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EDITORIAL

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MYOCARDITIS, COVID-19 AND ANTI-SARSCOV2 VACCINES IN ADOLESCENTS: ARE WE REALLY REPORTING THE TRUTH ABOUT REAL-WORLD ADVERSE DRUG REACTIONS?

ABSTRACT

In this editorial we will focus about epidemiology of myocarditis/pericarditis related to patients affected by COVID-19 disease or that underwent Anti-SarsCov2 vaccination.

We will evaluate VAERS and EudraVigilance data about myocarditis/pericarditis and we will spot the differences between passive and active pharmacovigilance; moreover we will accurately evaluate the real risk/benefit ratio related to administration to adolescents of COVID-19 vaccination drugs.

Myocarditis is commonly defined as an inflammatory process of the myocardium. Viral infections are most frequently the cause of myocarditis. Other less frequent causes of myocarditis are rheumatic carditis, Chagas disease or complications related to advanced HIV/AIDS, and myocarditis within the context of autoimmune systemic diseases.

The incidence of myocarditis in general population is approximately 1.5 million cases worldwide per year. Incidence is usually estimated between 10 to 20 cases per 100,000 people. The overall incidence is unknown and probably underdiagnosed as some cases can develop asymptomatically or mildly symptomatic and thus neglected [(1) (2)].

Myocarditis has been reported as a possible complication of COVID-19 confirmed disease[(3)] and as a side effect of administration of the so-called "anti-SarsCov2 vaccines", BNT162b2 mRNA-PfizerBioNTech (Comirnaty) and the mRNA-1273-Moderna (Spikevax)[(4)].

The prevalence of myocarditis purely related to COVID-19 affected patients is unclear, partly because the reports often lacked the specific diagnostic modalities to assess myocarditis, partly because non-specific increase in high-sensibility troponin dosage consequent to myocardial injury not necessary related to myocarditis[(3)].

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According to the United States Centers for Disease Control and Prevention (CDC), based on data derived from Vaccine Adverse Event Reporting System (VAERS), myocarditis/pericarditis rates could approximately be numbered about ≈12.6 cases per million doses of second-dose mRNA vaccine among individuals 12 to 39 years of age. VAERS is a passive pharmacovigilance system developed to collect, manage and analyze suspected adverse drug reactions (ADRs) reports for medicines approved in the United States by Food and Drug Administration (FDA).

The observed myocarditis/pericarditis reports associated with COVID-19 vaccination were higher than expected case rates for males compared with females, and higher at younger ages compared with older ages. In particular, in the population aged between 12 and 17 years old, over 2.189.726 doses of vaccines administered in females, and 2.039.871 doses of vaccines administered in males, 19 and 128 cases of myocarditis/pericarditis cases in 7-Day Risk window after second dose of mRNA Covid-19 vaccines were respectively diagnosed.
According to epidemiological overall population data, myocarditis/pericarditis clinical cases expected should be of 0-2 case in females and 0-4 in males in this age category.

In the population aged between 18 and 24 years old, over 5.237.262 doses of vaccines administered in females, and 4.337.287 doses of vaccines administered in males, 23 and 219 cases of myocarditis/pericarditis cases in 7-Day Risk window after second dose of mRNA Covid-19 vaccines were respectively diagnosed. According to epidemiological overall population data, myocarditis/pericarditis clinical cases expected should be of 1-6 case in females and 1-8 in males in this age category.

Thus, crude reporting rates of myocarditis/pericarditis cases per million doses after mRNA COVID-19 vaccination should respectively be 9.1 and 66.7 after second dose in female and males in the population aged between 12 and 17.
The above mentioned rates should respectively be 5.5 and 56.3 after second dose in female and males in the population aged between 18 and 24[(4)].

Many research articles by different authors report data that are approximately similar about myocarditis/pericarditis rates related to administration of mRNA Covid-19 vaccines and almost all authors declare that *the benefit of vaccination clearly outweighs the risk* of myocarditis/pericarditis in younger population as well, thus in favour of vaccination widespread overall population coverage despite any age [(5) (6) (7)].

