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Published in final edited form as: Lancet Child Adolesc Health. 2017 Oct;1(2):124-133
DOI: http://dx.doi.org/10.1016/S2352-4642(17)30010-X

Epidemiology of Blood Culture-proven Bacterial Sepsis in Children in Switzerland - a Population-based Cohort Study

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Abstract

Background

Sepsis is a leading cause of childhood mortality worldwide. We assessed population-based incidence and outcomes of blood culture-proven bacterial sepsis in children in Switzerland.

Methods

Multicenter national prospective cohort study including neonates and children <17 years with blood culture-proven bacterial sepsis from September 1, 2011, to December 31, 2015. Ten pediatric hospitals, including all five pediatric university hospitals, participated in the study. Children were eligible if they met criteria for systemic inflammatory response syndrome, as defined by 2005 pediatric consensus definition, at the time of blood culture sampling. Incidence was calculated by dividing the number of annual sepsis episodes in the study for the years 2012 to 2015 by the end of year resident pediatric population in Switzerland. The primary outcome was in-hospital mortality in the first 30 days after sepsis onset.

Findings

Of 1181 blood culture-proven bacterial sepsis episodes, 382 (32%) occurred in previously healthy children, 402 (34%) in neonates, and 397 (34%) in children with comorbidities. The incidence was 25·1/100'000 in children (95%-CI 23·8-26·4), and 146·0/100'000 in neonates (133·2-159·6). Central line-associated bloodstream infection and primary bloodstream infection accounted for 48% (569/1181) of episodes. The case fatality ratio (CFR) was 7% and was higher in neonates (11%, adjusted OR 4·41, 1·75-11·1) and children with comorbidities (7%, OR 4·97, 1·84-13·4) compared to previously healthy children (3%). The CFR was 1% in 726/1181 (61%) episodes without organ dysfunction and increased to 17% in 455/1181 (39%) episodes where an organ dysfunction was present (adjusted OR 4·84, 1·40-16·7).

Interpretation

The burden of blood culture-proven bacterial sepsis on child health remains considerable. We observed key differences in predominant organisms, severity, and outcome between neonates, previously healthy children and those with comorbidities. While the majority of blood culture-proven bacterial sepsis had no organ dysfunction, presence and number of organ dysfunctions were strongly associated with mortality.

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Funding

Swiss National Science Foundation (342730_153158/1). Swiss Society of Intensive Care. Bangerter Foundation. Vinetum and Borer Foundation. Foundation for the Health of Children and Adolescents.

Keywords

Bacteremia, Sepsis, Children, Pediatrics, Epidemiology, Case fatality rate

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Introduction

Invasive bacterial infections represent one of the leading causes of childhood mortality worldwide.[1] Neonates and young children are particularly susceptible to severe or lethal infections.[2] Recent studies from the United States reported that the incidence of severe sepsis in children increased from 0·56 to 0·89 cases per 1,000 children over the past decade.[3,4] In adults, bloodstream infections rank among the top seven causes of death in the US and Western Europe.[5] The incidence of bloodstream infections is highest at the extremes of age, in neonates and the elderly,[6] yet there is a lack of comprehensive population-based analyses on severe bacterial infections in childhood. In addition to age, host factors such as underlying disease are primary determinants of susceptibility and outcomes.[7,8] Importantly, epidemiology of invasive infections is subject to change as a result of vaccination campaigns,[9] and the increasing number of patients at risk of acquiring healthcare-associated infections including premature newborns, children with malignancies or after transplantation.[10] Considering the detrimental effect of delays in antimicrobial treatment in bacterial sepsis,[11] representative data on the contemporary burden of bacterial sepsis are key to guide national strategies for optimal antibiotic usage.[12]

Sepsis in adults was recently re-defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection.[13] In contrast, the pediatric definition of sepsis is still based on the 2005 consensus[2] requiring the presence of systemic inflammatory response syndrome (SIRS) in patients with suspected infection, which have been criticized for lack of specificity to identify patients subgroups with substantially higher mortality.[14] A limitation of larger studies on childhood sepsis consists in the use of clinical definitions of sepsis, with only a minority of sepsis episodes being microbiologically confirmed, and the lack of robust characterization of the presence and impact of organ dysfunction on outcomes.[3,4]

This population-based national prospective cohort study aimed to describe the epidemiology and severity of blood culture-proven bacterial sepsis, as defined by the 2005 consensus definitions,[2] in children in Switzerland. We investigated patterns of blood culture-proven bacterial sepsis in relation to incidence, pathogens, severity, organ dysfunctions, and outcomes.

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Methods

Study design

The Swiss Pediatric Sepsis Study[15] is a prospective national observational multicenter cohort study investigating blood culture-proven bacterial sepsis in children in Switzerland from September 1, 2011, to December 31, 2015. All ten major children's hospitals in the country participated in the study, including all five pediatric University hospitals, and the five largest regional pediatric hospitals. During the study, these centers accounted for 78% of all hospital admissions, and 98% of all pediatric intensive care unit (PICU) admissions with an International Classification of Diseases (ICD)-10 code for pathogen-specific sepsis in children below the age of 17 years in Switzerland (Supplementary Table 1). The ten study centers host all tertiary neonatal intensive care units (NICU) of the country and comprise all tertiary pediatric oncology and pediatric surgery services.

We obtained written informed consent from patients, or their legal guardians before study enrollment. In patients who fulfilled inclusion criteria but consent was not available, waiver from informed consent had been granted by the ethics commission for collection of anonymized clinical data. The study was approved by the ethics committees of all participating centers (Cantonal Ethics Committee, Inselspital, University of Bern, no. KEK- 029/11).

Study population and Definitions

All neonates and children <17 years of age with blood culture-proven invasive bacterial or fungal infection and SIRS, as defined by 2005 consensus definitions,[2] were eligible if they met SIRS criteria at the time of blood culture sampling. Blood cultures were processed according to the standard operating procedures of the local microbiological laboratories. At each study site, the clinician in charge of patient enrollment was notified by the microbiology laboratory using an automated alert process. We excluded children if blood culture isolates were considered to be contaminants (Supplementary Methods). Additionally, we excluded children after allogeneic bone marrow transplantation. SIRS criteria were assessed prospectively by clinicians. Data on demographics, perinatal and other risk factors, comorbidities, infection site, severity, and outcome were entered prospectively into an online database. Data monitoring and quality controls were performed by the local Clinical Trial Units under the guidance of SwissPedNet, a coordination platform for pediatric clinical research in Switzerland and member of the Swiss Clinical Trial Organization (www.scto.ch). We defined organ dysfunctions (cardiovascular,

respiratory, hepatic, renal, neurologic, hematologic) according to the 2005 consensus definitions;[2] organ dysfunctions were recorded from the time of blood culture sampling on. 30-day in-hospital mortality was the primary outcome. We defined a priori three patient groups: i) Previously healthy children, including term born infants ≥28 days of age; ii) Neonates, including term born neonates <28 days of age and prematurely born neonates <44 weeks postconceptional age at sepsis onset; and iii) Children ≥28 days of age with comorbidities, such as chronic inborn or acquired medical conditions, recent surgery or burns. Comorbidities were categorized according to the pediatric complex chronic conditions classification system version 2.[16] Hospital-acquired infection (i.e., blood culture obtained > 48h after admission) and central line-associated bloodstream infection (CLABSI) were defined according to the CDC criteria.[17]

Incidence calculation

To calculate incidence rates of blood culture-proven bacterial sepsis, we included only sepsis episodes recorded in full study years, between January 1, 2012, and December 31, 2015 (n=1126). To calculate age-specific incidence rates, we divided the number of annual sepsis episodes in the study by the end of year resident population in Switzerland in the respective age groups. Incidence rates were calculated for different age groups and age-standardized to the European standard population.[18] We estimated national incidence rates of blood culture-proven bacterial sepsis based on mandatory hospital statistics of Swiss children <17 years with an ICD-10 code for sepsis associated to a specific pathogen (Supplementary Methods and Supplementary Table 1).

