HHS Public Access

Author manuscript

Lancet Glob Health. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Lancet Glob Health. 2017 February ; 5(2): e157–e167. doi:10.1016/S2214-109X(17)30007-4.

Causes and Outcomes of Sepsis in Southeast Asia: A Multinational Multicentre Cross-sectional Study

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Abstract

Background—A better understanding of pathogens causing sepsis is important for management and antimicrobial selection. Here, we explored the causative pathogens of sepsis in Southeast Asia (SEA).

Methods—We prospectively recruited children (age≥30 days and <18 years) and adults (age≥18 years) at 13 public hospitals in Indonesia (n=3), Thailand (n=4) and Viet Nam (n=6). Hospitalised patients with suspected or documented community-acquired infection, with ≥3 diagnostic criteria for sepsis according to the Surviving Sepsis Campaign 2012, and within 24 hours of admission were enrolled. Blood from every patient, and nasopharyngeal swab, urine, stool and cerebrospinal fluid, if indicated, were collected for reference diagnostic tests. This study was registered with ClinicalTrials.gov, number NCT02157259.

Findings—From December 2013 to December 2015, 1,578 patients (763 children and 815 adults) were enrolled. Dengue viruses (n=122, 8%), *Leptospira* spp. (n=95, 6%), rickettsial pathogens (n=96, 6%), *Escherichia coli* (n=76, 5%) and influenza viruses (n=65, 4%) were commonly identified in both age groups, while *Plasmodium* spp. (n=12, 1%) and *Salmonella*

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Conflict of interest

We declare that we have no conflicts of interest.

enterica serovar Typhi (n=3, 0.2%) were rarely observed. Emerging pathogens identified included hantaviruses (n=28, 2%), non-typhoidal *Salmonella* spp (n=21, 1%), *Streptococcus suis* (n=18, 1%), *Acinetobacter* spp. (n=12, 1%), and *Burkholderia pseudomallei* (n=5, 0.3%). 28-day mortality was 2% in children (14/731) and 13% in adults (108/804). Severe sepsis was identified on enrolment in 27% of children (204/763) and 68% of adults (550/815), and was associated with increased mortality (adjusted odds ratio 5.3, 95% confidence interval 2.7–10.4, p<0.001).

Interpretation—Sepsis in SEA is caused by a wide range of known and emerging pathogens, and is associated with substantial mortality.

Funding—National Cancer Institute (HHSN261200800001E) and National Institute of Allergy and Infectious Diseases, National Institutes of Health, and Wellcome Trust (106680/B/14/Z and 106698/B/14/Z).

INTRODUCTION

Sepsis is the presence of systemic host responses to infection. Severe sepsis and septic shock are considered major healthcare problems and kill millions of people annually worldwide.[1–3] To reduce mortality, there is an urgent need to improve our understanding of causes of sepsis; however, this information is rarely available in tropical countries.[4] In Southeast Asia, a wide range of known and emerging pathogens may cause infections leading to sepsis and severe sepsis.[5] Several studies have examined causes of fever[6–10] and bacteraemia[11] in the region. However, none applied a pre-defined wide array of diagnostic tests and assessed the relative distribution of pathogenic bacterial, parasitic and viral agents identified in patients admitted with community-acquired sepsis. Also, none was conducted in multiple study sites in multiple countries in one single study.

The diagnostic criteria for sepsis and severe sepsis have been modified over time. The initial definition of sepsis was developed in 1991 through the concept of the Systemic Inflammatory Response Syndrome (SIRS), which was characterized by two or more of: body temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate of >20 breaths/min or a $PaCO_2$ of <32 mmHg; and a white blood cell count of >12,000 cells/μL or <4,000 cells/μL.[12] Recognizing limitations of the initial definitions, a 2001 task force expanded the list of criteria to diagnose sepsis to incorporate “general”, “inflammatory”, “hemodynamic”, “organ dysfunction” and “tissue perfusion” variables in addition to suspected or documented infection.[13] The expanded diagnostic criteria for sepsis have been adopted and recommended by the surviving sepsis campaign (SSC) in 2004, 2008 and 2012.[1–3] A 2014 task force concluded that the term “severe sepsis” was redundant and recommended that the new updated definitions and clinical criteria for “sepsis” should replace previous definitions so that the reported incidence and observed mortality are comparable worldwide, and early recognition and timely management can be provided for patients who are likely to have poor outcomes.[14] Here, we evaluated causes and mortality outcome of sepsis and severe sepsis patients based on the SSC 2012 definitions, and performed an additional analysis using the definition of the 2014 task force.

METHODS

Study sites and populations

We conducted a prospective observational study of community-acquired sepsis and severe sepsis in 13 public hospitals in Indonesia (Dr. Cipto Mangunkusumo Hospital, Jakarta; Dr. Sardjito Hospital, Yogyakarta; and Dr. Wahidin Soedirohusodo Hospital, Makassar), Thailand (Queen Sirikit National Institute of Child Health and Siriraj Hospital, Bangkok; Chiang Rai Prachanukroh Hospital, Chiang Rai; and Sappasithiprasong Hospital, Ubon Ratchathani) and Viet Nam (National Hospital of Paediatrics and National Hospital of Tropical Diseases, Hanoi; Hue Central Hospital, Hue; Children's Hospital 1, Children's Hospital 2 and Hospital for Tropical Diseases, Ho Chi Minh City) (Figure S1). All are tertiary public hospitals equipped with microbiology facilities and ICUs, with a median bed number of 1,200 (range 350–2,200). The study protocol and related documents were approved by regional and national Ethics Committees.

Study participants

We prospectively enrolled paediatric (age≥30 days and <18 years) and adult patients (age≥18 years) who were admitted with a primary diagnosis of suspected or documented infection made by the attending physician, were within 24 hours of hospital admission, and had at least three sepsis diagnostic criteria documented in the medical record. For adult patients, we used 19 variables which were consolidated from the 22 variables proposed as diagnostic criteria for sepsis by the Surviving Sepsis Campaign (SSC) 2012,[3] and included 'low oxygen saturation (SpO_2<95%)' (Table 1). This variable was added because 'Oxygen saturation determined by pulse oximeter' is recommended by the World Health Organization guidelines for limited-resource settings.[15] Altered mental status was defined as a Glasgow Coma Scale (GCS) score of <15, or <10 if intubated (<10T). For paediatric patients, in addition to three diagnostic criteria of fever or hypothermia, tachycardia and tachypnoea, patients had to have at least one of the following symptoms; altered mental status, hypotension, hypoxaemia and leukocytosis (Table 2). We excluded patients who were suspected of having hospital-acquired infections determined by the attending physician, had a hospital stay within 30 days prior to this admission, or were transferred from other hospitals with a total duration of hospitalization >72 hours. Due to concerns about the volume of blood drawn from each patient, we also excluded patients who had been enrolled into other clinical studies.

