THE LANCET Infectious Diseases

Supplementary webappendix

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Web appendix

Results

Pneumonia

Studies of pneumonia either prospectively investigated the role of PVL in a cohort of hospitalised patients or assessed the prevalence of PVL genes amongst heterogeneous isolates obtained from a hospital laboratory or reference unit. 11/12 studies reported the prevalence of PVL-positive strains amongst *S. aureus* pneumonia, two of which only enrolled children. The remaining study was a large case series.[1] Only three studies included more than 50 isolates in the analysis. The prevalence of PVL genes varied greatly in the eight studies of mainly adults with pneumonia, representing major regional differences in molecular epidemiology and heterogeneous study designs. In a study from Singapore only 0·3% of hospitalised patients with staphylococcal pneumonia were infected with PVL producing strains compared to 67% of specimens from community-onset infections referred to the French staphylococcal reference unit. Reference units receive highly biased samples from predominantly severe or unusual infections, whereas most included studies analysed samples submitted to the laboratory for routine diagnostic purposes, representing a spectrum of disease severity. However, even in hospital-based studies there was wide regional variation in the proportion of PVL-positive strains. Most studies used different inclusion criteria and without data on the proportion of infections that originated in the community and hospital settings, it is difficult to make comparisons between different studies. The two paediatric studies from China and America respectively reported 40% and 96% of MRSA pneumonias to contain the PVL genes, and almost all (92%) of the isolates in the American study were USA300.[2,3] Given that PVL-positive USA300 is endemic in the United States,[4] it is difficult to assess the role of PVL in these two studies independent of bacterial strain.

There were two studies of unselected *S. aureus* isolates from New Zealand and Singapore, both of which reported a negative association between PVL-positive strains and pneumonia compared to individuals with skin and soft tissue disease, although both these studies were small and did not reach statistical significance.[5,6] USA300 was the predominant clone in both studies from the United States, but outside of North America this strain was rare (3/3 studies).

Musculoskeletal infection

12 studies reported the prevalence of PVL-positive strains amongst *S. aureus* musculoskeletal infections. Six studies prospectively enrolled patients who were hospitalised or attending hospital with musculoskeletal disease,[7–12] three studies were from reference units,[13–15] and the remainder analysed isolates obtained from hospital microbiology laboratories.[5,16–18] Only three studies reported the prevalence of PVL genes amongst more than 50 isolates, reflecting the relative rarity of *S. aureus* musculoskeletal infection. In children PVL strains were highly prevalent (>70%) in three out of four studies of community onset infection, except in a study from the United States where PVL strains were less common amongst MRSA isolates (6/25) compared to MSSA strains (27/31).[17] The high prevalence was reported amongst both USA300 MRSA isolates in the United States,[8,16] and non-USA300 *S. aureus* isolates in a Tunisian study.[7] These four studies recruited a relatively homogeneous population of children with musculoskeletal infections, so differences in the proportion of MRSA strains producing PVL may be explained by geographical differences in molecular epidemiology or by different time periods, as the study reporting a comparatively low PVL gene prevalence was conducted before 2002. In adults the prevalence of PVL genes amongst *S. aureus* musculoskeletal disease ranged from 9-80%, in part explained by geographical differences in molecular epidemiology. Each of the four studies of adults attending or admitted to hospital were conducted in different continents,[9–12] and only one of these studies specified whether infection was community or hospital-acquired,[12] making it difficult to directly compare these studies. Estimates of PVL gene prevalence were similarly disparate (9-46%) from the four laboratory or reference unit based studies which all employed different inclusion criteria and study designs.[5,13,14,18]

In the single study of unselected isolates musculoskeletal infections caused by MSSA were less likely to be associated with PVL compared to skin and soft tissue disease (OR 0·48, 95% CI: 0·15-1·62).[5] Outside of the United States ST8 / USA300 was rare except in one study from the Finnish reference unit (30% USA300 variant).[13]

Bacteraemias

All 19 studies of bacteraemias sourced isolates from hospital laboratories or European reference units. Studies ranged in size from 65 to 474 isolates. European studies were mainly conducted at national or regional reference

units (four studies) or were hospital based (four studies). Although studies based at reference units are inherently biased because severe and unusual infections are over-represented we found good correlation between all European studies of bacteraemias with one exception. All studies reported a low (<2·5%) prevalence of PVL genes amongst *S. aureus* bacteraemias, except for a Spanish study where one third of MSSA strains produced PVL.[19] The Spanish study used a different sampling strategy collecting isolates from 21 hospitals, but it is unclear if specimens were systematically different to European reference unit or hospital based studies in terms of disease severity or the proportion defined as community-onset infection. Two studies from the United States investigated the relationship between PVL and infection-onset reporting high prevalence (>80%) of PVL genes amongst community-associated MRSA bacteraemias and lower prevalence (<30%) amongst healthcare-associated MRSA, almost entirely associated with USA300.[20,21] A further American study reported much lower prevalence (<20%) of PVL genes in both MRSA and MSSA strains, but did not specify whether infections were community or hospital-onset making it difficult to compare the estimates from this study. In three reports from Taiwan approximately one-third of community-acquired MRSA strains, [22,23] and 16% of healthcare-associated strains produced PVL.[24] The prevalence of PVL genes amongst *S. aureus* varied widely between the three remaining studies from Korea (0%), Australia (15%) and India (39%),[12,25,26] reflecting major geographical differences in molecular epidemiology and heterogeneous study designs.

