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Original Article

MRSA as an indicator of infection control measures in Turaif General Hospital, Northern Area-Saudi Arabia

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Abstract

Introduction: Saudi Arabia can be considered a hot spot for Methicillin-resistant *Staphylococcus aureus* (MRSA) infections with significant regional variations. As far as we know, this is the first study to evaluate the prevalence of MRSA in clinical samples obtained from Turaif general hospital (TGH), Northern Area-Saudi Arabia, and screening the resistance profile to the most regularly used antimicrobials as an indicator for evaluation of the implemented infection control measures.

Methodology: Totally, 410 Samples were collected from patients in TGH with clinically suspected nosocomial infections. MRSA isolates were identified by the classical bacteriological, biochemical, and cefoxitin-based methods as recommended by the Clinical Laboratory Standard Institute. Confirmation of isolates and testing of their antimicrobial susceptibilities were performed by the automated Vitek 2 compact system.

Results: Totally, 130 nosocomial isolates were detected. *Staphylococcus aureus* (29.23%) was the most frequently isolated Gram-positive pathogen. MRSA represented 39.47% of *Staphylococcus aureus* and 11.54 % of all isolates. MRSA-causing surgical site infections were the most predominant type of MRSA nosocomial infections representing (25.00%). Recent antibiotic therapy, prolonged hospital stays, and indwelling devices were significant risk factors for the development of MRSA infections. Although all MRSA isolates were sensitive to vancomycin, teicoplanin, linezolid, Fosfomycin, and tigecycline, many isolates were resistant to other tested antimicrobials.

Conclusions: Hospital administrators should strengthen the ideal use of antibiotics according to the local hospital policy to control the selective drug pressure on *Staphylococcus aureus* strains with minimizing exposure to the risk factors by implementing the proper infection control policies.

Key words: Antibiotics; infection prevention; methicillin-resistant *Staphylococcus aureus*; prevalence; resistance.

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Introduction

Staphylococcus resistance to Methicillin is explained by the acquisition of one of several staphylococcal cassette chromosomes (SCCmec), which carries the *mec A* gene that encodes an alternative penicillin-binding protein [1], or by the production of ß-lactamase [2]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major challenge to microbiologists due to the emergence and spread of clones with decreased sensitivity to multiple antimicrobials [3].

Hospital-acquired MRSA infections have a major burden on morbidities, mortalities, and healthcare resources. In humans, MRSA can cause minor to severe infectious diseases, such as pyogenic skin and soft tissue infections, food poisoning, suppurative pneumonia, pyogenic endocarditis, osteomyelitis, and otitis media. Continued isolation and characterization of this fatal organism are crucial for the proper prevention and control [4].

Initially, MRSA infections were limited to hospitals, however, it is now increasingly recovered in the community [5]. Hospital-Acquired (Nosocomial)-MRSA, is diagnosed when a culture isolates MRSA after 48 hours of patient admission to a health care facility [6]. The higher morbidity and mortality rates associated with MRSA are not necessarily due to increased virulence of resistant strains but rather may be due to other factors such as the delay in diagnosis [7]. Early detection of *Staphylococcus aureus* (SA) in clinical samples plays a major role in the definitive diagnosis of the etiology of infection and guiding its optimal treatment to avoid its fatal complications [8].

Many risk factors were reported for the development of MRSA infections such as non-optimal administration of antibiotics [9], prolonged hospitalization (especially in intensive care units; ICUs) [10], presence of indwelling devices [11], and previous MRSA colonization [12].

MRSA infections show significant international and national regional variations, which can be related to the implemented infection control efforts to decrease the colonization and spread of this organism. MRSA rate of 0.6% was reported in Sweden and most nearby countries due to proper infection control measures in these countries [13]. The worldwide prevalence of MRSA infections ranges between 13% and 74% [14], while the European range was from 0.9% to 56% in 2014 [15]. In the US, the Center for Disease Control and Prevention (CDC) reported an approximately 50% methicillin resistance rate among SA nosocomial infections in the ICUs [16]. A considerable variation was reported in MRSA prevalence among Gulf Corporation Council Countries (GCC), with the highest rate (29.9%) from Saudi Arabia and the lowest rate (3.3%) from Kuwait [17]. In Egypt, MRSA prevalence varies according to the geographical region. A low prevalence (24.4%) was reported from the AL-Minia-University hospital. On the other hand, higher prevalence rates were reported from Cairo university hospitals (47.9%) and Alexandria University hospitals (up to 75%) [4].

