

Current prevalence of multidrug-resistant organisms in long-term care facilities in the Rhine-Main district, Germany, 2013

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Multidrug-resistant organisms (MDRO) and in particular multidrug-resistant Gram-negative organisms (MRGN) are an increasing problem in hospital care. However, data on the current prevalence of MDRO in long-term care facilities (LTCFs) are rare. To assess carriage rates of MDRO in LTCF residents in the German Rhine-Main region, we performed a point prevalence survey in 2013. Swabs from nose, throat and perineum were analysed for meticillin-resistant *Staphylococcus aureus* (MRSA), perianal swabs were analysed for extended-spectrum beta-lactamase (ESBL)-producing organisms, MRGN and vancomycin-resistant enterococci (VRE). In 26 LTCFs, 690 residents were enrolled for analysis of MRSA colonisation and 455 for analysis of rectal carriage of ESBL/MRGN and VRE. Prevalences for MRSA, ESBL/MRGN and VRE were 6.5%, 17.8%, and 0.4%, respectively. MRSA carriage was significantly associated with MRSA history, the presence of urinary catheters, percutaneous endoscopic gastrostomy tubes and previous antibiotic therapy, whereas ESBL/MRGN carriage was exclusively associated with urinary catheters. In conclusion, this study revealed no increase in MRSA prevalence in LTCFs since 2007. In contrast, the rate of ESBL/MRGN carriage in German LTCFs was remarkably high. In nearly all positive residents, MDRO carriage had not been known before, indicating a lack of screening efforts and/or a lack of information on hospital discharge.

Introduction

Multidrug-resistant organisms (MDRO) are an increasing problem in hospital care worldwide. In Germany, according to data from the Antibiotic Resistance Surveillance System (ARS) and the European Antimicrobial Resistance Surveillance Network (EARS-Net) system, the meticillin-resistant *Staphylococcus*

aureus (MRSA) rates have not increased since 2008, with a slight decrease from 22% in 2010 to 16% in 2012 in the hospital setting [1-3]. However, an increase in the prevalence of multidrug-resistant Gram-negative organisms (MRGN) has been observed in the past decade [3,4], including a sharp increase in carbapenem-resistant organisms (CRO) [3,5,6]. MDRO are regarded as a potentially serious threat to elderly people living in long-term care facilities (LTCFs). Although various studies on the prevalence of MRSA in LTCFs in Germany [7-13] and other European countries [14-25] have been published (<1% in the Netherlands and Sweden, >20% in Ireland and the United Kingdom (UK)), studies on the prevalence of MRGN such as extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and vancomycin-resistant enterococci (VRE) among nursing home residents in German and in European LTCFs are scarce [7,14,24,26,27]. Although an increasing trend in the occurrence of ESBL-producing *Enterobacteriaceae* and even CRO is found in hospitals all over Europe [1,3,28,29], a lack of knowledge on multidrug-resistant organisms (MDRO) in nursing homes has to be stated. Notably, residents of LTCFs may present various risk factors for MDRO carriage and/or transmission (e.g. older age, comorbidities, medical devices or recurrent antibiotic treatments) [30,31]. To issue recommendations for MDRO screening of LTCFs residents, e.g. upon admission to hospital, a better knowledge of current colonisation rates and the most relevant clinical risk factors is needed. The aim of our study was to assess the current prevalence of MDRO, specifically MRSA, ESBL/MRGN and VRE, obtained by case history and by microbiological culture of swabs from nose, throat and perineum.

Methods

The study was approved by the Ethics committee of the Chamber of Physicians, County of Hesse, Germany. Inhabitants of 26 LTCFs in the Rhine-Main region were asked to take part in this study and to agree to having swabs from nose, throat and perineum taken for analysis for MDRO. Data on sex, age, health characteristics such as hospital stay, antibiotic therapy during the previous three months and surgery within the past 30 days, current healthcare-associated infection and/or antibiotic therapy, presence of urinary or vascular catheters, pressure sores and other wounds as well as case history for MDRO were obtained for all participants, using the well-established HALT questionnaire (healthcare-associated infections in LTCFs) in Europe [32]. An identical data set was obtained from non-participants in order to assess potential bias in participation. Information on healthcare-associated infections was obtained according to the McGeer criteria 1990 [33] and adapted by the HALT project, i.e. physician diagnosis of infection had been included as a criterion in all categories of infection in order to avoid underestimation of the infection rate due to lack of on-site diagnostic testing [32].

