UK Health Security Agency

The occurrence of venous thromboembolism among patients in hospitals with invasive Panton–Valentine Leukocidin *Staphylococcus aureus* infection

A rapid systematic review

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Main messages

1. This rapid systematic review (search up to 25 November 2024) identified and summarised evidence relating to the occurrence of venous thromboembolism (VTE) in hospital inpatients with invasive Panton-Valentine Leukocidin *Staphylococcus aureus* (PVL-SA) infection.

2. Four cohort studies were included (1 to 4). All were conducted in the United States of America (USA) in children aged 17 years or below. One cohort study specifically observed the development of VTE among hospital inpatients with staphylococcal osteomyelitis (2), while the others analysed clinical characteristics and outcomes for patients with *Staphylococcus aureus* infections in hospitals, including reporting invasive PVL-SA infections and development of VTE as a clinical presentation or complication (1, 3 and 4). All patients in the cohort studies were tested for the presence of PVL by polymerase chain reaction (PCR).

3. Three case series were included (5 to 7). One case series reported on adults (7) while the rest reported on children with invasive PVL-SA infections developing VTE (5, 6). One was reported from the UK (5), one from Germany (6) and one from USA ((7).

4. There were 12 case reports (8 to 19) each describing individual patients with invasive PVL-SA infections developing VTE. One case reported an adult patient (19) while the remaining cases were about children. Four cases were reported from Japan (11, 15, 16 and 19), 2 from Turkey (12, 13) and one each from Portugal (8), Spain (9), Slovenia (10), Greece (14), Italy (18), and Australia (17).

5. One cohort study reported that 18 out of 88 children with invasive PVL-SA developed VTE (20.4%) (3), and another reported that 5 out of 33 developed VTE (15.1%) (4). However, the other 2 cohort studies reported a higher occurrence of VTE with 7 out of 14 children (50%) developing VTE in one study (1), and 7 out of 7 (100%) children in the final cohort (2). The case series also reported a range of occurrence of VTE. One reported that 2 out of 8 children with invasive PVL-SA infections developed VTE (6), another found that 4 out of 11 children developed VTE (5), and a third documented 4 out of 4 adults developed VTE (7). Each case report described only one individual reporting VTE alongside invasive PVL-SA infection.

6. Studies reported that the majority of patients recovered, however one case series (5) reported that a 3 year old girl died. One cohort study (1) reported that 3 out of 14 children died but it was unclear whether those that died had VTE.

7. Risk of bias assessment of the cohort studies highlighted small sample sizes which were unlikely to be large enough to reliably estimate the incidence or rate of occurrence of VTE. The method of identification of VTE was only reported in 2 studies (2, 4). Most studies did

not report the individual demographics of included patients, and so it is not possible to assess if other factors may have influenced the outcome. Only 2 out of the 4 cohort studies (1, 2) discussed other possible factors that could increase risk of VTE.

8. Most of the case series and case reports described patients' medical history, symptoms, disease progression, method of VTE diagnosis and whether they recovered indicating a low risk of bias for these study designs. However, as case series and case reports are based on individual patient outcomes, they represent a low level of evidence and findings cannot be generalised to the broader population.

9. In summary, the review identified limited evidence on the occurrence of VTE among hospitalised patients with invasive PVL-SA infections. Most of the studies reported occurrence of VTE in children. Invasive bone and joint infections appeared as the most common presentation in hospitalised patients with invasive PVL-SA. However, since the majority of evidence was descriptive including case series and case reports, it was not possible to determine how common VTE occurrence is in patients with invasive PVL-SA infections.

Purpose

The purpose of this rapid systematic review was to identify and summarise the available evidence that reported on the occurrence of VTE in hospital inpatients with invasive PVL-SA infection.

The review question was:

1. What is the evidence of occurrence of venous thromboembolism among hospital inpatients with invasive Panton–Valentine Leukocidin *Staphylococcus aureus* infection?

Methods

A rapid systematic review was conducted, following streamlined systematic methods to accelerate the review process. A protocol was produced before the literature search was conducted, including the review question, the eligibility criteria, and all other methods. Full details of the methodology are provided in the protocol in Annexe A. To answer the review question, the following population, exposure, and outcome definitions were used:

1. Population: People with invasive PVL-SA infections being treated as hospital inpatients. The following invasive infections, as specified by subject matter experts were of interest for this review: osteomyelitis, necrotising fasciitis, pyomyositis, septic arthritis, deep seated tissue infections or abscesses, necrotising pneumonia, bacteraemia, abscesses and purpura fulminans. Only studies that used PCR testing to confirm invasive PVL-SA

infection in inpatients were included in the review. Where studies reported multiple PVL-SA invasive infections, only data for the eligible invasive infections was extracted.

2. Exposure: PVL-SA infection.

3. Outcome: Occurrence of VTE including incidence or count data (absolute number of people with invasive PVL-SA infections who developed VTE). VTE included deep vein thrombosis (DVT) or pulmonary embolism. Patients that developed infected or pus-filled blood clots in lungs were described as having septic pulmonary embolism. Septic thrombophlebitis (infected vein leading to blood clots and inflammation) was reported as a separate outcome.

4. As subject matter experts highlighted that VTE is more common in children, evidence for occurrence of VTE has been presented separately in this review for adults and children.

A literature search was undertaken to look for relevant primary observational studies, including case series and case reports, published up to 25 November 2024. Additionally, citation searching was performed by checking the reference lists of included studies to identify any studies that may not have been included in the initial search.

Screening title and abstract was undertaken in duplicate by 2 reviewers for 20% of the eligible studies, with the remainder completed by one reviewer. Full text screening was undertaken by one reviewer and checked by a second. Data extraction was performed by one reviewer and checked by a second. Disagreement was resolved by discussion.

Risk of bias assessment was conducted in duplicate by 2 reviewers. The JBI tools (20) for prevalence studies, case series and case reports were used for critical appraisal of included studies.

Evidence

In total, 5,299 studies were screened at title and abstract and 56 studies were screened at full text. Additionally, 18 studies were identified from citation searching of included studies and relevant reviews. As a result, 74 studies were screened at full text. Of these, 19 studies met the inclusion criteria. These included 4 cohort studies (1 to 4), 3 case series (5 to 7) and 12 case reports (8 to 19). All cohort studies, case series and case reports involved children aged 17 years or younger except one case series (7) and a case report (19) that included adults.

A PRISMA diagram showing the flow of studies through the review is shown in Annexe B, and studies excluded on full text screening are available with the reasons why in Annexe C. Study characteristics are available in Annexe D, and risk of bias assessments are available in Annexe E.

Adults

The evidence in adults described patients with invasive PVL-SA infections that developed VTE. All patients with VTE were male and recovered with treatment. Ethnicity of patients was not reported.

Case series

One case series reported 4 men with bacteraemia (mean age 50.5 years) between December 2005 to February 2007 (7). Patients had different invasive infections alongside bacteraemia: 2 cases had pyomyositis, one had an abscess and the fourth had osteomyelitis. Computed tomography (CT) scans confirmed that all patients developed septic pulmonary embolism. Septic thrombophlebitis could not be detected using the available scanning methods. Additional details of patients are reported in Table D.1.

Case report

One case report in Japan described a 20 year old man who developed multiple severe infections, including septic osteomyelitis of the hip joint, bacteraemia, and skin and soft tissue infections of the hip and thigh with abscesses. Abdominal CT scan revealed iliofemoral DVT (blood clot in the deep veins of the lower abdomen and thigh) and chest CT scan identified septic pulmonary embolism (19).

Children

Cohort studies

Four studies conducted in the USA between 2000 and 2014 at Texas Children's hospital reported VTE in children aged below 17 years (1 to 4). Two studies were retrospective (3, 4) and 2 were prospective cohort studies (1, 2). Ethnicity was only reported in one cohort study (2).

In one prospective cohort study, 14 previously healthy children (average age 12.9 years), all with invasive bone and joint infections, septic arthritis of the knee joint or multiple bone/joint involvement with pyomyositis of surrounding muscles were observed between September 2002 to January 2004 (1). Two out of 14 were girls. All but one child had bacteraemia. Four out of the 14 children developed DVT in different veins including: common iliac vein (in the lower abdomen and pelvis), saphenous (inside the leg) and popliteal vein (behind the knee) and the femoral vein (in the thigh). Method of DVT diagnosis was not reported. Chest radiographs of 7 out of 14 children showed signs of septic pulmonary embolism, seen as small lumps in both lungs. The study reported that the children did not have any predisposing factors leading to

VTE. Three of the children with septic arthritis died, but the study did not specify if they were the children that had VTE.

Another prospective cohort study conducted between August 2001 and December 2004 reported 9 children with osteomyelitis and pyomyositis, 7 of whom had infections caused by PVL-SA (2). The children aged between 3 to 14 years were all boys. Doppler ultrasound and CT showed VTE in all 7 children in the femoral, iliac, popliteal, and saphenous veins. Four out of 7 children developed septic pulmonary embolism. All the children recovered. Individual demographics of children have been reported in Table D.2.

A retrospective cohort study of 296 children with invasive staphylococcal infections during January 2007 to December 2014 found that 88 out of 296 children were PVL positive (3). Bone and joint infections were the most common presentation, followed by bacteraemia, pneumonia, myositis/pyomyositis and deep abscesses. All the cases had PVL gene. DVT was reported in 18 children (location not specified). Twelve of these children had concurrent bone and joint infections and 6 children had severe sepsis. Individual demographics, method of DVT diagnosis and whether the children recovered were not reported.

Another retrospective cohort study conducted between February 2000 and December 2002, studied 59 children with infections in the muscles, bones, or joints (4). Osteomyelitis was the most common invasive infection followed by septic arthritis and pyomyositis. PCR testing revealed that 33 children carried the PVL gene. Doppler ultrasound identified DVT in 5 children (location not specified). Demographics of individual cases or specific infection type in these children were not reported. All children with DVT recovered.

Case series

Between January 2004 and May 2008, a retrospective case series reported records of 11 children (median age 9 years) with invasive PVL-SA infections in the UK (5). Clinical presentations included septic arthritis, osteomyelitis, necrotising pneumonia, pyomyositis, retropharyngeal (space at the back of the throat, near the pharynx) abscess causing airway obstruction and bacteraemia leading to septic shock.

Four children developed DVT:

- a 3 year old girl with septic arthritis of the hip had femoral DVT
- a 7 month old girl with a retropharyngeal abscess causing airway obstruction developed internal jugular vein thrombosis (side of neck)
- a 9 year old boy with septic shock involving multiple sites including hips and chest also had femoral DVT
- another 9 year old boy with multiple infections and septic shock had multiple DVTs at the sites of central venous catheter insertion

The 3 year old girl died but all the other children recovered. Method of DVT diagnosis was not reported.

Another case series from Germany between January 2012 and December 2017 described records of 8 children (mean age 5.5 years) with severe PVL-SA infection (from a cohort of 75 children being treated for PVL-SA infection). Severe infection in this case series was defined as children requiring intravenous antibiotics, admission to an intensive care unit (ICU) or intermediate care unit (IMC) or undergoing major emergency surgery. Six out of 8 children were boys. Infections included necrotising pneumonia, necrotising fasciitis, pyomyositis, necrotising pneumonia and mastoiditis (infection of the mastoid bone located behind the ear). Two children developed DVT diagnosed by magnetic resonance imaging (MRI) scan:

- a 14 year old boy with necrotising pneumonia, pyomyositis and axillary abscess (armpit area) had femoral DVT. The boy developed swelling and pain on his left leg 3 days after hospital admission
- an 11 year old boy with mastoiditis and soft tissue infection had thrombosis of left sigmoid venous sinus (back of the head) and distal jugular vein (lower part of neck near collar bone)

Neither of them had any pre-existing health conditions. Both children made a full recovery (6).

Case reports

Eleven case reports documented VTE as a complication of invasive PVL-SA infections (8 to 18). Three of these cases were reported in Japan (11, 15 and 16) and 2 were reported in Turkey (12, 13). Individual cases were reported from Portugal (8), Spain (9), Slovenia (10), Greece (14), Italy (18) and Australia (17). Most reports were of children aged between 10 to 17 years, however, one case report presented a 22 month old child (10). Ethnicity was only reported in one case report (17). All cases recovered.

One case report described a 14 year old boy who developed an invasive PVL-positive infection following toe trauma progressing to soft tissue infection, septic arthritis, and bacteraemia (8). Doppler flow scans confirmed DVT in the right femoral vein. Doppler studies of inferior vena cava (large vein in the abdomen and lower chest, running alongside the spine) and ileo-femoral vessels also identified a large clot in the right iliac veins. Chest CT scan confirmed pulmonary embolism on day 3 after hospital admission.

Another case report described an 11 year old girl who developed an invasive PVL-positive infection following a fall while playing (9). Initially presenting with pain and swelling in the upper and inner side of leg, the condition progressed to osteomyelitis, fasciitis, cellulitis, and a large abscess that broke through the skin. As the condition got worse, the child developed DVT in the internal saphenous and popliteal veins. A second ultrasound scan revealed septic thrombophlebitis in the lower right leg.