Skin and soft tissue infections

Studies of skin and soft tissue infections either reported the prevalence of PVL genes amongst patients attending hospital (15 studies) or were laboratory-based investigating isolates from hospitals (21) or reference units (3 studies). One study was based in the community. 40 studies reported the prevalence of PVL strains amongst *S. aureus* skin and soft tissue infections in Europe (16), USA (10), Australia (7), Asia (5), Africa (2) and one global study. The prevalence of PVL genes amongst *S. aureus* skin and soft tissue infections in the European studies was heterogeneous ranging from <1% to >90%. This represents major differences in study design, inclusion criteria and sampling frame employed by these studies, precluding any attempt at an aggregate estimate of the association between PVL genes and skin and soft tissue infection by region. In five out of eight European studies of patients with comparatively severe skin and soft tissue disease attending or admitted to hospital, more than 70% of *S. aureus* specimens produced PVL.[27–31] Three of these studies only recruited patients with abscesses or furuncles,[27,28,30] and one study enrolled patients undergoing surgical drainage of SSTI.[29] The remaining three studies reported a lower PVL gene prevalence (12-21%) primarily amongst patients attending outpatient clinic with milder infections. In eight European studies based at hospital-laboratories and reference units the prevalence of PVL genes amongst *S. aureus* ranged from 21-51%, with the exception of a single cross-sectional study from France which reported less than 1% PVL gene prevalence amongst MRSA strains. This study included samples submitted to community laboratories which are likely to be derived from comparatively mild infections in comparison to specimens from more severe infections submitted to reference units and hospital laboratories. ST8 clones were identified in three out of seven studies and accounted for 13-33% of PVL strains from Germany,[32,33] and 33% of MRSA strains from France,[18] although typing was only conducted on a small number of isolates. This reflects the relative rarity of USA300/ST8 clones in Europe.[34]

In four studies of patients admitted to or attending hospital with skin and soft tissue infection in the United States more than 90% of *S. aureus* specimens produced PVL.[4,35–37] These studies were relatively homogeneous focusing on patients with acute purulent skin and soft tissue infections requiring surgery,[35,36] or attending the Emergency department.[4,37] More than 94% of MRSA isolates were classified as ST8/USA300 in the three studies where molecular typing was performed.[4,35,37] The prevalence of PVL genes was more variable amongst MRSA strains in the six laboratory-based studies from the United States, mainly due to differences in study design and inclusion criteria. Four out of six studies specified either community acquired or community onset infections, with PVL gene prevalence ranging from 33% (CO-MRSA) to 70-92% for CA-MRSA.[38–41] Of the two remaining studies, one was a clinical trial reporting a high prevalence (85%) of PVL-positive MRSA amongst SSTI isolates derived from an unspecified source, highly correlated with USA300.[42] The other study reported a relatively low (23%) prevalence of PVL genes amongst MRSA strains in a New York study of patients with skin and soft tissue infections.[43] Neither of these studies classified infection as community or hospital-onset making it difficult to draw comparisons with other studies.

Six studies were conducted in Australia, five of which were laboratory based studies of non-multiply resistant MRSA strains that were typically community-acquired,[44,45] or community-onset.[46–48] These studies used similar inclusion criteria with four out of five studies reporting high PVL gene prevalence (>80%). The fourth study based in Darwin reported 57% of MRSA strains to produce PVL. Compared to the other studies, a high

proportion of patients accessing Darwin hospital are indigenous Australians, so it is feasible that population differences underlie the variation in estimates of PVL gene prevalence. The remaining study investigated patients in the community with pyoderma reporting a relatively low prevalence of PVL genes (8%). PVL positive strains were rarely ST8/USA300. [44,46]

The five Asian studies from five different countries reported PVL prevalence ranging from 17-81%.[6,11,49–51] Geographical differences in molecular epidemiology and variation in study design and inclusion criteria make it difficult to draw comparisons between these estimates, particularly as the majority of studies did not distinguish between community and hospital onset infections. Two studies were conducted in Africa, one in Tunisia based at a single hospital (PVL gene prevalence 21%) and a further study which included samples from five African countries (PVL gene prevalence 56%). USA300/ST8 was rare amongst PVL strains in Asia and Africa, although data on bacterial strain was limited.

Odds ratios comparing skin and soft tissue infections to all other infection types could be calculated in ten European studies, nine of which demonstrated a clear association between PVL and skin and soft tissue disease. The strength of association was highly variable and mainly dependent on the comparator population. Four studies comparing skin and soft tissue isolates to diverse clinical specimens submitted to the hospital laboratory reported the odds of infection with a PVL-positive strain to be three to five times greater in patients with skin and soft tissue disease compared to all other manifestations of *S. aureus*.[18,52–54] By contrast the odds of infection with a PVL-positive strain were twenty times greater in those with skin and soft tissue infection when the comparator group was bacteraemias,[55] because PVL genes are rare amongst bacteraemias in Europe, see Table 3. Abscesses and furuncles were strongly associated with PVL in all included European studies (OR range: 17-140) with the strength of association largely dependent on the study design and comparator population.[13,14,27,55,56] Odds ratios could only be calculated for two studies from the USA which found the odds of PVL-positive infection to be seven times greater in abscesses compared to other types of skin and soft tissue infections,[41] and in skin and soft tissue infections compared to bloodstream infections.[43] PVL strains are not rare amongst bacteraemias in the United States, so using bacteraemias as the comparator group has less impact, highlighting the importance of geographical differences in molecular epidemiology. Two studies from New Zealand and Australia reported an association between skin and soft tissue infections and PVL genes, although the magnitude of the association varied (range 6·8-10·0), partly due to different study designs and comparator populations.[5,48] A further study suggested that the odds of PVL-positive infection were double in patients with skin and soft tissue infections, although failed to reach statistical significance.[47] Two Australian studies compared furuncles and abscesses respectively to other types of *S. aureus* skin infection reporting a strong association between PVL and furuncles (OR 40·0, 95% CI: 9·5-167·8), and abscesses (OR 12·1, 95% CI: 7·1-20·7).[46,47] Odds ratios could be calculated for four out of five studies from Asia which reported the odds of PVL-positive infection to be between four and eight times greater in patients with skin and soft tissue infection compared to other types of *S. aureus* infection.[6,11,49,50] These studies were all based at a single hospital and compared skin and soft tissue specimens to diverse clinical isolates submitted to the same laboratory. Only one study from Hong Kong classified infections as community or hospital-onset. Conversely both African studies failed to find an association between PVL and skin infections, which may be explained by differences in the proportion of infections sampled in Africa.[9] Three Asian or African studies included data on abscesses and/or furuncles all of which reported a strong but variable association with PVL (OR range 7·2-17·4) when compared to other manifestations of *S. aureus* disease.[6,11,57]

Overall eight studies included unselected *S. aureus* isolates, including samples from primary care. Five of these studies included sufficient information to calculate odds ratios comparing skin infections to all other types of *S. aureus* infection. In four out of five of these studies there was a clear association between PVL and skin and soft tissue infections when compared to all other types of *S. aureus* infection, (OR range: 3·4-6·8).[5,6,53,54]

