

Original Article

Consensus statements for influenza awareness, prevention, and vaccination in Pakistan

Bushra Jamil¹, Raeeffuddin Ahmed¹, Uzma Bashir², Shobha Luxmi³, Samreen Kulsoom⁴, Saadia Ashraf⁵, Muhammad H Hamid⁶, Fawad Farooq⁷, Ainan Arshad¹, Altaf Hussain⁸, Tabrez Ali⁹

¹ Department of Medicine, The Aga Khan Medical University Hospital, Karachi, Pakistan

² National Professional Officer (NPO), World Health Organization, Islamabad, Pakistan

³ Department of Infectious Disease, National Institute of Cardiovascular Diseases, Karachi, Pakistan

⁴ Department of Paediatric Infectious Diseases, Sind Institute of Infectious Diseases, Karachi, Pakistan

⁵ Department of Pulmonology and Critical Care, Khyber Teaching Hospital / Khyber Medical College, Peshawar, Pakistan

⁶ Department of Paediatric Medicine, King Edward Medical University and Mayo Hospital, Lahore, Pakistan

⁷ Department of Cardiology, National Institute of Cardiovascular Diseases, Karachi, Pakistan

⁸ Department of Otolaryngology, Head and Neck Surgery, Pakistan Institute of Medical Sciences, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan

⁹ Department of Medical Affairs, Established Pharmaceutical Division, Abbott Laboratories (Pakistan) Limited, Karachi, Pakistan

Abstract

Introduction: Influenza is a serious underestimated viral infection in Pakistan and influenza vaccination and vaccination awareness are low. The current work aimed to develop consensus on influenza epidemiology, prevention, vaccination, and awareness in Pakistan.

Methodology: A systematic literature search was conducted to develop recommendations on influenza vaccines in Pakistan. Experts' feedback was incorporated using the modified Delphi method. A three-step process was used, with 18 experts from different specialties from Pakistan who participated in voting rounds to achieve a minimum 75% agreement level.

Results: Pakistan has a low-immunization-rate and is susceptible to serious influenza outbreaks and influenza-related complications. Influenza circulates year-round in Pakistan but peaks during January and February. The subtype A/H1N1 is predominant. The experts urged vaccination in all individuals ≥ 6 months of age and with no contraindications. They highlighted special considerations for those with comorbidities and specific conditions. The experts agreed that the inactivated influenza vaccine is safe and efficient in pregnant women, immunocompromised, and comorbid respiratory and cardiovascular patients. Finally, the experts recommended conducting promotional and educational programs to raise awareness on influenza and vaccination.

Conclusions: This is the first regional consensus on influenza and influenza vaccination in Pakistan with experts' recommendations to increase influenza vaccination and decrease influenza cases and its associated detrimental effects.

Key words: influenza; vaccination; consensus; Pakistan.

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Introduction

Influenza is a widespread respiratory disease caused by viruses and affect people of all ages and origins. It is a public health concern, especially in low-and-middle-income countries, with a global estimation of 1 billion influenza cases yearly, out of which 5 million cases are severe [1]. Its manifestation varies from mild to severe and deadly, particularly among younger children, geriatrics, pregnant women, and people with pre-existing health conditions [2-7]. Influenza viruses are of three types, A, B, and C. Type A is the most prevalent and severe form [8].

An increasing influenza trend was detected in the Eastern Mediterranean Region (EMR) for the 2021-2022 analytical-period compared to reports from 2020-2021. The proportion of positive influenza specimens was still lower compared to the pre-coronavirus 2019 (COVID-19) period, due to the increased preventive measures [9-10]. However, influenza cases are anticipated to increase again following the lifting of COVID-19 restrictions. Therefore, influenza vaccination was recommended during the COVID-19 period, especially for high-risk people who may

develop severe complications when coinfecting by both viruses [11].

Several procedures were implemented to prevent influenza and its transmission or attenuate its symptoms and detrimental effects. Vaccination remains the gold standard in preventing infection; however, there are several challenges [12-13]. Seasonal influenza vaccines are of two types, inactivated influenza vaccines (IIV) and live-attenuated influenza vaccines (LAIV) [14]. With the advancements in preventive measures, diagnostic methods, and treatments, infectious diseases have been controlled to an extent, but specific populations are still medically vulnerable to outbreaks [15]. In addition, immunity wanes over time and the influenza strains evolve rapidly and continuously resulting in “drift and shift” of the strains, through surface protein mutations. This hinders the effectiveness of influenza vaccines [10,16].