Study procedures

The study was initiated in December 2013 in Thailand, March 2014 in Viet Nam and March 2015 in Indonesia. The study was closed in December 2015 in all three countries. The study team used a standardized case-report form to record the clinical symptoms and their respective durations, known chronic conditions, laboratory tests performed by the study hospital laboratories, and primary and final diagnoses made by attending clinicians. As per protocol, every patient was evaluated by the study team, and the following rapid tests were performed immediately after enrolment: a whole blood lactate RDT (Lactate Pro 2, Arkray Global Business Inc., Australia), a whole blood glucose RDT (ACCU-CHECK Performa, Roche Diagnostic, Germany), pulse oximeter (Nellcor N-65, Covidien plc., Ireland) and

dengue rapid diagnostic test (RDTs) (NS1 and IgM, Standard Diagnostics, South Korea). All children younger than 7 years old were evaluated using an influenza RDT (QuickVue, Quidel Corporation, USA), and all patients aged 7 years or older were evaluated using a leptospirosis RDT (Leptospira IgM/IgG, Standard Diagnostics). The results of all rapid tests were reported to the attending physicians. In all cases, blood samples (4 to 10 ml) were collected for culture on site and for serological tests and molecular tests at reference laboratory centres of each country. Pooled nasal and throat swabs were collected for respiratory viruses, if patients had respiratory symptoms. Stool samples were collected if patients had diarrhoeal symptoms. Residual cerebrospinal fluid (CSF) was collected if available. A set of reference diagnostic tests was performed for each patient according to clinical presentation (Table S1 and S2). This included complete blood count, blood culture, and urinary analysis and urine culture in every study patient, sputum Gram smears and sputum culture if patients have respiratory symptoms, stool examination and stool culture if patients have diarrhoeal symptoms, and CSF examination and CSF culture if patients have neurological symptoms and CNS infection is suspected (Table S1).

The study did not involve any clinical interventions. All treatment was provided by attending physicians and their medical teams. The rainy season was from November to March in Indonesia, July to October in Thailand, April to October in northern Viet Nam, September to January in central Viet Nam, and May to November in southern Viet Nam. The 28-day mortality was evaluated via telephone contact if subjects were no longer hospitalised and had been discharged alive.

Definition of clinical presentations

For each patient, the clinical presentations (in some cases, more than one) were defined based on the major presenting clinical symptoms. Acute respiratory infection was defined as manifestation of at least one respiratory symptom for no longer than 14 days. Acute diarrhoea was defined as diarrhoea for no longer than 14 days. Acute central nervous system (CNS) infection was defined as manifestation of CNS symptoms for no longer than 14 days or presence of signs of CNS infection on admission. Systemic infection was defined as absence of acute respiratory infection, acute diarrhoea and acute CNS infection.

Identification of the pathogens responsible of the sepsis

To maximize consistency and minimize subjectivity, the identification of the pathogens was generated using a computer-based algorithm (Table S3) and confirmed by adjudication committee. The blood culture result was considered contaminated if growth of coagulase-negative staphylococci, alpha-hemolytic streptococci, *Micrococcus* spp., *Propionibacterium* spp., *Corynebacterium* spp., *Burkholderia cepacia* or *Bacillus* spp. was detected without additional evidence of clinical diagnoses suggesting true infection (e.g. endocarditis, artificial material *in situ*). Rickettsial pathogens evaluated included *Orientia tsutsugamushi, Rickettsia typhi* and spotted fever group rickettsia (Table S1 and S2).

Statistical analysis

Data were entered into OpenClinica, Enterprise Edition (Waltham, USA), and all analyses were performed using STATA version 14.0 (StataCorp, College Station, USA). We

calculated that 125 participants per age group per study area (3 study areas per country [Figure S1] and a total of 750 participants per country) would provide adequate power (>90%) to observe a cause of sepsis which had a true prevalence of 2% or greater in each study age group in each study area. Differences in proportions among groups were evaluated using Fisher's exact test, and differences in medians by the Mann-Whitney test. Logistic regression models stratified by study sites and age group were used to evaluate the factors associated with mortality. 28-day mortality was defined as the proportion of patients who died within 28 days of hospital admission. Severe sepsis in adult patients was defined as described in SSC 2012,[4] and in paediatric patients as previously described.[16] We also additionally evaluated the association between sepsis defined by the 2014 task force (total SOFA score ≥2) and mortality in adult patients.[14] The additional analysis was restricted to only adult patients because the new sepsis definition is available only for adult populations.[14] The sensitivity analysis was conducted by including in the model only patients with a pathogen detected. The registry number of the study was NCT02157259. The final database and the data dictionary are publicly available online (https://figshare.com/s/2ee5d563e64953adc150).

Role of the funding source

All study procedures, data collection, data analyses, data interpretation, and writing of the report were performed without the sponsors' involvement. Full access to data was granted to the corresponding author. All authors participated in the study design or analysis, and approved the submission of the manuscript.

RESULTS

Baseline characteristics

A total of 4,736 patients (2,093 children and 2,643 adults) presenting at 13 study hospitals in three countries were screened by the study team during the study period (Figure 1). The common exclusion criteria were: being hospitalized in the past 30 days (719, 15%) and having less than three sepsis diagnostic criteria documented in the medical record (667, 14%). After giving informed consent, 1,582 community-acquired sepsis patients were enrolled. The enrolment target was reached for Thailand and Viet Nam (750 patients [375 children and 375 adults] per country). A total of 82 patients (16 children and 66 adults) were enrolled in Indonesia. The enrolment in Indonesia did not reach the target sample size because of competitive enrolment with other studies during the study period. Three enrolled children and one adult were retrospectively found not to fulfill the inclusion criteria and, therefore, were excluded from the analysis.

Table 3 and 4 show the characteristics of the 763 children and 815 adults included in the analysis, respectively. Table S4 shows the characteristics of patients by countries. Convalescent blood samples were obtained from 925 patients (415 children and 510 adults), and a total of 36,853 diagnostic tests were performed per protocol.

Clinical presentations

Per study protocol, 937 and 927 distinct clinical presentations were seen in 763 children (Figure 2) and 815 adults (Figure 3), respectively. Acute respiratory infection was the most frequent clinical presentation found in 481 (63%) children and 436 (54%) adults. Among those with acute respiratory infection, pneumonia was diagnosed by attending physicians in 280 (37%) children and 222 (27%) adults. Other clinical presentations were distributed as follows: 183 (24%) children and 168 (21%) adults had acute diarrhoea, 119 (16%) children and 80 (10%) adults had acute CNS infection, and 154 (20%) children and 243 (30%) adults had systemic infection. A total of 156 (20%) children and 105 (13%) adults had multiple clinical presentations.