Colonisation

There were five studies from Europe, two from the United States, two from Australia and New Zealand, eleven from Asia, and one from Africa. In Europe the prevalence of PVL genes in nasal specimens from healthy adults and children was low (<1%) in four studies,[30,58–60] whereas in a single study from Greece 8·2% of children were colonised with PVL-positive *S. aureus*.[31] This is consistent with previous research suggesting PVL-positive infections are relatively common in Greece compared to most of Europe.[61] In the United States National Health and Nutrition Examination Survey (NHANES) PVL genes were more frequently identified in MRSA (6/75) than MSSA isolates (3/297).[62] By contrast in a study of healthy children 16% of *S. aureus* specimens produced PVL.[63] Regional differences in molecular epidemiology or sampling over different time periods are possible explanations for this disparity. The remaining 13 studies were conducted in Australia, New Zealand, Taiwan (four studies), Indonesia, Malaysia, Korea and Gabon. The prevalence of PVL genes varied widely between and

within countries which may be partly explained by differences in the proportion of patients with healthcare contact, different populations and indigenous communities, regional variation in molecular epidemiology and varying study designs. Most studies reported the prevalence of PVL genes amongst MSSA strains with the exception of two studies in Taiwanese children, where PVL genes were present in approximately one third of MRSA colonising strains.[64,65]

Discussion

We have compared the proportion of *S. aureus* pneumonia, bacteraemias, musculoskeletal infections and colonisation associated with strains carrying PVL genes to skin and soft tissue disease to assess the relationship between PVL, colonisation, disease and outcome and acknowledge that without population-based studies it is impossible to know what absolute proportion of PVL-positive specimens are associated with colonisation and mild, moderate and invasive disease. We used meta-analysis to combine studies which were heterogeneous in terms of study design and acknowledge that this will have introduced bias into the summary estimates we derived, despite sensitivity analyses. Skin and soft tissue infections were chosen as the largest and most homogenous comparator group for all epidemiological analyses, but as each study used different or unstated inclusion criteria and often used different sampling frames for disease and skin and soft tissue isolates, it is difficult to assess the impact of bias on our estimates. In particular the proportion of infections classified as community and hospital-onset may have differed between disease and comparator skin and soft tissue infections, introducing selection bias with regard to community versus hospital-onset of disease. We excluded studies from meta-analysis where disease and comparator isolates were sampled differently, and compared our summary estimates to the subset of samples that had directly compared community-onset infections to community-onset skin and soft tissue disease to try and assess the impact of selection bias.

Laboratory sampling is biased towards more severe cases and this is likely to be most acute for skin and soft tissue infections, which are common, strongly associated with PVL, and are rarely sampled and sent for microbiological testing because most infections are mild.

Table 1. Studies reporting prevalence of PVL genes in *S. aureus* (SA) pneumonia

Author	Location	Year	Study setting	Inclusion criteria and provenance of pneumonia isolates	Prevalence of PVL genes (%) amongst *S. aureus*[1] isolates, healthcare-associated (HA), community-associated (CA) or community-onset (CO)	Comparator population of skin and soft tissue infections (SSTI)	Odds of infection with PVL-positive strain comparing pneumonia to skin & soft tissue infection OR (95% CI)[2]	Proportion of PVL strains identified as ST8 / USA300 (%)
Studies in children								
Carillo-Marquez (3)	USA	2001-09	Texas hospital	Children admitted to hospital with SA pneumonia. 79% community-acquired pneumonia.	79/82 (96.3) MRSA; 26/28 (92.3) MSSA	No comparator	No comparator data	75/82 (92) USA300 MRSA; 14/28 (50) USA300 MSSA
Geng (2)	China	2006-08	8 regional hospitals	Hospitalised children with community-acquired pneumonia.	22/55 (40.0) CA-MRSA	No comparator	No comparator data	N/A[3]
Studies in adults								
Badiou (18)	France		Lyon hospital	Patients with SA pneumonia in Lyon. Infection onset not specified.	6/18 (33.3) SA	144 pus samples from 6 countries.	0.63 (0.22-1.76)	0
Holmes (56)	England & Wales	2002-03	Reference unit	SA pneumonia specimens submitted to the reference unit. Infection onset not specified.	4/37 (10.9) SA	63 skin and soft tissue isolates submitted to reference unit.	0.39 (0.12-1.27)	0
Hsu* (6)	Singapore	2004	Singapore Hospital	Specimens submitted to hospital laboratory from adults with SA pneumonia. Community or hospital onset not specified.	1/30 (0.3) SA	95 specimens from adults with SSTI submitted to hospital laboratory contemporaneously.	0.17 (0.02-1.34)	N/A
Johnsson (52)	Sweden	1999-02	Orebro Hospital	SA isolates from patients in a prospective study of pneumonia aetiology. Community or hospital onset not specified.	2/23 (8.7) SA	43 specimens from patients attending hospital with SSTI. 73 isolates from severe or unusual SSTI's.	0.55 (0.12-2.58)	N/A
Lina (14)	France	1985-98	Reference unit	Pneumonia specimens submitted to reference unit. 68% community-acquired infection.	23/40 (57.5) SA; 0/13(0) HA-SA 27/40 (67.5) CA-SA	74 reference unit specimens from pyogenic infections. Onset of infection not stated.	1.28 (0.59-2.78)	N/A
Muttaiyah* (5)	New Zealand		Auckland hospital	Pneumonia specimens submitted to hospital laboratory. Community or hospital onset not specified.	2/11 (18.2) MSSA	234 SSTI specimens submitted to hospital laboratory contemporaneously.	0.24 (0.05-1.14)	N/A
Nickerson (11)	Thailand	2006-07	Sappasithipra-song hospital	Patients attending hospital with *S. aureus* pneumonia. Community or hospital onset not specified.	5/11 (45.5) SA	Specimens from patients attending hospital contemporaneously with SSTI.	0.44 (0.13-1.50)	N/A
Peyrani (66)	USA	2008-10	4 hospitals	Isolates from patients with hospital-acquired or ventilator-assisted pneumonia	29/109 (26.6) HA-MRSA	No comparator	No comparator data	29/29 (100) USA300
Wehrhahn (12)	Australia		Perth & Fremantle hospitals	Hospitalised patients with community-onset pneumonia.	5/22 (22.7) CO-SA	49 specimens from patients admitted with community-onset abscess, cellulitis or necrotising fasciitis.	0.26 (0.08-0.82)[4]	ST8-MRSA-IV less than 5%[5]

