Global initiative for meticillin-resistant *Staphylococcus aureus* pneumonia (GLIMP): an international, observational cohort study

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Summary

Background **Antibiotic resistance is a major global health problem and pathogens such as meticillin-resistant *Staphylococcus aureus* (MRSA) have become of particular concern in the management of lower respiratory tract infections. However, few data are available on the worldwide prevalence and risk factors for MRSA pneumonia. We aimed to determine the point prevalence of MRSA pneumonia and identify specific MRSA risk factors in community-dwelling patients hospitalised with pneumonia.**

Methods **We did an international, multicentre study of community-dwelling, adult patients admitted to hospital with pneumonia who had microbiological tests taken within 24 h of presentation. We recruited investigators from 222 hospitals in 54 countries to gather point-prevalence data for all patients admitted with these characteristics during 4 days randomly selected during the months of March, April, May, and June in 2015. We assessed prevalence of MRSA pneumonia and associated risk factors through logistic regression analysis.**

Findings **3702 patients hospitalised with pneumonia were enrolled, with 3193 patients receiving microbiological tests within 24 h of admission, forming the patient population. 1173 (37%) had at least one pathogen isolated (culture-positive population). The overall prevalence of confirmed MRSA pneumonia was 3·0% (n=95), with differing prevalence between continents and countries. Three risk factors were independently associated with MRSA pneumonia: previous MRSA infection or colonisation (odds ratio 6·21, 95% CI 3·25–11·85), recurrent skin infections (2·87, 1·10–7·45), and severe pneumonia disease (2·39, 1·55–3·68).**

Interpretation **This multicountry study shows low prevalence of MRSA pneumonia and specific MRSA risk factors among community-dwelling patients hospitalised with pneumonia.**

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Introduction

WHO recognises antibiotic resistance as a global public health threat because of its effect on health care, including higher costs, prolonged hospitalisation, and increased mortality.[1,2] Bacterial antibiotic resistance causes more than 25 000 deaths per year in the European Union, and costs more than €1·5 billion per year in health-care expenses and productivity losses.[3] Similarly, in the USA, about 2 million people acquire serious infections caused by bacteria resistant to at least one recommended antibiotic.[4] The emergence of antibiotic resistance and dearth of new antibiotics threaten the ability to treat patients with infectious diseases.[2]

Community-acquired pneumonia is the most common lower respiratory tract infection and the leading cause of death due to infection worldwide.[5,6] Increasing rates of antibiotic resistance in prevalent respiratory pathogens such as *Staphylococcus aureus* are a major public health concern due to few treatment options.[7–9] Previous scientific literature and clinical guidelines have emphasised the increasing prevalence of meticillin-resistant *S aureus* (MRSA) in patients with community-acquired pneumonia.[10,11] WHO highlights the need to optimise antibiotic usage by determining the true prevalence and associated risk factors of MRSA infection.[12,13] To bridge this gap in the literature, we did an international, multicentre study to determine the point prevalence and specific risk factors associated with MRSA infection in hospitalised patients with community-acquired pneumonia.

Methods

Study design and participants

The Global Initiative for MRSA Pneumonia (GLIMP) study is an international, multicentre, observational cohort study of adult patients in hospital with a diagnosis of community-acquired pneumonia. Medical centres and international researchers were invited to participate by email invitation sent individually and to members of different respiratory, infectious diseases, critical care, internal, and emergency medicine professional societies worldwide. This project was not funded and relied solely on voluntary site and investigator participation. This study was observational and clinicians were encouraged to treat all the patients according to the normal standard of care.

Research in context

Evidence before this study

We conducted two systematic reviews of papers published between 1947 and Jan 1, 2016, not limited by language, to assess the epidemiology of community-acquired pneumonia due to meticillin-resistant *Staphylococcus aureus* (MRSA) and its associated risk factors. The following keywords were selected in PubMed: "MRSA" AND "community-acquired pneumonia" AND "risk factors". We included observational and interventional studies in human beings and excluded editorials, letters, narrative, and conference abstracts. The search of MRSA community-acquired pneumonia with and without risk factors retrieved 603 manuscripts; among them, 49 met the inclusion criteria. For this systematic review, health-care-associated pneumonia was included in the definition of community-acquired pneumonia. Most of the current literature includes MRSA among the group of multidrug-resistant bacteria causing community-acquired pneumonia and evaluates prevalence and risk factors accordingly. Consequently, no study so far has aimed to determine the specific risk factors for MRSA community-acquired pneumonia. Furthermore, most past studies collected data from a few centres in the USA, Europe, and Asia, and the cohorts included patients with and without culture-positive pneumonia. Considering these limitations, MRSA community-acquired pneumonia prevalence broadly ranges from 0 to 30%, and no specific MRSA risk factors in patients with community-acquired pneumonia had been previously identified.

Added value of this study

To our knowledge, this is the first multicountry study to explore the prevalence of MRSA community-acquired pneumonia. The prevalence of MRSA was 3% among community-dwelling patients presenting with pneumonia. Substantial variability in MRSA-community-acquired pneumonia prevalence exists between different continents and among countries within the same continent. There were three specific risk factors for MRSA community-acquired pneumonia: previous MRSA infections or colonisation, recurrent skin infections, and severe pneumonia requiring higher level of care.

Implications of all the available evidence

Local pneumonia management guidelines should be developed that consider the local prevalence of MRSA in the community and presence of specific MRSA risk factors at the time of hospitalisation of patients with community-acquired pneumonia. This strategy could control the overuse of anti-MRSA antibiotics by guiding empirical initiation only in patients at risk of this hard-to-treat infection.

