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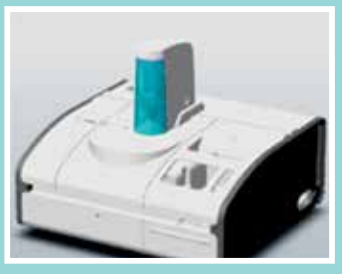

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Advantages of Subunit Influenza Vaccine: An Overall Perspective

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ABSTRACT

Influenza, a contagious respiratory infection, is caused by influenza virus A, B and C in humans. Chills, fever, headache, myalgia, fatigue and respiratory discomfort are the most commonly observed symptoms, whereas progression of illness may result in bronchitis, pneumonia, secondary bacterial infections, acute respiratory distress, cardiovascular diseases and even death. Management of influenza involves high treatment costs and functional losses. Therefore, immunization against influenza is the best method to prevent it. Seasonal trivalent influenza vaccine (TIV) formulations, i.e., whole inactivated virus (WIV) vaccines, "detergent"-split vaccines (SIV) and subunit vaccines (SUV), use inactivated influenza antigens. There are live attenuated influenza viruses vaccines also available, which we will not be discussed in this article. Administration of WIV vaccines leads to an increased rate of and more severe adverse reactions; therefore, less reactogenic forms of influenza vaccine, SIV and SUV are preferably being used. The present review compares SUV and SIV in terms of tolerability, and reactogenicity. Furthermore, the immunizing and reactogenicity profile of SUV in high-risk subgroups of the populations (children, elderly, pregnant women, liver transplant patients, asthmatics, diabetics and nursing home residents) has also been discussed.

Keywords: Subunit, vaccine, influenza, split, trivalent, whole, immunogenicity, reactogenicity

Influenza is a contagious respiratory illness, usually observed in humans and is caused by influenza virus A, B, C (Table 1).[1,2] The clinical manifestation observed in individuals with seasonal influenza includes chills, fever, headache, myalgia, fatigue and respiratory discomfort characterized by a cough, sore throat and rhinitis.[3] Untreated or progressed form of influenza may result in severe complications such as bronchitis, pneumonia, secondary bacterial infections, acute respiratory distress and cardiovascular diseases; which if further left untreated, can lead to death. Moreover, elderly, children, immunocompromised patients and individuals with weakened immune system are more vulnerable to such infections and are thus considered as high-risk populations.[3-6] Infection due to highly pathogenic strains of influenza virus (some of the avian H5 subtypes) may also cause severe respiratory distress and multi-organ failure in infected humans.[7] Other symptoms observed in patients during the attack of H1N1 virus in 2009 included gastrointestinal and neurological (encephalopathy, focal neurological findings, aphasia, and abnormal electroencephalographic findings) complications.[8,9]

Table 1. Influenza Virus A-C

Types	Results	Types	Reservoirs
A	Epidemics, pandemics	Based on the antigenic differences between two surface glycoproteins: H and N. Till date, 18 H subtypes (H1-H18) and 11 N subtypes (N1-N11) have been identified	Animals, humans
B	Epidemics	Only single subtypes of H and N	Humans
C	Infects humans but causes little or no disease	Only single subtypes of H and N	Humans

H = Hemagglutinin; N = Neuraminidase.

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Global influenza epidemics are highly influenced by the seasonal factors where it is commonly observed during the winter in the northern and southern hemispheres.[10] Globally, in 2016, the annual attack rate of influenza infection was reported to be 5-10% and 20-30% in adults and children, respectively, with a total of about 2,50,000 to 5,00,000 annual deaths along with 3-5 million cases of influenza-related severe illness.[11-13]

Though influenza disease can be shortened using various drugs, the high inpatient and outpatient treatment costs of influenza pose a socioeconomic burden on individuals, families and society. Moreover, the productivity and functional losses also add on to the economic burden associated with the diseases.[14] Besides, the severity of influenza infection outcomes along with the complications associated with it may lead to hospitalization or even death. Therefore, vaccination against influenza infection is the best and the most cost-effective way to prevent the influenza infection.[1]

Numerous types of influenza vaccine formulations are available these days. Seasonal trivalent influenza vaccine (TIV) formulations use inactivated influenza antigens and are available as whole inactivated virus (WIV) vaccines, "detergent"-split vaccines (SIV) and subunit vaccines (SUV).[15,16] The present review compares SUV and SIV in terms of tolerability, and reactogenicity. Furthermore, the immunizing and reactogenicity profile of SUV in high-risk populations (children, elderly, pregnant women, liver transplant patients, asthmatics, diabetics and nursing home residents) has also been discussed.

