

Sars-Co-2 Vaccine Adverse Effects

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Abstract

Introduction: Vaccine adverse effects VAE is one of the most vital areas of human mass vaccination programs. Covid-19 vaccines are not an exception to this theme. Covid-19 VAE occupied the forefront area in the current covid-19 vaccine research. It broadly categorized into simple and complex or serious VAE. The simple account for tender and swelling in muscle injection sites, as well as fever. The complex or serious VAE can be ramified into vaccine associated enhancement of disease VAE and Vaccine failure VF. Both of VAE and VF are a matter of debate in covid-19 vaccine manufacturing holds. Though they were currently reportable all over the world.

Methods : The present work aimed at a ; follow up report of VAED and VF cases in the post-vaccination period .

Results: Immune vascular embolism in lungs and in the lower left arterial embolism in leg , thrombocytopenia ,cardio-pathy, atopic and delayed skin hypersensitivity. While VF was as break through sars-cov-2 infection as pulmonary , gastric and long forms. A total of 20 cases which account for 0.026 per thousand of the total vaccine coverage during the study period in this area.

Conclusion: The immune mechanisms behind each of VAE cases were discussed. These findings stands as a novel contribution in this area.

Key Words: Allergy, Covid-19 vaccine, cardio-pathy, embolism ,thrombocytopenia.

INTRODUCTION

Vaccine Adverse Effects VAE is one of the most vital areas of human vaccination programs .Covid-19 is not an exception to this theme. Covid-19 VAE occupied the forefront area in the current vaccine research. It broadly categorized into simple and complex VAE. Simple VAE accounts for pain at the injection site, fever. While complex can be ramified into vaccine associated enhancement of the disease VAED and Vaccine failure .Iraq ,as other parts of the world have been affected by the current circulating covid-19 pandemic [1-6].The emergency licensed vaccines currently combats successfully the burden of the infection spread all over the world[1].However, there have been a scattered reported clinical vaccine adverse effects classified as; Vaccine associated enhancement of the disease VAED which is a case in which vaccination predispose the vaccinee in post vaccination period to more severe infection form when subsequently exposed to the live virus as compared with infection occur with- out prior vaccination. Vaccine induced biased TH2 humoral antibody and/or TH2 cellular immune responses leading to natural infection[1].Thus ,it is characterized by; i-Post vaccination period , ii-Subsequent exposure , iii-Induction of biased immune responses and iv-initiation of virus natural infection. Vaccine induced enhancement of the disease VIED, which is a case of molecular mimicry of some virus vaccine epitopes with host cellular antigenic epitope(s) occurring within the tissue niche of human vaccinee in post-vaccination period leading to an auto reactive pathologic immune responses ,in which a disease such that of covid-19 post vaccination thrombosis and thrombocytopenia and myocardiopathies. Thus it is characterized by ;i- 5-45 days Post-vaccination ii-Molecular mimicry of immune functioning epitopes of viral vaccine and host tissue antigenic epitope(s) , iii-heparin independent and iv- consequent natural infection is non-conditional. [7,8].And Vaccine Failure VF, which is apparent and real. The apparent can be due to host incubating the infectious agent during vaccination. While, the real failure can be due to an irresponsive host immune system or failure of the applied vaccine make with outcome of failure to combat the infectious disease burden [9,10].Thus ,its characterized by; i-Failure to combat infection ii- post vaccination host immune system failure or vaccine make failure[9,10]. VAED and VIED were

ensemble under the ambrella of VAED and break through infection with vaccine failure in this communication. The objective of the present work was to report on VAED and VF in Babylon Province/Iraq.

MATERIALS AND METHODS

A special information case sheet was designed Figure-1, by the main investigator of the team to match the vaccine associated enhanced diseases in this area. The 21 patients were interviewed by the medical internist of the research team. These patients were the attendance of Mergan Teaching And AL-Sadik hospitals. Patients consents were taken before the information sheets. Standard clinical criteria [11-22] were followed for the case diagnosis as follows; General clinical and laboratory investigation like, CT scan, NMRI, CRP, LDL, ferritin, D-dimer and IL6 [11,12,13], Thrombosis, four to 20 days post-vaccination and D-dimer [14], thrombocytopenia, five to 42 days post-vaccination, CBP including platelet count [15], cardio-pathy CT, ECHO, ECG, NMRI, troponin [16,17], allergy [18], long covid [19,20,21] and breakthrough infections [13,22].

