**Hand hygiene to reducing respiratory-tract infection transmission among Umrah and Hajj pilgrims: a feasibility trial**

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**Background**

Viral respiratory tract infections (RTIs) are a major public health burden, causing serious disease, especially in vulnerable populations. Influenza-associated lower respiratory tract disease alone causes over 54 million infections per year, eight million cases of severe illness, and 145,000 fatalities across all age groups,1 and currently COVID-19 has so far affected over 82 million people with about 1.8 million deaths (as of 30 December 2020) in less than one year of its emergence.2 Ever-increasing and faster international travel intensifies the transmission of respiratory viruses, especially in mass gathering settings.3-5 Non-pharmacological interventions such as hand hygiene (HH), have been used to complement pharmacological measures such as vaccinations against influenza and now also against COVID-19, and antiviral use in the prevention and control of viral RTIs.6

Systematic reviews of observational studies and randomised controlled trials (RCTs) in community and/or healthcare settings have demonstrated the role of HH in reducing the burden of viral RTIs.7,8 Summarising cluster-RCTs, a Cochrane systematic review reveals that the spread of the respiratory virus can be prevented by hand washing, especially around younger children.9 However, the studies were mostly conducted in developed world settings, had some risk of bias and included studies that originated from non-Hajj or non-Umrah settings. A previous systematic review assessed the uptake and effectiveness of non-pharmaceutical measures among Hajj pilgrims, including HH but provided no conclusive evidence on the role of HH in preventing RTIs.10

Only limited studies have explored the uptake and effectiveness of HH interventions among Hajj pilgrims. Surveys conducted by us and others show that the uptake of HH among Hajj pilgrims is currently suboptimal but improving steadily and that surfactant-based products are more popular than alcohol-based products.11 A focused systematic review published by our team showed that of 12 observational studies that assessed the uptake of HH among Hajj pilgrims, the uptake of hand washing with surfactant-based products (e.g., soap) ranged between 32% and 90% (pooled estimate 69%), while the uptake of alcohol-based sanitisers ranged between 31% and 77% (pooled estimate 51%).12

The effectiveness of HH against RTIs was investigated in six studies.12 The endpoints used to assess the effectiveness varied widely: three studies assessed the effect on clinical respiratory illnesses,13-15 and one on cough,16 using self-reported symptoms. Of these four studies, two found hand washing with soap to be effective against respiratory illnesses,14,15 and the other two found HH to be ineffective against respiratory symptoms.13,16 Only two of six studies that assessed effectiveness considered laboratory-proven viral or bacterial infections as an endpoint using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and both studies had limitations in design.4,17 In one of these studies, the prevalence of *S. pneumoniae* was found to be lower among participants using hand sanitiser compared to those who did not (odds ratio [OR]=0.4, 95% confidence interval [CI95%]: 0.2–0.9, P=0.02).17A study conducted by our team during Hajj in 2019 showed that while pilgrims have good knowledge and practice of HH only a minority used recommended HH products, and most preferred to use soap and water; overall HH to prevent contact transmission of RTIs is underutilised.18 To this end, we would like to conduct a pilot trial to evaluate the effect of HH against contact transmission of viral RTIs, including COVID-19, MERS-CoV and influenza, among Hajj and Umrah pilgrims.

**Objectives**

*Primary aim*

1. To evaluate the efficacy of HH against laboratory-confirmed viral RTIs (including influenza, SARS-CoV-2, MERS-CoV and other respiratory viruses).

*Secondary aims*

1. To investigate the transmission pattern of influenza and SARS-CoV-2 at Umrah/Hajj by studying the genetic relatedness between circulating viruses using deep genomic sequencing.
2. To assess Umrah/Hajj pilgrims’ hand hygiene knowledge, perception, and practice.

**Material and Methods**

***Design of the trial***

This study will be a pilot trial to test the efficacy of hand hygiene in preventing acute viral RTIs influenza and COVID-19. The trial will compare the ‘*use of supervised HH’ (i.e., researchers will provide HH products and follow the participants)* versus ‘*no use of* *supervised HH’ (i.e., standard care where researchers will not provide HH products but the participants may use their own)* among domestic Umrah and Hajj pilgrims (i.e., residents of Saudi Arabia) in Makkah/Madinah during thepeakperiod of Umrah in Ramadan 2021 and 2022 or during the peak Hajj week in 2021 and 2022.

***Recruitment and Data collection Procedure***

These procedures will be implemented by study volunteers (data collectors), who will be recruited through a Health Volunteering Platform (<https://volunteer.srca.org.sa/#!/ar/home>), trained and supervised by the study investigators.