Anterior bilateral nasal, throat and perianal swabs were collected from April to May 2013 using culture swabs with Amies collection and transport medium (Hain Lifescience, Germany). Swabs from nose, throat and perineum were taken from residents, with their written consent. The swabs from nose and throat were tested for MRSA, while perianal swabs were tested for the presence of VRE and ESBL/MRGN. All specimens were collected by the local nursing personnel. Collected swabs were processed within 24 hours by streaking on Brilliance MRSA 2 agar (Oxoid, Germany), ChromID VRE agar (bioMérieux, Germany) and CHROMagar ESBL (Mast Diagnostics, Germany) for the detection of MRSA, VRE and MRGN including ESBL-producing *Enterobacteriaceae*, respectively. Definite identification of presumptive *S. aureus*, enterobacterial species and enterococci was confirmed by the VITEK MS matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) automated system (bioMérieux, Germany). The determination of the antimicrobial susceptibility profiles and classification as ESBL/MRGN, MRSA and VRE was performed by the VITEK 2 identification system (bioMérieux, Germany), using either VITEK N263 (*Enterobacteriaceae*), P586 (*Enterococcus* spp.) or P580 (*Staphylococcus* spp.) antimicrobial susceptibility testing (AST) cards according to standard laboratory procedures under strict quality-controlled criteria (laboratory accreditation according to DAkkS and DIN15189:2007 standards; certificate number D-ML-13102-01-00, valid through 06.12.2015). MRSA phenotype was confirmed by detection of the *mecA* gene as described [34]. In addition, PCR for the *luk-PV* (encoding Panton-Valentine leukocidin) gene was performed as described [35]. MRSA *spa*-typing was used as first-line typing tool as described previously [36]. We used the BURP algorithm for attribution to

clonal complexes (www.ridom.de/staphtype/support). For isolates with *spa*-types which are not very often detected we used multilocus sequence typing (MLST) according to Enright et al. [37] as well as the *S. aureus* MLST database (www.mlst.net) for allelic profile analysis. Finally, prevalence rates, Kruskal–Wallis tests and univariate analysis (odds ratios) were performed with SPSS 15 software, IBM, Stanford University, United States (US).

Results

The total population, i.e. residents present in the 26 homes on the day of the survey, numbered 2,404. Of these residents, 690 (26%) took part in the MRSA analysis, while only 455 of them (19%) consented also in anal swabs for analysis of ESBL and MRGN. Characteristics of the total LTCF population and the final study participants are summarised in Table 1. There were no significant differences between participants and non-participants regarding sex, urinary and vascular catheters, pressure sores, impaired mobility, incontinence and disorientation, hospital stay in the past three months, surgery in the past 30 days, current infection or antibiotic therapy. The participants exhibited more ‘other wounds’, they were older, had more often a percutaneous endoscopic gastrostomy tube than the non-participants, and they had more often been treated with antimicrobials in the previous three months. Prevalence rates of positive MDRO anamnesis were lower in the group of the participants than in the total group (not significant). Prevalence for MDRO in swab cultures exceeded the prevalence of case history for MDRO by far: MRSA 6.5% vs 0.7%, ESBL 17.8% vs 0.7%, VRE 0.4% vs 0%.

From 45 detected MRSA-isolates, only 36, which all were positive for *mecA* gene but negative for *luk-PV* gene, could be recultured from stored samples and subjected to *spa*-typing. Of these 36, 21 were attributed to clonal lineage ST225, 10 to clonal complex 22, four to clonal complex 5 (other than ST225) and one to clonal complex 45. Antibiotic resistance phenotypes of the isolates were typical of those usually observed for MRSA attributed to ST225 and CC22 (resistance to beta-lactams, erythromycin, clindamycin, fluoroquinolones) [38]. Only one isolate exhibited mupirocin resistance, and three isolates of ST225 were in addition resistant to fusidic acid.