The study was conducted over 4 days in centres, with one day per month selected randomly during March, April, May and June of 2015. Random selection method was at the investigator's discretion. All adults (>18 years old) admitted to hospital with community-acquired pneumonia at participating centres during the study period were screened for study inclusion by investigators. Community-acquired pneumonia was defined by evidence of new pulmonary infiltrates on thoracic imaging (chest radiograph, CT, or ultrasound) during the first 48 h in hospital and at least one of the following criteria: new or increased cough with or without sputum production or with purulent respiratory secretions; fever (documented rectal or oral temperature ≥37·8°C) or hypothermia (documented rectal or oral temperature <36°C); and evidence of systemic inflammation, such as abnormal white blood cell count (leucocytosis [>10 000 cells per mL], leucopenia [<4000 cells per mL], or bandaemia [>10%]) and increased C-reactive protein or procalcitonin concentrations above the local upper limit of normal.[14] Only patients who received a microbiological test either from blood, sputum, or lower respiratory tract cultures within 24 h of hospital admission were included. Patients hospitalised with a diagnosis of hospital-acquired or ventilator-associated pneumonia were excluded.[15]

The project coordinating centre was located at the University of Texas Health Science Center, San Antonio (UTHSCSA) in San Antonio, TX, USA. The coordinating centre received expedited project approval by the institutional review board (number HSC20150184E). The review board waived the need for receipt of informed consent due to the nature of the study. Responsibility for institutional review board approval at each individual centre was that of the researchers.

Data collection and definitions

Study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application designed to support data capture for research studies hosted on the UTHSCSA server.[16] After study enrolment, participating centres were allowed 7 days to complete electronic data entry and confirm microbiological results. Attending physicians collected and processed all the appropriate diagnostic testing within the first 24 h of hospital stay, including collection of blood and respiratory cultures (eg, sputum, pleural fluid, endotracheal aspirate, and bronchoalveolar lavage), pneumococcus and legionella urinary antigen, and influenza testing according to local standard protocols.[17]

MRSA was defined according to the Clinical and Laboratory Standards Institute, in which the minimum

inhibitory concentration was 4 µg/mL or higher to oxacillin.[17–19] We defined severe community-acquired pneumonia as patients requiring any of the following: intensive care unit admission, invasive or non-invasive mechanical ventilation, or vasopressors or inotropes during the first 24 h of hospital admission. Previous MRSA infection or colonisation was defined as confirmed MRSA infection or colonisation during the past year as documented by the patient or the patient's information available at the time of evaluation (not based on MRSA colonisation by the presence of MRSA in the nares because it was not standardised as part of the study). We defined MRSA community-acquired pneumonia as patients with a diagnosis of community-acquired pneumonia in whom MRSA was isolated in any respiratory fluid (eg, sputum, bronchoalveolar lavage, or pleural effusion) or blood. All site investigators were provided with definitions before the study started.

Statistical analysis

We calculated MRSA prevalence using MRSA isolates from the study cohort with bacteriological testing done during the first 24 h of hospital admission. We compared categorical variables between groups using the χ^2 test. We did regression analyses to compare prevalence and determine odds ratios (OR) with 95% CIs to compare percentages and risk factors between groups. Logistic regression analyses assessed the relationship between MRSA pneumonia and 64 demographical, treatment, epidemiological, and clinical variables. We carried out a circular relation

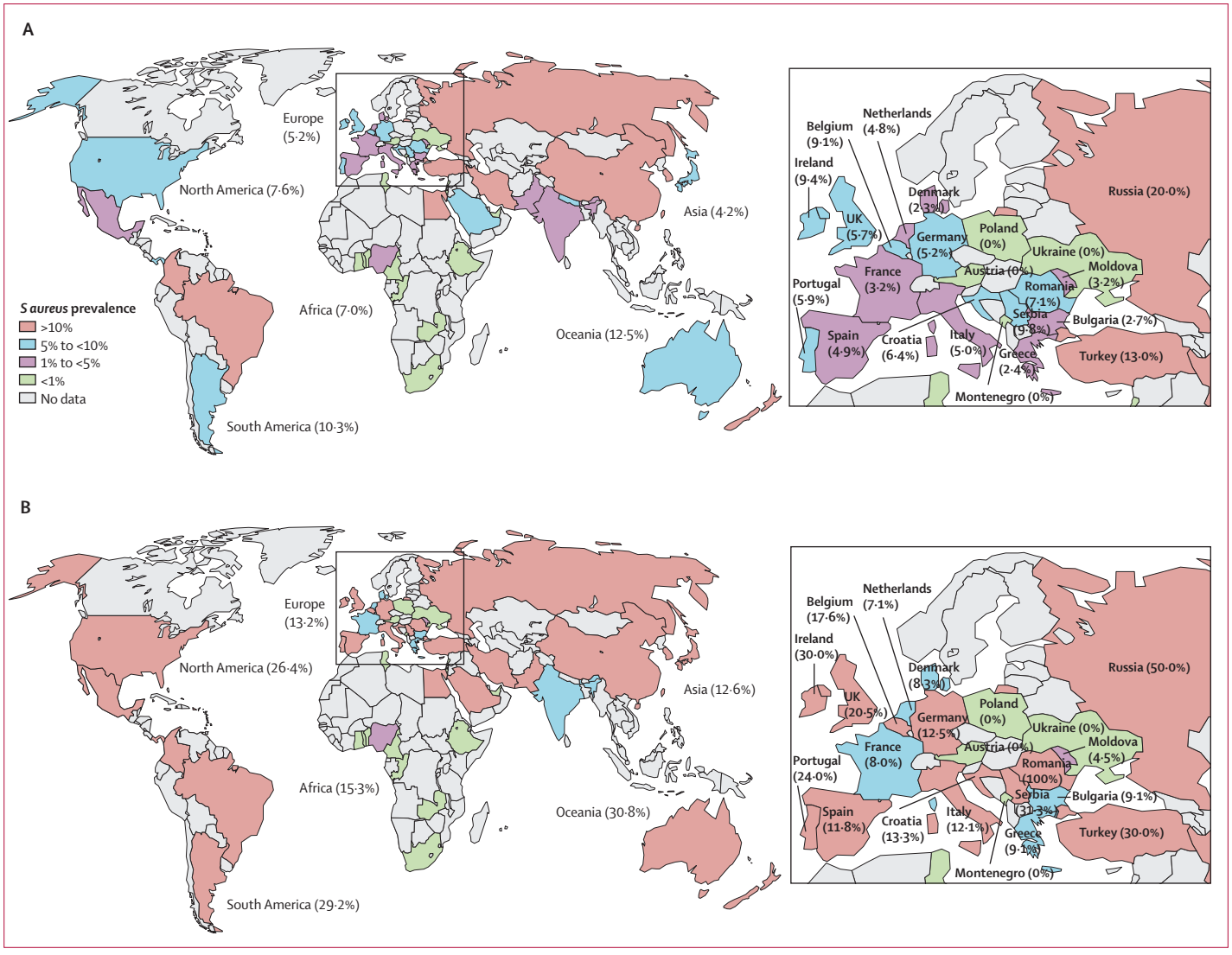

***Figure 1*: Prevalence of *Staphylococcus aureus* infection by continent and countries for participants in the entire cohort (A) and culture-positive cohort (B)**
Europe is shown in detail because of the high number of patients enrolled and the large number of participating countries.