Saudi Arabia can be considered a hot spot for MRSA infections because of many reasons. Saudi Arabia is one of the most populous countries with about 20% of its population who are expatriates. Furthermore, Mass gathering of more than four million Muslims from across the globe during the Umra and Hajj seasons increases the possibility of catching MRSA infections [3]. In Saudi reports, the overall estimated MRSA prevalence was 35.6% during the period between 2002 and 2012 with wide variations among the Saudi regions. MRSA rates varied from 5.97% in Dahran to 94 % in Riyadh cities. Furthermore, MRSA rates in the Makkah region varied from 4.16% to 57.93 % [18].

MRSA infections are usually difficult to treat due to the multi-antibiotic-resistance nature of the causative organisms leading to treatment failure with more complications [19]. The most effective treatment against the multi-antibiotic-resistant MRSA is vancomycin or linezolid. Vancomycin is a glycopeptide antibiotic that is active against Gram-positive bacteria, however, it is ineffective against Gram-negative bacteria, mainly due to their outer membranes [20-22].

While many reports of MRSA isolation and characterization from different countries and regions are available, more reports from different Saudi regions are essentials to assess the burden of MRSA disease among the Saudi population. As far as we know, this is the first study to evaluate the prevalence of MRSA in clinical samples obtained from Turaif general hospital (TGH), Northern Area-Saudi Arabia, and screening the antibiotics profile to the most regularly used antimicrobials as an indicator for evaluation of the implemented infection control measures.

Methodology

Study design and samples collection

Bioethical approval (number 03-07-42) was obtained from the local committee of bioethics of Jouf University, Saudi Arabia. Bioethical approval (number 1660321) was obtained from the local committee of bioethics of Northern Borders-Saudi Arabia.

According to the Northern Borders Health Affairs, TGH is a large hospital in the Northern Area-Saudi Arabia that serves thousands of outpatients, inpatients, and medical emergencies, in addition to performing thousands of one-day surgeries, laboratory tests, radiology examinations, and dialysis sessions [23]. A cross-sectional study was conducted on hospitalized patients in TGH for 6 months starting from November 01, 2020, to April 30, 2021, with the following inclusion and exclusion criteria.

Inclusion criteria

Signs and symptoms of infection became evident after > 48 hours following hospital admission e.g., purulent discharge, turbid urine, and chest X-ray consolidation; especially if patients had indwelling medical devices including intra venous catheter, urinary catheter, wound drains, orthopedic prosthesis, central venous pressure catheter and endotracheal tubes (ventilators); with local or systemic manifestations of infections related to the indwelling devices.

Exclusion criteria

(1) The presence of pre-admission infection (proved by history and clinical examination on admission). (2) Manifestations of infection developed during the first 48 hours following hospital admission.

Isolation and identification of SA

Wound specimens, purulent exudates, throat swabs, ear samples, eye (conjunctival) swabs, respiratory tract samples (including nasopharyngeal, oropharyngeal swabs, sputum if non intubated, bronchoalveolar lavage if intubated), whole blood samples, and urine samples were collected from patients with clinically suspected nosocomial infections, from different departments of TGH, including ICU, medical and surgical wards. All collected samples were processed according to the standard microbiological and biochemical methods in the microbiology laboratory of TGH. All media

included in this study were prepared according to the manufacturer's instructions. Samples were cultured on a suitable medium and incubated aerobically at 35 ºC for 48 hours. After incubation, colonies suspected to be SA were examined with Gram-stained films. The colonies with typical characteristics of SA (Gram-positive, cluster-forming, non-spore-forming, facultative anaerobe, produce β-hemolysis on blood agar with a golden yellow colony on nutrient agar) were sub cultured on Mannitol salt agar [24]. On Mannitol salt agar colonies are yellowish. Catalase and coagulase tests were done [25].

Identification and Confirmation of MRSA

MRSA isolates were preliminarily identified by cefoxitin-based method for detection of *mecA* mediated resistance [20] and interpreted according to the instructions and the guidelines of the clinical and laboratory standards institute (CLSI) [26] then confirmed by the automated method Vitek 2 compact system (BioMérieux, Marcy l'Etoile, France). The reference MRSA strain ATCC 33592 (Oxoid, Basingstoke, UK) was used as a positive control strain in all steps.