Statistics

Descriptive statistics are presented as median and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. We used χ^2 test of proportions and the Wilcoxon non-parametric rank sum test to compare covariates between children >28days with one or multiple comorbidities. Post-hoc Bonferroni correction was applied.

We fitted multilevel binomial regression models for potential determinants (patient group, number of organ dysfunctions, and gender) of death within the first 30 days after sepsis onset with the presence of organ dysfunctions using a random effect to correct for correlation between multiple observations at the same hospital. For this analysis we included only the first sepsis episode of each patient (n=1096), to avoid conditionality between repeat sepsis events in the same patient. We separately fitted univariable models for the patient group, the number of organ

dysfunctions present (such as any organ dysfunction, two and more organ dysfunctions, three and more organ dysfunctions), and gender. Then we fitted multivariable (adjusted) models containing all potential risk factors. We used backward stepwise selection with likelihood ratio tests to eliminate covariates with $p>0.1$ from the adjusted models. The best fitted model included the patient group and the presence of any organ dysfunction, two and more organ dysfunctions, four and more organ dysfunctions, and six organ dysfunctions. Due to the low number of observations with more than 4 organ dysfunctions, in the final selected model we adjusted for patient group and organ dysfunctions, categorized into no organ dysfunction, one organ dysfunction, two or three organ dysfunctions, and four or more organ dysfunctions. Corresponding area under the receiver operating characteristic curve (AUROC) was used to evaluate the performance of the model in assessing the risk for 30-day in-hospital mortality. Results of binomial multilevel regression analysis are presented as odds ratio (OR) with 95% confidence interval (CI) and p-value. We considered a 2-sided p-value of $<0{\cdot}05$ as significant. All analyses and plots were done using R version 3.4.0 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Results

We prospectively recorded 1204 eligible blood culture-proven sepsis episodes in 1110 children during the 52 months of the study (Figure 1). Twenty-three (2%) episodes with fungal septicemia were excluded for this analysis. Of the remaining 1181 blood culture-proven bacterial sepsis episodes, 382 (32%) occurred in previously healthy children, 402 (34%) in neonates, and 397 (34%) in children with comorbidities (Table 1). Seventy-nine (7%) children experienced two or more sepsis episodes (median 2, range 2-7).

Incidence

The crude annual incidence of blood culture-proven bacterial sepsis per 100'000 children was 19·1 (95%-CI 18·0-20·3), corresponding to an age-standardized incidence of 20·1 per 100'000 children (95%-CI 18·9-21·2). The estimated national age-standardized incidence of blood culture-proven bacterial sepsis was 25·1 per 100'000 children per year (95%-CI 23·8-26·4). The national incidence of blood culture-proven bacterial sepsis was strongly age-dependent, with highest estimates in neonates (146·0 per 100'000 neonates; 95%-CI 133·2-159·6), and infants (85·3 per 100'000 infants; 95%-CI 75·6-95·9) (Figure 2). The estimated national age-standardized incidence of blood culture-proven bacterial sepsis with any organ dysfunction was 8·3 per 100'000 children per year (95%-CI 7·5-9·1) (Figure 2).

Site of infection and pathogens

CLABSI and primary bloodstream infection were the most frequent sites of infection in the entire cohort (327/1181, 28% and 242/1181, 20%, respectively), in neonates (125/402, 31% and 146/402, 36%, respectively), and in children with comorbidities (202/397, 51% and 47/397, 12%, respectively) (Table 2). CLABSI-associated sepsis was primarily hospital-acquired (227/327, 69%). A distinct site of infection was identified in 333/382 (87%) previously healthy children (Table 2), frequently associated to a particular pathogen (Supplementary Figure S1).

E. coli (242/1181, 20%), *S. aureus* (177/1181, 15%), coagulase negative staphylococci (135/1181, 11%), and *S. pneumoniae* (118/1181, 10%) were the most prevalent pathogens in our study, accounting for 57% of episodes (Table 2). The distribution of infection sites and pathogens showed major differences pertinent to the three patient groups and age (Figure 3).

In 36/1181 (3%) episodes multi-resistant bacteria were cultured, including extended-spectrum beta-lactamase resistant bacteria in 23/1181 (2%), methicillin-resistant *S. aureus* in 8/1181 (1%), and carbapenemase resistant bacteria in 5/1181 (0%).

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Severity and outcome of sepsis

In 570/1181 (48%) episodes, children were treated in PICU or NICU, including 271/1181 (23%) episodes were children required intensive care admission because of blood culture-proven bacterial sepsis (Table 3). In 455/1181 (39%) episodes an organ dysfunction was present. Respiratory dysfunction (348/1181, 29%) and cardiovascular dysfunction (215/1181, 18%) were the most prevalent organ dysfunctions recorded (Supplementary Table S2), with inotropes required in 177/1181 (15%) episodes and new invasive ventilation required in 201/1181 (17%) episodes (Table 3).

Eighty-two children died within the first 30 days after the time of blood culture sampling, resulting in a case fatality ratio (CFR) of 7% (95%-CI 5·6-8·6) with a median time to death of 2 days (IQR 1-7) (Table 3). The CFR was lower in previously healthy children (10/382, 3% (95%-CI 1·3-4·9)) than in neonates (45/402, 11% (95%-CI 8·4-14·8)) and in children with comorbidities (27/397, 7% (95%-CI 4·6-9·9)) (Table 3). This was confirmed in regression analysis with an adjusted OR for death in neonates of 4·41 (95%-CI 1·75-11·1) and 4·97 (95%-CI 1·84-13·4)) in children with comorbidities compared to previously healthy children (Table 4 and Supplementary Table S3). In children with comorbidities, those with multiple comorbidities were more often treated in PICU than children with a single comorbidity (57/103, 55% vs. 82/294, 28%, $p < 0·0001$), more often required respiratory support (35/103, 34% vs. 35/294, 12%, $p < 0·0001$), and inotropes (29/103, 28% vs. 36/294, 12%, $p = 0·005$), and had a longer length of stay after sepsis onset (20 days (IQR 12-57) vs. 13 days (IQR 7-24), $p = 0·0009$), while the CFR was not different (10/103, 10% vs. 17/294, 6%, $p = 1·0$) (Supplementary Table S4). The CFR was lower in children with no organ dysfunction (5/726, 1% (95%-CI 0·3-1·7)) compared to those with at least one organ dysfunction (77/455, 17% (95%-CI 13·7-20·8)). The CFR increased with rising number of organ dysfunctions present (Figure 4, Supplementary Table S2, and Supplementary Figure S2).

In adjusted regression analyses, the CFR increased in the presence of one (OR 4·97 (95%-CI 1·43-17·2)), two or three (OR 49·5 (95%-CI 16·1-152)), and four or more organ dysfunctions (OR 275 (95%-CI 78·6-962)) (Table 4 and Supplementary Table S3). The model performed well to identify children with fatal outcome (AUROC 0·92, 95%-CI 0·89-0·92).

