



Post-Covid Vaccination and Non-Vaccination Complications

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Article History	Abstract
Received: 03 May 2023 Revised: 24 August 2023 Accepted: 07 Sept 2023	<p>Regarding the Covid-19 pandemic, researchers continue to be concerned about topics that have not yet been elucidated, the complications of serious patients during and after COVID, as well as their relationship with vaccination, are interesting. Studies show good acceptance of the vaccine by the general population, however, 15-20% have doubts about its safety. The most frequent complications are pulmonary, extrapulmonary and neurological, the latter due to the property of respiratory viruses neurotropism, which causes neurovirulence damage. The body shows strong reaction against COVID-19. Nonetheless, it is stronger with the OxfordAstraZeneca Vaxzevria vaccine than with the Pfizer-BioNTech Comirnaty vaccine, which also results in serious neurological disorders. We searched PubMed for the last 3 years. The search engine returned 147 abstracts, they were evaluated for selection and inclusion. They were classified according to how they described vaccine and non-vaccine complications. Through the theoretical foundation of the research, the main complications recorded in the literature consulted were identified. The rates of vaccine complications are low in relation to the immunized population. Vaccines continue to be the main measure to strengthen immunity, which is reflected in fewer serious patients and hospitalizations. In many cases, similar vaccine and non-vaccine complications are observed, so the organism's response to the virus or to other components of the vaccine is involved in the pathogenesis.</p>
CC License CC-BY-NC-SA 4.0	Keywords: Post-covid-19 vaccine complications, Non-vaccine complications

1. Introduction

Regarding the Covid-19 pandemic, researchers continue to be concerned about topics not yet elucidated, it is interesting the complications of serious patients during and after COVID, as well as their relationship with vaccination. The literature reports both manifestations resulting from the response produced between the virus and the host's immune system, as well as complications as a result of the vaccine. What are these complications? Are they frequent? What acceptance has the

vaccine had in the world population? What has been written about it? In the case of post-vaccination complications, are they prevalently related to a vaccine? These are some of the questions that generated this review.

Loza Chiriboga and collaborators in his studio... Pandemic in Ecuador: acceptance of the population before the application of the vaccine against covid-19, show that a large part of the population considers that the vaccine would be effective, but about half of the respondents do not know or deny wanting to be vaccinated, assuming that many mention that it would have adverse effects on health (3). This suspicion is likely due to lack of information or problems understanding the role of immunization in these pandemic cases.

According to the World Health Organization, vaccines against Covid 19, like any vaccine, can cause side effects, most of which are mild or moderate and disappear spontaneously within a few days, as a result of the immune response produced in our body, however, the results of clinical trials show that more serious or lasting side effects can also appear (4). Common side effects are injection site pain, fever, tiredness, headaches, myalgia, chills and diarrhoea. The likelihood of their occurrence varies depending on each vaccine and the host's response to it.

COVID-19 vaccines protect only against the SARS-CoV-2 virus, so it is important to also maintain good health and protect against other viral serotypes and other common diseases.

The truth is that according to the PAHO report to date in the Americas there have been more than 180,419,329 infected by the SARCov2 virus, to which is added 7,478 additional cases in the last 24 hours, more than 2,859,053 accumulated deaths, 44 in the last 24 hours (5). In Ecuador there are 999,837 confirmed cases of Covid-19, 112 in the last 24 hours]. In addition, 247,309 probable cases of being Covid-19 are registered, awaiting their result. In the last 24 hours, results of 406 tests are reported, of which 27.6% were positive. The cumulative national rate of Covid-19 cases is 5,709.9 per 100,000 inhabitants. 35,884 people died from Covid-19, 3 in the last 24 hours. The case fatality ratio of the virus (CFR) is 3.6% of the total confirmed cases while the cumulative mortality rate is 204.9 per 100,000 inhabitants (6). Deaths related to complications of severe forms. The most frequent complications are those related to risk factors such as age associated with chronic non-communicable diseases such as obesity, hypertension, diabetes mellitus, among others (7).