According to the criteria of the German Commission on Hospital Hygiene and Infection Prevention (KRINKO) [39], Gram-negative pathogens are classified as 3MRGN when resistant to three antibiotic groups (ureidopenicillins, third- and/or fourth-generation cephalosporins and fluoroquinolones) represented by piperacillin, cefotaxime and/or ceftazidime and ciprofloxacin as guiding agents to define resistance for each group. ESBL/MRGN were isolated from swabs from 81 residents; 25 of them tested positive for ESBL and 56 were 3MRGN. Among the 25 residents carrying ESBL-producing *Enterobacteriaceae*, we identified 22

TABLE 1

Characteristics of residents in 26 nursing homes, prevalence of infections, antibiotic therapy, MDRO anamnesis and colonisation status, Rhine-Main district, Germany, April–May 2013 (n = 2,404)

Population characteristics	All residents		Participants		KW test p-value participants vs non-participants
	n = 2,404	%	n = 690	%	
Age >85 years ^a	1,184	49.3	369	53.5	0.009
Male	679	28.2	200	29.0	0.620
Had urinary catheter	225	9.4	63	9.1	0.800
Had vascular catheter	10	0.4	4	0.6	0.430
Had pressure sores	86	3.6	28	4.1	0.424
Had other wounds	129	5.4	47	6.8	0.047
Were disoriented ^a	1,243	51.7	352	51.0	0.648
Had impaired mobility	1,197	49.8	362	52.5	0.102
Hospital stay in previous 3 months	333	13.9	101	14.6	0.486
Had surgery in the past 30 days	37	1.5	13	1.9	0.385
Were incontinent	1,683	70.0	484	70.1	0.958
Had percutaneous endoscopic gastrostomy tube	134	5.6	55	8.0	0.001
Had antibiotic therapy during previous 3 months	309	12.9	109	15.8	0.006
Prevalence of all infections	64	2.7	18	2.6	0.914
Prevalence of oral antibiotic therapy	33	1.4	6	0.9	0.178
Prevalence MDRO vs anamnesis					
MRSA	32	1.3	5	0.7	0.099
ESBL	18	0.7	5	0.7	0.929
VRE	0	0	0	0	1
Prevalence of MDRO colonisation (analysis)					
MRSA	NA	NA	45	6.5	NA
ESBL	NA	NA	81 ^b	17.8	NA
VRE	NA	NA	2 ^b	0.4	NA

ESBL: extended-spectrum beta-lactamase; KW: Kruskal–Wallis; MDRO: multidrug-resistant organisms; MRSA: methicillin-resistant *Staphylococcus aureus*; NA: not applicable/not available; VRE: vancomycin-resistant enterococci.

^a Information missing for one person.

^b 455 of 690 participants were tested for ESBL and VRE.

Escherichia coli, two *Klebsiella pneumoniae*, and one *Klebsiella oxytoca* isolate. Resistance against three antibiotic groups (3MRGN) was detected in 43 *E. coli*, eight *K. pneumoniae*, two *Acinetobacter baumannii*, one *Enterobacter* spp. and two *Pseudomonas aeruginosa* isolates. 4MRGN (Gram-negative *Enterobacteriaceae* resistant against four antibiotic groups, namely those mentioned above for 3MRGN plus resistance to imipenem and/or meropenem) according to the German KRINKO guideline [39] were not detected. Perianal carriage for VRE was observed in two residents (0.4%).

In 43 of 45 of the residents with MRSA colonisation, the colonisation status was previously unknown. Colonisation in both VRE cases and in 79 of 81 residents positive for ESBL-producing *Enterobacteriaceae* had not been known before this study either. In three of five residents with a documented MRSA history, detection of MRSA was not confirmed in our study.

In Table 2, patient numbers and odds ratios for MRSA and ESBL colonisation are shown. Medical history for MRSA (OR = 9.9; 95% CI: 1.6–61.1), urinary catheter (OR = 4.2; 95% CI: 2.1–8.7), percutaneous endoscopic gastrostomy tube (OR = 2.7; 95% CI: 1.2–6.2) and antibiotic therapy during the last three months (OR = 2.6; 95% CI: 1.3–5.1) proved to be significantly associated with MRSA colonisation. The odds ratios for ESBL/MRGN carriage were significantly increased by having a urinary catheter (OR = 1.9; 95% CI: 1.0–3.8). All other characteristics including anamnesis for MDRO (OR >4) proved not to be significant risk factors for ESBL colonisation. One of the two residents with VRE was bedridden and exhibited pressure sores, but neither of them had a catheter or exhibited other risk factors such as a hospital stay during the previous three months.

