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**Meningococcal vaccination and travel health in Hajj pilgrims – A
study of pilgrims to Mecca, Saudi Arabia**

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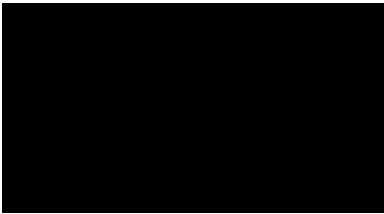
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Statement of own work

I, Abrar Alasmari, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Signature



April 2020

Abstract

Background

Hajj brings millions of pilgrims from different countries into a confined place. A number of outbreaks of meningococcal disease have been reported after the Hajj. All pilgrims are required to receive a quadrivalent meningococcal vaccine at least 10 days before the Hajj. They are also advised to follow travel health advice to reduce the risk of acquiring infections. We conducted a study to investigate the association between time of meningococcal vaccination and carriage of *Neisseria meningitidis* pathogenic serogroups A, C, W, and Y. Patterns of health problems encountered by pilgrims and preventive measures adopted during the Hajj were also investigated.

Methods

A cross-sectional oropharyngeal carriage survey was conducted in 2973 Hajj pilgrims in 2017. A two stage sampling method was used to select departing flights. An electronic data collection tool ('Open Data Kit' (ODK)), was used to gather demographic, health and exposure data through questionnaires. Real-time polymerase chain reaction (rt-PCR) was used to identify *N. meningitidis* and serogroups.

Results

The overall prevalence of *N. meningitidis* carriage was 4.6%. Meningococcal carriage of pathogenic serogroups A, C, W, and Y was not significantly associated with time of vaccination. A total 22.58 % were likely unvaccinated against meningococcal disease. 38.7% reported symptoms of upper respiratory tract infections and 5.4% of travel

diarrhoea. Compliance with facemask use was 50.2%. Changing facemask every 4 hours was found to be a significant protective factor for URTI's. No significant association was found between having a chronic disease and seeking pre-travel advice.

Conclusion

Whilst this study did not find any association between timing of meningococcal vaccination and carriage of *N. meningitidis*, it did highlight the issue of unvaccinated pilgrims and a need to strengthen compliance with the current vaccination policy. Early pre-travel health advice should continue to be enforced.

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List of acronym

CDC	Centre for Disease Control and Prevention
HIV	Human Immunodeficiency Virus
HCV	Hepatitis C Virus
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HbeAg	Hepatitis B e-antigen
IPV	Inactivated Poliovirus Vaccine
KAIA	King Abdulaziz International Airport
KSA	Kingdom of Saudi Arabia
KAUST	King Abdullah University of Science and Technology
LSHTM	London School of Hygiene & Tropical Medicine
MCV-4	Meningococcal Conjugate Vaccine (Quadravalent)
MOH	Ministry of Health
MPSV-4	Meningococcal Polysaccharide Vaccine (Quadravalent)
NM	<i>Neisseria meningitidis</i>
OPV	Oral Polio Vaccine
PCR	Polymerase Chain Reaction
UK	United Kingdom
US	United States
WHO	World Health Organization

Chapter 1: Background

1 Background

1.1 Introduction

Hajj, the spiritual journey that Muslims undertake to Mecca in Saudi Arabia is one of the largest annual events to occur globally. Performing Hajj is one of the religious obligations and rituals of worship for Muslims.¹ Every adult Muslim who is economically and physically capable of doing so should complete Hajj at least once during their lifetime.²

This particular religious ritual is based on the Islamic lunar calendar, meaning that the event moves back by approximately 10 or 11 days every year.³ Hajj begins on the 8th day of the last month of the Islamic lunar calendar and lasts for 5 days.⁴ Figure 1 illustrates the distinctive stages of the Hajj.⁵

Hajj gathers Muslims from across the world. Pilgrims from different ethnicities, age groups and socioeconomic status were reported to have come from more than 183 nations worldwide.^{6, 7} In 2019, a total of 2,489,406 Muslims, both residents and non-residents of Saudi Arabia performed the Hajj.⁸

Mecca is also a place where the less significant pilgrimage, the Umrah occurs. In contrast to the Hajj, the Umrah is of a shorter duration and can be undertaken at any time of the year.⁴

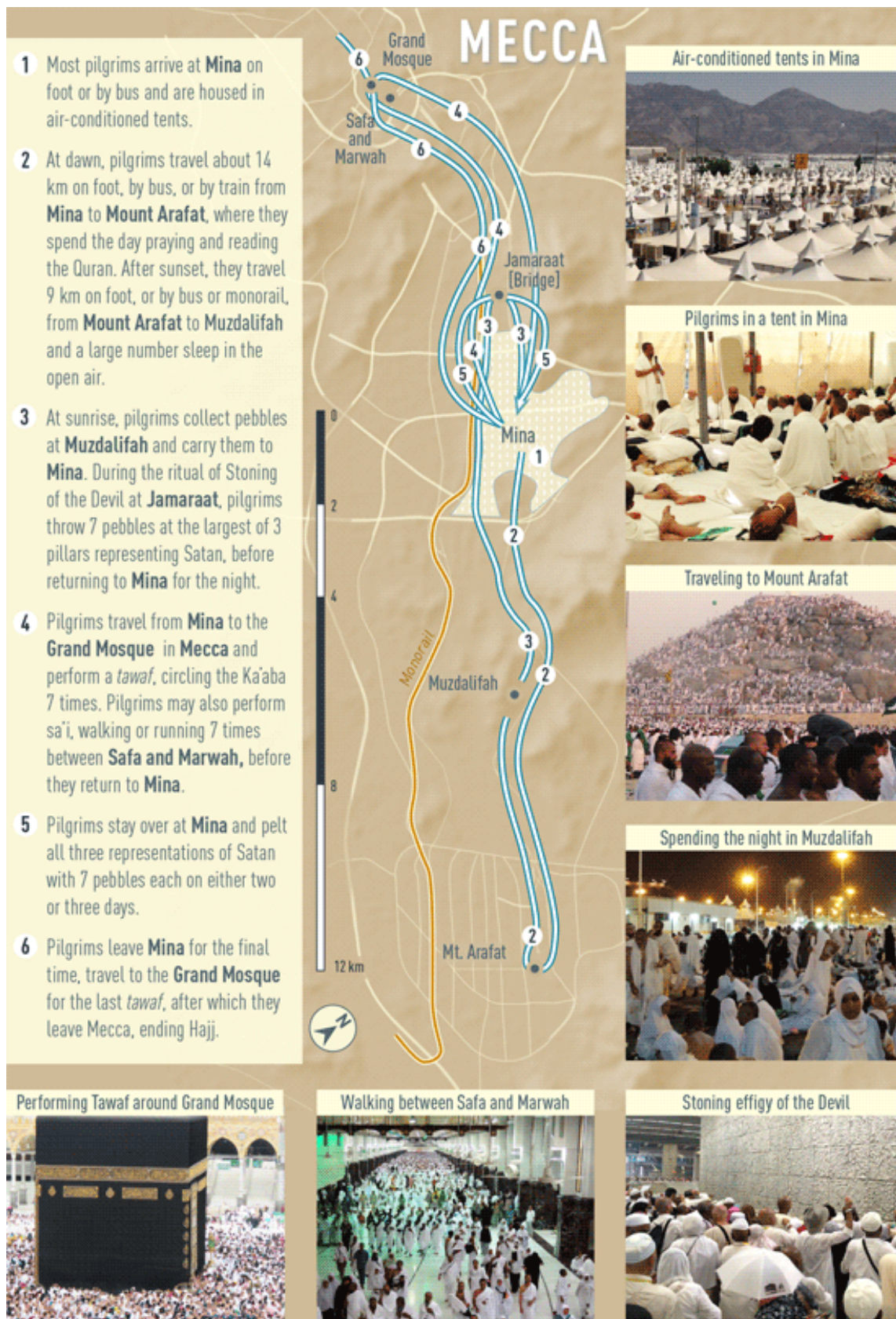


Figure 1: Stages of the Hajj.⁵

Developments in modern travel and religious tourism as well as the increase in the Muslim population worldwide have made travel to Mecca for the Hajj easier and more frequent. However, other challenges have been associated with the increase in the number of pilgrims attending the Hajj, particularly for those older and with comorbidities.^{9, 10}

All domestic and international pilgrims should register through an authorised Hajj agency by means of the Saudi authorities.^{11, 12} The agency has responsibility for providing food and accommodation for their Hajj travellers who usually share the same tent in Mina.^{13 14} Mina is the main Hajj location bordering on Mecca and is where pilgrims spend most of their time during Hajj.¹⁵ The tents have room for up to 100 or more pilgrims, although the number of pilgrims varies.¹⁶

1.2 Health risk associated with the Hajj

1.2.1 Communicable diseases

1.2.1.1 Meningococcal disease

Overcrowding during Hajj has in the past facilitated the spread of meningococcal disease.¹⁷ Consequently, there have been occurrences of meningococcal outbreaks during Hajj and Umrah pilgrimages, for example, the 1987 outbreak, which was caused by *Neisseria meningitidis* serogroup A. That particular epidemic led to a high attack rate, which was evident both among the pilgrims and their relatives or close associates.¹⁸ Consequently, the health authorities in Saudi Arabia made it obligatory for all Hajj pilgrims to receive bivalent AC vaccine, in order to obtain a visa and moreover, that all pilgrims from sub-Saharan Africa had to take oral ciprofloxacin upon arrival to eliminate nasal carriage.¹⁹

In 1992, two further outbreaks caused by serogroup A (ST5 clonal complex) occurred in Mecca and Jeddah and were both linked to the Umrah season. Furthermore, in 1997, there was a further epidemic during the Umrah season caused by serogroup A.¹⁸ Following the latest Hajj outbreaks in 2000 and 2001, which caused a shift in the epidemic pattern of the disease with phenotype W:2a:p1.5, 2 (ST11), Saudi authorities upgraded their Hajj vaccination policy to a mandatory quadrivalent meningococcal vaccine which must be administered to all Hajj pilgrims. This policy was upgraded to prevent future meningococcal disease outbreak.^{18, 19}

1.2.1.2 Respiratory tract infections

Respiratory tract infections are the most common observed health problem during the Hajj.^{2, 20, 21} The Hajj event is attended by a large number of pilgrims, both young and old, from different nations and ethnicities who can share the same tent. Consequently, the challenges in relation to accommodation and the provision of social amenities to the vast number of people attending the event have led to overcrowding at various Hajj sites, whilst the sharing of accommodation among other challenges has led to detrimental health effects, such as respiratory illnesses.^{22, 23}

Viral and bacterial upper and lower respiratory tract infections circulate among pilgrims during the Hajj,²⁴⁻³³ with hospital data indicate that pneumonia is the most common cause of hospital admission during the Hajj.^{24, 27, 29, 34, 35} It should be noted that the estimated occurrence of respiratory tract infections among pilgrims varies between 20-80%.³¹⁻³³ Simple physical non-pharmaceutical interventions such as wearing a facemask and maintaining hand hygiene are recommended to reduce the risk of respiratory infections.³⁶⁻³⁹ Furthermore, compliance with these personal preventive measures is challenging and varies between studies conducted among Hajj pilgrims.³⁶

Vaccination against respiratory tract infections such as influenzas and pneumococcal vaccines is also recommended to be taken prior to arriving at the Hajj. ^{33 5}

1.2.1.3 Diarrhoeal disease

Diarrhoeal disease is commonplace during Hajj seasons, even though few studies have reported its incidence and aetiology.² During the 1986 Hajj, gastroenteritis (n=381, 76.6%), was the most frequent cause of hospital admissions as regards pilgrims with an incidence rate of 4.4 per 10000. It was noted that 41% (156) of these patients were 60 years or older.⁴⁰ In a study conducted in 2002, gastrointestinal illness was ranked third (n=10,6.3%) after respiratory system (n=91, 57%) and cardiovascular disease (n=31, 19.4%) as reasons for pilgrims to be admitted.³⁰

Cholera, which is an acute bacterial enteric disease caused by vibrio cholerae accounted for a number of epidemics after the Hajj in 1984–86.^{41, 42} The Saudi Ministry of Health (MOH), has stated that cholera has reached Hajj areas and epidemics were recorded as long ago as 1846, with the last epidemic at the 1989 Hajj affecting 102 pilgrims.² The development of sewage systems and an improved water supply have eradicated cholera outbreaks, although few cases of cholera have still been identified in Saudi Arabia.^{43, 44}

Hepatitis A is also widespread in Saudi Arabia and is the most frequent vaccine-preventable illness contracted by visitors. ^{45, 46}

An additional notable cause of diarrhoea and vomiting during the Hajj is food poisoning.⁴⁷ Over the preceding 12 years, the number of cases of food poisoning reported has varied from 44 to 132 in each Hajj season.² Prevention of diarrhoeal diseases involves education of the pilgrims concerning hand hygiene, avoidance of

food (including ice) sold by street vendors, in addition to eschewing food that is made with fresh eggs. Authorities do not permit pilgrims to take food with them, apart from canned food that is enough for 24 hours.⁴⁸

The Ministry of Health scrutinises pilgrims arriving from countries where cholera is commonplace (identified in weekly reports released by the World health organization (WHO). If it is suspected that a pilgrim has the disease samples are collected and those identified as being infected are immediately quarantined. People who have been in contact with infected people are also tested.⁴⁸ It is recommended that pilgrims from developed countries have hepatitis A virus vaccine, though it is possibly needless for pilgrims from developing countries in view of the fact that they are likely to be immune owing to childhood exposure.²

1.2.1.4 Blood borne diseases

Head-shaving is one of the final rituals undertaken during the Hajj. Muslim men shave their heads and women cut a lock of their hair.¹⁶ Blood borne infections such as hepatitis B and C, as well as human immunodeficiency virus (HIV) ⁴⁹ can be transmitted by sharing shaving equipment.² The testing of barbers for blood-borne infections, including hepatitis B and C, besides HIV and the use of disposable sterile single use-blades are obligatory health regulations established by the Saudi authorities for all barbers operating during the Hajj.^{2, 50} However, unlicensed barbers continue to operate illegally during the Hajj regardless of the efforts made by the Saudi authorities to ensure only authorised barbers are working.⁵¹ A study conducted among 158 Hajj barbers indicated positive hepatitis serology results among those barbers; specifically, 10% were noted to be positive for hepatitis C virus (HCV) , 4% were positive for HBsAg (hepatitis B surface antigen), whilst 0.6 were perceived to be

positive for HbeAg (hepatitis B “e” antigen).^{2, 52} These results indicate the occupational risk of blood borne infections for both barbers and pilgrims.^{2, 52} The Saudi authorities urge pilgrims to be shaved only by licensed barbers and avoid sharing shaving equipment.²

The behaviour of re-using razor blades and using the services of unlicensed barbers has been observed among Hajj pilgrims in previous studies.^{53, 54} This sort of behaviour may place pilgrims at risk of spreading blood borne infections for example hepatitis B and C, as well as HIV^{16, 55, 56 57} as many pilgrims are from countries where hepatitis B and/or C are endemic.^{55, 58 59}

Vaccination remains the most effective measure to prevent hepatitis B virus.⁶⁰ However, it is still not recommended among Hajj travel vaccines by the Saudi government due to the cost and long administration schedule.² No vaccine is currently available for hepatitis C virus or HIV.^{61, 62}

1.2.1.5 Poliomyelitis

Poliomyelitis is a disease that can be prevented by vaccination. However eradication of this disease remains challenging due to the fact that it is still predominant in various countries and travellers across countries may play a role in the potential spread of Poliomyelitis.⁶³ Mathematical modelling has estimated 20 importations of poliovirus into Saudi Arabia associated with Hajj.⁶⁴ Pilgrims originating from polio endemic areas should be vaccinated against Poliomyelitis at least 4 weeks prior to their arrival in Saudi Arabia.³⁸

1.2.1.6 Yellow fever

Yellow fever disease is a vector borne disease caused by yellow fever virus and occurs in tropical regions of Africa and South America.⁶⁵ Hajj gathers millions of pilgrims from different countries and approximately 15% come from yellow fever endemic areas in Africa and Latin America.⁶⁶ Although Saudi Arabia has made good progress with respect to vector borne disease control by means of environmental spraying, the development of mosquitoes that carry resistant strains cannot be precluded.⁶⁶ Likewise, the vast crowds and compact accommodation at Mina that is characteristic of the Hajj can assist mosquitoes to breed and spread disease.⁶⁶ Researches undertaken on dengue fever have described the existence of mosquitoes in homes in cities close to the Hajj area (1% in Mecca, 63% in Medina, 47% in Jeddah).⁶⁷ Both mosquito control and vaccination with yellow fever vaccine can prevent the disease⁶⁸ and according to the most recent guidelines issued by the World Health Organisation (WHO), is valid for a lifetime.⁶⁹

1.2.2 Non-communicable diseases

1.2.2.1 Pre-existing comorbidities

Many Hajj pilgrims are older and have comorbidities.^{9, 70} In 2017, thousands of medical and surgical procedures were performed on pilgrims with comorbidities. Of those, 19 were open heart surgeries, 355 were cardiac catheterisation operations, whilst 1277 kidney dialysis procedures were also completed.⁷¹

During Hajj seasons, cardiovascular disease ranked the most common cause of death among Hajj pilgrims and accounted for (40 -60 %).⁷²⁻⁷⁵ The physical stress associated with the Hajj is even demanding for healthy adults and can lead to ischaemia in those

with pre-existing cardiac disease.^{2, 76} Pilgrims with cardiac disease are advised to consult their clinicians before planning for the Hajj. Avoiding Hajj is highly recommended for those with cardiac disease, although this is primarily left to the pilgrim to decide. Clinicians must ensure their cardiac patients have a sufficient supply of medication and that the compliance with these medications is maintained. Some Hajj rituals can be performed by proxy and therefore pilgrims with cardiac disease are advised to avoid crowds at certain sites and request healthier pilgrims to perform these rituals on their behalf.²

Nephrological diseases are a less common cause of hospital admission for Hajj pilgrims and accounted for 2%.⁷⁷ Pilgrims with kidney diseases are advised to receive pre-Hajj medical consultation and follow health tips for kidney patients published on the Saudi Ministry of Health website.⁷⁸

Diabetes mellitus is another health condition that pilgrims may have since many of them are elderly and originate from countries with a high prevalence of type 2 diabetes mellitus.⁷⁹ Changes in the everyday life of diabetic patients during Hajj (e.g. weather, diet, geography and physical activities) can be incredibly challenging.⁷⁹ It has been stated that diabetes is the leading cause of illness and mortality during the Hajj event.⁸⁰ In one recent study, 31.9% of a total of 689 patients admitted as an emergency had diabetes.⁸¹ Health tips for diabetic pilgrims are also published on the Saudi Ministry of Health website for them to follow.⁷⁸

1.2.2.2 Injuries

The risk of trauma is significantly increased owing to the mass movement of millions of pilgrims from one ritual place to another, over a short period and within a small

area.⁷⁶ It should be pointed out that Hajj pilgrims are at risk of falling over, slipping, as well as traffic accidents and even stampedes which have occurred in the past.⁸² Majority of injuries typically take place when pilgrims are completing the rituals of Tawaf, Saee and Ramy al-Jamarat in and around Mecca.⁸² Injuries represent 9.4%²⁶ of hospital admissions and 6.4%⁷³ of intensive care units (ICU) admissions during the Hajj. Fire is another cause of injuries during the Hajj.⁷⁶ The occurrence of burns was noted to be approximately 40/10,000.⁸² Nevertheless, pilgrims are not allowed to cook when residing in Mina, whilst smoking is prohibited during the Hajj, so as to reduce the risk of fires occurring.⁷⁶

1.2.2.3 Heat illnesses

Dealing with the excessive heat is one of the main complaints that pilgrims make during Hajj.⁸³ Exposure to the sun, high air temperatures in addition to the heat distributed by the vast amount of people and vehicles all contribute to the problem of heat stress.⁷⁶ The highest occurrence of heat fatalities arose when the maximum air temperature reached a scorching 48.7°C.⁷⁶ Over the past few years, the occurrence of heat stroke and exhaustion has been observed to be low. This is most likely attributable to improvements in climatic conditions as the Hajj seasons have been occurring in the winter when temperatures are not as high.⁷⁶ In 2017, death because of heat stroke & heat exhaustion accounted for 2.8% of all causes of death among Hajj pilgrims.⁸⁴ The increase number of cases of heat illnesses (995 cases in 2017 Hajj) probably due to the fact that 2017 Hajj season was in August when temperature reached the highest level. It is essential to reduce heat exposure by means of increasing awareness of the signs and symptoms associated with heat stress, avoiding excessive sun exposure by looking for shade and making use of umbrellas,

drinking sufficient fluids and ensuring that sun creams are utilised.^{2, 76} The Saudi authorities have established a number of preventative measures, for example making drinking water available for all pilgrims and supplying water mist sprayers that operate on a regular basis in the places where the Hajj rituals are carried out.^{2, 83}

1.3 Hajj and Umrah Health Regulations

The Saudi Ministry of Health (MOH), by way of its official website provides health regulations for those who wish to travel to Saudi Arabia for the purpose of Hajj or Umrah. These health regulations are in Arabic and English, Bangladeshi, Hausa, Indonesian, Turkish and Urdu language and are updated every year.^{38, 85} The Hajj and Umrah health regulations are divided into two main parts vaccination and personal preventative measures that can be adopted by pilgrims.³⁸

1.4 Hajj and Umrah vaccination policy

The Saudi Ministry of Health developed a Hajj and Umrah vaccination policy, which is upgraded annually depending on the current health conditions.³⁸ The current Hajj and Umrah vaccination policy includes mandatory vaccines such as meningococcal, polio and yellow fever vaccine which are required in order for an individual to be granted a visa to enter Saudi Arabia and recommended travel vaccines such as influenza and pneumococcal vaccine which pilgrims are advised to have.^{38 12}

1.4.1 Mandatory vaccines

These vaccines are mandatory for the Hajj and Umrah. Pilgrims are required to submit documents that confirm that they have received these vaccines when they apply for the Hajj or Umrah visa.^{12, 38}

1.4.1.1 Meningococcal vaccine

All pilgrims travelling to Saudi Arabia for the Hajj or Umrah, whether they are domestic or international must have a certificate of vaccination, which provides evidence that they have been vaccinated with the quadrivalent (ACYW) vaccine. In addition, this official document for the quadrivalent (ACYW) polysaccharide lasts 3 years, 5 years for the quadrivalent (ACYW) conjugate vaccine and should have been administered no less than 10 days prior to the pilgrim arriving in Saudi Arabia. The vaccine is also mandatory for all residents of Mecca and Medina and all those in contact with pilgrims, including health care workers, volunteers and personnel in other authorities, such as the national guard and civil defence.³⁸

1.4.1.2 Polio vaccine

The Saudi authority expects those coming from countries infected with Wild Polio Virus 1 or vaccine derived polio virus, such as Afghanistan, Nigeria and Pakistan, **countries at risk of re-infection, for instance** Cameroon, the Central African Republic, Chad, Guinea, Laos, Madagascar, Myanmar, Niger and the Ukraine and **countries which are still at risk of Polio, for instance** the Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Iraq, Kenya, Liberia, Sierra Leone, Somalia, South Sudan, the Syrian Arab Republic and Yemen to provide evidence that they have received at least one dose of oral polio vaccine (OPV) or inactivated poliovirus vaccine (IPV) 4 weeks to 12 months prior to departure before being granted a Hajj visa.⁸⁶ In addition, all travellers from these countries should receive one dose of OPV upon arrival at the port of entry in Saudi Arabia.^{86, 87}

1.4.1.3 Yellow fever vaccine

All pilgrims aged more than 9 months coming from countries in the Americas or Africa that pose a risk, should provide evidence that they have been vaccinated with yellow fever vaccine. The effect of yellow fever vaccine starts 10 days after administration lasts a lifetime.^{38 69}

According to the WHO International Travel and Health guidelines, the following countries are at risk of yellow fever transmission; in Africa (Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, the Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Sudan, the Republic of South Sudan, Togo and Uganda) and in the Americas: (Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Peru, Surinam, Trinidad and Tobago and Venezuela).³⁸

1.4.2 Recommended travel vaccines

1.4.2.1 Seasonal Influenza vaccine

Although the latest available seasonal influenza vaccine is mandatory for all domestic pilgrims and health care workers who serve at the Hajj and Umrah sites, it is still in the recommended vaccines category for international pilgrims and not required to enter Saudi Arabia.³⁸ The influenza vaccine is expected to be received ten days prior to arrival in Saudi Arabia for the Hajj or Umrah and is highly recommended for pregnant women, children under five years, elderly and those with chronic diseases or immune deficiency.³⁸

1.4.2.2 *Pneumococcal vaccine*

Pneumonia is one of the most common causes of hospital admission during Hajj seasons.³⁵ However, pneumococcal vaccine is still not among the vaccines recommended by the Saudi Ministry of Health for Hajj and Umrah pilgrims.³⁸ The Centre for Disease Control and Prevention (CDC) strongly recommends receiving pneumococcal conjugate or polysaccharide vaccines for pilgrims who are ≥ 65 years and for younger pilgrims with comorbidities.⁵

1.5 Preventive measures

A list of health preventive measures are published on the Saudi Ministry of Health website.³⁸

1.6 Visa application and Hajj permit

International pilgrims who are aiming to perform the Hajj should apply for a Hajj visa and domestic pilgrims for a Hajj permit prior to their arrival to Mecca.^{11, 12} In relation to every country that wishes to send pilgrims, Kingdom of Saudi Arabia (KSA) provides 1000 visas for every one million Muslims, even though countries with a small number of Muslims, are treated as a special case, by either having the quota waived or adjusting it to reflect the total population in those countries⁸⁸. Saudi Arabia also limits Hajj to once in every five years for all domestic and international pilgrims.^{88 89} Regarding visa applications, Saudi embassies worldwide start accepting them two months prior to the Hajj and up to two weeks before the Hajj commences.⁹⁰

1.7 Pre-travel preparation

Travellers are recommended to obtain pre-travel health advice at least 6-8 weeks prior to travelling to Saudi Arabia.⁹¹ Hajj pilgrims are also advised to obtain pre and post health counselling and screening for illnesses, particularly as many pilgrims are older and have various chronic diseases.⁹²

The Saudi Ministry of Health works with different travel agents, tour operators and Muslim councils in the areas from where pilgrims originate from to develop educational material and provide valuable information that is essential before and during the Hajj.⁹³ The application of educational materials and communication in the Hajj sites by the Saudi Ministry of Health during the 2009 pH1N1 season was associated with reduced occurrence and duration of respiratory illness.⁹⁴ Nevertheless, it should be mentioned that the influence and effectiveness of the educational programmes being conducted prior to arrival in Saudi Arabia is undetermined.³³

The aim of the pre-travel consultation is to promote risk reduction by way of undertaking an individual risk assessment, and recommending preventive measures, educating travellers on the anticipated health risks and methods for their prevention, in addition to providing vaccines for preventable diseases.^{95, 96}

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Chapter 2: Meningococcal carriage in Hajj and Umrah pilgrimage: A systematic review

2 Meningococcal carriage in Hajj and Umrah pilgrimage: A systematic review

Abstract

Meningococcal disease has been of concern for public health authorities for a considerable period. The invasive meningococcal disease is caused by *Neisseria meningitidis* which is transmitted via respiratory droplets. Asymptomatic carriers are the main source of infection. Overcrowding during Hajj and Umrah pilgrimage can facilitate the spread of meningococcal disease.

A systematic review of asymptomatic meningococcal carriage among Hajj and Umrah pilgrims was conducted. With certain outliers, most Hajj and Umrah carriage studies reported a low carriage rate similar to the rate in non-epidemic settings. Nonetheless, these results must be treated with caution considering the limitations that were identified within the studies.

The most dominant detected pathological serogroups among pilgrims were serogroups W and B which reflects the serogroups dominant in areas where most pilgrims come from.

The current meningococcal disease preventative measures used for Hajj and Umrah do not necessarily prevent the carriage and transmission of *Neisseria meningitidis*. As a consequence, this may cause local and international outbreaks among populations that are vulnerable. Monitoring the carriage states of pilgrims with the application of preventive measures that have an impact on carriage are justified so as to reduce the risk of Hajj and Umrah-related meningococcal disease outbreaks.

2.1 Introduction

Meningococcal disease is a serious infectious disease caused by *Neisseria meningitidis* and transmitted via respiratory droplets.¹ Annually, the disease affects 0.5-1.2 million people and causes between 50,000 and 135, 000 deaths globally.² There are 12 known serogroups of *N.meningitidis* although 6 serogroups (A,B,C,W,Y and X) cause the meningococcal disease.³ Meningococcal vaccines are available in both conjugate and polysaccharide forms.⁴ A vaccine that protects against four serogroups and which is currently available is the quadrivalent (groups A, C, Y and W) vaccine in both polysaccharide and conjugate forms. ⁴ Currently no vaccine exists that protects against all pathological serogroups.⁴

In contrast to meningococcal conjugate vaccines, polysaccharide vaccines can protect against meningococcal disease. However, they do not prevent the carriage of *N.meningitidis* which is the main source of infection.¹ The bacterium is typically present in the nose and throat of humans, which is normally considered as the only reservoir for *N.meningitidis*.⁵ Roughly 10% of the general population are asymptomatic carriers of *N. meningitidis* in the naso-oropharynx.⁶

Hajj, the Islamic pilgrimage that Muslims made to Mecca in Saudi Arabia is one of the largest annual events to occur globally.⁷ Mecca is also a place where the less significant pilgrimage, the Umrah occurs. In contrast to the Hajj, the Umrah is of a shorter duration and can be undertaken at any time of the year.⁸

Meningococcal carriage during the Hajj has been of concern for public health authorities for a considerable time, as pilgrims and their household contacts remain at an increased risk of meningococcal disease.

Overcrowding during Hajj has in the past facilitated the spread of meningococcal disease and several meningococcal outbreaks during and after Hajj and Umrah pilgrimages have occurred since 1987.^{9, 10} Consequently, the health authorities in Saudi Arabia made it obligatory for all Hajj pilgrims to receive the quadrivalent meningococcal vaccine, in order to perform the Hajj or Umrah and moreover, that all pilgrims from sub-Saharan Africa had to take oral ciprofloxacin upon arrival to eliminate nasal carriage.^{11, 12}

The aim of this systematic review is to describe the rate of meningococcal carriage in the Hajj and Umrah pilgrimages and the serogroups circulating among pilgrims. This review also aimed to update a current published systematic review by other authors related to meningococcal carriage in relation to Hajj and Umrah mass gatherings.¹³

2.2 Methods

A search was conducted to identify studies from electronic databases including Medline (Pubmed and Ovid), Embase and Global Health. Other databases such as Google Scholar and the Saudi Epidemiology Bulletin were also searched. A combination of MeSH terms and text words were used in the search including: 'Hajj' OR 'Umrah' OR 'Pilgrims' OR 'Pilgrimage' AND '*Neisseria meningitidis*' OR 'meningococcal' AND 'Carriage'. Reference lists belonging to the relevant studies were also hand searched to identify relevant studies. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to present the search results (Figure 2).

Studies considered for inclusion in the review were original studies involving Hajj or Umrah pilgrims of any age, gender and country of origin which measured the outcomes of interest, i.e. meningococcal carriage. Only English language studies from

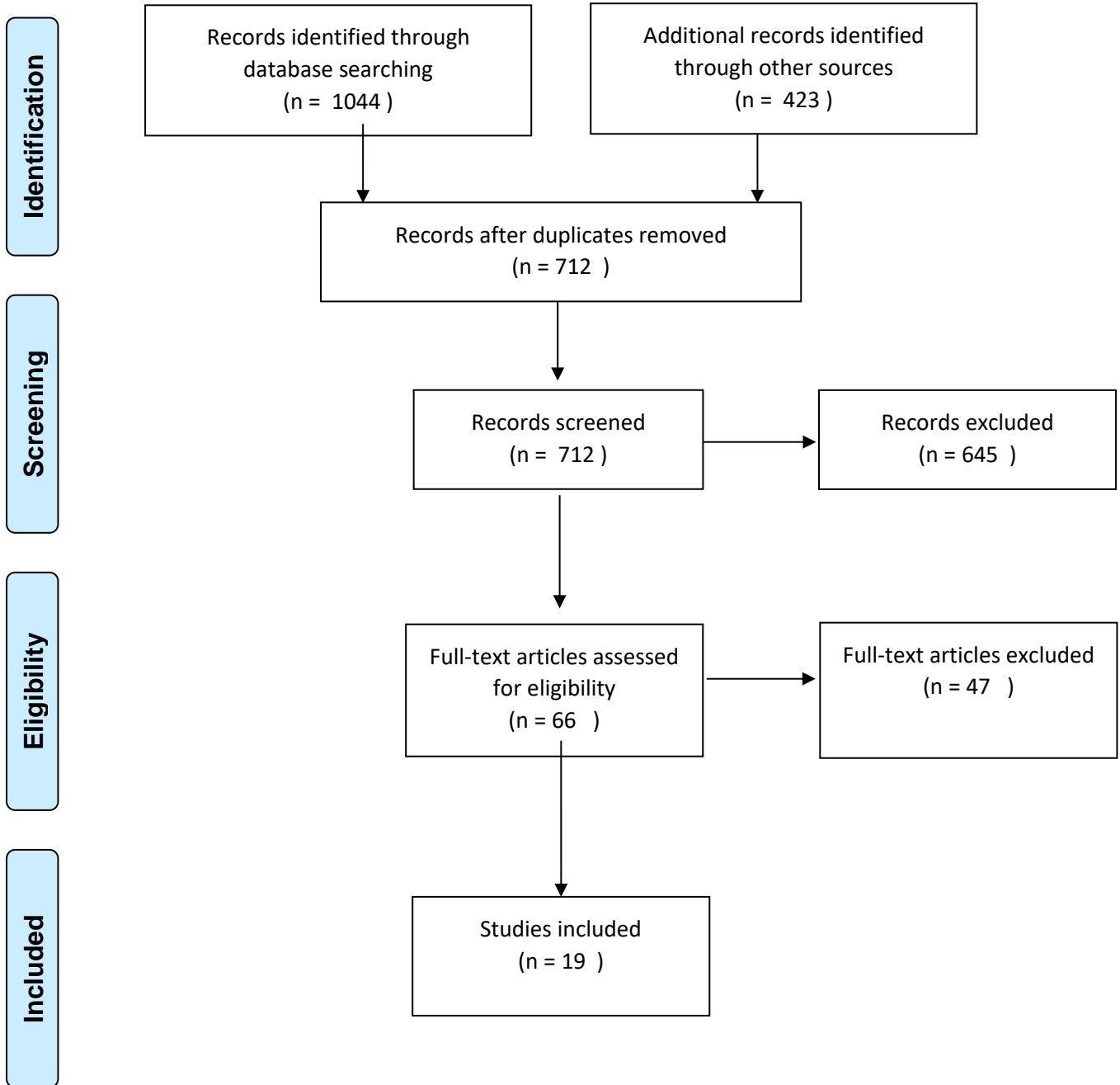
1987 till July 2020 were included. Excluded studies were those that involved healthcare workers or non-Hajj/Umrah pilgrims and studies not investigating the carriage of meningococcal among pilgrims.

The titles and abstracts were reviewed independently by the PI to identify potentially relevant papers. Full texts of all potentially relevant papers were reviewed to determine those which met the selection criteria.

Data was extracted from each study into a data extraction sheet which included: study design, year of data collection, country of origin, type of pilgrimage (Hajj or Umrah), age, meningococcal carriage rate, type of the meningococcal vaccine, antibiotic uptake, *Neisseria meningitidis* serogroups and laboratory work.

Modified ranking criteria based on Oxford Evidence Based Medicine (<http://www.cebm.net/>) was applied to undertake the quality assessment of the included studies. The studies were categorised into specific groups (e.g., A, B, C), where A stood for RCTs of an adequate sample size, B for observational studies of an adequate sample size with good quality, or pilot RCTs or a non-randomised trial and C denoted observational studies of an inadequate sample size or that were of poor quality.¹⁴

Figure 2:PRISMA Flow Diagram



2.3 Results

2.3.1 General description

The search results are shown in Figure 1. Of 1467 titles and abstracts, 19 studies were included. All reported the carriage of *Neisseria meningitidis* among Hajj and Umrah pilgrims. Of those included studies, three examined the effect of antibiotics on the carriage of *Neisseria meningitidis*. All studies were conducted between 1998 and 2018 involving pilgrims from different countries. Nearly all the included studies were conducted among Hajj pilgrims. Two were conducted among Umrah pilgrims.^{15, 16} Two (out of 19) studies focused on the effectiveness of conjugate vaccine on the carriage of serogroups A, C, W and Y.^{17, 18}

The study sample sizes varied ranging from 123 to 1458. Most of these studies were conducted in either airports or clinics. Only 5 studies reported selecting pilgrims using random sampling methods.¹⁹⁻²³ The study population varied depending on the study, 5 included multinational pilgrims, while the other 14 focused on a single nationality. Twelve studies were cohort, six cross-sectional, whilst one was a single-blinded randomised controlled trial (See table 2). All cohort and cross-sectional studies were considered Level B or C evidence using a modified ranking associated with the Oxford evidence-based medicine levels of evidence, while the single-blinded randomised controlled trial was considered Level A evidence.

