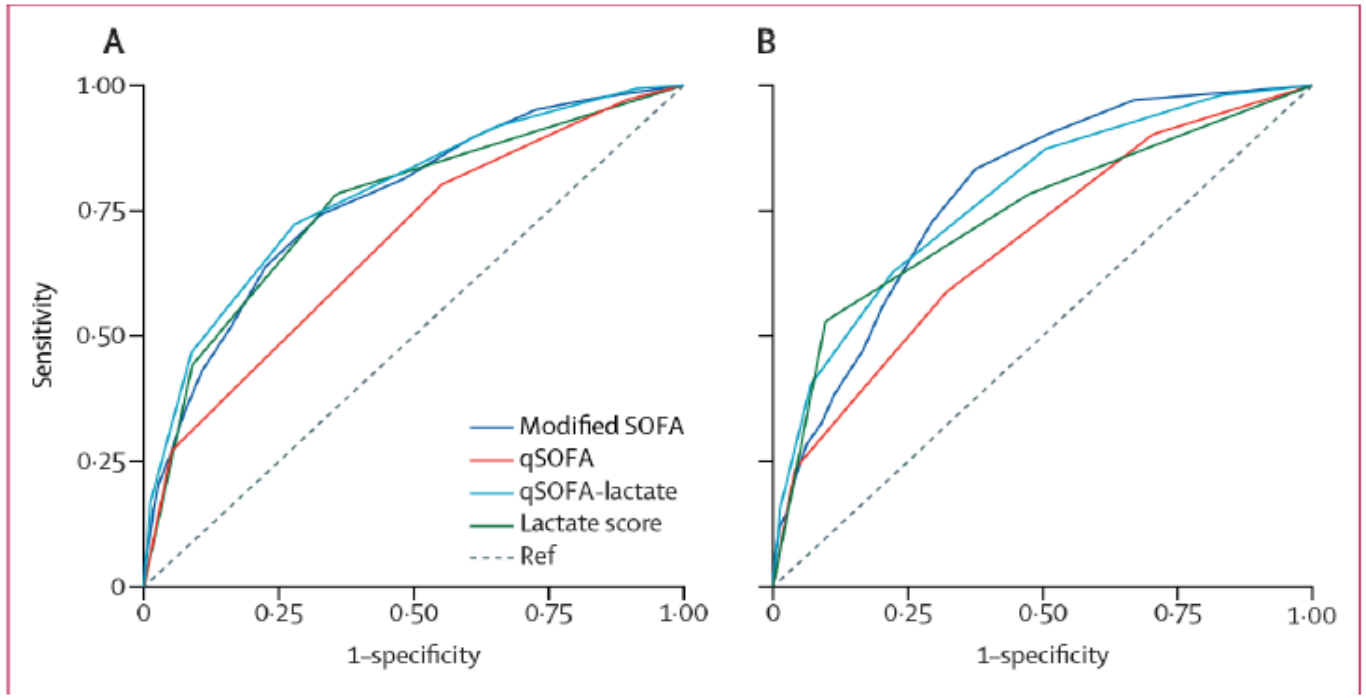

Figure 3: Receiver operating curves for mortality discrimination

Area under the receiver operating curves (AUROC) for the modified SOFA, qSOFA, qSOFA-lactate, and ternary lactate score models for 28-day mortality discrimination in the derivation cohort (A) and external validation cohort (B). SOFA=Sequential Organ Failure Assessment. qSOFA=quick Sequential Organ Failure Assessment.

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Step 1	• Recognizing sepsis
Step 2	• Start ATB

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Antibiotic Timing

Shock is present

Shock is absent

	Shock is present	Shock is absent
Sepsis is definite or probable	☑ Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.	☑ Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.
Sepsis is possible	☑ Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.	☑ Rapid assessment* of infectious vs. noninfectious causes of acute illness. ☑ Administer antimicrobials ***within 3 hours*** if concern for infection persists.

**Rapid assessment includes history and clinical examination, tests for both infectious and noninfectious causes of acute illness, and immediate treatment of acute conditions that can mimic sepsis. Whenever possible, this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.*

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Effect of the 1-h bundle on mortality in patients with suspected sepsis in the emergency department: a stepped wedge cluster randomized clinical trial