TABLE 2

Numbers and odds ratios of nursing home residents with MRSA and with ESBL/MRGN colonisation, Rhine-Main district, Germany, April–May 2013 (n = 690)

	MRSA-negative n = 645		MRSA-positive n = 45		MRSA OR		ESBL/MRGN-negative n = 374		ESBL/MRGN-positive n = 81		ESBL/MRGN OR	
	n	%	n	%	OR	95% CI	n	%	n	%	OR	95% CI
Aged >85 years ^a	343	53.2	25	55.6	1.097	0.597–2.015	201	53.7	44	54.3	1.024	0.632–1.658
Male	183	28.4	17	37.8	1.529	0.817–2.862	111	29.7	18	22.2	0.677	0.383–1.196
Had urinary catheter	51	7.9	12	26.7	4.228	2.058–8.686	36	9.6	14	17.3	1.962	1.003–3.837
Had vascular catheter	3	0.5	1	2.2	4.856	0.495–47.652	3	0.8	0	0.0	0.821	0.786–0.857
Had pressure sores	24	3.7	4	8.9	2.520	0.835–7.607	18	4.8	3	3.7	0.761	0.219–2.646
Had other wounds	41	6.4	6	13.3	2.263	0.905–5.654	29	7.8	7	8.6	1.125	0.475–2.667
Were disoriented ^a	323	50.1	28	62.2	1.637	0.879–3.049	199	53.2	48	59.3	1.279	0.786–2.083
Had impaired mobility	332	51.5	30	66.7	1.880	0.992–3.560	197	52.7	52	64.2	1.611	0.980–2.650
Had hospital stay in previous 3 months	95	14.7	6	13.3	0.889	0.366–2.158	61	16.3	9	11.1	0.641	0.304–1.351
Had surgery in the past 30 days	13	2.0	0	0.0	0.933	0.915–0.952	5	1.3	3	3.7	2.838	0.664–12.125
Were incontinent	453	70.2	31	68.9	0.934	0.486–1.794	254	67.9	61	75.3	1.441	0.832–2.497
Had percutaneous endoscopic gastrostomy tube	47	7.3	8	17.8	2.746	1.210–6.235	34	9.1	13	16.0	1.912	0.959–3.812
Had antibiotic therapy during previous 3 months	95	14.7	14	31.1	2.610	1.339–5.088	61	16.3	10	12.3	0.723	0.353–1.480
Prevalence of all infections	15	2.3	3	6.7	2.995	0.834–10.755	12	3.2	3	3.7	1.160	0.320–4.209
Prevalence of oral antibiotic therapy	6	0.9	0	0.0	0.934	0.916–0.953	4	1.1	0	0.0	0.820	0.786–0.857
Prevalence MDRO vs anamnesis												
MRSA	3	0.5	2	4.4	9.938	1.617–61.069	2	0.5	2	2.5	4.709	0.653–33.933
ESBL	5	0.8	0	0.0	0.934	0.916–0.953	1	0.3	1	1.2	4.663	0.289–75.329
VRE	0	0	0	0	NA	NA	0	0.0	0	0.0	NA	NA

CI: confidence interval; ESBL: extended-spectrum beta-lactamase; MDRO: multidrug-resistant organisms; MRSA: methicillin-resistant *Staphylococcus aureus*; NA: not analysed; OR: odds ratio; VRE: vancomycin-resistant enterococci.

^a Information missing for one person.

Discussion

Our point prevalence study on MDRO such as MRSA, ESBL/MRGN and VRE in residents of LTCFs in the Rhine-Main district in Germany revealed a high MRSA prevalence compared with hospital settings, rehabilitation and dialysis units in Germany [40], and a much higher prevalence for ESBL/MRGN carriage, whereas VRE had a very low prevalence in the studied LTCFs.