The most frequent complications produced in severe patients infected by the SARS-CoV-2 virus are pulmonary, extrapulmonary and neurological, the latter due to the property of respiratory viruses to affect the cells of nervous tissue, which is known as neurotropism, everything that causes neurovirulence, among these complications by COVID 19 virus are: taste and smell disorders, encephalopathies, encephalitis, acute hemorrhagic necrotizing encephalopathies, Guillain-Barré syndrome (8).

Regarding extrapulmonary complications, cardiovascular, hepatic, neurological, hematological, renal and inflammatory response syndromes were diagnosed in adults and children. Multicenter study of 1099 patients in China reported 83.2% lymphopenia, 36.2% thrombocytopenia and 33.7% leukopenia (34). In addition, the association between lymphopenia and the development of ARDS has been demonstrated (35). In addition, 2 studies were conducted in China which mentioned an association between lymphopenia and the need for admission to the ICU. (9) (10) (11). In Washington, lymphopenia was also notorious in critically ill patients (12)(13)14).

The most frequent post-vaccine complications are also neurological, hematological, cardiovascular, respiratory and gastrointestinal, due to the wide distribution of the angiotensin II receptor used by the virus to penetrate the cell.

Post-vaccine neurological complications with mRNA preparations appear to be induced by a pathophysiological basis shared with COVID-19 viral infection, by binding of viral proteins to human cells that trigger an inflammatory response. This inflammatory state can cause a hypercoagulable state manifested by ischemic or thrombotic stroke complicated by intracranial hemorrhage. Post-vaccine strokes responded better to treatment than those dependent on COVID-19 viral infection. The body's reaction to COVID-19 vaccines is stronger with the OxfordAstraZeneca Vaxzevria vaccine than with the Pfizer-BioNTech Comirnaty vaccine, resulting in serious neurological disorders. The study and

follow-up of these cases facilitates the identification of associated risk factors that make them susceptible to specific complications (15).

During pregnancy, no major adverse effects were reported in the mother or newborn, on the contrary, antibodies were found in these babies, which is an excellent result and allows pregnant women to be guided to use immunization with confidence (16).

Regarding post-cardiac vaccine complications, an analysis article in Singapore was reviewed where they combine cohort study and systematic review, with appearance of cardiac manifestations within 14 days after vaccination with COVID-19. Of the 30 patients included in the research, thirty 29 were diagnosed with acute myocardial infarction (AMI) and 1 myocarditis, 5 developed heart failure, two suffered cardiogenic shock, three were intubated and one presented cardiovascular mortality, in the review they found in 16 studies with 41 myocarditis and six cases of AMI. In the combined cohort analysis of the study and the systematic review, 35 patients had AMI and 42 had myocarditis, it turned out that patients with myocarditis presented symptoms 72 hours after vaccination, while patients with AMI were older and presented them 24 hours after vaccination. Most with AMI or myocarditis developed symptoms after the first and second doses of vaccination, respectively (17).

Acute transverse myelitis (ATM) is a very rare neurological disease, with an incidence of 1.34 to 4.6 cases per million / year, note the attention that during the pandemic there have been cases of TMJ associated with COVID-19. Román et al. studied 43 cases of acute installation, patients presented paralysis, sensory alterations and sphincter disorders caused by inflammatory injury of the spinal cord demonstrated by images. The disease occurs equally in both sexes aged between 20 and 75 years.

The researchers concluded that TMJ is an inexplicably common neurological complication in COVID-19 patients. The latency of the first symptoms was from 10 days to 6 weeks, whose pathogenic mechanism could be explained by the host response to the virus. The AZD1222 vaccine trials reported three cases of acute transverse myelitis out of 11,636 participants, which is considered high considering a global incidence of 0.5/million cases of TMJ associated with COVID-19 found in this report. The pathogenesis of TMJ is still being studied as many factors remain unknown, however, they must be common elements to the SARS-CoV-2 virus and the AZD1222 COVID-19 vaccine or its adjuvant that could be explained by the immune response of patients as a cause of myelitis (18).

