Journal of Vaccines, Immunology and Immunopathology
Rella S and Brooks BD. J Vaccines Immunol 9: 1115.
www.doi.org/10.29011/2575-789X.0001115
www.gavinpublishers.com

Commentary

Rethinking Risk of Adverse Events in Vaccination

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Citation: Rella S, Brooks BD (2024) Rethinking Risk of Adverse Events in Vaccination. J Vaccines Immunol 9:1115. DOI: 10.29011/2575-789X.0001115

Received Date: 25 March, 2024; **Accepted Date:** 29 March, 2024; **Published Date:** 01 April, 2024

Abstract

The growth of vaccine hesitancy, especially highlighted during the COVID-19 pandemic, has raised concerns over the safety and efficacy of vaccinations. Amidst accelerated vaccine development and widespread misinformation, public trust has been tested, underscoring the necessity for clear communication and evidence-based information on vaccine safety. This review delves into the incidences of serious adverse effects such as myocarditis, Guillain-Barre Syndrome (GBS), and Complex Regional Pain Syndrome (CRPS) post-vaccination, comparing these with the occurrence rates following natural infections. Utilizing data from the Vaccine Adverse Event Reporting System (VAERS) alongside various epidemiological studies, a detailed analysis of adverse events associated with recommended vaccines (COVID-19, HPV, herpes zoster, hepatitis B, and influenza) and the morbidity of the infectious diseases they treat is presented. Findings reveal that serious side effects from vaccines are exceedingly rare and occur at much lower rates compared to the complications from the diseases they aim to prevent. The commentary emphasizes the importance of continuous vaccine safety monitoring, advocating for targeted educational campaigns detailing actual vaccine risk versus infection and transparent communication to combat vaccine hesitancy and bolster public confidence in vaccination as a cornerstone of public health.

Keywords: Adverse Effects; Complex Regional Pain Syndrome; Guillain-Barre Syndrome; Myocarditis; Public Trust in Vaccination; Vaccine Hesitancy

Introduction

Since their development and introduction as a preventative health measure, vaccines have gained widespread acceptance as essential and beneficial for public health, with their efficacy and safety endorsed by regulatory bodies [1]. Vaccines effectively reduce the transmission, severity, and complications associated with the infections for which they are developed. Like all medications, vaccines are not free of adverse side effects. However, the side effects of vaccination have been deemed outweighed by a vaccine's benefits [2]. Many common side effects are associated with all vaccines, including administration site reactions, fever, chills, and allergic reactions [3].

While adverse events experienced by individuals are unfortunate, and efforts should be made to reduce their occurrence, the rarity of such events highlights vaccinations' overwhelming safety and efficacy for the broader population. This review explores the incidence of serious side effects such as myocarditis, Guillain-Barre Syndrome (GBS), and Complex Regional Pain Syndrome (CRPS), comparing the frequency of these adverse events in vaccination versus infection scenarios to support the justification for vaccination. The documentation of vaccine-associated adverse events has become more comprehensive and continuously grows, particularly with new monitoring programs introduced during the COVID-19 pandemic [4]. These initiatives have enhanced the ability to track and analyze vaccine side effects in real time, offering unprecedented insights into the safety profiles of COVID-19 vaccines and beyond. Such programs, including enhanced surveillance systems and expanded reporting databases, have been crucial in identifying, investigating, and addressing potential adverse events quickly and efficiently. Adverse events are also available to the public through online databases documenting adverse events following vaccination, such as the Vaccine Adverse

Event Reporting System (VAERS). Over the past three decades, the belief that vaccination is not beneficial and can be, in fact, harmful has unfortunately grown in popularity, especially after the COVID-19 pandemic [5] . Pfizer and Moderna's accelerated development and deployment of mRNA vaccines during the COVID-19 pandemic contributed to an increase in vaccine skepticism and anti-vaccination sentiment [6].

The side effects associated with vaccines have scared individuals to the point of refusing vaccines despite the education and encouragement from physicians. Recently, Faksova et al. reported serious side effects, such as myocarditis, are associated with the COVID vaccines (i.e., Moderna, Pfizer, and AstraZeneca) but occur at a lower rate than with COVID infection [7]. This article aims to expand on the notion that side effects, such as myocarditis, GBS, and CRPS, occur at lower rates with vaccination compared to their incidence with infection. In this commentary, records and VAERS assessments of common mRNA, killed, recombinant, and subunit vaccines in the United States, including those for COVID-19, HPV, herpes zoster, hepatitis B, and influenza, were examined. The analysis identified these vaccines' most common serious side effects and compared the incidence of these occurrences following vaccination to the incidence following infection.

