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Commentary

Influenza vaccination for Hajj for the next decade: A case for quadrivalent SH vaccine

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1. Introduction

Respiratory infections are common among Hajj pilgrims with nearly 60% reporting sick due to respiratory complaints [1]. Intense crowding (3–4 persons/m^2) of pilgrims, drawn from more than 185 countries, especially while circumambulating the holy Kaaba (Tawaaf) is conducive to acquiring and spread of acute respiratory infections (ARI) with a high attack rate (4–15%) [2]. Influenza virus is one of the commonest pathogens causing ARI in Hajis, with a reported prevalence of 4.5–13.9% [3–6]. Returing Hajj pilgrims are known to carry influenza viruses at times of low or no activity of influenza at home [7,8].

1.1. Seasonality of influenza in countries of origin and implications for spread of influenza in Hajj

Hajj pilgrims include foreign and domestic (Saudi, non-Saudi) pilgrims, the former registering a steep 2824 percent increase from 58,000 in 1920s to about 1.7 million in 2012 [9]. An undocumented number of natives/expats also join unofficially. The pilgrims come from different countries and geographies with diverse patterns of influenza circulation (Tables 1 and 2).

Hajj, scheduled in the last month of the Muslim lunar calendar, for the next decade, would fall in the months of April to August. These months demonstrate a higher influenza activity in the Southern hemisphere (SH) and in tropical/subtropical regions. Influenza circulation in the tropics and subtropics reveals a complex seasonal pattern with year-round circulation in some areas and biannual peaks in others. Surveillance data of 3,36,098 samples from 9 countries in South and South East Asia (Japan, Northern China, Southern China, Singapore, the Philippines, Thailand, India, Lao PDR, Cambodia, and Malaysia) revealed a latitude related pattern of circulation [10]. Influenza A circulation predominated between November and March during winters in areas lying above 30°N latitude, during monsoon months of June–November in areas between 10° and 30°N latitude, and exhibited no specific seasonality in areas lying closer to the equator. Influenza B matched influenza A seasonality in areas lying above 30°N latitude; whereas in areas south of 30°N Asia, influenza B circulated year round with less pronounced peaks during post-monsoon period [10]. Large land-mass countries (India, China) exhibit latitude related subregional variations [10–12] whereas countries like Indonesia, Malaysia, Singapore and Vietnam (near equator) exhibit year-round influenza activity [13].

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Table 1
showing the countries with the highest number of pilgrims for Hajj 2018, along with their latitudes, and the pattern of seasonality according to WHO flunet. NH: Northern hemispherical seasonality, SH = Southern hemispherical seasonality. Data of pilgrim numbers sourced from: Countries with highest number of Hajj pilgrims in 2017.

S. No	Country	Number of Pilgrims	Latitude	Pattern of influenza seasonality
1	Indonesia	221,000	-0.789^0	Year round
2	Pakistan	179,210	30.37^0	NH
3	India	170,000	20.59^0	SH*
4	Bangladesh	127,198	23.68^0	SH
5	Egypt	108,000	26.82^0	NH
6	Iran	86,000	32.43^0	NH
7	Nigeria	79,000	9.08^0	Year around
8	Turkey	79,000	-8.97^0	NH
9	Algeria	36,000	36.75^0	NH
10	Morocco	31,000	31.79^0	NH

Table 2
Countries Groups contributing to the Hajj 2018 (Data from Hajj Statistics 2018-1439. General Authority for Statistics, Kingdom of Saudi Arabia.).

Countries Groups	Number of Pilgrims (1439H)
GCC countries	35,794
Arab countries excluding GCC Countries	465,510
Asian countries excluding Arab Countries	1,083,528
African countries excluding Arab Countries	167, 959
European countries	89,368
North and South America countries and Australia	25,519
Total	1,867,678

While large number of pilgrims also originate from the GCC and African countries, scant data exist on circulations patterns of influenza there. Flunet data on the spatio-temporal patterns of seasonal influenza activity in 17 countries of the Middle East and North Africa (Afghanistan, Armenia, Bahrain, Algeria, Egypt, Georgia, Israel, Iraq, Iran, Jordan, Lebanon, Morocco, Oman, Pakistan, Qatar, Tunisia and Turkey) during 6 consecutive seasons (2010–2011 to 2015–2016), revealed a NH pattern of seasonality for most countries, with dominant primary peaks between January and March and no or nearly undetectable secondary peaks [14]. Jordan, however, exhibited a secondary peak in April whereas Bahrain and Qatar, located in the south-eastern part of the Arabian Peninsula, demonstrated earlier primary peaks (in November/December) and a very clear secondary peak in March, while Oman, located nearby, having two peaks with very similar amplitudes in January and April [14]. Limited data from Nigeria suggest an year-round circulation, whereas whatever data are available from large countries like Saudi Arabia, Yemen and Sudan, do not clearly depict a clear pattern of circulation.