Pathogens identified

The distribution of illnesses by pathogen type (bacterial, viral or parasitic) is presented in Figure 4. A total of 425 (56%) children and 388 (48%) adults had at least one pathogen identified, and a total of one child (0.1%) and 17 (2%) adults had final diagnosis of non-infectious causes. The numbers and proportion of children and adults with each pathogen identified are presented in Table S5.

Viruses—Dengue virus was identified in 55 (7%) children and 67 (8%) adults. Among the 481 children and 436 adults with acute respiratory infection, diagnostic tests were positive for at least one virus in 282 (59%) children and 74 (17%) adults. Those included influenza viruses (44 children and 20 adults), rhinovirus (92 children and 12 adults) and respiratory syncytial virus (52 children and 2 adults). A virus was identified in 42% (76/183) of children and 12% (20/168) of adults with acute diarrhoea. Those included rotavirus (12 children and 2 adults), adenovirus (8 children and 0 adults) and norovirus (3 children and 1 adult). Of 100 children and 70 adults who had clinical presentation of both acute respiratory infection and acute diarrhoea, 57 (57%) and 12 (17%) had diagnostic tests positive for at least one virus; including 20 children and 1 adult with rhinovirus identified (Figure 2). Among 119 children and 80 adults who had clinical presentation of acute CNS infection, 40 (34%) and 10 (13%) had viruses identified, respectively. Those included dengue virus (10 children and 8 adults), influenza virus (7 children and 1 adult), enterovirus (6 children and 0 adults) and adenovirus (3 children and 0 adults). Hantavirus was identified in both children (14/749; 2%) and adults (14/750; 2%).

Bacteria—Of 742 children and 789 adults for whom blood culture was performed, 15 (2%) and 37 (4%) were positive for contaminant bacteria and 35 (5%) and 96 (12%) were positive for pathogenic bacteria. The most frequent contaminants were coagulase-negative *Staphylococcus* (n=34). Overall, 12 children and 68 adults had blood culture positive for Gram-negative bacteria (including *Escherichia coli* [n=40], *Klebsiella pneumoniae* [n=9], *Acinetobacter* spp [n=9], *Enterobacter* spp [n=6] and *Burkholderia pseudomallei* [n=3]), and 22 children and 24 adults were blood culture positive for Gram-positive bacteria (including *Staphylococcus aureus* [n=21], *Streptococcus pneumoniae* [n=7], *Streptococcus suis* [n=5], and beta-haemolytic *Streptococcus* spp [n=11]) (Table S6). Among 1,444 patients with negative blood cultures, blood 16S PCR was positive in 44 (3%) patients. Products of 16S PCR could be identified in 14 cases; including *S. suis* (n=4), *Orientia tsutsugamushi* (n=4),

Pseudomonas spp (n=2), *Achromobacter* spp (n=1), *S. pneumoniae* (n=1), *K. pneumoniae* (n=1) and *Enterobacteriaceae* (n=1).

Among the 481 children and 436 adults with acute respiratory infection, diagnostic tests were positive for at least one bacterium in 93 children (19%) and 147 adults (34%). Those included *S. aureus* (10 children and 6 adults), *Mycoplasma* spp (14 children and 6 adults), *K. pneumoniae* (0 children and 9 adults), *S. pneumoniae* (2 children and 4 adults), *Leptospira* spp (11 children and 44 adults), *O. tsutsugamushi* (11 children and 14 adults) and *Mycobacterium tuberculosis* (2 children and 4 adults). A bacterium was documented in 22% (40/183) of children and 36% (60/168) of adults with acute diarrhoea. Those included *Salmonella enterica* serovar Typhi (0 children and 1 adult), non-typhi *Salmonella* spp (11 children and 7 adults), *E. coli* (7 children and 12 adults) and *Campylobacter* spp (2 children and 0 adults). Among 119 children and 80 adults with acute CNS infection, 17 (15%) and 42 (53%) had bacteria identified. Those included *Leptospira* spp (2 children and 9 adults), *E. coli* (3 children and 7 adults), *S. suis* (0 children and 10 adults), *S. pneumoniae* (4 children and 1 adult), spotted fever group rickettsia (2 children and 2 adults) and *O. tsutsugamushi* (0 children and 3 adults).

Overall, tropical bacterial infectious diseases were common, including leptospirosis and rickettsioses, in both children and adults.

Parasites—A total of 4 children and 8 adults had malaria, 2 patients had *Entamoeba histolytica*, 2 adults had strongyloidiasis, and 1 child had cryptosporidiosis.

Spatial and Temporal distribution—Pathogens identified in Indonesia, Thailand and Viet Nam were largely comparable, except non-typhi *Salmonella*, *Enterobacter* spp, *Acinetobacter* spp, beta-hemolytic *Streptococcus* spp, rickettsial pathogens, dengue viruses, influenza viruses, hantaviruses, rotavirus, cytomegalovirus and bocavirus (Table S7). We found that *S. suis* and respiratory syncytial virus were more commonly identified during rainy season, while influenza viruses and rotavirus more commonly identified during dry season (Table S8).

28-day mortality

The 28-day mortality was 2% (14/731) in children and 13% (108/804) in adults (Table 1). Mortality outcome was not available in 19 children and 5 adults who withdrew from the study prior to 28 days of follow-up, and in another 13 children and 6 adults who could not be contacted for 28-day outcome. The failure to obtain 28-day mortality data was higher in Thailand (4%; 29/750) than in Viet Nam (2%; 13/749) and Indonesia (1%; 1/79) (Table S4, p=0.03). Of 122 patients who died, 26% died within 2 days (n=32) and 40% between day 3 and 7 (n=49) of hospitalization. In the multivariable logistic regression model, severe sepsis on admission was strongly associated with mortality in both paediatric (6% [11/194] vs. 0.6% [3/537]) and adult patients (18% [99/546] vs. 3% [9/258]) (Table 5). Patients with viruses identified had a lower risk of death. These were also observed when only patients with pathogens identified were included in the model (Table S9). In the additional analysis, SOFA scores ≥2 were also associated with 28-mortality in adults (22% [99/454] vs. 3% [9/350], p<0.001) (Table S10).