GENERATIONS OF TRIVALENT INACTIVATED VACCINES: AN OVERVIEW

All generations of TIV (WIV, SIV, SUV) contain inactivated influenza viruses derived from two influenza A strains (H3N2 and H1N1) and one influenza B strain. The three major formulations differ in either structural organization or viral components (Fig. 1).[15,16]

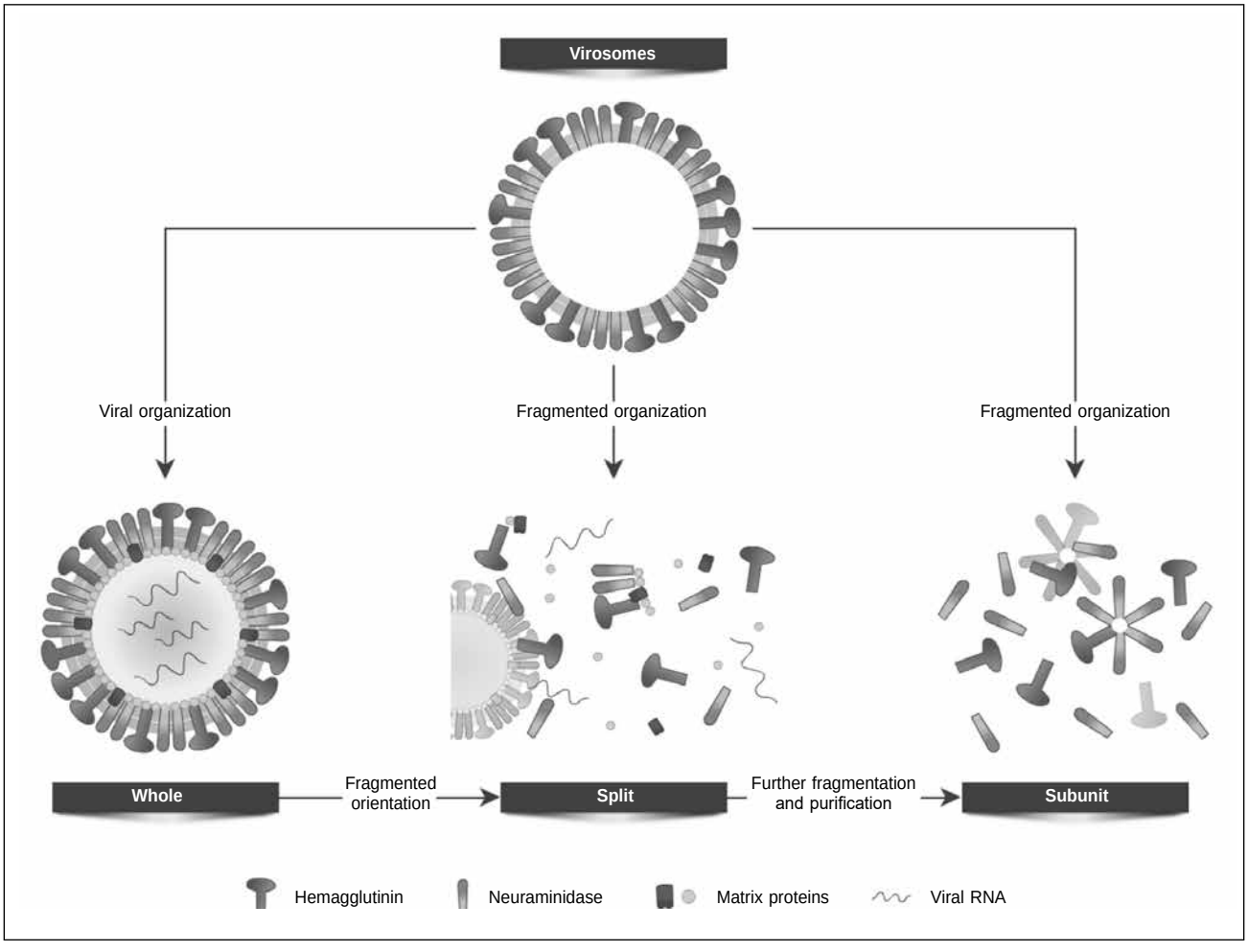

Figure 1. Structural difference in trivalent influenza vaccine formulations.

