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Acute respiratory tract infection symptoms and the uptake of dual influenza and pneumococcal vaccines among Hajj pilgrims

Najim Zafer[1]*, Camille Dulong[2]*, Adib Rahman[3, 4]*, Mohamed Tashani[3, 5, 6], Mohammad Alfelali[3, 7], Amani Salem Alqahtani[3, 8], Osamah Barasheed[3, 9], Mohammad Hassan Emamian[10], Harunor Rashid[3, 5, 11, 12]

[1]Department of Family and Community Medicine, Faculty of Medicine, University of Jeddah, Jeddah, Saudi Arabia
[2]Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, ON, Canada
[3]National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead, New South Wales, Australia
[4]The University of Queensland, Faculty of Medicine, Herston, Queensland, Australia
[5]Discipline of Child and Adolescent Health, The Children's Hospital at Westmead Clinical School, The University of Sydney, NSW, Australia
[6]Faculty of Medicine, University of Tripoli, Ain Zara, Tripoli, Libya
[7]Department of Family and Community Medicine, Faculty of Medicine in Rabigh, King Abdulaziz University, Jeddah, Saudi Arabia
[8]Saudi Food and Drug Authority, Riyadh, Saudi Arabia
[9]Research Centre, King Abdullah Medical City (KAMC), Makkah, Saudi Arabia
[10]Department of Epidemiology, School of Public Health, Shahroud University of Medical Sciences, Shahroud, Iran
[11]Marie Bashir Institute for Infectious Diseases and Biosecurity, School of Biological Sciences and Sydney Medical School, University of Sydney, Australia
[12]WHO Collaborating Centre for Mass Gatherings and High Consequence/High Visibility Events, Flinders University, Adelaide, Australia

ABSTRACT

Background: *Hajj pilgrims are encouraged to take influenza and pneumococcal vaccines prior to their travel to safeguard against acute respiratory tract infections (ARTIs). It is unclear whether dual immunisation with influenza and pneumococcal vaccines have had any impact on ARTI symptoms. To this end, we have examined the data of the last several years to assess whether combined influenza and pneumococcal vaccination has affected the rate of ARTI symptoms among Hajj pilgrims.*

Materials and methods: *Hajj pilgrims from United Kingdom, Australia, Saudi Arabia and Qatar who attended the congregation between 2005 and 2015 were included in this study. Data from surveillance studies or clinical trials involving Hajj pilgrims were used. In this analysis we have made use of the raw data to construct a trend line graph with the prevalence of combined cough and fever (as a proxy for ARTI) against the uptake of combined influenza and pneumococcal vaccines, and to estimate the relative risk (RR) of ARTI with 95% confidence interval (95% CI).*

Results: *Data of a pooled sample of 9350 pilgrims, aged 0.5–90 years with a male to female ratio of 1.1, were analysed. Although vaccination uptake did not rise significantly over the years, there was also no observed meaningful benefit of combined vaccination (RR = 1.1; 95% CI 0.8–1.4), the rates of ARTI symptoms demonstrated a decline over the last several years. The findings of this analysis highlight that the prevalence of 'cough and fever' among Hajj pilgrims is on decline but the uptake of combined influenza and pneumococcal vaccines remains unchanged over years, and the decline can not be attributed to dual influenza and pneumococcal vaccination.*

Conclusions: *Acute respiratory tract infections among Hajj pilgrims are decreasing, it is unclear if the reduction is due to vaccine uptake, but the data and analysis have some limitations.*

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Key words: acute respiratory tract infection, Hajj, influenza vaccine, mass gathering, pneumococcal vaccine

✉ Harunor Rashid, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), Kids Research Institute at The Children's Hospital at Westmead, Cnr Hawkesbury Road and Hainsworth Street, Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia, tel: +61 29845 1489, fax: +61 29845 1418, e-mail: harunor.rashid@health.nsw.gov.au

*Made equal contributions to the manuscript.

