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Title: Transmission of respiratory Tract infections at mass gathering events

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Abstract

PURPOSE OF REVIEW:

Mass gathering events bring people from across all continents increasing the risk of spread of aerosol transmissible respiratory tract infections. Respiratory tract infections for instance in pilgrims attending the world's largest recurring annual pilgrimage, the Hajj are common. We review recent literature on viral and bacterial infections diseases with special focus on the Hajj.

RECENT FINDINGS: The prevalence of bacterial and viral infections continue to increase, due to the acquisition of rhinovirus, coronaviruses (229E, HKU1, OC43), influenza A H1N1, *Streptococcus pneumoniae, Haemophilus influenzae and Staphylococcus aureus* during Hajj. Whilst MERS-CoV continue to circulate in the Middle East, no cases of MERS-CoV have yet been identified in pilgrims during Hajj.

SUMMARY: Respiratory tract infections are a major cause of morbidity in pilgrims attending mass gathering events. The management of severe respiratory infections should consider investigation and empirical coverage for most likely etiology based on syndromic surveillance data from hosting country and /or other relevant exposure history during events. Pneumococcal and Pertussis vaccines should be recommended for Hajj pilgrims.

Keywords: mass gathering medicine, respiratory infections, pneumococci, influenza

Introduction

A Mass Gathering (MG) has been defined by the World Health Organization (WHO) as an occasion, either organized or spontaneous where the "number of people attending is sufficient to strain the planning and response resources of the community, city, or nation hosting the event".[1] The WHO guidelines list diseases to be included in enhanced surveillance: “Have modes of transmission likely to be enhanced in a mass gathering situation (e.g. meningitis, gastrointestinal and respiratory diseases).

Some of the largest mass gathering event are religious. The Hajj is an annual Islamic pilgrimage to Mecca, Kingdom of Saudi Arabia (KSA). This event follows the lunar calendar with pilgrims coming from both northern and southern hemisphere gathering in Mecca bringing to the locally circulating infections imported group from a mixed seasonality and diseases epidemiology. In 2019, the number of pilgrims coming from in- and outside KSA to perform Hajj was 2,489,406.[2] The Kumbh Mela is the largest religious mass gathering in the world attracting over a 100 million Hindu pilgrims from all over India over 3 months every 12 years. The Arbaeen, Iraq, is the largest annual religious gathering in Iraq for Shia Muslims lasting for 14 days and attracting an estimated 15 million pilgrims in 2018. Other mass gathering event are the world Olympic games, football cups and other sports events.

Mass gathering events are bringing people close together from different area, regions and countries, which increases the risk of spreading aerosol transmissible diseases, including transmission of multidrug resistant bacteria.[3] A study of upper respiratory samples taken before and after the 2013 Hajj found that the prevalence of viruses and bacteria increased, from 7.4% and 15.4% before the Hajj to 45.4% and 31.0% after the Hajj, respectively, due to the acquisition of rhinovirus, coronaviruses (229E, HKU1, OC43), influenza A H1N1, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus.*[4]

Surveillance systems need to be in place and should be tailored to target selective diseases/events of public health significance, as no surveillance system can cover every possible event.[5]

In this review we will discuss recent literature on influenza, pertussis, measles, tuberculosis and Middle East Respiratory Coronavirus Syndrome, MERS-CoV at the annual Hajj pilgrimage.

Generic studies on Respiratory tract infections

A study of French Hajj pilgrins between 2014 to 2017 showed that 82.1% presented with Respiratory Tract Infections, RTIs.[6] Respiratory chronic diseases were associated with cough, Influenza-like illness (ILI) and the acquisition of *H. influenzae*. Vaccination against invasive pneumococcal diseases (IPD) and influenza was associated with a decrease in the acquisition of *S. pneumoniae* and prevalence of ILI and aRR = 0.69, 95%CI [0.52-0.92] respectively). Individuals carrying rhinovirus and *H. influenzae* - *S. pneumoniae* together were respectively twice and five times more likely to have respiratory symptoms. Individual with *H. influenzae* - *K. pneumoniae* carriage were twice (p = 0.04) as likely to develop a cough.[7],[8] The use of disposable handkerchiefs was associated with a decrease in the acquisition of *S. aureus* (aRR = 0.75, 95%CI [0.57-0.97]). The study confirmed the effectiveness of influenza and IPD vaccinations in reducing ILI symptoms and acquisition of *S. pneumoniae* carriage respectively.