Myocarditis

Myocarditis is inflammation of the heart muscle or myocardium. Although myocarditis can arise from various causes, in high-income countries, the predominant cause is viral infection [8]. Following the introduction of COVID-19 vaccines, mainstream, and social media circulated concerns that these vaccines might not meet the "safe and effective" standards promised by the FDA and healthcare professionals, highlighting potential side effects like myocarditis and blood clots. This coverage amplifies and expands public fears, increasing vaccine hesitancy among specific population segments [6]. The problem lies in the fact that these notable side effects are presented as only occurring in the setting of vaccination against COVID-19. However, evidence shows that these side effects occur not only in the setting of infection with the virus but also at higher rates than seen with vaccination. For example, according to a VAERS assessment of all COVID-19 vaccines, including Pfizer, Moderna, Novavax, and Johnson & Johnson, with dates ranging from 2020-2023, there were 3,091 documented cases of myocarditis. According to a published dataset, over 676 million COVID-19 vaccine doses have been administered in that time frame [9]. Based on this data, the incidence of myocarditis with vaccination in the United States is roughly $4.6x10^{-6}$ or 0.00046%. According to Whitberg et al., the estimated incidence of myocarditis after at least one dose of the BNT162b2 (Pfizer-BioNTech) mRNA vaccine is 2.13 cases per 100,000 (or 0.002%) according to the Clalit Health Services database in Israel [10]. Other epidemiological studies have suggested the incidence of myocarditis after COVID vaccination to range between 0.8 to 147 per million (or 0.00008%-0.0147%) (Table 1) [11-15].

Myocarditis with COVID-19 [10-14,16-18]		
Incidence with vaccine: 0.00008%-0.0157%	<	Incidence with infection: 0.12%-0.146%
8-1800x greater risk with infection*		
GBS with HPV [23,25,28,29]		
Incidence with vaccine: 0.00009%-0.00225%	<	Incidence in general population: 0.001-0.002%
Up to 22x greater risk with infection*		
GBS with Herpes Zoster [21,29,32,33]		
Incidence with vaccine: ~0.000549%	<	Incidence in general population: 0.001-0.002%
2-3x greater risk with infection*		
GBS with Influenza [20,29]		
Incidence with vaccine: 0.000022%-0.0005%	<	Incidence with infection: 0.0017%
3-77x greater risk with infection*		
CRPS with HPV [34–37]		
Incidence with vaccine: ~0.000024%	<	Incidence in general population: 0.0063-0.026%
260-1000x greater risk with infection*		

*based on calculations of incidence data presented in the table.

Table 1: Adverse Event Incidence in Vaccines vs Infection

In contrast, Tuvali et al. reported an incidence of myocarditis in a cohort of post-COVID-19 infected patients identified from the Clalit Health Services database in Israel at 0.0046% [16]. In a cohort of patients identified by admission to the hospital for COVID-19 in the United States, the incidence of developing myocarditis was 0.12% [17] . In an extensive database assessment performed by the CDC, it was found that the incidence of myocarditis with COVID-19 infection was 0.146%, and patients were found to have a 15.7x greater risk of developing myocarditis with COVID-19 infection when compared to those without COVID-19 [18]. Myocarditis is a common complication associated with viral infections, including COVID-19. The available data suggests that myocarditis with COVID-19 infection is approximately ten times higher than vaccination against COVID-19 [11-18]. Considering the significantly higher incidence of myocarditis associated with COVID-19 infection compared to vaccination, the data supports that the risk of developing myocarditis-and potentially other side effects-is considerably lower when opting for vaccination against COVID-19, underscoring the vaccines' safety and efficacy in preventing severe outcomes of the virus.

Guillain-Barre Syndrome

A potential side effect for many vaccines that was repeatedly seen in the literature is Guillain-Barre Syndrome (GBS) [19-23]. This autoimmune attack on the peripheral nervous system is commonly preceded by infection or an event that stimulates the immune system, such as vaccination [24]. The incidence of GBS with HPV vaccination, mainly Gardasil, has been reported to be low, with an estimated incidence between 0.55 and 2.25 cases per 100,000 people (or 0.00055% to 0.00225%) as per a recent meta-analysis [23]. According to a VAERS assessment of Gardasil, Gardasil-9, and Cervarix vaccination adverse events from 2006-2023, a total of 126 GBS events have been reported. According to the CDC, there have been over 135 million doses administered of Gardasil, Gardasil-9, and Cervarix in the United States, making the overall incidence of developing GBS after vaccination against HPV estimated to be 0.93 per 1 million (or 0.000093%). Multiple studies have shown limited association between GBS and HPV vaccination [25-28]. Furthermore, the incidence of GBS in the general population is estimated to be 1-2 cases per 100,000 people per year (or 0.001-0.002% annually) [29]. The incidence of GBS resulting from HPV infection remains unknown due to the absence of reported statistics and case studies on this matter. However, it is estimated that over 42 million people in the United States are infected with HPV, and an estimated incidence of disease-associated HPV infection in persons aged 15-59 years old is around 672 cases per 10,000 persons (or 6.72%) [30].