	Among CAP patients with microbiology testing (n=3193)						Among CAP patients with culture-positive pneumonia (n=1173)					
	Continent/country		Rest of the world		OR (95% CI)	p value	Continent/country		Rest of the world		OR (95% CI)	p value
	Prevalence (%)	n/N	Prevalence (%)	n/N			Prevalence (%)	n/N	Prevalence (%)	n/N		
Continents												
S aureus												
Africa	7·0%	9/128	5·8%	179/3065	1·21 (0·60–2·44)	0·575	15·3%	9/59	16·1%	179/1114	0·94 (0·45–1·94)	0·868
Asia	4·2%	17/405	6·1%	171/2788	0·67 (0·40–1·11)	0·122	12·6%	17/135	16·5%	171/1038	0·73 (0·42–1·24)	0·248
Europe	5·2%	100/1941	7·0%	88/1252	0·71 (0·53–0·96)	0·028	13·2%	100/754	21·0%	88/419	0·57 (0·42–0·78)	0·001
North America	7·6%	37/484	5·6%	151/2709	1·40 (0·96–2·03)	0·07	26·4%	37/140	14·6%	151/1033	2·09 (1·38–3·17)	0·001
Oceania	12·5%	4/32	5·8%	184/3161	2·31 (0·80–6·65)	0·11	30·8%	4/13	15·9%	184/1160	2·35 (0·71–7·73)	0·145
South America	10·3%	21/203	5·6%	167/2990	1·95 (1·20–3·14)	0·005	29·2%	21/72	15·2%	167/1101	2·30 (1·35–3·92)	0·002
Meticillin-sensitive *S aureus* (MSSA)												
Africa	3·9%	5/128	2·9%	88/3065	1·38 (0·53–3·47)	0·495	8·5%	5/59	7·9%	88/1114	1·08 (0·42–2·76)	0·873
Asia	1·7%	7/405	3·1%	86/2788	0·55 (0·25–1·21)	0·129	5·2%	7/135	8·3%	86/1038	0·60 (0·27–1·33)	0·21
Europe	2·8%	54/1941	3·1%	39/1252	0·89 (0·58–1·35)	0·585	7·2%	54/754	9·3%	39/419	0·75 (0·48–1·15)	0·192
North America	2·9%	14/484	2·9%	79/2709	0·98 (0·55–1·75)	0·977	10·0%	14/140	7·6%	79/1033	1·32 (0·73–2·44)	0·334
Oceania	9·4%	3/32	2·8%	90/3161	3·22 (0·96–10·71)	0·029	23·1%	3/13	7·8%	90/1160	3·56 (0·96–13·19)	0·057
South America	4·9%	10/203	2·8%	83/2990	1·82 (0·92–3·56)	0·078	13·9%	10/72	7·5%	83/1101	1·97 (0·97–4·00)	0·053
Meticillin-resistant *S aureus* (MRSA)												
Africa	3·1%	4/128	3·0%	91/3065	1·05 (0·38–2·91)	0·919	6·8%	4/59	8·2%	91/1114	1·22 (0·43–3·45)	0·703
Asia	2·5%	10/405	3·0%	85/2788	0·80 (0·41–1·56)	0·521	7·4%	10/135	8·2%	85/1038	0·89 (0·45–1·77)	0·754
Europe	2·4%	46/1941	3·9%	49/1252	0·59 (0·39–0·89)	0·012	6·1%	46/754	11·7%	49/419	0·49 (0·32–0·74)	0·001
North America	4·8%	23/484	2·7%	72/2709	1·82 (1·13–2·95)	0·012	16·4%	23/140	7·0%	72/1033	2·62 (1·58–4·35)	0·000
Oceania	3·1%	1/32	3·0%	94/3161	1·05 (0·14–7·79)	0·96	7·7%	1/13	8·1%	94/1160	0·94 (0·12–7·34)	0·957
South America	5·4%	11/203	2·8%	84/2990	1·98 (1·04–3·77)	0·034	15·3%	11/72	7·6%	84/1101	2·18 (1·10–4·30)	0·021
Countries												
S aureus												
Argentina	7·4%	13/176	5·8%	175/3017	1·30 (0·72–2·34)	0·37	26·5%	13/49	15·6%	175/1124	1·95 (1·01–3·76)	0·04
Bulgaria	2·7%	1/37	5·9%	187/3156	0·44 (0·06–3·23)	0·42	9·1%	1/11	16·1%	187/1162	0·53 (0·06–4·09)	0·53
Croatia	6·4%	6/94	5·9%	182/3099	1·09 (0·47–2·53)	0·83	13·3%	6/45	16·1%	182/1128	0·8 (0·33–1·91)	0·61
Denmark	2·3%	2/86	6·0%	186/3107	0·37 (0·09–1·53)	0·17	8·3%	2/24	16·2%	186/1149	0·47 (0·11–2·01)	0·31
France	3·2%	2/63	5·9%	186/3130	0·51 (0·12–2·13)	0·36	8·0%	2/25	16·2%	186/1148	0·45 (0·10–1·92)	0·28
Germany	5·2%	7/134	5·9%	181/3059	0·87 (0·40–1·90)	0·11	12·5%	7/56	16·2%	181/1117	0·73 (0·32–1·65)	0·46
Greece	2·4%	2/84	6·0%	186/3109	0·37 (0·09–1·55)	0·17	9·1%	2/22	16·2%	186/1151	0·51 (0·12–2·23)	0·37
India	2·7%	4/146	6·0%	184/3047	0·42 (0·15–1·16)	0·09	7·0%	4/57	16·5%	184/1116	0·38 (0·13–1·06)	0·06
Ireland	9·4%	3/32	5·9%	185/3161	1·66 (0·50–551)	0·40	30·0%	3/10	15·9%	185/1163	0·26 (0·58–8·842)	0·23
Italy	5·0%	19/381	6·0%	169/2812	0·82 (0·50–1·33)	0·42	12·1%	19/157	16·6%	169/1016	0·69 (0·41–1·14)	0·15
Moldova	3·2%	1/31	5·9%	187/3162	0·53 (0·07–3·91)	0·53	4·5%	1/22	16·2%	187/1151	0·24 (0·03–1·83)	0·17
Montenegro	0%	0/1	5·9%	188/3192	..	..	..	0/0	16·0%	188/1173	..	..
Netherlands	4·8%	2/42	5·9%	186/3151	0·77 (0·18–3·23)	0·72	7·1%	2/28	16·2%	186/1145	0·39 (0·09–1·68)	0·21
Pakistan	4·7%	5/107	5·9%	183/3086	0·77 (0·31–1·93)	0·58	19·2%	5/26	16·0%	183/1147	1·25 (0·46–3·36)	0·65
Portugal	5·9%	6/101	5·9%	182/3092	1·01 (0·43–2·33)	0·98	24·0%	6/25	15·9%	182/1148	1·67 (0·66–4·25)	0·27
Saudi Arabia	7·1%	3/42	5·9%	185/3151	1·23 (0·37–4·02)	0·72	17·6%	3/17	16·0%	185/1156	1·12 (0·32–3·95)	0·85
Serbia	9·8%	4/41	5·8%	184/3152	1·74 (0·61–4·94)	0·29	33·3%	4/12	15·8%	184/1161	2·65 (0·79–8·90)	0·11
Spain	4·9%	29/589	6·1%	159/2604	0·83 (0·54–1·21)	0·291	11·8%	29/246	17·2%	159/927	0·04 (0·42–0·98)	0·04
UK	5·7%	8/140	5·9%	180/3053	0·96 (0·46–2·00)	0·92	20·5%	8/39	15·9%	180/1134	1·36 (0·61–3·02)	0·43
USA	7·9%	35/443	5·6%	153/2750	1·46 (0·99–2·13)	0·05	27·1%	35/129	14·7%	153/1044	2·16 (1·41–3·31)	0·001
Meticillin-sensitive *S aureus* (MSSA)												
Argentina	4·0%	7/176	2·9%	86/3017	1·42 (0·64–3·11)	0·38	14·3%	7/49	7·7%	86/1124	2·01 (0·87–4·61)	0·09
Bulgaria	2·7%	1/37	2·9%	92/3156	0·92 (0·12–6·82)	0·93	9·1%	1/11	7·9%	92/1162	1·16 (0·14–9·18)	0·88
Croatia	2·1%	2/94	2·9%	91/3099	0·71 (0·17–2·96)	0·64	4·4%	2/45	8·1%	91/1128	0·53 (0·13–2·22)	0·39