2.3.2 Rate of meningococcal carriage among Hajj and Umrah pilgrims.

The overall carriage rate of *N.meningitidis* in most pilgrimage studies from 1987 to 2018 ranged between 5-10%²⁴ (Table 1) ,However, lower overall carriage rate (1.9%)²⁵ was reported during the meningococcal outbreak season in 2001 among pilgrims from the United States and in 2002 (1.7%)²⁶among pilgrims from Singapore. A higher overall carriage rate (18.7%) was detected among Turkish pilgrims in 2010. .²⁷

The uptake of antibiotics by pilgrims vary between studies, ranging from 7 -59% (Table 1). In one particular study, a single dose of ciprofloxacin (500 mg) administered to a cohort of Iranian pilgrims 24 hours prior to departing for Hajj reduced the carriage rate from 8.1% before Hajj to 0% post-Hajj.¹⁹ In a further study, *N. meningitidis* carriage was not detected post-Hajj among 177 Kuwaiti pilgrims, 83% of whom received one dose of ciprofloxacin before leaving Hajj.²⁸

A study by Wilder-Smith reported a lower carriage of meningococcal carriage among the Umrah cohort (1.3%) compared with the Hajj cohort (17%).¹⁶ Another cohort study conducted among Umrah pilgrims reported a higher rate of meningococcal carriage (5.7%) after the Umrah Ramadan season.²⁹

2.3.3 *N.meningitidis* serogroups circulating in Hajj and Umrah pilgrimage.

The most dominant detected pathological serogroups among pilgrims were serogroups W and B.²⁴ (See table 1) In a study conducted among Turkish pilgrims, 82.5% of the pre-Hajj isolates were positive for serogroup W and 91.3% were W positive after the Hajj.²⁷

Two studies were conducted among Singaporean Hajj and Umrah pilgrims and showed that serogroup W was not detected in any of the isolates from Umrah pilgrims,

while it was the dominant carried serogroup among Hajj pilgrims.^{16, 30} In a further study, serogroup W was identified from two Umrah isolates.¹⁵ This study was conducted among pilgrims from different countries and, after Umrah Ramadan season.

The overall carriage of Serogroup B *N. meningitidis* ranged between 9–25% among isolates (Table 1).²⁴ In one study, the prevalence of serogroup B among isolates from UK pilgrims was reported to be 24% pre-Hajj and 27% post-Hajj. It consisted of 22% of isolates retrieved from the household contacts of returning carrier pilgrims.^{24, 31}

Two studies investigated the effect of the quadrivalent conjugate meningococcal vaccine on serogroup A,C,W and Y. Non of these studies reported carriage of these serogroup from the swabs after the Hajj.^{17, 18}

The carriage rate of non-serogroupable *N. meningitidis* among pilgrims ranged between 28-75% (Table 1).²⁴ Eight studies reported the carriage of these isolates among pilgrims.^{15-17, 19, 23, 31-33}

Table 1: Summary of studies reporting meningococcal carriage among Hajj and Umrah pilgrims.

Study population	Pilgrimage	Overall carriage	Carriage pre-Hajj	Carriage post-Hajj	Antibiotic uptake	Type of meningococcal vaccine
Australia ³⁴	Hajj 2014	1% (3/276)	0.6% (1/183) 1 MenW	2.2% (2/93) 2 MenB	17.2% (16/183)	78.7% were vaccinated with the quadrivalent polysaccharide vaccine and 21.3% with the conjugate vaccine
France. ³⁵	Hajj 2013	0% (0/258)	0% (0/129)	0% (0/129)	-	-
Iran. ¹⁹	Hajj 2003	4.9% (66/1348)	5.2% (35/674) 9 MenB, 5 MenC, 5 MenD, 5 Men Y, 1 MenW and 10 NG	4.6% (31/674) 1 MenA, 2 MenB, 1 MenY, 8 NG and 3 MenZ	58.2% received antibiotics during the Hajj	All were vaccinated with the quadrivalent polysaccharide vaccine
Iran. ¹⁹	Hajj 2003	-	8.1% (10/123) 2 MenB, 1 MenC , 2 MenD, 1 MenX, 2 MenY and 2 NG	0% (0/123)	All received one dose of ciprofloxacin 500mg 24 h prior to leaving for the Hajj	All were vaccinated with the quadrivalent polysaccharide vaccine

Iran. ³⁶	Hajj 2012	0.7% (6/844)	0% (0/422)	1.4% (6/422)	58.5% received antibiotics during the Hajj	All were vaccinated with the quadrivalent polysaccharide vaccine
Kuwait. ²⁸	Hajj 2005	-	-	0% (0/177)	83% used Ciprofloxacin	92% were vaccinated with quadrivalent polysaccharide vaccine
29 countries. ³²	Hajj 2003 ¹	3.2% (11/344) 2 MenW, 1 MenB and 8 NG	-	-	-	44% were vaccinated in the last 4 years - 92% with the quadrivalent polysaccharide vaccine and 8% with the bivalent vaccine
14 countries. ¹⁵	Hajj 2009	7.3% (152/2046) 42 Poly (A,B,C,D), 16 MenB, 17 Poly (X,Y,Z) and 70 NG	6% (84/1433)	11% (68/613)	-	-
15 countries. ¹⁵	Umrah 2009	4% (80/1958)	2.5% (24/979)	5.7 (56/979)	-	-

Continued

		20 poly (A,B,C,D) 8 MenB, 2 MenW, 37 NG, 13 poly (X,Y,Z)				
8 countries. ³⁷	Hajj 2002	9.2% (134/1458)	8% (57/715) 3 MenA, 9 MenB, 4 MenY, 3 MenW, 8 MenX, 1 MenZ and 29 NG	10.4% (77/743) 3 MenB, 1 MenC , 34 MenW, 3 MenX and 36 NG.	-	-
Multiple countries. ³⁸	Hajj 2010	6%(103/1715)	5.7% (47/829) - the most common MenC followed by A and Y. The least were D, W, B then X	6.3% (56/886) the most common MenA followed by Y and C. Others namely W, D, B and X were less common	-	-
15 countries . ¹⁷	Hajj 2016/2017	0.1%(3/1878)	0.2%(2/1133) 1 MenB, 1 NG	0.1 (1/745) 1 MenB	-	Group A : all received the quadrivalent polysaccharide vaccine. Group B: all received the quadrivalent conjugate vaccine

Singapore. ¹⁶	Umrah 2001	0.6%(1/160)	-	0.6%(1/160) 1 NG	7%	All were vaccinated with the quadrivalent polysaccharide vaccine
Singapore. ³⁰	Hajj 2001	8% (30/375)	0.5% (1/204) 1 MenX	17% (29/171) Mostly the MenW epidemic strain	41%	All were vaccinated with the quadrivalent polysaccharide vaccine
Singapore. ²⁶	Hajj 2002	1.7% (6/346)	2.6% (4/193) 1 MenB and 3 NG	1.3% (2/153) 2 MenW	53%	All were vaccinated with the quadrivalent polysaccharide vaccine
Thailand. ³⁹	Hajj 2001	-	-	0% (0/374)	-	77.8% were vaccinated with the quadrivalent polysaccharide vaccine
Turkey. ²⁷	Hajj 2010	18.7% (144/768)	13.3% (63/472) 52 MenW, 9 MenB, 1 MenA and 1 MenY	27.4% (81/296) 74 MenW, 5 MenB, 1 MenA and 1 MenY	-	All were vaccinated with the quadrivalent polysaccharide vaccine
Turkey. ¹⁸	Hajj 2018	4.2% (19/458)	3.9% (9/229) 9 MenB	0.4% (1/299) 1 new MenB	9.3% prior to the Hajj and 57% during the Hajj	All were vaccinated with the quadrivalent conjugate vaccine

United Kingdom. ³¹	Hajj 2002	7.5% (32/427)	8.3% (21/253) 2 Men W (epidemic strain), 5 MenB and 14 NG	6.3% (11/174) 1 Men W (Non-epidemic strain), 3 Men B, One 29 E and 6 NG	21% (36/174)	Quadrivalent polysaccharide
United States. ⁴⁰	Hajj 1987	11.6% (37/318)	-	11.6% (37/318) 34 MenA	The use of rifampicin was reported by 15% of the 186 of travellers	17% were vaccinated with the Meningococcal vaccine
United States. ²⁵	Hajj 2001	1.9% (22/1153)	0.9% (4/452)	2.6% (18/701)	15% prior to the Hajj and 44.8% after the Hajj	97% were vaccinated with the quadrivalent polysaccharide vaccine

Table 2: Characteristics of included studies that reported meningococcal carriage in the Hajj and Umrah pilgrimage

Study population	Pilgrimage	Study design	Sample size	Sampling methods	Mean age	Laboratory work	Ranking
Australia ³⁴	Hajj 2014	Cohort	183	Mina tents	40	Conventional and molecular methods	C
France. ³⁵	Hajj 2013	Cohort	129	Private travel agency	61	Molecular methods	C
Iran. ¹⁹	2003	Cohort	674	Randomly at the airport	-	Conventional methods	B
Iran. ¹⁹	2003	Cohort	123	Randomly at the airport	-	Conventional methods	B
Iran. ³⁶	Hajj 2012	Cohort	422	Airport	50	Conventional methods	C
Kuwait. ²⁸	Hajj 2005	Cross-sectional	177	Post Hajj gathering	37	Conventional methods	C
29 countries. ³²	Hajj 2003 ²	Cross-sectional	344	National Guard Health Affairs clinics	-	Conventional methods	C
14 countries. ¹⁵	Hajj 2009	Cohort	1433	King Abdulaziz International Airport	-	Conventional and molecular methods	B
15 countries. ¹⁵	Umrah 2009	Cohort	979	King Abdulaziz International Airport	-	Conventional and molecular methods	B
8 countries. ³⁷	Hajj 2002	Cohort	1458	Random sampling	-	-	B

Continued

Multiple countries. ³⁸	Hajj 2011	Cross-sectional	886	-	-	-	C
15 countries . ¹⁷	Hajj 2016/2017	Single-blinded, randomised, controlled trial	1146	-	36	Conventional and molecular methods	A
Singapore. ¹⁶	Umrah 2001	Cross-sectional	160	Vaccination clinic	40	Conventional and molecular methods	C
Singapore. ³⁰	Hajj 2001	Cohort	204	Vaccination clinic	39	Conventional and molecular methods	C
Singapore. ²⁶	Hajj 2002	Cohort	193	Vaccination clinic	48	Conventional and molecular methods	C
Thailand. ³⁹	Hajj 2001	Cross-sectional	374	Random sampling (Hat Yai International Airport)	50	Conventional methods	C
Turkey. ²⁷	Hajj 2010	Cohort	472	Hacettepe University	-	Conventional and molecular methods	C
Turkey. ¹⁸	Hajj 2018	Cohort	229	Ankara Esenboğa Airport	56	Conventional and molecular methods	C
United Kingdom. ³¹	Hajj 2002	Cohort	253	East London mosque	42	Conventional methods	C

United States. ⁴⁰	Hajj 1987	Cross-sectional	318	Random sampling at JFK International Airport	43	Conventional methods	C
United States. ²⁵	Hajj 2001	Cohort	1153	Random sampling at JFK International Airport	-	Conventional and molecular methods	B

2.4 Discussion

This systematic review shows that the overall carriage rate of *N.meningitidis* in most pilgrimage studies ranged between 5-10%²⁴, which is similar to the rate in non-epidemic settings.⁴¹

There are several possible explanations for this low rate of meningococcal carriage from pilgrimage studies. First, most of these studies were conducted with a relatively small sample size and focused on certain nationalities (Table 2). Airports were the main location with respect to sample recruitment, although only five studies indicated the type of random sampling which was employed.¹⁹⁻²³ In order to provide unbiased and representative results, a probability random sampling method should be used.⁴² Random sampling based flights or Hajj/Umrah agencies may be the most appropriate sampling method to use in circumstances such as a pilgrimage.

Second, the demographic data of pilgrims reveal that the majority of them were older people which may explain the lower carriage rate among pilgrims. In the general population carriage prevalence increases through childhood, from 4-5% in infants to a peak of 23.7% in 19-year olds, then a decrease in adulthood to 7-8% in 50-year olds.⁴³

Third, most of these studies were conducted during or after the 2000 and 2001 meningococcal outbreak among Pilgrims (Table 1) . Consequently, they were performed in a period when various meningococcal disease prevention measures had been launched, both in Saudi Arabia and globally, with the aim of preventing potential outbreaks.²⁴ The mass vaccination of Hajj pilgrims caused a reduction in invasive meningococcal disease, which would have impacted carriage rates.^{44, 45}

Saudi Arabia implemented the first Hajj vaccination policy in 1987 after the outbreak of meningococcal serogroup A, following the Hajj season.¹¹ However, the Umrah pilgrims were not all vaccinated, which may possibly explain the two outbreaks of Serogroup A among the Umrah pilgrims in 1992 and 1997.^{46, 47} A vaccine that protects against all serogroups is currently unavailable.⁴ The existing Hajj and Umrah vaccination policy was upgraded in 2002 to include the quadrivalent (ACYW) vaccine however, it does not indicate the type of quadrivalent (ACYW) vaccine that should be administered, i.e., quadrivalent meningococcal conjugate vaccine (MCV-4) or quadrivalent meningococcal polysaccharide vaccine (MPSV-4).⁴⁸ MCV-4 is believed to have more advantages over (MPSV-4) in preventing the *acquisition of the bacterium*.⁴⁹ Only two studies have investigated the impact of the quadrivalent meningococcal conjugate vaccine on carriage among pilgrims and did not detect any *acquisition* of serogroups A, C, W or Y after the Hajj.^{17 18}

Fourth, self-medicating with antibiotics has been customary practice among pilgrims during the Hajj to protect against respiratory transmitted diseases.³² The uptake of antimicrobial drugs among pilgrims ranged between 7-59% (Table 1).⁵⁰ This may have played a role in eliminating carriage in previously reported Hajj studies conducted separately among Iranian and Kuwaiti pilgrims.^{19, 28} Conversely, this custom of non-prescribed antibiotics may contribute to antibiotic resistance.³²

To lower the carriage rate, there is a mandatory policy for all pilgrims coming from Africa's meningitis belt to receive a single dose of ciprofloxacin tablets (500 mg) as a chemoprophylaxis on arrival in Saudi Arabia.⁵¹ However, this policy does not include South Asian pilgrims who have been reported to have significantly higher carriage

rates in Hajj studies and who may have contributed to the increased rate in pilgrims from lower carriage rate countries.³⁸

Fifth, social activities and length of stay in Saudi Arabia may possibly affect the rate of meningococcal carriage among pilgrims. The concept of pilgrimage is to bring people from different age groups, ethnicities and socioeconomic status together in a confined place where they interact with each other socially and spiritually. Hajj in contrast to Umrah is longer in duration and involves spending 5 days in tents in Mina near Mecca. The tents at Mina can provide accommodation for up to 100 or more pilgrims, although the number varies.⁵² In addition, the numbers of people in these tents vary from a few to very crowded. This factor in conjunction with social activities may possibly play a part in the carriage rate of *N.meningitidis*. None of the Hajj or Umrah studies has investigated the effect of numbers of people inside the tents and social activities by pilgrims on carriage rate. Although the Hajj lasts for 5 days, pilgrims tend to spend longer in Saudi Arabia before and after completing Hajj. The acquisition of carriage of *N.meningitidis* may need longer time to be shown and detectable.⁵³ Additionally, length of stay inside KSA has not been investigated which may affect the carriage rate.

Sixth, the type of pilgrimage e.g. Hajj or Umrah may also affect the carriage rates. According to Wilder-Smith, the meningococcal carriage rate among the Umrah cohort was lower (1.3%) compared with the Hajj cohort (17%).¹⁶ The smaller number of pilgrims and the shorter duration of Umrah in contrast to Hajj may explain this difference in the carriage rate.¹⁶ However, some Umrah seasons, such as Ramadan are more crowded than Hajj.⁵⁴ This may explain the significantly high acquisition rate of meningococcal carriage of 5.7% among pilgrims who were swabbed before and after the Umrah Ramadan season.¹⁵ Further studies, determining factors associated

with acquisition of *N.meningitidis* in both types of pilgrimage, are required to provide a better understanding.

Seventh, Other factors such as sampling techniques , sample storage and transportation and laboratory methods could have influenced the reported meningococcal carriage rates among pilgrims.

The most dominant detected pathological serogroups among pilgrims were serogroups W and B which reflects the serogroups dominant in areas where most pilgrims come from.²⁴ Serogroup W (ET-37 clonal complex) which involved Hajj outbreaks was first identified in a child in Gambia which has majority Muslim population.⁵⁵ Since then, this serogroup has been regularly circulating among pilgrims after the meningococcal outbreak caused by serogroup W in 2000.²⁴ In a study conducted among Turkish pilgrims, 82.5% of the pre-Hajj isolates were positive for serogroup W and 91.3% were W positive after the Hajj.²⁷

The overall carriage rate of *N.meningitidis* serogroup B among pilgrims has been between 9-25%.²⁴ This is relevant as the current mandatory quadrivalent (ACWY) vaccine for Hajj and Umrah pilgrims does not cover serogroup B.²⁴ Although a vaccine against serogroup B is now available, it is still not among the mandatory Hajj and Umrah vaccines. ^{24, 48} It should be mentioned that countries with a large Muslim population are showing an increase in meningococcal disease caused by serogroup B which is causing concern as this may change the aetiology of meningococcal disease in Hajj and Umrah. ⁵⁶

Two studies were conducted among Singaporean Hajj and Umrah pilgrims and showed that serogroup W was not detected in any of the isolates from Umrah pilgrims, while it was the dominant carried serogroup among Hajj pilgrims.^{16, 30} In a further study,

serogroup W was identified from two Umrah isolates.¹⁵ This study was conducted among pilgrims from different countries and, after Umrah Ramadan season, which may explain the variation in the detected serogroups.

The carriage of non-serogroupable *N. meningitidis* among pilgrims ranged between 28% and 75% (Table 1).²⁴ Capsular polysaccharides are the outmost antigens on the meningococcal surface and the main target for mucosal and humoral immunity.^{57, 58} Patient strains are encapsulated - six of these serogroups (A, B, C, W, X and Y) produce more than 90% of the invasive meningococcal disease.⁵⁸ Conversely, in the region of 50% of the strains isolated from carriers lack the capsule and are therefore serologically not groupable.⁵⁸

The importance of these non-serogroupable isolates is not clear. In the past, non-serogroupable meningococci were thought to be non-pathogenic. However, it was found that capsule production in meningococcal strains can switch on and off at a high frequency and that phase variation in the expression of virulence factors which consist of the capsule is common.^{58, 59} The loss of the capsule may improve the ability of meningococci to colonise an individual's nasopharynx and circumvent the immune systems.⁵⁸

There is growing evidence of the pathogenic potential of strains that are not groupable by standard slide agglutination (SASG).⁶⁰ Number of carriage studies conducted on pilgrims and their contacts have made use of SASG methods to serogroup isolates.^{32, 33, 44, 61} Thus, the data obtained from such researches must be handled with a degree of caution, seeing as the carriage of potentially pathogenic strains may well have been underestimated.²⁴ This was highlighted in the research conducted by Dull et al., who assessed the carriage of *N. meningitidis* among travellers from the US who

participated in the 2001 Hajj.²² Concerning the 25 *N. meningitidis* isolates acquired, 15 (60%) were non-serogroupable when tested by means of SASG methods. Nevertheless, by employing PCR, nine (60%) of the non-serogroupable isolates were categorised as serogroups W (n=2), B (n=4), and Y (n=3). In one particular case, an *N. meningitidis* serogroup W isolate was obtained from an elderly male pilgrim. His wife was also a carrier, although her isolate was not groupable by means of SASG. When the two strains were further assessed by way of phenotypic and molecular methods, it was found that they were in fact identical apart from capsule expression.²²

2.5 Conclusions

Mass gatherings such as the Hajj and Umrah can facilitate the spread of meningococcal disease. Few outbreaks of meningococcal disease have been reported immediately after the Hajj and Umrah.⁵⁰ The current Hajj and Umrah vaccination policy can play a part in reducing the risk of meningococcal disease. However it does not cover all six pathological serogroups seeing as there is no vaccine at present that can protect against all these serogroups simultaneously.⁴ Meningococcal conjugate vaccines are proven to be more effective in preventing the acquisition of carriage compared to the polysaccharide vaccines.^{49, 62} Carriers of *N.meningitidis* remain the main source of infections.¹ Furthermore, although our review is demonstrating a lower carriage rate among pilgrims, the epidemiology of the carriage in Hajj and Umrah needs to be further explored taking into account the limitations in previous studies that might affect the carriage rate.

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Chapter 3: Knowledge gaps in previous literature, thesis aims, objectives and list of associated publications

3 Knowledge gaps in previous literature, thesis aims, objectives and list of associated publications

3.1 Knowledge gaps

It is important to note that only two studies have assessed the effect of the conjugate vaccine on meningococcal carriage among Hajj pilgrims.^{1 2} Moreover, no study has described the relationship between the timing of vaccine administration to the carriage rate of the pathological serogroups A, C, W and Y. Balkhy and colleagues³ recommended that further studies be performed with the aim of assessing the carriage patterns of pilgrims who had received the vaccine at different times.³ One study was conducted during the 2016-2017 Hajj seasons to compare the carriage patterns of pilgrims who had received the meningococcal conjugate vaccine and who had received the polysaccharide vaccine at different times.¹ Previous Hajj and Umrah meningococcal studies had not examined other factors that could possibly influence carriage rate among pilgrims, e.g. level of crowding, length of stay in KSA or social behaviour during the pilgrimage⁴. Therefore, calls have been made to conduct studies to determine the risk factors related to pilgrimage which possibly influence transmission of *Neisseria meningitidis*.⁵

Few studies have determined common acquired health problems among Hajj pilgrims and the preventive measures adopted by them during their pilgrimage. Studies that have been conducted were on small samples of pilgrims and focusing on specific countries. Seeking pre-travel health advice among pilgrims with co-morbidities has been investigated in one study only.

3.2 Aims

The aim of this study was to determine the uptake of meningococcal vaccine among pilgrims . It also aimed to investigate the overall carriage of *N.meningitidis* and the effect of timing of quadrivalent meningococcal vaccine administration for Hajj pilgrims on carriage of *N.meningitidis* serogroups ACWY. This is to inform further recommendations of the current Hajj vaccination policy in terms of the type and time of MenACWY vaccine uptake.

It also aimed to investigate pre-travel health preparation of pilgrims with chronic diseases and patterns of health preventive measures adopted by pilgrims and health problems among them.

3.3 Objectives

1. To determine the uptake of quadrivalent meningococcal vaccine among Hajj and Umrah pilgrims.
2. To determine the overall carriage of *N.meningitidis* among pilgrims.
3. To investigate the relationship between the time of quadrivalent meningococcal vaccine administration and the prevalence of carriage of *N.meningitidis* serogroups, ACWY.
4. To determine the uptake of influenza, pneumococcal, yellow fever and polio vaccines among Hajj pilgrims.
5. To determine the patterns of health problems experienced by pilgrims and describe the preventive measures adopted during the Hajj.

6. To examine the association between chronic disease status of pilgrims and timing of pre-travel preparation before Hajj

3.4 Associated publications related to this PhD

- 1- Research paper 1: Health preventive measures used by British pilgrims in the 2016 Hajj season. (Under preparation).
- 2- Research paper 2: Absence of an association between timing of meningococcal vaccination and *Neisseria meningitidis* carriage: a cross-sectional study of Hajj pilgrims to Mecca. (Submitted).
- 3- Research paper 3: Frequent facemask replacement may reduce the risk of acquiring upper respiratory tract infections in Hajj pilgrims . (Submitted)
- 4- Research paper 4: Pre-travel health preparation of pilgrims with chronic diseases. (Under preparation).

3.5 Associated conferences and presentations

- 1- Meningitis and Septicaemia in Children and Adults – 14 & 15 November 2017 (Poster Abstract ID: P10)
- 2- Meningitis and Septicaemia in Children and Adults – 5 & 6 November 2019 (Poster Abstract ID: P10)
- 3- American Society of Tropical Medicine and Hygiene (ASTMH) 68th Annual Meeting November 20-24, 2019 (Poster Abstract ID: LB-5451)
- 4- Advisory committee meeting at London school of hygiene and tropical medicine (Oral presentation)

- 5- Lab group meeting at King Abdullah University of Science and Technology (Oral presentation).
- 6- Clinical research department Lab group meeting at London school of hygiene and tropical medicine (Oral presentation)
- 7- Clinical research department meeting at London school of hygiene and tropical medicine (Oral presentation)
- 8- London School of Hygiene Tropical Medicine poster day on the 15th March 2020 (Abstract was accepted but poster day was Cancelled due to COVID-19 outbreak)

3.6 References

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Chapter 4: Methods

4 Methods

4.1 Introduction

This chapter summarises the methods used in the pilot study that was conducted after the 2016 Hajj and Umrah seasons in addition to the main study after the 2017 Hajj season. Statistical methods for each of the thesis objectives are described in detail in the statistical methods section in each research papers 1, 2, 3 and 4 and presented in respective chapters 7 to 10. Conceptual frameworks for each of the papers are attached in appendix 1,2,3 and 4. Estimation of probability weights for the sample survey in the main 2017 Hajj phase is described in Appendix 5. Missing data were summarised for the main exposures and potential confounders. Additionally, all missing data for a given variable were excluded from any analysis comprising that variable. In this study the numbers of participants responding to each variable have no meaning because the study did not use a simple random sample from the population. As described in the Methods section of each of the papers, two-stage random sampling was used to select pilgrims in the study. The numbers of pilgrims on each flight varied between flights and so the probability of selection into the survey sample was not equal for all pilgrims. The purpose of applying probability weights is to ensure that the probability of selection of each pilgrim into the survey sample is the same overall for all pilgrims. A survey analysis commands were used to take account of this unequal probability of selection and of the clustering of participants in our sample. Thus, only percentages have meaning in the analysis, as these are unbiased estimates of the population percentages.

4.2 Study design

A cross-sectional study among Hajj and Umrah pilgrims was conducted in two phases (See figure 3). The first phase was the pilot phase which was conducted after the 2016 Hajj and Umrah seasons among British Hajj pilgrims and Umrah pilgrims of different nationalities. This phase was followed by the second main phase which was conducted among pilgrims from different countries during the 2017 Hajj season.

In addition to objectives 1, 2 and 5, the aim of the pilot phase was to identify the most appropriate sampling methods to employ for the main study, so as to ascertain the best possible data collection methods and the most feasible logistics. Furthermore, the pilot phase sought to pilot the questionnaire and identify the optimal laboratory methods required to isolate and identify *N.meningitidis*. Besides assessing the feasibility and identifying the logistical challenges and deficiencies in the research questionnaire and protocol, the pilot study helped to discover several issues regarding the Hajj and Umrah vaccination policy that have not been recognised or discussed in previous Hajj or Umrah studies. Data was collected from Umrah pilgrims from different countries including (Algeria, India, Indonesia, Nigeria, Pakistan, Sudan, Turkey and Malaysia).

The second phase was conducted after the 2017 Hajj season and among a larger number of pilgrims from different countries. Besides objectives 3,4,5 and 6, the aim of the main phase was to investigate the research questions raised during the pilot phase in regard to the uptake of meningococcal vaccine and the issue of unofficial vaccination cards carried by a number of pilgrims.

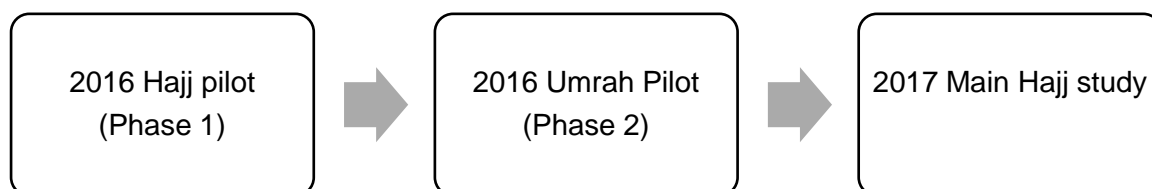


Figure 3: Stages of the study.

4.3 Study site

Both phases of the study were conducted at the King Abdulaziz International Airport ¹ in Jeddah, Saudi Arabia after the 2016/2017 Hajj and Umrah seasons. King Abdul Aziz International Airport is situated in Jeddah and covers an area of 105 km².² KAAI has three main terminals: The North Terminal which handles all foreign airlines, the South Terminal which processes domestic and international flights for Saudi Airlines, in addition to the Hajj terminal which manages up to 80 million Hajj and Umrah pilgrims that travel to Mecca every year.^{1 3}

Most Hajj and Umrah flights are managed in the Hajj terminal; however, several flights can depart from the north and south terminals e.g. flights departing to Europe, the Gulf States and North America.

The Hajj terminal which is the fourth largest airport terminal in the world, after Hong Kong, Bangkok and Seoul is the principal entry point into Mecca.² Most of the international pilgrims pass through this terminus, in order to arrive at the Sacred Mosque in Mecca.² The Hajj terminal at KAAI Airport consists of a large number of halls designed in the shape of tents that cover an area of approximately 465 000 m². The airport can accept in the region of 50 000 pilgrims a day during the Hajj season.² Every single one of its 14 arrival lounges can accommodate flights of pilgrims arriving to participate in the Hajj, whilst the same hall operates as a departure lounge for pilgrims travelling back home. ²

A total 2,352,122 pilgrims performed the 2017 Hajj, 600,108 of whom were domestic and 1,752,014 were international pilgrims.⁴ Pilgrims can travel to and from Saudi Arabia for the Hajj by several routes: 94% travel by air, 5% by land and 1% by sea.⁵ For logistic reasons and to focus on the main port of entry, only pilgrims who travelled by air and departed from the Hajj terminal at KAIA were included in the main phase of the study which was undertaken after the 2017 Hajj season.

4.4 Sampling

In order to provide unbiased and representative results, probability sampling method was employed in the main phase. Pilgrims included in the sample were determined by chance only. In this case, the possibility of introducing selection bias through the sampling approach was eliminated; however, such a method does not eliminate the likelihood of selection bias completely, as the sampled pilgrims may be unwilling to participate in this study or may withdraw from the sample once enrolled.⁶ The pilot

phase aimed to identify the most appropriate sampling method to use in the main study e.g. systematic sampling or clustering based on flights.⁶

The Hajj pilot phase one was the first and most challenging phase to be conducted in this pilot study. The intended sampling method was not carried out literally due to several logistical reasons. British pilgrims depart from different terminals; the Hajj, and north and south terminals and regularly travel as individuals not as group, unlike pilgrims from other countries with Muslim majorities. As a result, only flight clusters were selected. Conducting the pilot study helped to identify the optimal and logical sampling method to use both in the pilot Umrah study and the main Hajj study.

Clusters sampling methods e.g. Simple one-stage or Simple two-stage sampling⁶ are the only possible methods to use in the airport in Jeddah. Systematic sampling was excluded due to the substantial number of pilgrims distributed in different lounges, at various times.

British pilgrims use different airlines to travel from and to the United Kingdom. The most commonly used airlines are British Airways, Lufthansa, Saudi, Qatar and Emirates. Only flights from British Airways and Lufthansa depart from the North terminal. Saudi airlines departing from the South terminal and two Emirates flights from the Hajj terminal were selected as clusters. Subsequently, a systematic sampling from each flight cluster was used.

We planned to target one nationality (British) however, targeting one specific nationality at the airport in Saudi Arabia was challenging, particularly when the targeted nationality is a minority among other pilgrims.

While waiting for the British pilgrims to arrive at the airport, the PI used the opportunity to have several conversations with pilgrims from different countries. She was informed by several Egyptian Hajj pilgrims that they felt they had been deceived by their Hajj agencies; hence, they had not received the vaccines they were promised and had paid for at a cheaper price. Pilgrims reported to the PI that the vaccination cards were given in advance and that they were informed that they would then receive the vaccines prior to their departure for Hajj. Nevertheless, they did not receive the vaccines. Similar declarations were given by South Asia pilgrims who also encountered vaccination issues prior to travelling.

This was a warning sign to change the study protocol and targeted populations to establish if pilgrims had been vaccinated. Therefore, the plan was to conduct a phase two of the pilot study that targeted Umrah pilgrims without any nationality or vaccination status restrictions. Therefore, an ethical amendment form was submitted to both LSHTM and KAUST and was granted prior to the commencement of the Umrah.

Umrah pilgrims were sampled in the Hajj terminal only and by way of using a simple two-stage sampling method.⁶

Stage 1: select primary sampling units from Umrah flights from the daily flight schedule in the Hajj terminal by means of using simple random sampling

Stage 2: select Umrah pilgrims from each flight systematically.

4.5 Sample size

Sample size was calculated for all phases of the study separately and based on assumptions or findings from other studies . Software such as Stata and Epi Info were used in samples size calculation.^{7 8}

4.5.1 Sample size calculation for the Pilot phase

Epi Info software was used to calculate a sample size of 97 British Hajj pilgrims to estimate a meningococcal carriage rate of 10%, with precision of 5% and a confidence level of 90% and a sample size of 384 Umrah pilgrims to estimate 50% of non-meningococcal vaccinated pilgrims with precision of 5% and a confidence level 95%.

4.5.2 Sample size calculation for the main phase

The sample size for the main 2017 Hajj study was recalculated to compare the uptake of meningococcal vaccine proportions between pilgrims who have received the conjugate vaccine, polysaccharide vaccine and those who haven't received any meningococcal vaccine before the Hajj based on results from the Umrah phase of the pilot study. These results were used to estimate a sample of 2036 pilgrims comparing different proportions of meningococcal vaccine uptake between conjugate group, polysaccharide group and non-vaccinated group 2% , 42% and 51% respectively. The sample size was calculated to achieve 80% power at a 5% significance level.

Samples size was also recalculated to compare the carriage proportions between pilgrims who have received the conjugate vaccine, polysaccharide vaccine and those who haven't received any meningococcal vaccine before the Hajj. STATA was used to calculate sample size based on a number of results from previous meningococcal

carriage studies and assumption.⁹⁻¹¹ These results were used to estimate a sample of 2176 pilgrims comparing different proportions of meningococcal carriage between conjugate group, polysaccharide group and non-vaccinated group 0.0001%,2.6% and 10%, respectively.

Table (3) illustrates the sample size required to compare the proportion between the three groups based on the uptake of meningococcal vaccination and meningococcal carriage of serogroups A,C,W and Y . The laboratory results from the pilot study did not provide any results to be used as an estimate of the Intra-class Correlation Coefficient and design effect (DEFF), for this reason , a design effect =2 was assumed for planning purposes to estimate the sample size required for the main study.¹² This means estimating the sample size using standard method mentioned above (i.e. n=1088) and doubling it (i.e. n=2176) in order to provide the same precision and power to detect the hypothesized difference in carriage.¹²

For the ethical approval, the sample size was increased to involve 3000 pilgrims in the study.

Table 3: Estimated sample size for the three groups (conjugate, polysaccharide and unvaccinated).

Estimated sample size based on carriage of serogroups A,C,W and Y					
Total estimated Sample size	N::Conjugate group , 0% <i>Nm</i> carriage	N: Polysaccharide group , 2.6% <i>Nm</i> carriage	N: Unvaccinated , 10% <i>Nm</i> carriage	STATA command	Total sample size with design effect = 2
602	301	301	-	power twoproportions 0.0001 0.026, p(0.80) a(0.05)	1204 N1: 602 N2: 602
338	-	169	169	power twoproportions 0.026 0.1, p(0.80) a(0.05)	676 N1: 338 N2: 338
148	74	-	74	power twoproportions 0.0001 0.1, p(0.80) a(0.05)	296 N1: 148 N2: 148
Estimated sample size based on meningococcal vaccination status					
Total estimated Sample size	N::Conjugate group , 2% uptake	N: Polysaccharide group , 42% uptake	N: Unvaccinated , 51% uptake	STATA command	Total sample size with design effect = 2
32	16	16	-	power twoproportions 0.02 0.42, p(0.80) a(0.05)	64 N1: 32 N2: 32
962	-	481	481	power twoproportions 0.42 0.51, p(0.80) a(0.05)	1924 N1: 962 N2: 962
24	12	-	12	power twoproportions 0.02 0.51, p(0.80) a(0.05)	48 N1: 24 N2: 24

4.6 Study procedures

4.6.1 Pilot Phase

All sampled pilgrims were provided with written information regarding the aims of this study and were informed that this study will take place in the airport prior to their

departure. Upon their agreement to participate in the study, they were asked to sign a consent form. The PI took swabs from pilgrims after Hajj in a special room at KAIA. Well-structured open and closed questionnaires were completed by the pilgrim at the swabbing site after Hajj. The questionnaire was a 9 page, self-administered paper questionnaire. This consisted of contact information, demographic items, health status, common health illnesses during Hajj, preventive measures and several questions related to the type of quadrivalent MenACWY vaccine, time of administration, use of antibiotics, and the uptake of recommended vaccines. (Appendix 6)

Swabs taken from the posterior pharyngeal wall behind the uvula via the mouth have shown the best sensitivity in relation to detecting meningococcal carriage, according to limited evidence from previous studies.¹³ Therefore, posterior pharyngeal swabs were taken via the mouth from pilgrims after Hajj. A skimmed milk, tryptone, glucose and glycerin (STGG) medium was used to store the swabs. The participant was asked to tilt the head back, open the mouth wide and phonate an “ah”.¹⁴ A tongue depressor was used to provide a better view and a Dacron / polyester tip swab was gently rolled over the tonsils and posterior pharynx. It is recommended to plate swabs onto a solid culture medium on site immediately after collection.¹⁵ However this immediate plating was not undertaken. This is for the reason that this was challenging logistically and dangerous to use in closed places like airports, especially when a flame burner is commonly used when direct plating onto a solid culture to provide a clean environment for plating the swab. Upon agreement, a nasopharyngeal swab was taken from pilgrims and inserted in the transport medium (Triazol). The full swabbing protocol can be seen in Appendix 7.