DISCUSSION

Using a predefined set of diagnostic tests, we were able to identify the possible causative organisms of sepsis and severe sepsis in 56% of children and 48% of adults enrolled in our study. Viral, bacterial and parasitic agents were identified in 29%, 27% and 1% of the patients. Tropical infectious diseases are common causes of sepsis and severe sepsis in our setting. These include dengue virus, leptospirosis and rickettsioses. Typhoid fever was rarely identified. We also observed a number of emerging pathogens including hantavirus, non-typhoidal *Salmonella* spp, *S. suis*, *Acinetobacter* spp, and *B. pseudomallei*. Non-typhoidal *Salmonella* infection is increasingly recognised as an important cause of sepsis and diarrhoeal illnesses in the region.[17,18] Community-acquired *Acinetobacter* bacteraemia and pneumonia is also increasingly reported.[19,20] *B. pseudomallei* is known to be endemic but general underdiagnosed in the region,[21] and little is known about hantavirus[22,23] and *S. suis*.[24,25]

Our study emphasizes the need for rapid, inexpensive and accurate multi-disease diagnostic tests for tropical developing countries. For example, a number of both paediatric and adult patients with dengue in our study might have not been diagnosed if RDTs for dengue were not used in every participating patient. This is because diagnostic tests are usually used for a single disease based on clinical suspicion; therefore, patients presenting with atypical symptoms are commonly misdiagnosed or undiagnosed. For example, recent studies showed that rickettsioses, leptospirosis and dengue are commonly found in patients presenting with acute CNS infections in Southeast Asia,[26, 27] which is consistent with our results.

Our findings strongly support the recommendation of SSC to obtain blood cultures prior to administration of antibiotics within 3 hours for patients presenting with sepsis.[3] Bacteraemia is commonly observed in both age groups in our study (12% in adult patients and 5% in paediatric patients). Susceptibility testing of the bacterial agents identified from blood could be used to adjust or deescalate antimicrobial drugs.

Our findings indicate that severe sepsis is associated with higher mortality. This strongly suggests that patients suspected of infection should be routinely screened for signs of tissue hypo-perfusion or organ dysfunction, and severe sepsis patients should immediately receive intensive care and organ support.[3] We also show that adult patients with sepsis defined by the 2014 task force (SOFA score ≥2) are also associated with higher mortality, which supports the use of the new sepsis definition.[14]

Given the mortality associated with severe sepsis, clinicians must provide the most effective empirical management even before a microbiological diagnosis is confirmed. Our results highlight diverse causes of sepsis that should be considered in a patient's differential. For example, the clinical presentations of dengue and leptospirosis overlap, and both were common in our patient population. If a patient is managed for presumed dengue with supportive care but actually has leptospirosis, an opportunity for effective antimicrobial intervention will be missed. Awareness of the epidemiology of sepsis will help clinicians develop the most appropriate differential to guide empirical treatment before a microbiologic diagnosis is known.

Based on our findings, the first broad-spectrum antibiotics for patients with severe sepsis in Southeast Asia should cover both Gram-negative and Gram-positive bacteria, for example a combination of ceftriaxone plus doxycycline, or a combination of ceftazidime plus doxycycline. Doxycycline may need to be included as commonly used empirical antimicrobials such as beta-lactams and carbapenems are not effective against *Orientia tsutsugamushi*.[28,29] Doxycycline can be used even in children under the age of 8 years.[30] In areas where melioidosis is endemic, the third-generation cephalosporin may need to be ceftazidime as other third-generation cephalosporins are ineffective against *B. pseudomallei*.[21]

Only about half of sepsis patients had a pathogen identified. This finding is comparable to other studies in the region[6–10]. For examples, only 41%, 52% and 47% of fever episodes had a microbiological cause of fever identified in Southern Laos[6], two study sites in Laos[7] and Cambodia[8], respectively. D'Acremont et al[4] reported that 88% of paediatric patients in Tanzania had microbiological evidence, and the high proportion of microbiological evidence found could be due to the different diagnostic tests used and the different setting. In our study, it is possible that a proportion of patients without pathogen identified were actually infected by one of the agents we targeted, because the sensitivity of collected specimens and reference diagnostic tests is not 100%.[31] Also, many patients in our settings may have taken antibiotics prior to hospital admission. An alternative explanation is that patients were infected by pathogens that were not targeted by our diagnostic tests. Further studies in this group of patients are still required.

Our study has several potential limitations. First, the decision to perform some diagnostic tests in predefined subsets of patients with relevant symptoms could lead to misdiagnosis of some infectious diseases. However, this represents the variable clinical presentations of tropical infectious diseases. Second, in some patients, the pathogens identified might not be the cause of sepsis. It is possible that some pathogenic viruses and bacteria could be found in the nasopharyngeal cavity of healthy patients, and background sero-positivity for rickettsiosis and leptospirosis is also a possibility in people living in endemic areas. The presence of viruses in the nasopharyngeal cavity of healthy people in the previous studies conducted in China was not high[32]. Also, we used conservative criteria for microbiological evidence, such as high cutoffs for serological tests for ricketsiosis and leptospirosis (Table S3). Therefore, in most patients, the pathogens identified were likely to be the causes of sepsis. Further studies in healthy people in SEA are also needed. Third, the study did not reach the target sample size in Indonesia. Nonetheless, we did not observe major differences between the causes and outcomes of sepsis patients in Indonesia and in Thailand and Viet Nam. Fourth, the study was conducted at tertiary-care hospitals in Southeast Asia. Sepsis in other settings may be caused by different distribution of pathogens.

In conclusion, our study highlights the diverse causes of sepsis and their variable clinical manifestations, the need of multiplex RDTs for tropical infectious diseases, the substantial mortality of sepsis, and the utility of the sepsis diagnostic criteria and the SSC recommendations in three middle-income countries in SEA.

Panel: Research in context

Evidence before this study—We searched Pubmed for prospective studies that evaluated causes of fever and causes of sepsis and severe sepsis in less-resourced countries, and were published in English between Jan 1, 1984 and Dec 31, 2014 using the following terms “sepsis” *MeSH term+ AND (“Asia, Southeastern” *MeSH term]). We identified 34 studies. None of the studies applied inclusion criteria of surviving sepsis campaign (SSC) to patients presenting with sepsis in Southeast Asia. Several studies have examined causes of fever[6–10] and bacteremia[11] in Southeast Asia. However, none applied a pre-defined wide array of diagnostic tests and assessed the relative distribution of pathogenic bacterial, parasitic and viral agents identified in patients admitted with community-acquired sepsis in Southeast Asia.