A study of ill travelers returning from mass gathering events based on the GeoSentinel database found that respiratory diseases accounted for almost 80% of all diagnoses, with vaccine preventable illnesses such as influenza and pneumonia accounting for 26% and 20% of all diagnoses respectively.[9] A study of 9,350 pilgrims from United Kingdom, Australia, Saudi Arabia and Qatar voluntary taking influenza and pneumococcal vaccines prior to Hajj found no observed benefit of combined vaccination (RR = 1.1; 95% CI 0.8-1.4).[10]

Pneumococcal infections

A review of studies on the prevalence of *S. pneumoniae* carriage among Hajj pilgrims before and after participating in the Hajj activities showed a significant increase in nasopharyngeal carriage of pneumococci including antibiotic resistant strains following the pilgrimage, with acquisition rates ranging from 18 to 36%.[10] There was no significant difference observed in the prevalence ratio of pneumococcal carriage between vaccinated and unvaccinated pilgrims. Another study found that the Hajj may increase pneumococcal carriage-particularly conjugate vaccine serotypes and antibiotic non-susceptible strains, although the exact mechanism remains unknown. The Hajj may therefore provide a mechanism for the global distribution of pneumococci.[11] However, the efficacy and effectiveness of the current vaccines in the context of Hajj and Umrah have not been studied.[12]

Influenza

A review of studies of influenza in Hajj pilgrims found influenza vaccination to be significantly associated with a reduced prevalence of ILI (RR 0.5 [95% CI 0.4, 0.6], P < 0.01).[13] The vaccine benifits extend beyond protecting the individule during their ritual to prevention of outbreaks in home countries secondary to diffrent strains of influenza. A study of the uptake of influenza vaccines among Hajj pilgrims found the vaccine uptake was 2% and the attack rate of influenza was 8.2%.[14]

Middle East Respiratory Syndrome Corona virus – MERS-CoV

The MERS-CoV was first described from Saudi Arabia in 2012.[15] With a mortality rate of 59.8% in one study from Riyadh in people with co-morbidities like chronic lung diseases and renal failure.[16],[17] A study of 132 Hajj pilgrims found that influenza A, followed by non-MERS human coronaviruses, rhinoviruses, and influenza B was the most common virus acquired during the Hajj.[18] Regulations for screening all camels participating in racing and beauty competitions in KSA had limited spread of MERS-CoV during such gatherings and also from slaughtered camels at Hajj ritual. No cases of MERS-CoV have yet been identified in pilgrims during Hajj or upon return to their home countries. Other coronaviruses identified at the Hajj include alpha-coronavirus and beta-coronavirus, of which the 229E strain is most common cause of upper respiratory tract illnesses. A study from France evaluated the level of knowledge of Middle East respiratory syndrome coronavirus (MERS-CoV) among Hajj pilgrims before and after an education health programme during international vaccine consultations in France.[19] Less than 25% were aware of the routes of transmission, symptoms and preventive behaviours and remained less than 50% after the Hajj.

Tuberculosis

Tuberculosis remains the commonest cause of death from an infectious disease worldwide. Many people attending the Hajj and other religious mass gathering come from TB high endemic counties defined as an annual incidence of 150/100 000 population.[20] TB is a slowly evolving disease and it is not unusual for persons to have symptoms like cough for months before they are diagnosed with active, pulmonary TB. Thus, people with pulmonary TB will participate in mass gatherings and with the close contact with others, the risk of transmission is high. No pre-departure screening for active TB, for instance with a chest X-

ray, CXR, is currently practised for pilgrims attending the Hajj as most likely it will not be cost effective.

The incidence of tuberculosis in travelers have been reported. A study of peace corps volunteers from the U.S.A. found 0.02 cases of active TB (95% CI 0.01-0.03) per 1000 Volunteer-months, which is 24/100 000 persons per year.[21] An earlier study including travellers from The Netherlands to high endemic countries found that 1.8% converted from a negative to a positive skin test.[22]

These two study can not directly be extrapolated to mass gathering events, but mass gathering in TB high endemic countries or involved people from high endemic countries like the Hajj, must be assumed to have a higher risk.

One study including 352 pilgrims to the Hajj found that out of 149 with a negative interferon-gamma release assay, IGRA, pre-Hajj 10.4% had positive IGRA post Hajj.[23]

This indicate that 10% of the Hajj pilgrims is exposed to TB during the Hajj, which is an exordinary high number. As 90% of exposed people never develop active TB and it many take years before a latent TB infection develops into active TB. It is therefore difficult to access the real risk. In addition, issues relating to the standarization of the cut-off positive results for IGRA among pilgrims coming from over 180 countries need to be taken into consideration. Howver, there in urgent need for repeating this study using tuberculin skin test and IGRA test pre- and post Hajj to determine the risk and perhaps take steps to perform pre-Hajj screening for active TB for instance with a CXR.