All mouth and nasal swabs were kept at 4C for one hour followed by storage in a portable freezer at -20C. They were then kept securely at the airport for two weeks prior to being transported to KAUST to be stored at -80C.

The PI followed all safety precautions and wore a face mask which was changed every four hours, and used gloves and gel sanitizer every time she took a swab from a pilgrim. A bio hazard bag was used to collect all waste and was discarded daily following Ministry of Health guidelines.

Tracking and identification barcoded labels were printed for each participant. A special room in the airport was provided for swabbing and precautions were taken to guarantee such a procedure was conducted safely. the PI received the quadrivalent conjugate meningococcal vaccine two months prior to the field work.

The same swabbing protocol used in the Hajj phase was employed to swab all Umrah pilgrims from the mouth and nose. However, the 9 page English questionnaire was not completed and only information about vaccination status, gender, age, nationality, vaccination date, arrival and departure dates were collected.

4.6.2 Main phase fieldwork

4.6.2.1 Recruitment, selection and training of field staff.

The aim of the main study was to target a large sample size of pilgrims over a period of one month; therefore, a large medical team was necessary to achieve the data collection goals in the targeted period.

To improve the training of students who have graduated from medical schools and to facilitate logistical support for researchers in Saudi Arabia, the Saudi Commission for

Health Specialties requires every medical graduate to volunteer as a data collector for any ethically approved health research.¹⁶ Medical student volunteers are expected to be trained to meet study requirements and ethical standards. Moreover, at the end of each study, medical students are granted appreciation certificates from the research institutions to prove their contribution as data collectors to Saudi Commission for Health Specialties.¹⁶

4.6.2.1.1 Research advertisement

Social media was used to advertise the study and recruit medical students from May 2017. The advertisement was in Arabic and consisted of approximately 300 words, with a brief introduction to the study, in addition to the inclusion and exclusion criteria in the applicant selection. A WhatsApp group was created, and the link was disseminated among medical students primarily from Ibn Sina National College for Medical Studies in Jeddah, Saudi Arabia, who subsequently distributed it to other medical students from different medical institutions in Jeddah e.g. King Abdulaziz University, Batterjee Medical College, Al-Farabi Private College and Umm al-Qura University in Mecca, Saudi Arabia. The advertisement reached individual medical students from other cities e.g. Riyadh, Medina, Dammam and Abha.

Within five hours the number of applicants reached 226 male and female medical students; hence, the group had to be closed. A waiting list was created on WhatsApp for any new applicants to be added if any of the accepted applicants withdrew before the training date.

4.6.2.1.2 Selection of medical students

The selection of the medical students was based on certain inclusion and exclusion criteria to ensure that every applicant was eligible for training and data collection. The quota was divided into 50% female and 50% male in order for both sexes to be given equal opportunity; however, there were more female applicants than males, although the quota remained intact until the last final list was drafted. Other criteria e.g. 4th year medical student or above, ability to speak two or more languages, fieldwork experience, and moreover, based in Jeddah or Mecca, or at least based in Jeddah for the Hajj for those from outside Mecca province.

4.6.2.1.3 Interviewing students

All the applicants were briefly and informally interviewed by the PI in May, June and July 2017 to ensure that they were eligible and committed to work. Approximately 100 medical students were accepted to participate in the data collection and to be registered for the final approval.

Two female and two male medical students were selected to act as sub-leaders for the medical students and to provide logistical and management support for the fieldwork. The selection was based principally on previous experience in fieldwork on other Hajj projects they had been involved in over the last few years.

4.6.2.1.4 Training location

Saudi Vision 2030 and the National Transformation Program 2020 support private sector investment in areas that the Saudi government has mostly financed in the past.¹⁷ In recent years, the health sector has been reformed by the Saudi government

to provide high-quality public healthcare and health education to the public. Furthermore, to receive funding and support from the government, private hospitals in Saudi Arabia compete to advertise their contribution to health research.

Consequently, a business arrangement was made with the New Jeddah Clinic Hospital to host medical students and provide a free theatre and training materials for ten days in return for permitting the marketing team from the New Jeddah Clinic Hospital to photograph the training sessions to advertise the contribution of their hospital in research training programmes.

4.6.2.1.5 Registration

Medical students were asked to submit a copy of their Saudi National or resident identification card, university identification card, two photos, a certificate that confirmed receipt of the quadrivalent meningococcal vaccine not less than two weeks prior to the commencement of the data collection and insurance amounting to 200 Saudi Riyals.

The aim of the 200 Saudi Riyal (SAR) was to ensure students were committed to the training and fieldwork. All students were provided with an insurance invoice to refund the 200 SAR at the end of the fieldwork. Any student who withdrew after registration or training was not permitted a refund, and furthermore, any remaining finance was used to pay the four sub-leaders who were appointed for fieldwork management. Approximately 83 males and females registered for the training programme in New Jeddah Clinic Hospital; 52 females and 31 males.

The Hajj terminal is a semi-restricted military campus and only pilgrims, permitted vehicles and personnel have access to the Hajj terminal. Therefore, a request was

made to provide the research team with airport IDs and free movement within the Hajj terminal. All required documents e.g. Saudi national or resident identification card and two photos were collected from all students and sent to the airport security department so that the airport IDs could be issued. The Saudi Minister of the Interior spent three days checking the records of all medical students to ensure that none of them had committed any crimes or had any suspicious ideologies. This is undertaken to ensure the safety of the pilgrims and protect the Hajj terminal from any hostile behaviour. The Saudi Minister of the Interior then gave permission to the Hajj terminal to issue IDs for each of the medical volunteers. The IDs were eligible for one month from the 28th August 2017 to 6th October 2017.

4.6.2.1.6 Training materials

The training seminar consisted of a two-hour lecture followed by a practical session on how to use Tablets and the Open Data kit (ODK) system¹⁸ for the entire 10 days. Additionally, a video was recorded and sent to students to ensure that they had access to the training material any time

Training lasted from the 20th to the 30th of August 2017. The 83 eligible students were divided on these ten days to ensure in the region of 8 students were well trained each day. Twenty tablets were provided for the training.

The training lecture started by giving the background to the research and the aim of the study, followed by a lecture about research ethics and how to ethically approach participants. The PI attended two separate ethics courses at the London School of Hygiene and Tropical medicine; specifically, research ethics: *Making Your Application to the LSHTM Ethics Committee* and *Ethics and Good Research Practice for RD*

Students. Furthermore, a face-to-face meeting was undertaken with John Porter the head of the Ethics Committee to discuss any ambiguous or concerning issues that might arise during the fieldwork.

Special attention was given to ethical issues, principally informed consent, autonomy and privacy. All medical volunteers received special training designed for research ethics to ensure that the most stringent measures would be applied, so as to protect pilgrims throughout the entire research. In addition, all medical volunteers were asked to inform pilgrims that they are free to withdraw from the study at any stage and for any reason without any form of victimisation or humiliation occurring in any way, such as in relation to their performance at the Hajj/Umrah in the future or their leave from Saudi Arabia. Medical volunteers were also informed that the research was entirely voluntary and that pilgrims should not hesitate to report to the researcher or the Saudi authorities if they have been coerced or forced to participate in the study by the medical volunteers, in order to enable action to be taken.

A translated information sheet and informed consent forms in 15 different languages were shown to medical volunteers. The volunteers were also notified that typically, the tour operator who speaks the language of the targeted group of pilgrims would work as a translator to explain the research aim and approach pilgrims before each medical volunteer approached pilgrims individually. They were also informed that pilgrims were free to ask any questions in regard to the research and that the tour leader would act as a translator. It is worth mentioning that the medical volunteers were notified of the importance of obtaining written consent. Nevertheless, it was noted that verbal permission would be acknowledged if pilgrims felt awkward with regards to signing.

Additionally, for pilgrims who are not educated, a witnessed consent procedure was put in place to ensure their full understanding and that informed consent would be taken from parents or a guardian for pilgrims less than 18 years old.

The practical part of the training was on how to use the Tablets and how to choose an appropriate language for each targeted group of pilgrims. Every question in the questionnaire was discussed with the students and feedback was received for some students in regard to several questions.

Open data kit (ODK) is an electronic data capture tool, which has been setup to help scientific researchers in their projects.¹⁸ The Open data kit serves as a secure encrypted server and is available at LSHTM for researchers.¹⁸ ODK was chosen for its advantages that surmount conventional paper. These advantages include data accuracy, data completeness, video and picture capture options, in addition to speed of analysis.

Twenty Asus ZenPad Z380M tablets¹⁹ were purchased for the purpose of this project. All tablets were secured with passwords in order to prevent any unauthorised access.

4.6.2.1.7 Swab training

The medical student's primary task was to approach pilgrims ethically, obtain informed consent and collect data using the Tablets. It was intended that the PI would conduct the swabbing; however, around 20 medical students were trained on how to take oropharyngeal and nasopharyngeal swabs as a backup if the PI was unable to collect swabs. The use of one person to swab was to ensure that the technique used was consistent for all swabs taken. A training video was recorded on swabbing by the

LSHTM media team and the PI was shown the proper technique to employ when performing both oropharyngeal and nasopharyngeal swabs. This video was shown to medical students and a practical session was conducted on each of the training days. Figure 4 and appendix 8 illustrate the number of leaders and medical volunteers involved in data collection .

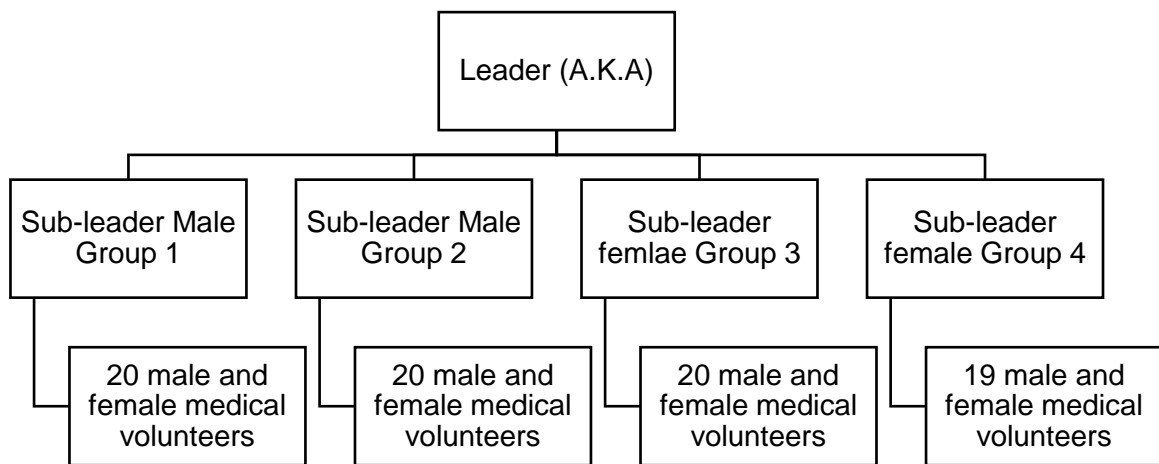


Figure 4: Number of leaders and medical volunteers involved in data collection.

4.6.2.1.8 Transportation

Only registered vehicles are allowed to enter the Hajj terminal campus; therefore, a 32-seater registered bus was hired for one month with a private driver to transport students to and from the Hajj terminal every day.

4.6.2.1.9 Field safety

A field work plan was prepared for health and safety issues that may be encountered in the field. All medical students were required to submit a quadrivalent meningococcal

vaccine certificate that verifies receipt of the vaccine not less than two weeks prior to the commencement of the data collection. The Saudi Ministry of Health collaborated with Uber taxi service to provide free influenza vaccines and quadrivalent meningococcal conjugate vaccines for all residents of Jeddah, Mecca and Medina, one month before Hajj began. This collaborative service saved considerable time, since it can be requested via a special App and transport a nurse to the precise location to administer the vaccine. All medical students who volunteered in the study received both the influenza and the quadrivalent meningococcal conjugate vaccines.

A meeting was undertaken with the head of the airport clinic and the medical team from the Ministry of Health to agree on a safety and medical plan to ensure that all the medical students had access to health care in the airport at any time and under any circumstances.

The security and military forces were informed by the head of the airport about the research to ensure the safety of both the pilgrims and research team. A special security force usually patrolled the area where the research took place. Students were informed that CCTV cameras are positioned everywhere to ensure that none of the students acted in an unethical when approaching pilgrims and to ensure that the data collection is monitored, and no misclassification bias carried out by the medical students, e.g. a student completing a questionnaire and attempting to pass it off as belonging to a pilgrim.

4.6.3 Data collection

The Hajj terminal began operating departing flights from 4th September to 6th October 2017. The majority of departures left Saudi Arabia in the first two weeks, starting from

the 4th of September 2017 and decreased gradually over the last two weeks to a few flights during the last few days. September the 4th was for local flights only that were departing for other cities across Saudi Arabia. The 5th was for local flights and flights going to any of the Arabian Gulf countries. Flights departing to the rest of the world started operating on 7th 2017.

Data collection took place from 5th to 29th September 2017. The medical students were divided into four groups and each group had a number of male and female students. Every shift had an attendance sheet and students were asked to sign in and out for each shift and make a note of the number of data they collected over the duration of each shift. Tablets were also numbered with codes and every student was allocated to a known code, so as to track any Tablet easily. Students were not allowed to take the Tablets home with them and were asked to return them to the PI at the end of each shift.

The PI was based primarily at the airport. She had an on-call room with full access to all Ministry of Health rooms in each of the 14 lounges at the Hajj terminal.

Fieldwork materials were stored in the storage room in lounge 14 in a freezer (-20 C). The freezer remained on at all times to keep the samples frozen.

4.6.4 Challenges

The main challenge concerning the fieldwork was that the PI had to swab all the pilgrims single-handedly and was based at the airport for most of the time ready for any selected flights to be sampled. In addition, general supervision was performed by

the PI with the help of the four sub-leaders, in regard to monitoring the work ethically and logistically.

One of the main challenges remained the constant use of facemasks by the PI which had to be removed several times throughout the day , which was a risk in the Hajj terminal when sick pilgrims were having swabs taken, and some coughed and sneezed over her on numerous occasions.

The work load on the medical students was divided fairly, so as not to allow students to work more than a maximum of six hours every day. Each student was asked to collect data from at least 35 pilgrims for the entire data collection period. This means every student worked for a maximum of one week. Students were asked to wear facemasks constantly and use hand sanitiser and gloves when necessary. None of the students developed any serious health issues during data collection period, principally because of the short exposure period every day and the emphasis placed on wearing a facemask and following health precautions.

4.7 Ethical considerations and permissions

4.7.1 Ethical approvals

Ethical approvals were granted from the London School of Hygiene and Tropical Medicine (LSHTM) in the United Kingdom and King Abdullah University of Science and Technology (KAUST) in Thuwal, Saudi Arabia prior to conducting the pilot study (see Appendix 9).

LSHTM approved the entire study (pilot and main phases) on June 16th, 2016. This contrasted with King Abdullah University of Science and Technology, which approved

the pilot study in two stages: the data collection stage approved on September 4th 2016 and the laboratory safety stage approved on May 12th 2017 followed by approval of the main study with regards to the 2017 Hajj.

4.7.2 Approval from the Governor of Mecca Province

Saudi Arabia is distinguished by its importance in the Islamic world due to the presence of the cities of Mecca and Madinah. Kings in Saudi Arabia have been crowned custodians of the Two Holy Mosques which serve Hajj and Umrah pilgrims, for decades. Saudi Arabia treats visiting pilgrims from all over the world with great care and is keen to treat them as guests. Accordingly, any contact with any pilgrim inside Saudi Arabia or conducting any research on pilgrims requires the approval of the governor of the Mecca region (in 2017, prince Khalid al-Faisal Al Saud), to avoid any harm to any guest and to allow the government to observe ethical procedures taken by the researcher.

The requested approval was made by Dr Abdullah M Assiri, the assistant deputy minister of preventive health at the Saudi Ministry of Health and was granted prior to the study.

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Chapter 5: Questionnaire development

5 Questionnaire development

“I came, I don't know from where or how I came to be I am, or why I came? I don't know! I saw a path in front of me I began to walk, I must keep on walking willingly or unwillingly, whether I agree or not. How did I come to be? How did I sighted my way? I can't perceive the matter, I don't know”¹

In this translated Arabic poem, Elia Abu Madi remarked that it is human nature to ask questions to find a suitable way and investigate any matter we are interested in. Asking questions is possibly the best method of gaining knowledge secondary to observation, and the most universal form of human communication.² However, determining the answers provided by respondents is influenced by the specific phrasing of questions. This precision of wording is not valued as completely as it should be, even in everyday conversations.³ Others also assume answers for certain questions, based on other information provided by the respondent. For instance, a physician colleague in the emergency room was taking the medical history of a Yemeni patient and assumed a low social economic status based on the external appearance. In fact, the patient belongs to one of the richest families living in Saudi Arabia. Another researcher was investigating the relationship between ethnicity and cigarette smoking by asking questions concerning nationalities and ignoring the fact that most countries now are multi-ethnic countries.

These two stories illustrate the challenges both researchers and questionnaire developers face when they construct questionnaires to answer research questions. They also demonstrate the importance of asking direct questions that clarify the meaning.

This chapter of the thesis presents the development of the questionnaire and piloting before finally using it to collect data for the purpose of this primary study. Additionally, it could possibly be used by other researchers as a standard Hajj and Umrah questionnaire, or in relation to other types of mass gatherings. The final version of the questionnaire progressed through three distinct stages, including questionnaire construction, pre-testing, piloting and translation.

5.1 Questionnaire construction

Developing a good questionnaire is challenging and time consuming; therefore, the PI had to attend two different questionnaire design courses in order to develop a valid, reliable and standardised questionnaire. One of these courses was at the London School of Hygiene and Tropical Medicine (LSHTM) and is called Introduction to data management and questionnaire design. The other course known as questionnaire design and testing was external and conducted by the Social Research Association. Advice was also taken from Dr Phil Edwards from LSHTM who is an expert in the field of surveys.

Existing questionnaires and guidelines concerning questionnaire design, as well as books were reviewed to construct this questionnaire.

A seven tasks framework for developing an effective questionnaire was used to construct this questionnaire.² Figure 5 illustrates the seven steps involved in questionnaire construction. Each of these stages took place at a separate time and in different places.

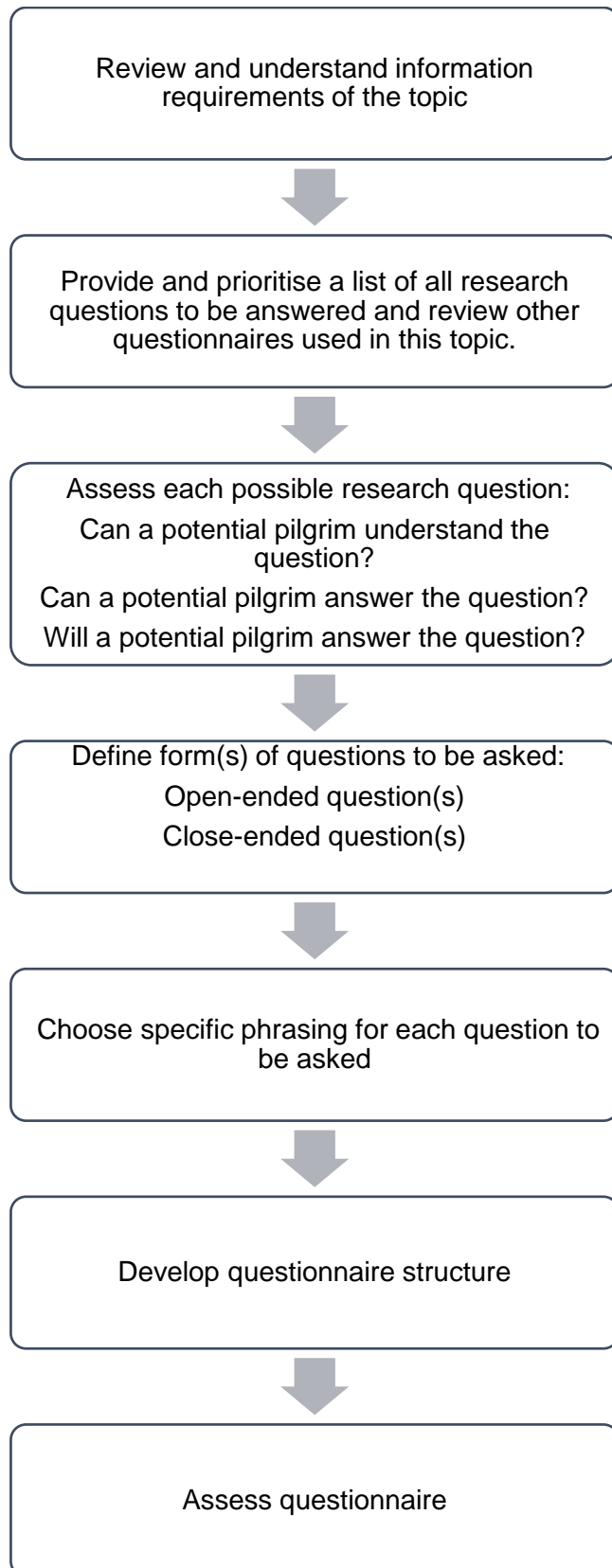


Figure 5: Stages of questionnaire construction. .²

5.1.1 Task one: Review and understand information requirements of the topic.

The literature related to meningococcal studies and other diseases found at Hajj and Umrah was reviewed comprehensively to gain the most recent and valuable information regarding disease, prevention and risk factors.

5.1.2 Task two: Provide a list of search questions.

Once the review of the literature was completed, a list of all potential research questions that are essential to deliver the required information were listed and prioritised so that the questions required to answer primary research objectives were listed first and subsequently followed by the secondary objectives. Various questionnaires used in other Hajj and Umrah studies ⁴ were reviewed and the author's permission asked for via e-mail so that specific aspects related to the questionnaire could be used as guidelines.

5.1.3 Task three: Assess each possible research question.

Three questions were asked to assess each possible question in the questionnaire: Can a potential pilgrim understand the question? Can a potential pilgrim answer the question? And, will a potential pilgrim answer the question? For a question to be used in the questionnaire the answer should be 'yes' for each of the three assessing questions.² Although these were evaluated based on the research experience, the questions were re-evaluated by means of a pre-test and piloting stages, where three people who had recently performed Umrah were involved in the evaluation of the pre-test stage and 140 British pilgrims in the piloting stage.

5.1.4 Task four: Define form(s) of questions.

Closed-ended questions and open-ended questions are the two basic forms of survey questions.² Choosing the form of survey questions and whether to use open-ended (allows respondents to answer in their own words) or closed-ended (respondents must choose an answer from listed answers) is a priority decision prior to constructing any questionnaire.⁵ Each form has advantages and disadvantages and none can be considered as superior to the other. Using both closed-ended and open-ended questions is common in many questionnaires.²

Both open-ended and closed-ended questions were used in developing this questionnaire. Most questions are closed-ended, either ticking a particular box or yes or no questions, and only 24% are open-ended questions. These open-ended questions include personal, tour group and flights date questions, such as name, e-mail address, mobile number, name of tour group, city of residence, arrival and departure dates, vaccination source and date of vaccination. Other open-ended questions comprise questions that have the option “other” in their categories.

5.1.5 Task five: Choosing specific phrasing.

Constructing survey questions might be the easiest part; however, minor changes in wording can cause huge variances in answers.³ Simple short questions with one or two clauses were used to avoid confusion and uncertainty and no jargon or negative questions were used. A separate question was used for each piece of information, for example instead of asking two pieces of information at the same time, e.g. have you shared toothbrushes and water bottles during Hajj? The question is separated into two

questions so the first can be, have you shared toothbrushes during Hajj? Whereas the second is have you shared water bottles during Hajj?

Variables and questions to measure socio-economic status (SES) were selected carefully; nevertheless, it was difficult to avoid the question related to monthly income. This is because it is an important variable to measure SES according to the National Committee on Vital and Health Statistics (NCVHS), which developed a standard to measure socio-economic status and identify the minimum and most important set of variables for measuring SES. These variables include income, education, occupation, family size and household composition. All these four variables were included in the questionnaire to measure SES.⁶

Simple terms were used to describe medical conditions such as diabetes (high blood sugar), hypertension (high blood pressure) and malignant disease (cancer). Sensitive medical conditions, for instance AIDS and HIV were completely avoided by the specific terms and replaced by immune deficiency. This term was further described as low immunity due to a disease or medication use, seeing as many people, especially the elderly in some cultures tend to describe fatigue as low immunity.

To identify at least one episode of a previously defined common health problem that may develop during Hajj, based on syndromic signs and symptoms, a list of syndrome definitions was identified for each common health problem. Table 4 illustrates the research objectives and items included in the questionnaire.

Table 4: Syndrome definitions.

Syndrome	Definition
Travel diarrhoea	Passage of 3 or more loose or liquid stools in 24 hours with or without at least one symptom of cramps, fever, nausea or vomiting during or after the Hajj. ⁷
Upper respiratory tract infections	Developing “at least one of the constitutional symptoms (fever, headache, myalgia) and one of the local symptoms (running nose, sneezing, throat pain, cough with/ or without sputum after reaching Mecca for the Hajj” ⁸ or within few days after Hajj.

To avoid misunderstanding, the medical symptom diarrhoea was described as a passage of 3 or more loose stools during 24 hours.^{7, 9} Travel diarrhoea is separately defined in the analyses as a passage of 3 or more loose stools in 24 hours with other enteric symptoms, such as abdominal pain, nausea, fever or/and vomiting.⁷

In questions related to preventive measures adopted during Hajj and facemask use, the type of face mask e.g. normal surgical facemask or N95 respirator mask was supported by adding a small picture of each type for those who cannot differentiate between the two different types of facemask.

5.1.6 Task six: Develop questionnaire structure.

A single sided self-administered questionnaire consisting of ten pages was constructed for the pilot study. The questionnaire begins with a short simple title (Your Health and Hajj Journey) and a brief introduction explaining the purpose of the study with a cartoon picture of couples performing Hajj (see Appendix 6).

The information sheet and informed consent were attached to each questionnaire. Thirteen possible questions with the questions that might be asked by pilgrims are given in the information sheet to ensure that every pilgrim understood the purpose of the study, benefits of taking part, risks and confidentiality. Reading instructions might be boring and time consuming for many pilgrims; thus, no instructions were added as the questionnaire is simple and does not require instructions. Pilgrims are told to ask for help to complete the questionnaire if required.

The questions were ordered logically, starting with personal and tour information, demographic information, health problems and preventive measures used during the Hajj.

Since white clothing is a symbol of Hajj, A4 white pages were used with Arial font and size 12 for greater vision.

5.1.7 Task seven: Assessing the questionnaire.

Evaluation of the questionnaire was undertaken in two stages, pre-testing and piloting. Each stage is described in more detail below.

5.2 Pre-testing

Three different people, an elderly male, a young female receptionist and a young male physician who performed Umrah were asked to complete and evaluate the questionnaire in London, in May 2016. Selection of participants involved in the testing was based on age, background and gender. Participants were assured that their comments and quotes would be anonymous.

“I think it’s a simple, easy questionnaire, it took me 10 minutes to complete it but I’m not really sure pilgrims will answer the income question. I might be wrong but personally I don’t feel comfortable providing such information. I don’t have any suggestions to provide, in fact I have learned from this questionnaire and my discussion with you that the facemask should not be used for more than six hours, do you know that I have used the same facemask for two days during Umrah, that’s why I am sick now”. (23 years, male, junior physician).

“The language is very easy to understand but I did Umrah last year and really can’t remember some of the answers, especially the preventive measures” (27 years, female, receptionist)

“I find it simple but long. If you want this questionnaire to be completed then you should give something to them, tea or a coffee would work perfectly. Remember those pilgrims are in the airport, done with their Hajj and they just want to travel back home” (69 years, male).

All these comments made by participants who contributed during the test were noted but not followed, the PI wanted to pilot it in a large sample during the Hajj before making a final decision and changes to the questionnaire. Furthermore, the PI wanted to ascertain the effect of incentives on the response rate, as this would be difficult to see if incentives were provided from the beginning.

5.3 Pilot testing

Pilot testing took place in King Abdul-Aziz International Airport (KAIA) in Jeddah, Saudi Arabia during the 2016 Hajj and Umrah seasons. 140 British Hajj pilgrims participated in the piloting test and 385 international Umrah pilgrims.

The single sided questionnaire made the questionnaire appear larger. Consequently, several British Hajj pilgrims hesitated when they saw the size of the questionnaire, although the questionnaire took only 10-15 minutes to complete.

The response rate was different from one nationality to the other, and different factors influenced the response rate positively. For example, British pilgrims were more willing to participate when coffee or tea were provided. Warm words and a humble attitude with pilgrims and kissing the foreheads of the elderly increased the response rate dramatically, regardless of nationality or ethnicity and made pilgrims encourage each other to participate. Some pilgrims were happy to participate if the laboratory results of their swabs were going to be sent to them via e-mail or mobile messages.

Some pilgrims were more willing to participate when free medication was provided for current symptoms.

Several British pilgrims were not able to complete the questionnaire due to time limits prior to their flights. Missing data were discovered, specifically those related to monthly income and number of household members.

One British pilgrim felt offended by the ethnicity question. Therefore, the PI apologised to that pilgrim. The PI explained to him that this question did not doubt his loyalty or patriotism to the UK and that the purpose of this question is to establish the relationship between ethnicity and meningococcal carriage and that the same point can be applied to level of education and other risk factors.

The English questionnaire was not translated to other languages in the pilot phase and Umrah pilgrims were not able to complete the entire questionnaire due to language barriers. Group leaders helped in translation; however, it was difficult to ask for their help when approaching each participant.

Pilgrims made a few suggestions, such as adding questions regarding their visit to Medina the second holiest city in Islam after Mecca and questions related to other recommended vaccines, or the hygiene of other pilgrims inside the tents.

The lessons learned from the piloting were considered and an amendment ethics form will be submitted to include incentives like coffee or tea .

5.4 Translation of the questionnaire

Changes that were required were made in the English version of the questionnaire prior to translation. Different professional translation agencies in the United Kingdom (UK), Romania and United Arab Emirates (UAE) were used to translate the questionnaire into 14 different languages, including Arabic, Albanian, Bengali,

Bosnian, Chinese, French, Hindi, Indonesian, Kurdish, Malay, Pashto, Russian, Turkish and Urdu. Table (5) shows the 15 different languages and their distribution by means of each individual country.

Table 5: list of official languages by countries.

language	Countries
Arabic	All Arab League countries (22 countries)
Albanian	Albania
Bengali	Bangladesh
Bosnian	Bosnia and Herzegovina
Chinese	China
English	United Kingdom, United States, Canada, Australia and some African countries
French	France and some African countries
Indonesian	Indonesia
Pashto	Afghanistan and Pakistan
Hindi	India
Kurdish	Kurdistan
Malay	Indonesia, Malaysia, Brunei and Singapore
Russian	Russia, Kazakhstan, Kyrgyzstan, Uzbekistan, Tajikistan and Turkmenistan
Turkish	Turkey
Urdu	Pakistan

An electronic data capture tool open data kit (ODK) was used in the main Hajj study.¹⁰ A.K.A received online training on how to request and design ODK forms pertaining to different languages. Designing data forms for 15 languages and uploading these to the Tablets took approximately one month of continuous work. Figure 6 below summarises the stages of the ODK setup prior to the commencement of the data collection.

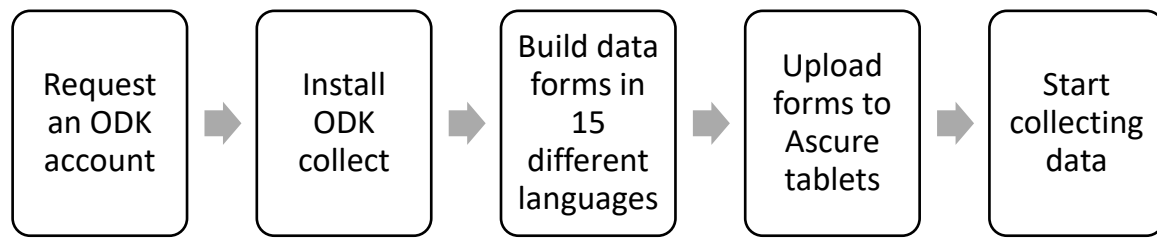


Figure 6: Stages of the ODK setup.

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Chapter 6: Laboratory methods

6 Laboratory methods

This chapter summarises laboratory techniques used in the isolation, identification and characterization of *Neisseria meningitidis* (meningococcus) from the oropharyngeal swabs collected from pilgrims who performed the 2016/2017 Hajj and Umrah . The techniques described in this chapter have been employed for many years and were selected by considering capability, time and cost. The PI performed all the laboratory testing in this chapter with the help of senior laboratory technician at King Abdullah University of Science and Technology (KAUST) and London School of Hygiene and Tropical Medicine (LSHTM)

6.1 Biosafety and trainings

Technicians working in laboratory places are at risk of laboratory acquired infections either as a result of accidents or unrecognised incidents. Different factors determine the degree of hazard including route of exposure, host resistance, virulence and dose of the biological agent, appropriate biosafety training, in addition to level of experience with biohazards. It is important to mention that laboratory-acquired infections can take place when microorganisms are ingested, inhaled or introduced into tissues unintentionally. ¹ Various cases of laboratory-acquired meningococcal infection with a high fatality rate have been reported.¹⁻³ Biosafety Level 2 (BSL-2) practices are required for work involving *N. meningitidis* .¹

The appropriate biosafety training and laboratory training required for working on *N. meningitidis* in BSL-2 was received by Dr. Fathia Ben Rached the laboratory safety representative from King Abdullah University of Science and Technology (KAUST) in Thuwal, Saudi Arabia and by Dr. Joanna Houghton the laboratory manager from

London School of Hygiene and Tropical Medicine (LSHTM) in London, the United Kingdom.

KAUST HEALTH provided medical clearance checks, spirometry and fit testing, all of which are prerequisites for being enrolled on the KAUST Respiratory Protection Programme (RPP) prior to working in the lab. A quadrivalent meningococcal conjugate vaccine was received in London six months before working on the samples.

6.2 Collecting and transporting of samples

Upon collection oropharyngeal swab samples were inserted into a screwed vial tube containing 1 mL skimmed milk, tryptone, glucose and glycerine (STGG) medium. This transport medium had been evaluated and used in other meningococcal and pneumococcal studies.⁴⁻⁶ All swabs were kept at 4 °C for 1 hour followed by storage in a portable freezer at -20 °C at the airport. They were then kept securely at the airport for two weeks prior to being transported and stored at -80 °C at KAUST for long-term storage.

The correct biosafety guidelines were followed while handling the collected potential infectious specimens. Mr Nader Al Farshooti a logistics officer from the research material logistics department at KAUST arranged for the safe transportation of the samples from the Hajj terminal at King Abdulaziz international airport (KAIA) to KAUST to be stored at -80 °C freezer in Professor Arnab Pain's lab and subsequently from the KAUST freezers to LSHTM. Samples were shipped on dry ice to maintain the -80 °C temperature. Material transfer agreement (MTA) was signed previously based on an established contract between LSHTM and KAUST. Samples reached LSHTM safely in September 2017 and were stored in a freezer at -80 °C prior to starting DNA extraction and the polymerase chain reaction (PCR) tests.

