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Review

Burden of clinical infections due to *S. pneumoniae* during Hajj: A systematic review

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ABSTRACT

The burden of pneumococcal disease at Hajj has not been precisely evaluated through a systematic review. To this end we have conducted a systematic review on the burden of clinical infections due to *Streptococcus pneumoniae* among Hajj pilgrims.

Major electronic databases including OVID Medline, Web of Science, OVID Embase, Social Sciences Citation Index, Google Scholar and relevant websites (e.g., online Saudi Epidemiology Bulletin) were searched by using MeSH terms and text words containing but not limited to 'Hajj', pneumonia and *S. pneumoniae*. This was buttressed by hand searching of reference lists of identified studies.

Of 21 full text papers reviewed, nine articles were included in this review. Seven studies reported the burden of pneumococcal pneumonia and the other two reported the burden of invasive pneumococcal diseases including meningitis and sepsis. The proportion of pneumonia that was pneumococcal ranged from 1% to 54% of bacteriologically confirmed pneumonias. The pneumococcus accounted for 2/3rd of bacteriologically diagnosed meningitis cases, and 1/3rd of confirmed cases of sepsis. Case fatality rate of pneumococcal pneumonia was recorded in only two studies: 33.3% and 50%. Only one study provided data on antimicrobial susceptibility of *S. pneumoniae* isolates, reporting 33.3% to be penicillin resistant. None of the included studies provided data on serotype distribution of *S. pneumoniae*.

This systematic review highlights the significance of pneumococcal disease during Hajj, and demonstrates paucity of data on its burden particularly on disease-causing serotype.

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1. Background

Each year during Hajj season, the Kingdom of Saudi Arabia hosts over two million pilgrims from all over the world. High population density, including crowded sleeping conditions, has facilitated infectious disease transmission and other health risks straining the healthcare resources of the host country [1].

Respiratory illness is the commonest cause of morbidity and an important cause of mortality at Hajj [2,3]. Pneumonia is the leading cause of hospital admission during Hajj [4,5]; it is also considered to be the second or third most common cause of admission to ICU during Hajj [6–8]. The point prevalence of pneumonia during the Hajj 1986 was about five per 100,000 pilgrims [9], but it reached to respectively 240 and 340 in the years 2004 and 2005 [10,11], and 450 in the years 2004–2009 [11]. More recently, a retrospective cohort analysis of clinical data at a Madinah hospital suggest that during the Hajj seasons between December 2004 and November 2013, 23% of total admissions to general wards and 20% of all ICU admissions were due to pneumonia [12]. Pneumonia accounted for 39% of total hospital admissions in 2002 [3], 20% of admissions in 2003 [2], and 27% of intensive care unit (ICU) admissions in 2009–2010 [7]. Microbiological analysis identifies *S. pneumoniae* to be a common cause for pneumonia, severe sepsis and septic shock among Hajj pilgrims [13,14]. Globally, pneumococcal disease accounts for perhaps millions of fatalities annually, especially at the extremes of age [15–17].

In many centres, including in Makkah (the key Hajj city), strains of *S. pneumoniae* are showing rising rates of resistance to penicillin and several other antibiotics [18–21]. Pharyngeal swab samples taken from otherwise asymptomatic Hajj pilgrims in 2011 and 2012 identified over 50 different serotypes, with the most prevalent serotypes being non-susceptible to antibiotics [22]. In a prospective study conducted during the Hajj 2013, over 30% of pharyngeal isolates from pilgrims were found to be non-susceptible to penicillin, and about 25% to erythromycin [23]. The studies also confirmed that pilgrims newly acquire *S. pneumoniae* carriage at Hajj and can potentially import the pathogen to their countries of origin [23,24].

Despite these important findings from carriage studies, the burden of pneumococcal disease at Hajj has not been precisely evaluated through a systematic review. With the availability of newer conjugate vaccines covering higher number of serotypes, vaccination could be an effective way to reduce morbidity and mortality from pneumococcal disease [25,26]. The aim of this systematic review is to synthesise data on the burden of confirmed clinical infections due to *S. pneumoniae* among Hajj pilgrims including data on antimicrobial resistance where available in order to quantify the burden of disease and inform vaccination policy.

2. Methodology

2.1. Search strategy and selection criteria

A search of electronic databases was conducted from database inception to February 28, 2018. Database searched include OVID Medline, Web of Science databases consisting of the Science Citation Index, OVID Embase, Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index- Science, and Conference Proceedings Citation Index- Social Science & Humanities. We used a combination of MeSH terms and text words including: 'Hadj' OR 'Hadz' OR 'Hajj' OR 'Mecca', OR 'Makkah' OR 'pilgrimage' AND '*Streptococcus pneumoniae*' OR 'pneumococcal infection' OR '*S. pneumoniae*' OR 'sepsis' OR 'meningitis' AND 'vaccines' OR 'vaccination' OR 'immunisation' OR 'polysaccharide' OR 'conjugate' OR 'pneumococcus vaccine' OR 'PCV' OR 'PPV' AND 'Hajj$' OR 'pilgrims' OR 'patients'. The same search terms were applied to each database after ensuring that the MeSH terms were consistent across the databases. Google Scholar and relevant websites including the online Saudi Epidemiology Bulletin were also searched for relevant studies. Finally, a manual search was performed reviewing reference lists of included studies to identify additional potentially relevant papers.

2.2. Study selection

Three reviewers (HR, IR and ASA) independently selected studies for inclusion. Any disagreement was resolved by discussion.

Inclusion criteria were any observational study that reported the burden of confirmed infection due to *S. pneumoniae* among Hajj pilgrims. The target population of this review were Hajj pilgrims of any age, gender and country of origin. Publications in all potential languages were searched. Studies that reported the carriage of *S. pneumoniae*, conducted in non-Hajj setting or that reported respiratory diseases without identifying the pathogens were excluded.

The 'preferred reporting items for systematic reviews and meta-analyses (PRISMA)' statement was used to guide and report the search methodology (Fig. 1).

2.3. Data extraction and quality assessment

Three authors (IR, ASA and MT) independently extracted the data from each study into a data extraction sheet, while another author (HR) arbitrated when a discrepancy occurred. Extracted data included: study design, year and country of conducting the study, sample size, age, diagnostic method used, burden of disease and antimicrobial resistance.

To evaluate the data quality, the Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used. Two authors (ASA and HR) independently evaluated the study quality; any disagreement was resolved through consensus.

3. Results

As shown in the PRISMA flowchart (Fig. 1), a total of 177 titles were screened; of 21 full text papers reviewed, nine articles were included in this review. All the included studies reported the burden of clinical infections due to *S. pneumoniae* during Hajj; the total population sample was 4026 people aged <10 years to 91 years. Males outnumbered females in most studies, ranging from 56.6% to 75%. Seven studies reported the burden of pneumonia caused by *S. pneumoniae* [7,12,14,27–30] and the other two reported the burden of invasive pneumococcal disease (IPD) including meningitis

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