Added value of this study—To our knowledge, this is the first study that aimed to identify potential causes of sepsis using a predefined set of diagnostic tests covering a wide range of viruses, bacteria and parasites in Southeast Asia. Typhoid fever and malaria was rarely identified in our study hospitals, which are situated in big cities in Indonesia, Thailand and Viet Nam. We observed a number of emerging pathogens including hantavirus, non-typhi *Salmonella* spp, *S. suis, Acinetobacter* spp, and *B. pseudomallei*. We observed that clinical presentations of many tropical infectious diseases, including dengue infection, leptospirosis and rickettsioses, were not specific. We show that mortality of sepsis in less-resourced countries in Southeast Asia is substantial, and severe sepsis defined by SSC 2012 is associated with mortality. We also conducted an additional analysis and showed that sepsis defined by the 2014 task force (total SOFA score ≥2) was associated with mortality in adult patients. One of the strengths of our study is that the mortality for sepsis observed is robust as we contacted participants to ascertain 28-day mortality outcomes. This is because there is a preference among people in many developing countries to die at home, and in-hospital mortality alone could underestimate the mortality of sepsis in developing countries.[20]

Interpretations of all the available evidence—To reduce mortality of sepsis in this region, rapid, inexpensive and accurate multi-disease diagnostic tests for tropical developing countries is urgently needed. The diagnostic criteria for sepsis and severe sepsis recommended by SSC are applicable to tropical less-resourced developing countries, and could be used to determine patients who are at high risk of death due to infectious diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the support provided by staff at all participating hospitals. This project was funded in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. This research was also supported in part by the National Institute of Allergy and Infectious Diseases, National Institutes of Health. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. DL was supported by a Wellcome Trust Public Health and Tropical Medicine Intermediate Fellowship, grant reference 101103/Z/13/Z. Mahidol-Oxford Tropical

Medicine Research Unit (MORU) in Thailand and Oxford University Clinical Research Unit (OUCRU) in Viet Nam were supported by Wellcome Trust grants 106698/B/14/Z and 106680/B/14/Z, respectively.

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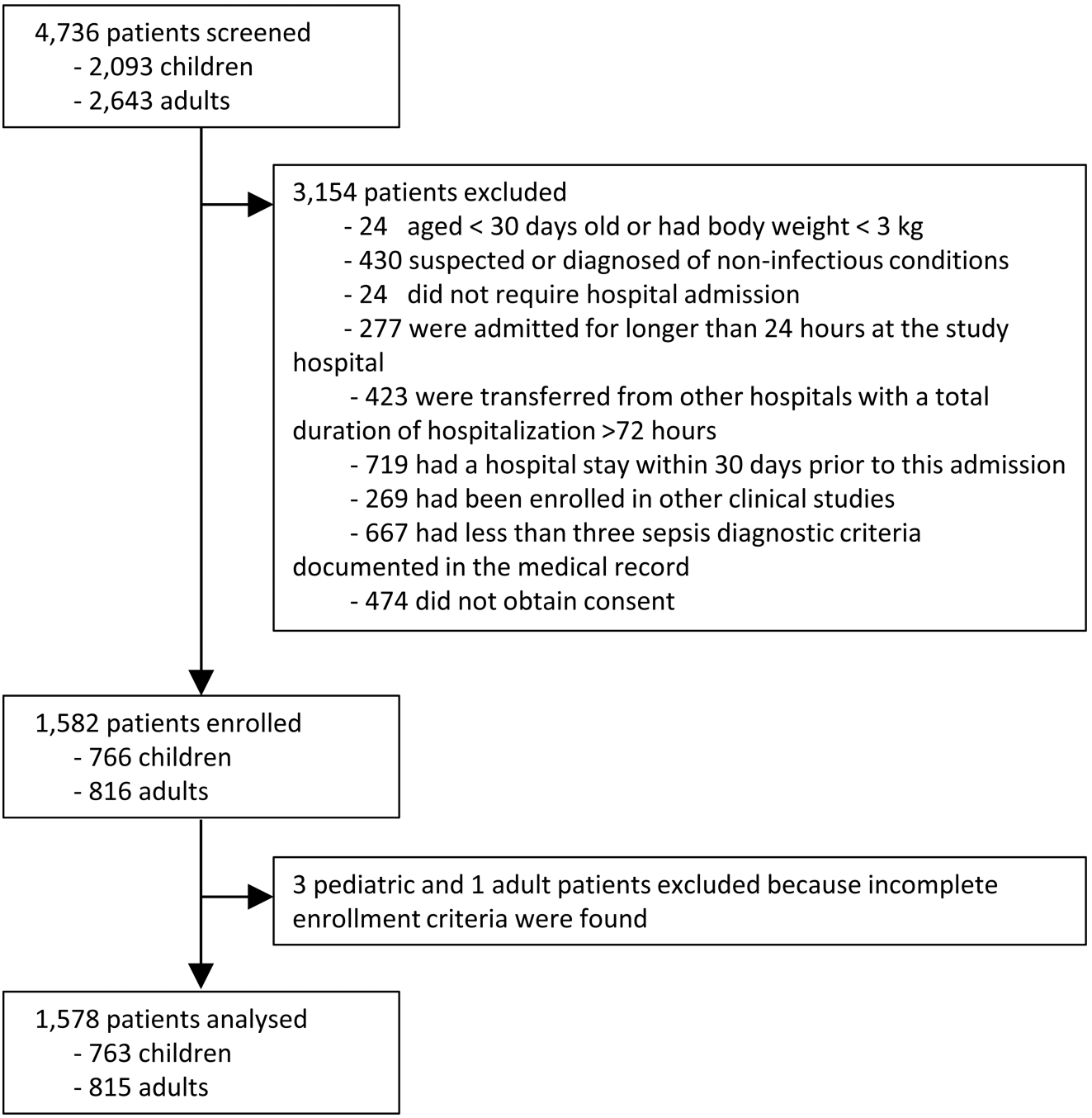