INTRODUCTION

Hajj is the largest annual religious mass gathering (MG) in which 2 to 3 million people assemble from different parts of the world in Makkah, the holiest city of Islam in the Kingdom of Saudi Arabia [1]. This event is spiritually significant for Muslims, being one of the five basic tenets of Islam and is found to increase belief in the quality and harmony among ethnic groups [2]. For over fourteen centuries, following the tradition of patriarch Abraham, Muslims from all corners of the world have been congregating in Makkah on specific dates of the 'Hajj month', the last month of the Arabic calendar [3]. Adult Muslims who are capable, both financially and physically, consider it a mandatory part of their religious duty to perform Hajj at least once in lifetime.

In this annual MG of more than two million people, the risk of communicable diseases is high [4]. Several large intercontinental outbreaks of infectious diseases have been linked to Hajj attendance [3–5]. Vaccinations against certain infections are routinely recommended for Hajj pilgrims, tour group officials, volunteers, healthcare workers, para-troops and seasonal workers [6]. Vaccination against four meningococcal serogroups (A, C, W, and Y) is mandatory for all Hajj pilgrims and the local residents of pilgrimage sites [7]. Following the vaccination policy, the incidence of the laboratory-confirmed meningococcal disease has declined significantly not only among pilgrims but also among residents [8]. Acute respiratory tract infections (ARTIs) can be caused by bacteria (e.g., *Streptococcus pneumoniae*), viruses (e.g., influenza) and other microbes. Children, elderly and individuals with lung and heart diseases, or other pre-existing medical conditions are at a higher risk of suffering from ARTIs. The risk of ARTIs, viral or bacterial, amplifies several times at Hajj [9]. In fact ARTIs are the leading causes of hospital attendance and admission among Hajj pilgrims [10]. Influenza and pneumococcal vaccines are viewed as the key preventive measures against these potentially serious diseases [11, 12]. The role of seasonal influenza vaccination in Hajj pilgrims is established [13, 14], but the role of combined influenza and pneumococcal vaccination in reducing ARTIs has not been assessed in a sufficiently large sample. To this end, we have examined the data of the last several Hajj years to assess whether dual influenza and pneumococcal vaccination has had any effect on the rate of ARTI among Hajj pilgrims.

Thus, the objectives of this study are to examine the frequency of ARTI symptoms and the uptake of influenza and pneumococcal vaccines among Hajj pilgrims, and to evaluate the effect of dual influenza and pneumococcal vaccination on ARTIs among Hajj pilgrims.

MATERIALS AND METHODS

DATA SYNTHESIS

The dataset used here comes from a database held by the senior authors of this publication at the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children's Hospital at Westmead, New South Wales, Australia). The database contains data from various surveys, surveillance studies and clinical trials involving Hajj pilgrims from Qatar, Saudi Arabia, Australia and United Kingdom conducted between 2005 and 2017. In the database, data for some years were incomplete or absent for this analysis. For instance, no, or only partial data (for this analysis) were available for the years 2006, 2008–2010, 2016 and 2017. For the pandemic year (2009), the data were retrieved from a published study [15], which provided data on participant demographics, uptake rate of influenza and pneumococcal vaccines, and prevalence of cough and fever symptoms. The study types, participant nationalities and Hajj years of the studies from where data have been used for this analysis are summarised in Figure 1.

Individual subject data for the included years 2005, 2007 and 2011–2015 were imported and combined in

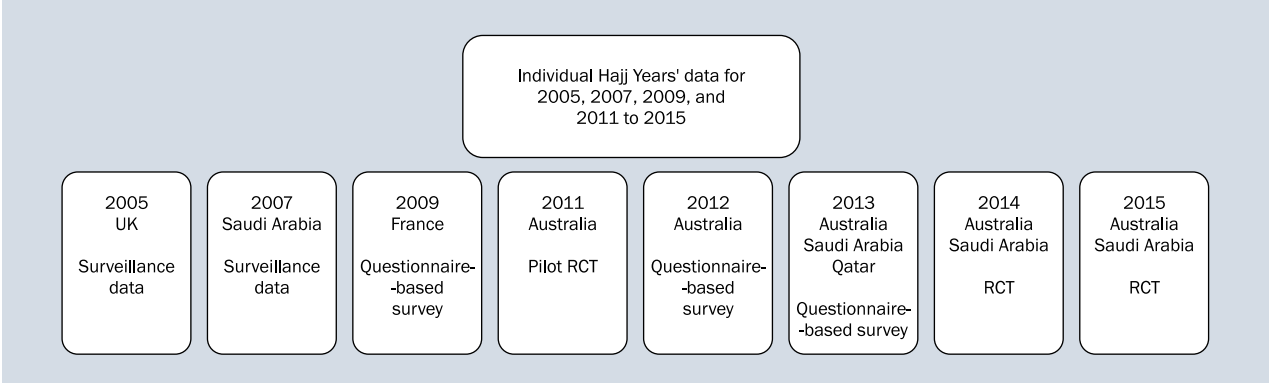

Figure 1. Studies from where individual subject data were collected for this analysis; RCT — randomised controlled trial