Pakistan is a low-middle-income EMR country and regularly reports influenza activity to the World Health Organization (WHO) FluNet and/or the Eastern Mediterranean Region Flu (EMFLU) platforms. Influenza, mainly of types A and B, circulates throughout the year in Pakistan but peaks during January and February, with subtype A/H1N1 being predominant [4,17-19].

Several risk-factors are associated with influenza morbidity and mortality [2]. For instance, septic shock, renal failure, and intensive care unit (ICU) stays were associated with in-hospital mortality in patients with influenza in Pakistan [4]. Due to the unavailability of influenza vaccine policies and lack of knowledge of the importance of vaccination, Pakistan has a low-immunization rate and is susceptible to serious influenza outbreaks and influenza-related complications [20-21]. Consequently, special considerations should be taken regarding influenza vaccines, in terms of formulation, administration, dosage and timing, and contraindications (Table 1); which are not yet available in Pakistan [12,22-24].

Thus, it is timely and important to develop a consensus that helps healthcare decision-makers in implementing well-informed influenza prevention

strategies and vaccination practices in Pakistan. Despite the availability of several guidelines and protocols for influenza control in Pakistan, there is still a need for an evidence-based approach to be implemented. Thus, we conducted a systematic review of literature based on a three-step modified Delphi method to develop this consensus.

Methodology

Literature review and survey development

A comprehensive and systematic literature search was conducted by the steering committee through the Medline via PubMed, UpToDate, and Cochrane Database, and included systematic reviews, randomized and non-randomized controlled trials, cohort studies, and international guidelines. All literature up to April 2022 were searched. Several combinations of relevant medical key words including “influenza”, “vaccine”, “prophylaxis”, “treatment”, and “Pakistan” were used. The recommendations were then developed while integrating experts’ feedback on statements chosen throughout this systematic literature search and the modified Delphi method. The level of evidence (LOE) of the retrieved statements was adopted from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Design and expert panel composition

We used a modified-Delphi method-based study and utilized a three-step process to reach a consensus. In order to achieve adequate content validation, 11 specialists from Pakistan were included [24]. These specialists had an active research profile and were affiliated with an academic or private institution that is involved in influenza and infectious disease management. The experts were contacted through email and invited to participate in the first voting round. This was followed by a hybrid in-person and video conference in the presence of all the experts to discuss the discrepancies between their voting results. Descriptive statistics were used to quantify experts’ responses to each statement and the responses were

Table 1. Contraindications for flu vaccination.

Key observations	Reference No
Patients with immunocompromised conditions or medications should not receive live-attenuated influenza vaccines. However, inactivated and quadrivalent recombinant influenza vaccines are considered safe and efficient.	[52]
There is an association between influenza infection and Guillain-Barré Syndrome (GBS) occurring within 3 months after the influenza-like illness. Patients who experienced GBS within 6 weeks of previous influenza vaccination should not be vaccinated.	[51]
Quadrivalent inactivated influenza vaccines or quadrivalent recombinant influenza vaccines may be used during pregnancy. Quadrivalent live attenuated influenza vaccines should not be used during pregnancy but can be used postpartum.	[24]
Patients with solid and hematological tumors have a serological response to influenza vaccine, thus protecting them against influenza-associated morbidity and mortality. Thus, influenza vaccination is recommended in oncology patients regardless of systemic or chemotherapy administration.	[47]

Table 2. Influenza epidemiology in Pakistan.

Key observations	Reference No
While influenza viruses are present year-round in Pakistan, the virus has peak activity in January and February.	[19]
All influenza types/subtypes, including A/H1N1, A/H3N2, influenza B, H5N1, and the novel A/H1N1pdm09 are present in Pakistan.	[17,29,30]
Influenza types A and B are continuously circulating in Pakistan; however, since 2009, H1N1pdm09 has become the predominant influenza A subtype.	[17,18]
In general, influenza type A is more common than influenza type B, with an approximate ratio of 3:1.	[32]
A/H1N1 and A/H3N2 were identified more frequently in Pakistani children < 10 years of age than A/(H1N1)pdm09 and influenza B	[26]
Influenza type A and B outbreaks are associated with significant morbidity and mortality in Pakistan.	[4]
Seasonal influenza viruses continuously evolve and yield new antigenic variants through surface protein mutations. Emerging strains evade pre-existing immunity and gain a competitive advantage.	[9]

considered a consensus if they achieved an agreement level of $\geq 75\%$.