*Study of unselected isolates which included all *S. aureus* specimens submitted to laboratory

[1] Prevalence of PVL-positive strains amongst *S. aureus* (SA), meticillin-resistant (MRSA) or meticillin-sensitive strains (MSSA)

[2] Odds ratio and 95% confidence interval

[3] Not applicable

[4] Less than 50 isolates of comparator skin and soft tissue infections. Skin and soft tissue data used to calculate odds ratios but excluded from tables 4 and 5

[5] For entire study, data unavailable for pneumonia isolates alone

Table 2. Studies reporting the role of PVL genes in staphylococcal musculoskeletal infections (MSI)

Author	Location	Year	Study setting	Inclusion criteria and provenance of samples	Prevalence of PVL genes (%) amongst healthcare-associated (HA), community-associated (CA) or community-onset (CO) *S. aureus*[1]	Comparator population of skin and soft tissue infections (SSTI)	Odds of infection with PVL-positive SSTI, OR (95% CI)[2]	Proportion of PVL strains identified as ST8/USA300 (%)
Abdel-Haq (8)	USA	2006-07	Michigan hospital	Hospitalised children with community-onset bone and joint infections.	20/22 (90.9) CO-MRSA	43 specimens from hospitalised children with SSTI. 98% community-onset.	0.49 (0.06-3.72)[3]	20/20 (100) USA300 MRSA
Badiou (18)	France		Lyon hospital	Patients with SA bone and joint infections in Lyon. Community or hospital onset not specified.	2/23 (8.7) SA	144 pus samples from 6 countries.	0.12 (0.03-0.53)	0
Breurec (9)	Africa	2007-08	Dakar	Patients hospitalised with myositis or osteomyelitis. Community or hospital onset not specified.	31/36 (86.1) MSSA	119 specimens from hospitalised patients with SSTI.	2.37 (0.76-7.42)[3]	Less than 5% ST8[4]
Dailiana (10)	Greece	2003-06	Thessalia hospital	Patients with MSI attending hospital. 85% community-onset.	58/81 (71.6) MRSA	No comparator	No data	0
Kanerva (13)	Finland	2004-06	Reference unit	Isolates from patients with bursitis or arthritis submitted to reference unit and defined as community-acquired.	5/11 (45.5) CA-MRSA	SSTI specimens submitted to reference unit defined as community-acquired.	0.97 (0.28-3.32)	33/90 (37%) ST8 MRSA-IV[9]
Kechrid (7)	Tunisia	2006-08	Tunis hospital	Children attending hospital with community-acquired osteomyelitis.	11/12 (91.7) CA- SA	No comparator	No data	0
Lina (14)	France	1985-98	Reference unit	Osteomyelitis specimens submitted to reference unit. Community or hospital onset not specified.	3/13 (23.1) SA	74 specimens from pyogenic infections submitted to reference unit.	0.28 (0.07-1.12)	N/A[5]
Martinez-aguilar (17)	USA	2000-02	Texas hospital	Children with community-acquired MSI.	6/25 (24.0) CA-MRSA 27/31 (87.1) CA-MSSA	No comparator	No data	N/A
Muttaiyah* (5)	New Zealand	2008	Auckland hospital	Specimens from bone or joint infections submitted to hospital laboratory. Infection onset not specified.	4/13 (30.8) MSSA	234 SSTI specimens submitted to hospital laboratory contemporaneously.	0.48 (0.15-1.62)	N/A
Nickerson (11)	Thailand	2006-07	Sappasithiporn-song hospital	Patients attending hospital with bone or joint infection. Community or hospital onset not specified.	12/25 (48.0) SA	Specimens from patients attending hospital with abscess or SSTI.	0.49 (0.21-1.14)	N/A
Pannaraj (16)	USA	2000-05	Texas hospital	Children hospitalised with community-acquired pyomyositis or myositis.	17/24 (70.8) CA-SA	No comparator	No data	13/13(100) USA300 MRSA; 1/9 (11) USA300 MSSA
Wehrhahn (12)	Australia		Perth & Fremantle hospitals	Consecutive hospitalised patients with community-onset invasive bone or joint infection.	14/76 (18.4) CO-SA	49 specimens of community-onset abscess, cellulitis or necrotising fasciitis.	0.20 (0.09-0.45)[8]	ST8-MRSA-IV less than 5%[9]

*Study of unselected isolates which included all *S. aureus* specimens submitted to laboratory

[1] Prevalence of PVL-positive strains amongst *S. aureus* (SA), meticillin-resistant (MRSA) or meticillin-sensitive strains (MSSA)

[2] Odds ratio and 95% confidence interval

[3] Less than 50 isolates of comparator skin and soft tissue infections. Skin and soft tissue data used to calculate odds ratios but excluded from tables 4 and 5

[4] Refers to entire study, data unavailable for bone, joint and muscle infections alone

[5] Not applicable

Table 3. Studies reporting the role of PVL genes amongst staphylococcal blood-stream infections (BSI)