Figure 1. Study Flow Diagram

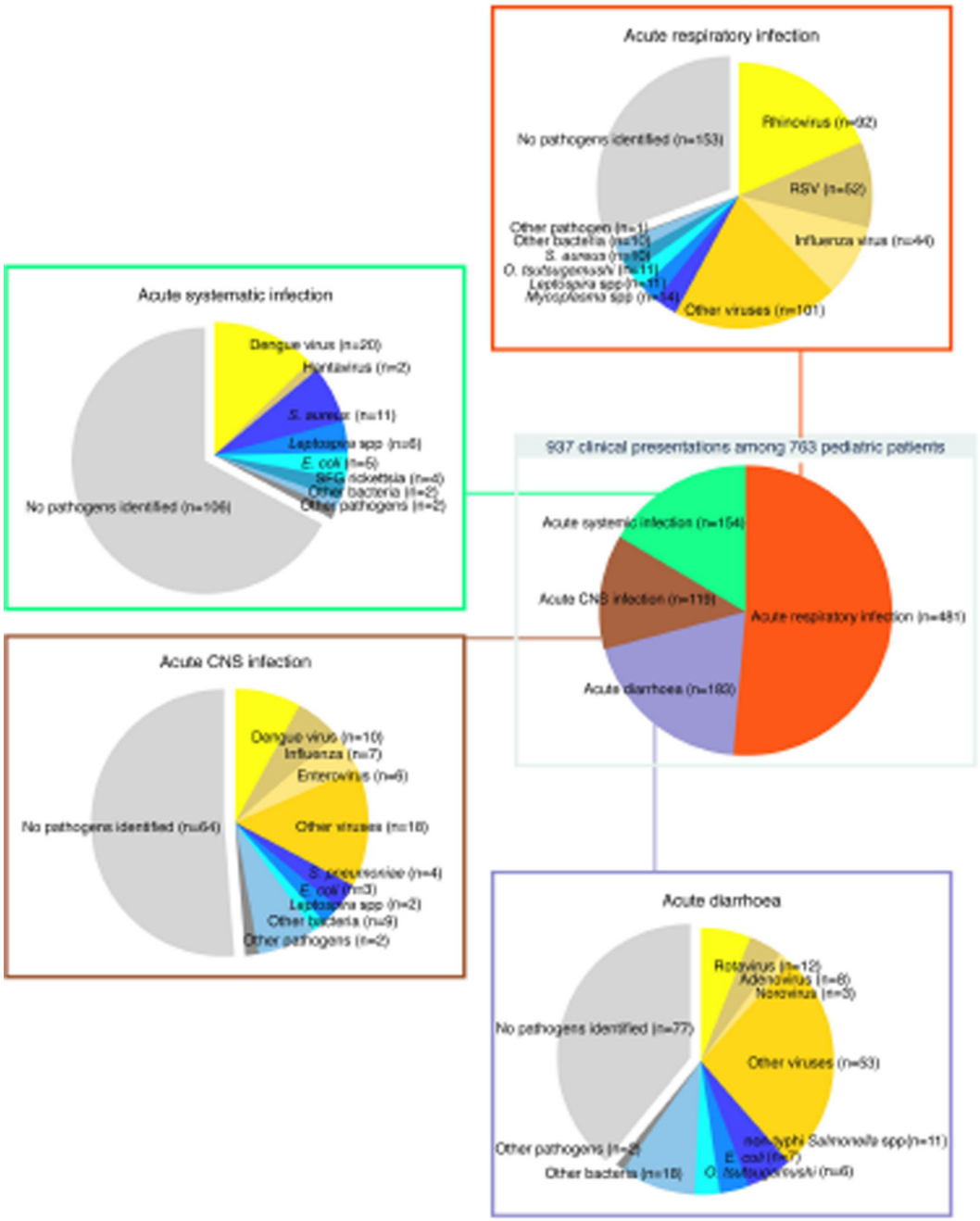


Figure 2. Distribution of clinical presentations and pathogens identified among 763 paediatric patients

Numbers are numbers of patients with each clinical presentation and of each pathogen identified. In some patients, there was more than one clinical presentation or more than one pathogen identified.