Frédéric Zuhorn and collaborators also found and presented a series of cases of post-vaccine encephalitis with the ChAdOx1 nCov-19 vaccine, the diagnosis of autoimmune cause was confirmed. Patients responded to immunosuppressive corticosteroid therapy. The estimated incidence is approximately 8 per 10 million doses of vaccine. The complication of post-vaccine encephalitis after vaccination with ChAdOx1 nCoV-19 still appears to be very rare, but should be properly diagnosed and treated (19).

In addition, the ophthalmological complications of COVID-19 were studied, with conjunctivitis being the most common manifestation. Among the proposed causes are direct injury to the virus or tissue damage mediated by the immune response, leading to the activation of the coagulation cascade. Viral ribonucleic acid (RNA) has been isolated from ocular tissues, but the role of the eyeball as a route of infection is not yet known. Ophthalmologists do not escape this disease and should prepare for the proper diagnosis and treatment of possible ocular complications from SARS-CoV-2 (20).

2. Materials And Methods

Modality of the research

This review of information was carried out from different bibliographic sources that theoretically supported the main complications of COVID-19 and post-vaccination.

We searched PubMed up to 2 November 2022 for the last 3 years for which we used the following keywords: post-COVID-19 complications vaccine or not. The search engine yielded 147 abstracts The abstracts and titles of each article were evaluated for selection and inclusion. 25 abstracts were selected for reading the extensive article. They were classified into those describing post-covid vaccine and non-vaccine complications.

3. Results and Discussion

As of November 2, 147 articles were found with the search terms. We found only 3 articles, which in general present clinical complications of Covid-19, a series of cases of acute transverse myelitis (TMJ), one of myelopathy and another on thrombosis and thrombocytopenia, which detailed the infrequency of the complication in the initial presentation of Covid-19 (21)(22).

All other studies analyzed referred to post-vaccination complications. Among the most frequent complications were neurological, hematological and cardiac. The vaccines with the highest adverse effect rates were AstraZeneca COVID vaccine, ChAdOx1 nCoV-19 COVID vaccine, AZD1222 COVID vaccine, Janssen COVID vaccine, Johnson & Johnson COVID vaccine, Ad26.COV2 COVID vaccine.

It is established that vaccination protects against hospitalization, ICU admission and death from COVID-19 (23), however, it has minimal adverse effects like any other drug. On the other hand, prior vaccination does not appear to change the picture of previously documented COVID-19 outcomes, such as prolonged COVID-19 sequelae, arrhythmia, joint pain, type 2 diabetes, liver disease, sleep disturbances, and mood and anxiety disorders, as well as maximal tiredness (24).

The absence of a protective effect against the long-lasting characteristics of COVID-19 is of concern given the high incidence and burden of these sequelae of COVID-19 (23). Relative differences in the incidence of individual characteristics of long COVID could explain why our findings differ from those of an app-based survey suggesting that vaccination generally protects against symptoms of long COVID (25).

In summary, current data shows that prior vaccination against COVID-19, especially after two doses, is associated with a significantly lower risk of severe COVID-19. These findings can inform service planning, contribute to forecasting the public health impacts of vaccination programs, and highlight the urgent need to identify or develop additional preventive and curative interventions for the aftermath of COVID-19.

The table below describes the reviewed articles.

Table 1: Information on reviewed articles.