The key steps of the study procedure are illustrated in figure 1. Data collectors will approach and invite pilgrims to join the study in their accommodation facilities (hotels in Makkah/Madinah or tents in Mina) and explain the study to them. If pilgrims agree to participate, a consent form will be signed after they have been assessed for the eligibility criteria:

***Inclusion criteria***

* Domestic Umrah and Hajj pilgrims (i.e., residents of Saudi Arabia) who are: aged ≥18 years in both genders.
* Have provided signed informed consent.

***Exclusion criteria***

* Children aged <18 years.
* Participation in another clinical trial investigating a medical intervention that may interfere with study outcome measures like proven viral RTI.
* Those who have flu-like symptoms during the time of recruitment.
* Known contraindication to HH product (e.g., allergy to any component of HH product).
* Individuals not having a full mental capacity to comprehend the consent form.
* Those who refuse to sign the consent form.

The participants will be randomly assigned to study groups (control group or intervention group). Randomisation to each arm will be in a 1:1 ratio and will be done according to accommodation unit (e.g., hotels in Makkah/Madinah or tents in Mina). A topographical list of accommodation units will be prepared after determining the Umrah/Hajj service providers (e.g., Towafa, Hamlah, and hotels) and obtaining their approval to conduct the study in their sites. Randomisation lists will be generated using an online software application (Sealed Envelope Ltd. 2021) by an offsite research coordinator who will not take part in the recruitment or assessment of participants. The randomisation will be stratified by gender to ensure balanced and proportionate recruitment. Allocation to study arm will be concealed before randomisation, afterwards, the subjects will know to which group they have been assigned.

**Figure 1:** Key steps of the trial

The study volunteers will send a self-administered online baseline questionnaire (Appendix 1) onsite and ask participants to fill it out. The questionnaire will include 3 major parts: part 1 to collect relevant socio-demographic information about the participant including gender, age, education, occupation, and nationality. Part 2 will collect data about the participants’ medical history such as vaccination history and clinical information such as respiratory symptoms with duration and presence of any pre-existing medical condition; while part 3 will comprise questions related to hand hygiene knowledge, perception and practice. The knowledge question will include true/false statements about practice of hand hygiene and the sum of knowledge scores will be calculated for each participant using a scale from 0 to 6, with a higher score indicating considerable knowledge level on hand hygiene and a lower score indicating poor knowledge. Additionally, participants’ perception regarding the effects of different hand hygiene methods including against respiratory tract infections will also be captured in section 3. Finally, participants will be asked how often they used different hand hygiene products (water only, soap and water, and alcohol-based hand rubs) to clean their hands per day in 2 weeks period before they come to Makkah.

For the pilgrims who assigned to the intervention group, 100 ml of a locally available non-scented HH product (alcohol-based hand sanitiser) will be provided to use for 7 days. The product is chosen in consultation with local religious jurists, so its use does not contradict with ‘Ihram’ conditions. Written information about the instructions for correctly using the HH product will be provided to the ‘intervention group’ (Appendix 2). These educational materials will be taken from reliable health sources such as the Saudi Ministry of Health (MoH) and the World Health Organisation (WHO). Study members will also practically demonstrate the correct method of how to use the HH product and help pilgrims to clean their hands for the first time. On the other hand, no alcohol hand sanitisers will be distributed to anyone in the ‘control group’ (although they can use their own supply), and we shall hand out brochures to them containing information about the correct technique of hand hygiene.

All pilgrims will be given an electronic health diary (Appendix 3) on a daily basis for a week (7 days) to follow up on their HH practice and respiratory symptoms, which contains questions about the presence or absence of respiratory symptoms and fever and how many times and when they have washed their hands.

Initially, the data collection tools (baseline questionnaire and health diary) will be drafted in English; after which, two of the study researchers will translate them to Arabic independently. Subsequently, professional linguists will perform proofreading to carefully checking for errors in the text and fix minor spelling, punctuation mistakes, typos, and inconsistencies.

***Specimen collection and testing***

In both groups, the study team members will actively search for pilgrims suffering from respiratory infections at least once every day. A study team member will collect nasopharyngeal (NP) swab (or throat swab if an NP swab is not doable) from anyone complaining of subjective fever and cough for subsequent molecular diagnostic testing for respiratory viruses. The swab used will be a Copan nylon flocked dry nasal swab. As a part of the routine care, pilgrims in both groups will be supplied with generic medications (such as acetaminophen and ibuprofen) for fever or aches. The swabs will be stored within 2-3 hours at subzero temperature for later molecular diagnostic testing at the NSW Health Pathology - Institute for Clinical Pathology and Medical Research, Westmead Hospital (ICPMR), Westmead Hospital, NSW, Australia. Pilgrims will provide their email addresses, phone numbers and mail addresses if they wish to receive the results of the laboratory test. Multiplex RT-PCR for influenza A and B, SARS-CoV-2, MRES-CoV and other coronaviruses, parainfluenza viruses (types 1,2, 3 and 4), RSV A and B, adenoviruses, human metapneumovirus (hMPV), and picorna viruses will be performed. The study staff who will take the swab will all have been trained to achieve an appropriate sample and maintain hygienic precautions including the use of personal protective equipment.