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Discussion

In this prospective, population-based study in a high-income country, the age-standardized incidence of pediatric blood culture-proven bacterial sepsis, as defined by 2005 consensus criteria,[2] was 25·1 per 100'000 children per year with an average 30-day in-hospital mortality of 7% (95%-CI 5·6-8·6). We observed major differences in clinical presentation, causative pathogen, disease severity, and outcome of sepsis between previously healthy children, neonates, and children with comorbidities. While the majority of blood culture-proven bacterial sepsis episodes had no organ dysfunction which was associated with a CFR of <1%, presence and number of organ dysfunctions strongly increased 30-day in-hospital mortality.

To the best of our knowledge, this is the largest population-based prospective study capturing blood culture-proven bacterial sepsis in all neonatal and pediatric age groups with detailed characterization of clinical host phenotypes. Our study fills an important knowledge gap, given that the majority of previous studies on sepsis in children included up to 50% of patients with suspected infections, lacking comprehensive microbiological diagnostics or including microbiological results that may represent colonization or viral infection.[19,20] In comparison, pathogen-specific sepsis, as captured by our study, accounted for 66% (1190/1813) of pediatric hospital admissions coded as sepsis in 2012-2015 in the ten study centers, in comparison to 56% (1534/2736) when assessing all pediatric hospital admissions in Switzerland using ICD-10 discharge coding (Supplementary Table 1). In agreement with a US and European study on bloodstream infections in adults,[5] our findings indicate that confirmed blood culture-proven bacterial sepsis represents a more severe infection phenotype, associated with significantly higher mortality compared to other studies based on clinical definitions of sepsis.[19]

Based on our data, 4% (95%-CI 3·5-5·4) of all childhood deaths in the years 2012 to 2015 in Switzerland[21] were associated with blood culture-proven bacterial sepsis, with blood culture-proven bacterial sepsis ranking 5th of all childhood death causes. This is lower than reported in previous studies in Finland,[22] a country with a very low childhood mortality, and Wales,[23] however, these were based on coding for any infectious cause using death registrations.

While bloodstream infections are likely to be underreported in hospital coding-based reports as patients may be coded according to the underlying focus of infection, our study was based on prospective screening by pediatric infectious disease teams and automated microbiology laboratory reporting.

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Our study demonstrates the importance of organ dysfunction to identify patient groups at substantially higher mortality risk, which can inform the translation of Sepsis-3[13] into future pediatric sepsis definitions. The current definition for pediatric sepsis and sepsis severity is based on the 2005 consensus statement, requiring the presence of suspected infection and SIRS[2]. Approximately two-thirds (61%, 95%-CI (58·6-64·2)) of bacteremia episodes in our cohort were classified as sepsis, despite the absence of organ failure, with close to zero mortality. Presence of SIRS in these cases may indeed represent an appropriate rather than dysregulated host response to infection.[14] In contrast, the recent Sepsis-3 consensus definition in adults discriminates sepsis from uncomplicated infection by the presence of organ dysfunction.[13] Our findings demonstrate that the majority of pediatric invasive bacterial infections respond to appropriate antimicrobial treatment without the development of organ dysfunction, confirming that timely recognition of infection and initiation of antibiotics remain the most important cornerstones of treatment.[24] In contrast, in approximately a third (39%, 95%-CI (35·8-41·4)) of sepsis episodes in our study new or worsening organ failure was present, associated with a dramatic increase in mortality to 17% (95%-CI 13·7-20·8) if at least one organ dysfunction was present, to 29% (95%-CI 22·9-34·9) if two or more organ dysfunctions were present. Our findings are supported by a recent international pediatric point prevalence study including 567 children with severe sepsis in 128 PICUs, which reported a mortality increase from 10% in children with single organ dysfunction to 28% in children with new multiple organ dysfunction syndrome, and a concomitant threefold increase in moderate to severe disability in survivors.[25] Importantly, while the 2005 consensus definitions[2] weighted cardiovascular failure higher than other organ dysfunctions (Supplementary Figure S3), our findings indicate that substantial mortality increase is seen in all types of organ failure. Future studies should investigate mechanisms, predictors, and markers to early identify which children are at risk for severe organ dysfunction as a result of dysregulated host response. In agreement with previous reports,[7,8] we observed that 57% of blood culture-proven bacterial sepsis deaths occurred within 48 hours of presentation, which has important implications for the design of interventional studies attempting to reduce sepsis mortality in children.

Our study provides insight into prevailing patterns and organisms for community-acquired and hospital-acquired sepsis. The incidence of sepsis in our study was highest in neonates, with approximately 1 per 1000 developing blood culture-proven bacterial sepsis. 54% of all sepsis episodes in our study occurred in neonates and infants, and 74% in children below five years of age, likely mirroring the maturation of the innate and adaptive immune system during the first

years of life. Despite the decline in invasive pneumococcal infections since the introduction of pneumococcal vaccination in Switzerland in 2006, the majority of sepsis cases in previously healthy children were caused by *S. pneumoniae*. Of note, few sepsis cases were due to *N. meningitidis*, in contrast to other cohorts where *N. meningitidis* was one of the most predominant organisms. *S. aureus* was the second most common pathogen for community-acquired sepsis in previously healthy children, with an estimated age-standardized incidence of 3·7 per 100'000 (95%-CI 3·2 – 4·2). In comparison, the recent Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis study reported an incidence of 8·3 per 100 000 population with a mortality of 4·7%.[26]

Approximately one-third of all blood culture-proven bacterial sepsis episodes in our study occurred in previously healthy children, frequently presenting with age-specific combinations of pathogens and sites of infection. The associated severity in previously healthy children was considerable, as 28% required PICU admission with a CFR of 8% (95%-CI 4%-16%). Underlying unrecognized primary immunodeficiencies, and other genetic and non-genetic host factors conferring increased susceptibility to fulminant sepsis have been shown to account for a proportion of severe infections in previously healthy children, but further studies are needed to elucidate the underlying host and pathogen interactions.[27,28] In addition our results indicate an urgent need for improved preventive strategies, including measures against *E. coli* and *S. aureus* infections which are responsible for an increasing proportion of sepsis cases given the decline in vaccine-preventable infections. In contrast, the majority of blood culture-proven bacterial sepsis episodes in neonates and children with comorbidities in our study were hospital-acquired or health-care associated, with CLABSI accounting for 53% of hospital-acquired sepsis. This is of particular relevance as most healthcare-associated infections have to be considered in principle preventable,[29] indicating an urgent need for improved bundle implementation, bundle maintenance, and benchmarking.[30]

Several limitations of this study have to be considered. First, while we included all the main pediatric hospitals in Switzerland, including all PICUs, NICUs, tertiary pediatric surgery, and oncology centers to estimate the population-based burden of disease, this may have led to a bias towards sepsis of greater severity, and sepsis in children with comorbidities, such as premature neonates and oncology patients. Second, geography, demography, epidemiology, and the organization of the healthcare system in Switzerland have to be considered, when attempting to generalize our findings. Third, we did not prospectively collect daily data on Sequential Organ

Failure Assessment Scores,[13] which have not been validated for children, and the timing of progression towards organ failure was not assessed. Fourth, the inclusion criteria required presence of blood-culture-proven sepsis as per 2005 consensus criteria,[2] and the study was therefore not designed to analyze contaminations and blood culture-proven infection in children without SIRS. Fifth, we defined 30-day mortality as main outcome, whereas longterm neurodevelopmental outcome and quality of health in sepsis survivors were not assessed. Sixth, our study excluded allogeneic bone marrow transplants which may have led to an underestimation of the incidence. Finally, despite the size of the study, the number of deaths was relatively low, limiting more extensive subgroup analyses when adjusting statistical models for potential covariates.