Results and discussion

Influenza epidemiology in Pakistan

Based on the review of published literature, we summarized the key findings related to influenza epidemiology in Pakistan (Table 2). All the experts agreed that the influenza virus peaks annually in January and February, and that there is a seasonal active window between October and April with sporadic occurrences throughout the summer [19,26,34]. Recently, a cross-sectional study in Islamabad reported that 74% of the patients diagnosed with influenza were type A, among which 62.2% were type A/H1N1. Most of these cases were detected during January and February [17,19]. This incidence is alarming, especially in an underprivileged population with a low-vaccination rate and weak immunity.

Between 2008 and 2011, influenza cases constituted 24% of patients who had influenza-like illnesses and severe acute respiratory illnesses at tertiary care hospitals in Pakistan. Influenza type A was detected in majority of the cases (72%) with A/H1N1pdm09 being the most abundant form exhibiting its peak activity during winter. Other influenza types were also detected, but with lower prevalence throughout the year [26]. The studies highlighted the drop in influenza cases after the COVID-19 pandemic, correlated with the preventive measures implemented during the pandemic; although

these measures were not fully implemented in Pakistan [9].

After identifying the influenza types and subtypes detected in Pakistan, it is crucial to understand the patterns of influenza infection and the strains in circulation to implement prevention and control strategies [18,27-30]. Therefore, all influenza types/subtypes, including A/H1N1, A/H3N2, influenza B, and the novel A/H1N1pdm09 that had been detected in Pakistan were summarized and it was determined that influenza types A and B have been in circulation since 2009, and H1N1, H1N1pdm09, and H3N2 are the predominant strains.

Special considerations should be given to children from lower resource countries, who are more vulnerable to severe complications from respiratory diseases [31]. In Pakistan, influenza types A/H1N1 and A/H3N2 were predominant in children less than 10-years-old and most often accompanied by other respiratory infections such as the respiratory syncytial virus [30,36]. Therefore, experts agreed that the detection of A/H1N1 and A/H3N2 was higher among Pakistani children less than 10-years-old than A/(H1N1)pdm09 and influenza-B.

Moreover, after extensively reviewing the literature [4,10], the experts came to a consensus that both the influenza types were associated with morbidity and mortality in Pakistan. In addition, the virus’s dynamic nature, in continuously evolving and yielding new antigenic variants, made control over its spread and

Table 3. Influenza vaccination in Pakistan

Key observations	Reference No
Annual influenza vaccination is the most effective prevention strategy against influenza infection in terms of preventing severe illness, secondary complications, and deaths.	[12]
Annual influenza vaccination is recommended for all Pakistani populations above 6 months of age with no apparent contraindications.	[2,14]
Due to its geographic location, seasonal influenza vaccination in Pakistan is recommended by the end of October or before the typical influenza season in January and February.	[33, 34]
Influenza vaccination is recommended in pregnant, potentially pregnant, and postpartum women before the influenza season	[5,6]
Children aged 6 months to 8 years who haven’t previously received ≥ 2 doses of trivalent or quadrivalent influenza vaccine require 2 doses, while adults and children aged ≥ 9 years need only 1 dose of influenza vaccine	[22]
Seasonal influenza vaccines can be co-administered with coronavirus disease 2019 (COVID-19) vaccines.	[35]
Chemoprophylaxis, including neuraminidase inhibitors, should not be considered a substitute for influenza vaccination.	[23]

COVID-19: coronavirus disease 2019.

management a challenging task and future outbreaks were possible.

Vaccination in Pakistan

Our literature review identified nine key findings regarding vaccination (Table 3). The experts highlighted the importance of implementing non-pharmaceutical preventive methods along with vaccines for effective influenza symptom management and to curb its transmission and outbreaks. Although they agreed that vaccines are not recommended between July and August, they also highlighted that vaccination is an opportunistic activity; and if a patient arrives in the clinic during a non-peak month, it would be safer to vaccinate the patient during the same visit instead of postponing till October. Thus, although it is preferable to get the influenza vaccine in the months leading to the peak season around October, there is flexibility for those who have special conditions and/or requests for an earlier vaccination [33-34]. The experts concluded that the annual influenza vaccine is crucial for all Pakistani populations and should be taken by the end of October or before the peak flu-season in January and February.