6.3 Methods used to detect *N.meningitidis*

Conventional and molecular methods are used to detect *N. meningitidis*. Conventional methods, such as culturing, the oxidase test and Gram stain are commonly used due to their lower cost compared to molecular methods. A combination of both methods has been used in different studies.⁷⁻⁹ Figure 7 summarises the methods used in both the pilot and the main study of the 2016/2017 Hajj and Umrah seasons.¹⁰

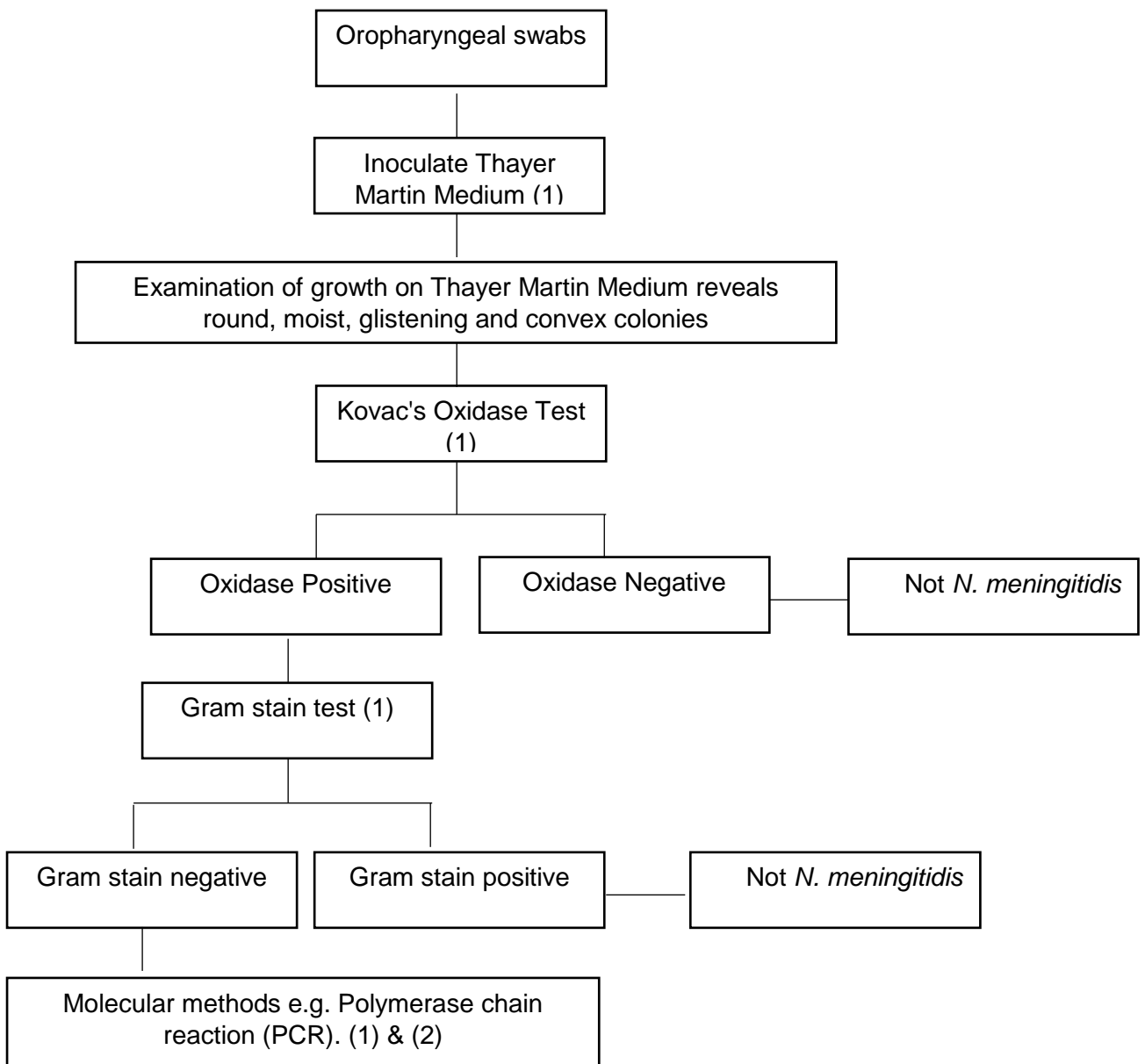


Figure 7: Methods used for identification and characterization of a *N. meningitidis* isolate. (1) methods used in the pilot study and (2) method used in the main.

6.3.1 Culture

N. meningitidis are gram-negative aerobic diplococcus bacteria with a “kidney” or “coffee-bean” shape¹¹ (Figure 8). It is a fastidious organism and will grow only if special nutrients are present in the culture medium at 35-37°C with ~5-10% CO₂ (or in a candle-jar).¹⁰ *N.meningitidis* grows on both a blood agar plate (BAP) and a chocolate agar plate (CAP), as well as selective medium for the bacterium *Neisseria*.¹² Colonies on BAP appear as grey unpigmented colonies, they look round, smooth, moist and convex with defined edges. On a CAP, they appear as large, colourless-to-grey opaque colonies.¹⁰

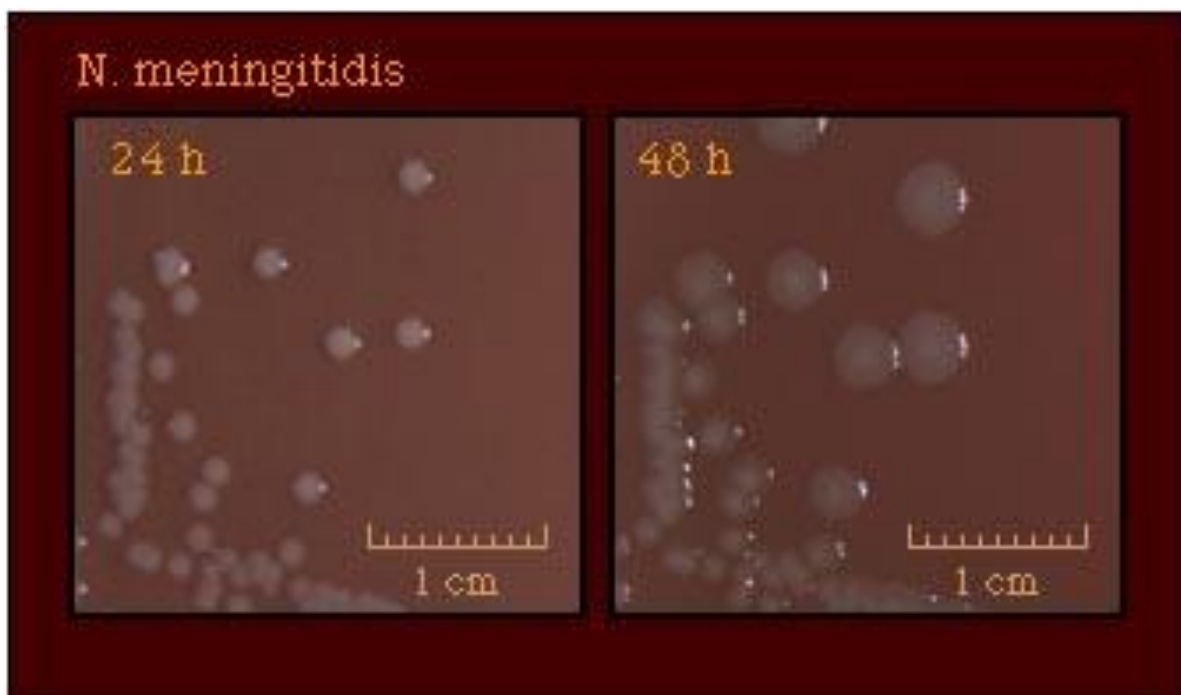


Figure 8: Colony Morphology of *N. meningitidis*.¹³

Both selective and non-selective mediums can be used to grow *N. meningitidis*. However, selective mediums such as Thayer Martin Medium (MTM), Martin-Lewis medium (ML) , GC-Lect medium and New York City (NYC) medium are used when the aim is to inhibit all other microorganisms and allow the selective recovery of *N.meningitidis*.¹² Antimicrobial agents are added to these mediums and are summarised in Table (5). The Thayer Martin Medium, which was used in the pilot stage of the study, contains a combination of antimicrobial agents: Vancomycin, Colistin, Nystatin and Trimethoprim (VCNT) inhibitor. Vancomycin inhibits most Gram-positive organisms except *Lactobacillus* and *Pediococcus* which are intrinsically resistant. Conversely, Colistin inhibits most Gram-negative organisms except for *Neisseria* and *Legionella*. Trimethoprim is added to inhibit Gram-negative organism “swarming *Proteus*” and Nystatin to inhibit most Fungi.¹²

Table 6:Antimicrobial agents in selective mediums for Neisseria bacterium.¹²

Antimicrobial agent	Media formulation (µg /mL)			
	MTM	ML	NYC	GC-L
Vancomycin	3	4	2	2
Lincomycin	-	-	-	1
Colistin	7.5	7.5	5.5	7.5
Nystatin	12.5	-	-	-
Anisomycin	-	20	-	-
Amphotericin B	-	-	1.2	1.5
Trimethoprim	5	5	5	5

Culture is an ideal method to confirm *N. meningitidis*. However, this method fails to detect all positives as it is negatively affected by factors such as storage, transportation conditions, culture practice and antibiotic usage prior to collection of the specimen.¹⁴

A culturing method was employed in the pilot stage of the study conducted at KAUST laboratory. Five hundred and five (128 samples from the 2016 Hajj season and 377 from 2016 Umrah season) collected swabs inserted in STGG were cultured by plating 100 µL of the STGG medium onto Thayer Martin Mediums and incubated for 24 hours at 37°C with ~5% CO₂. Suspicious colonies were sub-cultured to MTM for further identification. Suspicious colonies were isolated from the 268 Umrah samples and 64 from the Hajj samples.

6.3.2 Kovac's oxidase test

Kovac's oxidase test is used in microbiology to determine if a bacterium contains cytochrome c oxidases as a part of its respiratory chain.¹⁰ A positive dark purple result is obtained with the oxidase reagent, tetramethyl-p-phenylenediamine dihydrochloride. 1.0% Kovac's oxidase reagent is prepared by way of dissolving 0.1 g of tetramethyl-p-phenylenediamine dihydrochloride into 10 mL of sterile distilled water.¹⁰ A cotton swab can be used to rub a portion of the grown colonial from the MTM onto a filter paper with a few drops of the oxidase reagent. The results can be obtained within 10 seconds and a positive reaction is indicated by the dark purple colour on the filter paper¹² (Figure 9). This test is not a confirmatory test for *N.meningitidis* as some other genus *Neisseria* and unrelated bacteria may also provide a positive dark purple colour.¹⁰ Appendix 4 summarises steps used in the oxidase test.

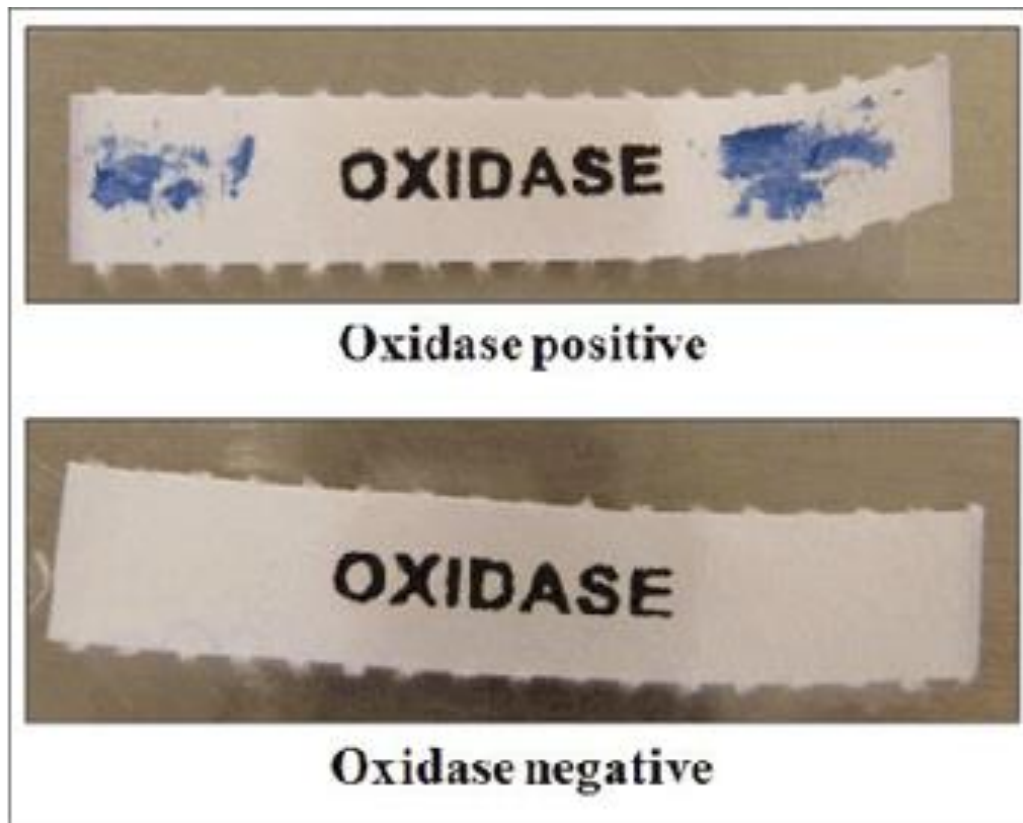


Figure 9: Negative and positive results of Kovac's oxidase test on filter paper. ¹⁰

All isolated bacterial colonies from the MTM were tested for oxidase. The positive reaction of oxidase test was observed in only 59 of the 64 pilot Hajj samples and 164 of the 268 pilot Umrah samples.

6.3.3 Gram stain

Gram stain is a method of staining developed by Hans Christian Gram that aims to distinguish between Gram negative bacteria and Gram positive bacteria based on the structure of their cell walls and by the red or violet colouring cells of the bacteria. ¹⁵

The morphology of the bacteria can be observed under the microscope. *N.meningitidis* appear as a red diplococci (Pairs) like kidney beans. ¹⁶

All isolated bacterial colonies that exhibited a positive oxidase reaction were tested for Gram stain. Out of the 59 Hajj samples and 164 Umrah samples that demonstrated a positive oxidase reaction, 20 were noted to be Gram stain negative as regards the Hajj and 73 for the Umrah.

6.3.4 Molecular methods: polymerase chain reaction (PCR).

All isolated bacterial colonies that exhibited Gram negative results were tested in KAUST using molecular methods and shipped to the Meningococcal reference unit (MRU) in the United Kingdom for further testing.

6.3.5 Molecular characterization: 16S PCR & Sanger sequencing in KAUST.

The isolated bacterial colonies were selected and placed in 50 μ L of sterile nuclease-free water in Eppendorf tubes and heated at 95°C for 10 min. The lysate was cleared by centrifugation for 5 min at 10000 rpm. The obtained supernatant was used to perform the PCR reaction for characterization of the 16S rRNA gene as follows:

1. 12.5 μ L of GoTaq® hot start Master Mix (Cat # M5006).
2. 1 μ L of each 10 μ M forward and reverse primers.
3. 5 μ L of supernatant from previous step.
4. Adjust the reaction volume up to 25 μ L with nuclease free water.
5. Place the PCR reactions in a thermal cycler (Applied Biosystems Veriti) using the following parameters:
 - initial denaturation step (1 cycle - 95°C for 3 min)
 - amplification step (35 cycles - 95°C for 30s, 50°C for 30s and 72°C for 45s)
 - post-extension step (1 cycle - 72°C for 5 min)

- hold at 4°C.

The sequences of the primers used are:

11 F forward primer (5'-GTTYGATYCTGGCTCAG-3') and 1492R reverse primer (5'-GGYTACCTTGTTACGACTT-3')¹⁷

After confirming the PCR by electrophoresis, the PCR products were purified using Wizard ® SV Gel and PCR Clean-up system (Promega). DNA concentration was quantified using Qubit® Broad Range DNA assay kit (Invitrogen), 40 ng of PCR products per isolate were submitted for capillary Sanger sequencing at the Bioscience Core Laboratory (BCL) at KAUST using 338F (5'-ACT CCT ACG GGA GGC AGC-3') as sequencing primer (10 µM).¹⁷

The results from the 16sPCR showed one positive Umrah sample for *N. meningitidis*. No Hajj samples were found positive for *N. meningitidis*.

6.3.6 Sub-culturing and Gram stain test at the Meningococcal Reference Unit (MRU)

All gram negative Hajj and Umrah isolated bacterial colonies were sub-cultured in MTM medium at KAUST and the isolated bacterial colonies were inserted in a transport medium that contains skimmed milk, glycerol and rabbit blood. These samples were shipped to the MRU on dry ice to maintain -80 °C cold chain.

Andy Walker from the MRU sub-cultured all samples onto a Neisseria selective agar (GCVCAT, Oxoid_Thermofisher) and non-selective agar medium, Columbia Blood

agar. All isolated bacterial colonies were tested for Gram stain and *N. meningitidis* was not confirmed.

6.4 Laboratory methods used in the Main study

Culture based identification of *N.meningitidis* did not detect any *N. meningitidis* from our pilot study and as a result we decided to use molecular methods for our main study samples to increase sensitivity. ¹⁴

6.4.1 DNA extraction and analysis

DNA extraction can be completed manually or by using an *automated DNA* extraction machine. ¹⁸ Extracted DNA must be of sufficient quality and quantity for detection in molecular studies. ¹⁴

DNA for the main study samples was extracted using QIAamp cador Pathogen Mini Kit (Cat No./ID: 54106) following manufacturer's Gram negative easy- to-lyse bacteria protocol. This extraction kit was selected as appropriate after review of the literature from similar studies. ¹⁹

Pre-treatment for easy-to-lyse bacteria was used to increase sensitivity. Up to 300 µL of the STGG fluid sample was added to 2 mL microcentrifuge tube and was centrifuged for 5 minutes at maximum speed (> 14,000 x g) and 100 µL of the supernatant removed and discarded. The pellet was then resuspended in the remaining liquid prior to commencement of the extraction protocol. Following the manufacturers protocol ,DNA was extracted from 2,357 STGG samples and was eluted in 100 µL of elution buffer and stored at -20°C.

6.4.2 Polymerase chain reaction (PCR) for the detection and characterization of *N. meningitidis*.

Diagnostic quantitative (qPCR) was used to detect *N. meningitidis* from all the 2,357 DNAs by targeting *ctrA*, *sodC*, and *porA* genes using primers and probes as described previously.^{14,20} A duplex real time PCR approach that targets both *porA* and *ctrA* genes is recommended as they are successful in detecting most *N. meningitidis* invasive strains. Nongroupable (NG) strains can also be detected by way of employing *sodC* assay which is better than *ctrA* assay in identifying NG strains of *N. meningitidis*.²¹ For this reason all three genes were targeted by qPCR for detection to increase the likelihood of detection.

All samples testing positive for *ctrA*, *sodC* and *porA* were subsequently tested for capsular biosynthesis genes for *N. meningitidis* serogroups A, B, C, W, X and Y employing primers and probes as previously described.¹⁴ All PCR reactions were completed with 5µL of extracted DNA, 10µL of qPCRBIO Probe mix Hi-ROX (PCR Biosystems PB20-22) in a reaction volume of 20 µL using the 7500HT ABI platform (Applied Biosystem, USA). Samples were tested in duplicate and counted as positive when the sample had a cycle threshold (Ct) value below 40.²² All samples were tested in parallel with positive control DNA for each serogroup (kindly supplied by Dr. Odile Harrison, University of Oxford).

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Chapter 7: Health preventive measures used by British pilgrims in the 2016 Hajj season.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	448680	Title	
First Name(s)	Abrar		
Surname/Family Name	Alasmari		
Thesis Title	Meningococcal vaccination and travel health in Hajj pilgrims – A study of pilgrims to Mecca, Saudi Arabia		
Primary Supervisor	Amaya Bustinduy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?			
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Please list the paper’s authors in the intended authorship order:	Abrar Alasmari , Phil Edwards , Abdullah Assiri , Ron Behrens , Amaya Bustinduy.
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Abrar Alasmari designed the study with support from Ron Behrens . Abrar Alasmari was responsible for data collection with logistic support from Abdullah Assiri. Abrar Alasmari did statistical analysis, with support from Phil Edwards .Abrar Alasmari wrote the first draft of the article with further contributions from other authors
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SECTION E

Student Signature	Abrar Alasmari
Date	20/04/2020

Supervisor Signature	Amaya Bustinduy
Date	20/04/2020

7 Research paper 1 : Health preventive measures used by British pilgrims in the 2016 Hajj season.

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Key words: Hajj, vaccines, facemask, hand hygiene, blood borne infections, pre-travel advice, chronic diseases.

Abstract

Background

The Hajj pilgrimage to Mecca, Saudi Arabia, is a profoundly spiritual journey undertaken by all physically and financially capable Muslims at least once in a lifetime. Thousands of pilgrims travel from the United Kingdom (UK) to Mecca every year to perform the Hajj. Communicable and non-communicable diseases have been reported during and immediately after the Hajj. In addition to vaccination, pilgrims are advised to adopt non-pharmacological preventive measures to protect themselves from these diseases. Little is known in regards to the health status of pilgrims from the UK and their compliance with preventive measures during the Hajj. Consequently, our study aimed to describe the health status of pilgrims from the UK and preventive measures adopted by them.

Method

A cross-sectional study was conducted among 136 British pilgrims at King Abdul Aziz International Airport (KAAI) in Jeddah and after the 2016 Hajj season. Pilgrims completed a self-administered paper questionnaire consisting of demographic items, health status, personal health preventive measures and several questions related to vaccination and the use of antibiotics.

Results

A total of 35.4% pilgrims reported having a chronic disease. One third of pilgrims 33.3% had started preparing for the Hajj more than two months in advance. The majority of pilgrims 83.5% were able to receive information regarding recommended travel vaccines and health preventive measures prior to the Hajj. The uptake of

influenza and pneumococcal vaccines were reported as 28.3% and 7.5%, respectively. Moreover, compliance with facemask use was low 23.4%.

Conclusion

Pilgrims are advised to receive recommended vaccines and to adhere with health preventive measures. Generally, our study shows that compliance with these is low among British pilgrims. This could be improved by providing pilgrims with health education prior to travelling to perform the Hajj and involving the appropriate stakeholders to ensure delivery of accurate health information to pilgrims.

Introduction

Every year millions of pilgrims from different age groups, ethnicities and socioeconomic status travel to Mecca, Saudi Arabia to perform the Hajj, one of the largest annual religious gatherings globally.¹ Pilgrims have to register through approved Hajj tour companies in order to perform the Hajj.² These tour companies are responsible for providing and supervising accommodation, food and transportation for pilgrims.³ Pilgrims are accommodated in tents in Mina the main location for the duration of Hajj and also where they spend most of their time during the Hajj.⁴

Overcrowding at various Hajj sites in addition to the sharing of accommodation helps to spread respiratory infections among pilgrims.⁵ Diarrhoeal illnesses have also been reported among Hajj pilgrims.⁶ Moreover, Mecca is also known for its extreme temperatures, which may reach 45°C in summer.⁷ Dehydration and illnesses caused by the extreme heat are among other health risks encountered during the Hajj.^{8, 9} A further Hajj ritual that presents a health risk relates to men shaving their heads on completion of the Hajj. Head shaving is undertaken with razors or blades which if used on several hajjis without being changed can transmit blood borne infections such as HIV, in addition to hepatitis B and hepatitis C.¹⁰

Hajj is a physically demanding pilgrimage and many older pilgrims with co-medical conditions can aggravate pre-existing health conditions such as diabetes mellitus, as well as cardiovascular and renal disease.⁹ Pilgrims, in particular those with co-morbidities are advised to seek pre-travel health advice before planning for the Hajj.^{11,}

The quadrivalent meningococcal vaccine is mandatory for all international and domestic pilgrims who are aiming to perform the Hajj.¹³ Influenza and pneumococcal vaccines are among recommended vaccines to be taken prior to the Hajj, in particular those who have an increased risk, such as pregnant women, children, the elderly and those with co-medical conditions.^{13, 14}

Approximately 20,000 of British pilgrims travel to Mecca each year to undertake the Hajj.¹⁵ There is a lack of evidence of the health status of British pilgrims and personal preventive measures adopted during the Hajj. Therefore, this study seeks to obtain data which will help to address these research gaps.

Methods and materials

A cross-sectional survey was conducted after the Hajj and from September 18th 2016 to October 2nd with respect to 136 British Hajj pilgrims. Departing flights carrying British pilgrims were selected from the Hajj terminal, in addition to the north and south terminals of King Abdul Aziz International Airport (KAAI) in Jeddah, Saudi Arabia. Pilgrims were informed about the aim of the study and only pilgrims aged 18 and above were included in the study. Upon their agreement to participate in the study, they were asked to sign a consent form and complete a self-administered paper questionnaire. These consisted of demographic items, health status, personal health preventive measures and several questions related to vaccination and the use of antibiotics. Stata version 16¹⁶ was used for all descriptive statistical analysis of the collected survey data.

Results

Basic characteristics

A total of 136 interviews were conducted with British pilgrims. Table 1 summarises pilgrim's basic characteristics.

Table 1: Demographic data of British pilgrims.

Characteristics	n (%)
Sex (n=132)	
Male	97 (59.8)
Female	53 (40.2)
Age in years (n=120)	
18-24	11 (9.2)
25-34	26 (21.7)
35-44	30 (25)
45 to 54	29 (24.2)
55 to 64	20 (16.6)
≥ 65	4 (3.3)
Education level (n=114)	
Illiterate	3 (2.6)
Can read and write	7 (6.2)
Less than high school	7 (6.2)
High school	26 (22.8)
Two years college	28 (24.6)
Bachelor degree	30 (26.3)
Master's degree	12 (10.5)

Doctoral degree	1 (1)
Ethnicity (n=118)	
Arab	8 (6)
South Asian	108 (92)
Caucasian	1 (1)
Mixed race	1 (1)
Employment (n=113)	
Full time employment	33 (29.2)
Part-time employment	20 (17.7)
Unemployed	22 (19.3)
Self-employed	30 (26.5)
Student	2 (2)
Retired	6 (5.3)
Smoking status (n=114)	
Smoker	13 (11.4)
Non-smoker	101 (88.6)

Pre-travel preparation and travel profile

A total of 77.7% (87/112) pilgrims indicated that they had experienced Hajj for the first time. More than one third of pilgrims 36% (39/108) started preparing for the Hajj one month before their arrival in Mecca, 30.7% (33/108) two months and 33.3% (36/108) more than two months. The majority of pilgrims 83.5% (86/103) had information regarding recommended travel vaccines and 67.4% (60/89) had information concerning personal preventive measures pertaining to health.

Vaccination

Most pilgrims (98.5% (135/136)) were vaccinated against meningococcal disease. Among those, 85.2% received meningococcal quadrivalent conjugate vaccine and 13.3% received polysaccharide vaccine. The uptake of influenza and pneumococcal vaccines were reported as 28.3% for the influenza vaccine and 7.5 % for the pneumococcal vaccine.

Health status of pilgrims

Distribution of chronic disease among British pilgrims is summarised in Table 2. A total of 35.4% (39/110) of pilgrims reported having a chronic disease. Table 2 summarises the distribution of chronic disease among British pilgrims. Antibiotic use was reported by 53/131 (40.5%) of pilgrims

Table 2: Distribution of chronic diseases among British pilgrims

Chronic disease	n	%
Any chronic disease (n=110)	39	35.4
Type of chronic disease (n=39)		
Diabetes	18	46.15
Hypertension	7	17.95
Asthma	12	30.77
Lung diseases other than asthma	1	2.56
Hypercholesterolemia	8	20.51
Cardiac disease	6	15.38

Immunodeficiency	3	7.69
Kidney disease	0	0
Malignant diseases	0	0
Medication use (n=39)	35	88
Travelled with medication (n=33)	32	97

Personal preventive measures

Face masks were used by 23.4% (25/107) of pilgrims. Approximately (4.7%) of the pilgrims said they use a face mask most of the time, (18.7%) occasionally, whilst (76.6%) said they had never used a face mask. Of those who used a face mask, 76% (19/25) reported using a normal surgical facemask, 12% (3/25) a N95 facemask, while 12% (3/25) could not identify the facemask they had used. Less than one fourth of pilgrims 13% (3/22) stated that they had changed their facemasks every 4 hours, 10% (2/22) every 6 hours, 64% (14/22) more than every 6 hours, whereas 13% (3/22) reported that they had never changed their facemask. The majority of those who reported using a facemask 92% (23/25) used it to cover both mouth and nose, 4% (1/25) their mouth only and 4% (1/25), claimed that they had wavered between both techniques related to wearing a face mask.

Most pilgrims 87.7% (93/106) washed their hands more than five times a day and 38.7% (41/106) used hand sanitisers. The majority of pilgrims 94.3% (100/106) consumed food provided by their tours. Raw food and vegetables were consumed by

42% (44/105) of pilgrims. The daily amount of water was measured by glasses per day and 71.7% (76/106) reported consumption of more than 8 glasses a day. The main source of drinking reported by pilgrims was bottled water 56.5% (61/108).

More than half of pilgrims 59.2% (61/103) revealed that they had shaved or cut their hair. Of those, 69.5% used the service of licensed barbers and 11.9% used the service of unlicensed barbers. One third of the pilgrims surveyed 31.5% (34/108) always covered their head with a hat or an umbrella, 22.2% (24/108) most of the time, 32.4% (35/108) occasionally, whilst 13.9% (15/108) claimed that they had never covered their head. Sunscreen products were used by 34.3% (36/105) of pilgrims.

Discussion

Our survey indicates that more than one third of British pilgrims had co-morbidities. Diabetes mellitus ranked first among these co-morbidities with a percentage of 46.15%. This is higher than that among French pilgrims (21%)¹⁷ but lower than domestic pilgrims in Saudi Arabia (55.7%)¹⁸. In our study, cardiac diseases ranked third (15.38%) after hypertension which is double the rate of that reported by domestic pilgrims.¹⁸ This is crucial as cardiovascular diseases ranked first among reasons for deaths during the Hajj.¹⁹⁻²² Muslims are among minority groups in United Kingdom (UK).²³ The rates of cardiovascular diseases and diabetes mellitus are higher among minority groups in the UK compared to the general population.²³

More than two thirds of pilgrims in our survey had started preparing for the Hajj two or more months in advance. Receiving pre-travel health advice is recommended at least two months prior to travel.²⁴ Most pilgrims in our study were able to receive information before the Hajj in regards to recommended travel vaccines and personal health

preventive measures. Our results are higher than those reported in other studies among Saudis (44%), Arabs (74%) and Australian pilgrims (65%).²⁵⁻²⁷ However, our study did not indicate the sources of health pre-travel advice. Accurate health advice from reliable sources should be encouraged to ensure pilgrims are receiving the correct health advice especially for those with comorbidities. Furthermore, medical screening for pilgrims with comorbidities is also encouraged.²⁸⁻³¹ Pilgrims who are medically illegible to perform the Hajj are advised to avoid performing the Hajj.²⁸ Medical screen of pilgrims has been implemented in some countries. This has shown a decrease in rates of hospital admission and mortality among pilgrims from these countries during the Hajj.^{28, 30, 31} Pilgrims with comorbidities who decide to undertake the Hajj should have their health monitored and should be supplied with sufficient medication before travelling to Mecca.⁹

The majority of pilgrims had received the quadrivalent meningococcal conjugate vaccine which is believed to be better than the quadrivalent polysaccharide vaccine in preventing acquisition of *Neisseria meningitides* and provides long lasting immunity.³² The only type of meningococcal quadrivalent vaccine that is available in the United Kingdom since 2014 is the conjugate type³³ , unlike other countries which are still providing the polysaccharide type. This could explain the high rate of conjugate vaccine received by British pilgrims in our study.

The uptake of influenza vaccine in our study was low (28%) compared to that found in another study conducted among British pilgrims which indicated that (37%) of pilgrims had received the influenza vaccine. Generally our results are among the lowest compared to the uptake of the vaccine in other studies conducted on the Hajj.³⁴

A total 7% of British pilgrims from our study reported receiving pneumococcal vaccine. This is slightly higher than the 5% reported by British pilgrims who attended the 2005 Hajj season.³⁵ Recommended vaccines such as influenza and pneumococcal vaccines are offered free of charge on the national health service (NHS) of the United Kingdom to people who are at risk.^{36, 37}

Several factors could explain this low rate of recommended vaccines including cost, misperception and lack of awareness regarding the risk of infection.³⁸

The cost of the vaccine could be one of the factors for those who are not at risk . A study conducted among French pilgrims revealed that pilgrims are willing to receive recommended vaccines if they were provided free of charge.³⁹ The uptake of recommended vaccines could be improved by advertising, pilgrims and medical staff education, pre-ordering to ensure a sufficient supply of vaccines, targeting people with comorbidities at their meetings, phone calls, besides offering home visits by nurses. Additionally, clinics established in cooperation with travel agents, community leaders and imams for pilgrims planning to perform Hajj may well further increase uptake.⁴⁰

Compliance with facemask use among British pilgrims in our study was noted to be low (23.4%). This percentage is among the lowest observed in previous studies conducted among Hajj pilgrims.⁴¹ Frequent changing of facemasks every six hours may reduce the risk of respiratory infections⁴² though our study shows that more than two thirds of pilgrims used the same facemask for more than 6 hours and moreover that 13% had never changed their facemask. Some Muslims believe that wearing a facemask can violate the state of Ihram (a sanctified state which pilgrims must experience in order to perform the pilgrimage).⁴² This may possibly explain the various

compliance rates as regards mask use among pilgrims, given that based on their religious viewpoints some pilgrims from different geographical places have distinct religious views. Wearing a facemask for the general public is not advised by the NHS in the UK ⁴³ and this could also influence the facemask uptake among British pilgrims. The majority of pilgrims stated that they washed their hands more than five times per day which is the standard frequency of hand washing completed by Muslims who perform the ablution prior to each of the five daily prayers.

Approximately 87.7% of the pilgrims in our study covered their heads with an umbrella to protect themselves from the intense sun. This is higher than that reported in a study conducted in 2017 among pilgrims from six countries in Africa, Asia and the Middle East, which demonstrated that 60% had used an umbrella.⁴⁴ Additionally, more than one third asserted that they had used sunscreen products. This was lower than the results obtained by a previous study which confirmed that 40% of pilgrims had used sun blockers when they were exposed to the sun during the day.⁴⁴

A number of factors could clarify these observations such as cultural and religious beliefs.⁴⁴ For example, a number of pilgrims think that certain actions such as using umbrellas, wearing hats or putting chemicals on the body are incompatible with the rituals performed during Hajj.⁴⁴ Education on these issues including the involvement of religious and community leaders is crucial to deal with such misunderstandings.⁴⁴ Also, it should be mentioned that pilgrim's origins and their common practices could also be an issue. For example, pilgrims originating from countries where exposure to the sun is much more common, such as Iraq and Egypt, were the least likely to make use of sunscreen.^{45, 46}

Drinking more than 8 glasses of water was reported by the majority of pilgrims in our study. Maintaining hydration during the Hajj is important so as to reduce the risk of illnesses as well as other health complications, in particular with respect to those who have co-morbidities such as diabetes mellitus and kidney illness.⁴⁴

Contrary to expected, a proportion of UK pilgrims had used the service of unlicensed barbers (11.9%). A similar finding was reported in a study conducted among domestic pilgrims in Saudi Arabia which indicated that 10% of pilgrims had used the service of unlicensed barbers.¹⁸ Unlicensed barbers work illegally during Hajj seasons and may re-use blades on different customers.⁴⁷ This may put pilgrims at risk of acquiring blood borne infections such as hepatitis B and C and HIV.⁹ The Saudi authorities urge pilgrims to use the service of licensed barbers and not to share blades with other pilgrims.⁹ The risk of blood borne infections in Hajj has not been investigated in previous studies⁴⁸ and the current findings indicate a need to explore this research gap.

Our survey provides valuable information on UK pilgrims but as it is based on a limited number of UK pilgrims, findings cannot be generalised to all UK pilgrims.

Conclusion

Health preventive measures are the most effective method of preventing diseases. Generally, compliance with these measures is low among British pilgrims and could be improved by providing pilgrims with health education prior to travelling to perform the Hajj.

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7.1 Supplementary data

Data was collected from 385 Umrah pilgrims from different countries including (Algeria, India, Indonesia, Nigeria, Pakistan, Sudan, Turkey and Malaysia) of whom (45.7%) were female and (54.3%) were male. Regarding Umrah pilgrims, a total of 51.4% declared that they had not been vaccinated despite carrying vaccination cards.

**Chapter 8: Meningococcal carriage among Hajj pilgrims,
risk factors for carriage and records of vaccination: a
study of pilgrims to Mecca.**

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	448680	Title	
First Name(s)	Abrar		
Surname/Family Name	Alasmari		
Thesis Title	Meningococcal vaccination and travel health in Hajj pilgrims – A study of pilgrims to Mecca, Saudi Arabia		
Primary Supervisor	Amaya Bustinduy		

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Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	AKA designed the study with support from RB, and DH. AKA was responsible for data collection with logistic support from AA. AKA did laboratory analysis of the samples with advisory support from JH. AKA did statistical analysis, with support from PE . AKA wrote the first draft of the article with further contributions from PE, BG, DH, RB, AB, JH, AA, FB, AP, and HL. All authors reviewed and approved the final version of the article.
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SECTION E

Student Signature	Abrar Alasmari
Date	20/04/2020

Supervisor Signature	Amaya Bustinduy
Date	20/04/2020

8 Research paper 2: Meningococcal carriage among Hajj pilgrims, risk factors for carriage and records of vaccination: a study of pilgrims to Mecca.

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Key words: Antibiotic, Hajj, meningococcal, *Neisseria meningitidis*, pharyngeal carriage, vaccination.

Abstract

Background

Hajj brings millions of pilgrims from different countries into a confined place of worship. A number of outbreaks of meningococcal disease have been reported immediately after the Hajj. The Saudi government requires that all pilgrims receive a quadrivalent meningococcal vaccine at least 10 days before the Hajj. We conducted a study to determine the uptake of meningococcal vaccine and antibiotic use. We also investigated risk factors of meningococcal carriage and carriage of *Neisseria meningitidis* pathogenic serogroups A, C, W, and Y.