In conclusion, this contemporary population-based cohort on pediatric blood culture-proven bacterial sepsis observed an ongoing burden of disease in a high-income country. The findings demonstrate distinct patterns in relation to epidemiology, host susceptibility, pathogen spectrum, and outcomes of pediatric sepsis. While the majority of bacteremia episodes had no organ dysfunction with close to zero mortality, we demonstrated the importance of organ dysfunction to characterize patients with substantially worse outcomes, which should be considered when reviewing pediatric sepsis definitions. These data may serve to inform current antimicrobial strategies and future sepsis trials and to identify high-risk populations most likely to benefit from targeted preventive and therapeutic interventions.

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Panel: Research in context

Evidence before this study: We searched PubMed for studies published in English, reporting longitudinal population-based data for incidence and mortality of bacteremia and sepsis in children <17 years published between 1990 and 2016. We used the search terms "bacteremia", "blood culture", "bloodstream infection", "mortality", "sepsis", "child", and "epidemiology". Invasive bacterial infections represent one of the leading causes of childhood mortality worldwide, and contribute to 11 - 20% of childhood deaths in high-income countries. The incidence of invasive infections is highest in neonates and children, yet there is a lack of population-based analyses on microbiologically confirmed severe bacterial infections in childhood. In addition to age, host factors such as underlying disease are primary determinants of susceptibility and outcomes. A limitation of larger studies on childhood sepsis consists in the use of clinical definitions of sepsis, with only a minority of sepsis episodes being microbiologically confirmed, and lack of robust characterization of comorbidities. Considering the detrimental effect of delays in antimicrobial treatment in bacterial sepsis, representative data on the contemporary burden of bacterial sepsis are urgently needed to guide national strategies for optimal antibiotic usage. **Added value:** We report specific patterns of clinical presentation, causative pathogen, disease severity, and outcome of sepsis which differed significantly between previously healthy children, neonates, and children with comorbidities. While the majority of bacteremia episodes had no organ dysfunction with close to zero mortality, presence and number of organ dysfunctions were strongly associated with mortality. **Implications of all the available evidence:** We demonstrate an ongoing high burden of pediatric bacterial sepsis and identify high-risk groups most likely to benefit from targeted preventive and therapeutic interventions, which can inform current management strategies and future sepsis trials, in particular in view of the next iteration of pediatric Surviving Sepsis Guidelines and pediatric-specific sepsis definitions.

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Authors and Contributions

The corresponding authors, Dr. Agyeman and Dr. Schlapbach, had full access to all the data in the study and had final responsibility for the decision to submit for publication. Dr. Agyeman, Dr. Schlapbach, and Dr. Berger were responsible for the study design, prepared the first manuscript draft and approved the final version. Dr. Kuehni and Dr. Schindler performed population-based analyses, revised the manuscript, and approved the final version. Dr. Korten and Dr. Agyeman performed statistical analysis. Dr. Aebi was supervising the study and involved in study design, analyses, manuscript preparation, and approval of the final version. Drs Posfay-Barbe, Giannoni, Stocker, Heininger, Konetzny, Hasters, Leone, Relly, Baer, Niederer-Loher, and Kahlert were involved in study design, patient recruitment, data analysis, and manuscript preparation, and approved the final version.

Declaration of interests

None of the coauthors declared a conflict of interest.

Role of funding source

This study was funded by grants from the Swiss National Science Foundation (342730_153158/1), the Swiss Society of Intensive Care, the Bangerter Foundation, the Vinetum and Borer Foundation, and the Foundation for the Health of Children and Adolescents. The funding sources had no involvement in the design, analysis, and writing of the present manuscript.

Acknowledgements

The authors would like to thank in particular the participating patients and their families. In addition, the authors would like to thank B. Spycher for assistance with statistical analysis, the study nurses at each study site, and PedNet.

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Funding

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References

1 Dellinger RP, Levy MM, Rhodes A *et al.* Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Medicine* 2013; **39**: 165–228.

2 Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2005; **6**: 2–8.

3 Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis*. *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2013; **14**: 686–93.

4 Ruth A, McCracken CE, Fortenberry JD, Hall M, Simon HK, Hebbar KB. Pediatric severe sepsis: Current trends and outcomes from the Pediatric Health Information Systems database. *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2014; **15**: 828–38.

5 Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 2013; **19**: 501–9.

6 Laupland KB. Incidence of bloodstream infection: A review of population-based studies. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 2013; **19**: 492–500.

7 Cvetkovic M, Lutman D, Ramnarayan P, Pathan N, Inwald DP, Peters MJ. Timing of death in children referred for intensive care with severe sepsis: Implications for interventional studies. *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2015; **16**: 410–7.

8 Schlapbach LJ, MacLaren G, Festa M *et al.* Prediction of pediatric sepsis mortality within 1 h of intensive care admission. *Intensive Care Medicine* 2017; published online Feb. DOI:10.1007/s00134-017-4701-8.

9 Henderson KL, Johnson AP, Muller-Pebody B, Charlett A, Gilbert R, Sharland M. The changing aetiology of paediatric bacteraemia in England and Wales, 1998-2007. *Journal of Medical Microbiology* 2010; **59**: 213–9.

10 Levy MM, Artigas A, Phillips GS *et al.* Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: A prospective cohort study. *The Lancet Infectious Diseases* 2012; **12**: 919–24.

11 Weiss SL, Fitzgerald JC, Balamuth F *et al.* Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Critical Care Medicine* 2014; **42**: 2409–17.

12 NICE antimicrobial stewardship: Right drug, dose, and time? *Lancet (London, England)* 2015; **386**: 717.

13 Singer M, Deutschman CS, Seymour CW *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801–10.

14 Vincent J-L, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. *Lancet (London, England)* 2013; **381**: 774–5.

15 Giannoni E, Berger C, Stocker M *et al.* Incidence and Outcome of Group B Streptococcal Sepsis in Infants in Switzerland. *The Pediatric Infectious Disease Journal* 2016; **35**: 222–4.

16 Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: Updated for ICD-10 and complex medical technology dependence and transplantation. *BMC pediatrics* 2014; **14**: 199.

17 Centers for Disease Control and Prevention. Surveillance for Bloodstream Infections. ACH Surveillance for BSI (CLABSI) NHSN CDC. 2016. https://www.cdc.gov/nhsn/acute-care-hospital/clabsi/index.html (accessed May 23, 2016).

18 Waterhouse J, Muir C, Correa P, Powell J, editors. Cancer incidence in five continents. Lyon: IARC, 1976.

19 Schlapbach LJ, Straney L, Alexander J *et al.* Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: A multicentre retrospective cohort study. *The Lancet Infectious Diseases* 2015; **15**: 46–54.

20 Weiss SL, Fitzgerald JC, Pappachan J *et al.* Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. *American Journal of Respiratory and Critical Care Medicine* 2015; **191**: 1147–57.

21 Federal Statistical Office Switzerland. Todesfälle nach Geschlecht, Staatsangehörigkeit, Zivilstand und Alter. 2016; published online June.

https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/todesfaelle-sterblichkeit-lebenserwartung.assetdetail.325569.html (accessed Feb 21, 2017).

22 Lantto M, Renko M, Uhari M. Changes in infectious disease mortality in children during the past three decades. *The Pediatric Infectious Disease Journal* 2013; **32**: e355–359.

23 Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M. Continuing impact of infectious diseases on childhood deaths in England and Wales, 2003-2005. *The Pediatric Infectious Disease Journal* 2010; **29**: 310–3.