Whole Influenza Vaccine

WIV is prepared from harvested allantoic fluid of hen's egg which is chemically inactivated with chemicals such as formalin or β-propiolactone or formaldehyde and subsequently concentrated and purified to remove the contaminants, i.e., non-viral proteins.[17] The procedure followed to prepare WIV does not destroy the viral envelope (Fig. 1).[18]

The WIV was introduced first among the other types, and was the most widely used TIV.[17] However, an association of WIV with painful local and systemic reactions has declined its use over a period of time. A recipient blinded study conducted by Al-Mazrou et al, 1991 compared the adverse drug reactions (ADRs) caused by WIV and SIV in 333 patients with influenza who received the vaccine for the first time. It was reported that WIV formulations caused more local and systemic adverse effects upon administration, as compared to SIV. Generalized aching was observed in 13% of the SIV recipients in comparison to 26% WIV recipients ($p < 0.01$). Moreover, SIV group reported fewer visible local reactions such as soreness (SIV vs. WIV; 68% vs. 78%), redness/swelling (SIV vs. WIV; 18% vs. 29%).[17]

The ADRs observed in patients taking WIV may be attributed to the presence of impurities in WIV in the form of egg proteins. Such studies also supported the restriction of WIV vaccines in the market and promoted the entry of SIV in the market.[19] SIV and SUV are being used since the 1970s.[20,21] Another study by Carle et al, 1988 comparing WIV (received by 49 subjects, males = 21, females = 28, average age: 70.20 ± 11.98 years) with SUV (received by 53 subjects, males = 23, females = 30, average age: 80.12 ± 7.25 years) reported a lower reactogenicity of SUV as compared to WIV, despite similar immunogenicity and sero-protection. Though, patients receiving WIV and SUV did not experience any systemic reactions (headache, malaise, fever), the proportion of patients experiencing local reactions (such as redness, swelling and pain at site of injection) was high in WIV group as compared to SUV group (SUV vs. WIV: 41.51% vs. 53.06%).[22] The immunogenicity demonstrated by WIV and SUV was comparable with reduced reactogenicity with SUV in comparison with WIV formulations.

Split Influenza Vaccine

SIV is prepared by following an additional step to the ones followed for WIV, i.e., treatment of vaccine with diethyl ether or detergent for the disruption of viral lipid envelope as well as for exposure to all viral proteins and subviral elements (Fig. 1). Though SIV contains complete viral protein content, the loss of organization of original viral particulates as well as viral single-stranded ribonucleic acid (ssRNA) which is required for the immunogenicity of the virus helps in the formulation of a lesser reactogenic vaccine as compared to WIV.[15,16] SIVs are more acceptable due to their adequate immunogenicity, lower reactogenicity and easy process of production.[23]

Subunit Influenza Vaccine

In SUV, the viral content is treated with diethyl ether or a detergent to separate hemagglutinin (H) and neuraminidase (N) surface proteins from the viral nucleocapsid and lipids. The H and N proteins are further purified by removing other viral components (Fig. 1).[24,25] Sometimes, adjuvants are also added to the antigens to attain adequate immunogenicity in the elderly.[26] A recent modification in SUV, a recombinant H protein SUV has been introduced. This contains a high dose of antigen, i.e., 45 μg per strain to attain adequate immunogenicity. However, high dose antigen results in high seroconversion rates among healthy adults (50-64 years)[27] and low seroconversion and efficacy rates in children (6-59 months).[28]

SUV has been considered to be the least reactogenic influenza vaccine as compared to the other types, till date.[29] A meta-analysis conducted in 1996 included 14 clinical studies which evaluated SUV and reported that 95% of the study population vaccinated with SUV experienced no or mild (clinically insignificant) adverse events (AEs), which lasted up to 2 days. It was also reported that among 1,800 subjects (females: 891; males: 909), 745 subjects experienced local symptoms (redness, swelling, itching, warmth, pain on contact, continuous pain, restricted arm movement), whereas, 378 subjects experienced systemic symptoms such as fever, increased sweating, headache, malaise, insomnia and inconvenience.