Methods

A cross-sectional oropharyngeal carriage survey was conducted in 2973 Hajj pilgrims in September 2017. A real-time polymerase chain reaction (rt-PCR) assay was used to identify *N. meningitidis* from the oropharyngeal swabs. A questionnaire investigated potential risk factors for carriage of *N. meningitidis*.

Results

Overall, 2,249 oropharyngeal swabs were obtained. The overall prevalence of carriage of *N. meningitidis* was 4.6% (95% CI: 3.4% - 6%). Carriage of pathogenic serogroups was not associated significantly with any of the meningococcal risk factors evaluated. A majority of pilgrims (77%) were vaccinated but 22.58 % said they were carrying unofficial vaccination cards

Conclusion

Carriage with serogroups A, C, W, and Y was not significantly associated with any of the risk factors investigated. Less than a quarter of pilgrims were unlikely to have been vaccinated, highlighting a need to strengthen compliance with the current policy of vaccination to prevent meningococcal disease outbreaks during and after the Hajj.

Introduction

Neisseria meningitidis is a gram-negative aerobic bacterium which causes invasive meningococcal disease, a communicable disease spread via respiratory droplets.¹ There are twelve identified serogroups of *N. meningitidis*, which can be distinguished from each other by their polysaccharide capsule. However, there are six serogroups (A, B, C, W, X, and Y) that cause invasive disease.² Meningococcal carriers who have bacteria in the oropharynx but do not present with any symptoms, are the main source of invasive infections.^{1, 3}

Over two million Muslims visit Mecca in Saudi Arabia every year to perform the Hajj, one of the largest mass gatherings in the world,⁴ Pilgrims typically stay in the tents during the five days of each Hajj season where they share accommodation with other pilgrims.⁵ Overcrowding during the Hajj and an increase in the number of pilgrims inside Hajj tents has, in the past, facilitated the spread of meningococcal disease, and there have been several meningococcal outbreaks during Hajj pilgrimage.⁴ As a consequence of these outbreaks, the Saudi authorities developed and upgraded their Hajj vaccination policy to mandatory quadrivalent meningococcal vaccination, which must be administered to all Hajj pilgrims before arriving to Saudi Arabia for the Hajj.⁶ A vaccine that protects against all serogroups is currently unavailable.⁷ The existing Hajj vaccination policy does not indicate the type of quadrivalent (ACYW) vaccine that should be administered, i.e., a quadrivalent meningococcal conjugate vaccine (MCV-4) or a quadrivalent meningococcal polysaccharide vaccine (MPSV-4).⁸ Meningococcal polysaccharide vaccination can prevent severe meningococcal illnesses but it does not prevent the acquisition of carriage.¹ A quadrivalent conjugate

vaccine may prevent acquisition of new carriage but it does not clear existing carriage which may take two months or more to clear naturally. A quadrivalent meningococcal ACWY glycoconjugate vaccine was shown to have little impact on carriage one month post vaccination.⁹ This may have an impact on Hajj vaccination policy, which currently only requires vaccination 10 days prior to travelling to the Hajj.¹⁰

Self-medicating with antibiotics has long been a custom among pilgrims during the Hajj period to protect themselves against diseases transmitted via the respiratory route.¹¹ This has most likely played a role in eliminating carriage in previously reported Hajj studies.^{12, 13} Conversely, this custom of administration of non-prescribed antibiotics by Hajj pilgrims may contribute to increasing antibiotic resistance.¹¹

The aim of this study was to determine the uptake of the meningococcal vaccine and the use of antibiotics by Hajj pilgrims. The study also aimed to investigate the rate of *N. meningitides* carriage among pilgrims and to determine the risk factors associated with the carriage of *N. meningitides* serogroups (A, C, W and Y).

Methods

Study design and setting

A cross-sectional study was conducted in Jeddah, Saudi Arabia at the Hajj terminal of King Abdulaziz International Airport (KAIA) after the 2017 Hajj. Most of the international pilgrims pass through the Hajj terminal when visiting the Sacred Mosque in Mecca.¹⁴

Sampling methods

Two stage cluster sampling was used in the Hajj terminal at KAIA to select participants for the study. Departing flights from the Hajj terminal were selected as clusters as the first stage using simple random sampling from the daily Hajj flight schedules.

Subsequently, at the second stage, systematic random sampling of each flight cluster was undertaken using seat numbering. Departing pilgrims were recruited in the airport lounge and only those who provided informed consent were included in the study.

Data collection

All pilgrims selected for inclusion in the study were provided with written information regarding the aims of the study. Upon their agreement to participate, they were asked to sign a consent form. An electronic data capture tool, 'Open Data Kit' (ODK) was used to collect questionnaire data.¹⁵ Assistance was provided to pilgrims with clarifying questions and on how to use electric tablets.

Questionnaire design, piloting and translation

Twenty electronic tablets (Asus Zenpad 8 Z580C) supported by designed data questionnaire forms for 15 languages including Arabic, Albanian, Bengali, Bosnian, Chinese, English, French, Hindi, Indonesian, Kurdish, Malay, Pashto, Russian, Turkish and Urdu were used to collect data from pilgrims. All translated questionnaire forms were piloted prior to conducting the study.

Samples collection and storage

A Dacron / polyester tip swab was gently rolled over the tonsils and posterior pharynx and inserted into a vial containing transport medium containing skimmed milk, tryptone, glucose and glycerine (STGG). All swabs were kept at 4°C in an ice box for one hour followed by storage in a portable freezer at -20 °C. They were then kept securely at the airport for two weeks prior to being transported to King Abdullah University of Science and Technology (KAUST) where they were stored at -80 °C and then shipped on a dry ice to London School of Hygiene & Tropical Medicine for laboratory investigations. No cold chain breakdown was recorded during shipment

Laboratory analysis

An aliquot of 300 µl STGG medium was extracted from each vial and purified using QIAamp cadon Pathogen Mini Kit (Cat No. /ID: 54106), following the manufacturer's protocol. Extracted DNA was eluted in 100 µl of elution buffer and stored at -20°C. Quantitative PCR was then used to detect *N. meningitidis* *ctrA*, *sodC*, and *porA* target genes separately using primers and probes as described previously.^{16, 17} It is recommended to use a duplex real time -PCR approach that targets both *porA* and *ctrA* genes as these two are effective in detecting most *N. meningitidis* invasive strains. Nongroupable (NG) strains can also be identified by using *sodC* assay, which is superior to *ctrA* assay in detecting NG strains of *N. meningitidis*.¹⁸

All positive samples were tested for capsular biosynthesis genes for *N. meningitidis* serogroups A, B, C, W, X, and Y using primers and probes as described previously.¹⁷ All PCR reactions were performed with 5µl of extracted DNA, 10µl of qPCRBIO Probe mix Hi-ROX (PCR Biosystems PB20-22) in a reaction volume of 20µl using the 7500 ABI platform (Applied Biosystem, USA). Samples were tested in duplicates and considered as positive when the sample had a cycle threshold (Ct) value below 40.¹⁹ All samples were tested in parallel with positive controls for each serogroup (kindly supplied by Dr Odile Harrison, University of Oxford).

Statistical analysis

A descriptive analysis of all survey variables was performed using Stata commands for survey data (SVY) to account for the multistage sampling design. All analyses were weighted for probability of selection. Flight numbers and number of pilgrims in each flight were used to calculate the weight used in the analysis to ensure that the

probability of selection for each pilgrim sampled from flight was the same as the overall probability of selection for all pilgrims. A logistic regression model was developed to examine the associations between risk factors for meningococcal carriage (age, sex, education, type of meningococcal vaccine, timing of meningococcal vaccination, smoking status, marital status, country classification by income, length of stay in Saudi Arabia and number of pilgrims inside the tent where the participant slept) and the binary outcome variable “meningococcal carriage of serogroup ACWY”. Vaccination time was calculated from the date of receiving vaccination until the Hajj dates and was categorised as 0: ≤ 60 days, 1: ≥ 61 days. It is suggested that two months are needed to naturally clear any existing carriage of *N. meningitidis* and therefore was used as a cut-off point.¹⁰ The Wald test was used to assess evidence for any associations between the outcome “meningococcal carriage of serogroup ACWY” and each of the potential variables mentioned above. Due to lack of observations in some categories of variables, variables such as age, education, and country classification by income were re-categorised to fit the regression model. Age was categorised as 0: ≤ 34 years, 1: 35 to 44 years, 2: 45 to 54 years, 3: 55 to 64 years, and 4: ≥ 65 years. Education was classified as 0: low (Illiterate pilgrims or those who could only read and write), 1: middle (pilgrims with qualification of two years college, high school, or less than high school), and 2: high (pilgrims with doctoral, master’s, or bachelor’s degree). The type of meningococcal vaccine was categorised as 0: bivalent A and C or quadrivalent polysaccharide, 1: quadrivalent conjugate, and 2: unknown type. Country classification by income, as defined by the World Bank report for 2017-2018,²⁰ was also categorised as 0: low and low middle-income countries, 1: upper middle-income countries and 2: high-income countries. Variables with a $p > 0.1$ were considered statistically insignificant. All analyses were conducted using the STATA 16 software.²¹

Results

Demographic and other baseline characteristics

Of the initial 2,973 participants, 2,249 (75.56%) completed the electronic questionnaire and agreed to be swabbed. Table 1 summarises pilgrims' demographic data. Participants came from China, Europe, East Africa, the Middle East, North Africa, North America, Post-soviet states, South Asia, Southeast Asia, West Africa, and South Africa. The total length of stay of pilgrims inside Saudi Arabia during the Hajj journey (n=2973) averaged 33.8 (SD: 12.92) days in the 2017 Hajj season.

Table 1: Demographic characteristics of pilgrims

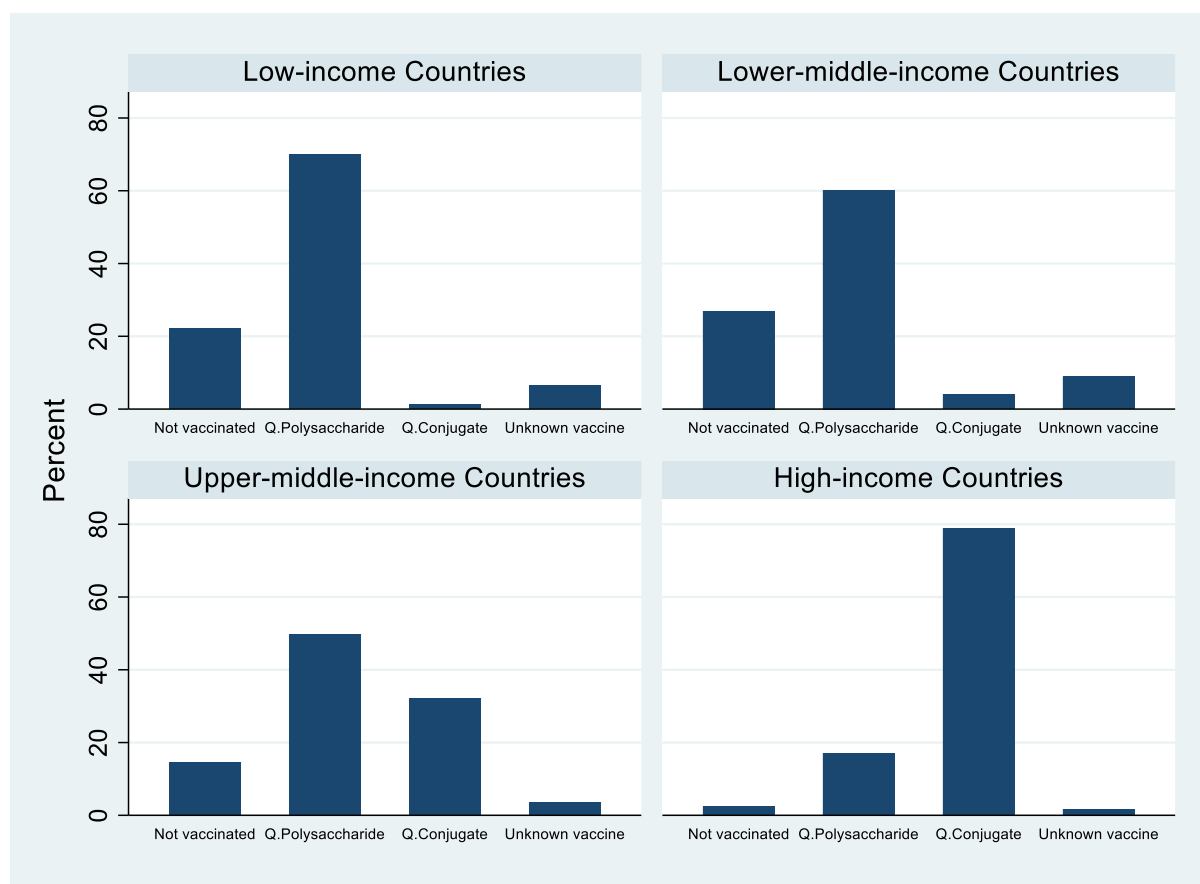
Characteristics	Total (%)
Sex	
Female	32
Male	68
Age in years	
11 - 17	0.5
18 - 24	2.9
25 - 34	12.6
35 - 44	26.7
45 - 54	26.3
55 - 64	22.5
65 or above	8.5
Education level	
Illiterate	5
Can read and write	11
Less than high school	9
High school	19
Two years college	9
Bachelor degree	27.5
Master's degree	15
Doctoral degree	4.5
Country classification by income	
Low	6
Low-middle	57

Upper-middle	28
High	9
Marital status	
Married	87
Unmarried	13

Meningococcal vaccination status and antibiotic use

The survey showed that 22.6 % of the study participants stated that they had not been vaccinated against meningococcal disease; 12.5 % of those were not vaccinated and not carrying any vaccination certificates and 11% self-reported that they were unvaccinated and carrying an unofficial purchased vaccination certificate. Very few pilgrims (0.5 %) had received the bivalent polysaccharide (A and C) meningococcal vaccine. A majority of pilgrims (71.2 %) had received the mandatory meningococcal quadrivalent vaccine. Most of the pilgrims (74.4) had received their vaccine from hospitals, (13.7%) from private clinics, (3.9%) from pharmacies, (3.4%) from mosques and (4.5%) from other places. Figure 1 illustrates the vaccination status of pilgrims by country classification by income.

Figure 1: Vaccination status of pilgrim by country classification by income.



Approximately one-third of all vaccinated participants (35.7%) received their vaccines at least two months before the Hajj. More than half of the participants (55.8%) said that they took antibiotics during and after the Hajj (Table 2).

Table 2: Pilgrim’s social and vaccination profile

Variable	Total percentage %
Vaccination status	
Unvaccinated without a vaccination card (self-reported).	12.6
Unvaccinated with a fake vaccination card (self-reported).	11

Bivalent (A and C) vaccine.	0.5
Quadrivalent polysaccharide vaccine	54.7
Quadrivalent conjugate vaccine.	16
Unknown meningococcal vaccine.	6.2
Time of vaccination before arrival in Saudi Arabia	
≤ 60 days	64.3
≥ 61 days	35.7
Antibiotic use	
Yes	55.8
No	44.2
Smoking status	
Smoker	10.6
Non-smoker	89.4
Number of pilgrims inside a tent	
6 – 8	16.4
10 – 20	13.9
50 – 100	39.5
≥ 100	30.3

Meningococcal carriage rate

A total (37%) of the 2,249 swabs were positive for *ctrA*, *SodC*, and *porA* genes. Target *ctrA* and *porA* genes characteristic of *N. meningitidis* were found among 103 of the total 2,249 samples tested, giving an overall carriage prevalence of 4.6%. (95% CI: 3.4% - 6%); 34 (1.13%) of these samples was positive for serogroups responsible for disease - serogroup A (n=2), B (n=10), C (n=10), W (n=3), X (n=6), and Y (n=3). Both *N. meningitidis* B and C were identified in seven pilgrims, A and B in one, and C and X in one.

Logistic regression analysis

The logistic analysis was restricted to the 1,736 pilgrims who received the meningococcal vaccine and provided an oropharyngeal swab. None of the variables studied was found to be associated with the outcome of carriage at 10% significant level. Meningococcal carriage of serogroup A, C, W, and Y *N. meningitidis* was higher among those who received a vaccine more than 60 days before the Hajj compared to

those who received it 60 days or less before the Hajj but the difference between groups was not statistically significant (adjusted OR 1.6; (0.55–4.8, *p*-value 0.36) (Table 3) No other statistically risk factors for *N. meningitidis* carriage were found.

Table 3: Risk factors for carriage of *Neisseria meningitidis* ACWY among pilgrims to Mecca, 2017

Exposure	Carriage of <i>Neisseria meningitidis</i> ACWY				
	Crude ratio (95% CI)	Odds	P value	Adjusted Odds ratio * (95% CI)	P value
Time of meningococcal vaccination					
≤ 60 days	Reference				
≥ 61	1 (0.34,3.26)		0.92	1.6 (0.55 –4.8)	0.36
Type of meningococcal vaccine					
Bivalent \ quadrivalent polysaccharide	Reference				
Quadrivalent Conjugate	0.73 (0.16,3.27)		0.8	0.8 (0.08 – 7.7)	0.8
Unknown	0.37 (0.05,2.77)		0.33	0.4 (0.05,4.3)	0.5
Sex					
Female	Reference				
Male	0.72 (0.26 - 2)		0.53	0.6 (0.22 –1.4)	0.25
Age in years					
≤ 34	Reference				
35 – 44	0.77 (0.11-5.11)		0.78	0.44 (0.04-4.2)	0.4
45 – 54	0.95 (0.14 –6.1)		0.95	0.7(0.08 – 6)	0.7
55 – 64	1.8 (0.32- 10.5)		0.47	1 (0.16- 6.4)	0.9
≥ 65	1.6 (0.31 – 8.3)		0.55	1.1 (0.25 -5.4)	0.8
Education level					
Low	Reference				
Middle	1 (0.20 – 5.6)		0.93	0.77 (0.15 - 4.)	0.7
High	0.5 (0.08 – 2.9)		0.44	0.53 (0.08-3.6)	0.5
Country classification by income					
Low/lower middle income	Reference				
Upper middle income	0.89 (0.24 –3.2)		0.85	1.1 (0.32,4.1)	0.8
High income	0.54 (0.06 –4.7)		0.57	2.3 (0.04,128)	0.6

Smoking status				
Non- smoker	Reference			
Smoker	1.3 (0.25 – 6.5)	0.74	1 (0.10 - 10)	0.9
Antibiotic use				
No	Reference			
Yes	1.2 (0.38 – 3.8)	0.72	1 (0.33-3.1)	0.9
Marital status				
Married	Reference			
Unmarried	0.57(0.07 – 4.2)	0.58	0.57 (0.07-4.4)	0.5
Length of stay in KSA	1 (0.9 – 1)	0.24	1 (0.9 – 1)	0.12
Number of pilgrims inside the tent				
6- 8	Reference			0.82#
10-20	0.66 (0.05 –8.3)	0.74	0.6(0.05-8.4)	0.7
50-100	0.74 (0.10 – 5)	0.76	0.8 (0.11, 6)	0.8
≥ 100	1.5 (0.29 – 7.6)	0.61	1.4 (0.3,7.3)	0.6

*The model was adjusted for variables (age, sex, education, type of meningococcal vaccine, timing of meningococcal vaccination, smoking status, marital status, and antibiotic use, length of stay in KSA, country classification by income and number of pilgrims inside the tents).

Overall Wald test

Discussion

According to the Hajj and Umrah vaccination policy, all pilgrims should receive the mandatory meningococcal quadrivalent (ACYW) vaccine at least 10 days before the Hajj.^{8, 22} Pilgrims are also required to submit a certificate to proof that they have received the vaccine.²² Surprisingly, a quarter of the pilgrims (22.6 %) in this study self-reported not having been vaccinated against meningococcal disease and of those 10.1 % were carrying unofficial vaccination certificates. The finding of a high percentage of pilgrims being unvaccinated was unexpected and indicates the need to determine whether pilgrims have been vaccinated prior to arrival for Hajj pilgrimage to prevent any future meningococcal outbreaks. The development of a Harmonised Hajj

Health Information System (HHIS), a synchronised information and data sharing platform among all Hajj stakeholders, would be beneficial.²³ The HHIS would capture pre-Hajj data, for instance pilgrims' demographic information, pre-existing health conditions and vaccination status.²³ To ensure that all pilgrims are receiving mandatory vaccines for the Hajj, vaccines could be given in specific vaccination centres authorised by the Saudi embassies in each country where pilgrims originate from and the vaccination status linked electronically to the HHIS.

Our study identified there were more carriers among those vaccinated more than two months prior to travelling to the Hajj than among those vaccinated less than two months before arrival, although the difference between groups was not statistically significant. Little information was found in the literature on the question of the association between time of meningococcal vaccination and carriage of *N. meningitidis*. Read et al. conducted the only published study that has investigated this association with regards to meningococcal conjugate vaccine and showed that the natural elimination of existing carriage may take two months or more and that the conjugate vaccine can only prevent acquisition of new carriage.⁹

There are a number of possible reasons for our findings. Firstly, the number of carriers was relatively small with only 18 being positive for a meningococcus of pathogenic serogroups A,C,W and Y, therefore a larger study might have found a significant effect. Secondly, over 50% of the pilgrims had received a polysaccharide vaccine and polysaccharide vaccines have little or no impact on carriage²⁴; only 16% were known to have received the quadrivalent conjugate vaccine which has been shown to prevent new acquisition of carriage. The Saudi Hajj vaccination policy does not indicate the type of quadrivalent vaccine required and leaves it to pilgrims to decide.⁸

As many pilgrims come from developing countries, the cost of the conjugate vaccine could influence uptake for many.⁸ Pilgrims from developing countries make life-long savings to be able to travel for the Hajj²⁵ and for many the option of receiving a cheaper polysaccharide vaccine is one that is more appropriate for their financial status.. Finally, although the analysis took into account reported use of antibiotics, it is possible that unreported use of antibiotics, which was likely widespread, might have confounded the difference between the groups. The high use of antibiotics reported in our study is consistent with other research which found that over 60% of pilgrims who travelled to Saudi Arabia carried antibiotics from their homeland with them and that 39.2% acquired non-prescribed antibiotics in Saudi Arabia.²⁶ Other studies have reported misuse and overuse of antibiotics among pilgrims²⁷ which, if continued, will make Hajj pilgrimage at risk of spreading antibiotic resistance.²⁸

The overall prevalence of meningococcal carriage in our study was low (4.6%), and that of serogroups A, B, C, W, X, and Y that cause the meningococcal disease was very low (1.13%) with many meningococci being non-groupable. This finding is in agreement with the findings of Memish et al. who also found a low prevalence of carriage of *N. meningitidis* in pilgrims attending the 2014 Hajj.²⁹ A surprising finding was the high proportion of carriers carrying meningococci of more than one serogroup. Carrying more than one serogroup of *N.meningitidis* in the throat is rare but can occasionally happen.³⁰ Contrary to expectations, we did not find any significant association between *N. meningitidis* (serogroupable and non-serogroupable) carriage and any of the risk factors found in other studies (age, sex, education level, smoking status, marital status, type of meningococcal vaccination, timing of vaccination ,country classification by income, and number of pilgrims inside the tents).³¹. Detection of serogroup X among the pilgrims is of concern as *N. meningitidis*

serogroup X has the potential to cause epidemics, as experienced recently in the African meningitis belt.³² Currently, there is no licensed vaccine against serogroup X *N. meningitidis*³³ although a pentavalent conjugate vaccine containing a serogroup X conjugate is being developed by the Serum Institute of India and is undergoing clinical trials.³⁴

This study had a number of limitations. Only pilgrims that had completed the Hajj were included and there was a lack information on events before the Hajj, for example those who attended a Hajj camps before the pilgrimage. Our findings are limited by the use of a cross-sectional design, given that conducting a large-scale longitudinal study is challenging and costly in circumstances similar to the Hajj. In addition, information on antibiotic use was self-reported and some pilgrims may have confused use of antibiotics with other non-antibiotic medications. The percentage of those unvaccinated is limited to those who have reported not being vaccinated and the number could be larger than recognised. Despite these limitations, this study was one of the largest studies undertaken on meningococcal carriage in pilgrims after completing the Hajj. Results have raised many questions regarding the need for further investigation including the issue of pilgrims traveling with unofficially purchased vaccination cards. Our study determined the prevalence of unvaccinated pilgrims, although it did not reveal the reasons why people had not been vaccinated or purchased unofficial vaccination cards. Pilgrims from different countries may possibly have different reasons. A future qualitative phase of the study may provide information to explore the issue of unofficial vaccination cards more comprehensively.

As one of the primary reasons for the authorities insisting on meningococcal vaccination prior to the Hajj is to prevent spread of meningococci among pilgrims during the Hajj, as well as to protect them against invasive meningococcal disease,

more studies are needed to ascertain the importance of using a conjugate rather than a polysaccharide vaccine and on the optimum vaccination time prior to traveling to the Hajj.

Contributions

AK.Alasmari wrote the first draft of the article with further contributions from all co-authors. A.K.Alasmari designed the study with support from R.Behrens, and D. Heymann. A.K.Alasmari was responsible for data collection with logistic support from A. Assiri. A.K.Alasmari did laboratory analysis of the samples with advisory support from J.H. Houghton. A.K.Alasmari did statistical analysis, with support from P. Edwards. All authors reviewed and approved the final version of the article.

Ethical approval

Ethical approvals were obtained from the ethics committees of the London School of Hygiene and Tropical Medicine (approval #11260) and King Abdullah University of Science and Technology prior to conducting the research (16IBEC21).

Conflicts of interest

We have no conflict of interest to declare.

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Chapter 9: Use of facemasks and other personal preventive measures by Hajj pilgrims and their impact on health problems during the Hajj.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	448680	Title	
First Name(s)	Abrar		
Surname/Family Name	Alasmari		
Thesis Title	Meningococcal vaccination and travel health in Hajj pilgrims – A study of pilgrims to Mecca, Saudi Arabia		
Primary Supervisor	Amaya Bustinduy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Travel Medicine Journal		
When was the work published?	September 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Travel Medicine Journal
Please list the paper's authors in the intended authorship order:	Abrar Alasmari , Phil Edwards , Abdullah Assiri , Ron Behrens , Amaya Bustinduy.
Stage of publication	Submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Abrar Alasmari wrote the first draft of the article with further contributions from Phil Edwrads, Ron Behrens , Amaya Bustinduy and Abdullah Assiri. Abrar Alasmari designed the study with support from Ron Behrens . Abrar Alasmari was responsible for data collection with logistic support from Abdullah Assiri. Abrar Alasmari did statistical analysis, with support from Phil Edwards .All authors reviewed and approved the final version of the article.
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SECTION E

Student Signature	Abrar Alasmari
Date	20/04/2020

Supervisor Signature	Amaya Bustinduy
Date	20/04/2020

9 Research paper 3: Use of facemasks and other personal preventive measures by Hajj pilgrims and their impact on health problems during the Hajj.

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Key words: Hajj, facemask, URTIs, travellers' diarrhoea , hand hygiene, blood borne infections.

Abstract

Background

The Hajj is one of the world's largest pilgrimage and gathers millions of Muslims from different nationalities every year. Communicable diseases have been reported frequently, during and following the Hajj and these have been linked to individual behavioural measures. This study aimed to measure the effect of personal preventive measures, such as facemask use, hand hygiene and others, adopted by pilgrims in reducing the acquisition of infectious diseases.

Methods

We conducted a cross-sectional study at the Hajj terminal in King Abdulaziz International Airport in Jeddah, Saudi Arabia. Pilgrims were approached in the airport lounges after the 2017 Hajj season and prior to the departure of their flights from Jeddah to their home countries. An electronic data collection tool ('Open Data Kit' (ODK)), was used to gather survey data in regards to health problems and preventive measures during the Hajj.

Results

2,973 Hajj pilgrims were surveyed. 38.7% reported symptoms of upper respiratory tract infections (URTI) and 5.4% reported symptoms of travel diarrhoea. Compliance with facemask use was 50.2%. Changing a facemask every 4 hours was found to be significantly associated with lower prevalence of URTIs (adjusted OR 0.56; (95% CI; 0.34 – 0.92), $p=0.02$). There was no statistical difference between overall facemask use and URTI acquisition. The main sources of food, eating raw vegetables/food, frequency of hand washing or use of hand sanitisers were not found to be significantly

associated with reported travellers' diarrhoea . Unlicensed barbers were used by 12% of pilgrims and 9.2% of pilgrims reported using blades that were re-used by other pilgrims.

Conclusion

Preventive measures are the most effective way to prevent infections Pilgrims can benefit from facemasks by changing them frequently . There is still limited information on the effect of the use of facemask in decreasing the risk of URTI in mass gatherings.

Introduction

Hajj, the Islamic annual pilgrimage to Mecca, is the fifth and last pillar of Islam and expected to be performed by physically and financially capable Muslims once during their lifetime.¹ Over two million Muslims from different ethnicities, age groups and socioeconomic status attend this religious gathering every year.² Domestic and international pilgrims should be registered through authorised Hajj agencies and via the Saudi authorities, in order to perform the Hajj.^{3, 4} The agency is responsible for providing accommodation and food for their Hajj travellers who typically share the same tent in Mina, the principal Hajj location close to Mecca, where pilgrims spend most of the Hajj period.⁵ The tents can accommodate up to 100 or more pilgrims, although this number varies.⁶ Overcrowding at various Hajj sites together with the sharing of accommodation, has led to adverse health effects such as the acquisition of respiratory illnesses.⁷ A key recommendation from the Saudi Ministry of Health (MoH), the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) to complement mandatory vaccinations, is the use of simple physical non-pharmaceutical interventions such as maintaining hand hygiene and wearing a facemask in crowds to reduce the risk of respiratory infections among pilgrims.⁸⁻¹¹

Gastroenteritis and diarrhoea have been a threat during previous Hajj seasons.¹² The reduction in travellers' diarrhoea in recent years likely reflects the Saudi government's efforts to improve sanitary conditions at Hajj sites. These initiatives have included for example restrictions on the food pilgrims are allowed to consume while at the Hajj.^{12,}
¹³ However, diarrhoea experienced by travellers and food-borne disease outbreaks

are still commonly reported among pilgrims.¹² Pilgrims are advised to maintain hand hygiene, avoid street vendors and wash vegetables and fruits prior to consumption.¹⁰

Shaving male heads is one of the rituals associated with Hajj and the majority of male pilgrims shave their heads as Hajj nears its end.⁶ Pilgrims who share razor blades for shaving or use the services of unlicensed barbers, are at risk of blood borne infections such as HIV and hepatitis B and C^{6, 14, 15 16}. The risk is higher in pilgrims who come from countries where such infections are highly prevalent.^{14, 17 18}

Few studies have analysed the role of personal preventive measures, such as facemask use, hand hygiene and others in the prevention of health problems during the Hajj.^{4 8, 19} Most have restricted their focus on certain nationalities and have relatively small sample sizes. This study aimed to measure the effect of personal preventive measures adopted by pilgrims from different countries in reducing the acquisition of infectious diseases during the 2017 Hajj season.

Methods and materials

The current study took place at the Hajj terminal in King Abdulaziz International Airport in Jeddah, Saudi Arabia. Pilgrims were approached in the airport lounges after the Hajj and prior to the departure of their flights from Jeddah to their home countries. An electronic data collection tool ('Open Data Kit' (ODK))²⁰, was employed to gather questionnaire data. Questionnaires were translated into a number of different languages including Arabic, Albanian, Bengali, Bosnian, Chinese, English, French, Hindi, Indonesian, Kurdish, Malay, Pashto, Russian, Turkish, and Urdu.

The electronic questionnaire consisted of demographic items, personal health preventive measures adopted by pilgrims and a list of symptoms pilgrims had during

and immediately after the Hajj. Upper respiratory tract infections and travellers' diarrhoea were diagnosed based on syndromic criteria and by combining diagnostic symptoms.

Ethical approval

Ethical approval was obtained from the ethics committee of the London School of Hygiene and Tropical Medicine (approval #11260).

Case definition

Travellers' diarrhoea

A recent graded expert panel report on the prevention and treatment of travellers' diarrhoea recommends using a functional impact severity definition rather than a frequency-based definition for travel diarrhoea.^{21, 22} To avoid any misunderstanding, medical symptoms for diarrhoea were described in the electronic survey tool (ODK) as a '*passage of 3 or more loose stools during 24 hours*'.^{23, 24} Travellers' diarrhoea was separately defined in the analyses as a '*passage of 3 or more loose stools in 24 hours with other enteric symptoms*'. Symptomatology could include abdominal pain, nausea, fever or/and vomiting during and after the Hajj and before leaving Saudi Arabia.²³

Upper respiratory tract infection

Upper respiratory tract infection was defined as developing "*at least one of the constitutional symptoms (fever, headache, myalgia) and one of the local symptoms (running nose, sneezing, throat pain, cough with/or without sputum)*"⁴.

Statistical methods

Descriptive statistics and regression analyses were performed using Stata 15 via the `svy` family of commands to incorporate survey weighting and clustering.²⁵ Flight numbers and number of pilgrims in each flight were used to calculate the weight used in the analysis to ensure that the probability of selection for each pilgrim sampled from flight is the same as the overall probability of selection for all pilgrims. We presented descriptive statistics for the preventive measures adopted by pilgrims. We examined the associations between the categorical exposure variable “facemask use” and the binary outcome variable “upper respiratory tract infections”. Facemask use was categorised as 0: never, 1: sometimes and 2: most of the time. The analyses were adjusted for potential confounders: age, sex, smoking status, type of facemask, facemask usage techniques, frequency of changing facemask, influenza vaccine status, pneumococcal vaccine status, antibiotic use, exposure to coughing, length of stay in Saudi Arabia, the numbers of pilgrims inside the tent where the participant slept and country classification by income, according to the World Bank report²⁶ for 2017-2018. We selected five times a day as a cut-off of hand washing because that is the standard frequency completed by Muslims who perform the ablution prior to each of the five daily prayers.

First, univariate analysis was performed to assess any associations between each of the explanatory variables and the outcome measure. Variables that were found to have a Wald test p-value of 0.1 and below were retained in the final model. Some of the remaining explanatory variables were considered to be relevant and therefore were used in the final model. Similar analyses were used to examine risk factors associated with travellers’ diarrhoea and were adjusted for potential confounders such

as sex, age, country classification by income, hand wash, use of hand sanitiser, antibiotic use, raw food and main sources of food.

Results

A total of 2,973 interviews were conducted with pilgrims from different nationalities (Figure1). Table 1 summarises the demographic data of pilgrims. The uptake of influenza and pneumococcal vaccines were reported as 50.18% and 22.7%, respectively.

The number of pilgrims living inside tents during the Hajj varied substantially. In this study, 16.3% of the interviewed pilgrims reported living in tents occupied by 6-8 pilgrims, 13.9% by 10-20 pilgrims, 39.5% by 50-100 pilgrims and 30.3% by 100 or more pilgrims. The total length of stay during the Hajj journey (n=2973) averaged 33.8 (SD: 12.92) days in the 2017 Hajj season. The majority (89.41%) of pilgrims were non-smokers. Additionally, over half (55.8%) reported that they had taken antibiotics during or immediately after the Hajj.

Symptoms of upper respiratory tract infections were reported by 38.7% and diarrhoea by 5.4% of pilgrims. During the Hajj trip, 44.35% of pilgrims reported that they were exposed to coughing. Table 2 summarises personal health preventive measures adopted by pilgrims.

After adjusting for potential confounders, the analysis did not show any significant association between the occurrence of diarrhoea among Hajj pilgrims and the main sources of food, eating raw vegetables/food, frequency of hand washing or use of hand sanitisers (Table 4).

Changing a facemask every 4 hours was found to be significantly associated with lower prevalence of symptoms of URTIs (adjusted OR 0.56; (95% CI; 0.34 – 0.92), *p*-value 0.02). However, there was no evidence of an association between URTIs and the overall use of a facemask. Having (symptoms) of URTIs was found to be significantly associated with country classification by income as shown in Table 3. More pilgrims with URTIs (symptoms) were reported from higher income countries, upper middle income countries and lower-middle income countries compared to those coming from low income countries; adjusted OR 3.2 (95% CI; 1.6, 6.4, *p*-value 0.001), 2.3 (95% CI; 1.3, 2.9, *p*-value 0.003) and 1.9 (95% CI; 1.2, 2.9, *p*-value 0.002) respectively.