A 22 month old boy with no significant medical history developed necrotising pneumonia with abscesses and osteomyelitis in the right thigh bone after a 2 day history of fever and painful swelling of the right hip (10). On day one after hospital admission, the child was found to have DVT in the right femoral vein.

Harada and others reported a 10 year old boy with no prior medical history or family history of immunodeficiency (11). The child developed acute osteomyelitis of the right ilium (forms upper portion of pelvic bone), along with pyomyositis and abscesses in the same region. During treatment, the infection progressed to include sacral (bone at the base of spine) osteomyelitis, additional abscesses around the right ilium, and septic arthritis of the right hip. CT of the pelvis revealed a blood clot that did not completely obstruct the blood flow (non-occlusive thrombosis) of the right common iliac vein. CT of the lungs showed several areas of infection and small lumps, which were signs of septic pulmonary embolism. Additionally, the child developed septic thrombophlebitis of the right common iliac vein.

Two cases of healthy teenage boys in Turkey who developed invasive infections complicated by pulmonary embolism were reported by Karli and others (12, 13). In the first case, a 13 year old boy had a deep tissue infection with an irregular, abscess in the buttock area, excess fluid in the joint, and inflammation of the top edge of the right pelvic bone. CT scans of the chest showed multiple empty spaces in the lungs consistent with septic pulmonary embolism (12).

The second case was a 12 year old boy with no significant medical or familial history. Physical examination revealed limited movement of the left hip and shallow breathing. Scans confirmed a left psoas muscle abscess (located in lower back) and osteomyelitis of the in the upper part of left thigh bone. Septic pulmonary embolism was also identified, which the authors stated had likely originating from the psoas abscess (13).

A 10 year old girl with no significant medical history presented with fever and impaired movement of her right leg following a mild injury during exercise (14). Ultrasound revealed inflammation in the right hip joint and MRI scans showed severe osteomyelitis in the right thigh bone and pyomyositis in the surrounding muscles. Five days after hospital admission, MRI showed DVT in the right femoral and external iliac veins.

Another case report was of a 17 year old sports player in Japan with no prior history of serious illnesses or predisposing factors, who developed a severe invasive infection following hard physical exercise (15). Blood cultures confirmed staphylococcal bacteraemia with infection that spread into the lungs. A chest scan showed fulminant embolic pneumonia (extensive lung problems and tissue damage indicating severe and quickly worsening lung infection caused by blood clots). The authors speculated that pulmonary embolism likely developed from hematogenous spread (spread through bloodstream), as the tissue damage resembled experimental pulmonary embolism.

A further case report from Japan described a 15 year old boy who had a history of furuncles (painful, red, swollen bumps on the skin) with pus discharge on the front side of his left knee

after an insect bite (16). MRI revealed pyomyositis in the one of the 4 muscles that make up the front thigh muscles and abscesses beneath the outer layer covering the bone of the left lower thigh, with suspected inflammation spreading to the bone marrow (osteomyelitis). On day 5 of admission, the child developed septic pulmonary embolism in the lungs, confirmed by CT scans, which also showed signs of pneumonia.

One case report described a 14 year old boy with a history of mild asthma who presented with a 7-day history of worsening left knee pain, swelling, fever, and severe chills and shivering (17). The child had multiple soft tissue and bone infections, including osteomyelitis, septic arthritis, and deep tissue abscesses. CT scan revealed DVT in the left popliteal vein (17).

Valentini and others reported a 15 year old boy with no significant medical history, aside from mild childhood asthma, who presented with a 4-day history of headache, fever, lumbar pain, and vomiting (18). The child had a small pus-filled sore on his back from a backpack rub during a trekking vacation. Imaging (scanning technique not reported) showed small lumps in both lungs and enlarged organs, and the child developed severe invasive infections including bacteraemia, necrotising pneumonia, and lung abscesses. A CT scan revealed DVT in the inferior vena cava and iliac veins.

Critical appraisal of evidence

Risk of bias assessment indicated that the cohort studies had some methodological limitations. All cohort studies were conducted in children and had small sample sizes, reporting limited or no demographic and clinical information for those who developed VTE. Therefore, the samples may not be fully representative of the broader patient population with invasive PVL-SA infections. The method of identification of VTE was not reported in 2 out of 4 cohort studies. It was also not clear whether patients had VTE from the start of the study. Two of the 4 cohort studies mentioned other possible factors in patients that may have led to development of VTE but there was no consideration of related factors in the remaining cohort studies.

Case series and case reports generally described patients' medical histories, symptoms, disease progression, VTE diagnosis method, and recovery outcomes. However, the time period and hospital setting were not provided in most case reports, except one (16). Details regarding ethnicity, psychosocial history, comorbidities were briefly mentioned or not reported at all.

As case series and case reports are based on individual patient observations, and the cohort studies did not provide sufficient information on effect size and variance, a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment for quality of evidence could not be conducted (21). However, the quality of evidence was generally considered low due to the descriptive nature of case reports, case series, and non-comparative cohort studies, which lacked control groups and could be prone to bias.

Health inequalities

The evidence presented in the review focused primarily on children, with only 2 studies reporting on the occurrence of VTE in adults. Most studies did not examine or report on socioeconomic factors, psychosocial history, ethnicity, or geographic disparities in patients with PVL-SA infections and VTE, limiting the ability to assess health inequalities. Variations in healthcare systems across different regions could influence VTE risk, but this factor was not explored in the included studies.

The inconsistent scanning methods across studies for detecting VTE raise concerns about potential health inequalities, as access to more sensitive techniques like doppler ultrasound could lead to earlier and more accurate detection of thrombosis, reducing the risk of underdiagnosis.

Limitations

This rapid systematic review used streamlined systematic methods to accelerate the review process. Sources of evidence searched included databases of peer-reviewed and preprint research, but an extensive search of other sources was not conducted and most article screening was completed without duplication, so it is possible relevant evidence may have been missed.

There were only 4 relevant cohort studies identified, which had some methodological limitations. These studies had small sample sizes, lacked sufficient demographic and clinical information, and were all conducted in children, limiting their generalisability to adults or the broader patient population with invasive PVL-SA infections. Additionally, 2 of the 4 studies did not report the method of VTE identification. While 2 studies mentioned possible predisposing factors for VTE, other studies did not consider these factors, further undermining the reliability of the findings.

Most of the evidence came from case series and case reports which described individual clinical presentations that may not be generalisable to the wider population even if they have the same characteristics.

With the evidence being mostly descriptive, no conclusions could be drawn about the relative frequency of occurrence of VTE in patients with invasive PVL-SA infections.

Although planned in the protocol, it was not possible to undertake a GRADE assessment for quality of evidence as none of the cohort studies reported effect sizes and variance, and the remainder of the evidence was from reports of individual cases.

Evidence gaps

There were a limited number of observational studies on the occurrence of VTE in patients with invasive PVL-SA infections. The evidence for adults was limited to a case series and a single case report with a total of 5 people included. No cohort studies were identified in adults. As most of the evidence in this review came from descriptive studies, it was not possible to establish the incidence of VTE in hospitalised patients with invasive PVL-SA infection. Among other invasive infections specified by the subject matter experts, none of the included studies reported purpura fulminans among inpatients and evidence for necrotising fasciitis was also very limited.

Conclusion

In summary, the review documented limited evidence on the occurrence of VTE in hospital inpatients with invasive PVL-SA infections. Invasive bone and joint infections appeared as the most common presentation in hospitalised patients with invasive PVL-SA. The available evidence is primarily from children. All of the included studies had small sample sizes, and were at risk of bias, therefore it is not possible to make firm conclusions on the incidence or frequency of occurrence of VTE in inpatients with invasive PVL-SA infections in the general population.

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Disclaimer

UKHSA's rapid systematic reviews and evidence summaries aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, and papers on preprint servers. Please note that the reviews:

- use accelerated methods and may not be representative of the whole body of evidence publicly available
- have undergone an internal independent peer review but not an external peer review
- are only valid as of the date stated on the review

In the event that this review is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

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Annexe A. Protocol

Review question

The review question is:

1. What is the evidence of occurrence of venous thromboembolism among hospital inpatients with invasive Panton–Valentine leukocidin *Staphylococcus aureus* infection?

A search for primary evidence to answer this review question will be conducted up to 25 November 2024.

Eligibility criteria

Table A.1. Inclusion and exclusion criteria

	Included	**Excluded**
Population	Patients with laboratory confirmed invasive Panton–Valentine Leukocidin *Staphylococcus aureus* (through polymerase chain reaction test) being treated as hospital inpatients Invasive will be defined as: • osteomyelitis • necrotising fasciitis • pyomyositis • septic arthritis • deep-seated tissue infections/abscesses • necrotising pneumonia • bacteraemia • abscesses • purpura fulminans	Patients with laboratory confirmed invasive Panton–Valentine Leukocidin *Staphylococcus aureus* who are not hospital inpatients Animals Non-invasive Panton–Valentine Leukocidin *Staphylococcus aureus*
Context	Any	
Settings	Hospitals	Laboratories Community
Intervention or exposure	Panton–Valentine Leukocidin *Staphylococcus aureus* infection	
Comparator	None required	

	Included	Excluded
Outcomes	Occurrence of venous thromboembolism in patients with Panton–Valentine Leukocidin *Staphylococcus aureus* 1. Incidence 2. Count data (absolute number of persons with the outcome)	
Language	English	Any other language
Date of search	Up to 25 November 2024	
Study design	Observational studies including cohort, case- control, cross-sectional studies, case series and case reports	Experimental studies including randomised-controlled trials, quasi-experimental studies, cross-over designs, before-and-after studies Modelling studies Quantitative research Qualitative research Mixed methods Reviews (all types)
Publication type	Peer-reviewed published research	Conference abstracts/presentations Editorials Letters News articles Grey literature Reports (for example, from governments, World Health Organization) Preprints

Identification of studies

The following databases will be searched for studies published up to 25 November 2024: Ovid Medline, Ovid Embase, Scopus, Cochrane Central Register of Controlled Trials, CINAHL. The search strategy is presented below. Backwards and forwards citation searching will be carried out using references that are included at full text screening as seed papers. Citation searching will use Lens.org via CitationChaser.

Screening

Title and abstract screening will be undertaken in duplicate by 2 reviewers for at least 20% of the eligible studies, with the remainder completed by one reviewer. Disagreement will be resolved by discussion or with involvement of a third reviewer where necessary. Screening on full text will be undertaken by one reviewer and checked by a second. Results of citation searching will be screened by one reviewer.

Data extraction

Summary information for each study will be extracted and reported in tabular form. Information to be extracted will include country, study period, study design, intervention, participants, results, and any relevant contextual data. This will be undertaken by one reviewer and checked by a second.

Risk of bias assessment

We will perform risk of bias assessment at the primary study level using the relevant JBI checklist (20). Risk of bias will be assessed by 2 reviewers independently with disagreements resolved through discussion or with a third reviewer.

Quality of evidence

The quality of evidence identified within this review will be assessed, if available evidence allows, using a modified version of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (21). Quality of evidence will be assessed at the outcome level, and be rated as one of 4 levels:

- very low (the true effect is probably different from the estimated effect)
- low (the true effect might be different from the estimated effect)
- moderate (the true effect is probably close to the estimated effect)
- high (the authors are confident that the true effect is similar to the estimated effect)

The quality of evidence will be assessed for each outcome across 4 domains:

1. Risk of bias: where results may not represent the true effect because of limitations in the design or conduct of the study. This will be measures as described under: Risk of bias assessment.

2. Inconsistency: where studies show different effects for the same outcome of interest. This will be assessed where there are 2 or more studies measuring the same outcome. Inconsistency will be rated down if the point estimates are not similar, or the confidence

intervals do not overlap. If there is only one study for the outcome of interest, then inconsistency will not be assessed. Inconsistency will be assessed by one reviewer and checked by a second.

3. Indirectness: where elements of the study differ from the intended elements in the review question (for example, the outcome of interest has not been directly measured). This will be rated down if the population, intervention, comparator, or outcome of interest have not been directly measured. Indirectness will be assessed by one reviewer and checked by a second.

4. Imprecision: a measure of how uncertain the estimate is. Imprecision will be rated down if the confidence intervals cross the line of no effect, or if the reviewer judges that the confidence intervals are overly wide and so the true effect is likely to be different at the upper versus the lower end of the confidence interval. Imprecision will be assessed by one reviewer and checked by a second.

If the studies only report count data without effect size measures like odds ratios (OR) or relative risks (RR), a full GRADE assessment will not be possible.

Synthesis

Where studies are similar enough to combine and present data in a consistent format, a narrative synthesis will be produced to interpret the findings. The number of studies, the number of participants in each study, effect size and variance and a summary of the risk of bias across studies reporting each outcome will be summarised and presented. Alternatively, if studies present methodological differences that would make synthesis inappropriate, a narrative summary of each study will be provided.

Health inequalities

Where available, data for children aged 17 years or below will be presented separately to that of individuals aged 18 years or above.