However, the percentage of patients who experienced each of the above mentioned local and systemic symptoms was not reported in the meta-analysis.[30]

KEY CLINICAL STUDIES COMPARING SUBUNIT INFLUENZA VACCINE WITH SPLIT INFLUENZA VACCINE

Several studies conducted in the past have compared SUV and SIV in terms of efficacy, immunogenicity, reactogenicity (common and expected AEs), and safety (relative freedom from harmful effect to

vaccine recipients, directly or indirectly). This section elaborates the literature comparing these two vaccines.

Many studies report SUV to be well-tolerated and associated with fewer AEs as compared to other vaccine types. A study comparing SUV (dosages: 700 and 2,100 International Units; IU) with SIV (800 IU/dose) and WIV (2,100 IU/dose) included 399 volunteers in the study and reported that SUV was well-tolerated as compared to WIV. SUV at both doses caused fewer AEs as compared to SIV and WIV.[31] A retrospective study, by Leeb et al, 2011, was conducted to compare the reactogenicity of SUV (Influvac®) with SIV (Fluvax®) among adults (≥18 years). Overall, 127 subjects received SUV and 156 received SIV. The study reported swelling (SIV vs. SUV; 18% vs. 7%, p = 0.009), muscle pain (SIV vs. SUV; 12% vs. 3%, p = 0.014) and use of anti-fever/pain medication after vaccination (SIV vs. SUV; 12% vs. 2%, p = 0.008) in both the groups. Moreover, SIV was considered to be a significant independent predictor of muscle pain and/or swelling (odds ratio, [OR] = 3.3, 95% confidence interval [CI] 1.5-7.4, p = 0.004).[32]

Another randomized, double-blind study compared the reactogenicity and serology of SUV and SIV in children (SUV: n = 249; SIV: n = 250; age 6-12 years). SIV-induced fever in a higher percentage of subjects (6.4%) as compared to SUV group (2.4%; p > 0.05). Blood samples collected from SUV group (n = 224) and SIV group (n = 223) demonstrated similar seroprotection (hemagglutination inhibition [HI] titer ≥1:40, SUV vs. SIV: H1N1, 99.6% vs. 100.0%; H3N2, 99.1% vs. 99.1%) and seroconversion rates (4-fold increase, SUV vs. SIV: H1N1, 95.1% vs. 97.8%; H3N2, 74.5% vs. 79.8%) with an increased geometric mean titer (GMT) (SUV vs. SIV: H1N1, 16.0 vs. 21.0; H3N2, 5.4 vs. 6.4) against the two A subtypes. A similar seroprotection rate (94.2% vs. 96.4%) and GMT increase (21.2 vs. 18.2) against the influenza B strain were also produced by both vaccines, showing that both vaccines were well-tolerated and presented effective immune response.[33]

Overall, SUV presents better safety as compared to SIV. SUV is also associated with a lower likelihood of local reactions among adults as compared to SIV.[32] This can be further supported by a meta-analysis (conducted in 1998), which included 22 randomized controlled trials (RCTs) describing 5,416 observations (local reactions: 2,858; systemic reactions: 2,990) with subjects of all age groups (children to elderly). The analysis compared SUV with SIV and WIV; and reported SUV to be superior than SIV and WIV in terms of lower reactogenicity.[34]

CLINICAL STUDIES ON SUBUNIT INFLUENZA VACCINE IN DIFFERENT SUBPOPULATIONS

van de Witte et al, 2012 reviewed 30 years of clinical experience with Influvac, which is an SUV. It was reported to be safe and clinically effective for all age groups (≥6 months of age).[35] Many other clinical trials have been conducted to assess the safety and immunogenecity of SUVs in different subpopulations such as children, elderly, pregnant women, etc.

Children

Children are at a higher risk of being infected with influenza virus as compared to elderly.[36,37] Moreover, school children play an important role in transmitting influenza infection.[38] The safety, immunogenicity and efficacy of influenza vaccines in children have demonstrated TIVs as well-tolerated vaccines in children.[39]

A randomized phase III trial was conducted on 205 healthy, unprimed children (aged 6 to <36 months) to evaluate the immunogenicity, safety and tolerability of a single 0.5 mL dose of the seasonal virosomal SUV, where 102 received one single 0.5 mL dose and 103 received the standard two 0.25 mL doses in a gap of 4 weeks. Both the doses enhanced the immune response against all three vaccine strains. Moreover, immunogenicity was maintained 7 months after the first vaccination with both the doses. Overall, the vaccine was found to be well-tolerated, where a single dose of 0.5 mL demonstrated long-term immunogenicity in terms of efficacy and safety in unprimed children, that too against all the influenza virus strains.[40]

