

Effectiveness of antibiotics for Panton-Valentine leukocidin-positive *Staphylococcus aureus* (PVL-SA) associated bacteraemia

A rapid systematic review

Contents

| Main messages | 3 |
|-------------------------------------|----|
| Purpose | 3 |
| Methods | 3 |
| Evidence | 4 |
| Health inequalities | 4 |
| Limitations | 4 |
| Evidence gaps | 4 |
| Conclusion | 5 |
| Acknowledgments | 5 |
| Disclaimer | 5 |
| References | 5 |
| Annexe A. Protocol | 6 |
| Annexe B. Study selection flowchart | 18 |
| Annexe C. Excluded full texts | 20 |
| About the UK Health Security Agency | 29 |

Main messages

- 1. This rapid systematic review (search up to 13 September 2024) aimed to identify and summarise evidence relating to the effectiveness of antibiotics to treat Panton-Valentine leukocidin-positive *Staphylococcus aureus* (PVL-SA) associated bacteraemia.
- 2. In total, 3,731 records from 5 databases were screened. No studies were identified for inclusion in this review.
- 3. In summary, no published randomised controlled trials, non-randomised control trials or observational studies (case control or cohort studies) were identified looking at the effectiveness of antibiotics in treating PVL-SA associated bacteraemia.

Purpose

The purpose of this rapid systematic review was to identify and summarise the available evidence that discussed the effectiveness of antibiotics to treat Panton-Valentine leukocidin-positive *Staphylococcus aureus* (PVL-SA) associated bacteraemia.

The review question was:

1. What is the effectiveness of antibiotics in treating people with Panton-Valentine leukocidin *Staphylococcus aureus* (PVL-SA) associated bacteraemia?

Methods

A rapid systematic review was conducted, following streamlined systematic methods to accelerate the review process (1). 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 <u>Annexe A.</u> There were no deviations from the protocol.

A literature search was undertaken to look for relevant interventional studies (randomised controlled trials, non-randomised controlled trials and cross over studies) and observational studies (case control and cohort studies) published up to 13 September 2024. The reference list of 2 systematic reviews identified during screening was also checked for any additional relevant primary studies.

The population of interest was adults or children with laboratory confirmed PVL-SA bacteraemia through a polymerase chain reaction (PCR) test, in inpatient settings. For this review, treatment could consist of any antibiotic or a combination of antibiotics, or antibiotic with immunoglobulin

(an antibody used by the immune system to recognise bacteria and viruses) used as treatment for PVL-SA bacteraemia through any route of administration. This was compared to other antibiotics, treatments such as supportive care, or placebo. Primary outcomes included mortality, morbidity and intensive care or high dependency unit admission. Adverse events, serious adverse events, or withdrawal due to adverse events ascribed to taking antibiotics were secondary outcomes that would have only been extracted from studies that had at least one of the primary outcomes.

Screening on title and abstract was undertaken in duplicate by 2 reviewers for 20% of the eligible studies, with the remainder completed by one reviewer. Screening on full text was undertaken by one reviewer and checked by a second.

Evidence

A total of 3,731 studies were screened at title and abstract and 82 studies were screened at full text. Of these, no studies met the inclusion criteria. A PRISMA diagram showing the flow of studies through the review is shown in <u>Annexe B</u>, and studies excluded at full text screening are available in <u>Annexe C</u> with the reasons why they were excluded. The main reasons for excluding records at full text were being in the wrong population (n=45) or wrong study type (n=20).

Health inequalities

Groups more likely to experience health inequalities, such as those with existing health conditions, children or young people were explicitly defined within the inclusion criteria in the review protocol. However, no studies were identified for inclusion in this review and therefore health inequalities could not be assessed.

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.

Evidence gaps

No studies were identified for inclusion in this review highlighting a clear evidence gap relating to the effectiveness of antibiotics to treat PVL-SA bacteraemia.

Conclusion

The aim of this review was to identify and assess available evidence that evaluated the effectiveness of antibiotics in treating people with PVL-SA bacteraemia. However, no relevant evidence (from interventional, case control or cohort studies) was identified and therefore this review is unable to inform on the effectiveness of antibiotics in treating this population.

Acknowledgments

We would like to thank colleagues within the All Hazards Public Health Response division who either reviewed or input into aspects of the review.

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.

References

- 1. Tricco AC and others. '<u>Rapid reviews to strengthen health policy and systems: a practical guide</u>' 2017
- 2. Aromataris E and others. 'JBI Manual for Evidence Synthesis. JBI' 2024
- Group T. '<u>GRADE handbook for grading quality of evidence and strength of</u> recommendations (updated October 2013)' 2013

Annexe A. Protocol

Review question

The review question is:

1. What is the effectiveness of antibiotics in treating people with Panton-Valentine leukocidin *Staphylococcus aureus* (PVL-SA) associated bacteraemia?

A search for primary evidence to answer this review question will be conducted up to 13th September.