The conclusion of most authors is then that given the known potential risk of complications following confirmed COVID-19 infection, including hospitalizations and death (mortality reported by CDC accounts to 0.1–1 per 100000 for people aged between 12 to 29 years old) vaccination should be recommended to all ages and sex people groups[(4)].
CDC confirms this data stating that though "*an elevated risk for myocarditis among mRNA COVID-19 vaccines has been observed, particularly in males aged 12–29 years […] continued use of mRNA COVID-19 vaccines in all recommended age groups will prevent morbidity and mortality from COVID-19 that far exceed the number of cases of myocarditis expected*"[(8)].

The common feature of the above mentioned and undoubtedly brilliant original researches is that all data are based on the same source that is VAERS. The intrinsic "bias" related to VAERS data is however remarkably interesting.

Prof. Vinay Prasad, haematologist-oncologist and associate professor in the Department of Epidemiology and Biostatistics at the University of California San Francisco, helps us getting deeper in understanding about this topic, pointing out the great epidemiological bias we risk to face, declaring that: "*VAERS is a suboptimal system of surveillance. It relies on providers making a mental connection and putting in effort. For truly extraordinary things such a system is good. It can find a needle in a haystack, but for meaningful excess in common events it is deeply suboptimal", adding that: "vaccination always serves two purposes, firstly to benefit the person who gets it and secondly to benefit others. We are willing to do things for the second purpose but not if they are a net harm to individuals*"[(9)].

VAERS is in fact based on what it is technically called passive pharmacovigilance surveillance.

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Before developing further discussion, we need to underline that the actual age-specific infection fatality rate (IFR) for COVID-19 according to specific studies is extremely low: the estimated age-specific IFR is very low for children and younger adults (e.g., 0.002% at age 10 and 0.01% at age 25). The IFR increases with the age but remains undoubtedly low in younger population[(10)].

Moreover, to have a wide vision of the global scenario, we should need to consider not only COVID-19 related IFR but all the ADRs and specifically related mRNA vaccine death reported by VAERS, recognizing the complexity of this multifactorial healthcare topic.

On the European side, EudraVigilance (EV) is a passive pharmacovigilance system developed to collect, manage and analyse suspected ADRs reports for medicines approved in the EU and it is operated by European Medicine Agency (EMA). Reports about ADRs are similar when compared data derived from VAERS.

As of 29 July 2021, a total of 244,807 cases of suspected side effects with Comirnaty were spontaneously reported to EudraVigilance from EU/EEA countries; 4,198 of these reported a fatal outcome[(11)].

As of 29 July 2021, a total of 48,788 cases of suspected side effects with Spikevax were spontaneously reported to EudraVigilance from EU/EEA countries; 392 of these reported a fatal outcome [(12)].

As of 29 July 2021, a total of 170,316 cases of suspected side effects with Vaxzevria were spontaneously reported to EudraVigilance from EU/EEA countries; 1,053 of these reported a fatal outcome [(13)].

As of 2 September 2021, a total of 20,206 cases of suspected side effects with COVID-19 Vaccine Janssen were spontaneously reported to EudraVigilance from EU/EEA countries; 138 of these reported a fatal outcome [(14)].
The total death account specifically related to administration of mRNA vaccines from the data collected above since the beginning of the vaccination campaign in Europe would result in 5781 cases to the dates above mentioned.

However both VAERS and EV clearly shows remarkable limitations about their actual activity to detect ADRs.

If we review the literature about pharmacovigilance before COVID-19 pandemic, the cornerstone of all the reviews of this system is the bias of *under-reporting*. This bias has not to be underestimated because if we consider this important interpretative key factor we should review all the data related to VAERS and EV reporting systems. Scientific literature about the quality of the above mentioned reporting systems raises remarkable questions. The estimated rate of under-reporting of ADRs to the spontaneous reporting systems ranged from 6% to 100%. The distribution of under-reporting rates was skewed towards the high end of this range with a median under-reporting rate of 94% across all studies [(15) (16) (17)].