Discussion

Upper respiratory tract infections are among relevant health problems during the Hajj. Based on syndromic criteria, the results of this study reveal that more than one third of pilgrims had URTI's (symptoms) during or immediately after the Hajj. Around half of pilgrims used the facemasks. Data from previous Hajj studies indicate a gradual increase in the use of face masks from 24% in 1999 to 64% in 2014.²⁷ In previous Hajj studies, avoiding exposure to infections and protection from air pollution were the most common reasons for compliance with facemask usage.^{27, 28} On the other hand, discomfort and difficulty with breathing were the most commonly reported reasons for non-compliance with facemask usage.^{27, 29, 30} The hot climate in Mecca³¹ may make it difficult for pilgrims to continually wear facemasks, especially for the elderly.⁸

Face mask and hand hygiene are low-cost physical measures that can be adopted to reduce the risk of respiratory infections.³² The ritual washing performed by Muslims before each of the five daily prayers involves washing the hands, which made the

recommendation of hand hygiene acceptable and easy to implement for most pilgrims.³³ The majority of pilgrims in this study (82.1%) reported hand washing more than five times a day. This finding is in agreement with a different study which demonstrated that 90.3% of domestic pilgrims had washed their hands more than five times per day.⁴

This study shows a significant lower frequency of URTIs (symptoms) among those who changed their mask every 4 hours compared to those who did not change masks. Gatrad et al. showed that facemasks should be changed on a regular basis, at least every six hours in order to remain effective.³⁴ Facemasks have been shown to be effective in preventing or decreasing nosocomial transmission of pandemic influenza since the time of the 1918 Influenza epidemic and could therefore play a role in other types of respiratory virus epidemics.^{35, 36} Lower infection rates have been observed among nurses using a well-designed face mask which were frequently changed every two hours.^{35, 36} The effectiveness of facemasks in reducing respiratory infections is influenced by several factors including quality, design, technique of application and frequency of face mask change.^{34, 37}

Effectiveness of facemasks in preventing URTI's has been examined in previous studies and data were observed either to be unconvincing or contradictory.³⁸⁻⁴⁹ Data from a large randomised controlled trial among Hajj pilgrims did not show any effect of facemask use against clinical or laboratory-confirmed viral respiratory infections.⁵⁰ Another observational study among French pilgrims found a higher prevalence of respiratory infections among those who reported wearing face masks. The authors argued that this could indicate that pilgrims with respiratory symptoms are more willing to wear a facemask to avoid spreading infections to others.⁵¹

More than half of pilgrims in this study, self-reported using antibiotic during and immediately after the Hajj. The prevalence of URTIs symptoms was higher among pilgrims who used antibiotic. URTIs are mainly caused by viruses, therefore antibiotics are not likely effective.^{52 53} The receipt of pneumococcal vaccine was also associated with an increased prevalence of URTIs symptoms. Pneumococcal vaccine is recommended for those at risk; including elderly travellers and those with chronic diseases.⁵⁴ Risk groups are shown to be at higher risk of respiratory infections.⁵⁵

URTIs symptoms were more frequently reported from higher, upper middle and lower-middle income countries compared to those coming from low income countries. These differences could be due to the lower numbers of pilgrims coming from low income countries. The size of the crowd inside tents of low income countries was lower than that from higher income countries, which could affect the transmission of respiratory infections among pilgrims inside the tents.

Proactive preventive measures have been taken by the Saudi government after the emerging Novel Coronavirus (COVID-19), by temporarily banning all Umrah pilgrimages to Mecca.^{56, 57} This raise additional challenges for Saudi and international authorities, as pilgrims arriving from all over the world could lead to the spread of this and similar new emerging infections.⁵⁸ Improve health security surveillance⁵⁹ and strict compliance with preventive measures such as facemask use and hand hygiene is highly recommended. Hajj agencies play an important role in pilgrim's health education.⁶⁰ Pilgrims have confidence in the advice provided by these agencies.⁶⁰

This study examined the effectiveness of facemasks on URTIs solely based on syndromic criteria. A future study could investigate the effectiveness of facemasks used by study participants on laboratory-confirmed respiratory pathogens. There is a

potential for recall bias in this study although the time between performing Hajj and departing home was usually a few days to weeks. The study is limited by the lack of information on the effect of beards for males and Niqab covering in females.⁴

In this study, diarrhoea was based on syndromic criteria and was self-reported among 5.4% of pilgrims. Gastroenteritis was in the past the most common cause of hospital admission in Hajj pilgrims.⁶¹ However, the rate of diarrhoea in the Hajj has been observed to be consistently decreasing in the last few years. The Saudi authorities do not allow pilgrims to travel with fresh food when arriving in Saudi Arabia.⁶² Pilgrims are only allowed to carry small quantities of canned food.^{1, 62}

In this study, 63.1% of pilgrims used the catering services provided by their Hajj tour operators. Although hand washing is a daily ritual practised by Muslims before every prayer, some authors argue that a more effective practice is using alcohol-based hand rubs regularly with respect to hand hygiene.¹² Alcohol-based hand rubs may be better than traditional hand washing as they are quicker and associated with better compliance and a lower rate of infections.⁶³⁻⁶⁵ This study indicates that more than half of the pilgrims (58.6%) used hand sanitisers, although the frequency of use was not captured in the questionnaire. As study conducted on local pilgrims in 2009 reported similar results of this studies findings which did not show any significant association between hand hygiene and diarrhoea.⁴ The daily main sources of food for the pilgrims was also not identified in this study. These gaps in information could have contributed to the lack of an association between all known risk factors and travellers' diarrhoea.

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Unlicensed barbers are still operating illegally during the Hajj season. We found that 12.3% of male pilgrims had their heads shaved by unlicensed barbers, while 9.9%

used other pilgrims' shaving tools to shave their heads. The findings of the current study are consistent with those obtained by Al-Jasser et al., who performed a study among domestic pilgrims confirming that 10% of pilgrims had used the services of an unlicensed barber.⁴ Reusing razor blades was also observed in an alternative study among pilgrims from 53 different nationalities revealing that 25% of pilgrims reused blades from other pilgrims.⁶⁷ This is relevant, as the behaviour of reusing blades from other pilgrims and using the services of unlicensed barbers who may use non-sterile blades can put pilgrims at risk of spreading blood borne infections such as hepatitis B and C as well as HIV.¹ Hepatitis B vaccine is not among the Hajj travel vaccines recommended by the Saudi authorities as it is difficult for many pilgrims to take due to the cost and time required to complete the vaccination course.¹ The risk of hepatitis B and C and HIV transmission using laboratory testing in pilgrims using unlicensed barbers was not investigated in our study. This is an important knowledge gap that needs to be investigated in further research based on laboratory confirmed results of blood samples from pilgrims before and after the Hajj .

This study is one of the largest studies conducted among Hajj pilgrims from different nationalities. Pilgrims were sampled using the most relevant random sampling method for the Hajj conditions. The survey was translated into several common languages and piloted before the main study was completed. This strengthened this study by ensuring that all pilgrims understood the survey questions.

Conclusion

Respiratory tract infections, travellers' diarrhoea and blood borne infections are among frequent health risks encountered during the Hajj. These diseases could potentially be prevented by adherence to personal preventive measures to minimise the

transmission of these diseases. The effect of facemasks on reducing URTIs in mass gatherings needs to be further investigated. The health education of pilgrims prior to their arrival in Saudi Arabia may play a role in increasing the compliance with preventive measures and decrease the risk of these diseases among hajj pilgrims.

Contributions

AKA designed the study with support from RB and AB. AKA was responsible for data collection with logistic support from AA. AKA did statistical analysis, with support from PE . AKA wrote the first draft of the article with further contributions from PE, AA, RB and AB. All authors reviewed and approved the final version of the article.

Conflicts of interest

The authors have declared no conflicts of interest

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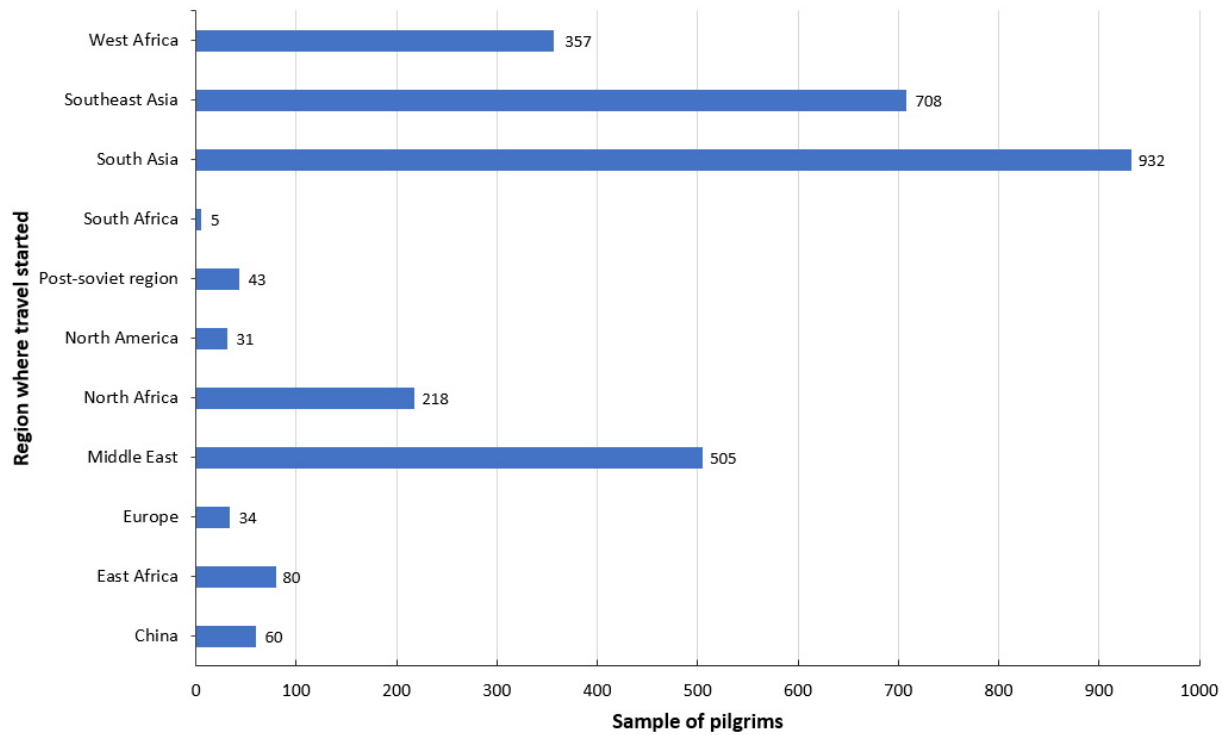


Figure 1: Number of sampled pilgrims and their regions.

Table 1: Pilgrims demographic profile.

Characteristics	%
Sex	
Male	68%
Female	32%
Age in years	
≤ 34	16%

35-44	27.7%
45 to 54	26.3%
55 to 64	22%
≥ 65	8%
Education level	
Low	16%
Middle	36.9%
High	47.1%
Ethnicity	
Arab	20.9%
African	15.8%
South Asian	30.3%
Caucasian	4.3%
Mixed race	2.5%
Other	26.2%
Country classification by income	
Low	5.84%
Low-middle	56.98%
Upper-middle	28.15%
High	9.02%
Employment status	
Employed	67
Unemployed	33

Education was classified as: low (Illiterate pilgrims or those who could only read and write), middle (pilgrims with qualification of two years college, high school, or less than high school), and high (pilgrims with doctoral, master's, or bachelor's degree).

All descriptive analysis were weighted

Table 2: Health preventive measures adopted by pilgrims

Preventive measures	%
Face mask use	
Most of the time	19.8%
Sometimes	30.4%
Never	49.8%
Type of face mask	
Surgical facemask	90%
N95 facemask	4%
Unknown facemask	6%
Face mask usage technique	
By covering the mouth only	3.6%
By covering both nose and mouth	84.7%
Using both ways	11.7%
Changing face mask	
Never	17.7%
Every 4 hours	26.8%
Every 6 hours	19.6%
Every more than 6 hours	35.9%
Eat raw food/vegetables	
Yes	44.3%
No	55.7%
Hand wash	
More than 5 times a day	82.1%
Less than 5 time a day	17.9%
Use of hand sanitiser	

Yes	58.6%
No	41.4%
Main source of food	
Canned	4.4%
Street	6.8%
Self-cooking	17.9%
Tour	63.1%
Other	7.8%
Shaves head for males	
Unlicensed barber	12.3%
Licensed barber	53.7%
Myself using my tools	11.4%
Myself using other's tools	2.6%
Fellow pilgrim shaved my head using other's tools	7.3%
Fellow pilgrim shaved my head using my tools	12.7%

All descriptive analysis were weighted

Table3: Risk factors of upper respiratory tract (symptoms)among Hajj pilgrims in 2017.

Exposure	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex				
Female	Reference			
Male	0.97 (0.74,1.2)	0.85	1.2 (0.9, 1.8)	0.15
Age				
<35	Reference			0.85 [#]
35-44	1.3 (0.83, 2)	0.23	1.2 (0.76, 2.)	0.35
45-54	1.3 (0.92,1.8)	0.12	1 (0.6, 1.6)	0.8
55-64	0.9 (0.6, 1.4)	0.8	1.1 (0.7, 1.9)	0.52
65 and above	1 (0.73, 1.5)	0.7	1 (0.56, 1.8)	0.93
Country classification by income				
Low income	Reference			0.001[#]
Lower middle income	1.2 (0.94, 1.7)	0.1	1.9 (1.2, 2.9)	0.002
Upper middle income	1.4 (0.85, 2.5)	0.16	2.3 (1.3, 4)	0.003
High income	1.4 (0.76, 2.6)	0.25	3.2 (1.6, 6.4)	0.001
Facemask use				
Never	Reference		-	-
Sometimes	1.7 (1.1 , 2.5)	0.004	Reference	-
Most of the time	1.3 (1 , 1.8)	0.05	0.8 (0.6 , 1.2)	0.45
Face mask frequency				
Never	Reference			0.05 [#]
Every 4 hours	0.47 (0.24,0.88)	0.02	0.56 (0.34,0.92)	0.02
Every 6 hours	0.73 (0.35,1.5)	0.41	0.74 (0.43, 1.2)	0.28
Every more than 6 hours	0.71 (0.43,1.2)	0.18	0.84 (0.54, 1.3)	0.44

Pneumococcal vaccine				
No	Reference			
Yes	1.5 (1, 2.3)	0.035	1.5 (1, 2.5)	0.02
Influenza vaccine				
No	Reference			
Yes	1.1 (0.86, 1.5)	0.32	1.3 (0.92, 1.8)	0.12
Antibiotic use				
No	Reference			
Yes	1.1 (0.92, 1.5)	0.16	1.3 (0.97, 1.7)	0.06
Exposed to coughing				
No	Reference			
Yes	0.89 (0.68, 1.2)	0.43	0.87 (0.62, 1.2)	0.4
N. of pilgrims in the tent				
6-8	Reference			0.09
10-20	1.2 (0.69, 2.1)	0.48	1.2 (0.72, 2.2)	0.38
50-100	1.5 (0.97, 2.5)	0.06	1.6 (0.98, 2.7)	0.05
More than 100	1.2 (0.76, 1.9)	0.4	1 (0.66, 1.7)	0.77

*Some selected potential confounders such as (Smoking status, type of facemask, facemask usage techniques, length of stay in Saudi Arabia) were found to have a Wald test p-value more than 0.1 and were removed in the final model. All analysis were weighted.

#Overall P-value

Table 4 : Risk factors of travel diarrhoea among Hajj pilgrims in 2017.

Exposure	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex				
Female	Reference			
Male	0.92(0.6, 1.4)	0.73	0.97 (0.64, 1.4)	0.88
Age				
<35	Reference			0.9 [#]
35-44	0.84 (0.43,1.6)	0.62	1 (0.53, 1.9)	0.9
45-54	0.72 (0.4, 1.3)	0.28	0.83 (0.48, 1.4)	0.49
55-64	0.76 (0.39,1.4)	0.42	0.9 (0.47, 1.7)	0.76
65 and above	0.75 (0.32,1.7)	0.51	0.83 (0.35, 1.9)	0.66
Country classification by income				
Low income	Reference			0.25 [#]
Lower middle income	1.1 (0.69, 2)	0.51	1.1 (0.6, 1.8)	0.7
Upper middle income	0.72 (0.37, 1.3)	0.33	0.69 (0.35, 1.3)	0.26
High income	0.85 (0.3, 2.3)	0.76	0.57 (0.17, 1.8)	0.35
Antibiotic use				
No	Reference			0.85 [#]
Yes	1.1 (0.74, 1.6)	0.6	1.1 (0.74, 1.6)	0.6
Hand wash				
More than 5 time a day	Reference			
Less than 5 time a day	1.4 (0.84, 2.3)	0.18	1.4 (0.75, 2)	0.39
Hand sanitiser				
No	Reference			
Yes	1 (0.62, 1.7)	0.86	1.1 (0.6, 1.7)	0.86

Raw food				
No	Reference			
Yes	1.3 (0.89, 2.1)	0.14	1.2 (0.78, 1.8)	0.38
Main source of food				
Canned	Reference			0.28 [#]
Street	1.3 (0.53, 3.2)	0.54	1 (0.4, 2.3)	0.99
Self	0.49 (0.19, 1.2)	0.15	0.5 (0.19, 1.2)	0.19
Tour	0.75 (0.34, 1.6)	0.47	0.7 (0.33, 1.5)	0.33
Other	0.49 (0.12, 1.8)	0.29	0.47 (0.12, 1.7)	0.12

All analysis were weighted.

[#]Overall p-value

Chapter 10: Pre-travel health preparation of pilgrims with chronic diseases.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	448680	Title	
First Name(s)	Abrar		
Surname/Family Name	Alasmari		
Thesis Title	Meningococcal vaccination and travel health in Hajj pilgrims – A study of pilgrims to Mecca, Saudi Arabia		
Primary Supervisor	Amaya Bustinduy		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Travel Medicine journal.
Please list the paper’s authors in the intended authorship order:	Abrar Alasmari , Phil Edwards , Abdullah Assiri , Ron Behrens , Amaya Bustinduy.
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Abrar Alasmari wrote the first draft of the article with further contributions from Phil Edwrads, Ron Behrens , Amaya Bustinduy and Abdullah Assiri. Abrar Alasmari designed the study with support from Ron Behrens . Abrar Alasmari was responsible for data collection with logistic support from Abdullah Assiri. Abrar Alasmari did statistical analysis, with support from Phil Edwards .All authors reviewed and approved the final version of the article.
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SECTION E

Student Signature	Abrar Alasmari
Date	20/04/2020

Supervisor Signature	Amaya Bustinduy
Date	20/04/2020

10 Research paper 4: Pre-travel health preparation of pilgrims with chronic diseases.

Authors

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Key words: Hajj, chronic diseases, travel preparation, influenza vaccine, polio vaccine, yellow fever vaccine, pneumococcal vaccine.

Abstract

Background

The Hajj pilgrimage to Mecca is the largest religious annual mass gathering which draws millions of Muslims from different nationalities, age groups, as well as health and socioeconomic status. Restricting the Hajj to only those who are physically fit to perform it is extremely difficult given that many pilgrims are elderly with chronic diseases. Early seeking of travel health advice is recommended for pilgrims, in particular pilgrims with chronic diseases who are advised to seek pre-travel health advice or avoid the Hajj depending on their health status. In this research we examined the association between having a chronic disease and pre-travel health preparation.

Methods

A cross-sectional study design was conducted using a two stage clustering method to approach 2,973 pilgrims at King Abdulaziz International Airport (KAIA) after the 2017 Hajj season. An electronic data capture tool: 'Open Data Kit' (ODK) was used to collect questionnaire data from pilgrims. The questionnaire was translated into 15 common and contained items related to demographic, health status, health travel preparation and travel profile.

Results

A total of 57.3% of pilgrims were ≥ 45 years old while 31% had chronic diseases. More than half of the pilgrims started preparing at least two months ahead of the Hajj and 80% received information on preventive measures and travel vaccines. A non-significant trend was noted between pilgrims with chronic disease; specifically that they were observed to be less likely to seek information on preventive health

measures, although more likely to seek information on recommended vaccines. There was no evidence of association between chronic disease status and early seeking of health advice.

Conclusion

Performing the Hajj is a life journey for many Muslims regardless of their background and health status. The high percentage of pilgrims with chronic disease in our study indicates the need for medical screen and to involve pre-travel health advice to all pilgrims in their home countries and involve relevant stakeholders to ensure the successful delivery of health advice.

Introduction

Hajj, the spiritual journey that Muslims undertake to Mecca in Saudi Arabia is one of the largest annual events to occur globally. Performing Hajj is one of the religious obligations and rituals of worship for Muslims.¹ Moreover, every adult Muslim who is economically and physically capable of doing so should complete Hajj at least once during their lifetime.² Hajj gathers Muslims from across the world even after recommendations to postpone Hajj during outbreak seasons.³ In 2017, a total of 2,352,122 Muslims, both residents and non-residents of Saudi Arabia performed Hajj.

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To manage the crowds at the Hajj and reduce the number of pilgrims attending every year, Saudi Arabia (KSA) provides 1000 visas for every one million Muslims⁵ and restricts Hajj to once in five years for all domestic and international pilgrims.^{5 6} Visa applications can be made between two months prior to the Hajj and until two weeks before the Hajj starts.⁷ This timescale may have an impact on pilgrims' preparation for the Hajj, and subsequently, their use of preventive health measures prior to attending the pilgrimage. The failure to use preventive measures may put pilgrims at risk of acquiring different types of diseases.

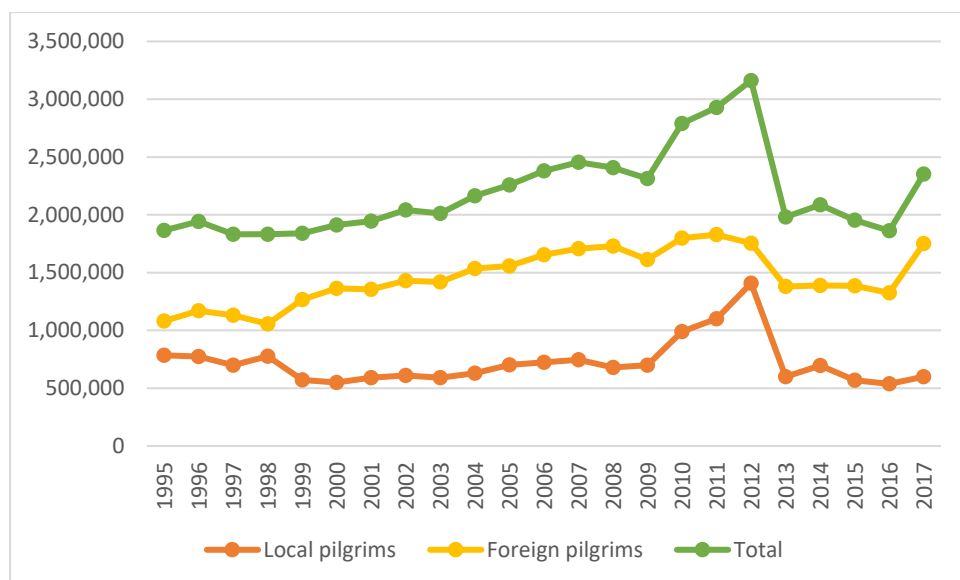
Previous studies reveal that last minute travellers have less time preparing their journey compared to those with more time, which may in turn impact on their knowledge and behaviour with respect to preventive measures.⁸⁻¹¹ Prospective pilgrims are advised to seek pre-travel health advice at least 6-8 weeks before the Hajj.¹²

The continuous increase in the number of pilgrims attending the event in the last two decades (Line chart 1), presents a significant challenge to the Saudi Arabian

administration which has been advising those suffering from chronic diseases to postpone the Hajj during outbreak seasons ¹³

Call by researchers has been made to limit Hajj based on non-communicable diseases (NCDs) and exclude those with high risk health conditions from performing the Hajj.¹⁴

Because of the cost of undertaking the Hajj, many will have had to save through their lifetime and will be an older population with a higher burden of NCD ¹⁵



Line chart 1: The number of local and foreign pilgrims from 1995 to 2017.⁴

Few studies have determined the prevalence of chronic health conditions among Hajj pilgrims.^{16 10, 17, 18 19-21} In addition, no research has investigated when pilgrims with chronic disease start preparing before the Hajj.

Few studies have explore pre-travel health advice received by pilgrims. These studies were mainly focusing on specific nationalities ²²⁻²⁶ and among these studies only one

have investigated the association between having a chronic disease and seeking pre-travel health advice.²³

This study, therefore intends to determine common chronic diseases among Hajj pilgrims and examine the association between having a chronic disease and seeking pre-travel health advice.

Methods and materials

This study was conducted as a cross-sectional study in Jeddah, Saudi Arabia at the Hajj terminal at King Abdulaziz International Airport (KAIA) after the 2017 Hajj season. Pilgrims were approached and asked to participate in the study using a two stage clustering method. Survey data was collected from pilgrims from different nationalities using an electronic data capture tool: 'Open Data Kit' (ODK).²⁷ Survey questions were translated into 15 languages and were piloted prior to conducting the study. The electronic questionnaire consisted of demographic items, health status and several questions related to the time taken for travel preparation before the Hajj as well as previous Hajj and Umrah history.

Statistical analysis

Descriptive and regression analysis were conducted using Stata 15 for survey data where clustering and weighting are accounted for via the svy family commands.²⁸ The association between the outcome and each of the potential confounders were investigated using the Wald adjusted test to account for cluster sampling design. Variables with a *p-value* ≤ 0.1 were selected to be included in a multivariable regression. The study classifies the following as chronic diseases: cardiovascular

disease, hypertension, diabetes mellitus, hypercholesterolemia, asthma, lung disease other than asthma, kidney diseases, immunodeficiency and cancer. We used logistic regressions to assess the association between the binary variable “chronic disease status” and gaining information regarding preventive measures (Model 1) and the association between chronic disease status and obtaining information about recommended travel vaccines (Model 2). Logistic regression was also fitted to examine the association between the exposure chronic disease status and the outcome variable pre-travel time preparation which was categorised as 0: < two months, 1: ≥ two months and more (Model 3).

Unadjusted and adjusted odds ratios (OR) for Models 1, 2 and 3 along with 95% confidence intervals (CI) were calculated. Model 1 was adjusted for sex, education level and country classification by income based on the World Bank classification for the year 2017-2018 ²⁹. Education level was categorised as 0: low level of education (illiterate pilgrims or those who can only read and write), 1: middle level (qualification of two years college, high school or less than high school, and 2: high level of education (doctoral, master or bachelor’s degree).

Model 2 included education level as a confounder, while Model 3 was adjusted for age, marital status, employment, country classification by income, previous Hajj, Umrah in the last 6-8 months and length of stay in Saudi Arabia.

Results

Demographic data and the travel profile of the 2,973 pilgrims involved in the study are summarised in Table 1. A total of 80.7% pilgrims reported that this was the first performance of the Hajj, while for 19.3% had undertaken a previous Hajj. Among pilgrims who reported a previous Hajj, 90.3% had done it once, 5.5% twice, 2.5%

three times and 1.7% more than 3 times. A total of 14.4% indicated visiting Mecca to perform Umrah in the last 6-8 months, prior to the 2017 Hajj. The majority of pilgrims (98.6%), were able to complete the Hajj successfully, while a small minority (1.4%), indicated that they had not due different reasons such as issues with their health. 77.4% of pilgrims reported they were vaccinated against meningococcal disease. Approximately half of the participants (48.4%), said that they received the polio vaccine and 21.4%, the yellow fever vaccine. The administration of recommended travel vaccines was reported by 25.9% for pneumococcal vaccine and 50.8% for influenza vaccine.

The majority of pilgrims (46.67%), reported that they started preparation for travel more than two months prior to the journey, 16.8% stated two months, 17.53% one month and 18.99% less than one month prior to the Hajj. Receiving information about recommended vaccines and health preventive measures was reported by (80%) and (81%) of pilgrims , respectively .

Chronic diseases were declared by 31% of participants. The distribution of chronic diseases among pilgrims is summarised in Table 2.

Table 1: Pilgrims characteristics profile.

Characteristics	%
Sex	
Male	68
Female	32
Age in years	
≤ 34	16
35-44	28
45 to 54	26
55 to 64	22
≥ 65	8
Education level	

Low	16
Middle	37
High	47
Ethnicity	
Arab	21
African	16
South Asian	30
Caucasian	4
Mixed race	3
Other	26
Country classification by income	
Low	6
Low-middle	57
Upper-middle	28
High	9
Employment status	
Employed	67
Unemployed	33

Table 2: Distribution of chronic diseases among 2017 Hajj pilgrims

Chronic disease status	%
With a chronic disease	31
Without a chronic disease	69
Type of chronic disease	
Diabetes	10.5
Hypertension	15.7
Asthma	3.4
Lung diseases other than asthma	0.6
Hypercholesterolemia	6.8

Cardiac disease	3
Immunodeficiency	0.7
Kidney disease	1.2
Malignant diseases	0.33
Medication use	
On medication	75
Not on medication	25
Travelled with medication	
Yes	24
No	76

Multivariate logistic regression analyses were employed to evaluate the association between chronic disease status and pre-travel time, gaining information related to preventive measures and travel vaccines outcomes. After adjustment for relevant potential confounding factors, the multivariate logistic regression analysis detected no significant associations (p -value 0.8 = for Model 1, p -value = 0.4 for model 2 and p -value = 0.2 for model 3) (see Tables 3 and 4).

In Models 1 and 2 and after adjusting for all other confounders, a non-significant trend was noted between pilgrims with chronic disease. They appeared to be less likely to seek information on health measures but more likely to seek information on recommended vaccines. Nevertheless, this should be carefully interpreted under our non-significant results: OR 0.97 (95% CI; 0.76, 1.2, p -value 0.8) and OR 1.14 (95% CI; 0.8, 1.6, p -value 0.4), respectively. Being a male, having a high level of education

and coming from upper middle income countries are factors significantly associated with seeking information about health preventive measures (Table 3).

In Model 2: We ascertained stronger evidence between education and seeking information regarding recommended travel vaccines, those with a high level of education more likely to be able to obtain information about travel vaccines. than those with a low level of education OR 2.8 (95% CI; 1.2, 6.6, *p*-value 0.01)

In Model 3 , there was no evidence of association between chronic disease status and the pre-travel time outcome. Other significant factors associated with pre-travel preparation time are summarised in Table 4.

Table 3: Multiple variables logistic regression analysis for associations between chronic disease status and gaining information about preventive measures and travel vaccines

	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Exposure	Model 1: Information about preventive measures *			
Chronic disease status				
Without a chronic disease	Reference			
With a chronic disease	0.97 (0.74,1.27)	0.83	0.97 (0.76,1.2)	0.81
Sex				
Female	Reference			
Male	1.3 (1.08,1.7)	0.008	1.2 (1.03,1.59)	0.02
Education level				0.007 [#]
Low	Reference			
Middle	1.16 (0.74,1.8)	0.48	1.2 (0.88,1.87)	0.18
High	1.72 (1.08,2.76)	0.02	1.9 (1.27, 2.86)	0.002
Country classification by income				0.03 [#]
Low income	Reference			
Lower middle income	0.95 (0.56,1.64)	0.8	0.9 (0.54,1.71)	0.9
Upper middle income	1.9 (0.97,3.87)	0.06	2.1 (1.06, 4.37)	0.033
High income	1.4 (0.66, 3.08)	0.35	1.3 (0.58, 3.09)	0.48
Exposure	Model 2: Information about travel vaccines *			
Chronic disease status				
Without a chronic disease	Reference			
With chronic disease	1.14 (0.76, 1.7)	0.5	1.14 (0.80,1.63)	0.4
Education level				0.003 [#]
Low	Reference			
Middle	1.86 (0.8, 4.3)	0.14	1.86 (0.8, 4.3)	0.14
High	2.82 (1.2, 6.5)	0.01	2.87 (1.24, 6.6)	0.01

* Model 1 was adjusted for potential confounders (sex, education level and country classification by income). Model 2 was adjusted for education level.

[#] Overall Wald test.

Table 4: Logistic regression analysis for associations between chronic disease status and pre-travel time preparation.

	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Exposure	Model 3: Pre-travel time preparation *			
Chronic disease				
Without a chronic disease	Reference			
With a chronic disease	0.9 (0.7 , 1.3)	0.8	0.8 (0.6,1.1)	0.2
Age in years				
<35	Reference			0.004 [#]
35-44	1.5 (1 , 2)	0.007	1.6 (1 , 2.5)	0.01
45-54	1.8 (1.2, 2.7)	0.003	1.8 (1.2, 2.8)	0.003
55-64	2.3 (1.5 , 3.5)	0.001	2.4 (1.5 , 3.8)	0.001
65 and above	2.7 (1.6 , 4.7)	0.001	2.7 (1.4 , 5.2)	0.002
Marital status				
Married	Reference			
Unmarried	0.5 (0.3 , 0.8)	0.007	0.6 (0.4 , 0.9)	0.02
Previous Hajj				
No	Reference			
Yes	0.5 (0.4 , 0.8)	0.001	0.5 (0.4, 0.7)	0.001
Umrah in the last 6-8 months				
No	Reference			
Yes	0.7 (0.5 , 0.9)	0.02	0.9 (0.8,1.2)	0.8
Having information about recommended vaccines				
No	Reference			
Yes	0.9 (0.6 , 1.3)	0.6	0.7 (0.4 , 1.2)	0.2
Having information about preventive measures				
No	Reference			
Yes	1.2 (0.9 , 1.5)	0.1	1.5 (1 , 2.3)	0.02
Country classification by income				
Low income	Reference			0.1 [#]
Lower middle income	1 (0.6 , 1.8)	0.7	1.3 (0.7 , 2.4)	0.3
Upper middle income	0.8 (0.4 , 1.5)	0.5	0.8 (0.4 , 1.6)	0.5
High income	0.4 (0.2 , 1.1)	0.09	1 (0.4 , 2.7)	0.8
Length of stay in KSA				
				0.001 [#]

<31 days	Reference			
31-70 days	1.6 (1.1, 2.4)	0.008	1.5 (1 , 2.2)	0.01
71 days and above	2.4 (1.4, 4)	0.001	2.6 (1.6, 4.3)	0.001

*Model 3 was adjusted for (age, marital status, previous Hajj, Umrah in the last 6-8 months, country classification by income , having information about vaccines and preventive measures and length of stay in Saudi). Start preparing for the Hajj less than two months before the Hajj was used as a reference group.

Overall Wald test.

Discussion

Many Hajj pilgrims tend to be older and have a chronic disease.^{15, 16} Our study shows that 57.3% of pilgrims were ≥ 45 years old and 31% with chronic diseases. This puts this older group of pilgrims at higher risk of health problems during Hajj. As Hajj is a profound spiritual journey for Muslims, it is difficult to restrict the Hajj based on non-communicable diseases (NCDs).¹⁵ It is therefore important that individuals with chronic diseases receive effective travel health advice along with recommended travel vaccines before departure. More than half of pilgrims started preparing at least two months before the Hajj and 80% sought information on preventive measures and travel vaccines. This is a higher proportion than reported in previous studies investigating Saudi, Arab and Australian pilgrims where 44% of Saudi, 74% of Arab and 65% of Australian pilgrims obtained some sort of pre-travel health advice ahead of the Hajj.²²⁻²⁴ However, our study did not indicate the source of pre-travel advice. Previous studies show that pilgrims usually seek pre-travel advice from their Hajj agencies and have confidence in these agencies along with friends and families who have undertaken Hajj in the past.^{23, 30} These Hajj agencies therefore play an important role in pilgrim's health education.

In our study, travelling with a chronic disease was not significantly associated with seeking pre-travel health information, unlike other study among Saudi pilgrims which shows it as a significant factor.²³ In addition, no significant trend was found between early seeking of health advice and having a chronic disease. This could be explained by the fact that our study lacked detailed information concerning the source of health advice received by pilgrims. Our study also targeted pilgrims from different nationalities, many of them from developing countries where access to health services and advice varies

between countries. It is worth stating that the demand that has been made to restrict the Hajj to those who are physically fit to perform is difficult to implement seeing as many pilgrims are elderly people with chronic diseases.¹⁵

To establish a balance between its diplomatic and service role, Saudi Arabia could aim to preserve its balanced policy but aim to improve the policy in terms of application times and the involvement of pre-travel health education for pilgrims in their home countries. Medical screening of pilgrims prior to travelling for the Hajj is important to identify pilgrims with chronic diseases and provide the necessary advice for each specific case.¹⁴

The uptake of the influenza vaccine in our study was 50.8% similar to the average published influenza vaccination uptake of pilgrims of 52%.³¹ Nearly half of those who received influenza vaccines in our study have a chronic disease. The influenza vaccine is recommended by the Saudi Ministry of Health, particularly for high risk individuals; children, the elderly and those with underlining medical conditions.¹³

There is no consensus on policy for administering pneumococcal vaccine for Hajj pilgrims with limited information on the burden of pneumococcal disease during the Hajj.³² Currently, the pneumococcal vaccine is still not among the list of recommended vaccines for Hajj by the Saudi Ministry of Health.¹³ However, our study demonstrates that, 25.9% of pilgrims had received the pneumococcal vaccine.

The uptake of polio vaccine was 48.42%, a higher rate compared to previous studies 8% of Australian pilgrims,³³ 15% of French pilgrims³⁴ and 42.5% of pilgrims from different countries³⁵.