Eligibility criteria

Table A.1 Inclusion and exclusion criteria

| | Included | Excluded |
|-----------------------------|---|---|
| Population | Adults and children with laboratory confirmed PVL-SA bacteraemia (through polymerase chain reaction test) | Animals |
| Context | Any context | |
| Settings | Hospital inpatient settings only | Laboratory settings |
| Intervention or exposure | Any antibiotic or combination of antibiotics, or antibiotic with immunoglobulin taken as treatment for PVL-SA bacteraemia Any route of administration | Any other form of treatment that does not include an antibiotic (such as monotherapy immunoglobulin) |
| Comparator | Comparison to other antibiotics or treatments such as supportive care, or placebo | |
| Outcomes | Primary outcomes: mortality (as reported by the study) morbidity, as measured by the following (and directly linked to having the infection): intensive care or high dependency unit admission | |

| Included | Evoludod |
|---|----------|
| | Excluded |
| need for intubation and ventilation | |
| \circ need for vasopressors | |
| clinical support with oxygen | |
| \circ end organ dysfunction | |
| Need for renal replacement therapy (to include dialysis and renal transplant) | |
| - Evidence of acute liver failure | |
| diagnosis of disseminated intravascular coagulation (DIC) | |
| Secondary outcomes (these will be extracted only from studies that have at least one of the primary outcomes): prevalence, incidence, risk (relative or absolute), or count data (individual or total) of any adverse event or serious adverse event or withdrawal due to adverse events ascribed to taking antibiotics for treatment of PVL-SA bacteraemia even if not stated as outcome of interest of the study | |
| Types of outcome as defined by the European Medicines Agency for adverse events (any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product) | |
| Or | |
| Serious adverse events (an adverse reaction that results in death, is life- | |

| | Included | Excluded |
|---------------------|--|--|
| | threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect) Or | |
| | As described by the review | |
| Language | English | Non-English language studies |
| Date of publication | Up to 13 September 2024 | |
| Study design | Interventional studies (Randomised Controlled Trials, Non-randomised controlled trials, cross over studies). Observational studies including case- control and cohort studies will only be included if there is no sufficient evidence presented in RCTs. Observational studies will still be included in the title and abstract stage of the review. | Systematic or narrative reviews Modelling studies Laboratory studies Case reports Case series Cross sectional studies Single-arm trials Qualitative research |
| Publication type | Peer-reviewed published research | Conference abstracts Editorials Letters News Articles Grey literature Preprints Books |

Identification of studies

The following databases and trial registries will be searched for studies published up to 13 September 2024: Ovid Medline, Embase, CINAHL, Scopus and Cochrane Central Register of Randomised Controlled Trials. The search strategy is presented <u>below</u>. Details of references that are included following full text screening will be used for backwards and forwards citation searching. Citation searching will be carried out using the Lens.org database via <u>CitationChaser</u>.

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 (including choice of antibiotic/regime according to any antibiotic resistance identified). 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 (2). 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 using a modified version of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (<u>3</u>). 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 <u>Risk of bias</u> <u>assessment.</u>
- 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.

Because the JBI checklist will be used to assess risk of bias, evidence from randomised controlled trials will start at high quality, and evidence from observational studies will start at low quality. Evidence may be downgraded one or 2 levels following the assessment of quality, or upgraded if there is a large magnitude of effect or clear dose-response gradient.

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

Variations across individuals with health inequalities will be considered, as these may produce different outcomes following treatment with antibiotics for PVL-SA associated bacteraemia (such as those with existing health conditions, or children or young people).

Search strategy

Ovid MEDLINE(R) ALL (1946 to 3 September 2024)

- 1. Leukocidins/ (1745)
- 2. leukocidin*.tw,kf. (2227)
- 3. leucocidin*.tw,kf. (557)
- 4. leukotoxin*.tw,kf. (995)
- 5. leucotoxin*.tw,kf. (53)
- 6. Panton Valentine.tw,kf. (2315)
- 7. PVL.tw,kf. (5093)
- 8. (LukS* or Luk S*).tw,kf. (458)
- 9. (LukF* or Luk F*).tw,kf. (351)
- 10. (LukPV* or Luk pv*).tw,kf. (76)
- 11. (LukSF* or Luk SF*).tw,kf. (54)
- Bacterial Toxins/ and (exp Staphylococcal Infections/ or exp Staphylococcus aureus/) (3574)
- 13. (bacteri* toxin* and (staph* or S* aureus)).tw,kf. (367)
- 14. or/1-13 (10043)
- 15. exp Sepsis/ (147419)
- 16. exp Bacteremia/ (33924)
- 17. (Bacteria/ or exp Staphylococcus aureus/ or Bacterial Infections/ or exp Staphylococcal Infections/) and exp Blood/ (16365)
- 18. ((bacter* or S* aureus or staph*) and blood*).tw,kf. (90785)
- 19. bacter?emi*.tw,kf. (40335)
- 20. sepsis.tw,kf. (130384)
- 21. septic*.tw,kf. (92541)
- 22. (infect* adj3 (blood or bloodstream)).tw,kf. (37292)
- 23. blood poison*.tw,kf. (60)
- 24. (bacteri* adj3 (blood or bloodstream)).tw,kf. (5605)
- 25. (S* aureus adj3 (blood or bloodstream)).tw,kf. (1370)
- 26. septic?emi*.tw,kf. (24074)
- 27. py?emi*.tw,kf. (264)
- 28. pyoh?emi*.tw,kf. (16)
- 29. or/15-28 (374763)
- 30. 14 and 29 (1933)

Embase (1974 to 3 September 2024)

- 1. leukocidin/ (1003)
- 2. leukotoxin/ (985)
- 3. Panton Valentine leukocidin/ (2747)
- 4. leukocidin*.tw,kf. (2736)
- 5. leucocidin*.tw,kf. (643)