Furthermore, the experts agreed that influenza and COVID-19 vaccines can be co-administered. Initially, WHO recommended a 14-day interval between COVID-19 vaccination and other vaccines. However, new evidence suggested that coadministration of the influenza and COVID-19 vaccines is supported [2]. WHO recommends coadministration of the vaccines for better management, especially since the symptoms resulting from the viruses are very similar [35-36].

Additionally, the experts recommended that the influenza vaccine should be considered in pregnant, potentially pregnant, or postpartum women since they are considered at high-risk of developing influenza complications [5]. In addition, special considerations should be taken when vaccinating these women, and

primary caregivers should make sure that no contraindications are present, and prescribe the suitable available influenza vaccine, and not receive LAIV (Table 4) [5,6]. For instance, the quadrivalent inactivated and quadrivalent recombinant influenza vaccines may be used in pregnant women; however, quadrivalent LAIV is contraindicated [24]. Thus, the experts agreed to recommend influenza vaccines for pregnant, potentially pregnant, and postpartum women.

Influenza vaccines in populations with comorbidities and special considerations

Fourteen key points were summarized regarding influenza vaccines in populations with comorbidities and special considerations (Table 4). Patients at high-risk of developing influenza-related serious adverse events, such as children, pregnant women, and patients with comorbidities, should be considered for annual vaccination. Previous studies have already established evidence supporting the need for annual vaccinations in special populations and highlighted the severity and extent of influenza infection in these groups.

The Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, recommended annual influenza vaccine for all eligible children who are ≥ 6-months of age and adults with no contraindications [2,14]. A recent multicenter study reported that vaccines are highly-effective in children against influenza-related hospitalizations and emergency department visits [37]. Debates around the safety and effectiveness of LAIV in children are still unclear [38-41]. However, IIV is recommended for all children and adults [38]. In addition, vaccines were safe and effective in asthmatic patients and have been shown to be associated with a decreased risk of respiratory failure in patients with chronic obstructive pulmonary disease (COPD) [41]. The experts also recommended annual influenza vaccines for patients with diabetes, cardiovascular diseases, chronic kidney diseases,

Table 4. Influenza vaccination in populations with comorbidities and special considerations.

Key observations	Reference No
Annual influenza vaccination is recommended for all children ≥ 6 months of age with no recorded contraindications.	[37]
Annual influenza vaccination is recommended in all asthmatic children (≥ 6 months of age) regardless of asthma symptoms or concurrent steroid therapy.	[38]
Seasonal influenza vaccinations are recommended in adult and elderly populations with asthma.	[57]
Annual Influenza vaccination is recommended for COPD patient population.	[58]
Annual influenza vaccination among Pakistani patients with diabetes is recommended regardless of age and severity of the diabetic disease.	[42, 44]
Seasonal influenza vaccination is recommended in patients with coronary artery diseases leading to a decrease in incidence, morbidity, and mortality from acute myocardial infarction.	[45, 49, 50]
Influenza vaccination significantly reduced the risks of death from cardiovascular causes and AMI/stroke in patients with hypertension. Hence, seasonal influenza vaccination is recommended in patients with hypertension.	[43, 46]
Seasonal influenza vaccination is recommended for patients with CKDs. However, nasal spray forms of live attenuated influenza vaccines are not recommended for people with CKDs.	[48, 59]
Seasonal influenza vaccines are recommended in cirrhotic and non-cirrhotic patients with chronic liver diseases.	[60]

COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease.

chronic liver diseases, immunocompromising conditions, and oncological disorders. The vaccine is highly-effective with a significant antibody response in patients with comorbidities [42-49]. These results were confirmed in a review of the observational studies that concluded that there was normal response to the influenza vaccine among diabetic patients [44]. The vaccine has a primary and secondary protective effect against cardiovascular events, especially since viral illnesses have been associated with myocardial infarction through specific inflammatory pathways [45,49-50]. In addition, a meta-analysis, concluded that there is a protection effect based on evidence from two randomized controlled studies where mortality pooled relative risk was 0.39 in favor of influenza vaccination versus no vaccination [45]. Previous studies have also shown that vaccination is effective in protecting hypertensive and chronic kidney disease patients through an association with reduced risks of mortality and morbidity in this population.