a MS Excel sheet for analysis. ARTI was defined as a combination of 'cough and fever'; such a definition was chosen because it contains a symptom of the lower respiratory tract (i.e., cough) and a constitutional symptom (i.e., fever) and covers two of the key symptoms produced by both influenza and pneumococcus. The rates of combined cough and fever (as proxy for ARTI) were plotted against the uptake rates of combined influenza and pneumococcal vaccines to construct a trend line graph. The relative risk (RR) of acquisition of ARTI among vaccinated versus unvaccinated pilgrims was estimated for each year with 95% confidence interval (95% CI) and finally for the pooled data. 'At risk' pilgrims were defined as those who were aged ≥ 65 years and/or had pre-existing medical conditions including heart, lung, kidney, liver, and neurological conditions and persons who were immunocompromised, including those with HIV infection, malignancy, functional or anatomical asplenia (which includes sickle cell disease, other haemoglobinopathies, congenital or acquired asplenia, splenic dysfunction), or chronic steroid users.

ETHICS APPROVAL

Ethical approval for the years 2013–2015 was obtained in Saudi Arabia from the Institutional Review Board (IRB) of King Abdullah Medical City, Makkah, (IRB Reference No: 15-205), in Australia from the Hunter New England Human Research Ethics Committee (HNEHREC Reference No: 13/07/17/3.04), and in Qatar from the Joint Institutional Review Board of Hamad Medical Corporation/Weill Cornell Medical College (JIRB Reference No: 13-00039). Ethics approvals for the other years were obtained from appropriate authorities in the UK (Reference No: MREC 02/2/12), Saudi Arabia (Reference No: KACST: H-01-R-012) and Australia (HREC Reference No: 11/SCHN/162).

RESULTS

The pooled sample size was 9350; in individual years or studies, the sample size varied considerably from 164 to 4428 (Table 1). The pilgrims' age ranged between 0.5 years and 95 years with comparable age range across the studies. Median ages across individual studies fell within the age band of 34–49 years. In the pooled sample male to female ratio was 1.1, but the ratio varied considerably across the years: males outnumbered females in the years 2005, 2007, 2012, and 2013, whereas in the remaining years females outnumbered males (Table 1). Overall, 19.2% of pilgrims were 'at risk', but this proportion varied from 12.8% in 2013 to 27.8% in 2005.

The uptake of combined influenza and pneumococcal vaccines ranged from 0.32% in 2007 to 24.4% in 2012, with the mean of 13.8% in the pooled sample with no significant trend of change (R^2 = 0.5), but the rate of ARTI (i.e., combined cough and fever) ranged from 2.2% in 2014 and 2.9% in 2015 to 46.3% in 2005 with the mean rate of 5.3% in the pooled sample and showed an overall declining trend (R^2 = 0.8) (Fig. 2). However, when the prevalence of ARTIs was computed against the uptake of vaccination, the RR showed a high variability from being ineffective in 2011 (RR 1.9, 95% CI 1.1–3.17) and 2014 (HR 2.2, 95% CI 1.1–4.5) to being effective in 2009 (RR 0.2, 95% CI 0.06–0.73), in the other years no significant effectiveness (or ineffectiveness) of vaccination was observed, and in the pooled sample vaccination was not effective (RR 1.1, 95% CI 0.8–1.4) (Table 1).

DISCUSSION

The findings of this analysis highlight that the prevalence of 'cough and fever' among Hajj pilgrims is on decline but the uptake of combined influenza and pneumococcal vaccines remains unchanged over years (Fig. 2), and the decline can not be attributed to dual vaccination (RR = 1.1, 95% CI 0.8–1.4).