Search strategy

Ovid MEDLINE(R) ALL (1946 to 25 November 2024)

1. Leukocidins/ (1750)
2. leukocidin*.tw,kf. (2240)
3. leucocidin*.tw,kf. (564)
4. leukotoxi*.tw,kf. (1109)
5. leucotoxi*.tw,kf. (73)
6. Panton Valentine.tw,kf. (2334)

7. PVL.tw,kf. (5140)
8. LukS.tw,kf. (374)
9. LukF.tw,kf. (330)
10. Luk pv.tw,kf. (49)
11. Bacterial Toxins/ and (exp Staphylococcal Infections/ or exp Staphylococcus aureus/) (3591)
12. or/1-11 (9899)
13. exp "Embolism and Thrombosis"/ (258642)
14. thrombo*.tw,kf. (458381)
15. Emboli*.tw,kf. (164502)
16. thromboembol*.tw,kf. (84536)
17. thrombus.tw,kf. (49699)
18. atherothrombo*.tw,kf. (6341)
19. blood clot*.tw,kf. (12299)
20. embolus.tw,kf. (6678)
21. (clot* adj3 (vein* or venous* or arter* or vascular* or cerebrovascular* or cardiovascular* or heart or brain or cardiac or cardio)).tw,kf. (1645)
22. or/13-21 (675978)
23. Pneumonia, Staphylococcal/ (2094)
24. Soft Tissue Infections/ (4427)
25. ((deep or invasiv*) adj3 infect*).tw,kf. (29552)
26. ((deep or invasiv*) adj3 staph*).tw,kf. (479)
27. ((deep or invasiv*) adj3 s aureus).tw,kf. (244)
28. ((deep or invasiv*) adj3 "s.aureus").tw,kf. (4)
29. ((deep or invasiv*) adj3 bacter*).tw,kf. (3759)
30. (deep tissue* adj3 infect*).tw,kf. (323)
31. (deep tissue* adj3 invasive*).tw,kf. (84)
32. (deep tissue* adj3 staph*).tw,kf. (6)
33. (deep tissue* adj3 s aureus).tw,kf. (6)
34. (deep tissue* adj3 "s.aureus").tw,kf. (0)
35. (deep tissue* adj3 bacter*).tw,kf. (65)
36. exp Osteomyelitis/ (25233)
37. osteomyelitis.tw,kf. (28442)
38. (bone* adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (11321)
39. (bone* adj3 S aureus).tw,kf. (143)
40. (bone* adj3 "S.aureus").tw,kf. (0)
41. Fasciitis, Necrotizing/ (3458)
42. necroti#ing fasciitis.tw,kf. (5516)
43. flesh eating bacter*.tw,kf. (42)
44. necroti#ing bacter*.tw,kf. (44)
45. (fascia adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (119)
46. (fascia adj3 S aureus).tw,kf. (0)
47. (fascia adj3 "S.aureus").tw,kf. (0)
48. Pyomyositis/ (468)

49. (intramusc* adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (568)
50. (intramusc* adj3 S aureus).tw,kf. (12)
51. (intramusc* adj3 "S.aureus").tw,kf. (0)
52. ((muscle* or muscular) adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (13341)
53. ((muscle* or muscular) adj3 S aureus).tw,kf. (11)
54. ((muscle* or muscular) adj3 "S.aureus").tw,kf. (0)
55. pyomyositis.tw,kf. (1290)
56. Myositis/ (10247)
57. myositis.tw,kf. (13405)
58. exp Arthritis, Infectious/ (16386)
59. (bacter* adj3 arthriti*).tw,kf. (856)
60. (septic* adj3 arthriti*).tw,kf. (7581)
61. (suppurat* adj3 arthriti*).tw,kf. (302)
62. (infect* adj3 arthriti*).tw,kf. (3037)
63. (staph* adj3 arthriti*).tw,kf. (317)
64. (S aureus adj3 arthriti*).tw,kf. (132)
65. ("S.aureus" adj3 arthriti*).tw,kf. (5)
66. (deep adj2 tissue* adj2 infect*).tw,kf. (413)
67. exp Tissues/ (2072117)
68. Pneumonia, Necrotizing/ (134)
69. pneumoni*.tw,kf. (245186)
70. ((lung or lungs or pulmonary) adj2 infection*).tw,kf. (24890)
71. ((lung or lungs or pulmonary) adj2 inflam*).tw,kf. (24354)
72. ((lung or lungs or pulmonary) adj2 (invasiv* or bacter* or staph*)).tw,kf. (7567)
73. ((lung or lungs or pulmonary) adj2 S aureus).tw,kf. (82)
74. ((lung or lungs or pulmonary) adj2 "S.aureus").tw,kf. (3)
75. exp Lung/ and Necrosis/ (1376)
76. ((pulmonary or lung*) adj3 necro*).tw,kf. (2324)
77. ((Alveolar* or airway* or respiratory* or lung* or bronch*) adj3 h?emorrhag*).tw,kf. (6267)
78. ((Alveolar* or airway* or respiratory* or lung* or bronch*) adj3 bleed*).tw,kf. (1718)
79. ((Alveolar* or airway* or respiratory* or lung* or bronch*) adj3 blood).tw,kf. (22729)
80. (multi lobar infiltrat* or multilobar infiltrat*).tw,kf. (77)
81. Respiratory Distress Syndrome/ (26136)
82. exp Respiratory Insufficiency/ (70372)
83. (respiratory adj (collapse* or distress or insufficiency or failure)).tw,kf. (106958)
84. (lung* adj (collapse* or distress or insufficiency or failure)).tw,kf. (1844)
85. (pulmonary adj (collapse* or distress or insufficiency or failure)).tw,kf. (2847)
86. Influenza, Human/ (60545)
87. influenza*.tw,kf. (143586)
88. Hemoptysis/ (6850)
89. h?emoptysis.tw,kf. (13343)
90. Leukopenia/ or Neutropenia/ (27517)
91. leukopeni*.tw,kf. (15027)
92. neutropeni*.tw,kf. (49570)

93. Oxygen Saturation/ (1112)
94. Oxygen/ and exp Blood/ (9960)
95. oxygen saturation.tw,kf. (36060)
96. (blood adj (oxygen or o2)).tw,kf. (10272)
97. SPo2.tw,kf. (9083)
98. exp Sepsis/ (148551)
99. exp Bacteremia/ (34147)
100. (Bacteria/ or exp Staphylococcus aureus/ or Bacterial Infections/ or exp Staphylococcal Infections/) and exp Blood/ (16424)
101. ((bacter* or S* aureus or staph*) and blood*).tw,kf. (92067)
102. bacter?emi*.tw,kf. (40738)
103. sepsis.tw,kf. (132294)
104. septic*.tw,kf. (93492)
105. (infect* adj3 (blood or bloodstream)).tw,kf. (37831)
106. blood poison*.tw,kf. (60)
107. (bacteri* adj3 (blood or bloodstream)).tw,kf. (5657)
108. (S* aureus adj3 (blood or bloodstream)).tw,kf. (1386)
109. ("S.aureus" adj3 (blood or bloodstream)).tw,kf. (5)
110. (Staph* adj3 (blood or bloodstream)).tw,kf. (1397)
111. septic?emi*.tw,kf. (24190)
112. py?emi*.tw,kf. (265)
113. pyoh?emi*.tw,kf. (16)
114. exp Abscess/ (60811)
115. abscess*.tw,kf. (93416)
116. Purpura Fulminans/ (363)
117. (purpura adj1 fulmina*).tw,kf. (1163)
118. h?emorrhagic vasculitis.tw,kf. (201)
119. henoch purpura*.tw,kf. (382)
120. henoch schoenlein purpura*.tw,kf. (181)
121. nonthrombocytopenic purpura*.tw,kf. (37)
122. non-thrombocytopenic purpura*.tw,kf. (37)
123. nonthrombopenic purpura*.tw,kf. (5)
124. non-thrombopenic purpura*.tw,kf. (4)
125. purpura h?emorrhagica.tw,kf. (264)
126. rheumatoid purpura*.tw,kf. (158)
127. or/23-126 (3249890)
128. 12 and 127 (3280)
129. 12 and 22 (237)
130. 128 or 129 (3423)

Embase (1974 to 25 November 2024)

1. leukocidin/ (1013)
2. Panton Valentine leukocidin/ (2761)

3. leukocidin*.tw,kf. (2749)
4. leucocidin*.tw,kf. (649)
5. leukotoxi*.tw,kf. (1184)
6. leucotoxi*.tw,kf. (82)
7. Panton Valentine.tw,kf. (2906)
8. PVL.tw,kf. (7859)
9. LukS.tw,kf. (489)
10. LukF.tw,kf. (414)
11. Luk pv.tw,kf. (56)
12. bacterial toxin/ and (exp Staphylococcus aureus/ or exp Staphylococcus infection/) (1543)
13. or/1-12 (12387)
14. exp thromboembolism/ (676295)
15. thrombo*.tw,kf. (685621)
16. Emboli*.tw,kf. (243545)
17. thromboembol*.tw,kf. (131989)
18. thrombus.tw,kf. (79961)
19. atherothrombo*.tw,kf. (9853)
20. blood clot*.tw,kf. (16481)
21. embolus.tw,kf. (10068)
22. (clot* adj3 (vein* or venous* or arter* or vascular* or cerebrovascular* or cardiovascular* or heart or brain or cardiac or cardio)).tw,kf. (2623)
23. or/14-22 (1118882)
24. exp staphylococcal pneumonia/ (1207)
25. soft tissue infection/ (16487)
26. ((deep or invasiv*) adj3 infect*).tw,kf. (40044)
27. ((deep or invasiv*) adj3 staph*).tw,kf. (614)
28. ((deep or invasiv*) adj3 s aureus).tw,kf. (350)
29. ((deep or invasiv*) adj3 "s.aureus").tw,kf. (3)
30. ((deep or invasiv*) adj3 bacter*).tw,kf. (4658)
31. (deep tissue* adj3 infect*).tw,kf. (386)
32. (deep tissue* adj3 invasive*).tw,kf. (84)
33. (deep tissue* adj3 staph*).tw,kf. (8)
34. (deep tissue* adj3 s aureus).tw,kf. (6)
35. (deep tissue* adj3 "s.aureus").tw,kf. (0)
36. (deep tissue* adj3 bacter*).tw,kf. (77)
37. exp osteomyelitis/ (49808)
38. osteomyelitis.tw,kf. (33282)
39. (bone* adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (14365)
40. (bone* adj3 S aureus).tw,kf. (170)
41. (bone* adj3 "S.aureus").tw,kf. (0)
42. necrotizing fasciitis/ (8235)
43. necroti#ing fasciitis.tw,kf. (7046)
44. flesh eating bacter*.tw,kf. (60)

45. necroti#ing bacter*.tw,kf. (59)
46. (fascia adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (156)
47. (fascia adj3 S aureus).tw,kf. (0)
48. (fascia adj3 "S.aureus").tw,kf. (0)
49. pyomyositis/ (1737)
50. (intramusc* adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (630)
51. (intramusc* adj3 S aureus).tw,kf. (13)
52. (intramusc* adj3 "S.aureus").tw,kf. (0)
53. ((muscle* or muscular) adj3 (invasive* or infect* or staph* or bacter*)).tw,kf. (22199)
54. ((muscle* or muscular) adj3 S aureus).tw,kf. (12)
55. ((muscle* or muscular) adj3 "S.aureus").tw,kf. (0)
56. pyomyositis.tw,kf. (1525)
57. exp myositis/ (56435)
58. myositis.tw,kf. (20603)
59. bacterial arthritis/ (12341)
60. (bacter* adj3 arthriti*).tw,kf. (1114)
61. (septic* adj3 arthriti*).tw,kf. (9930)
62. (suppurat* adj3 arthriti*).tw,kf. (285)
63. (infect* adj3 arthriti*).tw,kf. (4069)
64. (staph* adj3 arthriti*).tw,kf. (359)
65. (S aureus adj3 arthriti*).tw,kf. (155)
66. ("S.aureus" adj3 arthriti*).tw,kf. (7)
67. (deep adj2 tissue* adj2 infect*).tw,kf. (509)
68. exp *tissues/ (1106989)
69. necrotizing pneumonia/ (1281)
70. pneumoni*.tw,kf. (353624)
71. ((lung or lungs or pulmonary) adj2 infection*).tw,kf. (38558)
72. ((lung or lungs or pulmonary) adj2 inflam*).tw,kf. (35276)
73. ((lung or lungs or pulmonary) adj2 (invasiv* or bacter* or staph*)).tw,kf. (10987)
74. ((lung or lungs or pulmonary) adj2 S aureus).tw,kf. (118)
75. ((lung or lungs or pulmonary) adj2 "S.aureus").tw,kf. (8)
76. exp *lung/ and necrosis/ (488)
77. ((pulmonary or lung*) adj3 necro*).tw,kf. (3476)
78. ((Alveolar* or airway* or respiratory* or lung* or bronch*) adj3 h?emorrhag*).tw,kf. (10714)
79. ((Alveolar* or airway* or respiratory* or lung* or bronch*) adj3 bleed*).tw,kf. (3107)
80. ((Alveolar* or airway* or respiratory* or lung* or bronch*) adj3 blood).tw,kf. (30436)
81. (multi lobar infiltrat* or multilobar infiltrat*).tw,kf. (135)
82. exp *respiratory distress syndrome/ (45819)
83. exp *respiratory failure/ (28821)
84. (respiratory adj (collapse* or distress or insufficiency or failure)).tw,kf. (167381)
85. (lung* adj (collapse* or distress or insufficiency or failure)).tw,kf. (2788)
86. (pulmonary adj (collapse* or distress or insufficiency or failure)).tw,kf. (3784)
87. exp *influenza/ (59803)