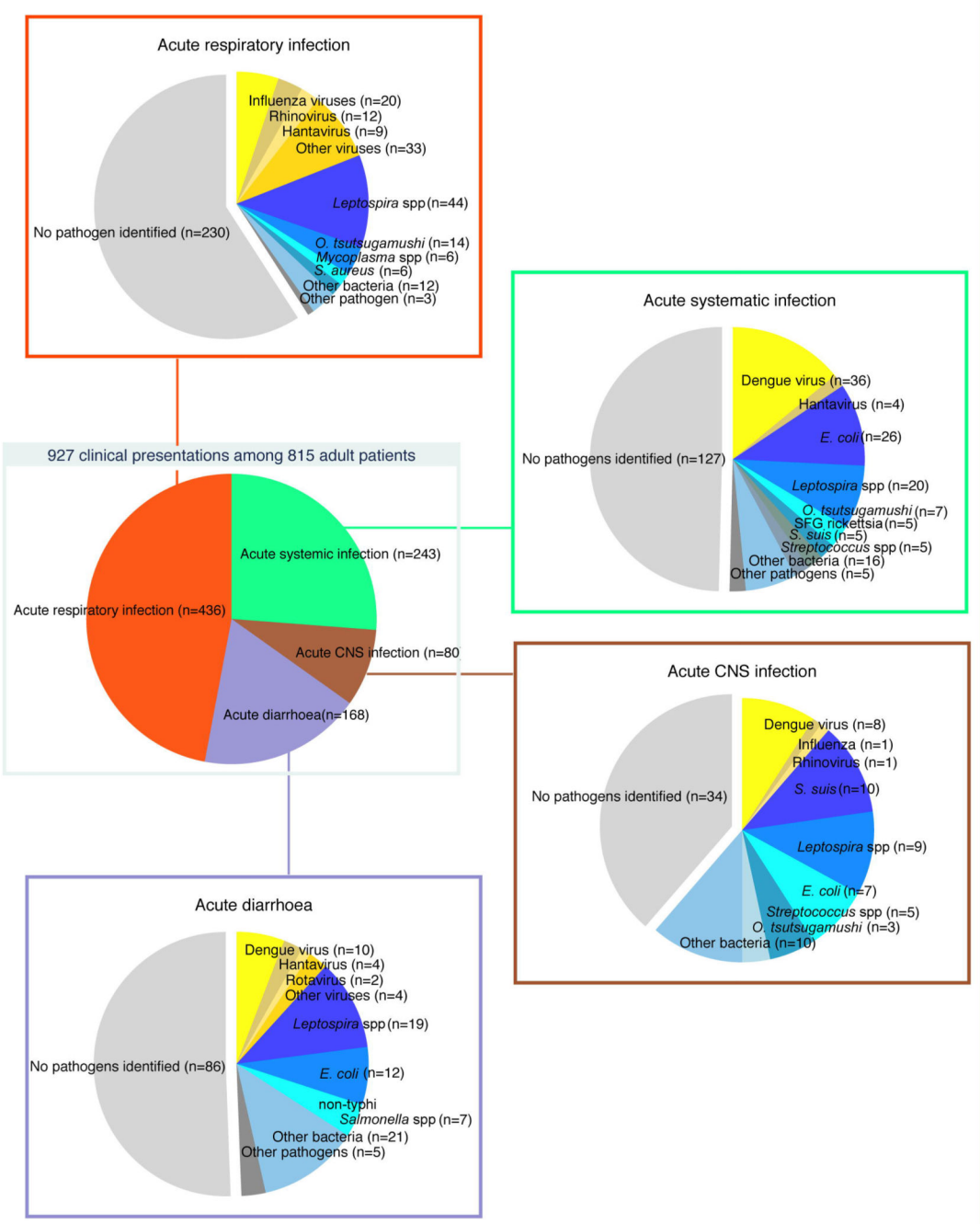
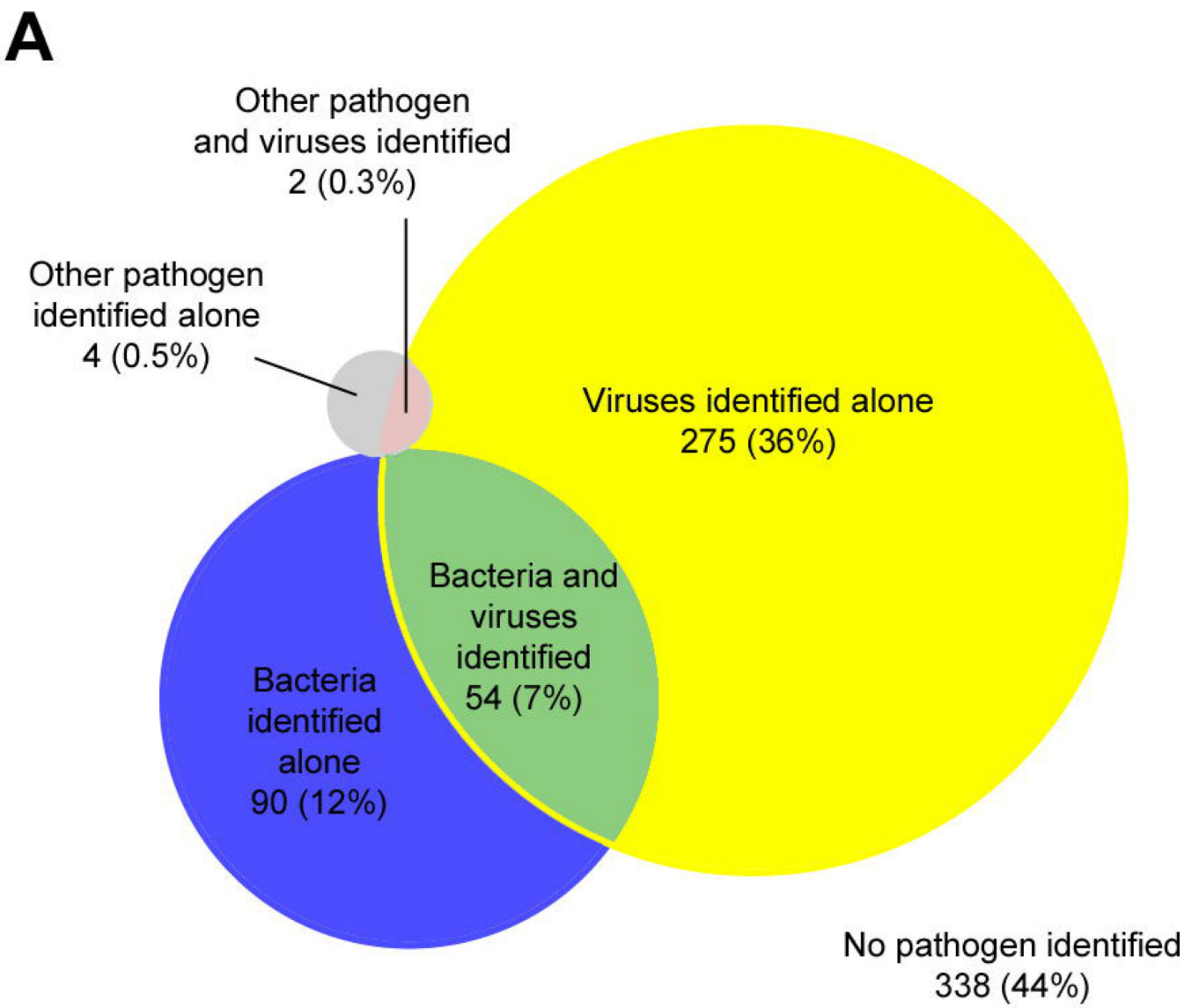


Figure 3. Distribution of clinical presentations and pathogens identified among 815 adult patients

Numbers are numbers of patients with each clinical presentation and of each pathogen identified. In some patients, there was more than one clinical presentation or more than one pathogen identified.