The decline in the prevalence of cough and fever symptoms could be purely because of influenza vaccination as was seen in previous analyses, including a meta-analysis of six studies (RR 0.56, 95% CI 0.41–0.75, $p < 0.001$) [13, 14, 16], or because of overall improvement in infection control programmes [17], or because of change in Hajj seasons from colder months a decade ago to warmer months in recent years, or it just could be an inexplicable chance finding.

Although no protective effect of dual influenza and pneumococcal vaccination was observed in this analysis, benefit of dual vaccination was noted in a cohort study involving 295 Iranian pilgrims during the Hajj 2005 when a significant reduction in the duration of cough, by almost 6 days, was noticed compared to no vaccination ($p < 0.01$) [18]. Beneficial effect was also noted in the French study included in this synthesis where fever was less frequently reported in pilgrims who were vaccinated against pneumococcal disease (plus influenza) (8.3% vs. 14.6%; RR = 0.22, 95% CI 0.06–0.73) [15].

Lack of apparent benefit of dual influenza and pneumococcal vaccination against ARTI may have stemmed from several reasons: a) in our analysis 'cough' and 'fever' have been used a proxy for ARTIs but those two symptoms may represent an array of respiratory and non-respiratory conditions not just influenza and pneumonia; b) only a small proportion of pilgrims (13.8%) received both vaccines, this small vaccination rate may not have a discernible impact on two common respiratory symptoms; c) the pneumococcal vaccine used here is a 23-valent polysaccharide vaccine which is primarily used to protect against invasive pneumococcal disease not necessarily pneumococcal pneumonia [19]. Systematic reviews of studies involving non-Hajj settings consistently showed that dual influenza

Table 1. Summary of the included raw data

	Hajj year								
	2005	**2007**	**2009**	**2011**	**2012**	**2013**	**2014**	**2015**	**Total**
1st day of Hajj	19th January	18th December	25th November	4th November	24th October	13th October	3rd October	22nd October	
Country	United Kingdom	Saudi Arabia	France	Australia	Australia	Australia, Saudi Arabia and Qatar	Australia and Saudi Arabia	Australia and Saudi Arabia	All included countries
Sample size	205	312	274	164	553	1180	2234	4428	9350
Male Female	9.3 1	1.3 1	1.1 1	1 1.3	1.8 1	1.9 1	1 1.4	1 1	1.1 1
Age range [years] (median)	01–83 (43)	0.5–90 (45.25)	23–83 (mean 58)	17–80 (48.9)	12–82 (47.4)	18–95 (36)	18–95 (34)	18–88 (36)	0.5–95
At risk pilgrims	57 (27.8%)	50 (16%)	135 (49.3%)	36 (22%)	103 (18.6%)	151 (12.8%)	353 (15.8%)	948 (21.4%)	2151 (23%)
Flu vaccine uptake	56 (27.3%)	22 (7.1%)	267 (97.4%)	111 (67.7%)	488 (88.3%)	242 (20.5%)	936 (41.9%)	2638 (59.6%)	4760 (51.2%)
Pneumococcal vaccine uptake	10 (4.9%)	1 (0.3%)	86 (31.4%)	46 (28.1%)	149 (26.9%)	67 (5.7%)	275 (12.3%)	535 (12.1%)	1169 (15.2%)
Flu and pneumococcal vaccine uptake	7 (3.4%)	1 (0.3%)	86 (31.4%)#	40 (24.4%)	135 (24.4%)	37 (3.1%)	203 (9.1%)	411 (9.3%)	920 (13.8%)
Fever*	8	132	30	57	57	N/A	N/A	N/A	284
Cough*	51	175	133	78	191	N/A	N/A	N/A	637
ARTI	95 (46.3%)	78 (25%)	30 (10.9%)†	44 (26.8%)	41 (7.4%)	35 (3%)	49 (2.2%)	124 (2.8%)	496 (5.3%)
RR (95% CI)	0.6 (0.1–2.0)	0.9 (0.1–11.0)	0.2 (0.06–0.73)	1.9 (1.1–3.17)	0.8 (0.4–1.7)	0.9 (0.1–6.4)	2.2 (1.1–4.5)	0.9 (0.5–1.7)	1.1 (0.8–1.4)