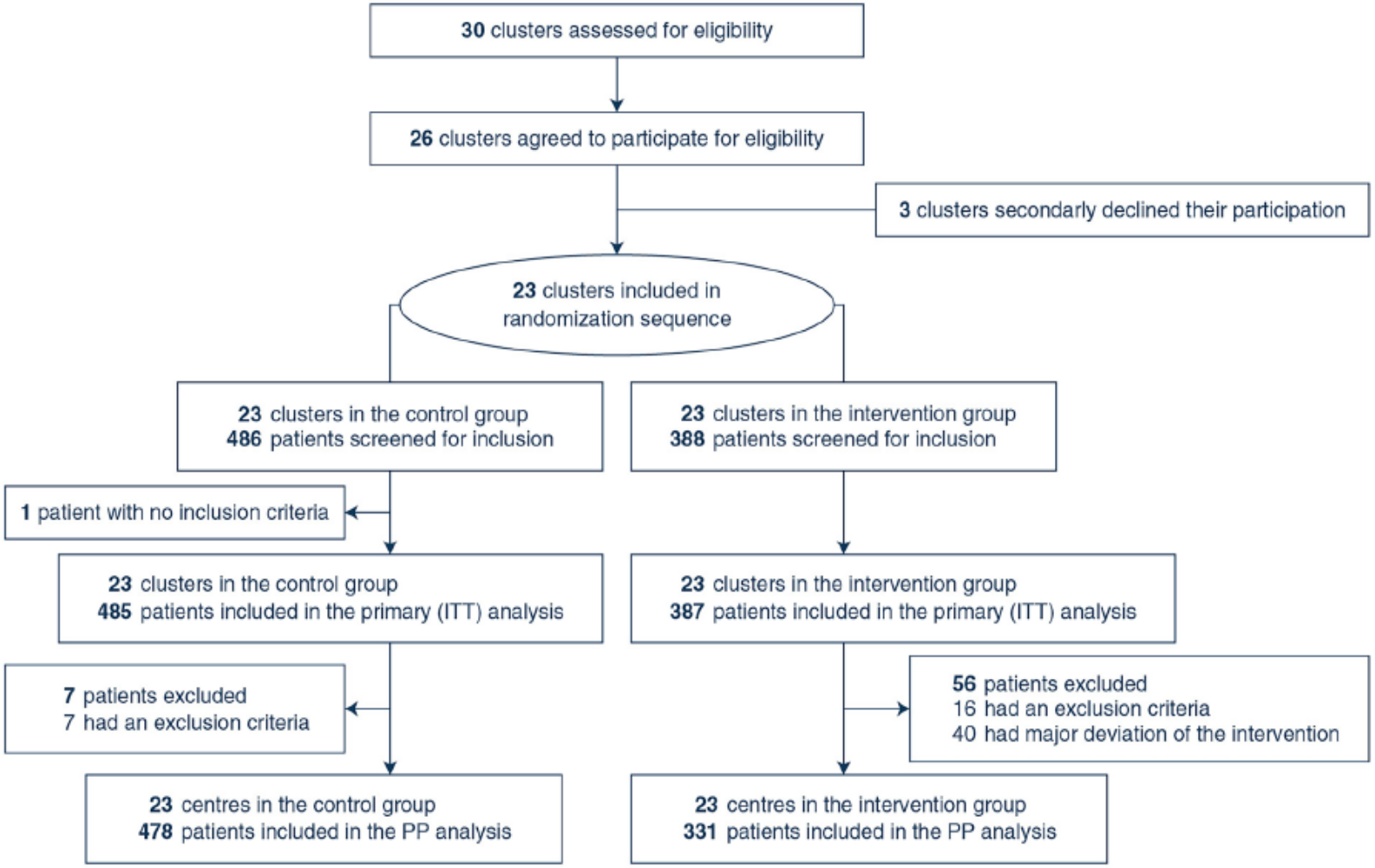

Fig. 1 Flow chart of clusters and patients. *ITT* intention to treat. *PP* per protocol

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Effect of the 1-h bundle on mortality in patients with suspected sepsis in the emergency department: a stepped wedge cluster randomized clinical trial

Table 2 Treatment received in the emergency department

Variable	Intervention		Control		Unadjusted difference	*p* value
	n = 387		*n* = 485			
Broad-spectrum antibiotics	*n*		*n*			
Broad-spectrum antibiotics, no (%)	386	371 (96.1)	485	432 (89.1)	7 (3.4 to 10.7)	0.0001
Broad-spectrum antibiotics within 1 h, no (%)	384	244 (63.5)	475	151 (31.8)	31.8 (25.1 to 38.4)	< 0.0001
Time between inclusion and broad-spectrum antibiotics initiation (minutes), median [IQR]	369	40 (10; 77)	422	113 (26; 241)	− 73 (− 92.6 to − 53.4)	< 0.0001
Fluid resuscitation						
Fluid resuscitation, no (%)	383	346 (90.3)	484	407 (84.1)	6.2 (1.6 to 10.9)	0.007
Fluid resuscitation within 1 h[a], no (%)	201	148 (73.6)	254	117 (46.1)	27.6 (18.5 to 36.7)	< 0.0001
Time between inclusion and fluid resuscitation (minutes), median [IQR]	305	16 (3; 44)	305	30 (4; 97)	− 14 (− 22.5 to − 5.5)	
Perfused volume in the first 3 h (mL), median [IQR]	379	1000 (500; 2000)	472	750 (250; 1500)	250 (− 100 to 600)	< 0.0001
Lactate						
Lactate performed, no (%)	383	371 (96.9)	485	421 (86.8)	10.1 (6.3 to 13.8)	< 0.0001
Lactate performed within 1 h, no (%)	382	221 (57.9)	479	212 (44.3)	13.6 (6.7 to 20.5)	< 0.0001