A randomized endpoint-blinded, parallel group trial was conducted to evaluate the immunogenicity and safety of two SUVs, Influvac and Agrippal, in healthy children (aged 3-12 years), adults (aged 18-60 years) and elderly (aged 60 years or more). Both, Influvac and Agrippal, induced high antihemagglutinin antibody titers in all the age groups. All the groups presented seroprotection and seroconversion rates of >85% and >70%, respectively for both vaccines and against all the three virus strains. Both vaccines were well-tolerated, immunogenic and safe for a population of all age groups.[41]

Grippol®, an SUV bound with polyoxidonium, received by the school children (aged 6-18 years) demonstrated low reactogenicity, high safety and adequate prophylactic effectiveness with no adverse effects. Moreover, the complaint of high morbidity rate due to

respiratory complications also decreased as compared to that of the control group (by 2.4 times).[42]

The efficacy of inactivated TIVs in 2,723 children aged 6-59 months at increased risk of severe disease was compared with children with no such risk by Blyth et al, 2016. It was reported that vaccine was found to be ≥70% efficacious in young children with and without risk factors for severe disease.[43]

An open, randomized, multicenter study compared the immunogenicity and safety of a single-dose regimen and a two-dose regimen of a trivalent virosome influenza vaccine (Inflexal Berna V) with those of an SUV (Influvac) in 11 young children (1-6 years old) and 53 older children and adolescents (>6 years old) with cystic fibrosis. The study reported that both the vaccines met all requirements, in terms of seroconversion, seroprotection and GMT, for influenza vaccine efficacy in all treatment groups. However, the rate of systemic ADRs reporting (mainly cough, fatigue, coryza or a headache) was less for SUV (71%) as compared to the other vaccine (84%).[44]

Another study assessing the humoral response of SUV in children (previously vaccinated with SUV [n = 25]; never vaccinated [n = 20]) with acute lymphoblastic leukemia also demonstrated high immunogenicity of SUV in patients with acute lymphoblastic leukemia. Previously vaccinated subjects exhibited a 13.2- and 21.1-fold increase in antibodies, respectively against H1N1; 10.8- and 20.5-fold increase, respectively against H3N2 and 9.2- and 15.6-fold increase, respectively, against influenza type B, at 3 weeks and 6 months post-vaccination. Children vaccinated for the first time showed a 8.3-fold increase in antibodies after three weeks of vaccination and 23.4-fold increase in antibodies after 6 months of vaccination against H1N1. An increase of 7.9- and 16.3-fold in antibodies was observed against H3N2 after 3 weeks and 6 months of vaccination, respectively, while, 5.5- and 14.4-fold increase against influenza type B. Moreover, none of the children vaccinated with influenza vaccine was observed with infection. The vaccine was found to be well-tolerated with no reported ADRs.[45]

Elderly

The influenza disease burden is high in elderly patients which is assumed to be a result of impaired immune system in this age group. Many countries generally recommend vaccination against influenza for the elderly, chronically ill and residents of health care facilities to prevent the occurrence of influenza in susceptible patients.[46]

Adjuvanted vaccines are reported to induce a stronger immune response in the elderly (>65 years old) population.[47,48] A study conducted to compare conventional SUV, MF59-adjuvanted and intradermal (ID) influenza vaccines in terms of safety and immunogenicity enrolled 335 healthy elderly volunteers who randomly received one of three seasonal TIVs. All the TIVs attained satisfactory protection against A/H1N1 and A/H3N2 strains but not for the B strain. ID vaccine demonstrated noninferior results as compared to the SUV, whereas MF59-adjuvanted vaccine exhibited superior results.[49] A randomized, observer-blind, three-arm, parallel group, multicenter trial including 386 elderly subjects compared immunogenicity and safety of a conventional SUV, MF59-adjuvanted SUV and a virosomal SUV. All the vaccines had similar immunogenicity and were found to be safe and well-tolerated. However, conventional SUV was found to be less reactogenic as compared to the MF59-adjuvanted vaccine in the elderly population.[50]