Antimicrobial susceptibility testing

It was done by the automated method Vitek 2 compact system (BioMérieux, Marcy l'Etoile, France) using AST580-GP in accordance with the manufacturer's instructions and CLSI guidelines [26]. MRSA strain ATCC 33592 (Oxoid, Basingstoke, UK) was used as a positive control reference strain. Triplicate testing was carried out for each isolate.

Data analysis

A Chi-square test was used to compare the likelihood of an event (methicillin resistance) occurring between 2 groups (methicillin-resistant/methicillin-sensitive). Statistical significance was considered at $p \leq 0.05$. The results were considered highly significant at $p < 0.001$).

Ethics statement

Bioethical approval (number 03-07-42) was obtained from the local committee of bioethics of Jouf University, Saudi Arabia. Bioethical approval (number 1660321) was obtained from the local committee of bioethics of Northern Borders-Saudi Arabia.

Results

During the period of the study, different samples were collected from patients with clinically suspected nosocomial infections, from different departments of TGH. A total of 410 clinical samples were collected. Samples were examined in the microbiology laboratory of TGH after being processed and cultured on appropriate media under appropriate incubation conditions. Infections were detected in 107 samples; 84 samples yielded a single pathogen whereas 23 samples yielded 2 pathogens. Consequently, the total number of isolated nosocomial pathogens was 130.

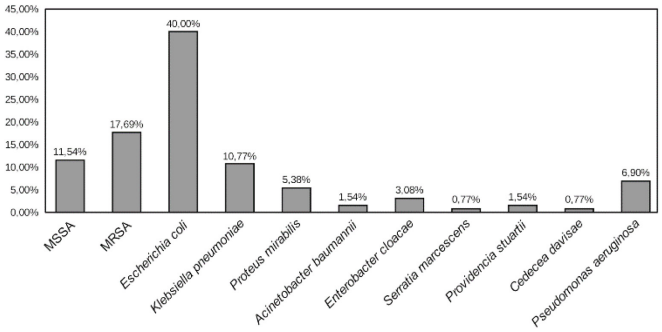
Respiratory tract infections (RTIs) constitute the most common nosocomial infection during the period of the study (37.70%) followed by urinary tract infections (UTIs), bloodstream infections (BSIs), and surgical site infections (SSIs) representing 30.77%, 19.23%, and 12.30% respectively.

SA was the most common Gram-positive organism accounting for 29.23% of all isolates (38 SA/130 isolates). MRSA represented 39.47% of SA (15 MRSA/38 SA) while Methicillin-sensitive *Staphylococcus aureus* (MSSA) represented 60.53% of SA (23 MSSA/38 SA). MRSA represented 11.54 % of all isolates (15 MRSA/130 isolates) (Figure 1).

The distribution of MRSA isolates according to the type of nosocomial infection in TGH is as the following; 6 MRSA isolates were detected from 40 UTIs (15.00%), 4 MRSA isolates were detected from 16 SSIs (25.00%), 3 MRSA isolates were detected from 25 BSIs (12.00%), and 2 MRSA isolates were detected from 49 RTIs (4.10%).

The medical history of the MRSA-infected patients was summarized in (Tables 1-2). Regarding the risk factors for methicillin resistance among SA isolates, it was clear that recent antibiotic therapy, prolonged hospital stays, and indwelling devices (such as IV lines,

Figure 1. Frequency of *Staphylococcus aureus* (SA) isolates among all isolated nosocomial pathogens: SA (MRSA and MSSA) was the most common Gram-positive organism accounting for 29.23% of all isolates (38 SA/130 isolates). MRSA represented 11.54 % of all isolates (15 MRSA/130 isolates). However, *E. coli* was considered the most frequently isolated pathogen during the study period accounting for 40.00% of all isolates.



CVP, and ventilators) were important risk factors for the development of MRSA infections (Table 3).

Regarding the antibiotic sensitivity patterns of MRSA isolates, variable degrees of decreased susceptibilities to some antibiotics were detected. All MRSA isolates were sensitive to tigecycline, fosfomycin, teicoplanin, vancomycin, and linezolid (Table 4).