Author	Location	Year	Study setting	Inclusion criteria and provenance of BSI samples	Prevalence of PVL genes (%) amongst healthcare-associated (HA) , community-associated (CA) or community-onset (CO) *S. aureus*[1]	Comparator population of skin and soft tissue infections (SSTI)	Odds of infection with PVL-positive strain comparing BSI to SSTI, OR (95% CI)[2]	Proportion of PVL strains identified as ST8/USA300 (%)
Budimir	Croatia	2001-02	10 hospitals in 7 cities	Hospital-acquired BSI isolates collected as part of EARSS[3].	0/82 (0) HA- MRSA	No comparator	No comparator	N/A
Chen (22)	Taiwan	2001-07	National Taiwan hospital	Adults treated in the Emergency department with community-acquired MRSA SCCmec IV or V.	43/115 (37.4) CA-MRSA	No comparator	No comparator	N/A
Chua (21)	USA	2005-07	Henry Ford hospital, Detroit	MRSA isolates from adults patients submitted to hospital laboratory. 24% community-associated BSI.	40/50 (80.0) CA-MRSA; 36/160 (22.5) HA-MRSA	No comparator	No comparator	74/76 (97) USA300
Couppie (55)	France		Strasbourg university hospital	BSI specimens from patients attending hospital. Community or hospital onset not specified.	1/87 (1.1) SA	184 SSTI specimens from patients attending hospital.	0.04 (0.006-0.32)	N/A
D'Souza (26)	India	2006-9	Mumbai hospital	BSI specimens from hospital and community patients in Mumbai.	20/51 (39.2) MRSA	No comparator	No comparator	N/A
Ellington (67)	UK & Ireland	2005	Reference unit	Isolates from hospitalised patients with BSI from 25 centres. Community or hospital onset not specified.	0/88 (0)MRSA	No comparator	No PVL strains	N/A
Holmes (56)	England & Wales	2002-03	Reference unit	Specimens from patients with SA BSI submitted to the reference unit. Community or hospital onset not specified.	1/65 (1.6) MSSA	63 SSTI isolates submitted to reference unit.	0.05 (0.006-0.39)	0
Huang (24)	Taiwan	1999-05	Taiwan university hospital	Random selection of health-care associated MRSA isolates submitted to hospital laboratory from patients with BSI.	11/69 (16.0) HA-MRSA	No comparator	No comparator	N/A
Johnsson (52)	Sweden	1999-02	Orebro University hospital	Specimens from hospitalised patients with BSI submitted to the hospital laboratory. Community or hospital onset not specified.	1/65 (1.6) SA	116 specimens from patients attending hospital with SSTI.	0.09 (0.01-0.70)	N/A
Kaltsas (43)	USA		Montefiore Medical centre	BSI specimens submitted to hospital laboratory. Community or hospital onset not specified.	2/45 (4.4) MSSA 9/54 (16.7) MRSA	101 specimens from SSTI submitted to laboratory.	0.11 (0.05-0.23)	N/A
Mee-marquet (68)	France	2003	Regional reference unit	BSI specimens from patients attending 31 hospitals with BSI. 35% community-acquired BSI.	0/69 (0) SA	No comparator	No PVL strains	No PVL strains
Melles (58)	Netherlands		University Medical Centre, Rotterdam	BSI isolates from patients in the Rotterdam area. Community or hospital onset not specified.	3/146 (2.1) MSSA	18 SSTI specimens collected contemporaneously.	0.03 (0.007-0.15)[4]	N/A
Peck (25)	Korea	2006	Samsung medical	BSI submitted to hospital laboratory.	0/70 (0) SA	No comparator	No PVL strains	No PVL strains

[1] Prevalence of PVL-positive strains amongst *S. aureus* (SA), meticillin-resistant (MRSA) or meticillin-sensitive strains (MSSA)

[2] Odds ratio, 95% confidence interval

[3] European Antimicrobial Resistance Surveillance System

[4] Less than 50 isolates of comparator skin and soft tissue infections. Skin and soft tissue data used to calculate odds ratios but excluded from tables 4 and 5

			centre, Seoul	Community or hospital onset not specified.				
Perez-Vazquez (19)	Spain	2006-7	21 hospitals	BSI specimens submitted to central laboratory. 33% community-onset BSI.	41/113 (36.3) MSSA; 1/90 (1.11) MRSA	No comparator	No comparator	1/42 ST8
Rossney (69)	Ireland	2003	28 hospitals	BSI isolates submitted to reference unit from hospitals participating in EARSS.[13]	2/474 (0.6%) MRSA	No comparator	No comparator	0
Seybold (20)	USA	2004	Grady memorial hospital, Atlanta	BSI specimens submitted to hospital laboratory. 58% community-onset BSI.	9/9 (100.0) CA-MRSA 30/107(28.0) HA-MRSA	No comparator	No comparator	USA300 (100%)
Von Eiff (70)	Germany	1993-94	Munster hospital	BSI specimens from hospitalised patients in 32 centres. Community or hospital onset not specified.	2/219 (0.9) MRSA	No comparator	No comparator	N/A
Wang (23)	Taiwan	2002-05	National Taiwan hospital	Community-acquired BSI specimens from adults submitted to hospital laboratory, defined on antibiotic susceptibility.	32/100 (32.0) CA-MRSA	No comparator	No comparator	N/A
Wehrhahn (12)	Australia		Perth & Fremantle hospitals	Hospitalised patients with community-onset BSI.	10/66 (15.2) CO-SA	49 specimens from hospital patients with community-onset severe SSTI.	0.16 (0.07-0.38)14	ST8-MRSA-IV less than 5%[1]

[1] Refers to entire study, data unavailable for BSI isolates alone

Table 4. Studies assessing prevalence of PVL genes amongst skin and soft tissue infections (SSTIs)