Type of item	Year	Complications		Methodology	Sample	Results
		Post-vaccination	No vaccines			
Systematic review	2021	Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) and Cerebral Venous Sinus Thrombosis (CVST)		Evaluation of abstracts and titles of each article for selection and inclusion	12 items	Among 49 patients with CVST, at least 19 patients died (39%) due to complications of CVST and VITT.
Scientist	2022	Cerebral venous sinus thrombosis. Bell's Paralysis Acute demyelinating polyneuropathy		Descriptive	62 items	Inconclusive Large collaborative prospective studies are needed to prove or disprove the causal association between the vaccine and neurological adverse events that occur with vaccination.
Scientist	2021	Ocular complications: 3 herpetic keratitis, 2 anterior scleritis, 5 anterior uveitis (UA), 3 toxoplasma chorioretinitis, 2		Retrospective study included patients with uveitis and other ocular complications following	34 patients	These complications could be related to the ability of SARS-CoV-2 vaccines to induce autoimmune

		<p>reactivations of Vogt-Koyanagi-Harada disease (VKH), 2 pars planitis, 2 retinal vasculitis, 1 newly occurring bilateral panuveitis. Behçet's disease, 3 multiple evanescent white spot syndromes (MEWDS), an acute macular neuroretinopathy (AMN), 5 retinal vein occlusions (VOR), non-arteritic ischemic optic neuropathy (NAION), 3 activations of chiascent choroidal neovascularization (CNV) secondary to myopia or uveitis, and central serous chorioretinopathy (CRSC)</p>		<p>COVID-19 vaccination between January 2021 and October 2021 at the Ocular Immunology Unit, Azienda Unità Sanitaria Locale (AUSL)-IRCCS, Reggio Emilia, Italy.</p>		<p>manifestations or thromboembolic events. Further epidemiological and clinical studies and longer follow-up of this cohort are needed to confirm the link between the COVID-19 vaccine and de novo recurrence or development of uveitis and other ocular complications.</p>
<p>Joint Clinical Case Study and Systematic Review</p>	<p>2021</p>	<p>Cardiac complications: AMI and Myocarditis</p>		<p>Patients admitted to a tertiary hospital in the first half of 2021, with cardiac manifestations within 14 days after vaccination with COVID-19, were studied. Systematic review, with access to PubMed, Embase, Research Square, MedRxiv and LitCovid databases from inception to 29 June 2021</p>	<p>30 patients were included in the study cohort of them 29 diagnosed with acute myocardial infarction (AMI) and 1 with myocarditis</p>	<p>We highlight the differences between the presentations of myocarditis and AMI in temporal association with vaccination.</p>
<p>Review of clinical cases</p>	<p>2021</p>	<p>3 TMJ adverse events reported among 11,636 participants in AZD1222 vaccine trials</p>	<p>Acute transverse myelitis (TMJ)</p>	<p>Case analysis in a patient from Panama with SARS-CoV-2 infection complicated by TMJ. Literature review of 43 patients with TMJ associated with COVID-19 from 21 countries published from March 2020 to</p>		<p>TMJ is an unexpectedly common neurological complication of COVID-19. The occurrence of 3 reported TMJ adverse events among 11,636 participants in the AZD1222 vaccine trials is extremely high considering a global incidence of</p>

				January 2021. In addition, 3 cases of TMJ were reported as serious adverse events during clinical trials of the COVID-19 vaccine ChAdOx1 nCoV-19 (AZD1222)		0.5/million ATM cases associated with COVID-19
Revision	2021	Vaccine-induced immune thrombocytopenia and thrombosis. (VITT)		Prospective study based on the National Cohort Study on the Efficacy and Safety of SARS-CoV-2/Covid-19 Vaccines	80 participants recently vaccinated (median 11 days [range 8-16] post-vaccination) with AZ (n=55, Oxford/AstraZeneca [AZD1222/ChAdOx1]) or mRNA (n=25 total: n=16 Pfizer/BioNTech [BNT162b2] and n=9 Moderna [mRNA-1273]) vaccines	the present study investigated the influence of different COVID-19 vaccines on inflammation, vascular endothelial activation, platelet activation and aggregation, whole blood clotting, thrombin generation, and PF4 antibodies to reveal potential differences between AZ vaccines and mRNA in individuals without VITT. The main findings were that the AZ vaccine induced a more pronounced increase in inflammation and platelet activation and increased thrombin generation compared to mRNA vaccines and that none of the vaccinated individuals developed PF4 antibodies. We speculate that specific components of the AZ adenovirus vector may serve as initial triggers of (hyper)inflammation, platelet activation, and thrombin generation.
Series Study of 3 clinical cases	2021	Post-vaccine encephalitis after ChAdOx1n Cov -19		Case series of three patients with autoimmune	3 cases	Very rare condition. Cass without sequelae, responded very