Discussion

The development of antimicrobial resistance, especially in developing countries, seems to be very much related to the irrational antimicrobial usage due to its injudicious use in hospitals, easy availability at the drug store without a prescription, and non-optimal use in agriculture, fisheries, and animal husbandry. MRSA infections impose a huge risk to public health in community and healthcare settings worldwide. Thus, rapid and accurate diagnosis of MRSA infections is of major importance [27].

The conducted study aimed to isolate MRSA from different sites of infection among patients admitted to TGH, Northern Area-Saudi Arabia and to screen the antibiotics profile of MRSA isolates against the most regularly used antibiotics as an indicator for evaluation of the implemented infection prevention and control measures.

During the period of the study, a total of 410 clinical samples were collected, and the total number of isolated nosocomial pathogens was 130. RTIs were the most common nosocomial infection in TGH during the conducted study (37.70%). This may be due, in part, to the exposure of hospitalized patients to respiratory interventions in ICUs, medical and surgical departments especially patients suffering from

Table 1. Antibiotic therapy, duration of hospitalization, and frequency of the used indwelling devices for MRSA infected patients.

Patients Infected	N (%)
Antibiotic therapy	
No Antibiotic Therapy	0 (0)
Single Antibiotic type (B-Lactams)	3 (20)
Single Antibiotic (Others)	2 (13.3)
More than one antibiotic type (including B-Lactams)	10 (16.7)
Duration of hospitalization	
3-7 Days	1 (6.7)
8-14 Days	5 (3.3)
> 14 Days	9 (60)
Number of devices used	
No Devices	0 (0)
Single Device Type	2 (13.3)
Two Different Devices	6 (40)
More than 2 Devices	7 (46.7)
Total	**15 (100)**

The table shows that the incidence of MRSA infection increases significantly with increased antibiotic prescription, hospitalization duration and number of the used indwelling devices. Prescribing more than one antibiotic type (including B-Lactams) is a high-risk factor (66.67%). Admission for more than 14 days is a high-risk factor (60.00%). Using ≥ two devices is a high-risk factor (86.67%).

Table 2. Age and gender distribution of the MRSA Infections.

Age groups (years)	Test group (15 MRSA)	
	Males	Females
< 12	1 (6.67%)	1 (6.67%)
13-18	1 (6.67%)	-
19-40	1 (6.67%)	1 (6.67%)
41-60	2 (13.33%)	2 (13.33%)
≥ 61	4 (26.66%)	2(13.33%)
Total	9 (60.00%)	6 (40.00%)

The table shows that the incidence of MRSA infection increases in elderly ages. The highest overall age incidence was in the age group ≥ 61 years (39.99%). MRSA infections were more common in males (60.00%).

Table 3. The risk factors for methicillin resistance among SA isolates.

Risk factor	15 MRSA	23 MSSA (control)	*p* value
Antibiotic therapy	15 (100.0%)	9 (39.1%)	< 0.001**
Hospitalization > 1 week	14 (93.3%)	7 (30.4%)	< 0.001**
Indwelling devices			
IV catheter	10 (66.6 %)	5 (21.7 %)	< 0.005*
Urinary catheter	7 (46.7%)	8 (34.8%)	0.339
Wound drains	7 (46.7%)	5 (17.4 %)	0.208
CVP	5 (33.3%)	1 (4.3%)	0.011*
ETT (ventilator)	6 (40.0%)	1 (4.3%)	0.004*
Old age (≥ 61)	6 (40.0%)	6 (26.1 %)	0.305
ICU patients	6 (40.0%)	5 (17.4 %)	0.166
Previous hospital admission	7 (46.7%)	5 (17.4 %)	0.086
Diabetes mellitus	7 (46.7%)	6 (26.1 %)	0.176
Surgical sutures	4 (26.7%)	3 (13.0%)	0.229
Pressure ulcers	2 (13.3%)	0 (0.0%)	0.057
Burn	1 (6.7%)	0 (0.0%)	0.154
Malignancy	2 (13.3%)	0 (0.0%)	0.057

The table illustrates the reported risk factors for infection with MRSA. Recent antibiotic therapy, prolonged hospital stays and indwelling devices (such as IV lines, CVP and ventilators) were important risk factors for the development of MRSA infections. (*Significant, **Highly Significant). MRSA; Methicillin-resistant *Staphylococcus aureus*. MSSA; Methicillin-sensitive *Staphylococcus aureus*.

underlying diseases and old age. On the other hand, it was reported that SSIs were the most common nosocomial infection in a university hospital in Egypt representing 36.0% [8]. Furthermore, in the Egyptian university hospital, MRSA causing SSI was the most predominant type of MRSA nosocomial infections representing 8.45% [8]. A higher rate of SSIs caused by MRSA was detected in the current study representing 25.00%.