88. influenza*.tw,kf. (164045)
89. exp hemoptysis/ (35042)
90. h?emoptysis.tw,kf. (23589)
91. leukopenia/ or neutropenia/ (180592)
92. leukopeni*.tw,kf. (23350)
93. neutropeni*.tw,kf. (95108)
94. oxygen saturation/ (94000)
95. oxygen/ and exp blood/ (26083)
96. oxygen saturation.tw,kf. (54999)
97. (blood adj (oxygen or o2)).tw,kf. (13105)
98. SPo2.tw,kf. (19029)
99. exp sepsis/ (366317)
100. exp bacteremia/ (66771)
101. (bacterium/ or exp Staphylococcus aureus/ or exp Staphylococcus infection/ or exp *bacterial infection/) and exp *blood/ (17934)
102. ((bacter* or S* aureus or staph*) and blood*).tw,kf. (133416)
103. bacter?emi*.tw,kf. (56726)
104. sepsis.tw,kf. (209535)
105. septic*.tw,kf. (131216)
106. (infect* adj3 (blood or bloodstream)).tw,kf. (52894)
107. blood poison*.tw,kf. (56)
108. (bacteri* adj3 (blood or bloodstream)).tw,kf. (7594)
109. (S* aureus adj3 (blood or bloodstream)).tw,kf. (2032)
110. ("S.aureus" adj3 (blood or bloodstream)).tw,kf. (20)
111. (Staph* adj3 (blood or bloodstream)).tw,kf. (2022)
112. septic?emi*.tw,kf. (27605)
113. py?emi*.tw,kf. (146)
114. pyoh?emi*.tw,kf. (2)
115. exp abscess/ (132372)
116. abscess*.tw,kf. (119464)
117. fulminating purpura/ (1619)
118. (purpura adj1 fulmina*).tw,kf. (1502)
119. h?emorrhagic vasculitis.tw,kf. (160)
120. henoch purpura*.tw,kf. (466)
121. henoch schoenlein purpura*.tw,kf. (301)
122. nonthrombocytopenic purpura*.tw,kf. (41)
123. non-thrombocytopenic purpura*.tw,kf. (41)
124. nonthrombopenic purpura*.tw,kf. (1)
125. non-thrombopenic purpura*.tw,kf. (2)
126. purpura h?emorrhagica.tw,kf. (32)
127. rheumatoid purpura*.tw,kf. (106)
128. or/24-127 (2957426)
129. 13 and 128 (3836)
130. 13 and 23 (507)

131. 129 or 130 (4142)
132. limit 131 to (conference abstract or conference paper or editorial or letter) (986)
133. 131 not 132 (3156)

CENTRAL

Date of search: 26 November 2024

ID	Search	Hits
#1	MeSH descriptor: [Leukocidins] explode all trees	9
#2	leukocidin*	21
#3	leucocidin*	5
#4	leukotoxi*	6
#5	leucotoxi*	0
#6	"Panton Valentine"	21
#7	PVL	480
#8	LukS	43
#9	LukF	0
#10	"Luk pv"	0
#11	MeSH descriptor: [Bacterial Toxins] explode all trees	4,264
#12	MeSH descriptor: [Staphylococcal Infections] explode all trees	1,562
#13	MeSH descriptor: [Staphylococcus aureus] explode all trees	1,191
#14	#12 OR #13	2,048
#15	#11 AND #14	22
#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #15	554
#17	MeSH descriptor: [Embolism and Thrombosis] explode all trees	10,978
#18	thrombo*	68,132
#19	Emboli*	14,617
#20	thromboembol*	13,426
#21	thrombus	3,403
#22	atherothrombo*	892
#23	blood NEXT clot*	7,193
#24	embolus	414
#25	(clot* NEAR/3 (vein* or venous* or arter* or vascular* or cerebrovascular* or cardiovascular* or heart or brain or cardiac or cardio))	1,812
#26	MeSH descriptor: [Pneumonia, Staphylococcal] explode all trees	45

ID	Search	Hits
#27	MeSH descriptor: [Soft Tissue Infections] explode all trees	189
#28	((deep or invasiv*) NEAR/3 infect*)	2,284
#29	((deep or invasiv*) NEAR/3 staph*)	14
#30	((deep or invasiv*) NEAR/3 s aureus)	15
#31	((deep or invasiv*) NEAR/3 s.aureus).	0
#32	((deep or invasiv*) NEAR/3 bacter*)	198
#33	(deep tissue* NEAR/3 infect*)	179
#34	(deep tissue* NEAR/3 invasive*)	13
#35	(deep tissue* NEAR/3 staph*)	1
#36	(deep tissue* NEAR/3 s aureus)	1
#37	(deep tissue* NEAR/3 "s.aureus")	1
#38	deep tissue* NEAR/3 bacter*	39
#39	MeSH descriptor: [Osteomyelitis] explode all trees	210
#40	osteomyelitis	849
#41	(bone* NEAR/3 (invasive* or infect* or staph* or bacter*))	1,056
#42	(bone* NEAR/3 S aureus)	3
#43	(bone* NEAR/3 "S.aureus")	1
#44	MeSH descriptor: [Fasciitis, Necrotizing] explode all trees	21
#45	necrotizing fasciitis	116
#46	flesh eating bacter*	4
#47	necrotizing bacter*	574
#48	(fascia NEAR/3 (invasive* or infect* or staph* or bacter*))	22
#49	(fascia NEAR/3 S aureus)	0
#50	(fascia NEAR/3 "S.aureus")	0
#51	MeSH descriptor: [Pyomyositis] explode all trees	1
#52	(intramusc* NEAR/3 (invasive* or infect* or staph* or bacter*))	192
#53	intramusc* NEAR/3 S aureus	1
#54	(intramusc* NEAR/3 "S.aureus")	1
#55	((muscle* or muscular) NEAR/3 (invasive* or infect* or staph* or bacter*))	2,140
#56	((muscle* or muscular) NEAR/3 S aureus)	0
#57	((muscle* or muscular) NEAR/3 "S.aureus")	0
#58	pyomyositis	18

ID	Search	Hits
#59	MeSH descriptor: [Myositis] explode all trees	314
#60	myositis	788
#61	MeSH descriptor: [Arthritis, Infectious] explode all trees	159
#62	(bacter* NEAR/3 arthriti*)	220
#63	(septic* NEAR/3 arthriti*)	182
#64	(suppurat* NEAR/3 arthriti*)	9
#65	(infect* NEAR/3 arthriti*)	380
#66	(staph* NEAR/3 arthriti*)	8
#67	(S aureus NEAR/3 arthriti*)	2
#68	("S.aureus" NEAR/3 arthriti*)	2
#69	(deep NEAR/2 tissue* NEAR/2 infect*)	36
#70	MeSH descriptor: [Tissues] explode all trees	44,748
#71	MeSH descriptor: [Pneumonia, Necrotizing] explode all trees	1
#72	pneumoni*	26,622
#73	((lung or lungs or pulmonary) NEAR/2 infection*)	3,134
#74	((lung or lungs or pulmonary) NEAR/2 inflam*)	1,868
#75	((lung or lungs or pulmonary) NEAR/2 (invasiv* or bacter* or staph*))	459
#76	((lung or lungs or pulmonary) NEAR/2 S aureus)	2
#77	((lung or lungs or pulmonary) NEAR/2 "S.aureus")	1
#78	MeSH descriptor: [Lung] explode all trees	6,524
#79	MeSH descriptor: [Necrosis] explode all trees	19,063
#80	#78 AND #79	20
#81	((pulmonary or lung*) Near/3 necro*)	197
#82	((Alveolar* or airway* or respiratory* or lung* or bronch*) NEAR/3 hemorrhage)	864
#83	((Alveolar* or airway* or respiratory* or lung* or bronch*) NEAR/3 bleed*)	485
#84	((Alveolar* or airway* or respiratory* or lung* or bronch*) NEAR/3 blood)	6,525
#85	(multi lobar infiltrat* or multilobar infiltrat*)	28
#86	MeSH descriptor: [Respiratory Distress Syndrome] explode all trees	3,658
#87	MeSH descriptor: [Respiratory Insufficiency] explode all trees	4,026
#88	(respiratory NEAR/1 (collapse* or distress or insufficiency or failure))	16,995
#89	(lung* NEAR/1 (collapse* or distress or insufficiency or failure))	807

ID	Search	Hits
#90	(pulmonary NEAR/1 (collapse* or distress or insufficiency or failure))	403
#91	MeSH descriptor: [Influenza, Human] explode all trees	3,658
#92	influenza*	11,747
#93	MeSH descriptor: [Hemoptysis] explode all trees	47
#94	hemoptysis	957
#95	MeSH descriptor: [Leukopenia] explode all trees	3,209
#96	MeSH descriptor: [Neutropenia] explode all trees	2,295
#97	leukopeni*	6,167
#98	neutropeni*	16,790
#99	MeSH descriptor: [Oxygen Saturation] explode all trees	148
#100	MeSH descriptor: [Oxygen] explode all trees	7,681
#101	MeSH descriptor: [Blood] explode all trees	21,418
#102	#100 AND #101	241
#103	oxygen saturation	19,999
#104	(blood NEAR/1 (oxygen or o2))	3,006
#105	SPo2	7,856
#106	MeSH descriptor: [Sepsis] explode all trees	6,615
#107	MeSH descriptor: [Bacteremia] explode all trees	1,322
#108	MeSH descriptor: [Bacteria] this term only	2,341
#109	MeSH descriptor: [Staphylococcus aureus] explode all trees	1,191
#110	MeSH descriptor: [Bacterial Infections] explode all trees	23,374
#111	MeSH descriptor: [Staphylococcal Infections] explode all trees	1,562
#112	#108 OR #109 OR #110 OR #111	25,559
#113	MeSH descriptor: [Blood] explode all trees	21,418
#114	#112 AND #113	588
#115	((bacter* or S* aureus or staph*) and blood*)	14,851
#116	bacteremi*	2,892
#117	bacteraemi*	790
#118	sepsis OR septic*	19,668
#119	(infect* NEAR/3 (blood or bloodstream))	4,092
#120	blood poison*	1,192
#121	(bacteri* NEAR/3 (blood or bloodstream))	1,520
#122	(S* aureus NEAR/3 (blood or bloodstream))	89

ID	Search	Hits
#123	("S.aureus" NEAR/3 (blood or bloodstream))	34
#124	(Staph* NEAR/3 (blood or bloodstream))	96
#125	septicemi* OR septicaemi*	1,319
#126	pyemi* OR pyaemi*	16
#127	pyohemi* OR pyohaemi*	6
#128	MeSH descriptor: [Abscess] explode all trees	842
#129	abscess*	5,227
#130	MeSH descriptor: [Purpura Fulminans] explode all trees	0
#131	(purpura NEAR/1 fulmina*)	20
#132	h*emorrhagic vasculitis	42
#133	henoch purpura*	144
#134	henoch schoenlein purpura*	10
#135	nonthrombocytopenic purpura*	7
#136	non-thrombocytopenic purpura*	5
#137	nonthrombopenic purpura*	0
#138	non-thrombopenic purpura*	0
#139	purpura h*emorrhagica	0
#140	rheumatoid purpura*	71
#141	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140	239,262
#142	#16 AND #141	290

Filtered to results from CENTRAL only (trials): 180

CINAHL

Date of search: 26 November 2024

ID	Search	Hits
S1	leukocidin*	291
S2	leucocidin*	80
S3	leukotoxi*	48
S4	leucotoxi*	5
S5	"Panton Valentine"	349
S6	PVL	759
S7	LukS	65
S8	LukF	11
S9	"Luk pv"	3
S10	(MH "Bacterial Toxins+")	13,004
S11	(MH "Staphylococcal Infections+")	12,018
S12	(MH "Staphylococcus Aureus+")	12,654
S13	S11 OR S12	18,599
S14	S10 AND S13	336
S15	(MH "Embolism and Thrombosis+")	53,777
S16	thrombo*	97,572
S17	Emboli*	44,375
S18	thromboembol*	23,743
S19	thrombus	14,090
S20	atherothrombo*	1,209
S21	"blood clot*"	8,866
S22	embolus	2,908
S23	(clot* N3 (vein* or venous* or arter* or vascular* or cerebrovascular* or cardiovascular* or heart or brain or cardiac or cardio))	464
S24	(MH "Pneumonia, Bacterial+")	5,397
S25	(MH "Soft Tissue Infections")	1,793
S26	((deep or invasiv*) N3 infect*)	6,645
S27	((deep or invasiv*) N3 staph*)	121
S28	((deep or invasiv*) N3 "s aureus")	42
S29	((deep or invasiv*) N3 "s.aureus")	0
S30	((deep or invasiv*) N3 bacter*)	555
S31	(deep tissue* N3 infect*)	52