Author	Location	Year	Study setting	Inclusion criteria and provenance of samples	Prevalence of PVL genes (%) amongst healthcare-associated (HA) , community-associated (CA) or community -onset (CO) *S. aureus*[1]	Comparator population	Odds of infection with PVL-positive strain for SSTI versus comparator population, OR (95% CI)[2]	Proportion of PVL strains identified as ST8/USA300 (%)
Badiou (18)	France		Lyon hospital	Pus specimens from 6 countries. Community or hospital onset not specified.	64/144 (44.4) SA	41 specimens from patients with SA pneumonia or bone and joint infection.	3.30 (1.43-7.64)[3]	8/24 (33) ST8 MRSA; 2/40 (5) ST8 MSSA
Couppie (55)	France		Strasbourg university hospital	1) Patients attending hospital with skin infections. Infection onset not specified.	39/184 (21.1) SA	Specimens from 87 patients attending hospital with BSI.	23.13 (3.12-171.40)	N/A
				2) Patients attending hospital with abscess or furuncle. Infection onset not specified.	36/126 (28.6) SA	Specimens from 134 patients attending hospital with SSTI and 87 patients with BSI excluding abscess or furuncle.	139.5 (43.48-447.61)	N/A
Del Giudice (28)	France	2003-08	Frejus hospital	Patients attending hospital with skin abscesses. Community or hospital onset not specified.	40/57 (70.2) SA	No comparator.		N/A
Del Guidice (27)	France	2003-10	Frejus hospital	Patients attending hospital with abscess or furuncle. Infection onset not specified.	72/80 (90.0) SA	Patients attending hospital with SSTI excluding abscess or furuncle.	44.64 (19.13-104.18)	N/A
Holmes (56)	England & Wales	2002-03	Reference unit	1) SSTI isolates submitted to the reference unit. Infection onset not specified.	15/63 (23.8) SA	407 diverse clinical isolates submitted to reference unit.	15.59 (6.28-38.68)	0
				2) Specimens from abscesses submitted to the reference unit. Infection onset not specified.	7/16 (43.8) SA	454 diverse clinical specimens excluding abscesses.	21.29 (7.04-64.4)	0
Issartel (29)	France	2002	Gaston Bourret hospital, New Caledonia	Patients admitted for drainage of community-onset soft tissue infections.	48/52 (92.3) CA-SA	No comparator	No comparator data	N/A
Jappe (33)	Germany	2003-05	University of Heidelberg	Patients attending outpatients with abscess or furuncle. Infection onset not specified.	20/108 (18.5) SA	Patients with SSTI excluding abscess or furuncle.	21.25 (6.38-70.82)	
Johnsson (52)	Sweden	1999-02	Orebro University hospital	Patients attending hospital with SSTI. Community or hospital-onset not specified.	17/146 (11.6) SA	88 specimens from hospitalised patients with BSI or pneumonia.	4.87 (1.38-17.17)	N/A

[1] Prevalence of PVL-positive strains amongst *S. aureus* (SA), meticillin-resistant (MRSA) or meticillin-sensitive strains (MSSA)
[2] 95% confidence interval
[3] Comparator sample contained less than 50 isolates

Kanerva (13)	Finland	2004-06	Reference laboratory, Helsinki	1) Community-acquired SSTI specimens submitted to reference unit	72/156 (46.2) CA-MRSA	Diverse clinical specimens submitted to reference unit, defined as community-acquired.	2.14 (0.96-4.76)18	33/90 (37%) ST8 MRSA-IV[1]
				2) Specimens from community-acquired abscesses submitted to reference unit.	54/65 (83.1) MRSA	Community-acquired mixed clinical specimens submitted to reference lab, excluding abscesses.	17.18 (7.94-37.20)	
Lina (18)	France	1985-98	Reference unit	1) Specimens from pyogenic infections submitted to reference unit. Infection onset not specified.	38/74 (51.4) SA	Diverse clinical specimens submitted to reference laboratory.	2.92 (1.54-5.54)	N/A
				2) Specimens from abscess and furuncles submitted to reference unit. Infection onset not specified.	28/30 (93.3) SA	Mixed clinical specimens submitted to reference laboratory, excluding furuncles.	41.2 (9.35-181.73)	
Masiuk (30)	Poland	2002-08	Pomeranian University, Szczecin	Patients with furunculosis attending hospital. Infection onset not specified.	64/74 (86.5) SA	No comparator	No comparator data	N/A
Maugat *(71)	France	2003	Labville network of 69 laboratories	SSTI isolates submitted to laboratory. Infection onset not specified.	1/142 (0.7) MRSA	No comparator	No comparator data	0
Monecke (32)	Germany		University of Dresden	Consecutive SA isolates from skin infections. Infection onset not specified.	30/100 (30.0) SA	No comparator	No comparator data	1/3 (33) USA300 MRSA
Sdougkos (31)	Greece	2005-06	Karamandaneion & Patras hospitals	Hospitalised children with community-acquired SSTI.	81/96 (84.4) CA-SA	No comparator	No comparator data	0 MRSA
Shallcross * (53)	England	2007	Royal Free Hospital, London	SSTI isolates submitted to hospital laboratory. Infection onset not specified.	22/106 (20.8) SA	Diverse clinical specimens submitted to hospital laboratory.	4.38 (2.20-8.73)	N/A
Vorobieva* (54)	Russia	2004	Regional hospital in Arkhangelsk	SSTI isolates submitted to hospital laboratory. Infection onset not specified.	34/66 (51.5) SA	Diverse clinical specimens submitted to hospital laboratory.	3.36 (1.19-9.49)[2]	0
United States of America								
Bhattacharya * (38)	USA	2000-02	San Francisco & Stanford Hospitals	Randomly selected community-onset SSTI specimens from adults submitted to hospital laboratory.	91/277 (32.9) CO-MRSA	No comparator	No comparator data	34/91 (37) USA300
Crum* (39)	USA	1990-04	US military clinic and hospital, San Diego	Subset of SSTI submitted to laboratory. 62% community-onset SSTI.	93/134 (69.4) CA-MRSA; 0/85 (0) HA-MRSA	No comparator	No comparator data	69/93 (74) ST8

[1] Refers to entire study

* Study of unselected isolates which included all S. aureus specimens submitted to laboratory