The prevalence of HPV in the United States is high, but GBS is rare. While accurate epidemiological data is missing, it may be safe to assume the incidence of developing GBS is likely similar in those with or without vaccination against HPV, and thus, the vaccines do not pose any higher risk of harm in regards to GBS. Furthermore, GBS has been documented with other vaccines, including herpes Zoster. The Shingrix vaccine has had 62 documented events reported per a VAERS assessment of GBS and mononeuropathy multiplex between 2017 and 2019. During that same time frame, roughly 11.3 million doses of Shingrix were administered, with 7.1 million first and 4.2 million second doses, as per a recent study [31]. These statistics show that the calculated incidence rate for developing GBS is 5.49 per 1 million (or 0.000549%). A small number of case reports documenting the development of GBS with primary or secondary infection with VZV [32,33] Islam et al. found that 1.7% of patients in their study with GBS had chickenpox cases within four weeks of onset of symptoms [33]. The incidence of GBS associated with VZV infection had minimal data, but compared to the incidence of GBS in the general population, which is 1-2 cases per 100,000 people per year (or 0.001-0.002% annually), the incidence with vaccination is significantly lower.

Expanding on the above, the development of GBS post-influenza vaccination compared to infection further strengthens our argument. Influenza vaccination is among the most commonly distributed annual vaccines in the United States, with over 173.4 million doses administered in 2022-2023, per the CDC. Per a VAERS assessment of intramuscular influenza vaccination, excluding intranasal spray, 39 cases of GBS reports occurred during the 2022-2023 period. Hence, the incidence rate for developing GBS following the influenza vaccine is determined to be 0.22 per 1 million doses (or 0.000022%). A recent review examining the incidence of GBS with influenza vaccination reported the incidence to be between 1-5 cases per million doses of vaccine administered, with the highest risk occurring within 2-3 weeks post-vaccination. The estimated incidence of GBS after influenza infection was 17.2 cases per 1 million patients hospitalized with influenza [20]. The incidence of GBS associated with influenza infection is considerably higher than with influenza vaccination. Additionally, the incidence of GBS in the general population, which is 1-2 cases per 100,000 people per year, is higher than in association with influenza vaccination. The data mentioned above demonstrates that serious complications associated with vaccination in this GBS occur at higher rates than in the rates associated with infection.

Complex Regional Pain Syndrome

Complex Regional Pain Syndrome (CRPS) is still not completely understood by medical professionals, and while it's considered rare, its actual occurrence may be more common than presently acknowledged. CRPS is a condition where patients experience a level of nerve pain that is much more intense than what would typically be expected from the initial tissue damage. This pain continues longer than the normal healing time, with

symptoms and intensities varying greatly from one individual to another [34]. In recent years, there have been documented cases of CRPS appearing after receiving the HPV vaccine. Huygen et al. identified 18,391 adverse event reports regarding persons who received the HPV 16/18 vaccine. Of these, 17 were reports of CRPS, but only five were classified as confirmed CRPS [35].Additionally, according to a VAERS assessment of Gardasil, Gardasil-9, and Cervarix vaccination adverse events from 2006-2023, 32 cases of CRPS post-vaccination were reported. More than 135 million combined doses of Gardasil, Gardasil-9, and Cervavix have been administered in the United States, according to the CDC website [36]. The incidence of CRPS in association with HPV vaccination appears to be insignificant. The incidence of CRPS in the general population of the United States is estimated to range between 6.28 and .2 per 100,000 person-years, which is much greater than what is seen in association with HPV vaccination [37]. Unsurprisingly, there is no data reflecting the incidence of CRPS in association with HPV infection. This probable underestimation might stem from the fact that, according to the CDC, over 42 million Americans are currently infected with HPV, and more than 13 million Americans contract the virus annually. The data for the association of CRPS with HPV infection is missing because it is highly likely that an individual being diagnosed with CRPS is infected with HPV. Additionally, the causes of CRPS are usually related to prior trauma or surgery. It would be disingenuous to say that CRPS can be caused by HPV vaccination, as the disease process is not fully understood, and the usual causes of the condition are traumatic events, not infection.

Conclusions

Vaccination has played a crucial role in public health for decades. They effectively reduce transmission, severity, and complications associated with infectious diseases. While vaccines, like any medication, have potential adverse effects, their benefits far outweigh the risks. The analysis of extensive documentation and adverse event reports, including data from the Vaccine Adverse Event Reporting System (VAERS), revealed that these serious side effects occur at lower rates with vaccination compared to their incidence with infection. Despite isolated cases, the rarity of these serious adverse events reinforces the overall safety of vaccination. Contextualizing the risk-benefit balance becomes crucial for enhancing public understanding and bolstering confidence in vaccination programs. With vaccine hesitancy on the rise, the analysis underlines the significance of leveraging evidence-based information to nurture informed decision-making and uphold societal health collectively. The review emphasizes the critical importance of ongoing vaccine safety surveillance and focused educational efforts as foundational strategies for enhancing public confidence in vaccination initiatives. These approaches are key to fostering trust, as they involve systematic monitoring for potential adverse effects and the deployment of clear, factual campaigns in the context of risk to educate the public. By communicating the real risks associated with vaccines compared to the greater risks posed by infectious diseases, such strategies effectively address and dispel fears and misconceptions. This, in turn, plays a significant role in motivating a broader segment of the population to accept vaccination, thereby bolstering public health defenses against infectious outbreaks.

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