The experts discussed the role of influenza vaccination in Guillain-Barré syndrome (GBS) and agreed that the vaccine should not be administered to patients who had a history of GBS within 6 weeks of a previous influenza vaccine administration since there is an increased incidence of GBS after vaccination [51].

Moreover, the experts agreed that LAIV is not recommended for immunocompromised patients or pregnant women, while inactivated and quadrivalent recombinant influenza vaccines are safe and recommended for these patients. Further considerations from the discussion and scientific literature are presented in Figure 1.

Finally, the experts agreed that special considerations should be taken before influenza vaccine

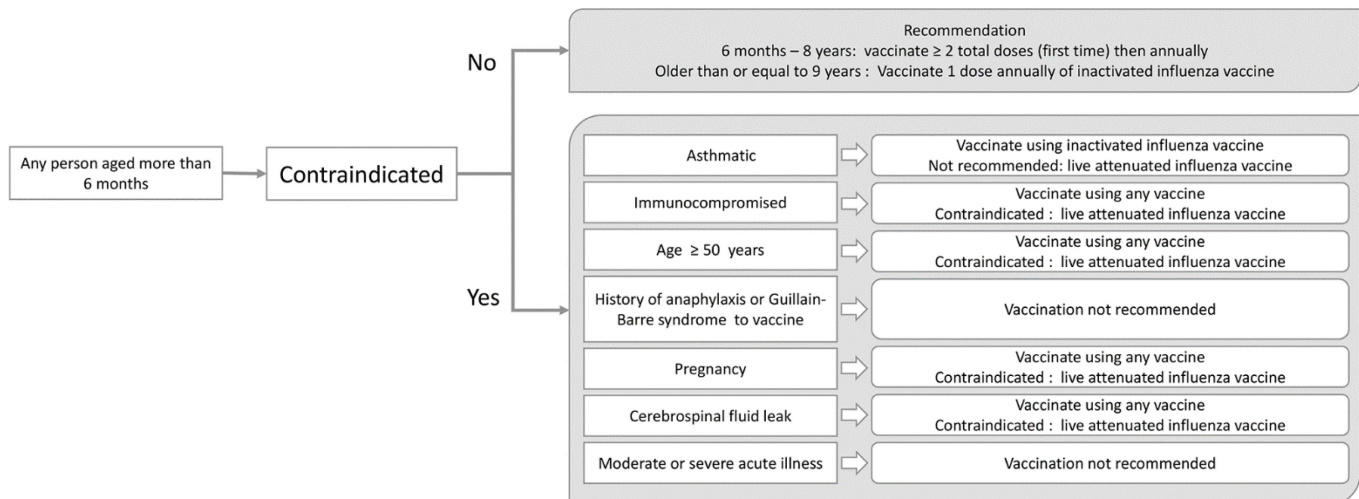
administration to specific populations. The vaccine should be administered after proper assessment, screening for contraindications and precautions, and consideration of administration method by healthcare providers [55].

Consensus on the need of awareness on influenza vaccines among Pakistani population

The experts agreed on 9 statements regarding the need for vaccination awareness among Pakistani population (Table 5). All the experts agreed that the vaccination rate is low, which is in line with what has been reported by local studies [20,52]. They associated low vaccination rates with misconceptions and lack of awareness regarding influenza manifestation and severity. This may be attributed to the lack of national immunization programs, policies, and recommendations by the Expanded Program on Immunization in Pakistan [20,52]. Although the parents had positive attitudes towards vaccination in general, lack of awareness about the influenza vaccine is common among Pakistanis, and very few are aware of its availability [20]. Pediatricians and physicians are the primary sources of information for parents and patients while considering vaccinations. However, some information is also obtained through other sources such as social media [54-55]. A cross-sectional study was conducted to evaluate the attitude, awareness, and behavior of parents towards influenza vaccination in Pakistan. The study concluded that there was a very low vaccination rate, which is probably due to a lack of knowledge of vaccine availability and a negative perception of the influenza vaccine [20].