RESULTS

1-Demography:

The male female ratio was 2.5:1. The incidence of VAED in the age groups; (20-29), (30-39), (40-49), (50-59), (60-69), (79-79) and (80-89) were, 2, 2, 4, 3, 5, 4, 0 and 1 respectively. While it was clustered around the age range of 40-79 years. The occupation of the female patients was mainly state employed. While male patients were spanned between state employed, officer, physician and retired subject.

2-Prevaccination Immune State: The co-morbidity records was one with arterioseclerosis 1:21 [], one with multiple sclerosis. The other 19:21 were of normal immune status as they were interviewed from the care giving vaccine authority. The in use vaccine types were Pfizer 18:21, AstraZeneca 2:21 and Synopharm 1:21. Vaccine coverage in this area was presented in the Table 3. Up to March 23, 2022. The total Iraqi coverage was at least one dose 10,266,670, fully vaccinated 7,121,524. Booster given 148,708 [Our world in data, March 19, 2022 [23]]. The overall numbers of the vaccinated subjects at Babylon province till March 21 was 808,389 [24].

3-The nature of the vaccine adverse effects;

Vaccine adverse effects were simple common effects like fever, headache and malaise and complicated which ensemble in two major categories; Vaccine associated enhancement of disease and vaccine failure. The duration of the onset of the vaccine adverse effects as vaccine failure VF and vaccine associated enhancement of the disease VAED were ranging from three days up to eight months and incidence percentages were 57% and 43% accordingly figure-1. These 21 cases accounts for 0.026 per thousands.

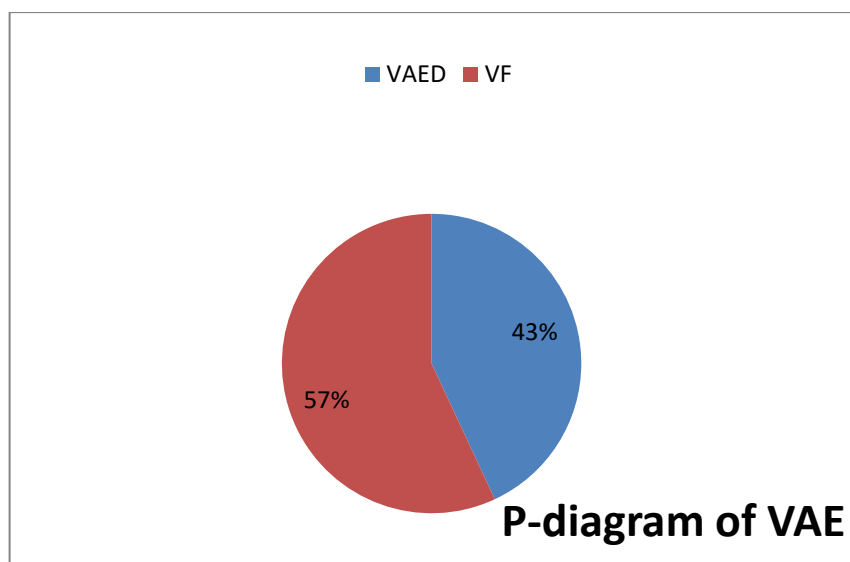


Figure -1: The percentages of vaccine adverse effects VAE as; failure VF to the Vaccine Associated Enhancement of the disease VAED.

3-1: Vaccine Associated Enhancement of Disease:

Immediate atopic allergy reaction with the onset of one to eight hours in one case .Delayed ``type of skin hypersensitivity with onset of one week post to first and second shot of Pfizer vaccine. Three cases with vascular thrombosis of leg artery and two of lung vessels. One with heart attack and the other with ischemic heart disease. Two were dead as a result of lung immune-thrombotic consequences .One with thrombocytopenia case. Table - 1.