- 6. leukotoxin*.tw,kf. (1075)
- 7. leucotoxin*.tw,kf. (65)
- 8. panton valentine.tw,kf. (2890)
- 9. PVL.tw,kf. (7790)
- 10. (LukS* or Luk S*).tw,kf. (619)
- 11. (LukF* or Luk F*).tw,kf. (441)
- 12. (Luk pv* or LukPV*).tw,kf. (89)
- 13. (LukSF* or Luk SF*).tw,kf. (66)
- 14. (exp Staphylococcus aureus/ or exp Staphylococcus infection/) and bacterial toxin/ (1533)
- 15. (bacteri* toxin* and (staph* or S* aureus)).tw,kf. (448)
- 16. or/1-15 (12699)
- 17. exp sepsis/ (360949)
- 18. exp bacteremia/ (65753)
- 19. exp staphylococcal bacteremia/ (3814)
- 20. (exp bacterium/ or bacterial infection/ or exp Staphylococcus aureus/ or exp Staphylococcus infection/) and exp blood/ (149431)
- 21. ((bacter* or S* aureus or staph*) and blood*).tw,kf. (131557)
- 22. bacter?emi*.tw,kf. (56074)
- 23. sepsis.tw,kf. (206733)
- 24. septic*.tw,kf. (129736)
- 25. (infect* adj3 (blood or bloodstream)).tw,kf. (52197)
- 26. blood poison*.tw,kf. (55)
- 27. (bacteri* adj3 (blood or bloodstream)).tw,kf. (7512)
- 28. (S* aureus adj3 (blood or bloodstream)).tw,kf. (2008)
- 29. septic?emi*.tw,kf. (27439)
- 30. py?emi*.tw,kf. (145)
- 31. pyoh?emi*.tw,kf. (2)
- 32. or/17-31 (694930)
- 33. 16 and 32 (2589)

CINAHL Complete

| # | Query | Results |
|----|--------------------|---------|
| S1 | leukocidin* | 288 |
| S2 | leucocidin* | 80 |
| S3 | leukotoxin* | 38 |
| S4 | leucotoxin* | 2 |
| S5 | "Panton Valentine" | 347 |
| S6 | PVL | 753 |
| S7 | LukS* OR Luk S* | 79 |
| S8 | LukF* OR luk F* | 70 |

| # | Query | Results |
|-----|---|---------|
| S9 | "Luk pv*" OR Lukpv* | 4 |
| S10 | (MH "Bacterial Toxins") | 1,586 |
| S11 | (MH "Staphylococcus Aureus+") | 12,558 |
| S12 | S10 AND S11 | 269 |
| S13 | "luk SF*" OR LukSF* OR ("bacteri* toxin*" AND (staph* OR "S* aureus")) | 327 |
| S14 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S12 OR S13 | 1,171 |
| S15 | (MH "Sepsis+") | 32,820 |
| S16 | (MH "Bacteremia") | 6,592 |
| S17 | (MH "Bacteria+") | 83,689 |
| S18 | (MH "Staphylococcus Aureus+") | 12,558 |
| S19 | (MH "Bacterial Infections") | 11,164 |
| S20 | S17 OR S18 OR S19 | 92,291 |
| S21 | (MH "Blood+") | 81,213 |
| S22 | S20 AND S21 | 3,286 |
| S23 | bacter#emi* OR ((bacter* or S* aureus or staph*) and blood*) | 25,672 |
| S24 | sepsis OR septic* | 47,091 |
| S25 | (infect* N3 (blood or bloodstream)) | 13,012 |
| S26 | "blood poison*" | 10 |
| S27 | (bacteri* N3 (blood or bloodstream)) | 2,833 |
| S28 | ("S* aureus" N3 (blood or bloodstream)) | 329 |
| S29 | septic#emi* | 2,032 |
| S30 | py#emi* | 9 |
| S31 | pyoh#emi* | 0 |
| S32 | S15 OR S16 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 | 79,010 |
| S33 | S14 AND S32 | 198 |

Cochrane Central Register of Controlled Trials (CENTRAL)

Date run: 4 September 2024 17:20:32

| ID | Search | Hits |
|----|--|------|
| #1 | MeSH descriptor: [Leukocidins] explode all trees | 9 |

| ID | Search | Hits |
|-----|---|-------|
| #2 | leukocidin* | 20 |
| #3 | leucocidin* | 5 |
| #4 | Leukotoxin* | 2 |
| #5 | leucotoxin* | 0 |
| #6 | "Panton Valentine" | 20 |
| #7 | PVL | 474 |
| #8 | (LukS* or Luk NEXT S*) | 188 |
| #9 | (LukF* or Luk NEXT F*) | 7 |
| #10 | (Luk NEXT pv* or LukPV*) | 0 |
| #11 | (LukSF* or Luk NEXT SF*) | 1 |
| #12 | MeSH descriptor: [Bacterial Toxins] this term only | 144 |
| #13 | MeSH descriptor: [Staphylococcal Infections] explode all trees | 1551 |
| #14 | MeSH descriptor: [Staphylococcus aureus] explode all trees | 1186 |
| #15 | #13 OR #14 | 2036 |
| #16 | #12 AND #15 | 14 |
| #17 | (bacteri* toxin* AND (staph* OR S* aureus)) | 98 |
| #18 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 | 766 |
| #19 | MeSH descriptor: [Sepsis] explode all trees | 6556 |
| #20 | MeSH descriptor: [Bacteremia] explode all trees | 1311 |
| #21 | MeSH descriptor: [Bacteria] this term only | 2326 |
| #22 | MeSH descriptor: [Staphylococcus aureus] explode all trees | 1186 |
| #23 | MeSH descriptor: [Bacterial Infections] this term only | 3787 |
| #24 | MeSH descriptor: [Staphylococcal Infections] explode all trees | 1551 |
| #25 | #21 OR #22 OR #23 OR #24 | 7706 |
| #26 | MeSH descriptor: [Blood] explode all trees | 21338 |
| #27 | #25 AND #26 | 207 |
| #28 | ((bacter* or S* aureus or staph*) and blood*) | 14716 |
| #29 | bacteremi* OR bacteraemi* | 3359 |
| #30 | sepsis | 15658 |
| #31 | septic* | 7436 |
| #32 | (infect* NEAR/3 (blood or bloodstream)) | 4045 |
| #33 | blood NEXT poison* | 93 |