[2] Comparator sample contained less than 50 isolates

Davies (42)	USA		Worldwide clinical trial	Part of clinical trial of patients with a complicated skin infection. Infection onset not specified.	196/231 (84.8) MRSA	No comparator	No comparator data	>95% USA300
Faden (35)	USA	2006-8	Buffalo hospital, New York	Specimens from children with abscesses requiring surgery.	59/60 (98.3) SA	No comparator	No comparator	57/59 (97) USA300
Frazee (37)	USA	2003-04	Alameda county medical centre, California	Patients with SSTI attending the emergency department. 76% community-acquired SSTI.	80/85 (94.1) MRSA	No comparator	No comparator data	76/80 (95) ST8
Gupta (40)	USA	2004-6	Yale New Haven hospital	Patients with CA-MRSA defined on susceptibility to specified antibiotics.	73/79 (92.4) CA-MRSA	No comparator	No comparator	Cannot calculate
Jahamy (41)	USA	2005-06	St. John hospital, Michigan	Specimens from patients admitted to hospital with soft tissue foci of infection. 74% community-acquired SSTI.	82/99 (82.9) CA-MRSA; 3/44 (6.8) CA-MSSA; 11/33(33.3) HA-MRSA; 0/18 (0) HA-MSSA	Specimens from patients with soft tissue foci of infection excluding abscesses.	7.46 (3.95-14.07)	N/A
Kaltsas (43)	USA		Montefiore medical centre	Specimens from patients with SSTI. Infection onset not specified.	37/58 (63.8) MSSA; 10/43 (23.3) MRSA	Specimens from 99 patients with BSI.	6.96 (3.32-14.58)	7/10 USA300 MRSA
Moran (4)	USA	2004	Emergency Departments in 11 cities	Adults with purulent SSTIs of less than one week's duration attending the Emergency department. Infection onset not specified.	213/218 (97.7)MRSA; 23/55 (41.8) MSSA	No comparator	No comparator data	212/213 (100) USA300 MRSA; 17/17 (100) USA300 MSSA
Rajendran (36)	USA	2004-05	ISIS clinic, San Francisco	Adults with a surgically drainable abscess. Infection onset not specified.	80/86 (93.0) MRSA	No comparator	No comparator data	N/A
Australia & New Zealand								
Costello (44)	Australia	2008-09	Queensland medical laboratory	Community-acquired SSTI specimens from adults, (defined as non-multi drug-resistant MRSA) submitted to hospital laboratory.	233/238 (97.9) CA-MRSA	No comparator	No comparator data	7/223 (3) USA300
Gubbay (45)	Australia	2001-02	Westmead hospital Sydney	Specimens from children with Gentamicin -sensitive MRSA submitted to hospital laboratory. 98% community-acquired SSTI.	51/59 (86.4) CA-MRSA	No comparator	No comparator data	0
McDonald (72)	Australia	2004-05	3 remote communities in the Northern territory	Patients with pyoderma resident in community.	19/239 (7.9) CO-SA	No comparator	No comparator data	N/A
Munckhof (48)	Australia	2004-05	Eight hospitals in south-west Queensland	Clinical isolates of non-multi-resistant MRSA, multi-resistant MRSA and MSSA SSTI submitted to	79/96 (82.3) CO-MRSA	44 specimens from BSI and pulmonary infections submitted to hospital laboratory contemporaneously.	9.96 (4.37-22.67)[20]	N/A

				hospital laboratory. Infection onset not specified.				
Muttaiyah * (5)	New Zealand	2008	Auckland hospital	Clinical MSSA isolates. Infection onset not specified.	112/234 (47.9) MSSA	101 specimens from diverse clinical isolates submitted to hospital laboratory.	6.81 (3.54-13.11)	N/A
Nimmo (46)	Australia	2008	Hospitals in Queensland	Community-onset non-multi resistant furunculosis isolates.	115/117 (98.3) CO-MRSA	182 diverse isolates (90% SSTI) from community-onset non-multi-resistant specimens submitted to laboratory contemporaneously.	40.00 (9.54-167.80)	2/207 (1) USA300 variant[1]
Tong (48)	Australia	2006	Royal Darwin hospital, Northern Territory	1) SSTI specimens of non-multiresistant MRSA (nmMRSA) and MSSA	121/212 (57.1) CO-MRSA; 89/207 (43.0)MSSA	40 specimens of pneumonia and BSI submitted to laboratory contemporaneously.	1.87 (0.95-3.67)[2]	N/A
				2) Abscess specimens of non-multiresistant MRSA (nmMRSA) and MSSA.	64/72 (88.9) CO-MRSA; 46/57 (80.7) MSSA	349 Non-multiresistant MRSA (nmMRSA) and MSSA SSTI specimens submitted to laboratory contemporaneously, excluding abscesses.	12.09 (7.07-20.67)	
Asia and Africa								
Breurec (9)	Africa		5 hospitals in Madagascar, Morocco, Niger, Senegal, Cameroon	Hospitalised patients with SSTI. Community or hospital-onset not specified.	67/119 (56.3) MSSA	109 diverse clinical specimens submitted to hospital laboratories contemporaneously.	0.94 (0.56-1.59)	Less than 5% ST8[3]
Cheung (49)	Hong Kong	2006	Hong Kong reference laboratory	CA-MRSA SSTI isolates submitted to laboratory.	37/83 (44.6) CA-MRSA	57 diverse specimens of CA-MRSA submitted to laboratory contemporaneously.	8.36 (3.03-23.07)	0
Hsu (6)*	Singapore	2004	Singapore General Hospital	SSTI specimens from adults submitted to hospital laboratory. Infection onset not stated.	16/95 (17%) SA	68 Diverse specimens from adults submitted contemporaneously to hospital laboratory.	4.39 (1.23-15.72)	N/A
				Abscess specimens from adults submitted to hospital laboratory. Infection onset not stated.	14/34 (41.2) SA	129 diverse specimens from adults submitted contemporaneously to hospital laboratory, excluding abscesses.	17.36 (5.64-53.5)	
Lo (50)	Taiwan	2003-05	Triservice hospital, Taipei	SSTI specimens from hospitalised children submitted to laboratory. Infection onset not stated.	54/67 (80.6) SA	72 diverse specimens from hospitalised children submitted to hospital laboratory.	5.39 (2.62-11.12)	N/A
Mesrati *(57)	Tunisia	2005-07	Charles Nicolle hospital, Tunis	SSTI specimens submitted to hospital laboratory. Infection onset not stated.	11/54 (20.4) SA	89 diverse clinical specimens submitted to hospital laboratory.	0.88 (0.39-2.02)	N/A

* Study of unselected isolates which included all *S. aureus* specimens submitted to laboratory

[1] Refers to entire study, data unavailable for furunculosis

[2] Less than 50 comparator isolates

[3] Refers to entire study, data unavailable for SSTI alone

				Specimens from abscesses and furuncles submitted to hospital laboratory. Infection onset not stated.	11/20 (55.0) SA	124 diverse clinical specimens submitted to hospital laboratory excluding abscesses and furuncles.	7.15 (2.56-20.00)	
Nickerson (11)	Thailand	2006-07	Sappasithiprasong hospital	1) Specimens from patients attending hospital with *S. aureus* SSTI. Community or hospital onset not specified.	99/151 (65.6) SA	97 diverse clinical specimens from patients attending hospital.	6.13 (3.44-10.90)	N/A
				2) Specimens from patients attending hospital with abscess. Infection onset not specified.	91/123 (74.0) SA	125 specimens from patients attending hospital with mixed clinical infections excluding abscess.	8.62 (4.87-15.28)	
Yao (51)	China	2002-8	Wenzhou hospital	Pus samples from patients with community and hospital acquired SSTI	13/63 (20.6) HA-SA; 13/48 (27.1) CA-SA	No comparator	No comparator	0
Global Trials								
Goering (73)	10 countries	2004-05	5 global clinical trials	Community-onset uncomplicated SSTI. Infection onset not specified.	55/105 (52.4) MRSA; 118/187 (63.1) MSSA	No comparator	No comparator data	49/55 (89) USA300 MRSA; 5/118 (4) USA300 MSSA