Table 1 : VAED case information

Pt. Number	Sex	Age	First shot	Second shot	onset	Diagnostic evaluations	Diagnosis
2	Both	40-62		+	1-7 months	CT angiography	Vascular pulmonary embolism with an without atrial enlargement
1		70 years		+	Two days	CT angiography	Lower left leg popliteal artery embolism
2		70 years		+		Serum troponin elevation ,D-dimer elevation, PCR +	One with heart attack and the other with ischemic heart disease
1		45		+	up to eight hours	-Redness ,itch in skin and eye	-Skin & eye atopic allergy
1		71	+	+	One week post to first and second shot	Redness, raised papule like lesions	Skin delayed allergy
1	male	60		+		Low platelet count .covid 19 CT	Thrombocytopenia and covid-19 30% CT
1	female	26		+	Two weeks post second vaccine shot	Muscle pain, low grade fever Lethargy Joint pain	

3-2:Vaccine Failure :

The remaining were break through infections of various grades due to the state of vaccine failure, Table-2.

Table 2 :Vaccine failure break through covid-19 infections

Number of patients	Sex	Age years	First dose	Second dose	Onset/months	Diagnostic evaluation	Diagnosis
1	female	32		+	8 hrs	Abdominal pain, fever ,vomits,	Covid-19 gastritis

						Diaarhoea	
1	Male	24		+		Flu like, Cough ,chest pain	Pulmonary covid-19
1	Male	67		+	Eight months	Cough, fever ,SOB, elevated WBC,PLT 111	Covid-19 infection
1	male	59		+		CT 85% pCR +	Infection ,severe ,death
1	male	70		+		CT 90%	Severe infection ,death
7	both	30-90		+		CT scan 30-90%	Moderate to severe covid-19

4-Vaccine Adverse Effects Entities:

4-1: Vaccine Associated Enhancement of Disease Entities:

4-1-1:Vascular Embolism:

i-A 62 years old male, married ,have the first shot of Pfizer vaccine at Dec.5th.2021 and the second shot was at Jan.5th.2022.One month post to second shot, chest pain ,hemabmesis ,blood vomits and dark black hossey stool. ECO study revealed enlarged right atrium. Computed tomography for lung arteries have shown vascular embolism ,D-dimer assay has revealed elevation in concentration to10670 ng/dl.

ii-A 40 years old female, married, fully vaccinated with mRNA Pfizer vaccine six months post vaccination she developed respiratory symptom of cough and fever. Manual steathoscop chest check has shown loud second heart sound .Echo study have revealed enlargement of both right atrium and ventricle . Computed tomography has shown lung vascular embolism. The case showed a comorbidity with multiple sclerosis diagnosed three years ago through MRI investigation.

iii-A 70 years old female ,married .She got her first shot at Jan2022 and second dose at Feb.2022.Two days post to the second dose ,she developed fever and lower left leg pain .Computed tomographic angiography has shown vascular thrombosis in the popliteal artery.

4-1-2:Coagulopathy;

iv-Thrombocytopenia

A 65 years old male married, have covid-19 family contact. He got his full vaccination at Dec.2021.post to his second shot. He developed chest pain ,cough, cerpt chest ,ecchymosis and Hypertensive neuropathy, with blood coagulation problem due to low thrombocyte count ,abnormal thrombin and pro-thrombin time .The clinical diagnosis was thrombocytopenia. Chest CT scan revealed 30% covid-19 pathology.

4-1-3;Allergy:

v-Atopy:

A 45 years old male,married,covid-19 family contact, got his full vaccination with mRNA Pfizer vaccine atDec.21 and Ja.2022.Post to the first shot he developed skin redness, itching and redness of the eye .After full vaccination he developed a flu like sickness .CT investigation to chest has shown 25% covid -19 pathology.

vi-Delayed Skin Allergy

A 71 years old male ,he got his first shot of Pfizer mRNA vaccine at may.2021 and second shot at Jun.2021. A week post to the first and second shots he developed skin redness, rash and itching with raised red papule like lesions on his dorsal body plain skin face skin redness. Dermatologist diagnoses as post vaccination skin delayed allergy.