*For the Hajj 2013, 2014 and 2015, the data have been derived from a cluster randomised controlled trial; data on individual symptom (e.g., cough and fever) were not available, but data on combined 'fever and cough' were.
#In this study 97.4% were vaccinated against seasonal flu plus 5.8% against A(H1N1)pdm09, and 31.4% against pneumococcus. It was not mentioned precisely how many received both flu and pneumococcal vaccines. So we considered that all (100%) received flu vaccine, and the uptake of combined flu and pneumococcal vaccine was estimated to be 31.4%.
†It was estimated that of all those who complained of subjective fever, 10.9% had also cough, and 8% had a triad of cough, sore throat and fever.
ARTI — acute respiratory tract infections; N/A — not available; RR — relative risk

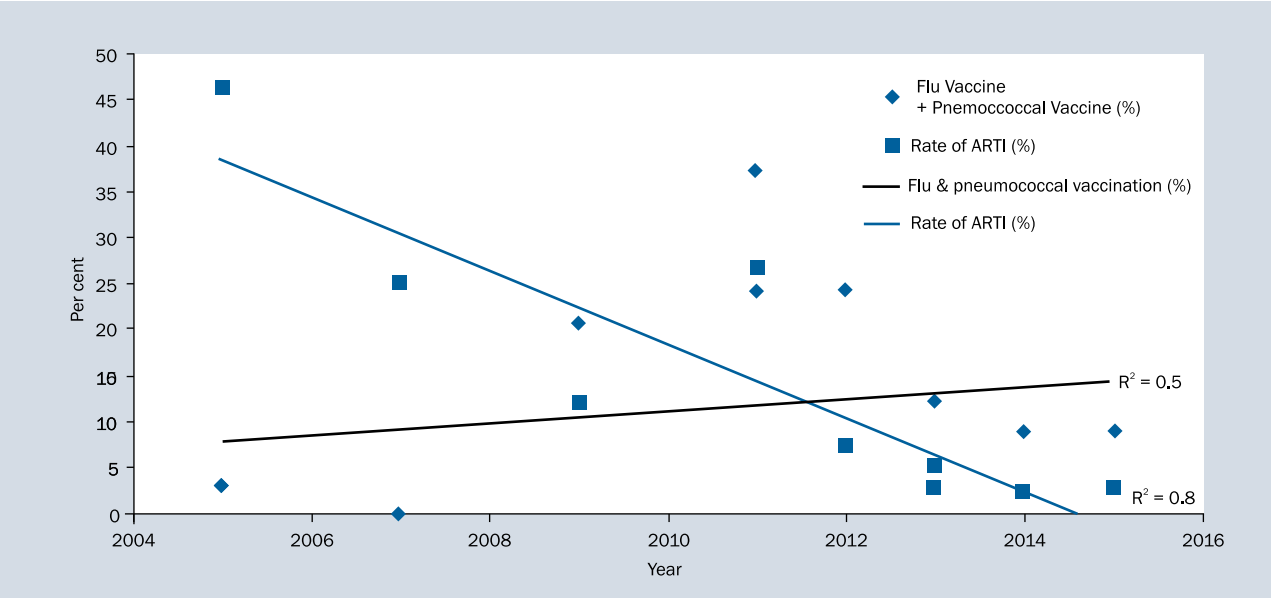

Figure 2. Line diagram showing the prevalence of cough and fever (proxy for acute respiratory tract infections [ARTIs]) against the uptake of combined influenza and pneumococcal vaccines among Hajj pilgrims (the vaccination rate did not increase significantly, however, the prevalence of cough and fever decreased)

and pneumococcal vaccination is associated with a significantly lower pneumonia rate and significantly lower pneumonia-associated mortality than influenza vaccination alone [20, 21]. No apparent effect of combined influenza and pneumonia vaccines among Hajj pilgrims observed in this analysis, compared to significant effect of influenza vaccine alone observed in other analyses, brings this synthesis into question. Despite this non-conclusive finding vaccinations are highly desirable. Serious epidemics such as the outbreaks of meningococcal group A in 1987 and then group W in 2000–2001 have been brought under control by mandatory vaccinations [5, 22], actually the effect was so sustained that the mean annual meningococcal disease rates decreased from 0.20 cases/100,000 in pre-epidemic era to 0.06 cases/100,000 in post-epidemic period and mean numbers of Hajj-related cases from 13 to 2 cases/year ($p < 0.01$) [8].