| ID | Search | Hits |
|-----|---|-------|
| #34 | (bacteri* NEAR/3 (blood or bloodstream)) | 1516 |
| #35 | (S* NEXT aureus NEAR/3 (blood or bloodstream)) | 98 |
| #36 | septicemi* OR septicaemi* | 1320 |
| #37 | pyemi* OR pyaemi* | 16 |
| #38 | pyohemi* OR pyohaemi* | 6 |
| #39 | #19 OR #20 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 | 36622 |
| #40 | #18 AND #39 | 205 |

Cochrane Central Register of Controlled Trials (CENTRAL)

Date run: 16 September 2024

| ID | Search | Hits |
|-----|---|------|
| #1 | MeSH descriptor: [Leukocidins] explode all trees | 9 |
| #2 | leukocidin* | 20 |
| #3 | leucocidin* | 5 |
| #4 | Leukotoxin* | 2 |
| #5 | leucotoxin* | 0 |
| #6 | "Panton Valentine" | 20 |
| #7 | PVL | 474 |
| #8 | (LukS* or Luk NEXT S*) | 188 |
| #9 | (LukF* or Luk NEXT F*) | 7 |
| #10 | (Luk NEXT pv* or LukPV*) | 0 |
| #11 | (LukSF* or Luk NEXT SF*) | 1 |
| #12 | MeSH descriptor: [Bacterial Toxins] this term only | 144 |
| #13 | MeSH descriptor: [Staphylococcal Infections] explode all trees | 1551 |
| #14 | MeSH descriptor: [Staphylococcus aureus] explode all trees | 1186 |
| #15 | #13 OR #14 | 2036 |
| #16 | #12 AND #15 | 14 |
| #17 | (bacteri* toxin* AND (staph* OR S* aureus)) | 98 |
| #18 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 | 766 |
| #19 | MeSH descriptor: [Sepsis] explode all trees | 6556 |

| ID | Search | Hits |
|-----|---|-------|
| #20 | MeSH descriptor: [Bacteremia] explode all trees | 1311 |
| #21 | MeSH descriptor: [Bacteria] this term only | 2326 |
| #22 | MeSH descriptor: [Staphylococcus aureus] explode all trees | 1186 |
| #23 | MeSH descriptor: [Bacterial Infections] this term only | 3787 |
| #24 | MeSH descriptor: [Staphylococcal Infections] explode all trees | 1551 |
| #25 | #21 OR #22 OR #23 OR #24 | 7706 |
| #26 | MeSH descriptor: [Blood] explode all trees | 21338 |
| #27 | #25 AND #26 | 207 |
| #28 | ((bacter* or S* aureus or staph*) and blood*) | 14716 |
| #29 | bacteremi* OR bacteraemi* | 3359 |
| #30 | sepsis | 15658 |
| #31 | septic* | 7435 |
| #32 | (infect* NEAR/3 (blood or bloodstream)) | 4046 |
| #33 | blood NEXT poison* | 93 |
| #34 | (bacteri* NEAR/3 (blood or bloodstream)) | 1516 |
| #35 | (S* NEXT aureus NEAR/3 (blood or bloodstream)) | 98 |
| #36 | septicemi* OR septicaemi* | 1319 |
| #37 | pyemi* OR pyaemi* | 16 |
| #38 | pyohemi* OR pyohaemi* | 6 |
| #39 | #19 OR #20 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 | 36622 |
| #40 | #18 AND #39 | 205 |

Filtered to CENTRAL only: 100 results

Scopus

TITLE-ABS-KEY(leukocidin*) OR TITLE-ABS-KEY(leucocidin*) OR TITLE-ABS-KEY(leukotoxin*) OR TITLE-ABS-KEY(leucotoxin*) OR TITLE-ABS-KEY("panton valentine") OR TITLE-ABS-KEY(PVL) OR TITLE-ABS-KEY((LukS* or "Luk S*")) OR TITLE-ABS-KEY((LukF* or "Luk F*")) OR TITLE-ABS-KEY(("Luk pv*" or LukPV*)) OR TITLE-ABS-KEY((LukSF* or "Luk SF*")) OR TITLE-ABS-KEY(("bacteri* toxin*" and (staph* or "S* aureus")))