4-1-4:Cardiopathy:

vii-A 70 years old male ,married .He got first dose at oct and second dose at Nov.2021 .post to second dose, he was presenting dysnea ,SOB ,vomition and chest pain. ECHO,ECG and elevated serum troponin level have revealed Ischemic heart disease. Covid lung pathology at level of 40% in CT scan investigation.

viii- A 41 years old male , married with history of family covid-19 contact .He got his first and second, and present respiratory symptom post to the second dose .His clinical picture suggest a heart attack in addition to CT scan results indicate 85% covid-19 pathology. PCR for covid-19 mRNA was positive .D-dimer elevated to more than four folds the normal range value

4-1-5:Long Covid

ix:-A 26 years old female resident physician ,married. She has her first astrazinica vaccine shot at April-2021 and the second at Aug.2021.Two weeks post to the second shot she developed; low grade fever, arthralgia, myalgia, and lethargia.

4-2: Vaccine Failure Disease Entities

4-2-1:Extrapulmonary Break Through Infection

x- A 32 years old married female physician. She got his first mRNA covid-19 pfizer vaccine in July.2021 and second shot at Aug,2021.Eight hours post to second shot she was being feverish ,severe abdominal pain diarrhea ,tender a swelling site of injection. The clinical diagnosis was Gastritis.

xi- A 24 years old single male with history of family covid- 19 contact. Fully covid-19 mRNA vaccination. Developed flu like illness ,cough post taking the vaccine.

xii-A 67 years old male ,married ,He finished two shots of mRNA covid-19 vaccination at May.2021.Eight months post to second shot he complained fever ,cough associated with SOB and leukocytosis 9.05 cells/ml.

4-2-2: Severe Covid-19 break through infection with bad prognosis of death;

xiii- A 59 years old married male with history of covid-19 family contact. He was fully vaccinated with the multi-epitopic inactivated covid-19 synopharm vaccine .He complained illness post to second shot of the vaccine. Cough, chest pain, fever ,shortness of breath .CT investigation showed 75% covid-19 pathology, patient was resident in ICU, ventilation and ends with death.

xiv-A 70 years old married male with history of family covid-19 contact .He got his first and second shots of Pfizer mRNA covid-19 vaccine at July andAug.2021.Ten days post to second shot .His complaining was fever, cough ,shortness of breath, resident in ICU with aided ventilation. CT investigation has shown 90% covid-19 pathology. Patient ends with death.

4-2-3: A break through covid-19infection with comorbidity of Arterioseclerosis:

xv- A 53 years old married female having her first shot of Pfizer co vid -19 mRNA vaccine at Dec.2021 and the second shot at Jan.2022.Five days post to second shot she complain fever, cough chest pain D –dimer elevation. PCR mRNA covid-19 genes was negative. CT investigation has shown 60% covid-19 pathology .ECO studies showed arterio-seclerosis.

4-2-4: A break through moderate to severe covid-19 illness:

xvi- A series of six post vaccinee break through patients from both of sex with an age range of40 to 90 years. They complained; cough ,chest pain ,shortness of breath and fever post to second vaccine shot of Pfizer covid-19 mRNA vaccine. elevated D-dimer to a various degrees were noted and the CT investigation has shown covid-19 pathology of 30 up to 85 %.

Discussion

The pathology and immunopathology of human and zoonotic viruses can be attributed to the virus virulence factors or to the host immune responses to these factors. The virus infection and virus vaccination may induced humoral ,cellular and/or humoral and cellular immune responses. The immunity to virus infection can be a tripartite immunity as; innate ,cross-road ,and adaptive immunity .The nature of immune response time curve of human infection and human vaccinee are primary and secondary immune responses. The secondary immune responses in both cases resulted in both of effector and memory immunity[25].].Human immunity to vaccines are analogous but not homologous to infection immunity.Both immunity to virus infected and virus vaccinee human subjects can be in association with vaccine associated enhancement of the disease or with immune failure but those with vaccinee are more profound than the infected[1].Virus vaccine efficacy is either complete or partial in a sense of prevention of infection , modulation of the disease severity and/or change in death risk. The virus vaccine immunogenicity and vaccine efficacy are either associated or dissociated [26-28].