The factors that contribute towards low influenza vaccination rates in Pakistan include lack of official

Figure 1. Algorithm of influenza vaccination recommendation in Pakistan.



policies, unavailability of the vaccine in the EPI, high healthcare costs, traditional beliefs and customs, illiteracy, and reliance on healthcare providers recommendations [21]. The healthcare providers in Pakistan do not encourage and advocate for influenza vaccination due to misconceptions about the vaccine’s side effects [55]. Educating the healthcare providers on the benefits and efficacy of the vaccine is crucial because people rely on them as the primary source of information on healthcare and refer to them for medical advice [15,20,]. The experts advocated for educational programs in healthcare institutes and media to increase public awareness of influenza vaccination. In addition, they recommended training courses to improve medical students’ and healthcare workers’ attitudes toward vaccination. Such training programs have already been initiated and are anticipated to be effective in increasing public vaccination by engaging more people. These training programs highlight the importance of vaccination and the severity of the side effects of influenza in people with underlying risk factors. These campaigns include the “Flu Awareness Campaign” organized by WHO/Europe in October every year and the national influenza vaccination week organized by the National Foundation for Infectious Diseases [56].

Clinical pathway algorithm

Based on the findings from literature and their own clinical experience, the panel agreed on the set of decision criteria that may be used when determining whether the annual influenza vaccine should be administered to Pakistani individuals. The vaccine can be administered to individuals ≥ 6 months of age and it can be co-administrated with COVID-19 vaccines, when applicable. Children between 6 months and 8 years should receive ≥ 2 total doses of trivalent or quadrivalent influenza vaccine, and individuals ≥ 9 years should receive one dose of the influenza vaccine. The vaccine can be administered to patients with asthma, COPD, diabetes, coronary artery disease

(CAD), hypertension, chronic kidney disease (CKD) (except for LAIV nasal-spray forms), chronic liver disease, and cancer. LAIV should not be administered to asthmatic children who are between 2-4 years old, or immunocompromised patients. Quadrivalent LAIV is not recommended for pregnant women. A flow chart with these recommendations is presented in Figure 1.

Conclusions

In this Delphi-based consensus, clinical-experience and evidence-based research were combined to reach a novel consensus statement on influenza vaccination status and awareness in Pakistan. The expert panel discussed and agreed on statements regarding epidemiology, vaccinations, conditions and special considerations, and awareness of the vaccine in Pakistan. The findings will help healthcare workers and policy makers understand the importance of vaccination and assist with development of awareness and vaccination implementation programs for underprivileged populations who are at a higher risk of developing severe complications from influenza.

Our literature review and expert consultations concluded that influenza is common in Pakistan and the subtype A/H1N1 of the virus is predominant. Influenza vaccination and awareness about the vaccine are low in Pakistan. Therefore, educational programs are recommended to raise awareness on influenza and its vaccine.

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Table 5. Consensus on the need of vaccination awareness among Pakistani population.

Key findings	Reference No.
The rate of influenza vaccination is very low in Pakistan; most probably due to the lack of knowledge about the importance and availability of vaccines.	[4,20]
The majority of the Pakistani population is not aware about the seasonal influenza vaccination due to lack of an official influenza vaccine policy in Pakistan.	[20, 21]
Annual influenza vaccination should be included in the expanded program on immunization (EPI) in Pakistan to decrease childhood influenza-related morbidity and mortality.	[4]
Hospital authorities should mandate influenza vaccination for all healthcare staff.	[21]
Promotional and educational programs in healthcare institutes and media should be conducted to increase awareness on influenza vaccination.	[15]
Flu awareness campaigns like the National Influenza Vaccination Week (NIVW) could increase public awareness on vaccination.	[56]
A low rate of influenza vaccinations among Pakistani healthcare workers is mainly due to misconceptions regarding side effects.	[55]
Training on influenza vaccination are recommended to enhance medical students' and healthcare workers' attitudes towards vaccination	[55, 56]

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Corresponding author

Tabrez Ali, MD, MSc, MBA
Department of Medical Affairs, Established Pharmaceutical Division, Abbott Laboratories (Pakistan) Limited,
8th Floor, Faysal House, Main Sharah e Faisal Road, Karachi, Pakistan.
Tel: 0092-21- 32799307
Email: tabrez.ali@abbott.com

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