And:

```
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(septic*emi*) OR TITLE-ABS-KEY(py*emi*) OR TITLE-ABS-KEY(py*emi*) OR TITLE-ABS-KEY(py*emi*) OR TITLE-ABS-KEY(py*emi*))

2,477 results

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 n=0 studies.

From identification of studies via databases and registers, n=6,870 records identified from databases:

- Medline (n = 1,935)
- Embase (n = 2, 159)
- CINAHL (n = 199)
- CENTRAL (n = 100)
- Scopus (n = 2,477)

From these, records removed before screening:

• duplicate records removed using Deduklick (n = 3,139)

n=3,731 records screened, of which n=3,651 were excluded, leaving n=80 papers sought for retrieval, of which n=0 were not retrieved.

n=2 studies were identified from a trial registry included at full text, of which n=0 were not retrieved.

Of the n=82 papers assessed for eligibility, n=82 reports were excluded:

- no comparator (n=6)
- not English Language (n=1)
- wrong intervention (n=7)
- wrong population (n =45)
- wrong publication type (n=3)
- wrong study type (n=20)

n=0 papers included in the review.

Annexe C. Excluded full texts

No comparator (6 studies)

Imauven and others. '<u>Paediatric and adult patients from New Caledonia Island admitted to the</u> <u>ICU for community-acquired Panton-Valentine leucocidin-producing *Staphylococcus aureus* <u>infections</u>' Scientific Reports 2022: volume 12, issue 1, article number 11,024</u>

Isendahl and others. '<u>Prevalence of community-acquired bacteraemia in Guinea-Bissau: an</u> <u>observational study</u>' BMC Infectious Diseases 2014: volume 14, article number 3,859

Kok and others. '<u>AsSOCIATION OF VANCOMYCin MIC and molecular characteristics with</u> <u>clinical outcomes in methicillin-susceptible *Staphylococcus aureus* acute hematogenous <u>osteoarticular infections in children</u>' Antimicrobial Agents and Chemotherapy 2018: volume 62, issue 5, page 5</u>

McGuire and others. '<u>Is Panton-Valentine leucocidin (PVL) toxin associated with poor clinical</u> <u>outcomes in patients with community-acquired *Staphylococcus aureus* bacteraemia?' Journal of Medical Microbiology 2023: volume 72, issue 4</u>

Neuner and others. '<u>Clinical, microbiologic, and genetic determinants of persistent methicillin-</u> resistant <u>Staphylococcus aureus bacteremia</u>' Diagnostic Microbiology and Infectious Disease 2010: volume 67, issue 3, pages 228 to 233

Qu and others. 'Epidemiological and clinical features of Panton-Valentine leukocidin-positive <u>Staphylococcus aureus bacteremia: a case-control study</u>' PLoS ONE [Electronic Resource] 2022: volume 17, issue 3, article e0265476

Not English language (one study)

Šimkovičová and others. '<u>Coagulase negative staphylococci isolated from haemocultures</u>' Epidemiologie, Mikrobiologie, Imunologie 2001: volume 50, issue 3, pages 117 to 120

Wrong intervention (7 studies)

Adhikari and others. 'Lower antibody levels to *Staphylococcus aureus* exotoxins are associated with sepsis in hospitalized adults with invasive *S. aureus* infections' Journal of Infectious Diseases 2012: volume 206, issue 6, pages 915 to 923

Alvarez and others. '<u>Nosocomial infections caused by community-associated methicillin-</u> <u>resistant *Staphylococcus aureus* in Colombia</u>' American Journal of Infection Control 2010: volume 38, pages 315 to 318

Blaine and others. '<u>Progression to bacteremia in critical care patients colonized with methicillin-</u> resistant <u>Staphylococcus aureus</u> expressing Panton-Valentine leukocidin' Diagnostic Microbiology and Infectious Disease 2010: volume 68, issue 1, pages 28 to 33

Chantratita and others. '<u>Comparison of community-onset Staphylococcus argenteus and</u> <u>Staphylococcus aureus sepsis in Thailand: a prospective multicentre observational study</u>' Clinical Microbiology and Infection 2016: volume 22, issue 5, pages 458.e411 to 459

Eshwara and others. '<u>Staphylococcus aureus bacteremia in an Indian tertiary care hospital:</u> observational study on clinical epidemiology, resistance characteristics, and carriage of the <u>Panton-Valentine leukocidin gene</u>' International Journal of Infectious Diseases 2013: volume 17, issue 11, e1051 to 1055

Gonzalez and others. '<u>Severe Staphylococcal sepsis in adolescents in the era of community-acquired methicillin-resistant *Staphylococcus aureus*' Pediatrics 2005: volume 115, issue 3, pages 642 to 648</u>

Knudsen and others. '<u>Increased age-dependent risk of death associated with lukF-PV-Positive</u> <u>Staphylococcus aureus bacteremia</u>' Open Forum Infectious Diseases 2016: volume 3, issue 4, ofw220

Wrong population (45 studies)

Calderwood and others. '<u>Staphylococcal enterotoxin P predicts bacteremia in hospitalized</u> patients colonized with methicillin-resistant *Staphylococcus aureus*' Journal of Infectious Diseases 2014: volume 209, issue 4, pages 571 to 577

Campbell and others. '<u>Clindamycin adjunctive therapy for severe *Staphylococcus aureus* treatment evaluation (CASSETTE): an open-labelled pilot randomized controlled trial' JAC-Antimicrobial Resistance 2022: volume 4</u>

Campo and others. '<u>Panton Valentine leukocidin exotoxin has no effect on the outcome of</u> <u>cancer patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections</u>' Medicine 2011: volume 90, issue 5, pages 312 to 318

Carrillo-Marquez and others. '<u>USA300 is the predominant genotype causing *Staphylococcus* <u>aureus septic arthritis in children</u>' Pediatric Infectious Disease Journal 2009: volume 28, issue 12, pages 1,076 to 1,080</u>