The nature of the Immunity to sars cov-2 virus infection in human being during the recovery time can be of ;Lost ,waning ,sterile and /or functional types[25,26] .While the immunity to sars-cov-2 vaccine might be similar/or different from that of infection post recovery immunity to date it is not clear cut evident. The sars-cov-2 vaccine efficacy have been found spanning between 55 up to 85% this range of efficacy depends onto vaccine design, menu of vaccination, population demography and eco-geographic determinants[25,26,27].Sars-cov-2 vaccine in post-vaccination periods may and may not be in association with vaccine associate enhancement of the disease VAED and/or vaccine failure VF (break through infection)[[1].The second or repeated infection with sars-cov-2 virus can be due reactivation of tissue resident inactive stealth virus ,co-infection and /or real re-infection[].While post-vaccination illness can be due vaccine failure or vaccine associated enhancement of the disease[29].Sars-cov-2 vaccine antigens may bears; immune over-reactive epitopes ,hyper-inflammatory epitopes ,immune-thrombotic epitopes ,immune mimicry epitope and/or immunosuppressive epitopes[25-28].The frequency of vaccine associated enhancement of the disease post-to second vaccine shot appeared to be more severe than that of post to first shot[].Now ,there are some debate about the possibility for VADE and VF in case of covid-19 vaccine. Workers believe that it is happening due to the day by day current reporting all-over the world ,others try to deny this believe due to manufacture oriented attitudes[Vaccine manufacturers].To the team believe it is possible and happening in this area.

Immuno-thrombosis and thrombocytopenia were reported ,Table -1 ,The possible mechanisms behind these haem-disorders post to covid-19 mRNA full vaccination with Pfizer make ,can briefly be stated in the followings;

Sars-cov-2 spike protein expressed from the mRNA vaccine within the human cells may serve as an initial trigger(s) of hyper-inflammation ,platelet activation and generation of thrombin a state which potentially lowering the threshold for a cascade that both trigger complement related to excessive inflammation, platelet and coagulation activation that promote “ vaccine induced immunothrombosis thrombocytopenia VIIT when combined with high titre functionally active PF4 antibodies[7,8].This stands as a new syndrome named” vaccine induced immunothrombosis thrombocytopenia VITT[7].

The hypothesis of VIIT syndrome holds the idea that IgG specific antibodies recognize the multi-molecular complex ofPF4-cationic and heparin anionic elements as foreign, such recognition causing multicellular activation and in particular the activation of monocyte and platelets through FcRgIIA receptor with the release of pro-coagulant ,metallo-proteins as well as direct activation of the endothelium by antibody complexes leading to increase thrombogenicity with the release of selectin P and E, Von-Wellbrand factor,IL6,and thrombosis with the consequent thrombocytopenia from the platelet consumption and severe thrombogenicity. Vaccination probably also can induce the formation of antibodies against platelet antigens as a part of the inflammatory reactions to cluster and form immune complexes through electrostatic interactions which in turn cause FcgRIIA massive dependent platelet activation ,increase of PF expression ,and subsequent generation of thrombin regardless the presence of heparin[7]

Two cases of post mRNA covid-19 vaccination were noted ,Table- 5 ,One atopic and the second was of delayed hypersensitivity. The immune mechanisms behind each of which was outlined in the followings;

The in the first exposure to the allergen ,atopic epitope that may be present in or on the mRNA vaccine components may induce DC. Dc in turn, activate naive T cells to be differentiated to TFH IL4 producing cells. TFH IL4 producing cells activate B cells to grow ,proliferate and expand as an effector B cells producing initially IgM the class switched into IgE.The B cell IgE producing do synthesis and secret IgE that bind to mast cell FceR this occurred within minutes after the exposure .In the second exposure ,however, IgE bind to mas cells receptors induce secretion of mediators ,this occurs within 2 to 4 hours[30].