In the present study, SA was the most common Gram-positive organism (38 SA/130 isolates). MRSA represented 39.47% of SA (15 MRSA/38 SA). This result is nearly similar to the results of two researches in which MRSA accounts for 30-50% and 31.3% of all SA isolates respectively [28,29]. Higher rates were reported from Riyadh and Qassim hospitals-Saudi Arabia where methicillin resistance represented 77.5% and 90.0% of SA isolated respectively [30,31]. These higher rates could be attributed to the vulnerable groups in the studies. Lower rates were reported from Egypt where methicillin resistance represented 20.0% and 25.4% of SA isolates respectively [8,27].

The prevalence of MRSA infection shows marked variation. In the current study, MRSA represented 11.54% of all nosocomial isolates (15 MRSA/130 isolates). The low MRSA prevalence detected could be attributed to the implementation of effective infection control measures in TGH such as optimal hand hygiene, antimicrobial stewardship policy, active surveillance to identify MRSA reservoirs with decolonization, proper isolation, and contact precautions with regular education of healthcare workers regarding infection control policies and procedures. This result is consistent with the reports from Taiwan and Japan where MRSA accounts for 9.3% and 11.8% of the total nosocomial infections respectively [32,33]. Lower rates were reported from Egypt, Turkey, Ghana, Mexico, South Africa, and Uganda where MRSA accounts for 6.48%, 1.30%, 0.00%, 0.08%, 1.20%, and 3.00% of the total nosocomial infections respectively [8,34-38]. Higher rates were reported in Taiwan where there was a rapid increase in nosocomial MRSA rates (from 26.3% in 1986 to 77% in 2001) [39]. Furthermore, Arega and his colleagues reported that MRSA accounts for 28.00% of the total nosocomial infections in a study conducted in Ethiopia [40].

Saudi Arabia can be considered a hot spot for MRSA infections with significant regional variations as reported in the following studies. In the Riyadh region, the MRSA rates were 94.0 and 24.00% [41,42] respectively. In the Al-Qassim region, the MRSA rate was 52% [43]. In the Makkah region, the MRSA rates were 39.5 and 55.00% [44,45] respectively. In the Al-sharqia region, the MRSA rates were 5.97, 38.38, and 28.00% [46-48] respectively. In the Assir region, the MRSA rates were 43.00 and 61.72% [49,50] respectively. In the Hail region, the overall MRSA rate was 17.33% [51]. In the Al-Gouf region, the MRSA rates were 13.0 and 8.50% [52,53] respectively.

The prevalence of MRSA infection shows marked variation according to the diagnostic methods (some investigators used the culture of clinical specimens only, and others used active surveillance cultures), studied populations, host factors, environmental factors, and the implemented infection prevention and control measures (some hospitals are stricter than the others).

Regarding the risk factors detected in the current study, it was clear that MRSA infections were more common in males (60.00%) and increase significantly with an increased antibiotic prescription, increased hospitalization duration, and increased number of the used indwelling devices as well as in elderly ages. Prescribing more than one antibiotic type (including B-Lactams) is a high-risk factor (66.67%). Admission for more than 14 days is a high-risk factor (60.00%). Using ≥ 2 devices is a high-risk factor (86.67%). The highest overall age incidence was in the age group ≥ 61 years

Table 4. Antibiotic sensitivity of the MRSA isolates by Vitek 2 compact system.