Chen and others. '<u>Differences between methicillin-resistant *Staphylococcus aureus* bacteremic isolates harboring type IV and type V staphylococcal cassette chromosome mec genes based on prior patient healthcare exposure' European Journal of Clinical Microbiology and Infectious Diseases 2010: volume 29, issue 12, pages 1539 to 1546</u>

Chen and others. '<u>Epidemiological and genetic diversity of *Staphylococcus aureus* causing <u>bloodstream infection in Shanghai, 2009-2011</u>' PLoS ONE [Electronic Resource] 2013: volume 8, issue 9, article e72811</u>

Chen and others. '<u>National surveillance of antimicrobial susceptibilities to ceftaroline,</u> <u>dalbavancin, telavancin, tedizolid, eravacycline, omadacycline, and other comparator</u> <u>antibiotics, and genetic characteristics of bacteremic *Staphylococcus aureus* isolates in adults: <u>results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART)</u> <u>program in 2020</u>' International Journal of Antimicrobial Agents 2023: volume 61, issue 4, 106745</u>

Colque-Navarro and others. '<u>Antibody response in *Staphylococcus aureus* septicaemia--a prospective study</u>' Journal of Medical Microbiology 1998: volume 47, issue 3, page 217 to 225

Crum and others. '<u>Fifteen-year study of the changing epidemiology of methicillin-resistant</u> <u>Staphylococcus aureus</u>' American Journal of Medicine 2006: volume 119, issue 11, pages 943 to 951

Davis and others. 'Epidemiology and outcomes of community-associated methicillin-resistant <u>Staphylococcus aureus infection</u>' Journal of Clinical Microbiology 2007: volume 45, issue 6, pages 1705 to 1711

Davis and others. '<u>A method for detection of anti-drug antibodies to a biotherapeutic (CSL112)</u> with endogenous counterpart (apolipoprotein A-I) using a novel sample pre-treatment electrochemiluminescence assay' Journal of Immunological Methods 2023: volume 513, 113411

Desachy and others. '<u>Role of superantigenic strains in the prognosis of community-acquired</u> <u>methicillin-susceptible</u> *Staphylococcus aureus* bacteraemia' Clinical Microbiology and Infection 2007: volume 13, pages 1,131 to 1,133

Doudoulakakis and others. '<u>Methicillin-resistant Staphylococcus aureus transmission and</u> <u>hospital-acquired bacteremia in a neonatal intensive care unit in Greece</u>' Journal of Infection and Chemotherapy 2022: volume 28, issue 2, pages 176 to 180

Ejlertsen and others. '<u>Epidemiology of toxic shock syndrome toxin-1 production in</u> <u>Staphylococcus aureus strains isolated in Denmark between 1959 and 1990</u>' Scandinavian Journal of Infectious Diseases 1994: volume 26, issue 5, pages 599 to 604

Fortunov and others. '<u>Community-acquired Staphylococcus aureus infections in term and near-term previously healthy neonates</u>' Pediatrics 2006: volume 118, issue 3, pages 874 to 881

Furuno and others. '<u>Community-associated methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis among HIV patients: a cohort study' BMC Infectious Diseases 2011: volume 11, article number 298</u>

Gopal Rao and others. '<u>Outbreak report of investigation and control of an outbreak of Panton-</u> Valentine leukocidin-positive methicillin-sensitive *Staphylococcus aureus* (PVL-MSSA) infection in neonates and mothers' BMC Infectious Diseases 2019: volume 19, issue 1, article number 178

Gosbell and others. '<u>Non-multiresistant methicillin-resistant *Staphylococcus aureus* bacteraemia in Sydney, Australia: emergence of EMRSA-15, Oceania, Queensland and Western Australian <u>MRSA strains</u>' Pathology 2006: volume 38, issue 3, pages 239 to 244</u>

Haji and others. 'Epidemiology of serious bacterial infection in febrile infants under 3 months of age and diagnostic management in Mayotte: Serious bacterial infection in febrile infants under 3 months of age in Mayotte' Archives de Pediatrie 2021: volume 28, pages 553 to 558

Horvath and others. '<u>Characterisation of antibiotic resistance, virulence, clonality and mortality in</u> <u>MRSA and MSSA bloodstream infections at a tertiary-level hospital in Hungary: a 6-year</u> <u>retrospective study</u>' Annals of Clinical Microbiology and Antimicrobials 2020: volume 19, issue 1, article number 17

Huang and others. '<u>Genomic characterization and outbreak investigations of methicillin-resistant</u> <u>Staphylococcus aureus in a county-level hospital in China</u>' Frontiers in Microbiology 2024: volume 15

Hulten and others. '<u>Analysis of invasive community-acquired methicillin-susceptible</u> <u>Staphylococcus aureus infections during a period of declining community acquired methicillin-</u> <u>resistant Staphylococcus aureus infections at a large children's hospital</u>' Pediatric Infectious Disease Journal 2018: volume 37, issue 3, pages 235 to 241

Jacobsson and others. '<u>Antibody responses in patients with invasive Staphylococcus aureus</u> <u>infections</u>' European Journal of Clinical Microbiology and Infectious Diseases 2010: volume 29, issue 6, pages 715 to 725

Jung and others. '<u>Emergence of Panton-Valentine leucocidin-positive ST8-methicillin-resistant</u> <u>Staphylococcus aureus (USA300 clone) in Korea causing healthcare-associated and hospital-</u> <u>acquired bacteraemia</u>' European Journal of Clinical Microbiology and Infectious Diseases 2016: volume 35, issue 8, pages 1,323 to 1,329