On concurrent chronic exposure to the vaccine allergenic epitopes. These epitopes activate TH1 responses. These responses activate macrophages but fails to eliminate the allergen .A case in which both activated macrophage and growth and T cells continue to produce cytokines and growth factors that amplify the reactions of both of both cell types and progressively modify the local tissue environment.

This results in a cycle of tissue injury and chronic inflammation followed by replacement with connective tissue (fibrosis). In this setting of chronic DTH reactions, activated macrophages change in response to cytokine signals, will develop an increase in cytoplasm and cytoplasmic organelles and become like epithelial cells (Epithelioid Cells), these epithelioid cells may fuse together to form multicellular giant cells. The pathologic immune mechanisms involved both CD4 T cell and TH17 cells as well as CTLs. The first cells lead to cytokine-mediated inflammation and the second cells lead to direct cell killing and cytokine-mediated inflammation. Helper T cells also stimulate the production of antibodies that damage the tissue and initiate inflammation [30].

The two cases of post-covid-19 mRNA vaccination cardiopathy reported in this communication were consistent with other reports published elsewhere in the world. The first possible mechanism holds the idea that mRNA may induce the immune cell events and derive the activation of the aberrant innate and adaptive immune responses. The exposure of the Toll-like receptor bearing cells or DC to vaccine mRNA might have the capacity to express cytokines and activation of cell markers in certain individuals. A case in which the immune system may recognize mRNA as antigen resulting in activation of pro-inflammatory cascade and immunogenic pathways that play in the development of cardiac myopathy as a part of the systemic reaction to vaccine material in certain individuals. The second possible mechanism by which circulating autoantibodies sharing specificity heart antigens were usually directed to the heart multiple antigens, some of which may be capable to affect cardiac myocytes [16,17,31,32].

One case of long covid was reported Table-7. The possible mechanism was described to be multi-factorial immune effectors [33], accounts for nine possible causes of long covid. Though other workers favor the molecular mimicry for interpretation of post-vaccination long covid-19 as the spike epitope can be of sharing antigenicity with tissue antigens of brain, lung, gut, joints, kidneys, muscles and heart [34]. Another possible mechanism was to believe that remnants of the virus in the body frequently released facing the immune system cells inducing immune responses that collaterally impact post-vaccinee multiple organs [35]. The reported 21 cases, Table-1 are in agreement with what have been documented by other workers abroad [36-42].

The reported VF in form of break through infections of various severity was depicted in, Table -2, were also reportable by other workers all over the world [43-47]. There was an interesting debate whether the covid-19 exposure post-covid-19 vaccination stands as a booster or a risk. The virus exposure in post vaccination may act same as a booster in one holding, in the other holding that there is still concern of exposure to virus may trigger long covid [35].

Conclusion

The total Iraqi covid-19 vaccine coverage among the Iraqis was 7,121,524 for the fully vaccinated and booster given was 148,708. While the Babylon Province coverage was 808,389 till March, 2022. Vaccine make types from the more to the lower applied was Pfizer, AstraZeneca and Sinopharm. Complicated vaccine adverse effects were either vaccine failure and/or vaccine associated enhancement of the disease. The study vaccine associated enhancement of the disease were; lung thrombosis, lower leg intravascular thrombosis, thrombocytopenia, and cardio-pathy. Thrombosis and thrombocytopenia cases associated with Pfizer vaccine make. While the vaccine failure was noted in the form of break through infection forms were respiratory and gut patho-type. Vaccine failure break through infections dominates on vaccine associated enhancement of disease and the immune-thrombotic cases dominates the others of VAED in the reported cases. The observable incidence of VAE was 0.026 in each thousands of vaccinee. Such percentage seems to be parallel that of the abroad studies. These findings appeared to novel as concerned to this area.

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