ID	Search	Hits
S32	(deep tissue* N3 invasive*)	2
S33	deep tissue* N3 staph*	0
S34	deep tissue* N3 s aureus	0
S35	deep tissue* N3 "s.aureus"	0
S36	deep tissue* N3 bacter*	18
S37	(MH "Osteomyelitis")	4,496
S38	osteomyelitis	6,579
S39	(bone* N3 (invasive* or infect* or staph* or bacter*))	2,445
S40	(bone* N3 "S aureus")	21
S41	(bone* N3 "S.aureus")	0
S42	(MH "Fasciitis, Necrotizing")	1,460
S43	"necroti?ing fasciitis"	1,401
S44	"flesh eating bacter*"	17
S45	"necroti?ing bacter*"	5
S46	(fascia N3 (invasive* or infect* or staph* or bacter*))	56
S47	fascia N3 "S aureus"	0
S48	fascia N3 "S.aureus"	0
S49	(intramusc* N3 (invasive* or infect* or staph* or bacter*))	49
S50	(intramusc* N3 S aureus)	1
S51	(intramusc* N3 "S.aureus")	0
S52	((muscle* or muscular) N3 (invasive* or infect* or staph* or bacter*))	2,836
S53	((muscle* or muscular) N3 S aureus)	3
S54	((muscle* or muscular) N3 "S.aureus")	0
S55	pyomyositis	240
S56	(MH "Myositis+")	4,578
S57	myositis	3,896
S58	(MH "Arthritis, Infectious")	2,321
S59	(bacter* N3 arthriti*)	162
S60	septic* N3 arthriti*	1,666
S61	suppurat* N3 arthriti*	27
S62	infect* N3 arthriti*	2,835
S63	staph* N3 arthriti*	51
S64	"S aureus" adj3 arthriti*	0

ID	Search	Hits
S65	("S.aureus" N3 arthriti*)	1
S66	(deep N2 tissue* N2 infect*)	90
S67	(MH "Pneumonia, Necrotizing")	21
S68	pneumoni*	61,567
S69	((lung or lungs or pulmonary) N2 infection*)	4,034
S70	((lung or lungs or pulmonary) N2 inflam*)	3,593
S71	((lung or lungs or pulmonary) N2 (invasiv* or bacter* or staph*))	1,790
S72	((lung or lungs or pulmonary) N2 S aureus)	10
S73	((lung or lungs or pulmonary) N2 "S.aureus")	0
S74	(MH "Lung+")	27,602
S75	(MH "Necrosis+")	68,722
S76	S74 AND S75	220
S77	((pulmonary or lung*) N3 necro*)	377
S78	((Alveolar* or airway* or respiratory* or lung* or bronch*) N3 h#emorrhag*)	1,539
S79	((Alveolar* or airway* or respiratory* or lung* or bronch*) N3 bleed*)	407
S80	((Alveolar* or airway* or respiratory* or lung* or bronch*) N3 blood)	7,781
S81	("multi lobar infiltrat*" or "multilobar infiltrat*")	9
S82	(MH "Respiratory Distress Syndrome, Acute")	8,877
S83	(MH "Respiratory Failure+")	17,619
S84	(respiratory N1 (collapse* or distress or insufficiency or failure))	35,205
S85	(lung* N1 (collapse* or distress or insufficiency or failure))	726
S86	(pulmonary N1 (collapse* or distress or insufficiency or failure))	981
S87	(MH "Influenza, Human+")	9,976
S88	influenza*	35,766
S89	(MH "Hemoptysis")	1,568
S90	hemoptysis	2,845
S91	(MH "Leukopenia")	888
S92	(MH "Neutropenia+")	5,229
S93	leukopeni* OR neutropeni*	13,172
S94	(MH "Oxygen Saturation")	5,986
S95	(MH "Oxygen")	12,887
S96	(MH "Blood+")	82,064

ID	Search	Hits
S97	S95 AND S96	381
S98	"oxygen saturation"	12,471
S99	(blood N1 (oxygen or o2))	7,202
S100	SPo2	2,280
S101	(MH "Sepsis+")	33,150
S102	(MH "Bacteremia")	6,642
S103	(MH "Bacteria+")	84,267
S104	(MH "Staphylococcus Aureus+")	12,654
S105	(MH "Staphylococcal Infections+")	12,018
S106	(MH "Bacterial Infections+")	136,947
S107	(MH "Blood+")	82,064
S108	S103 OR S104 OR S105 OR S106	174,911
S109	S107 AND S108	4,562
S110	((bacter* or "S* aureus" or staph*) and blood*)	19,990
S111	bacter#emi*	10,274
S112	sepsis	37,481
S113	septic*	18,696
S114	(infect* N3 (blood or bloodstream))	13,212
S115	"blood poison*"	10
S116	(bacteri* N3 (blood or bloodstream))	2,843
S117	("S* aureus" N3 (blood or bloodstream))	334
S118	(Staph* N3 (blood or bloodstream))	410
S119	septic#emi*	2,043
S120	py#emi*	9
S121	pyoh#emi*	0
S122	(MH "Abscess+")	8,415
S123	abscess*	15,420
S124	(MH "Purpura, Schoenlein-Henoch")	1,015
S125	(purpura N1 fulmina*)	243
S126	"h#emorrhagic vasculitis"	1
S127	"henoch purpura*"	873
S128	"henoch schoenlein purpura*"	875
S129	"nonthrombocytopenic purpura*"	868

ID	Search	Hits
S130	"non-thrombocytopenic purpura*"	5
S131	"nonthrombopenic purpura*"	0
S132	"non-thrombopenic purpura*"	0
S133	"purpura h#emorrhagica"	2
S134	"rheumatoid purpura*"	868
S135	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S14	1,192
S136	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134	400,702
S137	S135 AND S136	396

Scopus

Date of search: 25 November 2024

TITLE-ABS-KEY(thrombo*) OR TITLE-ABS-KEY(Emboli*) OR TITLE-ABS-KEY(thromboembol*) OR TITLE-ABS-KEY(thrombus) OR TITLE-ABS-KEY(atherothrombo*) OR TITLE-ABS-KEY("blood clot*") OR TITLE-ABS-KEY(embolus) OR TITLE-ABS-KEY((clot* W/2 (vein* or venous* or arter* or vascular* or cerebrovascular* or cardiovascular* or heart or brain or cardiac or cardio)))

Or:

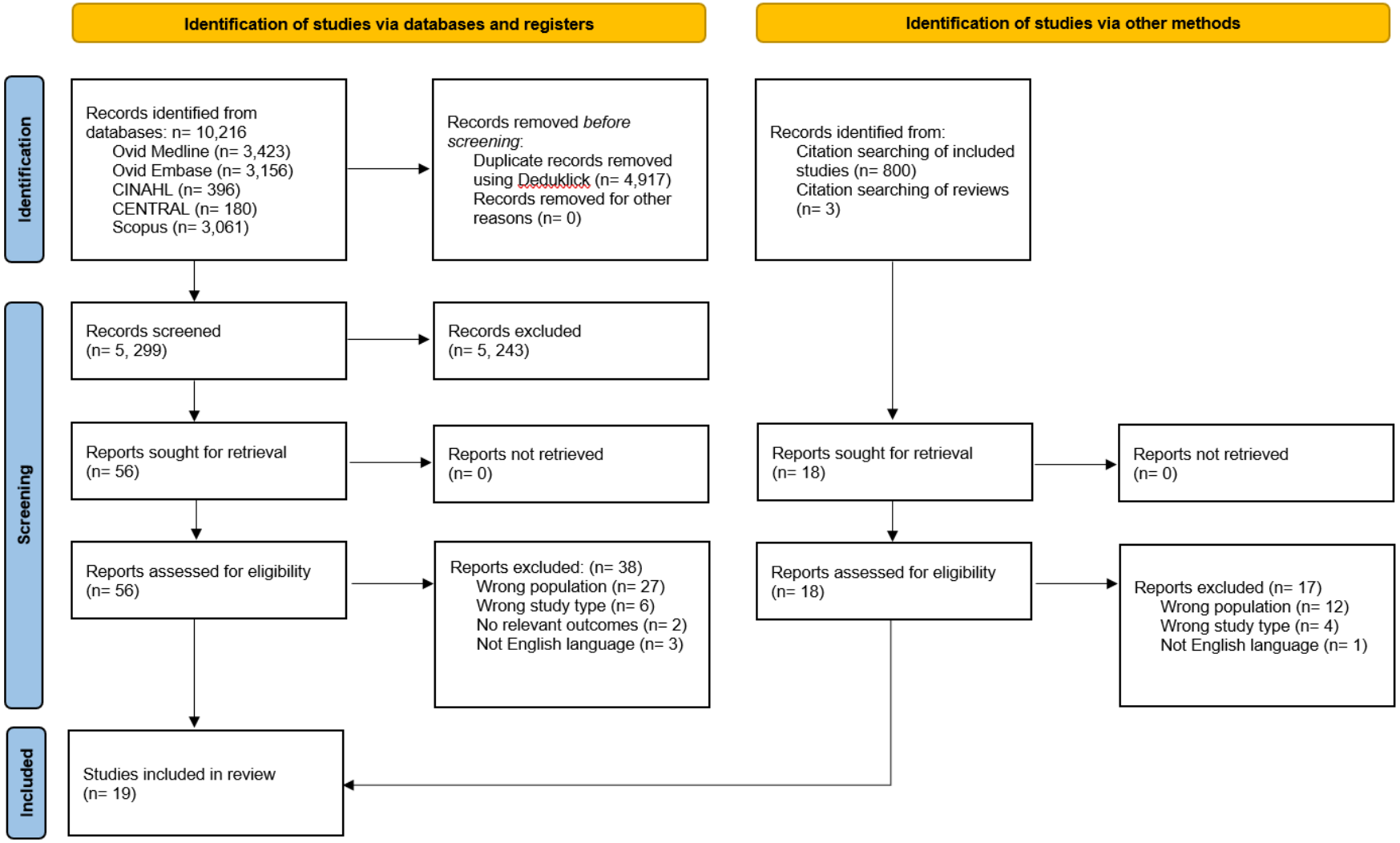
TITLE-ABS-KEY(((deep or invasiv*) W/2 infect*)) OR TITLE-ABS-KEY(((deep or invasiv*) W/2 staph*)) OR TITLE-ABS-KEY(((deep or invasiv*) W/2 "s aureus")) OR TITLE-ABS-KEY(((deep or invasiv*) W/2 "s.aureus")) OR TITLE-ABS-KEY(((deep or invasiv*) W/2 bacter*)) OR TITLE-ABS-KEY(("deep tissue*" W/2 infect*)) OR TITLE-ABS-KEY(("deep tissue*" W/2 invasive*)) OR TITLE-ABS-KEY(("deep tissue*" W/2 staph*)) OR TITLE-ABS-KEY(("deep tissue*" W/2 "s aureus")) OR TITLE-ABS-KEY(("deep tissue*" W/2 "s.aureus")) OR TITLE-ABS-KEY(("deep