Another randomized, controlled evaluator-blinded study comparing ID, MF59-adjuvanted and SUV formulations of equal potency and strain composition on 887 non-frail adults, annually TIV-immunized (≥65 years old) reported redness at the site of injection in the following order: ID (75%) > MF59-adjuvanted (13%) > SUV (13%); whereas pain was observed as MF59-adjuvanted (38%) > ID (29%) > SUV (20%). Seroprotection rates of MF59-adjuvanted vaccine were highest, and all the vaccines were well-tolerated.[51]

Patients with Cardiovascular Diseases

According to the Centers for Disease Control and Prevention (CDC), patients with cardiovascular disorders are considered as high-risk population group for developing complications related to influenza infection. The inpatient record for influenza during 2015-2016 reports heart disease (such as heart attacks and stroke) as the most commonly occurring chronic condition affecting 41% of total influenza-infected hospitalized adults. Therefore, vaccination against influenza is highly recommended in patients with cardiovascular disorders.[52]

A randomized prospective double-blind placebo-controlled Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease (FLUCAD) study was conducted to compare humoral response in patients with coronary artery disease

receiving SUV (n = 325) and placebo (n = 333). The post-vaccination antibody titers were significantly higher (4.9- to 5.7-fold for antihemagglutinin; 3.5- to 4.2-fold for neuraminidase antibodies) and post-vaccination protection rates ranged from 56.4% to 60.3% and response rates from 62.8% to 68%. Moreover, immunoglobulin G and M levels were high in patients receiving the vaccine.[53]

Diabetics

Patients with diabetes are vulnerable to influenza and are prone to influenza-related complications resulting due to impaired immune system. Vaccination against influenza is therefore highly recommended in this subgroup of patients.[54,55] Type 2 diabetes subjects (n = 105) were compared with nondiabetic controls (n = 108) in a randomized controlled study to evaluate the long-term immunogenicity and safety of SUV (intramuscular). The vaccine achieved adequate seroprotection after 1 month except for the A/H1N1 influenza virus strain, which was lower in the elderly diabetic group than that in the elderly nondiabetic group (diabetic group vs. nondiabetic group [p value], A/H1N1: 69.5% vs. 76.9% [0.227], A/H3N2: 99.0% vs. 98.1% [0.578], B: 56.2 vs. 60.2 [0.555]). The post 6-month seroconversion (diabetic group vs. nondiabetic group [p value], A/H1N1: 26.7% vs. 19.4% [0.211], A/H3N2: 34.3 vs. 29.6 [0.466], B: 32.4% vs. 24.1 [0.178]) and GMT levels (mean titer diabetic group vs. mean titer non-diabetic group [95% confidence interval or CI], A/H1N1: 33.3 [27.5-38.0] vs. 34.8 [29.7-40.8], A/H3N2: 161.1 [127.1-204.2] vs. 159.0 [128.9-196.0], B: 22.7 [19.6-26.2] vs. 18.6 [16.2-21.5]) were well-tolerated in both the groups. Moreover, the ADRs observed post-vaccination were mild-to-moderate with its reduced incidence in the diabetic group. The study reported the association of long-term immunogenicity with age and pre-vaccination titer, instead of diabetes status.[56] Another study comparing the cytotoxic T-cell and humoral immune response of an influenza A-H1N1 SUV among 27 subjects (patients with type 1 diabetes mellitus [T1DM]: 14; healthy subjects: 13) reported poor cytotoxic T-cell response to vaccination in both the groups.[55] A pilot study conducted to evaluate inactivated TIV in juvenile diabetics and matched healthy controls reported no difference in both groups in terms of the humoral immune response.[57]

Another study evaluating the effect of SUV in combination with pneumococcal vaccination in children and adolescents (group vaccinated with pneumococcal vaccine: 100 out of which 28% were vaccinated with SUV also; unvaccinated group = 30; age: 2-18 years) with T1DM who were on intensified insulin treatment did not report any activation of autoimmune process or increase in levels of autoantibodies to n-DNA, d-DNA and pancreatic tissue in group receiving vaccination. In addition, there was no disease progression observed in the subjects, while the immune system of the vaccinated patients was found to be positively influenced by a tendency to shift towards normalization.[58]