(Table 1 continues on next page)

	Among CAP patients with microbiology testing (n=3193)						Among CAP patients with culture-positive pneumonia (n=1173)					
	Continent/country		Rest of the world		OR (95% CI)	p value	Continent/country		Rest of the world		OR (95% CI)	p value
	Prevalence (%)	n/N	Prevalence	n/N			Prevalence (%)	n/N	Prevalence (%)	n/N		
(Continued from previous page)												
Denmark	2·3%	2/86	2·9%	91/3107	0·78 (0·19–3·25)	0·74	8·3%	2/24	7·9%	91/1149	1·06 (0·25–4·56)	0·94
France	1·6%	1/63	2·9%	92/3130	0·53 (0·07–3·88)	0·53	4·0%	1/25	8·0%	92/1148	0·48 (0·06–3·58)	0·47
Germany	2·2%	3/134	2·9%	90/3059	0·75 (0·23–2·41)	0·63	5·4%	3/56	8·1%	90/1117	0·64 (0·19–2·11)	0·46
Greece	1·2%	1/84	3·0%	92/3109	0·39 (0·54–2·83)	0·35	4·5%	1/22	8·0%	92/1151	0·55 (0·07–4·12)	0·56
India	1·4%	2/146	3·0%	91/3047	0·43 (0·10–1·79)	0·25	3·5%	2/57	8·2%	91/1116	0·41 (0·98–1·7)	0·22
Ireland	9·4%	3/32	2·8%	90/3161	3·52 (1·06–11·80)	0·04	30·0%	3/10	7·7%	90/1163	5·11 (1·29–20·09)	0·02
Italy	2·1%	8/381	3·0%	85/2812	0·68 (0·33–1·43)	0·31	5·1%	8/157	8·4%	85/1016	0·59 (0·28–1·24)	0·16
Moldova	0%	0/31	2·9%	93/3162	..	..	0	0/22	8·1%	93/1151	..	..
Montenegro	0%	0/1	2·9%	93/3192	..	..	0	0/0	7·9%	93/1173	..	..
Netherlands	4·8%	2/42	2·9%	91/3151	1·64 (0·39–6·88)	0·49	7·1%	2/28	7·9%	91/1145	0·89 (0·21–3·81)	0·876
Pakistan	0·9%	1/107	3·0%	92/3086	0·30 (0·04–2·22)	0·24	3·8%	1/26	8·0%	92/1147	0·46 (0·06–3·42)	0·45
Portugal	5·0%	5/101	2·8%	88/3092	1·77 (0·70–4·47)	0·22	20·0%	5/25	7·7%	88/1148	3·01 (1·1–8·22)	0·031
Saudi Arabia	7·1%	3/42	2·9%	90/3151	2·62 (0·79–8·62)	0·11	17·6%	3/17	7·8%	90/1156	2·54 (0·71–8·99)	0·15
Serbia	2·4%	1/41	2·9%	92/3152	0·83 (0·11–6·11)	0·85	8·3%	1/12	7·9%	92/1161	1·05 (0·13–8·27)	0·95
Spain	3·4%	20/589	2·8%	73/2604	1·22 (0·74–2·03)	0·42	8·1%	20/246	7·9%	73/927	1·04 (0·62–1·73)	0·89
UK	2·9%	4/140	2·9%	89/3053	0·98 (0·35–2·70)	0·96	10·3%	4/39	7·8%	89/1134	1·34 (0·47–3·87)	0·58
USA	2·9%	13/443	2·9%	80/2750	1·01 (0·55–1·83)	0·96	10·1%	13/129	7·7%	80/1044	1·35 (0·73–2·50)	0·34
Meticillin-resistant *S aureus* (MRSA)												
Argentina	3·4%	6/176	2·9%	89/3017	1·17 (0·50–2·70)	0·71	12·2%	6/49	7·9%	89/1124	1·62 (0·67–3·92)	0·28
Bulgaria	0%	0/37	3·0%	95/3156	..	..	0	0/11	8·2%	95/1162	..	..
Croatia	4·3%	4/94	2·9%	91/3099	1·47 (0·52–4·08)	0·46	8·9%	4/45	8·1%	91/1128	1·11 (0·39–3·17)	0·84
Denmark	0%	0/86	3·1%	95/3107	..	..	0	0/24	8·3%	95/1149	..	..
France	1·6%	1/63	3·0%	94/3130	0·52 (0·07–3·79)	0·52	4·0%	1/25	8·2%	94/1148	0·47 (0·06–3·49)	0·46
Germany	3·0%	4/134	3·0%	91/3059	1·00 (0·36–2·77)	0·99	7·1%	4/56	8·1%	91/1117	0·86 (0·30–2·45)	0·78
Greece	1·2%	1/84	3·0%	94/3109	0·38 (0·05–2·77)	0·34	4·5%	1/22	8·2%	94/1151	0·53 (0·07–4·02)	0·54
India	1·4%	2/146	3·1%	93/3047	0·43 (0·10–1·75)	0·23	3·5%	2/57	8·3%	94/1116	0·40 (0·09–1·66)	0·208
Ireland	0%	0/32	3·0%	95/3161	..	..	0	0/10	8·2%	95/1163	..	..
Italy	2·9%	11/381	3·0%	84/2812	0·96 (0·51–1·82)	0·91	7·0%	11/157	8·3%	84/1016	0·84 (0·44–1·60)	0·59
Moldova	3·2%	1/31	3·0%	94/3162	1·08 (0·14–8·06)	0·93	4·5%	1/22	8·2%	94/1151	0·53 (0·07–4·02)	0·54
Montenegro	0%	0/1	3·0%	95/3192	..	..	0	0/0	8·1%	95/1173	..	..
Netherlands	0%	0/42	3·0%	95/3151	..	..	0	0/28	8·3%	95/1145	..	..
Pakistan	3·7%	4/107	2·9%	91/3086	1·28 (0·46–3·54)	0·63	15·4%	4/26	7·9%	91/1147	2·11 (0·71–6·25)	0·17
Portugal	1·0%	1/101	3·0%	94/3092	0·32 (0·44–2·31)	0·25	4·0%	1/25	8·2%	94/1148	0·46 (0·06–3·49)	0·46
Saudi Arabia	0%	0/42	3·0%	95/3151	..	..	0	0/17	8·2%	95/1156	.	.
Serbia	7·3%	3/41	2·9%	92/3152	2·62 (0·796–8·66)	0·11	25·0%	3/12	7·9%	92/1161	3·87 (1·03–14·55)	0·045
Spain	1·5%	9/589	3·3%	86/2604	0·45 (0·22–0·91)	0·03	3·7%	9/246	9·3%	86/927	0·37 (0·18–0·75)	0·006
UK	2·9%	4/140	3·0%	91/3053	0·95 (0·32–2·64)	0·93	10·3%	4/39	8·0%	91/1134	1·31 (0·45–3·76)	0·61
USA	5·0%	22/443	2·7%	73/2750	1·92 (1·18–3·13)	0·01	17·1%	22/129	7·0%	73/1044	2·74 (1·63–4·58)	0·001