[a] Fluids resuscitation among patients with systolic blood pressure < 90 mmHg or a lactate > 4 mmol/L

IQR interquartile range

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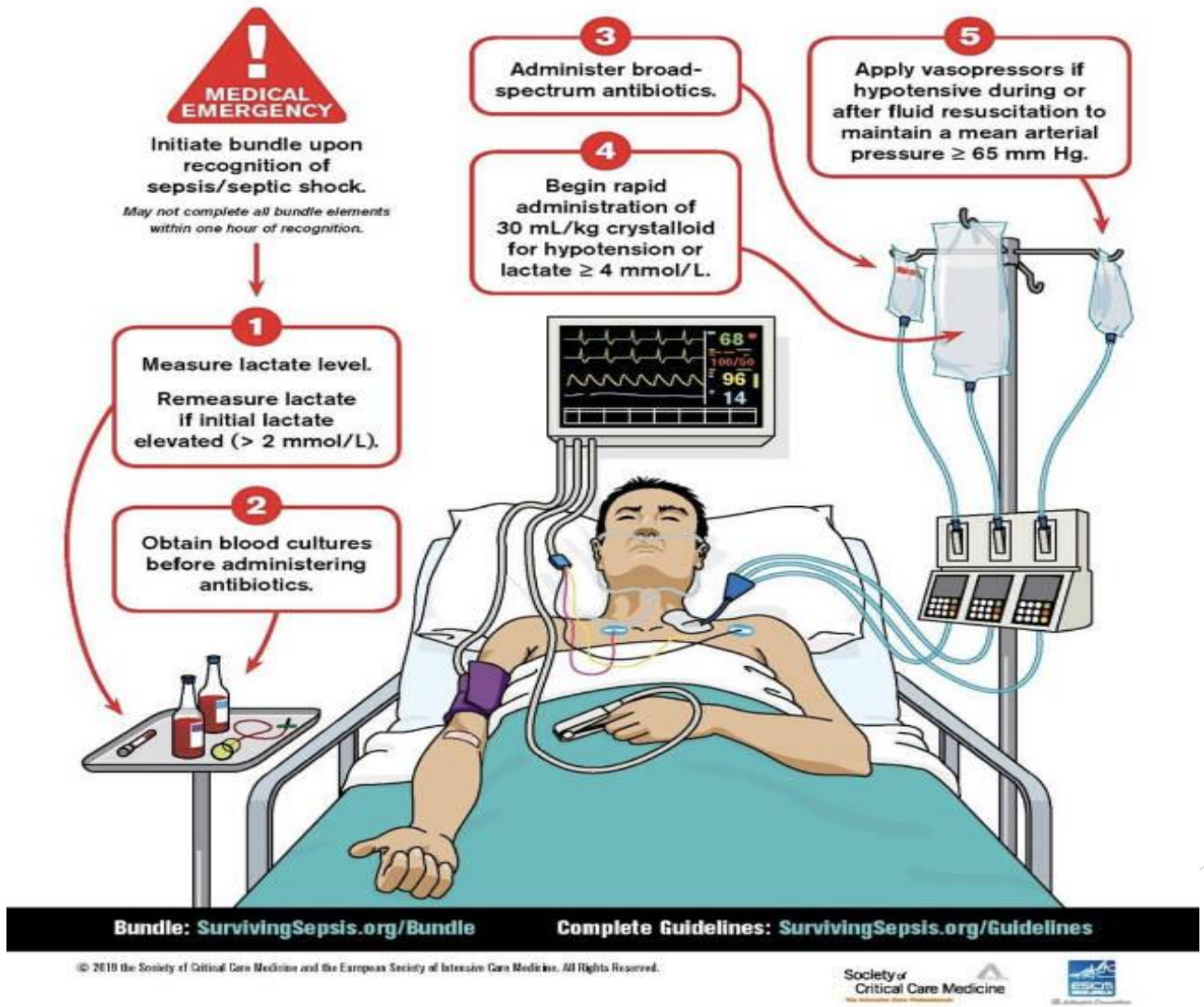
Hour-1 Bundle

Initial Resuscitation for Sepsis and Septic Shock

Surviving Sepsis Campaign



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