The uptake of the yellow fever vaccine among pilgrims in our study was (21.4 %). The yellow fever vaccine is a mandatory vaccine for pilgrims coming from Africa and South and Central America. Pilgrims from these countries are expected to show a valid vaccination card for yellow fever vaccine at the port of entry in Saudi Arabia.³⁶ The current World Health Organisation (WHO) guidelines for yellow fever vaccine indicate that the vaccine is valid for a lifetime for the vaccinated person.³⁷ Data from the 2013 Hajj reveals that 14% of pilgrims travelled to Saudi from 46 countries where yellow fever is endemic.³⁸ Previous research shows that some factors influence the decision among pilgrims to accept or refuse recommended vaccines.³⁹ Our study did not explore the factors influencing the uptake or refusal of recommended vaccines by pilgrims. The study also included pilgrims from different backgrounds and nationalities, therefore the factors may differ between country of origin.

The majority (80.7%) of pilgrims have experienced the Hajj for the first time. Previous studies among Australian and French pilgrims found most arrival were travelling for their first Hajj.^{33, 40} Saudi administration advice all pilgrims who have completed the Hajj once to be content that they have met the requirements of one of the 5 pillars of Islam, which is to do it once in a life time .⁴¹

This study is the first and largest study conducted among Hajj pilgrims to investigate the timing to pre-travel preparation. Our survey covered travellers internationally using questionnaires in 15 main common languages. The study did not include to the sources of pre-travel preparation plans and of pre-travel information. Future studies on the current topic are therefore recommended, seeing that a well-designed longitudinal trial would

provide valuable data for policy makers on the effect of pre-travel preparation timing on the health of pilgrims with chronic diseases.

Conclusion

Performing the Hajj is a life journey for many Muslims regardless of their background and health status. The high percentage of pilgrims with chronic disease in our study indicates the need to involve pre-travel health advice to all pilgrims in their home countries and involve relevant stakeholders to ensure the successful delivery of health advice. Hajj is an opportunity to reach large numbers of people to provide health information that may also have an impact on their health and not only restricted to the Hajj period.

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Chapter 11: Discussion

11 Chapter 11: Discussion

11.1 Preface

This chapter discusses the main results and interpretation of the PhD work, the policy and research implications resulting from it, as well as the strengths and limitations encountered. This PhD comprises two distinct phases (pilot and main), which were conducted in two separate Hajj seasons; specifically 2016 and 2017. The principal aim of the study was to determine the uptake of the meningococcal vaccines and investigate the association of early meningococcal vaccination on the carriage of *N.meningitidis* serogroups A, C, W and Y . It also aimed to investigate the association between early seeking of pre-travel health advice and having a chronic disease. Patterns of acquired health problems and personal health preventive measures adopted by pilgrims were also investigated.

11.2 Summary and interpretation of the main results

11.2.1 Vaccine uptake rates

The Hajj and Umrah vaccination policy includes vaccines that are compulsory and those that are recommended for pilgrims.¹ Compulsory vaccines are required for international pilgrims to be granted visas or for domestic pilgrims to be granted Hajj permits.¹⁻³ Recommended vaccines on the other hand are advised but not required for the entry into Saudi Arabia. The meningococcal quadrivalent vaccines ACWY (polysaccharide or conjugate) are compulsory for all pilgrims whether they are international or domestic.¹

Pilgrims should receive the meningococcal quadrivalent vaccine at least ten days prior to arrival in Saudi Arabia.¹ Influenza and pneumococcal vaccines are among the vaccines that pilgrims are recommended, in particular those who are at risk, such as the elderly, pregnant women, children and those with comorbidities.¹

Previous studies have shown that the meningococcal conjugate vaccine is more effective in reducing the carriage of *N.meningitidis*, although it remains uncertain whether conjugate vaccines clear the existing carriage or are only able to prevent acquisition of new *N.meningitidis*⁴⁻⁶ which could reduce the incidence of the disease and help to protect large mass gatherings from being the source of infection. The Saudi Hajj and Umrah policy does not indicate the type of quadrivalent vaccine required and leave it to pilgrims to decide. Many pilgrims are coming from developing countries where the cost of the conjugate vaccine would be an issue for many of them.⁷ Since 2003, it has been a requirement that both Saudis and other expatriates residing in Saudi Arabia who aim to perform Hajj must apply for a Hajj permit in conjunction with a MenACWY vaccine receipt.⁸ Despite this, illegal domestic pilgrims frequently enter Hajj sites without holding a permit and without officially registering with an accredited Hajj agency.⁸ Pilgrims who perform the Hajj illegally are highly likely to be unvaccinated seeing as they do not go through the requirement process for registration for the Hajj.

In our study, a total of 77.4% pilgrims from the main Hajj study, self-reported receiving a meningococcal vaccine (Chapter 8). Of these, 71.2% had reported receiving the mandatory meningococcal quadrivalent vaccine, 0.5% received the bivalent polysaccharide (A and C) meningococcal vaccine, whilst 6.2% were given an unknow

type of meningococcal vaccine. Of note, not being vaccinated against meningococcal disease was self-reported by 22.6% of pilgrims; 12.6% of those were not vaccinated and did not carry any vaccination certificate and 11% self-reported that they were unvaccinated and carried a purchased unofficial vaccination certificate. In the pilot study conducted among British pilgrims (Chapter 7) the uptake of the mandatory meningococcal quadrivalent vaccine was higher (98.5%) and among those, 85.2% received the meningococcal quadrivalent conjugate vaccine. Since 2014, meningococcal quadrivalent conjugate is the only type of meningococcal quadrivalent vaccine available in the UK, unlike other countries, who still offer the polysaccharide vaccine.⁷ This could explain the high rate of conjugate vaccines received by British pilgrims in the pilot study in 2016 compared to pilgrims from countries in the main study in 2017.

As expected, the majority of pilgrims in our study had received the quadrivalent polysaccharide (ACWY) vaccine. Over 60% of pilgrims came from low and low middle income countries (Chapter 8). Pilgrims from developing countries save long-term in order to be able to perform the Hajj⁹. For many people, as a result of their financial status, the choice of receiving a low-cost polysaccharide vaccine is one that is more suitable for them. The cost of the vaccine and socioeconomic status of the pilgrims may explain not being vaccinated against meningococcal disease or carrying unofficial vaccination certificates. The issue of not being vaccinated was also identified in another study conducted among domestic pilgrims.⁸

Vaccine shortages may be another explanation as to why some pilgrims choose to purchase unofficial vaccination certificates. Our study shows that very few pilgrims have

received the bivalent polysaccharide (A and C) vaccine due to quadrivalent meningococcal vaccine shortage in their home country. In an informal conversation with a number of pilgrims, several reported the issue of vaccine shortage. The challenge of achieving an optimum supply of meningococcal vaccines has been a pressing issue in various countries.^{10 11} The cost of the vaccine and vaccine availability are among these challenges.^{10 11}

The results from our main and pilot study highlight many issues in regard to the compliance, vaccine shortage and the type of quadrivalent vaccine.

Although our study did not show any significant association between time of MenACWY vaccination and carriage of serogroup A, C, W and Y, Pilgrims stated that a lack of preparation time prior to the Hajj remains a significant factor affecting the uptake of meningococcal vaccine.⁸ A study conducted among domestic Hajj pilgrims revealed that lack of time was the second most relevant barrier to vaccination.⁸

The uptake of other recommended vaccines such as influenza and pneumococcal vaccines was generally low in our study. The uptake of influenza and pneumococcal vaccines among British pilgrims in the pilot phase of the study were reported as 28.3% for the influenza vaccine and 7.5 % for the pneumococcal vaccine (Chapter 7). The rates were higher among pilgrims from different nationalities in the main phase of the study; specifically 50.17% for the influenza vaccine and 22.7% for the pneumococcal vaccine (chapters 9 and 10). Our study did not determine the factors and reasons for low uptake

of recommended vaccines among Hajj pilgrims. However, other studies have investigated these in different populations.¹²

The uptake of recommended vaccines among Hajj pilgrims has been generally low in previous Hajj studies.¹² A study conducted in London, UK, found that the rate of influenza vaccine uptake was 20.8% among the study population of 96 Hajj pilgrims, with the uptake rate being statistically significantly higher among at risk pilgrims.¹³ Particularly, older pilgrims aged over 60 years old and those with underlying conditions tended to have a statistically significantly higher uptake of recommended vaccines.¹³ An earlier study in France reported an influenza vaccination rate of 27.3% which also increased with the age of the pilgrim.¹⁴ However, our study did not reveal any significant association between the age or chronic disease status of pilgrims and the uptake rate of recommended vaccines (Chapter 10).

In the Netherlands, researchers found that from the year 2007, 2,156 pilgrims had been advised to have recommended vaccines.¹⁵ Of this number, roughly a quarter of them (24%) agreed to take the trivalent diphtheria, tetanus and poliomyelitis vaccine (dTP), which is a recommended vaccine.¹⁵ This was a higher rate compared to the one among French pilgrims from Marseille.¹⁶ Gautret and colleagues investigated vaccine uptake for the three vaccines individually (diphtheria, tetanus and poliomyelitis). They discovered that the rate was 14.7% (diphtheria), 18.9% (tetanus) and 15.0% (poliomyelitis).¹⁶

Likewise, Gautret, and colleagues reported an acceptance rate of 41% for the pneumococcal vaccine.¹⁷ This rate was much greater than that recorded among Australian pilgrims.¹⁸ Tashani and colleagues who completed a study among Australian

pilgrims to the 2011, 2012 and 2013 Hajj determined that the pneumococcal vaccine uptake rate for the three years was 28.5%, 28.7% and 14.2% respectively .¹⁸

The cost of vaccines has been identified as a possible reason for the low uptake of recommended vaccines. Keles et al., observed that the reason for the low uptake of recommended vaccines among pilgrims departing from the Amsterdam travel clinic may well have been the costs of the vaccines.¹⁵ Similarly, other researchers observed that Muslim communities in France belong to a low socioeconomic class and as such they are a disadvantaged minority group.¹⁷ Aware of the disadvantaged status of Muslims in European countries including France, Gautret et al., made a decision to offer free dTP and influenza vaccines at their Marseille-based travel clinic. They established that from 2007 to 2009, all pilgrims departing from Marseille, France accepted the updated dTP vaccine.¹⁷ Moreover, during the same period, 97%-100% accepted the seasonal influenza vaccine after being informed about the benefits of the vaccine.¹⁷ The findings by Gautret et al., underline that the cost of vaccines is a serious determinant to the uptake of recommended vaccines.¹⁷ Gautret et al., attributed the low acceptance rate of pneumococcal vaccine to the fact that the vaccine was not freely available at their clinic.¹⁷

11.2.2 Health status and pre-travel preparation of pilgrims

Many Hajj pilgrims come from developing countries and because of the cost of undertaking the Hajj, many will have had to save through their lifetime and will be an older population with a higher burden of chronic diseases ⁹

As Hajj is a profound spiritual journey for Muslims, it is difficult to restrict the Hajj based on chronic diseases .⁹ It is vital that pilgrims understand the need for travel health advice

prior to travelling for the Hajj, seek travel health advice in an appropriate manner, obtain travel health advice from a qualified source and primarily, adhere to preventive measures recommended to preventive against most relevant illness during the Hajj.^{19, 20}

As expected , both the pilot and main phases of our study indicate that less than two third of pilgrims are 45 years or older and around one third of pilgrims have chronic diseases (chapters 7 and 10). More than half of the pilgrims started preparing at least two months prior to the Hajj and the majority of pilgrims sought information on travel vaccines and health preventive measures. Importantly, our study did not show any significant association between pre-travel health advice and the uptake of recommended vaccines or the adoption of preventive measures during the Hajj by pilgrims. Having a chronic disease was not a significant predictor of seeking pre-travel advice ahead of the Hajj. Unlike other studies, among domestic pilgrims, found that having a chronic disease was a significant factor for seeking pre-travel health advice.²⁰ Our study did not reveal the origin of pre-travel advice

A study conducted among US pilgrims during the 2009 pH1N1 season illustrates that receiving health messages issued by the Saudi Ministry of Health at the various Hajj sites was associated with lower occurrence and duration of respiratory illness.²¹

However, it is worthwhile mentioning that the influence and effectiveness of the health educational programmes being conducted in advance of arrival in Saudi Arabia is undecided.²²

Earlier studies demonstrate that pilgrims typically obtain pre-travel advice from their Hajj agencies and they have confidence in the advice provided by these agencies, as well as friends and families who have performed Hajj previously.^{20, 23} It is clear that Hajj agencies play a crucial role in pilgrim's health education.

Saudi health authorities recommend that people at risk of emerging conditions such as elderly, pregnant women and those with chronic disease to postpone the Hajj during outbreaks seasons.²⁴ At risk pilgrims may choose to defy the advice and proceed to perform the Hajj. For instance, Gautret et al. ascertained that among the 179 at risk French pilgrims who reported to their clinic for pre-Hajj vaccination, none of them chose to postpone the Hajj.²⁵ This was despite the fact that most of them were aware of the Saudi health ministry recommendation, despite the advice issued by the travel clinic.²⁵

Saudi Arabia planned to host the Hajj in 2020 just a few months after the novel coronavirus (SARS-CoV2) emerged in China.²⁶ This raised additional challenges for Saudi and international authorities as Hajj gathers pilgrims from all over the world and could potentially spread new emerging infections.

Recognising that many pilgrims are elderly with chronic underlying diseases and the compliance with the recommendations to postpone in previous Hajj seasons was not followed, proactive preventive measures have been taken by the Saudi government to control the spread of coronavirus (SARS-CoV2), by temporarily banning all Umrah pilgrimages to Mecca.²⁷ The 2020 Hajj season will also be banned if coronavirus (SARS-CoV2) is still not under control.^{28, 29} These strict measures have been undertaken to prevent pilgrims from contracting the virus that is spreading globally.^{28, 29}

11.2.3 Compliance with personal preventive measures

Upper respiratory tract infections, diarrhoeal disease and blood borne infections are frequent health risks at the Hajj.³⁰ Pilgrims are advised to comply with preventive measures to protect themselves against these infections.¹ Non-pharmaceutical interventions such as wearing a facemask, hand hygiene as well as the use of sterile blades when shaving are among the preventive measures recommended.^{1, 30-32}

Approximately half of the pilgrims conformed with the use of facemask in the main phase of the study and one fourth in the pilot phase of the study. Data obtained from earlier Hajj studies suggest a steady increase in the utilisation of face masks from 24% in 1999 to 64% in 2014.³³ The low compliance rate with regards to face masks among British pilgrims in the pilot stage of the study (chapter 7) could be explained by means of cultural or alternative religious views. Some Muslims believe that faces should remain uncovered during the Hajj. Hence, most do not find it essential to wear a mask and therefore observed a low rate of facemask use.³⁴

Hand hygiene and face masks are inexpensive physical measures that can be implemented with the aim of reducing the risk of respiratory infections.³⁵ The ritual washing completed by Muslims prior to each of the five daily prayers requires washing the hands, which made the hand hygiene recommendation tolerable and straightforward for most pilgrims to implement.³⁶ Most of the pilgrims in our research (82.1%) reported that they washed their hands more than five times a day. This is

consistent with a another study which revealed that 90.3% of domestic pilgrims had washed their hands more than five times per day.³⁷

Importantly, our research confirmed a significant lower frequency of URTI's symptoms among those who changed their mask every 4 hours in comparison to those who did not change masks. Gatrads et al. mentioned that facemasks should be changed on a regular basis, at least every six hours so as to remain useful.³⁴ Facemasks have been demonstrated to be effective in inhibiting or reducing nosocomial transmission of pandemic influenza since the deadly 1918 flu pandemic and may well play a role in other types of respiratory virus epidemics.^{38, 39} The effectiveness of facemasks in reducing respiratory infections is affected by a number of factors that include design, quality, how they are applied to the face and how frequently they are changed.^{34, 40} Facemasks need to be worn correctly and must be of a high quality and standard and replaced every six hours to be completely effective .³⁴ Our study did not indicate any significant association between the type of facemask used e.g., surgical or N95 and URTIs symptoms among Hajj pilgrims.

Regarding previous studies that investigated the effectiveness of facemasks concerning preventing URTI's, the data gathered were noted either to be unconvincing or inconsistent.⁴¹⁻⁵²

In our research, 63.1% of pilgrims made use of the catering services their Hajj tour operators provided. Although Muslims perform hand washing prior to every prayer, certain authors maintain that a more effective method is to use alcohol-based hand rubs on a regular basis as regards hand hygiene.⁵³ Alcohol-based hand rubs may possibly be more

effective than conventional hand washing as they result in improved compliance as well as a lower rate of infections,, in addition to being easier and quicker to use.⁵⁴⁻⁵⁶ Our research suggests that more than half of the pilgrims (58.6%) used hand sanitisers. However, frequency of use was not investigated in the questionnaire. A study performed on local pilgrims in 2009 documented similar results to our findings which did not demonstrate any significant association between hand hygiene and diarrhoea.³⁷

Unlicensed barbers continue to operate illegally during the Hajj season. We reported that 12% of pilgrims had their heads shaved by unlicensed barbers, while 9.2% used other pilgrims' shaving implements to shave their heads. The findings collected by the current study are in accordance with those gathered by Al-Jasser et al., who completed research among domestic pilgrims verifying that 10% of pilgrims had used the services of an unlicensed barber.³⁷ Reusing razor blades was also noted in a separate survey undertaken among pilgrims from 53 different nationalities showing that 25% of pilgrims reused blades from other pilgrims.⁵⁷ This is significant, as the practice of reusing blades from other pilgrims and using the services of unlicensed barbers who may use non-sterile blades, suggests that pilgrims are at risk of acquiring blood borne infections such as hepatitis B , C and HIV.³⁰ Hepatitis B vaccine is not among the Hajj travel vaccines proposed by the Saudi authorities given that it is not easy for many pilgrims to get owing to the cost and time necessary to complete the vaccination course.³⁰

11.3 Study Limitations

We are aware that this study may have certain limitations and it is plausible that these limitations could have influenced the results obtained. First, these findings are limited by the use of a cross-sectional design, given that conducting a large scale longitudinal study is challenging in circumstances similar to the Hajj. Furthermore, in the short-term, due to the 'loss of follow-up, it was extremely difficult to contact the substantial numbers of pilgrims who participated in this study, as they are spread throughout the world. Therefore, the cross-sectional study conducted after the Hajj was unable to determine the rate of *N.meningitidis* carriage before the Hajj in order to compare it with that post-Hajj. It is not clear whether the carriage that the study detected was a pre-existing carriage of the bacterium or an acquired carriage during the Hajj.

Second, the data collected from pilgrims were limited to those departing from the Hajj terminal at King Abdul-Aziz Airport in Jeddah . Pilgrims can travel to and from Saudi Arabia to perform the Hajj by means of several routes: 94% travel by air, 5% by land, whilst 1% travel by sea.⁵⁸ Air routes are managed by King Abdul-Aziz Airport in Jeddah and Prince Mohammad bin Abdulaziz Airport in Medina. Most Hajj and Umrah flights are managed in the Hajj terminal of King Abdul-Aziz Airport.. Pilgrims who departed from Prince Mohammad bin Abdulaziz Airport in Medina and by other ports, e.g. by sea and land were not involved in the data collection in this study. Therefore, these data must be interpreted with caution and generalisation cannot be applied.

Thirdly, the survey did not include detailed questions in relation to pre-travel preparation plans and the source of pre-travel information. It also lacked questions on the reasons for not being vaccinated against the meningococcal disease and reasons for obtaining

unofficial vaccination cards. The issue of unofficial vaccination cards was not recognised when designing the pilot study. In the main study, the aim was to determine the prevalence of unvaccinated pilgrims more than the reasons for not being vaccinated or the reasons for purchasing unofficial vaccination cards. Information on antibiotic use was self-reported, thus subject to recall bias. A number of pilgrims may have confused use of antibiotics with other non-antibiotic medications or the type and dose of antibiotic which could have influenced the results.⁵⁹

Missing data at interview was a major limitation in the pilot study on British pilgrims. This limitation was primarily avoided in the main study by using an electronic data collection tool (ODK). Main survey questions that are essential for the objectives of the main study were compulsory in the ODK. Interviewers could not proceed to the next question without answering the previous one. However, answering certain secondary important questions was optional for the respondents; therefore, some avoided these questions in the electronic survey.

Data were missing for several important variables used to measure socioeconomic status (SES), such as monthly income. Monthly income variable was missing for 1,724 (58%) of the pilgrims in the main Hajj study. These variables were omitted from the analysis, although SES could be one of the risk factors that could influence the results. The study focused on other variables that are also used to measure SES such as education and employment status. Regression analysis could have provided valuable information on the significance of the results obtained in regard to the association between timing of meningococcal vaccination and carriage of serogroups A, C, W and Y if the confounder antibiotic uptake was controlled. It is extremely difficult to control this especially as many

pilgrims do take antibiotics for protection or treatment against respiratory disease. The study could not also detect any significant association between diarrheal disease among Hajj pilgrims and the various known risk factors, source of food, eating raw vegetables/food, frequency of hand washing or use of hand sanitisers. The small number of pilgrims (172/2,973), who suffered diarrheal disease could have influenced the results and a larger sample may provide a significant association.

The survey did not include detailed questions in regard to the daily food source of pilgrims. This could also explain the absence of a significant association between hand washing and having diarrhoea. Ablution, the ritual washing performed by Muslims prior to each of the five daily prayers involves washing hands with water and does not require the use of soap. Although the majority of pilgrims had washed their hands more than five times a day, this is however limited to water use .

Fourth, the study examined the effectiveness of facemasks on upper respiratory tract infections solely based on syndromic criteria. Investigating the effectiveness of facemask use supported by laboratory confirmed findings would provide strong evidence to support the findings.

Finally, the study successfully highlighted the issue of using unlicensed barbers and sharing shaving tools by some pilgrims which may place many pilgrims at high risk of blood borne infections, such as hepatitis B and C as well as HIV. However, the risk of blood borne infections in this study has not been investigated based on . A cross-sectional study is not the best study design to determine the risk of blood borne disease. Collecting biological samples for laboratory investigations would be the optimal scientific method to confirm these infections.

11.4 Study Strengths

This is the largest study to date on meningococcal carriage among Hajj pilgrims and the largest pertaining to patterns of diseases and personal health preventive measures adopted by pilgrims. This study also examined the association between timing of meningococcal vaccination and carriage of *N.meningitidis* serogroups A, C, W and Y. The study examined several of the significant risk factors that may affect the carriage, such as length of stay in Saudi Arabia, level of crowd inside the tent and various social activities pilgrims undertake. This study is also the first Hajj study to investigate when pilgrims with chronic diseases start preparing for the Hajj in terms of their health.

Despite the cross-sectional design of the study which have limited the findings in regard to meningococcal carriage, it did demonstrate for the first time, the issue of unofficial vaccination cards held by a number of pilgrims. This is relevant as those unvaccinated pilgrims put themselves and others at risk of meningococcal disease. Targeting pilgrims after the Hajj and prior to their return flight to their various countries helped encourage many to admit to using fake vaccination cards and their concerns as regards being unable to enter Saudi Arabia to perform the Hajj has been eliminated.

The study was conducted using an appropriate random sampling method (clustering method) for the circumstances, given that systematic sampling was not possible at the airport and during Hajj. The study also targeted pilgrims of various nationalities and the questionnaire was translated into 15 of the most common languages used by pilgrims. Language barrier may have been one of the issues in previous Hajj studies. However, one of the strengths of this particular study was to make the questionnaire understandable

by the majority of the pilgrims, although it is practically impossible to ensure that respondents answer every single question.

It should be stated that employing an electronic data capture tool, such as open data kit (ODK), reduced missing data particularly of (monthly income) and ensured 'no missing data' the primary variable, such as meningococcal vaccination and time of vaccination.

The ODK reduced data entry time need for dual -entry whilst minimising entry errors.

The ODK was also fun to use and many pilgrims were encouraged to participate by means of using the tablets provided.

The technology used in the ODK supported a number of questions with pictures to avoid confusion, such as that showing the type of facemask that was used by pilgrims e.g. N95 or surgical facemask.

Choosing the airport as a site to approach pilgrims to participate in the study also permitted advantages, as it help us to target large numbers of pilgrims in one primary site.

Many pilgrims were also encouraged to participate so as to 'kill waiting time' before their flights back to their countries.

11.5 Research implications

The association between timing of meningococcal vaccination and carriage of *N. meningitidis* serogroups A, C, W and Y remains understudied. Our study was limited to the use of a cross-sectional design and was unable to control the confounder antibiotic used by pilgrims.. There is a need for further studies (with appropriate longitudinal study design and appropriate data analysis methods controlling for potential confounders and

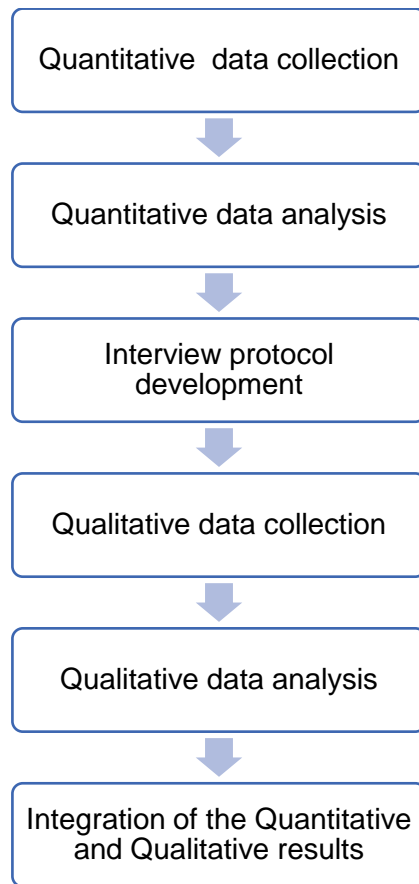
mediators). The issue of purchasing unofficial vaccination certificates by some pilgrims could be further investigated by means of conducting a mixed methods study involving a qualitative phase, where the initial results from the quantitative stage are explained in more depth and to develop new questions based on the results which cannot be answered by quantitative data. Our study determined the prevalence of unvaccinated pilgrims, although it did not reveal the reasons why people had not been vaccinated or purchased unofficial vaccination cards. Pilgrims from different countries may possibly have different reasons.

The investigator had informal conversations with several pilgrims in the pilot study phase two (Umrah phase) regarding this issue. Pilgrims from different countries mentioned different reasons for purchasing unofficial cards or not being vaccinated. These reasons include cost, vaccine availability, safety concerns, lack of time and fraud by the Hajj agency. These factors need to be investigated in a scientific way and by conducting a study with appropriate design and sampling methods so that these particular reasons can be fully understood. The prevalence of unvaccinated pilgrims in our study may allow us to provide certain recommendations but these are still restricted to the limited data we have obtained. The vaccination process involves many stakeholders, starting with the pilgrims themselves and comprising the Hajj agency, medical team based in the home country, Saudi embassy visa staff and the Saudi medical authority at the port of entry in Saudi Arabia. In order to fully investigate the issue of unofficial cards, a qualitative study needs to be conducted with these stakeholders so as to explore this issue and be able to provide necessary recommendations.

The qualitative stage which will involve focus group discussions and in-depth interviews with the following: pilgrims, pilgrims who have travelled for the Hajj, staff working for Hajj agencies, medical staff at ports of entry in Saudi Arabia and with visa issuing staff at Saudi embassies, in order to explore factors affecting the uptake of meningococcal vaccines by some pilgrims as well as their perceptions regarding recommended travel vaccines and preventive measures.

The proposed study will be conducted as explanatory sequential mixed methods. In mixed methods, both quantitative and qualitative data are merged or combined to provide comprehensive analysis or to explain the results of one method more thoroughly by conducting the other.⁶⁰ In contrast to other types of mixed methods, the explanatory sequential mixed methods design gives precedence to the quantitative stage. Therefore, this suggests that it starts with collecting and analysing quantitative data, which is subsequently followed by the gathering and examination of the qualitative data.⁶¹ Flow chart 1 explains the stages of explanatory mixed methods design.

Flow chart 1: Stages of explanatory design.⁶¹



Whole genome sequencing (WGS), is a laboratory technique that allows researchers to determine the genetic and epidemiological characteristics of bacterial pathogens, in addition to antibiotic resistance and vaccine coverage.⁶² Our STGG mediums which contain the collected swabs are still stored in LSHTM at - 80°C for further laboratory investigations, e.g. whole genome sequencing (WGS), which will also detect antibiotic resistance.

We also collected nasopharyngeal swabs from approximately 900 pilgrims involved in our main Hajj study to investigate all other pathogens. The nasopharyngeal swabs are stored

in a Trizol/DNA Shield medium which inactivates all viable cells. DNA and RNA extraction will be performed by researchers at KAUST followed by metagenomic library preparations. The libraries will be then sequenced in different platforms (Miseq, Hiseq) in the Bioscience core lab. Additionally, bioinformatic analysis will allow characterisation of microbial communities in the collected samples.

These laboratory results can provide valuable data which can be used to examine the effectiveness of facemask use, facemask type, mode of wearing face mask and the frequency changing facemask as regards these respiratory pathogenies.

A significant health risk at the Hajj to be further investigated in future studies is the risk of blood borne infections. Our survey results demonstrated that a number of pilgrims used the service of unlicensed barbers and shared shaving tools although these results were not supported by laboratory findings. Future experimental investigations based on laboratory findings are therefore required to determine the risk of blood borne infections in the Hajj.

In future investigations, it could be possible to employ a different survey tool in which the focus is on the pre-travel plan and source of health information pilgrims with chronic disease obtain.

Future studies on the association between having chronic disease and seeking health information are recommended, seeing that well-designed longitudinal quantitative studies would provide valuable data on the effect of pre-travel health advice and preparation on pilgrims health during the Hajj. In future investigations, it may well be possible to employ a separate survey tool in which the focus is on the pre-travel plan and source of health

information pilgrims with chronic disease obtain. To further the research, conducting a qualitative study to explore the pre-travel preparation experiences of pilgrims with chronic diseases may possibly give the results depth.

11.6 Policy recommendations

Hajj is the most organised mass gathering and migration globally. International and domestic pilgrims should register with a Hajj travel agency to participate in the Hajj and be granted a visa if they are an international pilgrim or a Hajj permit if they are a domestic pilgrim. Those Hajj agencies are responsible for pilgrims in terms of visa applications, accommodation in KSA, transportation, food and medical care..⁶³ In some countries, Hajj camps are organised in different cities where pilgrims gather to receive information concerning the requirements of the Hajj prior to performing the Hajj.

Having this large number of pilgrims gather in an organised way is an opportunity to medically screen pilgrims and follow up with those with chronic diseases to ensure that they are capable of performing the Hajj and are supplied with sufficient medication for their conditions before travelling. Many of those pilgrims are elderly and suffering from chronic diseases.

Developing a Harmonised Hajj Health Information System (HHIS), a platform for sharing synchronised data and information among Hajj pilgrimage stakeholders,⁶⁴ may play a role in resolving the issue of unofficial vaccination cards held by some pilgrims. The HHIS would capture data related to pilgrims before, during and after the Hajj. Data such as pilgrims' demographic information, pre-existing health conditions and vaccination status

can be captured before the pilgrims' arrival in Saudi Arabia for the Hajj.⁶⁴ To ensure that all pilgrims are receiving mandatory vaccines for the Hajj, vaccines can be received in specific vaccination centres authorised by the Saudi embassies in each country where pilgrims originate from and the vaccination status linked to the HHIS. Providing electronic evidence for vaccination from an authorised vaccination centre may reduce the number of unvaccinated pilgrims traveling with unofficial vaccination cards. The HHIS is also benefiting during and after the Hajj as it captures data related to pilgrim's health during the Hajj journey and tracks their health status after the Hajj in their home countries.⁶⁴

The HHIS would be a substantial assignment presenting a variety of tasks for those involved, including the creation of the human resources and infrastructure that are essential to assist such a system both in Saudi Arabia and the countries where pilgrims originate from.⁶⁴ Similarly, it will guarantee that rigorous regulations and safeguards are prepared to assure the security and appropriate access to and exploitation of the health information within the system along with the governance provided by the HHIS.⁶⁴ Besides, the HHIS would involve a high degree of collaboration and mediation universally between the various national and international stakeholders.⁶⁴ Nevertheless, the task could be achieved if it receives the required funding and backing from each of the participating organisations in conjunction with strong political will and support.⁶⁴

Another recommendation is to evaluate and authorise Hajj and Umrah agencies based on the health services and education provided by these respective agencies. Hajj agencies are responsible for submitting visa applications on behalf of pilgrims and providing accommodation, transportation, health care and advice, as well as food for their

Hajj travellers.⁵³ Every year the Ministry of Hajj and Umrah in Saudi Arabia updates their list of approved and authorised Hajj and Umrah agencies based on an annual evaluation.^{2, 3} The current evaluation of these agencies is not necessarily based on the health services provided. Involving Hajj agencies in health education and ensuring their customers are vaccinated and that each pilgrim holds an official vaccination card may also play a role in resolving the issue of unofficial vaccination cards being used by some pilgrims.

Religious leaders have respected positions in society and people tend to follow their views. Religious leaders may play a role in educating pilgrims on the importance of receiving vaccines before the Hajj to protect themselves and others. It may be possible to involve religious leaders in educating people on the risks of obtaining unofficial vaccination cards without being vaccinated.

Media and Hajj handlers play a critical role in the uptake of recommended vaccines. They have to ensure that pilgrims are properly informed about recommended vaccines, including their safety and effectiveness. Keles et al. observed that pilgrims are scarcely informed about the health risks involved before they visit vaccination clinics for compulsory vaccines.¹⁵ The role of informing pilgrims on the subject of health risks and the importance of recommended vaccines rests with the media, government and Hajj travel agencies. Barasheed et al. found that more than half of their participants (65%), reported having accepted the influenza vaccine prior to departing for the 2012 Hajj following a recommendation from tour group leaders.⁶⁵ Keles et al. also acknowledged the importance of Hajj agencies in vaccine uptake.¹⁵ They observed that Islamic

organisations handling Hajj pilgrims need to be well-informed regarding both mandatory and recommended vaccines .¹⁵ In France, Gautret et al. reported that 35.3% of the 360 French pilgrims they studied were aware of the recommendation to postpone the Hajj if they were at risk.²⁵ They attributed this awareness to the extensive media coverage of the issue by French newspapers.²⁵

Currently the Hajj and Umrah policy does not indicate the type of meningococcal ACWY vaccine that should be received, for example conjugate or polysaccharide⁷, although the conjugate vaccine has shown more benefits in contrast to the polysaccharide vaccine. ⁶⁶

⁶⁷ The cost of the conjugate vaccine may possibly be one of the reasons for leaving it optional for pilgrims to choose between two types depending on their financial ability, since many pilgrims come from developing countries and the cost could be a barrier.

There may be a need to reassess the current Hajj and Umrah vaccination policy in terms of the type and time of the vaccination and compliance with the vaccine.

Zakat is known as alms-giving in Islam and is a religious obligation or tax for more wealthy people.⁶⁸ Travellers and the poor are among the eight types of people who should receive Zakat.⁶⁸ Involving the Zakat house of countries where pilgrims originate from may possibly help to increase vaccination compliance by covering the cost of the vaccine and by choosing the more beneficial conjugate vaccine for pilgrims. Other recommended vaccines such as influenza and pneumococcal vaccines for high risk groups might also be offered free of charge by Zakat houses. Moreover, medical and financial screening of pilgrims may be performed in order to identify those in need and involve stakeholders

who may play a role in the vaccination of pilgrims. Sufficient time is necessary in order to achieve that and therefore early preparation for the Hajj is still recommended.

Saudi Arabia employs two meningococcal meningitis epidemic control approaches as regards Hajj pilgrims. ¹⁰ Visa-linked meningococcal vaccination certification (A, C, Y, W-135) is compulsory for all Hajj pilgrims. Furthermore, for those coming from the 'meningitis belt countries', a single dose of oral ciprofloxacin is dispensed at arrival ports in advance of the immigration process with the aim of reducing meningococcal nasopharyngeal carriage.¹⁰

Antibiotic uptake among Hajj pilgrims is high and could possibly lead to antibiotic resistance if continued.⁶⁹ The current antibiotic policy being undertaken by the Saudi authorities may need to be reassessed to balance the advantages and disadvantages associated with the policy.

Currently there is no meningococcal vaccination that protects against all the six pathological strains of *N.meningitidis*. However, a meningococcal ACYWX conjugate vaccine is under development.⁷⁰ Including the meningococcal ACYWX conjugate vaccine in the Hajj and Umrah vaccination policy once it is developed and licensed may play a role in decreasing the carriage of *N.meningitidis* and replace the use of antibiotic which is given as a prophylaxis for those coming from the meningitis belt countries.

Countries with significant Muslim populations have now begun to identify a trend in relation to increased serogroup B meningococcal disease; a serogroup for which a vaccine is available.^{71 72} This increase rate in meningococcal carriage caused by serogroup B should be considered by the Saudi authorities to reassess the current vaccination policy, so as to avoid any future outbreak of serogroup B.

11.7 Lessons learned

Conducting large studies involving international participants is challenging and is more challenging in mass gatherings such as the Hajj which is restricted to a specific and limited time each year.

One of the most important lessons learned from this PhD was the importance of establishing strong partnerships with different parties, both locally and internationally to ensure that contracts are established which explain the roles of each party with a timeline that must be adhered to.