CAP=community-acquired pneumonia. OR=odds ratio.

Table 1: **Prevalence of positive testing for *Staphylococcus aureus*, meticillin-sensitive *S aureus* and meticillin-resistant *S aureus* among patients with CAP among the six continents and the 20 higher enrolling countries**

analysis using the χ^2 test to compare the prevalence between countries and continents. A CHAID (χ^2 automatic interaction detector) decision tree was done to obtain variables most strongly associated with MRSA presence in patients with community-acquired pneumonia. A decision tree was generated with four terminal nodes and two levels deep. Statistical significance was defined as a p value of less than 0·05. Prevalence maps were created using Stat Planet software. All statistical analyses were done with IBM

	Patients with MRSA CAP (n=95)	Patients with non-MRSA CAP (n=3098)	p value
Demographic characteristics			
Median age (years)	71 (55–80%)	68 (54–80)	0·60
Men	59 (62%)	1818 (59%)	0·50
Underweight	1/60 (2%)	149/1995 (7%)	0·13
Obese	16 (17%)	494 (16%)	0·81
Respiratory past medical history			
Active lung cancer	4 (4%)	88 (3%)	0·35
Asthma	11 (12%)	223 (7%)	0·11
Bronchiectasis	4 (4%)	164 (5%)	0·82
Chronic aspiration	5 (5%)	213 (7%)	0·54
COPD	18 (19%)	816 (26%)	0·11
FEV_1 ≤30%	5 (5%)	85 (3%)	0·14
Current or former smoker	25 (26%)	1089 (35%)	0·08
Interstitial lung disease	4 (4%)	87 (3%)	0·35
Obstructive sleep apnoea	4 (4%)	119 (4%)	0·79
Oxygen therapy at home	6 (6%)	202 (7%)	0·94
Lung transplantation	0 (0%)	7 (<1%)	1·00
Tracheostomy	6 (6%)	44 (1%)	<0·0001
Cardiovascular past medical history			
Arrhythmia	19 (20%)	436 (14%)	0·10
Coronary artery disease	23 (24%)	503 (16%)	0·04
Heart failure	14 (15%)	404 (13%)	0·63
Hypertension	45 (47%)	1399 (45%)	0·67
Stroke	8 (8%)	242 (8%)	0·83
Chronic medications			
Inhaled corticosteroids use	17 (18%)	527 (17%)	0·82
Proton-pump inhibitor use	28 (29%)	879 (28%)	0·82
Statins use	20 (21%)	650 (21%)	0·99
Glucocorticoid use	4 (4%)	264 (9%)	0·19
Chronic interventions			
Enteric tube feeding	2 (2%)	46 (1%)	0·65
Haemodialysis	2 (2%)	49 (2%)	0·66
Indwelling catheter	6 (6%)	61 (2%)	0·004
Immunosuppressive conditions			
Active solid tumour	11 (12%)	234 (8%)	0·15
AIDS	2 (2%)	55 (2%)	0·69
Aplastic anaemia	0	13 (<1%)	1·00
Asplenia	0	12 (<1%)	1·00
Biological drug use	0	35 (1%)	0·63
Chemotherapy in the previous 3 months	5 (5%)	129 (4%)	0·60
Haematological malignancy	1 (1%)	149 (5%)	0·13
HIV infection	3 (3%)	104 (3%)	1·00
Immunocompromised	17 (18%)	570 (18%)	0·90
Neutropenia	1 (1%)	43 (1%)	1·00
Other immunosuppressive disorder	3 (3%)	122 (4%)	1·00