tissue*" W/2 bacter*)) OR TITLE-ABS-KEY(osteomyelitis) OR TITLE-ABS-KEY((bone* W/2 (invasive* or infect* or staph* or bacter*))) OR TITLE-ABS-KEY((bone* W/2 "S aureus")) OR TITLE-ABS-KEY((bone* W/2 "S.aureus")) OR TITLE-ABS-KEY("necroti?ing fasciitis") OR TITLE-ABS-KEY("flesh eating bacter*") OR TITLE-ABS-KEY("necroti?ing bacter*") OR TITLE-ABS-KEY((fascia W/2 (invasive* or infect* or staph* or bacter*))) OR TITLE-ABS-KEY((fascia W/2 "S aureus")) OR TITLE-ABS-KEY((fascia W/2 "S.aureus")) OR TITLE-ABS-KEY(intramusc* W/2 (invasive* or infect* or staph* or bacter*)) OR TITLE-ABS-KEY((intramusc* W/2 "S aureus")) OR TITLE-ABS-KEY(intramusc* W/2 "S.aureus") OR TITLE-ABS-KEY(((muscle* or muscular) W/2 (invasive* or infect* or staph* or bacter*))) OR TITLE-ABS-KEY(((muscle* or muscular) W/2 "S aureus")) OR TITLE-ABS-KEY(((muscle* or muscular) W/2 "S.aureus")) OR TITLE-ABS-KEY(pyomyositis) OR TITLE-ABS-KEY(myositis) OR TITLE-ABS-KEY((bacter* W/2 arthriti*)) OR TITLE-ABS-KEY((septic* W/2 arthriti*)) OR TITLE-ABS-KEY((suppurat* W/2 arthriti*)) OR TITLE-ABS-KEY((infect* W/2 arthriti*)) OR TITLE-ABS-KEY((staph* W/2 arthriti*)) OR TITLE-ABS-KEY(("S aureus" W/2 arthriti*)) OR TITLE-ABS-KEY(("S.aureus" W/2 arthriti*)) OR TITLE-ABS-KEY((deep W/1 tissue* W/1 infect*)) OR TITLE-ABS-KEY(pneumoni*) OR TITLE-ABS-KEY(((lung or lungs or pulmonary) W/1 infection*)) OR TITLE-ABS-KEY(((lung or lungs or pulmonary) W/1 inflam*)) OR TITLE-ABS-KEY(((lung or lungs or pulmonary) W/1 (invasiv* or bacter* or staph*))) OR TITLE-ABS-KEY(((lung or lungs or pulmonary) W/1 "S aureus")) OR TITLE-ABS-KEY(((lung or lungs or pulmonary) W/1 "S.aureus")) OR TITLE-ABS-KEY(((pulmonary or lung*) W/2 necro*)) OR TITLE-ABS-KEY(((Alveolar* or airway* or respiratory* or lung* or bronch*) W/2 h*emorrhag*)) OR TITLE-ABS-KEY(((Alveolar* or airway* or respiratory* or lung* or bronch*) W/2 bleed*)) OR TITLE-ABS-KEY(((Alveolar* or airway* or respiratory* or lung* or bronch*) W/2 blood)) OR TITLE-ABS-KEY(("multi lobar infiltrat*" or "multilobar infiltrat*")) OR TITLE-ABS-KEY((respiratory W/0 (collapse* or distress or insufficiency or failure))) OR TITLE-ABS-KEY((lung* W/0 (collapse* or distress or insufficiency or failure))) OR TITLE-ABS-KEY((pulmonary W/0 (collapse* or distress or insufficiency or failure))) OR TITLE-ABS-KEY(influenza*) OR TITLE-ABS-KEY(h*emoptysis) OR TITLE-ABS-KEY(leukopeni*) OR TITLE-ABS-KEY(neutropeni*) OR TITLE-ABS-KEY("oxygen saturation") OR TITLE-ABS-KEY((blood W/0 (oxygen or o2))) OR TITLE-ABS-KEY(SPo2) OR TITLE-ABS-KEY(((bacter* or "S* aureus" or staph*) and blood*)) OR TITLE-ABS-KEY(bacter*emi*) OR TITLE-ABS-KEY(sepsis) OR TITLE-ABS-KEY(septic*) OR TITLE-ABS-KEY((infect* W/2 (blood or bloodstream))) OR TITLE-ABS-KEY("blood poison*") OR TITLE-ABS-KEY((bacteri* W/2 (blood or bloodstream))) OR TITLE-ABS-KEY(("S* aureus" W/2 (blood or bloodstream))) OR TITLE-ABS-KEY("S.aureus" W/3 (blood or bloodstream)) OR TITLE-ABS-KEY((Staph* W/2 (blood or bloodstream))) OR TITLE-ABS-KEY(septic*emi*) OR TITLE-ABS-KEY(py*emi*) OR TITLE-ABS-KEY(pyoh*emi*) OR TITLE-ABS-KEY(abscess*) OR TITLE-ABS-KEY((purpura W/0 fulmina*)) OR TITLE-ABS-KEY("h*emorrhagic vasculitis") OR TITLE-ABS-KEY("henoch purpura*") OR TITLE-ABS-KEY("henoch schoenlein purpura*") OR TITLE-ABS-KEY("nonthrombocytopenic purpura*") OR TITLE-ABS-KEY("non-thrombocytopenic purpura*") OR TITLE-ABS-KEY("nonthrombopenic purpura*") OR TITLE-ABS-KEY("non-thrombopenic purpura*") OR TITLE-ABS-KEY("purpura h*emorrhagica") OR TITLE-ABS-KEY("rheumatoid purpura*")

Results: 3,061

Annexe B. Study selection flowchart

Figure B.1. PRISMA diagram



Text version of Figure B.1. PRISMA diagram

A PRISMA diagram showing the flow of studies through this review, ultimately including 19 studies.

From identification of studies via databases and registers, n=10,216 records identified from databases:

- Ovid Medline (n=3,423)
- Ovid Embase (n=3,156)
- CINAHL (n=396)
- CENTRAL (n=180)
- SCOPUS (n=3,061)

From these, records removed before screening:

- duplicate records removed using deduklick (n=4,917)
- records removed for other reasons (n=0)

n=5,299 records screened, of which n=5,243 were excluded, leaving n=56 papers sought for retrieval, of which n=0 were not retrieved.

n=18 studies were identified from citation searching of included studies and reviews, of which n=0 were not retrieved

Of the n=74 papers assessed for eligibility, n=55 reports were excluded:

- wrong population (n=39)
- not English language (n=4)
- wrong study type (n=10)
- no relevant outcomes (n=2)

n=19 papers included in the review.

Annexe C. Excluded full texts

Wrong population (39 studies)

Backes J and others. 'Septic knee-induced deep venous thrombosis in a young adult' Orthopedics 2010: volume 33, issue 10, pages 770 to 770

Bouchoucha S and others. 'Deep venous thrombosis associated with acute hematogenous osteomyelitis in children' Orthopaedics & Traumatology: Surgery & Research: OTSR 2010: volume 96, issue 8, pages 890 to 893

Bukhari EE and others. 'Severe community-acquired infection caused by methicillin-resistant Staphylococcus aureus in Saudi Arabian children' Saudi Medical Journal 2009: volume 30, issue 12, pages 1,595 to 1,600

Camargo JF and others. 'Septic pulmonary embolism of unknown origin in patients with Staphylococcus aureus bacteremia; A case report and review of 18 cases' Infectious Diseases in Clinical Practice 2013: volume 21, pages 217 to 221

Cherian MP. 'Invasive community-acquired methicillin-resistant Staphylococcus aureus infection causing bacteremia and osteomyelitis simultaneously in two Saudi siblings' Journal of Pediatric Infectious Diseases 2015: volume 3, issue 2, pages 131 to 135

Crary SE and others. 'Venous thrombosis and thromboembolism in children with osteomyelitis' The Journal of Pediatrics 2006: volume 149, issue 4, pages 537 to 541

Gencpinar P and others. 'Nonketotic hyperglycinemia: novel mutation in the aminomethyl transferase gene. Case report' Archivos Argentinos de Pediatria 2016: volume 114, issue 3, pages e142 to 146

Green K and others. 'Panton-Valentine Leukocidin Producing Staphylococcus Aureus Facial Pyomyositis Causing Partial Cavernous Sinus Thrombosis' Pediatric Infectious Disease Journal 2017: volume 36, issue 11, pages 1,102 to 1,104

Hoehn SK and others. 'Lemierre-like syndrome caused by community-associated methicillin-resistant Staphylococcus aureus complicated by hemorrhagic pericarditis' Pediatric Critical Care Medicine 2010: volume 11, issue 3, pages e32 to 35

Hollmig TS and others. 'Deep venous thrombosis associated with osteomyelitis in children' The Journal of Bone & Joint Surgery. American volume 2007: volume 89, issue 7, pages 1,517 to 1,523

Honarpisheh H and others. 'Staphylococcal Purpura Fulminans: Report of a Case' American Journal of Dermatopathology 2015: volume 37, issue 8, pages 643 to 646

Jain V and others. 'Acute osteomyelitis associated with Deep vein thrombosis in a patient of acute abdomen: A diagnostic dilemma' Journal of Clinical Orthopaedics and Trauma 2012: volume 3, issue 2, pages 112 to 114

Kramkimel N and others. 'Septic facial vein thrombosis due to Panton-Valentine leukocidin-positive Staphylococcus aureus' Archives of Dermatology 2009: volume 145, issue 12, pages 1,460 to 1,461

Kravitz GR and others. 'Purpura fulminans due to Staphylococcus aureus' Clinical Infectious Diseases 2005: volume 40, issue 7, pages 941 to 947

Kuhfahl K and others. 'Scapular abscess, septic emboli, and deep vein thrombosis in a healthy child due to community-acquired methicillin-resistant Staphylococcus aureus: case report' Pediatric Emergency Care 2009: volume 25, issue 10, pages 677 to 680

Lee C-Y and others. 'Musculoskeletal Sepsis Associated with Deep Vein Thrombosis in a Child' Pediatrics and Neonatology 2013: volume 57, issue 3, pages 244 to 247

Letts M and others. 'Atrial and venous thrombosis secondary to septic arthritis of the sacroiliac joint in a child with hereditary protein C deficiency' Journal of Pediatric Orthopedics 1999: volume 19, issue 2, pages 156 to 160

Ligon J and others. 'Differentiation of Deep Venous Thrombosis Among Children With or Without Osteomyelitis' Journal of Pediatric Orthopedics 2018: volume 38, issue 10, pages e597 to e603

Lu M and others. 'Septicaemia with deep venous thrombosis and necrotising pneumonia caused by acute community-acquired methicillin-resistant Staphylococcus aureus in an infant with a three-year follow-up: a case report' BMC Infectious Diseases 2022: volume 22, issue 1, pages 189 to 194

McDonald JE and others. 'Upper-extremity deep venous thrombosis associated with proximal humeral osteomyelitis in a child: A case report' The Journal of Bone & Joint Surgery. American volume 2010: volume 92, issue 11, pages 2,121 to 2,124

Menif K and others. 'Community-associated methicillin-resistant Staphylococcus aureus infections in a pediatric intensive care unit' Journal of Infection in Developing Countries 2011: volume 5, issue 8, pages 587 to 591

Mitchell PD and others. 'Panton-Valentine leukocidin-secreting Staphylococcus aureus causing severe musculoskeletal sepsis in children. A new threat' Journal of Bone & Joint Surgery - British Volume 2007: volume 89, issue 9, pages 1,239 to 1,242

Moriya M and others. 'A risk as an infection route: Nasal colonization of methicillin-resistant Staphylococcus aureus USA300 clone among contact sport athletes in Japan' Journal of Infection and Chemotherapy 2020: volume 26, issue 8, pages 862 to 864

Moue I and others. 'Community-Acquired Methicillin-Resistant Staphylococcus aureus Strain Positive for the Panton-Valentine Leucocidin Gene in a Middle-Aged Patient with Multiple Septic Pulmonary Emboli' Cureus 2024: volume 16, issue 3, e56243

Nourse C and others. 'Community-acquired methicillin-resistant Staphylococcus aureus causes severe disseminated infection and deep venous thrombosis in children: literature review and recommendations for management' Journal of Paediatrics and Child Health 2007: volume 43, issue 10, pages 656 to 661

Oberdorfer P and others. 'Deep vein thrombosis associated with Staphylococcus aureus septicemia' Chiang Mai Medical Journal 2012: volume 51, issue 3, pages 87 to 91

Ogata H and others. 'Psoitis and multiple venous thromboses caused by Panton Valentine Leukocidin-positive methicillin-sensitive Staphylococcus aureus in a 12-year-old girl: A case report' Journal of Infection and Chemotherapy: volume:25, issue 8, pages 630 to 634

Oymak FS and others. 'The prevalence of upper extremity deep venous thrombosis' Turkish Journal of Thoracic and Cardiovascular Surgery 2012: volume 20, issue 2, pages 312 to 322

Poddar B and others. 'Deep-vein thrombosis and septic pulmonary emboli in methicillin-sensitive Staphylococcus aureus infection' Paediatrics and International Child Health 2013: volume 33, issue 1, pages 49 to 52

Raval H and others. 'CASE REPORT: A RARE PRESENTATION OF DEEP VEIN THROMBOSIS WITH ACUTE HEMATOGENOUS OSTEOMYELITIS IN ADULT' Journal of Evolution of Medical and Dental Sciences 2015: volume 4, issue 65, pages 11,423 to 11,427

Riascos-Pinchao GA and others. 'Rare complications of Staphylococcus aureus infection in children: Case reports' Revista de la Facultad de Medicina 2019: volume 67, issue 4, pages 527 to 530

Rutar T and others. 'Ophthalmic manifestations of infections caused by the USA300 clone of community-associated methicillin-resistant Staphylococcus aureus' Ophthalmology 2006: volume 113, issue 8, pages 1,455 to 1,462

Schaub RL and others. 'Deep vein thrombosis and septic pulmonary emboli with MRSA osteomyelitis in a pediatric patient' Pediatric Emergency Care 2012: volume 28, issue 9, pages 911 to 912

Stein C and others. 'Rethinking the Molecular Diagnostics for Methicillin-Resistant Staphylococcus aureus' Infection Control and Hospital Epidemiology 2018: volume 39, issue 4, pages 495 to 496

Thabet FC and others. 'Septic pulmonary embolism secondary to Staphylococcus aureus septic thrombophlebitis in a pediatric patient' Saudi Medical Journal 2013: volume 34, issue 10, pages 1,080 to 1,082