				encephalitis related to previous vaccination with ChAdOx1 nCoV-19		well to immunosuppressive steroid therapy.
Report Review	2021	Allergic reactions. Pfizer-BioNTech Anaphylaxis		Descriptive cross-sectional study summarizes the clinical and epidemiological features of case reports of allergic reactions, including anaphylaxis and non-anaphylaxis allergic reactions, after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine between December 14 and 23, 2020 in the United States.	We identified 175 case reports for further review as possible cases of severe allergic reaction, including anaphylaxis	The prevalence of such adverse effects is minimal. There are at least 4 biases in the data
Systematic review and meta-analysis	2021	TTS-associated thrombocytopenia and thrombocytopenia syndrome (TTS) and cerebral venous sinus thrombosis (CVST)		Systematic review and meta-analysis of clinical trials, cohorts, case series, and registry-based studies	69 studies Qualitative analysis comprising 370 patients with CVST out of 4182 patients with any thrombotic event associated with administration of the SARS-CoV-2 vector-based vaccine. A further 23 studies were included in the quantitative meta-analysis.	About half of TTS patients have TSVC; almost one-third of patients with TTS do not survive. More research is required to identify independent predictors of TTS after adenovirus vector-based vaccination.
Experimental study	2021	The first dose of the AstraZeneca vaccine causes banal side effects more often than any dose of the Pfizer vaccine.		Analysis of the results of the application of a survey to a group of 705 vaccinated people.	705 people. 196 vaccinated with Pfizer and 509 with AstraZeneca	Side effects are frequent, evidence of immune system response. The first dose of the AstraZeneca vaccine causes side effects more often than any dose of the Pfizer vaccine.
Literature review	2022	Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)/thrombosis with	Thrombosis and thrombocytopenia is uncommon in the initial	Literature review of current knowledge on thrombotic and/or	Information found on the topic until July 2022	

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		Thrombocytopenia Syndrome (TTS) after administration of adenovirus-vectored vaccine. VITT/TTS	presentation of Covid -19	thrombocytopenic disorders reported with COVID-19 vaccines		
Literature review	2021	Cancer, safety and immunogenicity of COVID-19 vaccines			21 studies with a total of 5012 cancer patients, of whom 2676 (53%) had haematological malignancies, 2309 (46%) had solid cancers and 739 were healthy controls.	Cancer patients are a high-priority subgroup for COVID-19 vaccination and emphasize the need for longer-term data.
Systematic Review and Meta-Analysis	2021	Myocarditis in vaccinated		Systematic search in PubMed, Embase, Web of Science and Google Scholar of literature published between January 1, 2020 and July 17, 2021	69 patients from 25 qualified case reports and case series.	Myocarditis following mRNA vaccination is predominantly seen in young men a few days after the second dose of vaccination.
Case Series Study	2022	Hyperglycemia and pancreatic damage		Search for cases with reported hyperglycemia after vaccination		There is insufficient evidence in this regard
Reporting a case	2021	Neuromyelitis optica spectrum disorder (NMOSD)		Literature search to support the evidence found		NMOSD is severe and curative, it is important to know the symptoms of NMOSD after vaccination. Consider patients with pre-existing systemic autoimmune abnormalities in vaccination for COVID-19.
Original article	2022	Post-vaccination side effects		Publicly available data from the U.S. Vaccine Adverse Event Reporting System (VAERS) collected between January 1, 2021 and June 14, 2021.	Analysis of reported effects in 306,907,697 patients vaccinated during the study time period.	Few adverse effects if we analyze it in relation to the number of doses of inoculated vaccines
Original article	2022	Post-vaccine effects		Retrospective cohort study	10,024 emerging infections	COVID-19 vaccination is associated with a lower risk of COVID-19 sequelae in people with advanced