Vaccinations

Every year the Saudi Arabian Ministry of Health issues updated guidelines on travel immunisation recommendations for pilgrims (Table 1).[24] Apart from three mandatory vaccines are the quadrivalent meningococcal vaccine for all pilgrims and the Yellow fever and Polio vaccines for pilgrims coming from countries with active polio transmission, recommended vaccines include influenza vaccine and pneumococcal vaccine. Owing to the high incidence of pertussis seen among Hajj pilgrims in 2003, *Bordetella pertussis* is considered a risk in pilgrims, especially those who have not completed their immunisation schedule.

The KSA Ministry of Health recommends that all pilgrims attending the Hajj be up to date with their adult immunizations, inclusive of all vaccine preventable diseases. But no studies

have been conducted in KSA to check compliance of pilgrims with pertussis immunization or the percent of pilgrims who demonstrate pertussis acute infection or immunity.

Non-Influenza Vaccine preventable diseases

Pertussis. Pertussis (whooping cough), is an infectious disease of the respiratory tract caused by *Bordetella pertussis*, and is endemic in all countries. In 2014 the WHO reported an estimated 24.1 million pertussis cases and 160 700 deaths from pertussis in children < 5 years of age globally. Increase of pertussis attack rates have been observed during community outbreaks , even in populations with a high rate of immunization due to the waning of immunity conferred by childhood vaccination.[25]

In a prospective seroepidemiological study among 358 adult Malay pilgrims from Singapore to determine the incidence of pertussis, 5 (1.4%) were found to have acquired pertussis during the Hajj. [21] Of the 40 pilgrims who had no pre-Hajj immunity to pertussis, 3 (7.5%) acquired pertussis.[26] The vaccination coverage for pertussis for example was found to be 30% among Australian pilgrims who attended pre-travel clinics.[27] This is a public health concern as returning pilgrims may present a reservoir transmitting infection to susceptible infants in their home countries who are prone to most severe form of infection.[28] Extrapolating from the reported high incidence in travellers to the Hajj, the risk may be more substantial than thought. There are no universal recommendations for pertussis vaccination for adult travellers, and studies are needed to develop evidence-based guidelines.

Measles. Measles is an air born viral infection that can rapidly spread resulting in serious disease in non-immune individuals especially infants. The infection had re-emerged at global level due to fall in vaccination coverage in many countries and there had been reports of outbreaks in different settings including mass gathering events. Measles outbreaks has occurred among unvaccinated participants in 2005 at a church gathering in the USA,[29] international youth sporting event in Pennsylvania in 2007, in France during the Taizé festival in 2010, , during the international dog show in Slovenia in 2014 and at the Disney theme parks in California.[30],[31],[32] . Most of these outbreaks involved secondary cases through the participants spreading the illness upon return to their country of origin.

The re-emergence of measles became a major public health issue which had ignited the concerns about travel related spread of measles and special concerns were raised about mass gathering events. For Hajj 2019 we reviewed measles vaccine coverage, measles incidence and number of pilgrims attending Hajj from each of the countries. Based on the expected age of pilgrims we assumed that 70% of pilgrims were measles-immune (born before 1957) and calculated the number of susceptible pilgrims based on the vaccine coverage based on 2018 Hajj data. An estimated 110 measles importations was predicted to occur during the Hajj 2019 but KSA Ministry of Health did not report any cases nor there reported cases or outbreaks outside KSA from returning pilgrims.[22]

The unintentional 'mass gatherings' such as refugees sheltering in very crowded camps with poor hygiene and vaccines coverage (e.g. Syrian camps post displacement from civil war) are not usually regarded as mass gathering events, but nevertheless they pose great risk of aerosol transmissible diseases transmission like tuberculosis, measles, and polio.[33] Mumps outbreaks had been rarely reported following mass gathering events like the one happened after Easter festival in Austria in 2006 and resulted in 214 individuals been affected.[34]

The recommendations from WHO and CDC for health consultation prior to travelling to a mass gathering had been associated with a twofold increase in vaccinations among Hajj pilgrims who seek such advice compared to those who do not.[23]

Multidrug resistant bacterial infections

The potential spread of drug resistant bacterial infections between participants in mass gathering event – whether symptomatic or not – is a concern where many of nations now experiencing upsurge in prevalence of such superbug adding to that the unrestricted access to antibiotics from private pharmacies. A recent study in hospitalized Hajj pilgrims in Mecca found that *Escherichia coli* (28%), followed by *Klebsiella pneumoniae* and Pseudomonas were most commonly encountered antibiotics resistant bacterium. Methicillin-resistant *Staphylococcus aureus* (MRSA) was found in 9.6%.[35] Nasal swabs were taken from 979 Umrah visitors before and after events to evaluate the transmission of *Staphylococcus aureus* showed an increase in the carriage rate from 15.8% to 24%.[36]

Prevention and Management of respiratory infection in participants at mass gathering activities

A cross-sectional study of 225 Malaysian Hajj and Umrah pilgrims assessed the knowledge, attitude and practice towards prevention of RTIs during the 2018 Hajj.[37] Using a validated self-administered questionnaire showed good knowledge of RTIs among Malaysian pilgrims. However, a poor attitude was reflected in their preventive practice behaviours and the study highlighted the need for an educational health campaigns to raise pilgrims to awareness of RTIs.