Vamsidhar V and others. 'Bilateral subretinal abscess in community-acquired meticillin-susceptible Staphylococcus aureus infection' Journal of the Royal College of Physicians of Edinburgh 2020: volume 50, issue 1, pages 42 to 45

Walsh S and others. 'Deep Vein Thrombosis Associated with Pediatric Musculoskeletal Sepsis' Journal of Pediatric Orthopaedics 2002: volume 22, issue 3, pages 329 to 332

Wu C-Tand others. 'Cutaneous pustular manifestations associated with disseminated septic embolism due to a Panton-Valentine leukocidin-producing strain of community-acquired methicillin-resistant Staphylococcus aureus' International Journal of Dermatology 2008: volume 47, issue 9, pages 942 to 943

Yüksel H and others. 'Septic pulmonary emboli presenting with deep venous thrombosis secondary to acute osteomyelitis' Pediatrics International: official journal of the Japan Pediatric Society 2004: volume 46, issue 5, page 621to 623

Wrong study type (10 studies)

Altobelli MG and others. 'When should DVT be suspected in children with osteomyelitis' Hospital Pediatrics 2012: volume 2, issue 3, pages 167 to 172

Copley LA and others. 'A proposed scoring system for assessment of severity of illness in pediatric acute hematogenous osteomyelitis using objective clinical and laboratory findings' The Pediatric Infectious Disease Journal 2014: volume 33, issue 1, pages 35 to 41

Hensinger RN. 'Impending danger: Community-acquired methicillin-resistant Staphylococcus aureus' Journal of Pediatric Orthopaedics 2006: volume 26, issue 6, pages 701 to 702

Kaplan SL. 'Recent lessons for the management of bone and joint infections' The Journal of infection 2013: volume 68, pages S51 to 56

Mantadakis E and others. 'Deep venous thrombosis in children with musculoskeletal infections: the clinical evidence' International Journal of Infectious Diseases : IJID : official publication of the International Society for Infectious Diseases 2012: volume 16, issue 4, pages 236 to 243

Martin E and others. 'The role of hypervirulent Staphylococcus aureus infections in the development of deep vein thrombosis' Thrombosis Research 2012: volume 130, issue 3, pages 302 to 308

Méndez-Alvarez MI and others. 'Pediatric cases from Colombia caused by a Panton-Valentine leukocidin-positive community-acquired methicillin-resistant Staphylococcus aureus ST8-SCCmecIVc clone' Pediatric Infectious Disease Journal 2009: volume 28, issue 10, page 935

Oschman A and others. 'Venous thromboembolism in the pediatric population' Orthopedics 2010: volume 33, issue 3

Pendleton A and others. 'Methicillin-resistant Staphylococcus aureus bone and joint infections in children' The Journal of the American Academy of Orthopaedic Surgeons 2015: volume 23, issue 1, pages 29 to 37

Purcell and others. 'Community-acquired methicillin-resistant Staphylococcus aureus: a growing public health problem' Pediatric Health 2007: volume 1, issue 1, pages 95 to 105

No relevant outcomes (2 studies)

Gonzalez BE and others. 'Panton-Valentine leukocidin-positive methicillin-resistant Staphylococcus aureus necrotizing pneumonia presenting as fever of unknown origin' Infectious Diseases in Clinical Practice 2009: volume 17, pages 55 to 57

Kumari HBV and others. 'A variant epidemic methicillin resistant Staphylococcus aureus-15 cavernous sinus thrombosis and meningitis: a rare occurrence with unusual presentation' Indian Journal of Medical Microbiology 2010: volume 28, issue 3, pages 255 to 257

Not English language (4 studies)

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Fernandez-Lopez and others. 'Acute osteomyelitis due to Panton-Valentine leukocidine-producing methicillin-susceptible *Staphylococcus aureus* with deep vein thrombosis and

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Annexe D. Data extraction tables

Abbreviations: CT = computed tomography, DVT = deep vein thrombosis, L2 = lumbar 2 vertebra, MRI = magnetic resonance imaging, MRSA = methicillin-resistant *Staphylococcus aureus*, PCR = polymerase chain reaction, pvl = Panton-Valentine Leukocidin, USA = United States of America

Table D1. Data extraction table for adults

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
Lin and others, 2008 (7)	USA, December 2005 to February 2007	Case series	Sample size: 4 Mean age range: 36 to 65 years Sex: 100% male Ethnicity: not reported Case 1: Age: 36 years Prior medical history: Diabetes mellitus, obesity Case 2: Age: 55 years Prior medical history: hypertension, benign prostatic hypertrophy and chronic rectal haemorrhoids Case 3: Age: 46 years Prior medical history: none Case 4: Age: 65 years Prior medical history: alcoholism, prior assault resulting in prolonged exposure to cold temperatures, homelessness	Case 1: bacteraemia, pyomyositis in the front side of upper left leg Case 2: bacteraemia, prostatic abscess Case 3: bacteraemia, vertebral osteomyelitis with pyomyositis Case 4: bacteraemia, pyomyositis of the front side of upper legs All 4 isolates carried genes for PVL toxin, confirmed using a PCR assay	Case 1: • CT scan of the chest revealed septic pulmonary emboli (nodules on both sides of lungs and some cavitary) Case 2: • CT scan of the chest revealed septic pulmonary emboli (nodules on both sides of lungs) Case 3: • CT scan of the chest revealed septic pulmonary emboli (infected infiltrates on both sides of lungs) Case 4: • CT scan of the chest revealed septic pulmonary emboli All 4 patients recovered
Yokomori and others, 2020 (19)	Japan, time period not reported	Case report	Sample size=1 Age: 20 years Sex: male Ethnicity not reported Medical history: no previous medical or travel history	• skin and soft tissue infections, abscesses, septic osteomyelitis (hip joint), and bacteraemia • shortness of breath, abrasions from rugby, shadows in both lungs, and pneumonia with cavity (right upper lobe)	Abdominal CT showed iliofemoral DVT and chest CT revealed septic pulmonary embolism The case recovered

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
				• the isolate was positive for PVL (detected through PCR)	

Abbreviations: CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*, CA-MSSA = community-acquired methicillin-sensitive *Staphylococcus aureus*, CT = computed tomography, DNA = deoxyribonucleic acid, DVT = deep vein thrombosis, MRI = magnetic resonance imaging, MRSA = methicillin-resistant *Staphylococcus aureus*, PCR = polymerase chain reaction, PICU = paediatric intensive care unit, pvl = Panton-Valentine Leukocidin, PVL- SA = Panton-Valentine Leukocidin-*Staphylococcus aureus*, *S. aureus* = *Staphylococcus aureus*, VTE = venous thromboembolism, USA = United States of America

Table D2. Data extraction table of cohort studies in children

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
Gonzalez and others, 2005 (1)	USA, September 2002 to January 2004	Prospective cohort study	Sample size: 14 Average age range: 10 to 15 years Sex: 2 out of 14 were female (14.2%) Ethnicity not reported Medical history: all were previously healthy 12 children (86%) had no underlying medical condition, one had mild intermittent asthma, and one had history of patent ductus arteriosus with a coil placed one year before the present disease onset	Bone and Joint infections: • 13 out of 14 (93%) had bone and joint infections • 3 (29%) had septic arthritis of the knee joint • 10 (71%) had multiple bones and joints involved with >2 sites affected simultaneously (range: 2 to 10) Of the 10 children with more than 2 bones and joints affected, 8 also had pyomyositis of the neighbouring muscles 13 out of 14 (93%) were bacteraemia. These children also had more than 2 bone/joint sites affected and had pulmonary lesion Genes for PVL were present in all the isolates (detected through PCR)	• 4 out of 14 (29%) children had vascular complications, which included: • common iliac vein in one case, saphenous and popliteal vein thrombosis in 2 patient, femoral vein thrombosis in one patient • 2 of these children had chest radiographs consistent with septic emboli. None of the children had a family history of thrombosis • 7 out of 14 (50%) children had nodular densities in both lungs consistent with septic emboli seen on chest radiographs; these patients also had bone and joint infection and bacteraemia • 3 of the 14 patients with invasive PVL infection died
Gonzalez and others, 2006 (2)	USA, August 1, 2001 to December 31, 2004	Prospective cohort study	Sample size: 7 with invasive PVL infection (of 9 total in the study [one was negative for PVL gene, and the other was not reported]) Mean age: 12.6 years Sex: 100% male	Osteomyelitis and pyomyositis All 9 children had osteomyelitis and pyomyositis located next to the site of the venous thrombosis	The majority of the VTEs were detected when scanning was performed to evaluate the osteomyelitis/pyomyositis • case 2 (occurred in 2001, 3 years of age, black, osteomyelitis in the right femur): MRI revealed

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
			Ethnicity: 2 black, 1 Hispanic, 4 white Medical history: 6 children had no family history of predisposing conditions, 2 had relatives with history of VTEs or acute myocardial infection and one patient's history was unknown Records from the prior 3 years were also reviewed. No children with invasive PVL were identified from the 3 prior years	Stored isolates were cultured, and DNA was extracted for detection of PVL through PCR	right common femoral and right external iliac veins thrombosis • case 4 (occurred in 2003, 10 years of age, white, osteomyelitis in the left ischium, pubis and iliac bone): CT revealed left common iliac vein thrombosis • case 5 (occurred in 2003, 14 years of age, white, osteomyelitis in the right femur and tibia): MRI revealed right femoral vein thrombosis extending to right popliteal vein Septic emboli were observed in lungs • case 6 (occurred in 2003, 13 years of age, white, osteomyelitis in the left femur and tibia): MRI revealed left saphenous vein thrombosis • case 7 (occurred in 2003, 14 years of age, white, osteomyelitis in the left tibia): MRI revealed left popliteal and left saphenous vein thrombosis Septic emboli were observed in lungs • case 8 (occurred in 2004, 11 years of age, Hispanic osteomyelitis in the left femur): MRI revealed left femoral vein thrombosis Septic emboli were observed in lungs • case 9 (occurred in 2004, 14 years of age, white, osteomyelitis in the right femur): MRI revealed right common femoral thrombosis extending to right popliteal veins Septic emboli were observed in lungs All patients recovered.
Hulten and others, 2018 (3)	USA, January 1, 2007 to December 31, 2014	Retrospective cohort study	A total of 296 children with invasive CA-MSSA infections were identified from the surveillance database at Texas Children's Hospital,	• bone and joint infections n=62 • pneumonia n=11	12 patients with invasive bone and joint infections developed DVT

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
			representing 84.8% of all such infections during the study period. 88 out of 296 (29.7%) had the PVL gene Demographics of patients with invasive PVL only not reported	• myositis/pyomyositis n=4 • deep abscesses n=5 • other infection with sepsis/septic shock: n=6 Invasive CA-MSSA isolates were analysed by PCR for detection of the PVL genes	14 patients presented with severe sepsis/septic shock (out of which 8 had a DVT and 10 had septic emboli) All 18 patients with DVT and/or septic shock in addition to the bone and joint infection had PVL gene positive isolates Recovery of patients with DVT is not reported
Martínez-Aguilar and others, 2004 (4)	USA, February 2000 to December 2002	Retrospective cohort study	59 children with bone and muscle infections had community-acquired *Staphylococcus aureus* n=31 had MRSA n=28 had MSSA 33 cases were PVL-positive (27 MRSA, 6 MSSA) Demographics of patients with invasive PVL not reported	Osteomyelitis, pyomyositis and septic arthritis Breakdown not reported All patients had a positive culture of the affected tissue and/or positive blood culture for *S. aureus*, PVL gene was detected using PCR	Doppler ultrasound showed that 5 children (all with invasive PVL) developed deep vein thrombosis (age, sex, type of invasive infection in patients not reported) All patients recovered

Abbreviations: CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*, CA-MSSA = community-acquired methicillin-sensitive *Staphylococcus aureus*, CT = computed tomography, DNA = deoxyribonucleic acid, DVT = deep vein thrombosis, mm = millimetre, MRI = magnetic resonance imaging, MRSA = methicillin-resistant *Staphylococcus aureus*, p = probability value, PCR = polymerase chain reaction, PICU = paediatric intensive care unit, PVL = Panton-Valentine Leukocidin, PVL-SA = Panton-Valentine Leukocidin-*Staphylococcus aureus*, *S. aureus* = *Staphylococcus aureus*, SSTI = skin and soft tissue infection, USA = United States of America, X-ray = X- radiation

Table D3. Data extraction table of descriptive studies in children

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
Cunnington and others, 2009 (5)	England, January 2004 to May 2008	Case series	Sample size: 11 Age range: 7 months to 13 years Sex: 7 males (64%), 4 females (36%) Ethnicity (as reported by the study): 2 white, 9 non-white Medical history: no patients had any significant past medical problems of immunodeficiency	• necrotising pneumonia n=1 • septic arthritis n=3 • osteomyelitis n=1 • pyomyositis of thigh n=1 • upper obstruction from retropharyngeal abscess n=1	4 patients developed DVT: • one case (3 years, female, non-white, septic arthritis of the hip, sites involved hip and chest) had femoral DVT next to the presenting site of infection • another case (7 months, female, non-white, upper airway obstruction from a retropharyngeal