A further lesson learned was gained from conducting the pilot phase as this allowed us to determine the most appropriate random sampling method to use in the Hajj and Umrah studies. Cluster sampling methods e.g. simple one-stage or simple two-stage sampling are the only methods that can be used in airports. Targeting one specific nationality at the airport in Saudi Arabia was challenging, particularly when the targeted nationality is a minority among other pilgrims. Another possible location to recommend for future studies is to recruit pilgrims in Mina using cluster sampling methods based on the nationality and numbers in each individual tent. Pilgrims spend most Hajj days in their tents in Mina, the main Hajj location situated near Mecca. Mina is known as the 'City of Tents', seeing that it has more than 100,000 air-conditioned tents which provide temporary accommodation for approximately 3 million pilgrims during Hajj.⁷³ Each individual tent is numbered and colour-coded by country, with the pilgrims expected to wear badges that comprise their number and colour.⁷³ It should be noted that Mina is also a suitable location to collect data for studies based on daily diaries during the Hajj days, such as data investigating

respiratory and gastrointestinal symptoms as well as the preventive measures used every day.

Learning how to manage funds appropriately was also another skill that was learned from this study. Hence, costs were reduced by setting up business arrangements with organisations in the private sector who were willing to provide their services free of charge in return for permitting their marketing teams to advertise their contributions in research training programmes.

The data collection was limited to a short and specific period after the Hajj, which made data collection more challenging and required the presence of a team of medical volunteers to work continuously to collect the required data on time. Involving medical students to participate as data collectors also contributed to cutting costs and time and allow us to play a role in educating students in regard to research ethics, sampling methods and data collection. In return, the students received certificates as evidence of their contribution as data collectors for the Saudi Commission for Health Specialties.

Medical students were trained to build trusting and respectful relationships with the pilgrims so that any barriers that could prevent pilgrims from expressing their experience with the meningococcal vaccine were removed. Conducting a cross-sectional study after the Hajj when pilgrims were leaving Saudi Arabia was also beneficial as pilgrims generally felt comfortable about admitting to using unofficial cards.

For the first time, this particular study highlighted the issue of unofficial vaccination cards being held by a number of pilgrims. The lesson learned from these findings is that holding a vaccination card is not necessarily an indicator of being vaccinated. This is an important

issue to raise with policy makers and the scientific community. The issue of purchasing unofficial vaccination cards is more wide-ranging than the meningococcal vaccines and could be expanded to other vaccines against other fatal infections.

Currently, researchers are working to develop a safe and effective vaccine against SARS-CoV-2. ⁷⁴One of the most challenging missions after approving and licensing the vaccine is to ensure that people are vaccinated against the SARS-CoV-2. Markets that provide unofficial vaccination cards may in fact become more active as a result of SARS-CoV-2. Therefore, clear strategies should be put in place to curb the business of selling unofficial vaccination cards.

The outbreak of SARS-CoV-2 has also highlighted another preventive measure such as facemask use that can be used to prevent respiratory infections. This study has highlighted that frequent facemask replacement every four hours may reduce the risk of acquiring symptoms of upper respiratory tract infections. This is important for pilgrims and non-pilgrims as facemask use, hand hygiene and social distancing are the only available preventive measures which can prevent the acquisition of SARS-CoV-2. ^{75, 76}

11.8 Conclusion

This observational study has demonstrated that i) high rate of pilgrims carrying unofficial vaccination cards ; ii) low rate of meningococcal carriage among Hajj pilgrims ; iii) early vaccination of meningococcal vaccination was not significantly associated with the carriage of *N. meningitidis* serogroup A, C, W and Y; iv) the uptake of personal health preventive measures remains low among Hajj pilgrims and uptake needs to be increased

; v) changing facemask every four hours was significantly associated with a lower rate of URTIs self-reported symptoms among pilgrims; vi) having a chronic disease was not associated with seeking health advice early.

Whilst this study did not find any association between any of the meningococcal risk factors and the carriage of *N. meningitidis*, it did highlight the issue of unvaccinated pilgrims and a need to strengthen compliance with the current vaccination policy.

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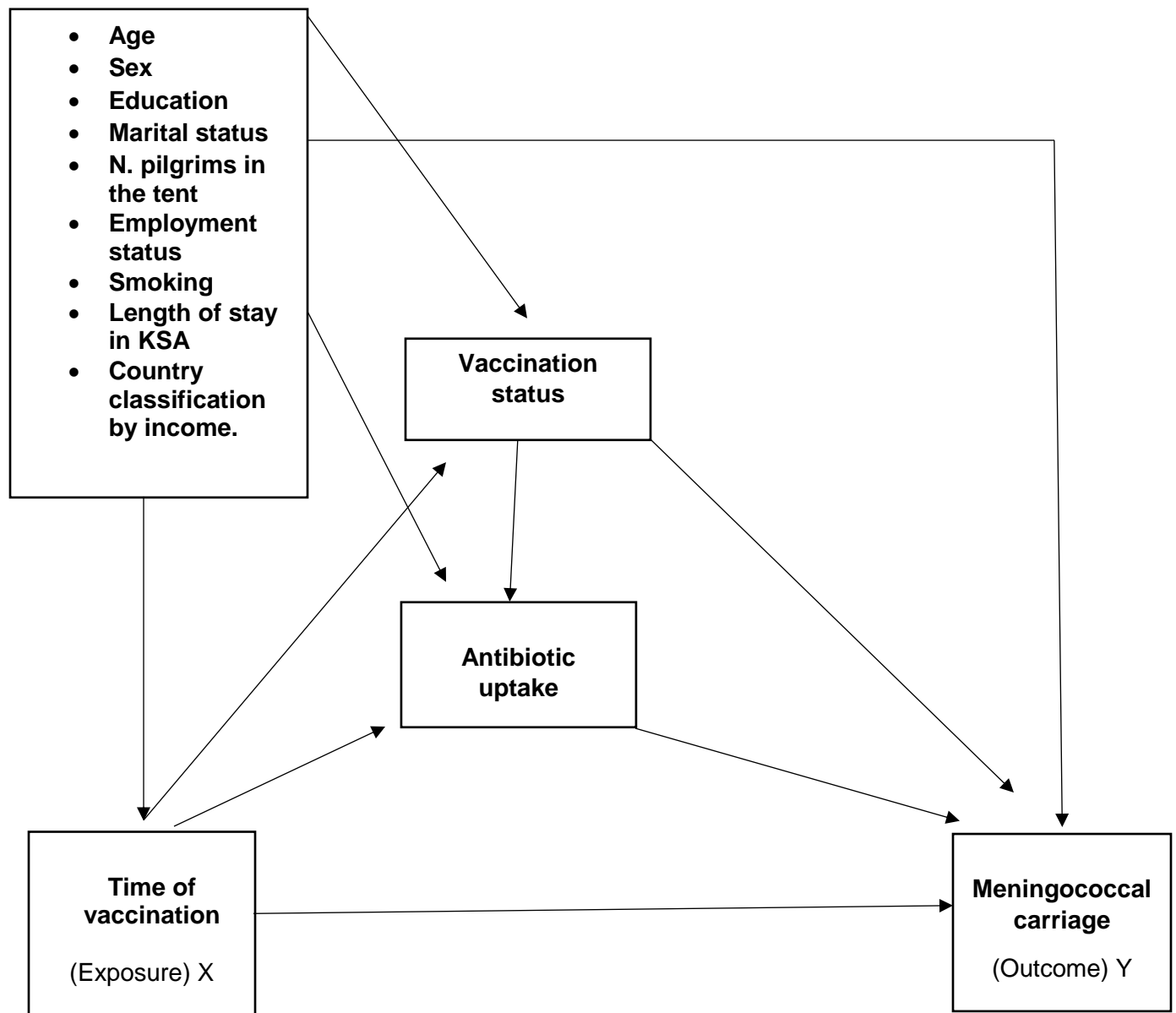
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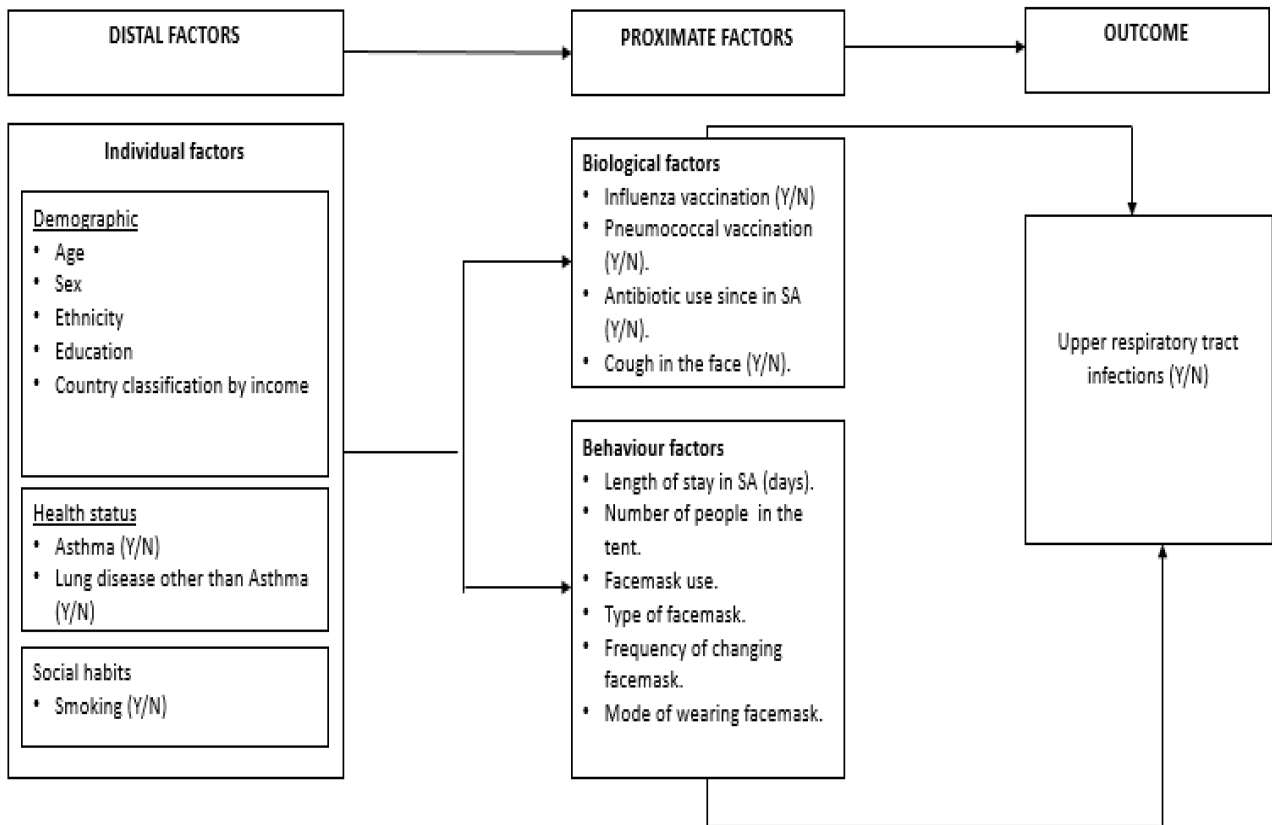
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12 Appendices

12.1 Appendix 1: Conceptual framework for the association between the timing of quadrivalent meningococcal vaccines administration and the carriage rate of serogroups, ACWY.

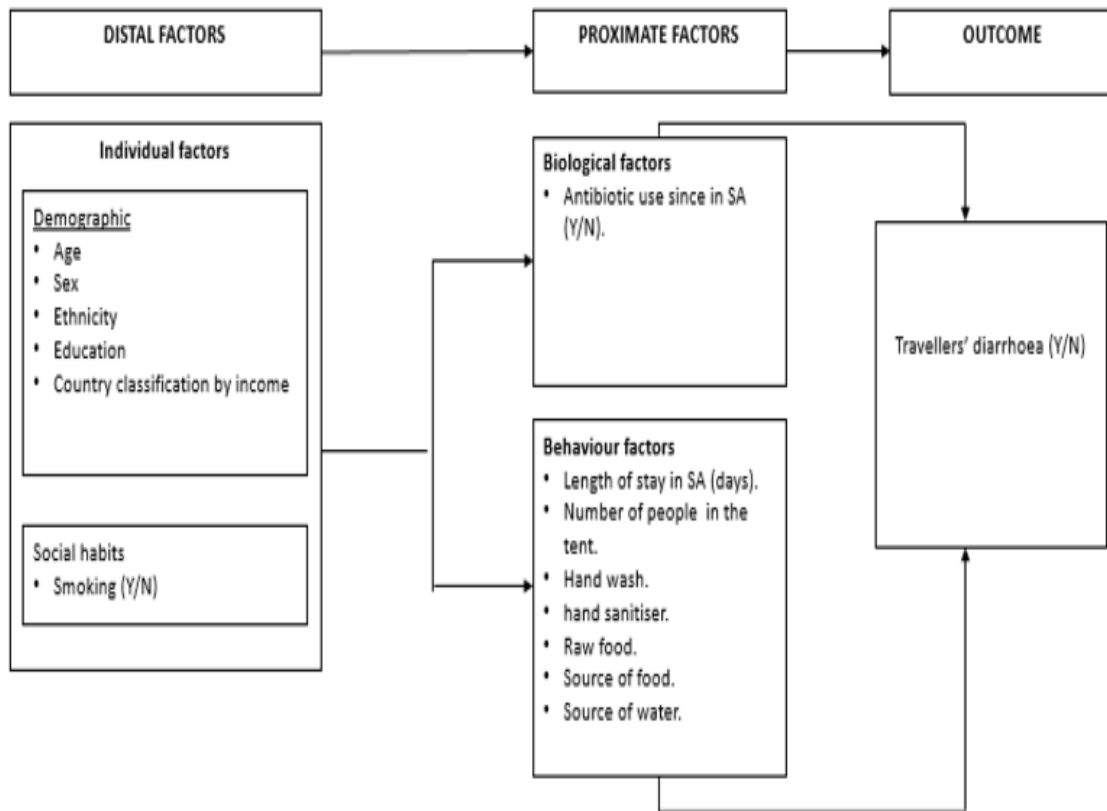


12.2 Appendix 2: Conceptual Framework for the association between upper respiratory tract infections and other risk factors.



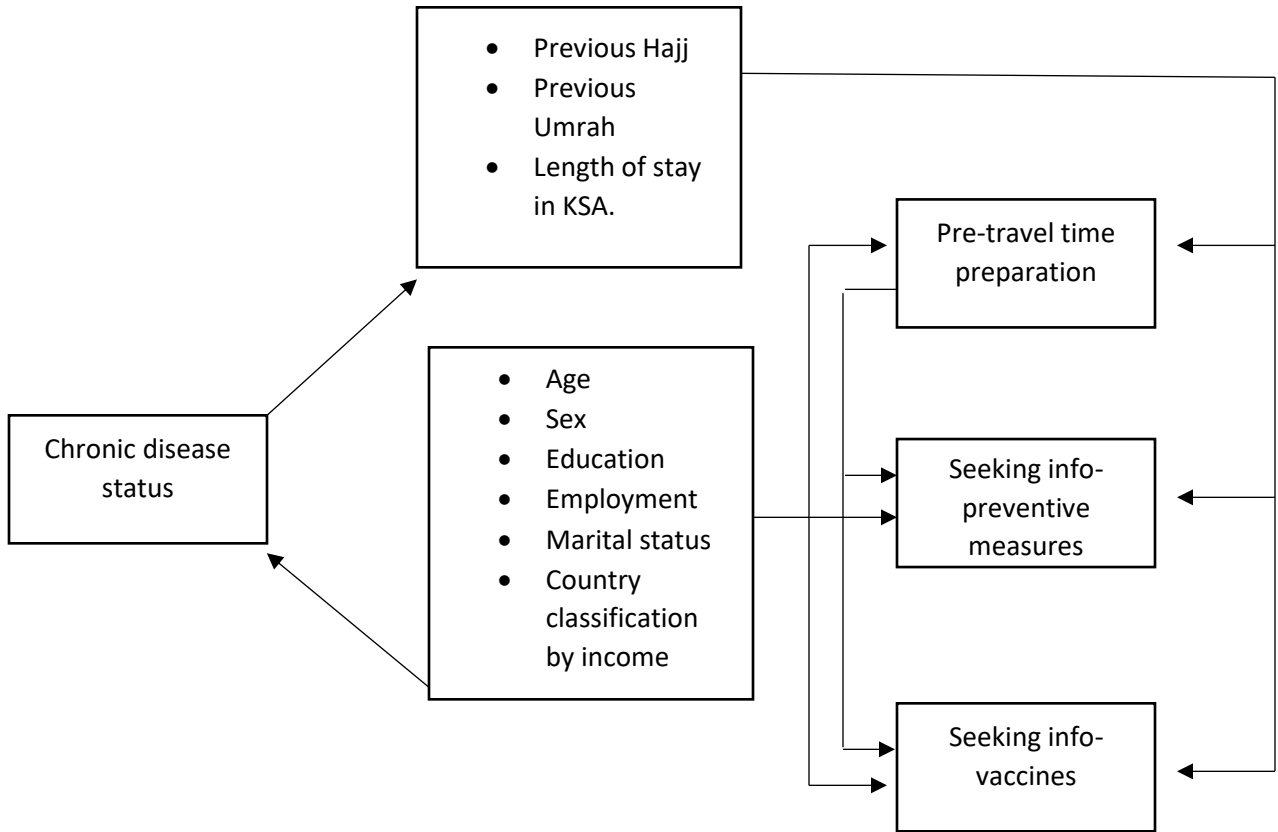
Y/N – Yes or No;

12.3 Appendix 3 : Conceptual Framework for the association between traveller's diarrhoea and other risk factors.



Y/N – Yes or No;

12.4 Appendix 4: Conceptual framework for the association of pre-travel preparation and chronic disease status.



12.5 Appendix 5: Estimation of probability weights

Estimation of probability weights for Abrar's sample survey in the Hajj 2017

A draft document prepared by Phil Edwards to advise Abrar Alasmari 18-03-18

Background

In Abrar's sample survey in the Hajj 2017, a two-stage random sample of 2,973 pilgrims was selected. At the first stage, a simple random sample of 74 flights departing from the Hajj terminal was selected. At the second stage a systematic random sample of pilgrims was selected from each flight. The numbers of pilgrims on each flight varied between flights and so the probability of selection into the survey sample was not equal for all pilgrims.

Probability weights

The purpose of the probability weights is to ensure that the probability of selection of each pilgrim into the survey sample is the same overall for all pilgrims.

Let w_i = probability weight for each pilgrim sampled from flight i

we must calculate the w_i such that the probability of selection for each pilgrim sampled from flight i is the same as the overall probability of selection for all pilgrims.

Target population

I assume that the *target population* is all pilgrims who attended the Hajj 2017 and who arrived by air. To calculate our probability weights, we need to know what is the size of this target population and how many flights were used to bring this population to the Hajj. Let us suppose that 835,980 pilgrims arrived on 3,125 flights and let us suppose that these 835,980 pilgrims were your target population.

Overall probability of inclusion in the sample

as your sample size is 2960, the overall probability of selection into your sample would be $=2960/835,980 = 0.003541$ (this will change if your target population is greater than or less than 835,980).

Probability of selection from each flight

Let n_i = number of pilgrims sampled from flight i

Let P_i = number of pilgrims on flight i

the probability of selection at the second stage was therefore $= \frac{n_i}{P_i}$

Overall probability of selection for each pilgrim sampled from flight i

if we assume that the total number of flights was 3,125 then the probability of selection at the first stage was $74/3,125$

the overall probability of selection for each pilgrim sampled from flight i would therefore be

$$74/3,125 \times \frac{n_i}{P_i}$$

we must now calculate the w_i such that the probability of selection for each pilgrim sampled from flight i is the same as the overall probability of selection for all pilgrims.

$$\text{So, } 74/3,125 \times \frac{n_i}{P_i} \times w_i = 0.003541$$

$$\text{So } w_i = 0.003541 \times P_i/n_i \times 3,125 /74$$

Example: If there were 300 pilgrims on flight i and you sampled 40 of them, then the probability weight for each of these 40 pilgrims in your data set would therefore be 1.121516.

Your Health and Hajj Journey



London School of Hygiene and Tropical Medicine collaborated with King Abdullah University of Science and Technology to conducting a study assessing your health at Hajj. Please take time to read both the information sheet and the informed consent before you start answering the questions in this questionnaire.

Please let us know if you need any help while completing the questionnaire.

Q1 Are you male or female?

Male Go to Q3

Female Go to Q2

Q2 Are you pregnant?

Yes

No

I don't know

Q3 How old are you?

18-24

25-34

35-44

45-54

55-64

65 and above

Q4 What is your ethnicity?

African

Arab

Asian (Indian, Pakistani or Bangladeshi)

White

Mixed

Other

If other, Please specify

Q5 Which of the following best describes your marital status?

Married and living with husband/wife

Married and separated from husband/wife

Divorced

Widowed

Single

Q6 What is your highest educational level?

Illiterate

Read and write only

Less than high school

High school

2 years college

Bachelor's degree

Master's degree

Doctoral degree

Q7 What is your current employment status?

Full-time employment

Part-time employment

Unemployed/Looking for job

Unemployed/Not looking for job

Self-employment

Student

Retired

Other

If other, Please specify

Q8 What is your monthly household income? (After income tax, rent/ mortgage interest, and council tax)?

Under £800

£800 to £1350

Over £ 1350

Q9 What is the total number of people (children and adults) in your household?

Q10 Do you smoke?

Yes

No

Q11 Are you in close contact with someone who smokes?

Yes

No

Q12 Do you have any of these disease?(Please mark all that apply)

Diabetes (High blood sugar)

Hypertension (High blood pressure)

High cholesterol

Asthma

Lung disease other than asthma

Heart disease

Kidney disease

Malignant disease (Cancer)

Immune deficiency (Low immunity due to a disease or medication)

Q13 Do you take any medication for the above diseases?

Yes -----Go to Q14

No ----- Go to Q 15

I don't have any of these diseases -----Go to Q 15

Q14 Have you taken your medication with you?

Yes

No

Q15 Have you received influenza (flu) vaccine in 2016?

Yes

No

I don't know

If other, Please specify

Q16 Have you received pneumococcal vaccine (for pneumonia) in the last 5 years?

Yes

No

I don't know

Q20 Have you done Umrah in the last 6-8 months?

Yes

No

Q17 Do you need support/assistance from anyone or any device to manage your everyday activities?

Yes -----Go to Q 18

No----- Go to Q 19

Q21 Have you performed Hajj before?

Yes

No

If yes, please specify the year

Q18 Please explain how do you need support to manage your daily activity?

Q 22 Are you currently suffering from any of these symptoms (problems)? (Please mark all that apply)

Fever

Sore throat

Cough

Runny nose

Headache

Breathing difficulty

Diarrhoea

Abdominal pain

Muscle pain

Vomiting

Nausea

Injuries

Other

If other, please specify

Q19 Where did you get the vaccine required for the visa application from?

Doctor/GP (Including nurse)

Council of British Hajjis

Pharmacy

Travel clinic

Mobile clinic (e.g. in mosque)

Place of work

Hospital

Other

Q23 Have you had any of these symptoms during Hajj? Please mark all that apply.

- Diarrhoea (Passage of 3 or more unformed stool during 24 hours)
- Abdominal pain
- Nausea
- Vomiting

Q24 Did you seek any medical advice or care treatment for these symptoms?

- Yes
- No
- No symptoms

Q25 Where did you usually eat your food during Hajj?

- Street vendor
- Tour group food
- Self-cooked food
- Canned food
- Other

If other, Please specify

Q26 Have you eaten any raw food/vegetables during Hajj?

- Yes
- No

Q27 How often have you washed your hands during Hajj?

- Less than 5 times a day
- More than 5 times a day

Q28 Have you used a hand sanitizer during Hajj?

- Yes
- No

Q 29 Have you had any of these symptoms during Hajj? Please mark all that apply

- Cough
- Shortness of breath
- Chills
- Sore throat
- Fever
- Lethargic or tired
- Coughing up blood
- Runny nose
- Sneezing
- Headache
- Pain in muscle

Q30 Did you seek any medical advice or care treatment for these symptoms?

- Yes
- No

No symptoms

Q31 Have you used a facemask during Hajj?

Most of the time

Sometimes

Never -----Go to Q35

Q32 What type of facemask have you used during Hajj?

Normal surgical facemask



N95 respirators mask



I don't know

Q33 How often did you change your face mask in a typical Hajj day?

Never

Every 0-4 hours

Every 6 hours

More than 6 hours

Q34 How did you wear your face mask?

I covered my nose and mouth

I covered my mouth only

I used both ways

Q35 Have you had any of these problems during Hajj? Please mark all that apply

Profuse sweating

Weakness

Hot skin with or without sweating

Coma

Confusion

Loss of body control

Slow and unclear speech

Q36 Did you seek any medical advice or care treatment for these problems?

Yes

No

No problems

Q37 How much water did you drink in a typical Hajj day?

More than 8 glasses

Less than 8 glasses

Less than 4 glasses

Less than 2 glasses

Often none

Q38 What was your source of drinking water?

Bottled water (unshared)

Shared water

Public water

Q39 During Hajj and when you were under the sun, have you covered your head by a hat, scarf or an umbrella?

Always

Most of the time

Sometimes

Never

Q40 During Hajj and when you were under the sun, Have you used any type of sunscreen?

Always

Most of the time

Sometimes

Never

Q41 Have you had any of these problems during Hajj? Please mark all that apply

Fractures (Broken or cracked bone)

Cut wounds on the skin

Contusions (Bruise)

Strain or sprain

Burn due to fire

Inflammation of the skin on the inner side of the thigh

Q42 Did you seek any medical advice or care treatment for these symptoms?

Yes

No

No symptoms

Q 43 Have you shaved your head?

Yes Go to Q 44

No Go to Q 45

Q44 Who shaved your head?

Licensed barber

Unlicensed barber

Another Hajji/using my tools

Another Hajji/using his tools

Myself /using others tools

Myself /using my tools

Q45 How did you behave in crowding during Hajj?

I have never avoided crowding

I avoided severe crowding only

I tried to do rituals at night

I asked another person to throw the stones at Jamrat Bridge Instead of myself

Q46 Were you able to perform the pillars (Arkan) of Hajj ((Staying at Arafah, Tawaful Ifadha and Sa'y)?

- Yes. All pillars
- Yes. Some pillar----- Go to Q 47
- No -----Go to Q 47

20 – 90

100 – 300

Q47 What was the main reason for not performing all or some of the Hajj pillars?

- I was sick and hospitalised
- Other reasons than illness prevented me from performing the Hajj pillars

Q50 Have you got any of these symptoms before the Hajj? (Please mark all that apply)

- Fever
- Sore throat
- Cough
- Runny nose
- Headache
- Breathing difficulty

Q48 Were you able to perform the duties (wajibat) of Hajj (throwing the stones, spending the night at Muzdalifa, spending night at Mina and Tawaf al wada)?

- Yes. All duties
- Yes. Some duties -----Go to Q49
- No -----Go to Q 49

Q49 What was the main reason for not performing all or some of the Hajj duties (wajibat)?

- I was sick and hospitalised
- Other reasons than illness prevented me from performing the Hajj duties.

Q50 How many people were living in your tent during Hajj?

- 6- 8

Swabbing Protocol

Materials

- Tongue depressors
- Facemask
- Gloves
- Oropharyngeal swab (OP), sterile plastic swabs with Dacron tips
- Nasopharyngeal (NP) swab
- Tissue
- Nasopharyngeal (NP) medium.
- STGG tubes
- Trizole tubes
- Biosafety bag
- Soap and water or alcohol based hand gel.
- Portable freezer
- Questionnaires/Tablet
- Consent and information sheets
- Subject ID labels
- Pen

Procedure

1. Inform the pilgrim about the questionnaire and sampling, verify signed consent forms and either signed assents forms or verbal assent.
2. Give one copy of signed consent form to the pilgrim (and one copy of signed assent form where relevant to the pilgrim), keep one copy for study records.
3. Ask questions of the pilgrim first. If the pilgrim is unable to answer due to language barriers, ask the relative/tour operator to translate.
4. Take the ID number labels. Stick one on the top right hand corner of each page of the questionnaire, each page of the consent form.
5. Thaw frozen tubes of STGG before use.
6. Label the tube with appropriate pilgrim and specimen information.
7. Check pilgrim's vaccination certificate and complete the first page of the questionnaire (Contact information, type of the vaccines, time of vaccination and antibiotic use).
8. Wash hands sterile with soap and water or an alcohol based gel.
9. Put on the facemask and gloves.
10. Position the pilgrim in a comfortable position, if possible place head against the wall to ensure he/she does not move during the sample collection process.
11. Remove the Oropharyngeal swab (OP) from the packaging and insert it into the posterior pharynx and tonsillar areas, rub swab over both tonsillar pillars and posterior oropharynx and avoid the touching tongue, teeth and gums.
12. Inset swab to the bottom of the STGG medium in thawed (room temperature) tube.

13. Raise the swab slightly and cut the wire portion (i.e., the shaft, or using a disinfected scissor) of the swabs at the top level of the container. Allow the bottom portion of the swab (i.e., the tip) to drop into the tube. Discard the remaining shaft into Biosafety bag.
14. Tighten the screw-cap top securely.
15. Vortex on high speed for 10–20 seconds.
16. Freeze specimen immediately in upright position at -20°C, if possible (place specimen on ice or in portable freezer).
17. Ask the pilgrim to blow his/her nose and dispose the tissue in a safety bag.
18. Tilt the pilgrim's head back slightly (about 70°) to straighten the passage from the front of the nose to the nasopharynx to make insertion of the swab easier.
19. Remove the Nasopharyngeal (NP) swab from the packaging and gently insert the swab along the medial part of the septum, along the base of the nose, until it reaches the posterior nares – gentle rotation of the swab may be helpful. (If resistance is encountered on one side, try the other nostril, as the patient may have a deviated septum).
20. Rotate the swab several times to dislodge the columnar epithelial cells, and then remove the swab. Note – insertion of the swab usually induces a cough or sneeze.
21. Put the NP swab into the transport medium (Triazol) and break it at the score mark on the shaft so that it does not protrude above the rim of the container. Failure to do so will result in the transport medium leaking and the sample being discarded.
22. Ensure that the lid of the container is screwed on tight.

23. Label the tube with appropriate pilgrim and specimen information.
24. Remove facemask and discard gloves. Perform hand hygiene by washing hands with soap and water or using alcohol hand rub.
25. Ask the pilgrim to complete the questionnaire.
26. After collection, immediately transport specimen to the laboratory and store it frozen at -70 °C until use for microbiological tests.

12.8 Appendix 8: A list of all medical students who participated in data collection.

Abdulaziz Ahmed Alharbi
Abdullah Ammash Aldawsari
Abdullah Mufarrih Algahtani
Abdulelah Tawfiq Fardus
Abdulmjeed Oqla Alnosair
Abdulrahman Waheed Aldossary
Abdullah Ammash Aldawsari
Abdulmohsin Ahmed Alghamdi
Aseel Osamah Murshid
Ashwaq Azhari Bangar
Afnan Shukri a Sharourou
Albaraa Sami Faden
Alanoud Khalid Nasri
Ahlam Ahmed Abu melha
Areej Omar Badawood
Anan Ibrahim Alturkustani
Amal Mohammed Alharthi
Asma Mohammed Alghamdi
Amirah Abdulbari Foad
Badr Ghassan Mahrous
Bashayer Ali Alshawi
Bayader Abuali Shami
Bayan Abdulrahman Alwaht

Esraa Abdulgader Abdulgader
Esraa Khalid Alharbi
Eman Osamah Murshid
Fatimah ahmed almahmoudi
Fai Salem Alkhelaiwi
Hanoof Hasan Ramadan
Hazem Mohammed Alotheid
Hamza Abdulaziz Mohammed
Haneen Mohamed Estantoli
Hootf Saeed Bafhaid
Hadeel Mohmoud Alomarni
Jenan Tajuddin Jawi
Khalid Rabai Muminah
Khalid Anwar Aboalela
Khulood Khaled Alzahrani
Mohammed Abdullah Alageeli
Mohammed Abubakr Badughesh
Mohammed Ali Gedthnan
Mohammed Saeed Algthaiae
Mohammed Fahad Alsabhani
Maram Ahmed Aljezani
Meshal Ahmed Algahtani
Auath Salem Binghafra
Malak Ahmed Alkaf

Mlouk Bassam Shabrawishi
Manal Saad Aldossary
Mansour Ali Alghuri
Muhannad Saleh Alzhrani
Mohammed Tariq Shata
Naif Ghassan Mahrous
Nada Anwar Aboalela
Nizar Othman Wali
Noora Salim Talib
Noor Hussain Bantan
Najwa Faraj Aljehani
Omar Abdullah Basfar
Ohood Abdulraouf Shrouro
Osamah Mohammed Aamer
Rlaf Abdullah Alzahrani
Rawan Nashaat Joharji
Raghad Ali Albalwi
Rahmah Mohammed Alasmari
Raghadh Faisal Al hatim
Raghad Yousef Neyaz
Raghad Hani Qutub
Reham Ahmed Fouad Saber
Rahaf Hakeem Ali Hakeem
Rawan Ezzi Abufaia

Rayan Mohsen Ismaeel

Reem Hussain Alamri

Rawan Talal Hejazi

Sarah Mohammed Alghfari

Salem Tawfiq Alasmi

Saud Abdulaziz Alsharif

Salha Saeed Asiri

Tala Ahmed Ali Alomari

Tala Khaled Alahdab

Taghreed Faisal Alawi

Wed Ahmed Alsubhi

Wafa Saleh Alghamdi

Wafaa Ahmed Alkaf

Wafa Ahmed Fouad Saber

Ziad Eidhah Sharaf Alzahrani

12.1 Appendix 9: Ethical approvals



Observational / Interventions Research Ethics Committee

Dr. Abrar Alasmari
LSHTM

16 May 2018

Dear Abrar,

Study Title: Impact of vaccination time on meningococcal carriage and effect of health problems on Hajj performance: A Cohort Study of Pilgrims Traveling from United Kingdom

LSHTM Ethics Ref: 11260 - 4

Thank you for your letter responding to the Observational Committee's request for further information on the above amendment to research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	16IBEC21_Pain	19/12/2017	1
Other	Informed Consent English ethics (1)	19/12/2017	1
Covering Letter	KAUST LEGAL ISSUE	30/04/2018	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: <http://leo.lshtm.ac.uk>

Additional information is available at: www.lshtm.ac.uk/ethics

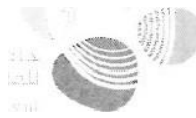
Yours sincerely



Professor John DH Porter
Chair

ethics@lshtm.ac.uk
<http://www.lshtm.ac.uk/ethics/>

Improving health worldwide



Institutional Biosafety and Bioethics Committee Approval Letter

Principal Investigator: Professor Arnab Pain, BESE Division

Project Title: "Assessing the effect of the quadrivalent conjugate (MenACWY) vaccine on the carriage of meningococci and other Bacteria during Hajj and Omra pilgrims - Phase (II)". IBEC Number: 16IBEC21_Pain_PHASE (II) - Project extension

Approval Date: August 22, 2017

Dear Professor Pain,

IBEC has reviewed your updated application for review for the research project entitled "Assessing the effect of the quadrivalent conjugate (MenA CWY) vaccine on the carriage of meningococci and other Bacteria during Hajj and Omra pilgrims - Phase a cross sectional study during 2016-2017 Hajj/Umrah seasons" in collaboration with the London School of Hygiene and Tropical Medicine, UK.

According to the information included in the submission, the project involves:

Study to identify the optimal time of quadrivalent meningococcal conjugate vaccine administration to inform the further assessment of the current Hajj & Omra vaccination policy in terms of the type and time of MenACWf vaccine uptake.

This application refers to the main study (16 IBEC21 Pain Phase I & 16 IBEC21 Pain Phase II) already approved by IBEC with the change of two following points:

1. The number of samples will be collected from 3,000 pilgrims and from all nationalities as long as they satisfied the inclusion criteria as mentioned in the application.
2. Minors (if <18 years of age) will also be included in the main study and for that informed consents will be taken from their parents (template of informed consent and information sheet provided).

Safety procedures will remain the same as for main application.



Dr. Abrar Alasmari, as a non-advertised lab worker, will be fully trained and supervised by Dr. Fathia Ben Rached (with almost 6 years of experience with BSL-2 agents handling), to handle biohazard specimen for all the experiments.

Laboratory personnel from KAUST working with the collected samples have completed required biosafety training and have acknowledged reading the standard operating procedure in the lab safety manual. The person incharge of samples transfer and storage has extensive experience working with infectious biological agents.

A Research Collaboration Agreement (RCA) between London School of Hygiene and Public Health (LSHTM) and KAUST has been signed to cover the project and amendment in the proposal have been obtained for the above mentioned changes.

Accordingly, IBEC has approved this project. Please submit your applications to IBEC for the use and/or shipping of samples as soon as possible.

We kindly ask you to inform IBEC if there is any further change to the research plan or the conditions listed above or if any new research team members join this project. It is important that you ensure that new members have completed their required biosafety training and acknowledged reading the SOP before handling infectious agents.

It is important to report any suspected laboratory acquired infection to researchsafetu@kaust.edu.sa.

IBEC wishes you and your team successful research.

Best regards,

Professor Mark Tester

IBEC Chairperson