24 Launay E, Gras-Le Guen C, Martinot A *et al.* Why children with severe bacterial infection die: A population-based study of determinants and consequences of suboptimal care with a special emphasis on methodological issues. *PloS One* 2014; **9**: e107286.

25 Lin JC, Spinella PC, Fitzgerald JC *et al.* New or Progressive Multiple Organ Dysfunction Syndrome in Pediatric Severe Sepsis: A Sepsis Phenotype With Higher Morbidity and Mortality. *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2017; **18**: 8–16.

26 McMullan BJ, Bowen A, Blyth CC *et al.* Epidemiology and Mortality of Staphylococcus aureus Bacteremia in Australian and New Zealand Children. *JAMA pediatrics* 2016; **170**: 979–86.

27 Davila S, Wright VJ, Khor CC *et al.* Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. *Nature Genetics* 2010; **42**: 772–6.

28 Asgari S, McLaren PJ, Peake J *et al.* Exome Sequencing Reveals Primary Immunodeficiencies in Children with Community-Acquired Pseudomonas aeruginosa Sepsis. *Frontiers in Immunology* 2016; **7**: 357.

29 Zingg W, Holmes A, Dettenkofer M *et al.* Hospital organisation, management, and structure for prevention of health-care-associated infection: A systematic review and expert consensus. *The Lancet Infectious Diseases* 2015; **15**: 212–24.

30 Gilbert RE, Mok Q, Dwan K *et al.* Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): A randomised controlled trial. *Lancet (London, England)* 2016; **387**: 1732–42.

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Tables

Table 1 - Demographic and clinical characteristics of neonates and children with blood culture-proven bacterial sepsis

	All episodes (n = 1181, in 1096 children)	Episodes in previously healthy children (n = 382, in 379 children)	Episodes in neonates (n = 402, in 391 infants)	Episodes in children with comorbidities (n = 397, in 341 children)
Demographics				
Age at sepsis onset (months)	7·6 (0·6-63·6)	44·3 (6-108·2)	0·3 (0·2-0·7)	37·4 (9·7-98·7)
Age groups				
Preterm newborn <44 weeks postconceptional age	266 (22·5%)		266 (66·2%)	
Term newborn <28 days	136 (11·5%)		136 (33·8%)	
28-365 days	237 (20·1%)	126 (33·0%)		111 (28·0%)
1-4 years	235 (19·9%)	96 (25·1%)		139 (35·0%)
5-9 years	148 (12·5%)	76 (19·9%)		72 (18·1%)
10-16 years	159 (13·5%)	84 (22·0%)		75 (18·9%)
Male	705 (59·7%)	220 (57·6%)	254 (63·2%)	231 (58·2%)
Ethnicity[a]				
Caucasian	915 (85·1%)	300 (89·6%)	313 (87·2%)	302 (79·3%)
Asian	39 (3·6%)	12 (3·6%)	6 (1·7%)	21 (5·5%)
African	49 (4·6%)	13 (3·9%)	9 (2·5%)	27 (7·1%)
other	72 (6·7%)	10 (3·0%)	9 (2·5%)	31 (8·1%)
Clinical characteristics				
Comorbidities[b]				
Neurologic and neuromuscular	41 (3·5%)		10 (2·5%)	31 (7·8%)
Cardiovascular	90 (7·6%)		20 (5·0%)	70 (17·6%)
Respiratory	56 (4·7%)		16 (4·0%)	40 (10·1%)
Renal and urologic	46 (3·9%)		8 (2·0%)	38 (9·6%)
Gastrointestinal	92 (7·8%)		17 (4·2%)	75 (18·9%)
Haematologic or Immunologic	18 (1·5%)		0 (0%)	18 (4·5%)
Metabolic	18 (1·5%)		5 (1·2%)	13 (3·3%)
Other congenital or genetic defect	39 (3·3%)		14 (3·5%)	25 (6·3%)

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Malignancy	144 (12·2%)		0 (0%)	144 (36·3%)
Neonatal[c]	209 (17·7%)		209 (52·0%)	0 (0%)
Surgery or burn	86 (7·3%)		28 (7·0%)	58 (14·6%)
Technology dependence[d]	42 (3·6%)		26 (6·5%)	16 (4·0%)
Solid organ transplantation	17 (1·4%)		0 (0%)	17 (4·3%)
> 1 condition	159 (13·5%)		56 (13·9%)	103 (25·9%)
Hospital acquired sepsis	431 (36·5%)	16 (4·2%)	243 (60·4%)	172 (43·3%)
CVAD present at time of sepsis onset	452 (38·3%)		176 (43·8%)	276 (69·5%)
Length of stay after sepsis onset[e] (days)	13 (8-29)	9 (5-13)	21 (12-65)	14 (8-29)
Antibiotic therapy				
Adequate empiric antibiotic treatment[f]	1020 (86·4%)	350 (91·6%)	343 (85·5%)	327 (82·4%)
Length of antibiotic treatment[g] (days)	14 (10-15)	14 (10-21)	11 (8-14)	14 (10-15)

CVAD=central venous access device

Categorical variables are given as frequencies and percentages, continuous variables as median and interquartile range. Column percentages are given. Percentages are based upon available data for each variable.

[a]data not available in 106. [b]More than one comorbidity may be present in a child, numbers and percentages do not add up. [c]Gestational age <27 weeks, birthweight <750g, history of mechanical ventilation, history of necrotizing colitis. [d]Central line, or urinary catheter, or ventriculo-peritoneal shunt system present at sepsis onset, or total parental nutrition in a child that does not have any other comorbidity. [e]data not available in 11 episodes (discharge to another facility; still hospitalized). [f]data not available in 1 episode (child died before receiving antibiotic treatment). [g]data not available in 4 episodes.

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Table 2 - Site of infection and pathogens identified in neonates and children with blood culture-proven bacterial sepsis

	All episodes (n = 1181, in 1096 children)	Episodes in previously healthy children (n = 382, in 379 children)	Episodes in neonates (n = 402, in 391 infants)	Episodes in children with comorbidities (n = 397, in 341 children)
Site of infection				
Primary bloodstream infection	242 (20·5%)	49 (12·8%)	146 (36·3%)	47 (11·8%)
Central line-associated bloodstream infection	327 (27·7%)	0 (0%)	125 (31·1%)	202 (50·9%)
Urinary tract infection	128 (10·8%)	56 (14·7%)	35 (8·7%)	37 (9·3%)
Pneumonia	112 (9·5%)	76 (19·9%)	22 (5·5%)	14 (3·5%)
Central nervous system infection	85 (7·2%)	53 (13·9%)	25 (6·2%)	7 (1·8%)
Bone and joint infection	68 (5·8%)	59 (15·4%)	4 (1·0%)	5 (1·3%)
Gastrointestinal system infection	72 (6·1%)	18 (4·7%)	22 (5·5%)	32 (8·1%)
Skin and soft tissue infection	51 (4·3%)	25 (6·5%)	12 (3·0%)	14 (3·5%)
Surgical site infection	17 (1·4%)	1 (0·3%)	4 (1·0%)	12 (3·0%)
Ear, Nose, and Throat infection	29 (2·5%)	23 (6·0%)	4 (1·0%)	2 (0·5%)
Cardiovascular system infection	10 (0·8%)	1 (0·3%)	1 (0·2%)	8 (2·0%)
Toxic shock Syndrome	8 (0·7%)	6 (1·6%)	0 (0%)	2 (0·5%)
Other specific infection type	32 (2·7%)	15 (3·9%)	2 (0·5%)	15 (3·8%)
Pathogens				
Gram positive bacteria	729 (61·7%)	260 (68·1%)	261 (64·9%)	208 (52·4%)
S. aureus	177 (15·0%)	66 (17·3%)	48 (11·9%)	63 (15·9%)
Coagulase negative staphylococci	135 (11·4%)	0 (0%)	86 (21·4%)	49 (12·3%)
S. pneumoniae	118 (10·0%)	90 (23·6%)	4 (1·0%)	24 (6·0%)
Viridans group streptococci	59 (5·0%)	15 (3·9%)	9 (2·2%)	35 (8·8%)
Group A streptococci	53 (4·5%)	47 (12·3%)	3 (0·7%)	3 (0·8%)
Group B streptococci	105 (8·9%)	24 (6·3%)	79 (19·7%)	2 (0·5%)
Enterococcus species	42 (3·6%)	6 (1·6%)	16 (4·0%)	20 (5·0%)
Other Gram positive bacteria	40 (3·4%)	12 (3·1%)	16 (4·0%)	12 (3·0%)
Gram negative bacteria	452 (38·3%)	122 (31·9%)	141 (35·1%)	189 (47·6%)
E.coli	242 (20·5%)	62 (16·2%)	96 (23·9%)	84 (21·2%)