In this analysis the uptake of combined influenza and pneumococcal vaccines among Hajj pilgrims was poor. Recommendation of these vaccines for pilgrims also varies while the routine use of influenza vaccination is considered very important (even mandatory by some authorities) [11], pneumococcal vaccine is primarily considered for 'at risk' pilgrims [12, 23]. Hence individually, even though influenza vaccination rate has increased over the years in pilgrims from resource-rich countries [13, 24, 25], the uptake of pneumococcal vaccine remains suboptimal [26, 27]. Lack of awareness about the availability of the vaccines was the main reason for non-receipt of pneumococcal vaccine [28].

It is surprisingly disappointing to note that in 2 years (2011 and 2014), receipt of influenza and pneumococcal vaccines was associated with a significant risk of ARTIs (Table 1). The reason for this paradoxical finding is unclear but the analysis has major limitations. First: smaller sample sizes in some years (e.g., in 2011 and 2005) are significant limitations. Data are unavailable for the years 2006, 2008, 2009, 2010, 2016 and 2017, and the 2009 data have been obtained from a published study where the definition of ARTI has deviated slightly from the rest of the analysis [15]. The constructed trend line, therefore, would not represent the real effect of vaccinations on ARTI. Furthermore, some data generated from clinical trials that examined the effect of an intervention (e.g., facemask) [29, 30], so the observed effect (decline in ARTI prevalence) could also be attributed to the effect of those interventions.

Second: there are variations in the participants' gender in the studied sample; it was skewed towards male gender in some years (2005, 2007, 2012, and 2013) and towards female in the other years. However, this variation was buffered in the pooled sample where female to male ratio was close to one.

Third: although pneumococcal vaccine is mostly recommended for Hajj pilgrims aged ≥ 65 years and individuals with pre-existing medical conditions [12], this analysis encompassed individuals of all age groups and irrespective of risk conditions; therefore, does not indicate a true relationship between pneumococcal vaccination and ARTI.

Fourth: ARTI was defined by a presence of cough and subjective fever. These symptoms could be caused by

viruses and bacterial infections besides influenza and pneumococci; sensitivity and specificity of this definition may not be optimum.

Fifth: vaccination data are subject to recall bias since the data were obtained by asking pilgrims about their vaccination history, not from their medical or vaccination records. This affects the validity of the data.

Sixth: the original studies from where these data were obtained differed widely in their designs (i.e., surveillance data, questionnaire-based survey, pilot clinical trial, and randomised controlled trial). This variation may have affected the quality of the aggregated data.

Seventh: the last 2 years (2014, 2015) disproportionately represented a large proportion (73.4%) of the pooled data skewing the results.

Finally, the studies were conducted in different seasons involving varying populations with varying health behaviours, nutritional status, immunity and background pre-existing illnesses compromising the homogeneity of the data and quality of the synthesis.

Despite these limitations, there are a couple of unique strengths of this study. This is the first ever analysis of dual influenza and pneumococcal vaccination among Hajj pilgrims with a relatively large sample of over 9000 pilgrims, and a large part of the data have been taken from meticulously conducted clinical trials (2013–2015, and 2011).

The pneumococcal vaccine studied here is a 23-valent polysaccharide vaccine, currently conjugate pneumococcal vaccines of different valencies covering 7, 10 and 13 serotypes are available [31]. The effectiveness of the newer conjugate vaccines against ARTI among Hajj pilgrims remains unclear at this stage but the significant burden of pneumococcal disease at Hajj means that such vaccines will make a difference [32].

CONCLUSIONS

The risk of ARTI against the uptake of influenza and pneumococcal vaccines among Hajj pilgrims is still unclear. The coverage of these vaccines together is very low, but the prevalence of 'cough and fever' seems to have declined in the last several years. The data and their synthesis have limitations, so it is not known whether the decline in prevalence is due to slight (non-significant) increase in vaccine coverage or because of other factors. Further studies with more validated and homogenous data are needed to dispel the myth.

CONFLICT OF INTEREST

Harunor Rashid has received fees from Pfizer, Sanofi and Novartis for consulting or serving on an advisory board. The other authors have no competing interests to declare.

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