						SARS-CoV-2 infection. It is also associated with low hospitalizations, ICU admissions, and death from COVID-19. In addition, vaccination against COVID-19 is associated with a lower risk of respiratory failure, hypoxemia, oxygen requirement, venous hypercoagulopathy or thromboembolism, seizures, psychotic disorder and hair loss.
Clinical case presentation	2022	Post-vaccine gastrointestinal effects: acute diverticulitis and colon microperforation		Case Study		The complication occurs one day after the reinforcement of vaccination with Moderna.
Clinical case presentation	2021	Post-vaccine inflammatory myositis Anti-Jo-1 syndrome		Case Study		Post-vaccine inflammatory myositis second dose of COVID-19 vaccine (Oxford-AstraZeneca)
Systematic review	2021	Post-vaccine myelopathy COVID-19.	Myelopathy related to COVID-19.	Systematic review	18 items	In all cases the diagnosis was verified
Original article	2022	Musculoskeletal adverse effects		Cross-sectional study in India using a properly validated and approved survey	2334 study participants	More than 50% of vaccinated people experienced some form of musculoskeletal side effects
Reporting a case	2022	Aortic dissection complicated with histiolympocytic pericarditis and aortic inflammation after COVID-19 mRNA vaccination		Analysis of a post-autopsy report		Histological findings were compatible with those of post-vaccine myocarditis
Original article	2022	Side Effects and Risks of Outbreaks in Patients with BNT162b2 Post-Vaccine SLE (BioNTech & Pfizer)		Descriptive observational study in patients with SLE from the Department of Immuno-Rheumatology of the Cayetano Heredia Hospital, Lima, Peru, immunized with the BNT162b2		Episodes of reactivation after vaccination against SARS-CoV-2 (mainly mild) are described, we advise that the COVID-19 vaccination process remains a priority for patients with SLE.

				vaccine from May 21 to June 30, 2021		
Original article Cases- controls		Behavior of serum antibodies against SARS-CoV-2 in patients with chronic liver diseases such as cirrhosis		Consecutive patients who visited the hepatology outpatient clinic of the General Hospital "Laikon" of Athens, Greece, from March 1 to May 31, 2021, were recruited for the evaluation of serum anti-SARS-CoV-2 antibodies at 3 time points: before the first dose of the vaccine, 1 month after the second dose of vaccine and 3 months after the second dose of vaccine. Inclusion criteria included the presence of chronic liver disease and planned vaccination with the Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273 vaccines		New mRNA-based SARS-CoV-2 vaccines found to be effective and safe in patients with liver disease
Incidence study	2022	Exacerbation of autoimmune bullous diseases after vaccination against severe acute respiratory syndrome coronavirus 2		Longitudinal descriptive study	446 patients with autoimmune bullous diseases (AIBD)	Not enough evidence was gathered that the risk of exacerbation of AIBD post-COVID-19 vaccine to prevent vaccination.

. Source: author

4. Conclusion

Through the theoretical foundation of the research, the main vaccine and non-vaccine complications recorded in the literature consulted were identified. Vaccine complication rates are low in relation to the vaccinated population. Vaccines remain the main medicine for strengthening immunity and therefore are reflected in fewer serious patients and hospitalizations. In many cases, similar vaccine and non-vaccine complications are observed, so the pathogenesis of these manifestations involves the body's response to the virus or other components of the vaccine.

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