(Table 2 continues in next column)

(Continued from previous column)

	Patients with MRSA CAP (n=95)	Patients with non-MRSA CAP (n=3098)	p value
Other chronic medical disorders			
Chronic renal failure	9 (9%)	340 (11%)	0·64
Dementia	12 (13%)	321 (10%)	0·48
Diabetes mellitus	24 (25%)	657 (21%)	0·34
Liver disease	2 (2%)	127 (4%)	0·59
Malnutrition	10 (11%)	279 (9%)	0·59
Mental disorders	8 (8%)	212 (7%)	0·55
Prosthetic material	5 (5%)	95 (3%)	0·23
Recurrent skin infections	6 (6%)	49 (2%)	<0·0001
Other non-medical conditions			
Bedridden	20 (21%)	333 (11%)	0·002
Contact sport	1 (1%)	4 (<1%)	0·14
Health-care worker	2 (2%)	42 (1%)	0·38
Homeless	1 (1%)	30 (1%)	0·61
Use of injection drugs	2 (2%)	35 (1%)	0·30
Living in crowded conditions	25 (26%)	646 (21%)	0·20
Nursing home resident	19 (20%)	239 (8%)	<0·0001
Worker in livestock meat industry	1 (1%)	28 (1%)	0·59
Previous infections or colonisation			
Previous mycobacterial diseases	2 (2%)	87 (3%)	1·00
Previous MRSA infection or colonisation	18 (19%)	63 (2%)	<0·0001
Previous ESBL-producing bacterial infection	1 (1%)	53 (2%)	1·00
Previous *Pseudomonas* spp infection	6 (6%)	90 (3%)	0·06
Previous health-care exposure			
Antibiotic infusion at home during the previous 12 months	10 (11%)	110 (4%)	0·004
Emergency room admission in the previous 12 months	35 (37%)	2700 (87%)	0·03
Hospitalisation during the previous 12 months	41 (43%)	985 (32%)	0·048
Intravenous antibiotics during the previous 12 months	38 (40%)	774 (25%)	0·007
LRTI in the previous 12 months	36 (38%)	2756 (89%)	0·15
Oral antibiotics during the previous 12 months	49 (52%)	1170 (38%)	<0·0001
Current pneumonia episode			
Severe CAP	51 (54%)	914 (30%)	<0·0001
Concurrent pathogen			
Influenza virus infection	3 (3%)	151 (5%)	0·45

Data are median (IQR) or n (%). CAP=community-acquired pneumonia. MRSA=meticillin-resistant *Staphylococcus aureus*. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. CAD=coronary artery disease. ESBL=extended-spectrum β lactamases. LRTI=lower respiratory tract infections.