Our study has the following limitations: Of the 214 LTCFs located in in the Rhine-Main district, the 83 members of the MDRO-network Rhine-Main were asked to participate and 26 of them finally participated in this study. With informed consent being necessary for investigation of MDRO colonisation in nursing home residents in Germany, we were able to enrol only 690 (29%) of all residents in the MRSA study and 455 (19%) in the

ESBL/MRGN study. Our study has features of cluster sampling, which could lead to wider confidence intervals. Participants had significantly more often reported on antibiotic therapy in the past three months than non-participants and were more often supplied with a percutaneous endoscopic gastrostomy tube. However, no significant differences between participants and non-participants were found regarding sex, impaired mobility, disorientation, faecal or urinary incontinence, urinary and vascular catheter etc. Residents with a positive case history for MRSA, ESBL or VRE were not represented more than other residents in the MDRO analysis. Therefore, the hypothesis that residents with positive MDRO anamnesis may take advantage of the opportunity to receive an MDRO analysis free of charge and thus would be overrepresented in the study did not prove to be true. Thus, although the number of

TABLE 3
MDRO in residents of long-term care facilities in Frankfurt am Main compared with other studies in Germany and abroad 2000–13

Country	Year of investigation	LTCFs	Residents tested	MRSA	ESBL	VRE	Reference
		n	n	%	%	%	
Germany							
Berlin	1999	NR	NR	NR	NR	4.2	[26]
Different regions	2000	32	1,342	2.4	NR	NR	[8]
Frankfurt am Main	2000	8	159 ^a	2.5	NR	NR	[8]
Heidelberg	2000/01	47	3,236	1.1	NR	NR	[13]
North Rhine-Westphalia	2000/01	30	1,057	3.1	NR	NR	[11]
Frankfurt am Main	2001	6	319	0.3	NR	NR	[9]
Frankfurt am Main	2007	8	178	9.0	11.2	0	[7]
Hessen	2010/11	11	240	NR	9.6	NR	[27]
Brunswick	2011	32	1,827	7.6	NR	NR	[12]
Frankfurt am Main	2012	8	184	9.2	26.7	2.7	[10]
Rhine-Main region	2013	26	690 ^b	6.5	17.8	0.3	This study
Europe							
France	2004	1	109	37.6	NR	NR	[20]
Slovenia	2005	1	107	9.3	NR	NR	[18]
Belgium	2005	60	2,953	19.9	NR	NR	[19]
Spain	2005	9	1,377	16.8	NR	NR	[23]
Italy	2006	2	551	7.8	NR	NR	[17]
United Kingdom	2007	39	715	22.0	NR	NR	[16]
Ireland	2007	45	1,111	23.3	NR	NR	[15]
Italy	2008	1	120	38.7	64	NR	[24]
Spain	2009/10	17	744	10.6	NR	NR	[21]
Luxembourg	2010	19	954	7.2	NR	NR	[25]
Sweden	2010	9	495	0	3.0	0	[14]
The Netherlands	2011	NR	1,268	0.3	NR	NR	[22]
Other countries							
United States	1998	1	117	24	33	3.5	[45]
Australia	2000	8	292	NR	NR	3.1	[55]
United States	2008	1	84	28	51	4	[43]
United States	NR	1	160	27.5	NR	NR	[41]
United States, California	2008/09	NR	1,000	30.7	NR	NR	[44]
Australia, Melbourne	2010	3	119	NR	12	2	[52]
United States	2006/07	1	161	11.8	22.8	0.6	[42]
China	2011	40	2,020	21.6	NR	NR	[46]

ESBL: extended-spectrum beta-lactamase; LTCF: long-term care facility; MDRO: multidrug-resistant organisms; MRSA: methicillin-resistant *Staphylococcus aureus*; NR: not reported (in the main text or abstract only); VRE: vancomycin-resistant enterococci.

^a Residents were a subgroup of 1,342 residents tested by Heuck et al. [8] all over Germany, 2000.

^b 455 of them were tested for both ESBL and VRE.

participating LTCFs and the response rate of 29% (19% for the ESBL study) among residents was rather low, there is no obvious indication for bias in our study, so that the data can be regarded as representative for LTCFs in the Rhine-Main region in Germany in 2013.

The point prevalence of MRSA colonisation was 6.5% and thus much higher than in earlier studies in 2000–01 in Germany [8,9,11,13], but since 2007, the MRSA prevalence in LTCFs in Germany has not increased further and remained between 6.5% and 9.2% [7,10,12].

The MRSA prevalence we observed was lower than in MRSA surveys in recent years in the US [41–45], China [46], the UK [16], France [20], Ireland [15], and Italy [24], but higher than in the Netherlands and Sweden [14,22] (Table 3).