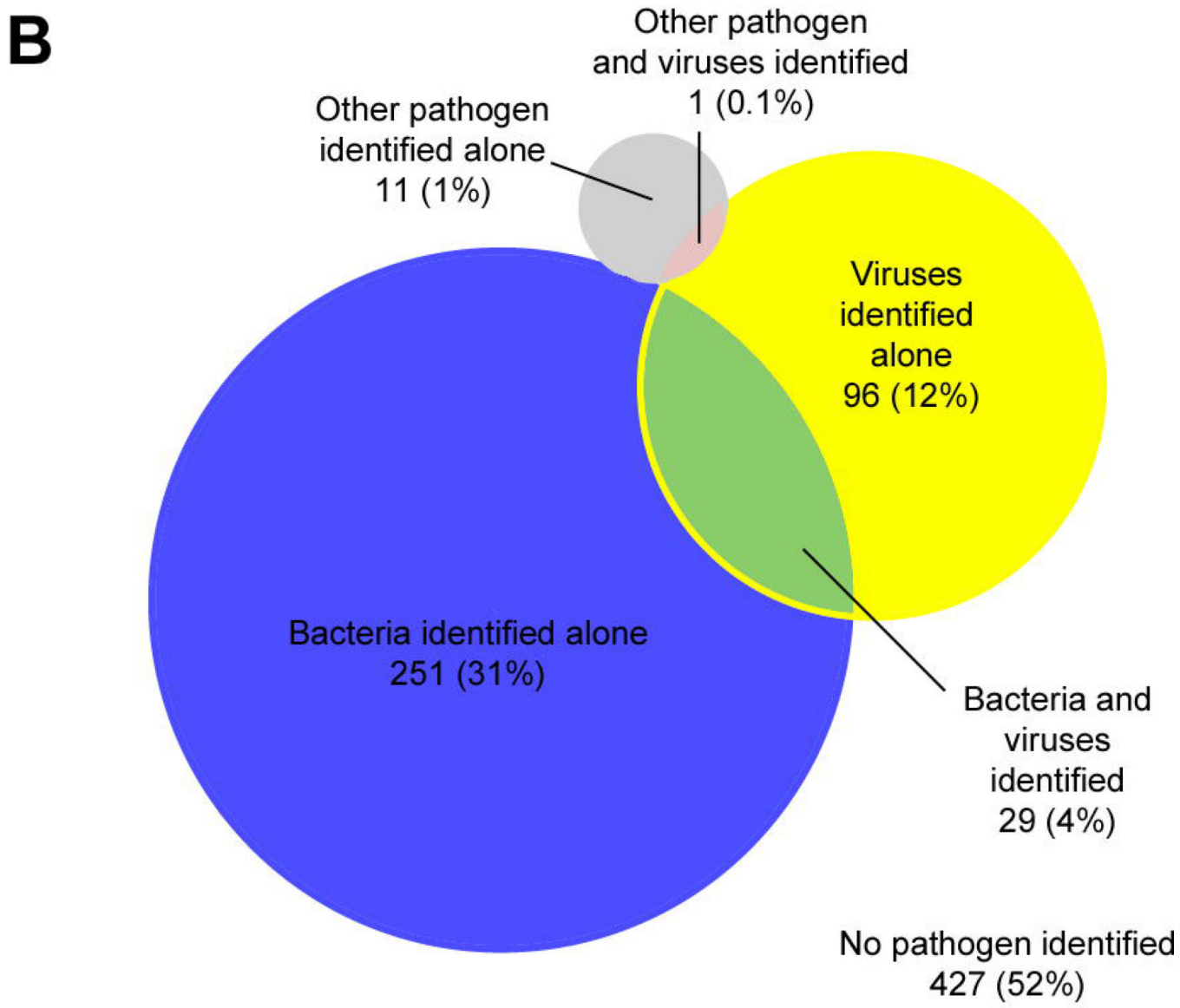


Figure 4. Overlap among pathogens identified in (A) 763 paediatric patients and (B) 815 adult patients

Table 1

Diagnostic criteria for sepsis in adult patients

Infection, documented or suspected, and some of the following:
General variables
Fever or hypothermia (body temperature >38.3°C or <36°C) *
Heart rate >90/min
Tachypnoea (respiratory rate >20/min)
Altered mental status (Glasgow Coma Scale <15 or <10T) †
Significant oedema or positive fluid balance (20 mL/kg over 24 hr)
Hyperglycaemia (plasma glucose >140 mg/dL) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12,000 u/L), Leukopenia (WBC count <4,000 u/L), or immature forms >10% ‡
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Haemodynamic variables
Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg or an SBP decrease >40 mmHg)
Organ dysfunction variables
Low oxygen saturation determined by pulse oximetry (SpO_2 <95%) §
Arterial hypoxaemia (PaO_2/FiO_2 <300)
Acute oliguria (urine output <0.5 mL/kg/hr for at least 2 hrs) ¶
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR >1.5 or aPTT >60s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000 u/L)
Hyperbilirubinaemia (plasma total bilirubin >4 mg/dL)
Tissue perfusion variables
Hyperlactataemia (>1 mmol/L)
Decreased capillary refill or mottling

Adapted from Dellinger et al, Surviving Sepsis Campaign: International Guideline for Management of Severe Sepsis and Septic Shock: 2012 [3]

*Variables fever and hypothermia were consolidated into a single variable.

†Glasgow Coma Scale <15 or <10T was defined for the altered mental status variable.

‡Variables leukocytosis, leukopenia and immature forms >10% were consolidated into a single variable.

§Variable low oxygen saturation determined by pulse oximetry (SpO_2 <95%) was added.

¶There is a condition of 'despite adequate fluid resuscitation' for this criterion in the SSC 2012 diagnostic criteria for severe sepsis.

Table 2

Diagnostic criteria for sepsis in paediatric patients

Infection, documented or suspected, with all three of the following:
Fever or hypothermia (rectal temperature >38.5°C or <35.0°C [or equivalent])
Tachycardia (heart rate > 2 SD above the normal value for age. This could be absent in hypothermic subject
Tachypnoea (respiratory rate > 2 SD above the normal value of age)
AND at least one of the following parameters
Altered mental status (e.g., drowsiness, poor quality of cry, poor reaction to parent stimuli, and poor response to social overtures)
Systolic blood pressure < 2 SD below the normal value for age, narrow pulse pressure (<20 mmHg), or poor perfusion (capillary refill > 2 sec)
Low oxygen saturation determined by pulse oximetry (SpO_2 <95%)
Leukocytosis (WBC count >12,000 u/L), leukopenia (WBC count <5,000 u/L), or immature forms >10%

Adapted from Goldstein et al, International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics [16]

Table 3

Baseline characteristics of paediatric patients with sepsis

Characteristics	Paediatric patients (%, n=763)
Sex, male	433 (57%)
Age	
1 mo - <1 year	171 (22%)
≥1 - <5 years	385 (50%)
≥5 - <18 years	207 (27%)
Country	
Indonesia	14 (2%)
Thailand	375 (49%)
Viet Nam	374 (49%)
Preexisting known conditions	
Diabetes	1 (0.1%)
Hypertension	0
Chronic kidney disease	0
Chronic lung disease	1 (0.1%)
HIV/AIDS	2 (0.3%)
28-day mortality	
Survived	717 (94%)
Died	14 (2%)
Unknown *	32 (4%)

* Mortality outcome was not available in 19 children who withdrew from the study prior to 28-days of follow-up, and in another 13 children who could not be contacted for 28-day outcome.

Table 4

Baseline characteristics of adult patients with sepsis

Characteristics	Adult Patients (%, n=815)
Sex, male	462 (57%)
Age	
≥18 - <40 years	261 (32%)
≥40 - <60 years	270 (33%)
≥60 years old	284 (35%)
Country	
Indonesia	65 (8%)
Thailand	375 (46%)
Viet Nam	375 (46%)
Preexisting known conditions	
Diabetes	124 (15%)
Hypertension	217 (27%)
Chronic kidney disease	50 (6%)
Chronic lung disease	36 (4%)
HIV/AIDS	2 (0.3%)
28-day mortality	
Survived	696 (85%)
Died	108 (13%)
Unknown *	11 (1%)

* Mortality outcome was not available in 5 adults who withdrew from the study prior to 28-days of follow-up, and in another 6 adults who could not be contacted for 28-day outcome.

Table 5

Risk factors for 28-day mortality in adult patients with sepsis

Factors	Outcome		Odds ratio (95% CI) *	
	Non-survivors (n=122)	Survivors (n=1,413)	Univariable analysis	Multivariable analysis
Severe sepsis	110 (90%)	630 (45%)	5.1 (2.6–10.0)	5.3 (2.7–10.4)
Bacteria identified	45 (37%)	364 (26%)	1.1 (0.7–1.8)	1.0 (0.6–1.5)
Viruses identified	13 (11%)	434 (31%)	0.5 (0.3–1.0)	0.5 (0.3–0.9)

* Stratified by age groups and study sites