Liver Transplant Patients

Like other subgroups of the population at risk, patients with liver transplant also warrant immunization against influenza vaccine. However, the response of recipients receiving immunosuppressive therapy is controversial. A study assessing efficacy of first and second vaccination using SUV in 61 immunocompromised adult liver transplant recipients, 35 liver cirrhosis patients and 45 healthy spouses of these patients reported a significant rise in GMT of all three antigens after one vaccination (H3N2, ranges, controls: 194-375, cirrhosis: 207-531, liver transplant 53-103; $p < 0.001$; H1N1, ranges, controls: 292-655, cirrhosis: 484-1303, liver transplant: 132-278, $p < 0.001$; B, ranges, controls: 65-166, cirrhosis: 61-199; liver transplant: 37-83, $p = 0.058$), without further significant increase in patients with cirrhosis (ranges: H3N2: 215-533, H1N1: 461-1,219, B: 73-204) and control subjects (ranges: H3N2: 181-354, H1N1: 291-630, B: 119-246) after second vaccination. Patients with liver transplant were observed with a rise in GMT after the second vaccination. The overall antibody response to all three influenza virus strains was lower in the liver transplant recipients as compared to control group. Despite immunosuppressive therapy, liver transplant recipients were effectively vaccinated using SUV.[59]

Pregnant Women

The CDC recommends vaccination against influenza infection for pregnant women due to the likelihood of getting infected because of weakened immune system and risk of pregnancy complications associated with influenza. Vaccination may be done anytime during pregnancy.[60] Studies have suggested a reduction in preterm birth and low birth weight in babies with mother getting vaccinated during pregnancy.[61,62] A recent meta-analysis conducted by Nunes et al, 2016, included five studies to assess the effect of vaccination in pregnant women. The study reported an association between maternal influenza vaccination and decreased risk of preterm birth (odds ratio [OR]: 0.87; 95% CI: 0.77-0.98) and low birth weight (OR: 0.74; 95%

CI: 0.61-0.88).[63] Pregnant women (second trimester) immunized against influenza A (H1N1) using SUV were evaluated to assess alterations in immune response and possible risk of antenatal development of the fetus in post-vaccination period. Mild local reactions were observed in 13% cases during vaccination, whereas 26.1% subjects presented general systemic reactions such as weakness, dizziness and headaches. The SUV demonstrated comparable reactogenicity with the control group and was considered safe to be used in pregnant women.[64]

Nursing Home Residents

A cohort study comparing the SUV vaccinated 10,739 elderly (older than 65 years; patients receiving one dose: 2,027; patients receiving two doses: 8,712) nursing home residents and 11,723 control subjects during an influenza A (H3N2) epidemic in 1998 to 1999 reported decrease in the number of cases diagnosed with influenza infection among the vaccinated group. Out of 950 cases diagnosed clinically with influenza infection, only 256 infected cases, 32 hospital admissions and one death were observed in vaccinated group as compared to the unvaccinated controls with 694 infected cases, 150 hospital admissions and five deaths. An equal efficacy was observed in patients receiving one or two doses of vaccine with no serious adverse reactions.[65]

Asthma Patients

Asthmatic patients infected with influenza virus may present worsened symptoms and other complications. Vaccination of asthma patients is recommended by physicians as well as the CDC. In a study, a total of 95 children (male: 52; female: 43; age range: 7 months to 12 years) suffering from moderate-to-severe asthma received SUV (Aggripal, IV). No sign of fever was observed till 48 hours after vaccination. Only three children (age: 7-30 months) showed signs of local side effects such as pain, restricted movement) at the site of injection for 8-12 hours. Overall, no side effects were observed till 2 months following the vaccination along with no worsening effect on asthma.[66]

Another study conducted on 14 asthmatic patients (12 men; 2 women; age range: 24-65 years) to assess the efficacy of SUV (Influvac, subcutaneous) reported SUV as well-tolerated vaccine in patients with asthma and was found to be immunogenic. No local or systemic side effects were observed following vaccination. Moreover, no change in the asthma symptoms was observed.[67]

CONCLUSION

Influenza virus infects individuals of all age groups and is associated with a diverse clinical presentation. Influenza is associated with several complications, which can be adverse to a considerable extent. Vaccination against influenza infection is therefore highly recommended. All the TIVs, i.e., WIV, SIV and SUV have been considered immunogenic; however, SUV presents better tolerability and lower reactogenicity as compared to other vaccine types. In addition, SUV has demonstrated high immunizing and favorable safety profile in clinical studies conducted on high-risk subgroups of population which include children, elderly, pregnant, liver transplant patients, asthmatics, diabetics and nursing home residents.

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