All MRSA isolates were attributed to clonal lineages (ST) and/or clonal complexes (CC) that are prevalent in German hospitals, in particular ST225 is widely disseminated in the west of Germany [47]. These results indicate primary hospital origin. Prevalence of these

clonal lineages was also reported in a study from 2006 in the west of Germany bordering the Netherlands [48]. None of the isolates reported here were attributed to community-associated MRSA (CA-MRSA) or livestock-associated MRSA (LA-MRSA). That CA-MRSA can represent a substantial proportion of MRSA in nursing home residents has been reported from the US [49], and LA-MRSA has been identified among isolates from Dutch nursing homes [50]. In Germany, CA-MRSA is not common so far, nor is LA-MRSA as nasal coloniser and infectious agent in regions of Germany with low density of livestock farming such as the Rhine-Main region [51]. As all our isolates were susceptible to antibiotics that are recommended as treatment alternatives for MRSA infections, e.g. vancomycin, teicoplanin, linezolid, daptomycin, tigecycline, rifampicin and cotrimoxazol, calculated therapy of severe infections should be unproblematic.

Regarding ESBL and VRE carriage, only two other studies in German LTCFs, not done in Frankfurt am Main [7,10], have been published since 1999 [26,27]. ESBL/MRGN prevalence in our studies was 11.2% up to 26.7% [7,10] and therefore much higher than MRSA prevalence. Three studies from LTCFs in the US and one in Italy exhibited higher prevalence rates for ESBL-producing bacteria than our study [24,42,43,45], whereas in Australian and especially in Swedish LTCFs, ESBL prevalence rates were lower than in the Rhine-Main region [14,52] (Table 3). However, in all studies, ESBL rates exceeded those of MRSA by far [7,10,24,42,43,45]. Prevalence rates of MRSA and ESBL/MRGN in the LTCF residents in our study were even higher than those in a survey on 750 ambulatory patients undergoing haemodialysis enrolled in the Rhine-Main area in summer 2012, presenting 2.1% MRSA, 7.5% ESBL and 5.5% VRE prevalence [53].

Compared with studies on MRSA in LTCFs, only few studies on ESBL/MRGN have been published so far, with a maximum of 495 participants per study. Our study encompassing 455 participants was a comparatively large study. In Germany, up to now, MDRO prevalence rates in residents from nursing homes have only been published for the Rhine-Main region [7,10] and the federal state of Hesse [27]. This is striking because of the well-known and published increase in MRGN in the hospital setting in Germany and abroad.

In Germany, guidelines for hygiene and infection prevention in LTCFs have been published in 2005 [51], including recommendations for the care of residents with MRSA colonisation. According to these guidelines, isolation of those persons is recommended for hospitals but does not need to be applied in LTCFs. A single room (no isolation), however, is recommended if the resident with MRSA colonisation or their roommate exhibits risk factors such as medical devices or wounds. In 2012, KRINKO published a guideline on the management of patients carrying 3MRGN and 4MRGN [39]. It recommends that patients with 3MRGN are

isolated in risk areas such as intensive care units only, whereas patients with 4MRGN must be cared for in single rooms in combination with barrier nursing in all hospital wards. Although the guideline primarily addresses the hospital setting, the KRINKO expert panel recommends that in other healthcare settings such as LTCFs, hygienic measurements for MRGN should not exceed those defined for MRSA [39]. Therefore, a high standard of hygiene should be applied to residents with ESBL/MRGN, but restriction of their mobility in the home and their contact to other residents is not necessary. Staff, however, need to be well informed about new and emerging antibiotic-resistant organisms and must observe good hygiene for the protection of other residents and themselves. Although 4MRGN have as yet not been detected in the residents in our studies, it can be hypothesised that this may soon be the case as 4MRGN rates are continuously increasing in Germany and Europe [54].

In conclusion, the data suggest that MRSA prevalence in LTCFs in the Rhine-Main region is stable, but a high ESBL/MRGN carriage in LTCFs is recognised. No CRO have been detected yet. In nearly all residents with MDRO, the MDRO carriage had not been known before, indicating a lack of screening and/or a lack of information on hospital discharge.

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Conflict of interest

None declared.

Authors' contributions

PP, DM and UH were responsible for the study design, statistical analysis, and did the literature search. MH, PP, DM, CC, VAK and UH contributed to data collection and analysis as well as writing and review of the manuscript.

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