1.2. Co-circulation of influenza A and B, two lineages of influenza B and the vaccine mismatch

Influenza B often co-circulates with influenza A and can be the dominant circulating virus in some seasons. The seasonality of influenza B is different from that of influenza A from the areas that contribute to the largest contingent of the pilgrims for Hajj [13]. In the Global Influenza B study (GIBS) that studied characteristics of influenza B in 26 countries from NH (n = 7), SH (n = 5) and the inter-tropical belt (n = 14) from 200 to 2013, influenza B contributed to a median of 22.6% of the 935 673 influenza cases, being <20% in 90 seasons, 20–50% in 82 seasons and $\geq$ 50% in 28 seasons [15]. The proportion of influenza B was 17·8% in 39 seasons in the SH, 24·3% of 94 seasons in the inter-tropical belt, and 21·4% in 67 seasons in the NH. During the seasons of co-circulation (>20% of total detections) or dominant circulation of influenza B; B/Victoria and B/Yamagata predominated in 64% and 36% of seasons, respectively [15]. In Indonesia, influenza B was seen in 36% of the 3653 influenza detections from 2003 to 2007. In a more recent literature review of influenza B circulation in 15 countries from the Asia-Pacific region including Indonesia and Malaysia [16], influenza B circulated in a varying proportion (0–92%) in different seasons. Pre-Hajj global influenza activity based on reported data to FluNet for the period from 16 April 2018 to 29 April 2018 revealed a circulation of influenza viruses that included influenza A (56%) as well as influenza B (44%) [17]. Of the current global influenza activity, 1503 (54.6%) of the influenza A viruses were influenza A/H1N1pdm09 and 1252 (45.4%) were influenza A/H3N2 whereas of the characterized B viruses, 428 (84.9%) were of the B/Yamagata lineage and 76 (15.1%) were of the B/Victoria lineage [17]. Pertinently, influenza B causes similar morbidity as influenza A [18] and can result in more hospitalizations than influenza A across all age groups.

Even as vaccination is the best strategy for prevention of influenza, mismatch between the vaccine strains and circulating strains are common. Mismatching between the circulating and trivalent influenza vaccine (TIV) strains between 2003 and 2014 was reported in both NH and SH regions, ranging from 3% to 68% [19]. More recently, Jennings et al in a literature review of influenza circulation from 15 countries from the Asia Pacific region, reported co-circulation of influenza B in all seasons, constituting 0–92% of the influenza virus strains, with a co-circulation of the B/Yamagata and B/Victoria lineages and a consequent mismatch with the TIV [16]. The earlier GIBS study demonstrated a high (upto 24–25%) mismatch in 11 of 36 seasons in the NH (31%), six of 22 seasons in the SH (27%), and two of 21 seasons in the inter-tropical belt (10% or 14%) [15]. A mismatch of the TIV vaccine was responsible for 42% of all influenza B infections throughout 12 seasons since 1992 in Hajj [20].

1.3. Recommendations for influenza vaccination and adherence and challenges to adherence

Vaccination is recommended as a standard measure for Hajj pilgrims, especially those at high risk for complications of influenza. In a systematic review of reported that despite mismatching, TIV was efficacious against laboratory-confirmed influenza with the pooled efficacy of 56% (95% CI 43% to 66%) [21]. Enhanced vaccination rates are expected to result in higher benefit herd immunity, especially in case of a vaccine match.

Despite the recommendations, the vaccine uptake has, however, been variable ranging from 30% during the pandemic year to about 89% among Australian pilgrims in 2012 [22]. Background seasonality and vaccination status likely affect the incidence of respiratory infection in Hajj. In a study comparing incidence of ARI among Saudi pilgrims and those from UK, the incidence of influenza was 10% in Saudi pilgrims and 7% and 14% among vaccinated and unvaccinated pilgrims from the UK, respectively [4].

Importantly supported national influenza immunization programs do not exist in countries like Indonesia, Malaysia, India, Pakistan and Bangladesh that contribute to bulk of the foreign pilgrims. The vaccine uptake is poor even in high risk populations like health care workers, pregnancy, or those with chronic conditions consequent on a number of barriers that include differences in climate and geographical conditions at sub-regional level, poor awareness about vaccine, poor education, misperceptions and misconceptions about safety and efficacy of the influenza vaccine and economic considerations [23].

1.4. A case for a quadrivalent SH influenza vaccine for the next decade

Co-circulation of the 2 lineages in variable proportion in most of seasons in countries of the origin of the pilgrims results in mismatch of lineage between the circulating influenza B virus and the TIV. The B/Yamagata and B/Victoria lineages of the influenza B virus are antigenically distinct and vaccines against one lineage induce low levels of cross protection against the other lineage. Against this backdrop, it makes sense to recommend a quadrivalent influenza vaccine (QIV) rather than a TIV. However, the relatively lower prevalence of influenza B in Hajj in the recent years strongly argues for adoption of other preventive measures like hand washing, nasal masks, etc to reduce the burden of influenza at Hajj.

Against this backdrop, the Government of Saudi Arabia could consider recommending routine administration of SH QIV vaccine to Hajj pilgrims from all countries for the next decade. This would entail procurement of the SH vaccine by health authorities in countries/geographies that normally follow a NH vaccination schedule (like the North American and European continents and areas north of 30° latitude). There is an expected additional value of SH vaccine in those who previously received the NH vaccine as the protective antibody titres would have expectedly fallen and there is an additional possibility of a changed strain of the vaccine with an obvious added advantage of the vaccination. Hence recommending procurement and administration of the SH QIV vaccine for prospective pilgrims from diverse geographies seems the likely way forward for Hajj pilgrims arriving into coming to Saudi Arabia for the next decade.

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Declaration of competing interest

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Author contributions

PAK conceived the project. NKB and HPK performed the literature search and contributed to the data compilation and initial write-up of the manuscript. All the authors approved the final version for submission and take responsibility for the manuscript.

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