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H. influenzae	21 (1·8%)	17 (4·5%)	1 (0·2%)	3 (0·8%)
Klebsiella species	55 (4·7%)	0 (0%)	20 (5·0%)	35 (8·8%)
N. meningitidis	28 (2·4%)	26 (6·8%)	0 (0%)	2 (0·5%)
P. aeruginosa	24 (2·0%)	2 (0·5%)	4 (1·0%)	18 (4·5%)
Other Gram negative bacteria	82 (6·9%)	15 (3·9%)	20 (5·0%)	47 (11·8%)

Data are n (%). Column percentages are given.

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Table 3 - Severity of sepsis episodes in neonates and children with blood culture-proven bacterial sepsis

	All episodes (n = 1181, in 1096 children)	Episodes in previously healthy children (n = 382, in 379 children)	Episodes in neonates (n = 402, in 391 infants)	Episodes in children with comorbidities (n = 397, in 341 children)
Organ dysfunctions				
No organ dysfunction present	726 (61·5%)	281 (73·6%)	174 (43·3%)	271 (68·3%)
1 organ dysfunction	224 (19·0%)	43 (11·3%)	132 (32·8%)	49 (12·3%)
2 organ dysfunctions	111 (9·4%)	25 (6·5%)	51 (12·7%)	35 (8·8%)
3 organ dysfunctions	56 (4·7%)	9 (2·4%)	23 (5·7%)	24 (6·0%)
4 organ dysfunctions	30 (2·5%)	9 (2·4%)	14 (3·5%)	7 (1·8%)
5 organ dysfunctions	20 (1·7%)	10 (2·6%)	5 (1·2%)	5 (1·3%)
6 organ dysfunctions	14 (1·2%)	5 (1·3%)	3 (0·7%)	6 (1·5%)
PICU/ NICU admission[a]	570 (48·3%)	108 (28·3%)	323 (80·3%)	139 (35·0%)
PICU/ NICU admission due to sepsis	271 (23·0%)	103 (27·0%)	100 (24·9%)	68 (17·1%)
Length of PICU stay[b] **(days)**	14 (4-52)	4 (2-9)	25 (8-66)	14 (3-68)
Length of PICU stay due to sepsis[c] **(days)**	4 (2-11)	4 (2-9)	6 (4-17)	3 (1-9)
Invasive ventilation[a]	307 (26·0%)	54 (14·2%)	183 (45·5%)	70 (17·6%)
Invasive ventilation due to sepsis	201 (17·0%)	51 (13·4%)	109 (27·1%)	41 (10·3%)
Non-invasive ventilation	178 (15·1%)	17 (4·5%)	141 (35·1%)	20 (5·0%)
Non-invasive ventilation due to sepsis	70 (5·9%)	14 (3·7%)	50 (12·4%)	6 (1·5%)
Inotrope requirement[a]	177 (15·0%)	46 (12·0%)	66 (16·4%)	65 (16·4%)
Case fatality	82 (6·9%)	10 (2·6%)	45 (11·2%)	27 (6·8%)
Time to death from sepsis onset (days)	2 (1-7)	2 (0-2)	1 (1-5)	6 (1-16)

PICU=pediatric intensive care unit. NICU=neonatal intensive care unit.

Categorical variables are given as frequencies and percentages, continuous variables as median and interquartile range. Column percentages are given. Percentages are based upon available data for each variable.

[a]data not available in 1 episode. [b]data not available in 31 episodes. [c]data not available in 14 episodes.

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DOI: http://dx.doi.org/10.1016/S2352-4642(17)30010-X

Table 4: Risk factors for death in neonates and children with blood culture-proven bacterial sepsis

	sepsis episodes in which children survived n = 1023	sepsis episodes in which children died n = 73	Unadjusted model		Adjusted model	
			OR (95% CI)	p value[b]	OR (95% CI)	p value[b]
Patient group				0·0003		0·0007
Previously healthy children[a], n=375	366 (97·6%)	9 (2·4%)				
Neonates, n=391	349 (89·3%)	42 (10·7%)	4·19 (1·94-9·04)		4·41 (1·75-11·1)	
Children with comorbidities, n=330	308 (93·3%)	22 (6·7%)	2·86 (1·28-6·40)		4·97 (1·84-13·4)	
Number of organ dysfunctions				<0·0001		<0·0001
No organ dysfunction[a], n=671	667 (99·4%)	4 (0·6%)				
1 organ dysfunction, n=207	198 (95·7%)	9 (4·3%)	5·78 (1·68-19·9)		4·97 (1·43-17·2)	
2 or 3 organ dysfunctions, n=160	127 (79·4%)	33 (20·6%)	56·7 (18·6-173)		49·5 (16·1-152)	
4 to 6 organ dysfunctions, n=58	31 (53·4%)	27 (46·6%)	212 (64·0-704)		275 (78·6-962)	

OR=odds ratio. CI=confidence interval. Data are n (%) unless otherwise specified. Row percentages are given.

Unadjusted and adjusted OR for death investigating potential risk factors patient group and number of organ dysfunctions in multilevel binomial regression. The adjusted model was adjusted for all variables listed. Outcome was death within the first 30 days after sepsis onset (yes/no).

[a]reference category. [b]p value from likelihood ratio test

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Figures

Figure 1: Flow chart of sepsis episodes included in the Swiss Pediatric Sepsis Study