To determine the transmission patterns of influenza viruses among Umrah and Hajj pilgrims, a complete genome sequence of influenza and SARS-CoV-2 viruses will be obtained using a next-generation sequencing protocol – using the Illumina MiSeq sequencer available at Westmead Hospital – and which will generate multiple reads per host (~1000X coverage per host; that is, ‘deep’ sequencing). All sequence data generated will be assembled and aligned using the Geneious (http://www.geneious.com) and VICUNA packages,19 with downstream phylogenetic (and other evolutionary) analysis undertaken using the Geneious, Seminator,20 and PhyML packages.21 With these data in hand we will be able to determine; (i) whether the study participants were infected prior to or during their Umrah or Hajj attendance, (ii) whether there was a direct viral transmission among the study participants (such that they harbor both ‘majority’ and ‘minority’ genetic variants), and (iii) if direct transmission is established whether this occurs more frequently in the intervention versus control groups. Respiratory samples will not be stored or banked for more than it is necessary (e.g., to revalidate any result). Any leftover sample will be disposed according to the standard operating procedure of the ICPMR.

***Data management and analysis***

To ensure the confidentiality of participants, all responses from the baseline questionnaires and daily health forms will be recorded and stored on a highly protected cloud-based survey application (Microsoft Forms). Apart from investigators or their authorised delegates, no one else will have access to the records. All data will be destroyed in about 10 years and disposed as per the KAMC data management guideline.

All the collected data in the software will be exported to a master Excel spreadsheet for cleaning and coding before importing to Statistical Package for Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, version 26.0, IBM Corp, Armonk, NY, USA).

Frequencies and percentages will be used to present the categorical variables, while the mean (or median with range) ± standard deviation (SD) will be used to summarise continuous variables. A p-value ≤ 0.05 will be considered to be statistically significant. Exploratory multivariable analyses will examine the effect of randomised treatment on outcomes in models adjusted for demographic factors, HH use and compliance with treatment. Subgroup analyses will be attempted to compare the effect of treatment between groups of participants: male vs. female, those with known risk factors vs. those without risk factors or risk status unknown for viral respiratory infections, vaccinated against influenza and COVID-19 vs. unvaccinated (or vaccination status reported as unknown), smoker vs. non-smoker, and by pilgrim’s country of origin.

Data available from questionnaires, diaries and laboratory tests will be analysed anonymously to examine whether HH use makes a significant difference in reducing the frequency of laboratory-confirmed respiratory virus infection (including influenza, coronavirus or other respiratory viruses). The primary endpoints (effectiveness and efficacy of HH against clinical and laboratory-confirmed viruses respectively) will be analysed by intention to treat.

The self-reported uptake rates of vaccination against influenza and COVID-19 will be determined and vaccine effectiveness will be estimated based on the case-negative case-control methodology. The results from the genomic sequencing of influenza and SARS-CoV-2 viruses will assist us in understanding the genetic relatedness of circulating virus strains at Hajj and the transmission pattern of these viruses among pilgrims.

***Sample size calculation***

Assuming that the prevalence of symptomatic RTIs is 30% in the controls and the prevalence of laboratory-proven viral RTIs in controls is approximately 12% the HH arm could be considered clinically worthwhile if it can reduce the prevalence of syndromic or proven viral RTI by 50%.22,23

Assuming a moderate intra-cluster correlation of 10% and a mean of 75 participants per cluster, and inflating the sample by a factor of 8.4 to account for clustering, the sample size required for an ideal cluster RCT to detect a reduction from 12% to 6% with 80% power at 5% significance is 3000 per arm. However, this being a pilot trial, from our previous experience, one-tenth of it i.e., about 300 participants in each arm (totaling 600) would provide just sufficient sample for pilot analysis. It is expected that about 15% of these will be symptomatic thus roughly about 100 samples will be available for virological analysis.

***Publication policy***

We expect to publish a synopsis of the research results in KAMC website, this will not have any named data, and all participants will have access to this. Any participant interested to know about the study outcome in general, and outcomes of his or her laboratory tests will be provided the results only via postal mail in order to avoid breach of privacy.

 The results of this study will be submitted for publication to an established high-impact peer-reviewed medical journal, and again no named/identifiable data will appear in any public domain.

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