***Table 2*: Characteristics of patients who underwent at least one microbiology test for MRSA pneumonia**

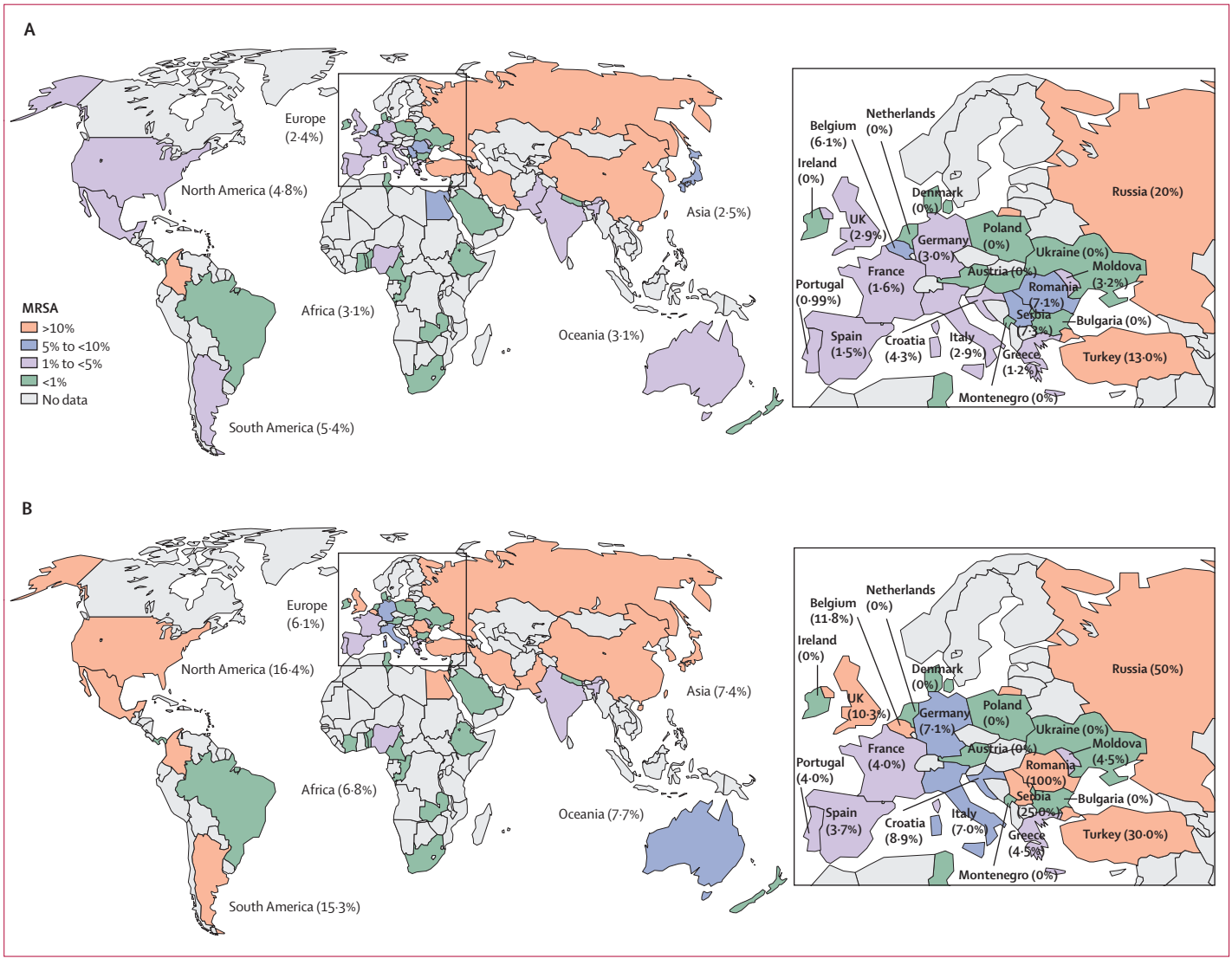

***Figure 2*: Prevalence of meticillin-resistant *Staphylococcus aureus* (MRSA) infection by continents and countries for participants in the entire cohort (A) and culture-positive pneumonia cohort (B)**

Europe is shown in detail because of the high number of patients enrolled and the large number of participating countries.

SPSS, Statistics for Mac, version 22.0, and Stata version 13.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

See Online for appendix

Investigators enrolled 3702 patients among 222 hospitals in 54 countries. Most patients were enrolled from European hospitals (appendix p 9). The final study population consisted of 3193 patients that underwent at least one bacterial microbiological test within the first 24 h of hospitalisation. Cultures were done from blood samples (n=2211 [69%]) and respiratory samples (sputum [n=1630; 51%], bronchoalveolar lavage [n=311 [10%], endotracheal aspirate (n=274 [9%]), and pleural fluid cultures (n=117 [4%]). In 1173 (37%) patients, a pathogen was identified as causative of community-acquired pneumonia (forming the culture-positive community-acquired pneumonia cohort).

S aureus was identified in 188 patients (6%), corresponding to 16% of patients with an identified pathogen. The prevalence of *S aureus*-positive pneumonia was highest in Oceania and lowest in Europe (figure 1). The prevalence of *S aureus* varied widely by country and continent (table 1).

MRSA community-acquired pneumonia was identified in 95 patients (prevalence 3·0%; 8·1% among those with an identified pathogen; tables 1, 2). Respiratory samples (n=67; 71%) were the most common culture confirmations of MRSA pneumonia (sputum [n=30; 32%], endotracheal aspirate [n=21; 22%], bronchoalveolar lavage [n=15; 16%], and pleural fluid culture [n=1; 1%]), followed by blood cultures (n=28; 29%). By continent, the prevalence of MRSA community-acquired pneumonia ranged from 2·4% in Europe to 5·4% in South America (figure 2) and the prevalence in patients with an identified pathogen ranged from 6·1% in Europe to 16·4% in North America (figure 2). North America (4·8%) and South America (5·4%) had a higher prevalence of MRSA than other continents, whereas Europe (2·4%) had a lower prevalence than other continents (table 1). The only country with a significantly higher prevalence of MRSA community-acquired pneumonia than other participating countries was the USA (table 1; appendix p 13). The only country with a significantly lower prevalence of MRSA community-acquired pneumonia was Spain (table 1). These differences remained statistically significant in the group of patients with an identified pathogen (table 1).

Overall, among all the *S aureus* isolates, 51% were meticillin resistant (MRSA) and 49% were meticillin sensitive (MSSA; appendix p 12). The highest MRSA to MSSA prevalence ratio was in North America (with a MRSA/MSSA ratio of 1·64 for *S aureus* pneumonia patients) followed by Asia and South America (appendix p 12). The countries with the highest MRSA to MSSA ratio were Pakistan, Croatia, and the USA (appendix p 12).

Previous MRSA infections or colonisation, recurrent skin infections, and severe pneumonia were the only risk factors independently associated with MRSA community-acquired pneumonia, including in culture-positive patients (appendix p 4, 6; table 3). This analysis showed that previous MRSA infection and severe pneumonia were the most important risk factors among the 64 possible risk factors for MRSA community-acquired pneumonia. Previous MRSA infection or colonisation was the first node that determined the different prevalence rates of MRSA community-acquired pneumonia, with a range from 2% among participants with no previous MRSA infection or colonisation hospitalised in a non-ICU setting, to 32% among participants with previous MRSA infection or colonisation admitted with severe pneumonia requiring high level of care (appendix p 14).

	Microbiological-tested cohort		Culture-positive cohort	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (categorised)	..	..	1·01 (0·99–1·02)	0·45
Bedridden	1·32 (0·75–2·33)	0·33	1·52 (0·86–2·71)	0·15
Nursing home resident	1·63 (0·89–3·00)	0·12	1·72 (0·89–3·32)	0·11
Tracheostomy	1·84 (0·67–5·08)	0·24	..	..
Arrhythmia	..	..	1·59 (0·87–2·89)	0·13
CAD	1·35 (0·81–2·24)	0·25	..	..
Indwelling catheter	1·35 (0·50–3·62)	0·55	..	..
Recurrent skin infections	2·87 (1·10–7·45)	0·03	3·07 (1·10–8·56)	0·03
Previous MRSA	6·21 (3·25–11·85)	<0·0001	5·05 (2·48–10·26)	<0·0001
Severe CAP	2·39 (1·55–3·68)	<0·0001	1·87 (1·20–2·94)	0·006
Hospitalisation during the previous 12 months	0·95 (0·65–1·37)	0·77	1·11(0·75–1·63)	0·61
Intravenous antibiotics treatments during the previous 12 months	0·98 (0·55–1·74)	0·94	0·83 (0·44–1·55)	0·55
Oral antibiotics treatments during the previous 12 months	1·44 (0·90–2·32)	0·13	1·54 (0·95–2·49)	0·08

CAP=community-acquired pneumonia. OR=odds ratio. CAD=coronary artery disease. MRSA=meticillin-resistant *Staphylococcus aureus*.

***Table* 3: Independent risk factors for CAP due to MRSA in multivariate logistic regression analysis among all the patients who underwent at least one microbiological test and among all patients with an identified pathogen**

Discussion

This international, multicentre, point-prevalence study showed that patients with community-acquired pneumonia have a low prevalence of MRSA, but that the rates of MRSA-positive pneumonia varied among participating centres from all six continents and among countries within the same continent. Previous MRSA infections or colonisation, recurrent skin infection, and severe community-acquired pneumonia were specific risk factors independently associated with MRSA community-acquired pneumonia.