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
				• septic shock n=4 (one also had necrotising pneumonia) Toxin gene profiling was performed by multiplex PCR to detect PVL	abscess) also had DVT (internal jugular vein thrombosis) near the site of infection • a further case (9 years, male, non-white, septic shock, sites involved both hip joints, femur, humerus, elbow joint, mandible, vertebra, chest) also had a femoral DVT next to the presenting site of infection • one case (9 years, male, non-white, thigh pain with septic shock, site involved hip joint, femur, tibia, thigh muscle, pelvis, chest) developed multiple DVTs at sites of central venous catheter insertion The patient that was 3 years of age with femoral DVT died. All other patients recovered
Hoppe and others, 2019 (6)	Germany, January 2012 to December 2017	Case series	Sample size: 8 (of a total 75 children treated for PVL-SA infection in the study) Reported sample size is for eligible invasive infections only Age range: 0 to 15 years Sex: 6 males (75%), 2 females (25%) Ethnicity not reported Medical history: one case had neonatal drug withdrawal and congenital cyto-megalovirus	• necrotising pneumonia: n=4 • necrotising fasciitis: n=2 • pyomyositis: n=2 (1 also had pneumonia) • mastoiditis and cerebellitis: n=1 Where reported, PVL-SA was cultured from blood samples. PVL was detected using commercial PCR (eazyplex MRSAplus)	Of 8 children with invasive PVL, 2 children developed deep vein thrombosis: • case 1 (14 years, male, no pre-existing health conditions, necrotising pneumonia after drainage of an axillary abscess, pyomyositis and fasciitis also present): Case initially presented with extensive thrombosis of the left communal femoral vein • case 7 (11 years, male, no pre-existing health conditions, presented with mastoiditis and cerebellitis: An MRI revealed a thrombosis of the left sigmoid venous sinus and the distal jugular vein, as complication of mastoiditis and SSTI of the neck Both patients recovered

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
Esteves and others, 2010 (8)	Portugal, not reported	Case report	Sample size: 1 Age: 14 years Sex: male Ethnicity not reported Medical history not reported	Septic arthritis and bacteraemia PVL genes detected in the isolated MSSA strain on PCR assays	DVT in the right femoral vein (confirmed by venous doppler ultrasound) Later, the second CT showed signs of pulmonary embolism. Doppler studies of inferior vena cava and ileo-femoral vessels identified a large thrombus in the right iliac veins The case recovered
Gomez and others, 2020 (9)	Spain, not reported	Case report	Sample size: 1 Age: 11 years Sex: female Ethnicity not reported Medical history: no relevant medical or family history	Tibial osteomyelitis, fasciitis, cellulitis, with a large pretibial abscess fistulising toward the skin *S. aureus* strain tested positive for the PVL gene through PCR	Ultrasound scan revealed superficial venous thrombophlebitis (septic) in the lower right limb. A further ultrasound showed thrombosis of the internal saphenous vein and popliteal vein permeability Chest radiograph also showed alveolar and nodular infiltrates in both lungs, indicating pulmonary involvement The case recovered
Groselj-Grenc and others, 2011 (10)	Slovenia, not reported	Case report	Sample size: 1 Age: 22 months Sex: male Ethnicity not reported Medical history: uneventful medical history and up to date immunisation	Necrotising pneumonia with abscesses (developed on day 16) and osteomyelitis of the right femur (developed on day 25) *S. aureus* was isolated from both blood cultures and joint fluid, *S. aureus* isolate was PVL-positive through PCR	DVT in the right femoral vein was recognised on day one The case recovered
Harada and others, 2023 (11)	Japan, not reported	Case report	Sample size: 1 Age: 10 years Sex: male Ethnicity not reported Medical history: previously healthy with no family history of immunodeficiency	Osteomyelitis, pyomyositis and septic arthritis *S. aureus* was isolated from both blood cultures and joint fluid, PVL-positive through PCR	Septic thrombophlebitis of the right common iliac vein Additionally, the case had septic pulmonary embolism as a complication The case recovered

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
Karli and others, 2015 (12)	Turkey, not reported	Case report	Sample size: 1 Age: 13 years Sex: male Ethnicity not reported Medical history: previously healthy	Irregular abscess with thick septae, suggesting a deep-seated infection in the gluteal region Positive for MSSA. PVL detected through PCR	Thorax CT revealed multiple, widespread cavitary lesions with air and fluid levels, located in the upper lobe of the right lung, consistent with septic pulmonary embolism Diagnostic tests for DVT were not performed The case recovered
Karli and others, 2016 (13)	Turkey, not reported	Case report	Sample size: 1 Age: 12 years Sex: male Ethnicity not reported Medical history: clear familial history and previously in good health	Osteomyelitis and muscle abscess MSSA isolated from blood and bone marrow culture. PCR was performed for PVL on DNA extracted from *S. aureus* strains	Septic pulmonary embolism attributed to Psoas abscess The case recovered
Kefala-Agoropoulou and others, 2010	Greece, not reported	Case report	Sample size: 1 Age: 10 years Sex: female Ethnicity not reported Medical history: clear history except a mild injury during exercise on the day of disease onset	Osteomyelitis and pyomyositis PCR testing confirmed PVL gene and was characterised as MRSA	5 days after hospital admission, MRI revealed DVT of the right femoral and right external iliac vein The case recovered
Miyashita and others, 2002 (15)	Japan, not reported	Case report	Sample size: 1 Age: 17 years Sex: male Ethnicity not reported Medical history: no history of serious illnesses and no symptoms of influenza or a history of smoking, alcohol abuse, or drug use	Bacteraemia with metastatic infection in the lungs *Staphylococcus aureus* identified from blood, sputa, and pleural effusions. PCR testing detected the PVL gene	Authors speculate that the case developed pulmonary embolism from fulminant embolic pneumonia due to blood borne spread. Chest X-ray and CT showed diffused multilobular opacities and cavernous changes. Pathological features resembled an experimental pulmonary embolism The case recovered
Sawanobori and others, 2015 (16)	Japan, August 2010	Case report	Sample size: 1 Age: 15 years Sex: male Ethnicity not reported Medical history: patient developed a furuncle accompanied by pus discharge twice on the anterior surface of the left knee after an insect bite but showed improvement 15 days before	Osteomyelitis and femoral pyomyositis Cultures of blood and pus revealed PVL positive MSSA. Virulence genes were analysed by PCR	Septic pulmonary embolism on day 5 based on CT findings. CT scan also showed posterior pleural and pulmonary infiltrates suggesting pneumonia. The case recovered

Study	Country, time period	Study type	Population	Invasive infection and PVL detection	Outcomes
			admission, no other previous medical history reported		
Swaminathan and others, 2006 (17)	Australia, not reported	Case report	Sample size: 1 Age: 14 years Sex: male Ethnicity: Samoan background Medical history: clear medical history apart from mild asthma controlled with inhalers	Osteomyelitis, septic arthritis, and deep tissue abscesses PVL-positive *S. aureus*, confirmed by PCR amplification of the PVL genes from the blood culture isolate	A venous phase scan revealed a DVT (left popliteal vein thrombosis) The case recovered
Valentini and others, 2008 (18)	Italy, not reported	Case report	Sample size: 1 Age: 15 years Sex: male Ethnicity not reported Medical history: no significant medical history, except for mild asthma during childhood	Bacteraemia, necrotising pneumonia and lung abscess MRSA isolated from blood cultures. The MRSA isolate was PVL-positive	CT scan revealed DVT (thrombosis in the inferior vena cava below the renal veins and both iliac veins) An investigation into his underlying health revealed that he had inherited thrombophilic defects, which likely contributed to the development of DVT The case recovered

Annexe E. Risk of bias assessment

Table E.1. Risk of bias assessment for prevalence studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Comments
Gonzalez and others, 2005	No	Yes	No	Yes	Yes	Unclear	Unclear	NA	Yes	Q1: Sample size not representative of target population Q3: Study did not conduct any subgroup analysis Q6: Study does not discuss method of identification of outcome Q7: Study does not discuss method of identification of outcome, therefore it was unclear if the condition was measured in a standard, reliable way for all participants
Gonzalez and others, 2006	No	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Q1: Sample size not representative of target population Q3: Study did not conduct any subgroup analysis
Hulten and others, 2018	No	Yes	No	Yes	Yes	Unclear	Unclear	NA	Yes	Q1: Sample size not representative of target population Q3: Study did not conduct any subgroup analysis Q6: Study does not discuss method of identification of outcome Q7: Study does not discuss method of identification of outcome, therefore it was unclear if the condition was measured in a standard, reliable way for all participants
Martinez-Aguilar and others, 2004	No	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Q1: Sample size not representative of target population Q3: Study did not conduct any subgroup analysis

Note: Q8 marked as non-applicable as statistical analysis for relevant outcomes was not conducted.

Critical appraisal was done using the JBI checklist for prevalence studies (20).

List of questions:

Question 1: Was the sample frame appropriate to address the target population?
Question 2: Were study participants sampled in an appropriate way?
Question 3: Was the sample size adequate?
Question 4: Were the study subjects and the setting described in detail?
Question 5: Was the data analysis conducted with sufficient coverage of the identified sample?
Question 6: Were valid methods used for the identification of the condition?
Question 7: Was the condition measured in a standard, reliable way for all participants?
Question 8: Was there appropriate statistical analysis?
Question 9: Was the response rate adequate, and if not, was the low response rate managed appropriately?

Table E.2. Risk of bias assessment for case series

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Comments
Cunnington and others, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	
Hoppe and others, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	NA	Q9: Only location of the presenting site stated, no information on demographic information of patients or surrounding area
Lin and others, 2008	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	NA	Q4: Study doesn't state at which point during the timeframe patients were treated, and therefore it is unclear if the case series had consecutive inclusion of participants Q5: Study does not explicitly state whether all eligible cases from the time period were included

Note: Q10 marked as non-applicable as no statistical analysis was conducted.

Critical appraisal was done using the JBI checklist for case series (20).

List of questions:

Q1: Were there clear criteria for inclusion in the case series?
Q2: Was the condition measured in a standard, reliable way for all participants included in the case series?
Q3: Were valid methods used for identification of the condition for all participants included in the case series?
Q4: Did the case series have consecutive inclusion of participants?
Q5: Did the case series have complete inclusion of participants?
Q6: Was there clear reporting of the demographics of the participants in the study?
Q7: Was there clear reporting of clinical information of the participants?
Q8: Were the outcomes or follow up results of cases clearly reported?
Q9: Was there clear reporting of the presenting site(s) or clinic(s) demographic information?
Q10: Was statistical analysis appropriate?

Table E.3. Risk of bias assessment for case reports

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Comments
Esteves and others, 2010	Yes	No	Yes	Yes	NA	Yes	NA	Yes	Q2: Patients history not clearly reported Q5: Dosage and treatment regime of intervention not reported
Gomez and others, 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	No	Q5: Dosage of intervention not stated Q8: Case report provides no takeaway lessons relevant to outcomes
Groselj-Grenc and others, 2011	Yes	Yes	Yes	Yes	NA	Yes	NA	No	Q5: Dosage of intervention not stated Q8: Case report provides no takeaway lessons relevant to outcomes
Harada and others, 2023	Yes	Yes	Yes	Yes	NA	Yes	NA	No	Q5: Dosage and route of administration of intervention not stated Q8: Case report provides no takeaway lessons relevant to outcomes
Karli and others, 2015	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	
Karli and others, 2016	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	
Kefala-Agoropoulou and others, 2010	Yes	Yes	Yes	Yes	NA	Yes	NA	No	Q8: Case report provides no takeaway lessons relevant to outcomes
Miyashita and others, 2002	Yes	Yes	Yes	Yes	NA	Yes	Na	Yes	
Sawanobori and others, 2015	Yes	Unclear	Yes	Yes	NA	Yes	NA	Yes	Q2: History of events preceding invasive infection given but medical history of case not reported
Swaminathan and others, 2006	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	
Valentini and others, 2008	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	
Yokomori and others, 2020	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Q5: Dosage of intervention not stated

Note: Q5 marked as non-applicable as intervention or treatment procedures were not being assessed. Q7 marked as non-applicable as adverse events or unanticipated events of said intervention/treatment were not assessed

Critical appraisal was done using the JBI checklist for case reports (20).

List of questions:

Q1: Were patient's demographic characteristics clearly described?
Q2: Was the patient's history clearly described and presented as a timeline?
Q3: Was the current clinical condition of the patient on presentation clearly described?
Q4: Were diagnostic tests or assessment methods and the results clearly described?
Q5: Was the intervention(s) or treatment procedure(s) clearly described?
Q6: Was the post-intervention clinical condition clearly described?
Q7: Were adverse events (harms) or unanticipated events identified and described?
Q8: Does the case report provide takeaway lessons?

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