Kang and others. '*agr* functionality affects clinical outcomes in patients with persistent <u>methicillin-resistant</u> *Staphylococcus aureus* bacteraemia</u>' European Journal of Clinical Microbiology and Infectious Diseases 2017: volume 36, issue 11, pages 2,187 to 2,191

Katsarou and others. '<u>Fatality of Staphylococcus aureus infections in a Greek university</u> hospital: role of inappropriate empiric treatment, methicillin resistance, and toxin genes' presence' European Journal of Clinical Microbiology and Infectious Diseases 2020: volume 39, issue 3, pages 443 to 450

Lee and others. '<u>Outbreak among healthy newborns due to a new variant of USA300-related</u> <u>meticillin-resistant *Staphylococcus aureus*</u>' Journal of Hospital Infection 2014: volume 87, pages 145 to 151

Lee and others. '<u>Clinical features and risk factors of mortality for bacteremia due to community-onset healthcare-associated methicillin-resistant *S. aureus*' Diagnostic Microbiology and Infectious Disease 2013: volume 76, issue 1, pages 86 to 92</u>

Maeda and others. '<u>Analysis of staphylococcal toxins and clinical outcomes of methicillin-</u> <u>resistant *Staphylococcus aureus* bacteremia</u>' Biological and Pharmaceutical Bulletin 2016: volume 39, issue 7, pages 1,195 to 1,200

Nickerson and others. '<u>Factors predicting and reducing mortality in patients with invasive</u> <u>Staphylococcus aureus disease in a developing country</u>' PLoS ONE [Electronic Resource] 2009: volume 4, issue 8, article e6512

Nunez and others. '<u>Molecular and phylogenomic analysis of a vancomycin intermediate</u> resistance USA300LV Strain in Chile' Microorganisms 2024: volume 12, issue 7, page 25

Omid and others. '<u>Molecular epidemiology, virulence factors, antibiotic resistance and risk</u> factors for nasal carriage of *Staphylococcus aureus* in a teenage student population: high prevalence of oxacillin-susceptible MRSA isolates' Jundishapur Journal of Microbiology 2021: volume 14

Park and others. '<u>Community-associated MRSA strain ST72-SCCmecIV causing bloodstream</u> <u>infections: clinical outcomes and bacterial virulence factors</u>' Journal of Antimicrobial Chemotherapy 2015: volume 70, issue 4, pages 1,185 to 1,192

Petraitiene and others. '<u>Prevalence, clinical expression, invasiveness and outcome of</u> <u>Staphylococcus aureus containing Panton-Valentine leukocidin in children treated in a university</u> <u>hospital of Lithuania</u>' Infectious Diseases 2020: volume 52, issue 7, pages 464 to 472

Rose and others. '<u>Cytotoxic virulence predicts mortality in nosocomial pneumonia due to</u> <u>methicillin-resistant *Staphylococcus aureus*</u>' Journal of Infectious Diseases 2015: volume 211, issue 12, pages 1,862 to 1,874

Ruffin and others. '<u>Black and white patients with *Staphylococcus aureus* bacteremia have similar outcomes but different risk factors</u>' Clinical Infectious Diseases 2023: volume 76, pages 1,260 to 1,265

Scribel and others. '<u>Clinical and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* carrying SCCmecIV in a university hospital in Porto Alegre, Brazil' Diagnostic Microbiology and Infectious Disease 2009: volume 65, pages 457 to 461</u>

Sharma-Kuinkel and others. '<u>Associations of pathogen-specific and host-specific characteristics</u> with disease outcome in patients with <u>Staphylococcus aureus</u> bacteremic pneumonia' Clinical and Translational Immunology 2019: volume 8

Skiest and others. '<u>Community-onset methicillin-resistant *Staphylococcus aureus* in an urban <u>HIV clinic</u>' HIV Medicine 2006: volume 7, issue 6, pages 361 to 368</u>

Vallejo and others. '<u>Staphylococcus aureus central nervous system infections in children</u>' Pediatric Infectious Disease Journal 2017: volume 36, pages 947 to 951

Walraven and others. '<u>Site of infection rather than vancomycin MIC predicts vancomycin</u> <u>treatment failure in methicillin-resistant *Staphylococcus aureus* bacteraemia</u>' Journal of Antimicrobial Chemotherapy 2011: volume 66, issue 10, pages 2,386 to 2,392

Welsh and others. '<u>Clinical characteristics, outcomes, and microbiologic features associated</u> <u>with methicillin-resistant *Staphylococcus aureus* bacteremia in pediatric patients treated with <u>vancomycin</u>' Journal of Clinical Microbiology 2010: volume 48, issue 3, pages 894 to 899</u>

Welsh and others. '<u>Predictors of relapse of methicillin-resistant *Staphylococcus aureus* bacteremia after treatment with vancomycin' Journal of Clinical Microbiology 2011: volume 49, pages 3,669 to 3,672</u>

Wu and others. '<u>Comparison between patients under hemodialysis with community-onset</u> <u>bacteremia caused by community-associated and healthcare-associated methicillin-resistant</u> <u>Staphylococcus aureus strains</u>' Journal of Microbiology, Immunology and Infection 2013: volume 46, issue 2, pages 96 to 103

Zheng and others. '<u>Pharmacometric analyses to characterize the effect of CSL112 on</u> <u>apolipoprotein A-I and cholesterol efflux capacity in acute myocardial infarction patients</u>' British Journal of Clinical Pharmacology 2021: volume 87, issue 6, pages 2,558 to 2,571

Wrong publication type (3 studies)

<u>Successful treatment of Panton-Valentine leukocidin-positive methicillin-resistant</u> <u>Staphylococcus aureus pneumonia with high doses of linezolid administered in continuous</u> <u>infusion</u>Liu and others. '<u>Overview of panton-valentine leukocidin-expressing staphylococcus</u> <u>aureus pneumonia and its therapeutic strategy</u>' Advances in Biology 2022: volume 1, pages 123 to 151