The low prevalence of MRSA community-acquired pneumonia is the result of a low prevalence of *S aureus* as the pathogen of the pneumonia. Additionally, the rate of MRSA community-acquired pneumonia was lower than that previously reported from administrative databases and retrospective or prospective cohort studies of patients with pneumonia.[7,20,21] This difference in prevalence rates could be driven by several factors, such as the characteristics of the patients evaluated, presence of risk factors among specific communities, and microbial ecology of the region. As presented in our study, the prevalence rate for MRSA is much higher among culture-positive patients with community-acquired pneumonia, consistent with the previous literature.[6] We suggest against using culture-positive patients as a real-life denominator, because this does not represent at risk patients among all the patients with the disease. For instance, all patients with community-acquired pneumonia that have had microbiological testing represent the same patients for whom empirical antibiotic coverage for MRSA would be considered at the time of hospitalisation while waiting 48–72 h for culture results. Thus, clinicians aware of low prevalence rates of MRSA community-acquired pneumonia might not initiate empirical anti-

MRSA therapies, despite the presence of certain clinical characteristics.

Another major finding of our study is that prevalence rates of MRSA community-acquired pneumonia vary from 0% to 18·5% across different continents (appendix p 12) and among countries on the same continent (appendix p 13). The differences observed between continents suggest that Europe has a much lower prevalence rate of MRSA pneumonia than North America, South America, and Asia. However, among the highest participating countries in Europe, Spain had more MSSA than MRSA, by contrast with what was observed in Germany or Italy, where the proportion of MRSA was higher than MSSA (appendix p 12). These differences among continents and countries might be driven by multiple factors, such as differences in microbial ecology (eg, different circulating strains such as USA300 community-associated MRSA in the USA), patient risk factors, antimicrobial resistance patterns, and health-care systems. The immediate implication of these findings is that continent-level antimicrobial guidelines might be inadequate because of differences in prevalence among countries from the same continent (appendix p 13). Furthermore, these findings suggest that recommendations for appropriate antibiotic use should be driven by local MRSA prevalence rates in the community before adopting a generic "one size fits all" recommendation.

Empirical antibiotic coverage against MRSA in patients with community-acquired pneumonia should be initiated on the basis of the presence of specific risk factors.[22] We identify three independently associated risk factors for MRSA community-acquired pneumonia: previous MRSA infection or colonisation, recurrent skin infections, and severe pneumonia. These risk factors were identified consistently in both evaluated cohorts that included patients that underwent microbiological testing or had culture-positive pneumonia. Although previous MRSA infection and recurrent skin infections are well known risk factors for MRSA infection,[23,24] they have not been previously associated with MRSA community-acquired pneumonia to our knowledge. The presence of previous MRSA infection or colonisation, whether by history or MRSA colonisation of the nares, could assist clinicians in stratifying patients at risk for MRSA-positive pneumonia, especially in critically ill patients with severe disease. The high negative predictive value (99%) of MRSA nasal swabs observed in populations with low prevalence of the MRSA community-acquired pneumonia as in our study, suggests that a negative test will preclude the need of empirical anti-MRSA antibiotic coverage.[25] Additionally, some studies suggest that empirical antibiotic therapy against multidrug-resistant pathogens including MRSA pneumonia were associated with worse survival.[22,26] This approach could simplify identification of patients in whom empiric antibiotic coverage is justified and shift the focus to selecting appropriate anti-MRSA antimicrobial drugs.

This study has important strengths and limitations. A strength is the enrolment of a large and diverse group of patients from different continents and countries around the world in GLIMP. However, differences in health-care systems, hospital facilities, and local or regional protocols for the management of community-acquired pneumonia in these centres could limit our findings. Additionally, we were not able to include a high number of investigators from Asia and Africa resulting in a modest assessment of MRSA pneumonia prevalence on these continents. However, GLIMP is the first study to our knowledge to enrol patients across six continents. Despite this large cohort of patients enrolled in 4 days, the sample size could have been larger for the nature of this multicountry study. These results might be due to the characteristics of the study design and the uncertainty about how many patients with pneumonia were admitted at one point in time to the different hospitals. Therefore, this new evidence regarding the prevalence rate of MRSA may inform future observational studies to consider larger sample sizes. Patients included in this study might also have recall bias that would affect the patients' ability to report previous recurrent skin infections or MRSA colonisation. Additionally, not all participating centres universally tested for MRSA colonisation on hospital admission. The number of patients enrolled in some centres was low, which might be explained by the size of the hospital or because the number of patients admitted with community-acquired pneumonia on a particular day was low. Furthermore, seasons differed by country during this study. Some countries were in the autumn on the first day of enrolment, which might explain the low number of patients hospitalised due to community-acquired pneumonia. To mitigate the effects of seasonal variation, we enrolled patients through June to include patients during the southern hemisphere's winter season. It is possible that patients with positive blood cultures for MRSA might also have positive sputum samples, but the dataset only allowed choice of the predominant pathogen from the most likely source of infection and this was not documented.

In conclusion, the global prevalence of MRSA as an aetiological pathogen in community-dwelling patients hospitalised with pneumonia is lower than has been previously estimated. There are important differences in MRSA prevalence between different continents and among countries within the same continent. A better understanding of this variability at a local level is crucial to develop protocols, policies, and guidelines to identify patients at risk for MRSA-positive pneumonia. Finally, the specific risk factors for MRSA community-acquired pneumonia identified in this study might help to assist clinicians when deciding to initiate empiric antibiotic coverage against MRSA. Future epidemiological studies

to assess the fluctuations of microbial ecology of drug-resistant pathogens are needed to improve our understanding of how these pathogens evolve around the world.

Contributors

SA, LFR, PF, and MIR designed the study and invited researchers to participate in the study. SA, LFR, PF, NJS, and MIR enrolled patients in the study, alongside the GLIMP investigators. SA, LFR, PF, GS, SD, AHR, and MIR performed statistical analysis. SA, LFR, PF, GS, SD, AHR, NJS, and MIR wrote and edited the manuscript and contributed intellectually.

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Declaration of interests

We declare no competing interests.

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