Antibiotic	Resistant: No. (%)	Intermediate: No. (%)	Sensitive: No. (%)
Benzylpenicillin	15 (100%)	0	0
Cloxacillin	15 (100%)	0	0
Oxacillin	15 (100%)	0	0
Cefaclor	15 (100%)	0	0
Levofloxacin	9 (60.00%)	1 (6.67%)	5 (33.33%)
Gentamicin	7 (46.67%)	3 (20.00%)	5 (33.33%)
Erythromycin	7 (46.67%)	5 (33.33%)	3 (20.00%)
Clindamycin	8 (53.33%)	3 (20.00%)	4 (26.67%)
Tetracycline	3 (20.00%)	0	12 (80.00%)
Tigecycline	0	0	15 (100%)
Fosfomycin	0	0	15 (100%)
Teicoplanin	0	0	15 (100%)
Vancomycin	0	0	15 (100%)
Linezolid	0	0	15 (100%)

(39.99%). This may be due, in part, to the greater likelihood over time of becoming colonized with MRSA from either horizontal nosocomial transmission or endogenous emergence of resistance. These results were supported by many reports, in which the majority of nosocomial MRSA infections occur in persons with multiple risk factors and this could explain the differences among hospitals in MRSA rates [8,54,55].

Regarding the antibiotic sensitivity patterns of the isolated MRSA strains, all isolates are resistant to benzylpenicillin, cloxacillin, oxacillin, and cefaclor. These findings agree with the results of Taha and his colleagues and Noto who reported MRSA resistance to ampicillin, penicillin, and cephradine antibiotics [8,56].

During the study, MRSA was found to be resistant to levofloxacin (60%), clindamycin (53.33%), gentamicin (46.67%), and erythromycin (46.67%). Higher rates of resistance were reported by many studies. Adwan and his colleagues reported that up to 82.1% of nosocomial MRSA isolates were resistant to erythromycin and therefore, the macrolides cannot be considered first-line therapy for serious *Staphylococcal* infections [57]. Al-Tawfiq reported that nosocomial MRSA isolates showed resistance to ciprofloxacin (76.6%), clindamycin (76.6%), and erythromycin (68%) [46]. Taha and his research team reported that MRSA was found to be resistant to ciprofloxacin (65%), clindamycin (89%), gentamicin (80%), and erythromycin (88%) [8].

In the current study, most (80.00%) MRSA isolates were sensitive to tetracycline. This result agrees with Colakoglu and his colleagues who found that all MRSA isolates were sensitive to tetracycline [58]. On the other hand, it was reported that 92% of MRSA isolates were resistant to tetracycline in the Egyptian university hospital mentioned above [8].

Fortunately, in the current study, all (100.00%) MRSA isolates were sensitive to tigecycline, fosfomycin, teicoplanin, vancomycin, and linezolid. Glycopeptides are the antibiotics of choice for MRSA infections. Clinical failure with vancomycin has been already observed in many studies conducted in Egypt [8,59] and Saudi Arabia [59,60] where many MRSA isolates showed multidrug drug resistance patterns.

The variations in the reported antimicrobial resistance patterns among different national and international sites can be explained by the selection pressure of certain drugs used according to the local hospital policy. Moreover, the variations may be due to the irrational use of antimicrobial agents in food-producing animals', chickens' and fishes industry as documented in the Al-Qassim region of Saudi Arabia [31].

A limitation of our study was that the local laboratory of TGH does not have facilities for molecular approaches. Molecular-based typing method of MRSA isolates is essential during outbreaks of healthcare-associated infections.

Conclusions and recommendations

As far as we know, this is the first study to evaluate the prevalence of MRSA in clinical samples obtained from TGH, Northern Area-Saudi Arabia as an indicator for evaluation of the implemented infection prevention and control measures. Low MRSA prevalence, with susceptibility to the most regularly used antimicrobials, was detected indicating well-implemented infection control measures in TGH.

The appearance of some MRSA strains with variable degrees of reduced susceptibilities to some antibiotics should alarm the hospital administers to strengthen the optimal use of antibiotics according to the local hospital policy to limit the selective drug pressure on SA strains with minimizing exposure to the risk factors by continuing implementing of the proper infection control policies. The control of the extremely adaptive MRSA organism must be a continuous team effort among all healthcare workers.

More studies of MRSA prevalence from different Saudi regions are required with a comparison of the results to assess the burden of MRSA disease among the Saudi population and try to improve the overall implemented infection control measures to limit the spread of such fatal organisms.

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Authors' Contributions

All authors designed and performed the research and the manuscript.

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