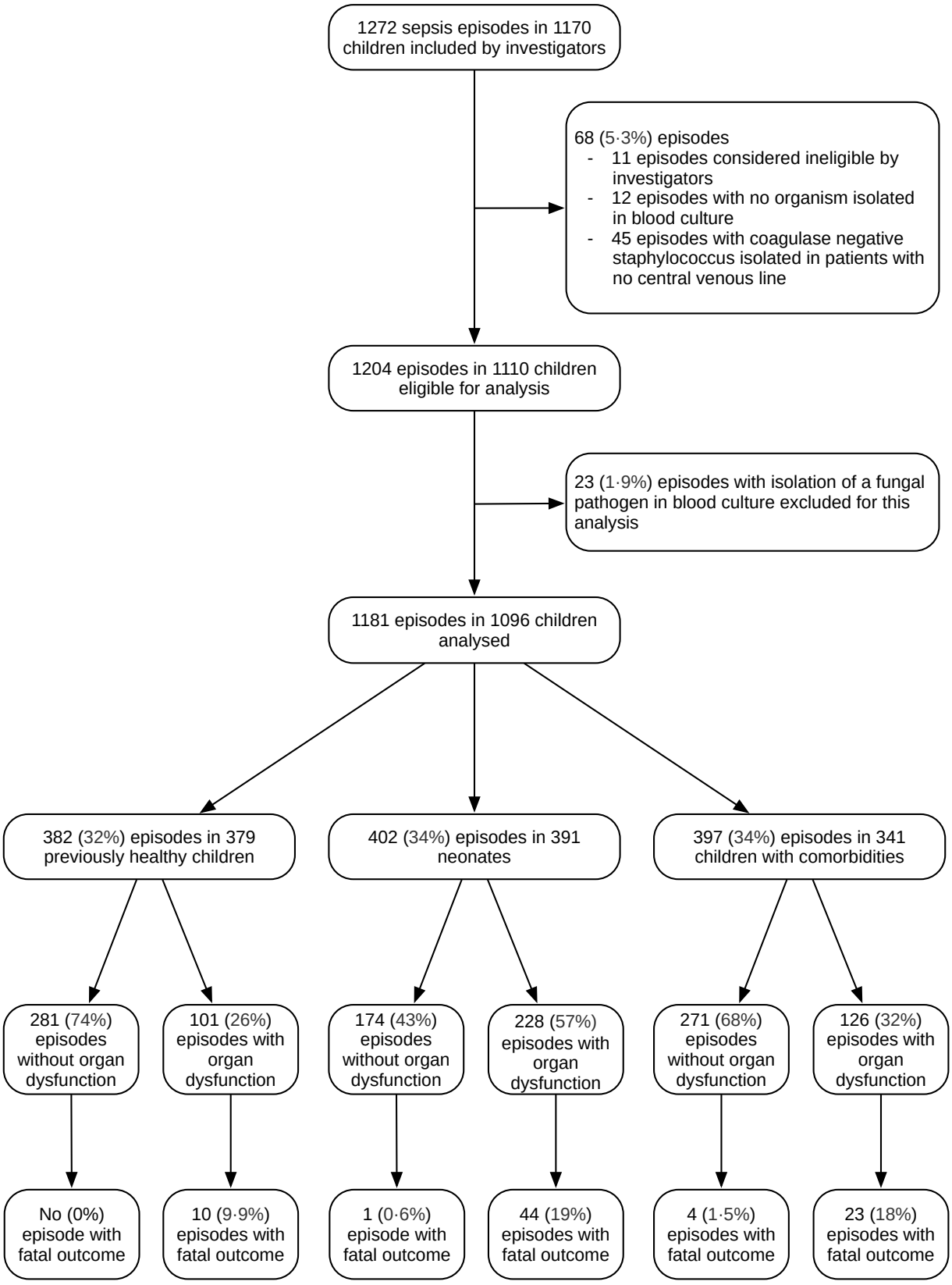

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Figure 2: Incidence of blood culture-proven bacterial sepsis in the years 2012-2015 in Switzerland, grouped by age.

Red horizontal lines show the crude incidence (n=1126), as measured in the ten participating study centers, black horizontal lines the estimated national incidence of all blood culture-proven bacterial sepsis in Switzerland (Panel A), and blood culture-proven bacterial sepsis with organ dysfunction (n=439) (Panel B). The estimate of national sepsis incidence is based on the assumption that participating hospitals captured 80% of all sepsis episodes in children up to 16 years in Switzerland and 90% of all episodes with organ dysfunction (irrespective of age). Vertical lines represent the 95% confidence intervals around the point estimates for each age group.