When we consider the data derived from VAERS and EV systems of pharmacovigilance combined with the scientific literature regarding the sensitivity of the reporting systems we should necessarily raise remarkable doubts about the genuine reliability of the data themselves and necessarily speculate that all the data are remarkably underestimating the real world ADRs data.
Common reasons for not reporting include a lack of time of the physicians, different care priorities, uncertainty about the drug causing the ADRs, difficulty in accessing reporting forms, lack of awareness of the requirements for reporting and lack of understanding of the purpose of spontaneous reporting systems. Moreover well known and trivial ADRs are less likely to be reported.
Finally physicians' attitudes towards reporting ADRs contribute to under-reporting believing that serious reactions would certainly already be clearly well documented by the time a drug is marketed or that one case reported by an individual doctor will not contribute to overall medical knowledge [(16)].

If we hypothetically switch from passive to active pharmacovigilance we could speculate that ADRs surveillance necessarily amplifies and gets more accurate.

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There are few scientific articles comparing active vs passive pharmacovigilance; in a small study conducted on patients affected by tuberculosis the yield of ADRs was fourfold using active method during therapy administration [(18)].

Another study clearly proves that active surveillances about traditional vaccines administration allows to reach more accurate results and explains the global trends in identifying ADRs through computational system software to increase sensibility and implemented data in terms of efficiency in detecting ADRs when compared to passive pharmacovigilance systems [(19)].

In august 2021 CDC published an active pharmacovigilance report named "*v-safe*" enrolling 129.059 adolescents aged 12-17 in the next 7 days after first and second COVID-19 vaccination doses with Pfizer BioNTech COVID-19 vaccine, using mobile smartphone reporting apps available for study participants to signal and track any ADRs [(20)]. The results were of concern: 63.4% of participants aged 12-15 reported "*any systemic reaction*", 69.9% of participants aged 16-17 reported "*any systemic reaction*" (*systemic reaction* = abdominal pain, myalgia, chills, diarrhea, fatigue, fever, headache, joint pain, nausea rash, vomiting); 25.4% of participants aged 12-15 reported "*any health impact*", 28.6% of participants aged 16-17 reported "*any health impact*" (*health impact* = unable to perform normal daily activities, unable to work or attend school, needed medical care, telehealth, clinic, emergency department visit, hospitalization).

If we would speculate and hypothetically extend these data to all the adolescent population of Italy, for example, we should face an impressive arise in ADRs in young people aged 12 to 17, independently from specific data already reported about myocarditis/pericarditis.
For example, if we obligatorily administer double dose of an mRNA vaccine to all people aged 12-17 in Italy (approximately 3.400.000 inhabitants according to ISTAT census bureau) we could extrapolate the hypothesis of possible serious ADRs in approximately 1 every 1800 adolescent, requiring hospitaliziation. These numbers should seriously be taken in consideration before stating that COVID-19 vaccination is *absolutely safe and effective in young population. We should then seriously reconsider the risk/benefit ratio* of such administration of immunomodulant drugs. If this scheme is adopted for general ADRs, we should necessarily speculate that we should witness an increase of myocarditis/pericarditis as well.

It is therefore necessary to remind that adolescents are rarely severely affected by Sars-Cov2, that often if they get the infection do not carry risk of contagion more than seven days maximum interval time, and that they develop natural, durable, efficacious and stronger immunity when compared with artificial vaccines-related immunity [(21) (22)] .

In conclusion, it is recommended to be *extremely cautious* before stating that benefit of mRNA COVID-19 vaccination in young population clearly outweights the risks. The data collected so far definitely need to be carefully evaluated because of the statements reported above and considering also that *no data are available about mid and long term effect* of the new developed mRNA COVID-19 vaccines.

Younger people need an accurate and individual, specific, clinical evaluation before rushing into simplistic and universal solutions. Let's always remember that one of the major statement for the healthcare professional is "*primum non nocere*" ("*the first thing to do is not to make damage*").

COVID-19 so-called pandemic implied a huge geopolitical and economic upheaval of the planet with enormous economic incomes for many industries, companies and many other subjects involved in it.

Personally, I hope the scientific community recover the necessary wisdom and calmness to provide harmonious and mutually shared solutions and effective conclusions, refusing any conflict of interest, any business, merchandise or any kind of whatever profit related to the so-called pandemic with all the subsidiaries implications it has involved. We are healthcare professional: to save and aid lives is our mission. Nothing else…at least in my opinion.

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