Proper planning and preparation for the participation in mass gathering event is the most important step in minimizing risk of contracting infections. Each individual should consider his vulnerability and discuss ahead of time with his physician possible strategies in mitigating the risks based also on understanding the geographical epidemiology and season of the event. The participants need for vaccines like influenza, meningococcal, measles, pertussis among others should be assessed and given at least two weeks prior to the event. Routine infection prevention and control (IPC) measures like practicing hand and respiratory hygiene are important tools in reducing the transmission of infections and it should be in educational and advocacy materials for the event.

Returning participants should seek medical attention if they develop acute respiratory illness with fever and cough during the two weeks after their return, or cough persisting more than three weeks especially if symptoms are severe enough to interfere with their daily activity. They need to be reminded about respiratory hygiene practice when ill (covering mouth and nose when coughing or sneezing; washing hands and or cleaning it with alcohol-based hand rubs after contact with respiratory secretions; and keeping a distance of one meter from other persons) to prevent speeding infection. The management of a mass gathering participants with severe respiratory infection should consider investigation and empirical coverage for most likely etiology based on syndromic surveillance data from hosting country and /or other relevant exposure history during events.

Conclusion: Respiratory infections are common among Hajj pilgrims with viral etiology identified in most of them, but bacterial infections are also possible. The management of severe respiratory infections should consider investigation and empirical coverage for most likely etiology based on syndromic surveillance data from hosting country and /or other

relevant exposure history during events. Pneumococcal and Pertussis vaccines should be recommended for Hajj pilgrims.

Bullet Points:

- Respiratory infections are common during Mass Gathering events with viral etiology being common.
- Syndromic surveillance and management should be applied during Mass Gathering events.
- Vaccination of people attending Mass Gathering events against influenza, pneumococcal disease and pertussis should be reccomended

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** Evaluate the effect of infection preventive measures.

Table 1. Vaccination requirements for the 2019 Hajj.[24]

	Pilgrims coming from	**Vaccination**
Yellow fever	**Africa:** Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Guinea, Guinea-Bissau, Gambia, Ghana,	• Yellow fever vaccination (≥ 10 days after the date of vaccination). • If no proof of vaccination, Pilgrims will be placed under surveillance for 6 days from the last date of potential exposure.

	Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, South Sudan, Togo and Uganda. **South and Central America:** Argentina, Venezuela, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Paraguay, Peru, Bolivia, Suriname, and Trinidad and Tobago.	
Meningococcal Vaccine (polysaccharide or conjugate)	**a) Any visitor** **b) Visitors from African meningitis belt:** Benin, Burkina Faso, Cameroon, Chad, Central African Republic, Côte d'Ivoire, Eritrea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal and Sudan **c) Pilgrims from within Saudi and the Hajj workers,** all citizens and residents of Medina and Makkah	**a) V**accination with ACYW135: vaccine within the last 3 years (polysaccharide vaccines); within 5 years (conjugate vaccines), and > 10 days before arrival to Saudi Arabia. **b)** ACYW135 vaccine (as above) **c)** ACYW135 vaccine (as above)

Poliomyelitis	**A) Pilgrims from areas with active poliovirus transmission of a wild or vaccine-derived poliovirus:** Afghanistan, Nigeria and Pakistan. **B) Countries at risk of polio reintroduction:** Cameroon, Central African Republic, Chad, Guinea, Laos People's Democratic Republic, Madagascar, Myanmar, Niger, and Ukraine. **C) Countries which remain vulnerable to Polio:** Afghanistan, Nigeria, Pakistan, Papua New Guinea, Syria, Myanmar, Yemen and Somalia	**A)** At least one dose of bivalent oral polio vaccine (bOPV), or inactivated **A)** poliovirus vaccine (IPV), in the last 12 months and $\geq$ 4 weeks prior to departure **B)** As above **C)** As above and additionally those pilgrims will receive 1 dose of OPV on arrival to Saudi Arabia.
Seasonal influenza	All pilgrims (internal and international) and all health-care workers in the Hajj area	A recommendation
Cholera		No specific vaccine requirement

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