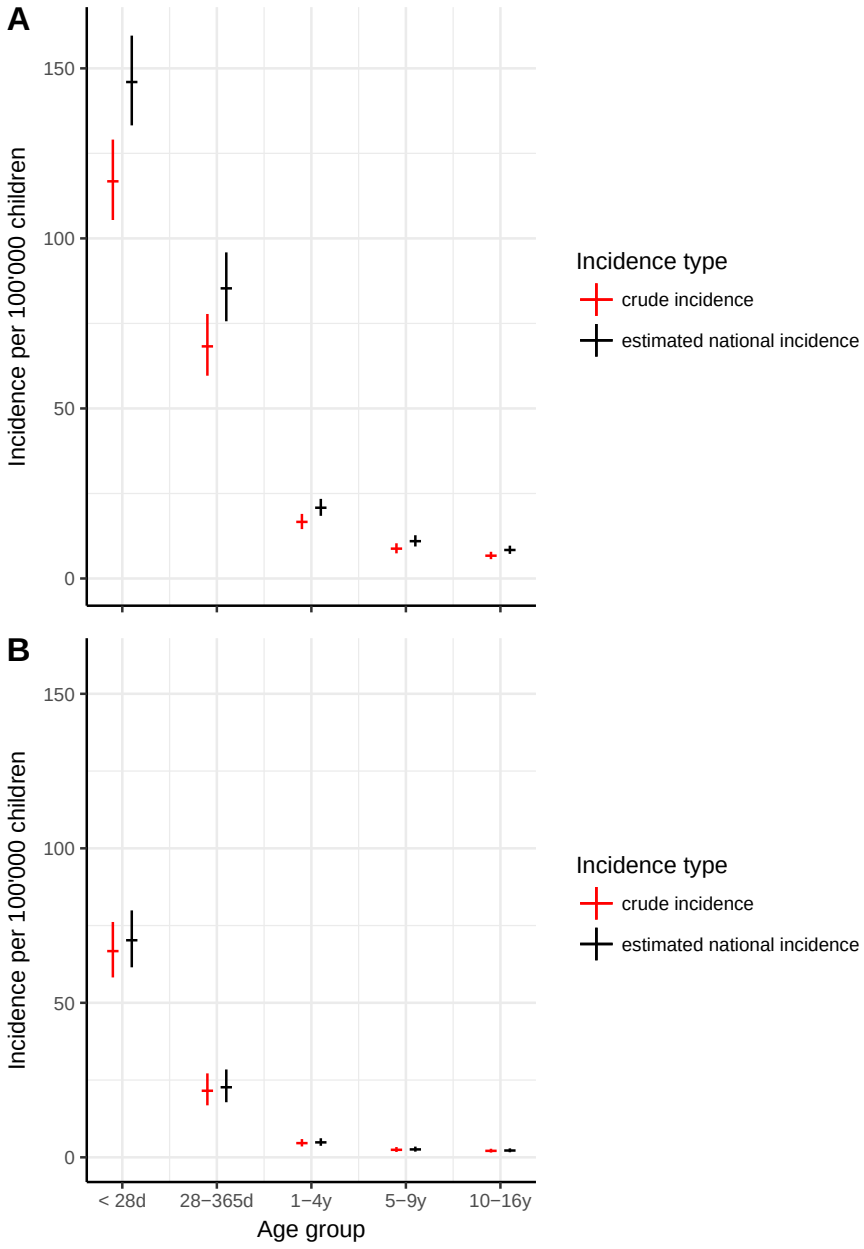

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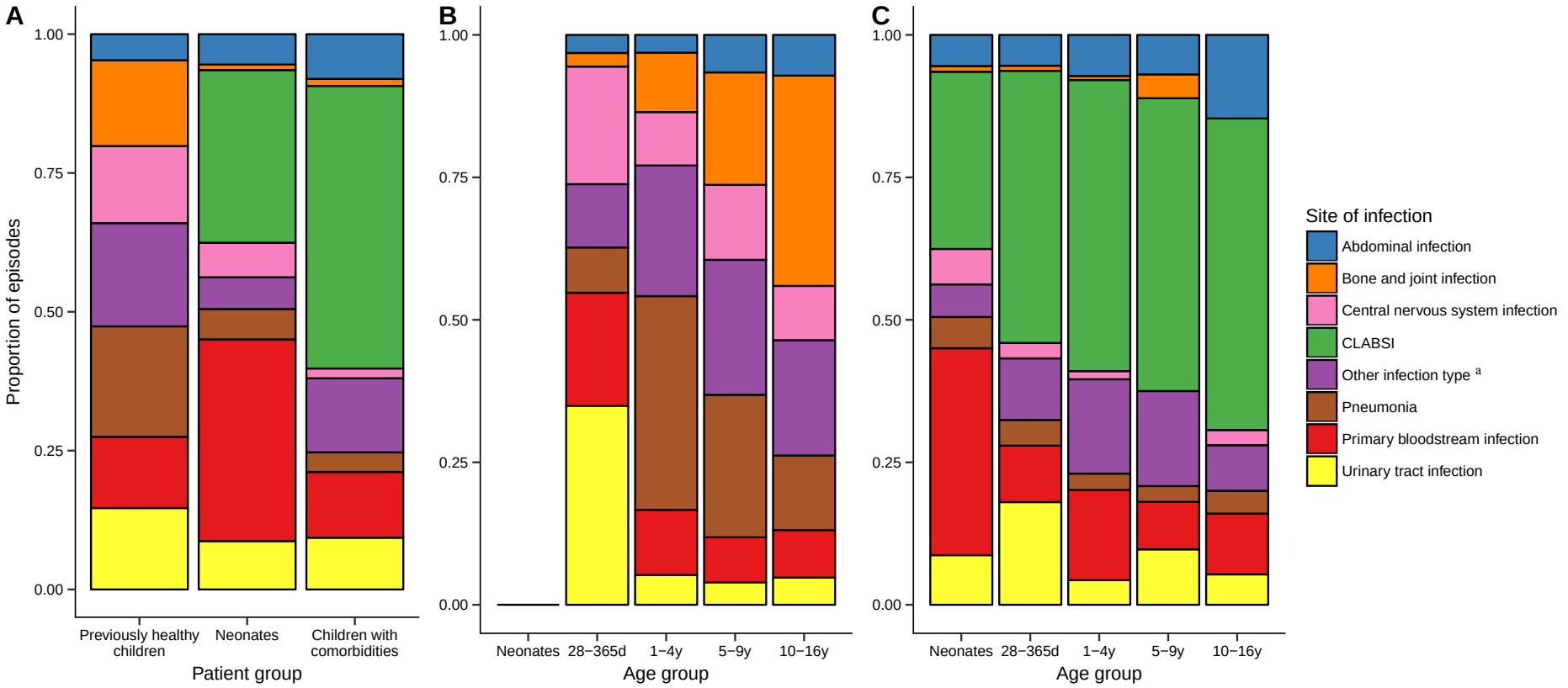
Figure 3: Age distribution of sites of infection and responsible pathogens causing blood culture-proven bacterial sepsis in children.

Sites of infection are shown for the three patient groups (A) and separately for previously healthy children ≥28 days of age (B), and for neonates, and children with comorbidities ≥28 days of age (C) grouped by age. Pathogens isolated in blood culture are shown for the three patient groups (D), and separately for previously healthy children ≥28 days of age (E), and for neonates, and children with comorbidities ≥28 days of age (F) grouped by age. CLABSI=central line-associated bloodstream infection. CoNS=coagulase negative staphylococci. [a]Skin infection, wound infection, endocarditis, toxic shock syndrome, ear-nose-throat infection, other non-specified focal infection. [b]*P. aeruginosa*, *Klebsiella spp.*, *N. meningitidis*, *H. influenzae*, other Gram-negative pathogens. [c]*Enterococcus spp.*, viridans group streptococci, other Gram-positive pathogens



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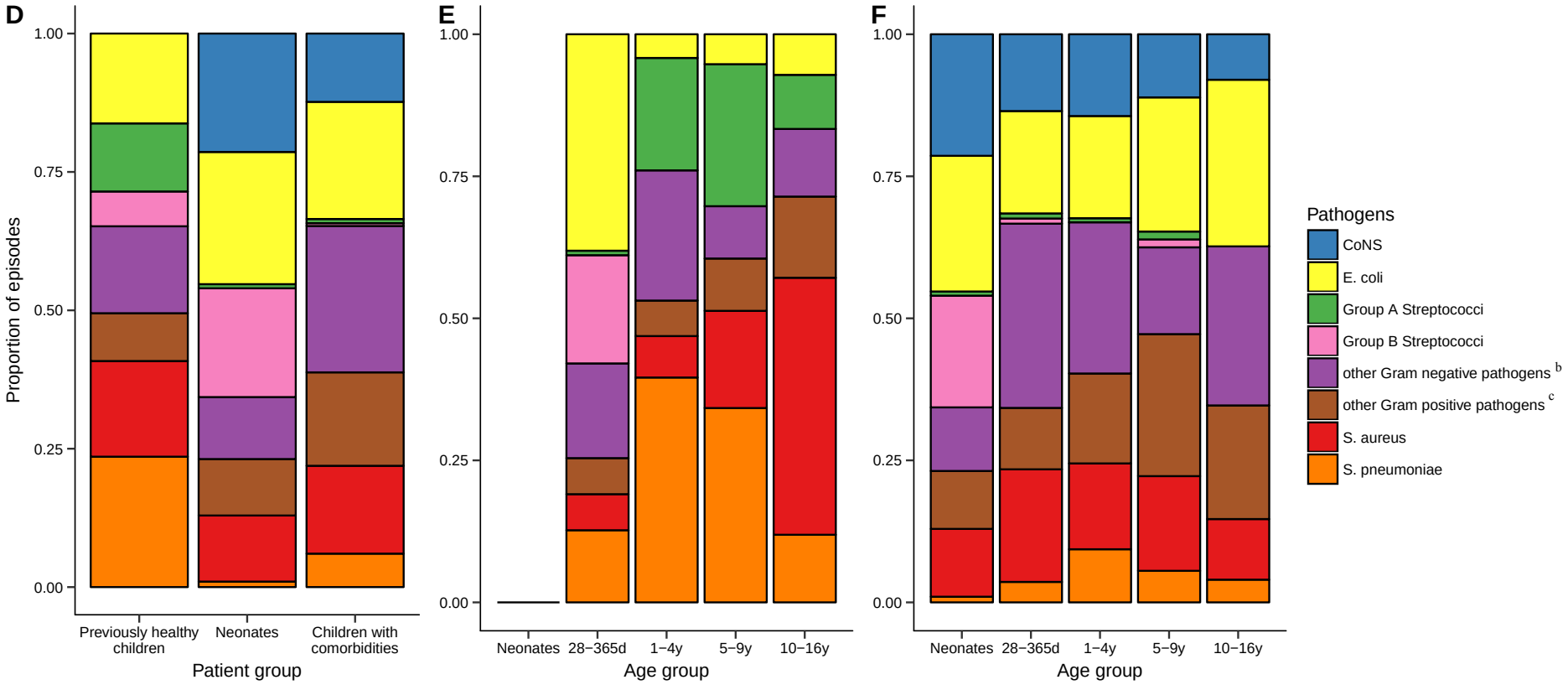

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Figure 4: Impact of organ dysfunction on case fatality ratio in children with sepsis.

Horizontal lines represent point estimates of the case fatality ratio in children with sepsis stratified by number of organ dysfunctions present. Vertical lines represent the 95% confidence intervals around the point estimates for each group.