Table 5. Studies assessing the role of PVL genes in *S. aureus* colonisation

Author	Location	Year	Study setting	Inclusion criteria and provenance of carriage isolates	Prevalence of PVL gene (%) amongst *S. aureus*[1] colonisation isolates	Comparator population of skin and soft tissue infection (SSTI) isolates	Odds of infection with PVL-positive strain comparing pneumonia to skin & soft tissue infection OR (95% CI)[2]	Proportion of PVL strains identified as ST8 / USA300 (%)
Comparative studies								
Lo (50)	Taiwan	2003-05	Triservice hospital, Taipei	Nasal specimens from healthy children in the community.	18/300 (6.0) SA	67 SSTI specimens from hospitalised children submitted to laboratory.	0.02 (0.007-0.03)	N/A
Masiuk (30)	Poland	2002-08	Pomeranian University, Szczecin	Nasal specimens from healthy blood donors excluding those with skin infection in the prior 2 years.	1/108 (0.9) SA	74 specimens from patients with furunculosis.	0.001 (0.0002-0.01)	0
Melles (58)	Netherlands		University Medical Centre, Rotterdam	Nasal specimens from healthy children and healthy adults aged >55 years in Rotterdam area.	5/829 (0.6) MSSA	18 SSTI specimens from patients in Rotterdam area.	0.01 (0.003-0.03)[3]	N/A
Muttaiyah * (5)	New Zealand	2008	Auckland hospital	Nasal specimens from healthy volunteers in community with no hospital contact in the prior 3 months.	29/93 (31.2) MSSA	234 SSTI specimens submitted to hospital laboratory.	0.49 (0.30-0.82)	0
Schaumburg (74)	Gabon	2008-10	Lambarene region	Nostril, axilla and groin specimens from inpatients, outpatients, hospital personnel and participants without healthcare contact.	66/163 (40.5) SA	21 specimens from abscesses and wounds submitted to Lambarene hospital.	0.28 (0.12-0.64)	1/163 (0.6)
Thomsen (63)	USA	2003-8	Vanderbilt hospital	Nasal specimens from children attending health maintenance visits.	17/105 (16.2) SA	113 specimens from children with localised SSTI.	0.03 (0.01-0.06)	0
Sdougkos (31)	Greece	2005-06	Karamandaneion & Patras hospitals	Nasal swabs from healthy uninfected children attending outpatients.	6/73 (8.2) SA	Specimens from 96 hospitalised children with community-acquired SSTI.	0.02 (0.006-0.05)	0
Prevalence studies								
Deurenberg (75)	Indonesia	2006	Yogyakarta area	Nasal specimens from patients attending outpatients and their companions attending with them.	10/62 (16.1) MSSA	No comparator	No comparator	0
Fan (76)	China	2005	Chengdu	Nasal specimens from children attending kindergartens	33/147 (18.4) SA	No SSTI comparator	No comparator	0
Ghasemzadeh Moghaddam (77)	Malaysia	2008	Serdang	Nasal specimens from healthy individuals who lack risk factors for healthcare contact.	9/110 (8.1) MSSA	No comparator	No comparator	N/A
Huang(64)	Taiwan	2005-6	Linko, Kaohsiung and Taichung hospitals	Nasal specimens from healthy children aged less than 5 years attending a well-child health care visit.	60/212 (28.3) MRSA	No comparator	No comparator	N/A

*Study of unselected isolates which included all *S. aureus* specimens submitted to laboratory

[1] Prevalence of PVL-positive strains amongst *S. aureus* (SA), meticillin-resistant (MRSA) or meticillin-sensitive strains (MSSA)

[2] Odds ratio and 95% confidence interval

[3] Comparator population contains fewer than 50 isolates

Kuehnert (62)	USA	2001-2	National Health & Nutrition Survey (NHANES)	Nasal swabs from US population participating in NHANES.	3/297 (1.0) MSSA 6/75 (8.0) MRSA	No comparator	No comparator	N/A
Lee (78)	Korea	2008	Seoul	Nasal specimens from healthy pre-school children attending daycare centres.	0/60 (0) SA	No comparator	No comparator	0
Lo (65)	Taiwan	2004-6	Triservice hospital	Nasal specimens from healthy children attending 57 kindergartens or a health maintenance visit.	123/371 (33.2) MRSA	No comparator	No comparator	N/A
Lozano (59)	Spain	2009	La Rioja	Nasal specimens from healthy volunteers who lacked risk factors for healthcare or animal contact.	0/53 (0) SA	No comparator	No comparator	0
Monecke (60)	Germany	2005-8	Saxony	Nasal specimens from medical students, inpatients admitted for conditions unrelated to *S. aureus* and employees of a biomedical facility.	1/155 (0.7)	No comparator	No comparator	0
Munckhof (79)	Australia	2005-6	Brisbane suburbs	Nasal specimens from patients attending General Practice without an infectious condition and healthy volunteers selected from electoral roll.	2/191 (1.0) SA	No comparator	No comparator	N/A
Neela (80)	Malaysia		Selangor	Nasal specimens from Orang asli community and rural population.	4/88 (4.5) MRSA	No comparator	No comparator	0
Peck (25)	Korea	2006	Seoul	Nasal specimens from children attending outpatients.	0/95 (0) SA	No comparator	No comparator	N/A
Severin (81)	Indonesia	2001-2	Semarang and Surabaya	Nasal specimens from inpatients, patients attending primary care and healthy relatives.	35/329 (10.6) SA	No comparator	No comparator	0
Wang (82)	Taiwan	2007	Taiwan hospital	Nasal specimens from adults attending mandatory health examinations as part of workplace health promotion.	2/119 (1.7) MRSA	No comparator	No comparator	N/A

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