<u>Community-associated meticillin-resistant</u> *Staphylococcus aureus* in injecting drug users and the homeless in south London

Wrong study type (20 studies)

Anderson and others. '<u>Community-associated methicillin-resistant Staphylococcus aureus</u>' U.S 2007: pages HS3 to HS12

Anpalagan and others. '<u>Does adjunctive clindamycin have a role in *Staphylococcus aureus* bacteremia? A protocol for the adjunctive treatment domain of the S. aureus Network Adaptive Platform (SNAP) randomized controlled trial' Clinical Infectious Diseases 2024: volume 27, pages 626 to 634</u>

Beaumont and others. '<u>Clinical impact and public health challenges of a PVL-MRSA</u> <u>bacteraemia outbreak amongst people who inject drugs in South Yorkshire, UK</u>' Access Microbiology 2024: volume 6, issue 2

Cunnington and others. '<u>Severe invasive Panton-Valentine Leucocidin positive Staphylococcus</u> <u>aureus infections in children in London, UK</u>' Journal of Infection 2009: volume 59, issue 1, pages 28 to 36

Darboe and others. '<u>Prevalence of Panton-Valentine leukocidin (PVL) and antimicrobial</u> resistance in community-acquired clinical *Staphylococcus aureus* in an urban Gambian hospital: <u>a 11-year period retrospective pilot study</u>' Frontiers in Cellular and Infection Microbiology 2019: volume 9, page 170

Dotel and others. '<u>CASSETTE-clindamycin adjunctive therapy for severe *Staphylococcus* aureus treatment evaluation: study protocol for a randomised controlled trial' Trials [Electronic Resource] 2019: volume 20, issue 1, article number 353</u>

Duckworth. '<u>Controlling methicillin resistant *Staphylococcus aureus*' British Medical Journal 2003: volume 327, pages 1,177 to 1,178</u>

Ellington and others. '<u>Is Panton-Valentine leucocidin associated with the pathogenesis of</u> <u>Staphylococcus aureus bacteraemia in the UK?</u>' Journal of Antimicrobial Chemotherapy 2007: volume 60, issue 2, pages 402 to 405

Gosbell. '<u>Managing MRSA infections in the community</u>' Medicine Today 2012: volume 13, pages 69 to 73

Hoppe and others. 'Severe infections of Panton-Valentine leukocidin-positive Staphylococcus aureus in children' Medicine 2019: volume 98, issue 38, e17185

Jones. '<u>Key considerations in the treatment of complicated staphylococcal infections</u>' Clinical Microbiology and Infection 2008: volume 14, pages 3 to 9

Levison and others. '<u>Community-associated methicillin-resistant Staphylococcus aureus:</u> reconsideration of therapeutic options' Current Infectious Disease Reports 2006: volume 8, pages 23 to 30

Maltezou and others. '<u>Community-acquired methicillin-resistant Staphylococcus aureus</u> infections' International Journal of Antimicrobial Agents 2006: volume 27, issue 2, pages 87 to 96

Mehra and others. '<u>Whole-genome sequencing links cases dispersed in time, place, and person</u> while supporting healthcare worker management in an outbreak of Panton-Valentine leucocidin meticillin-resistant *Staphylococcus aureus*; and a review of literature' Journal of Hospital Infection 2023: volume 141, pages 88 to 98

Miller and others. '<u>Necrotizing fasciitis caused by community-associated methicillin-resistant</u> <u>Staphylococcus aureus in Los Angeles</u>' New England Journal of Medicine 2005: volume 352, issue 14, pages 1,445 to 1,453

Nygaard and others. '<u>Fatal SARS-CoV-2-associated Panton-Valentine leukocidin-producing</u> <u>staphylococcal bacteremia: a nationwide multicenter cohort study</u>' Pediatric Infectious Disease Journal 2022: volume 41, issue 4, pages e142 to e145

Rojo and others. '<u>Community-associated Staphylococcus aureus infections in children</u>' Expert Review of Anti-Infective Therapy 2010: volume 8, pages 541 to 554

Salliot and others. '<u>Panton-Valentine leukocidin-producing *Staphylococcus aureus* infections: <u>Report of 4 French cases</u>' Scandinavian Journal of Infectious Diseases 2006: volume 38, pages 192 to 195</u>

Soderquist and others. '<u>Community-acquired pneumonia and bacteremia caused by an unusual</u> methicillin-resistant *Staphylococcus aureus* (MRSA) strain with sequence type 36,

staphylococcal cassette chromosome mec type IV and Panton-Valentine leukocidin genes' European Journal of Clinical Microbiology and Infectious Diseases 2006: volume 25, issue 9, pages 604 to 606

Tong and others. '<u>Community-associated methicillin-resistant Staphylococcus aureus skin</u> infections in the tropics' Dermatologic Clinics 2011: volume 29, pages 21 to 32

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation health secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

© Crown copyright 2025

Prepared by Georgia Towson, Stefano Brini, Jennifer Hill, Mikhailia McIntosh Maman, and Serena Carville.

For queries relating to this document, please contact: enquiries@ukhsa.gov.uk

Published: May 2025 Publication reference: GOV-18426 (CPHR29b)

Suggested citation: Towson G, Brini S, Hill J, McIntosh Maman M, Carville S. Effectiveness of antibiotics for Panton-Valentine leukocidin-positive *Staphylococcus aureus* (PVL-SA) associated bacteraemia: a rapid systematic review. UKHSA; 2025

OGL

You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. To view this licence, visit <u>OGL</u>. Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned.



UKHSA supports the UN Sustainable Development Goals

