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Incidence of cerebral venous thrombosis and COVID-19 vaccination: possible causal effect or just chance?

On 7 April, the European Medical Agency (EMA) declared as justified the concern about serious adverse events of the Astra-Zeneca vaccine, ChAdOx1nCoV-19, based on 62 cases of cerebral venous thrombosis (CVT) and 24 cases of splanchnic venous thrombosis, among the near 25 million people vaccinated in the UK. In addition, in the past few days, safety issues on the last approved vaccine (Johnson & Johnson/Janssen, Ad26.COV2.S) have been raised due to the same potential adverse events as the Astra-Zeneca's. However, the same type of events might have occurred also after (not because of) mRNA vaccines.[1]

Also on April 7, *New England Journal of Medicine* published two papers,[2,3] reporting that in vaccinated subjects the rare acute CVT was associated with platelet activation causing thrombus formation. Although no study has shown a causal relationship, the evidence that some strains of adenovirus have a particular tropism for platelets, and enhance their aggregability,[4] increases suspicions against vaccines using viral gene-transfer technique, though it is well known that unfavourable characteristics can be eliminated.[5]

What is still missing in the viral vector-based vaccine mosaic, however, is the most important epidemiological piece, the comparison with the expected incidence rates of CVT in the general, unselected population.

We compared specifically the incident 62 CVT cases that EMA officially reported after the ChAdOx1nCoV-19 vaccine administration to the uncertain expected incidence, to verify whether they could be potentially due to chance. If the incidence rate of CVT after the administration of the vaccine exceeds the number of new cases that during the same period might be expected to occur in the general population, then a cause–effect relationship between vaccination and occurrence of CVT may be thought as possible and biologically plausible, albeit not yet certain.

Based on the data provided by the EMA, the crude incidence rate of CVT in vaccinated people is **2.6 cases per million people**, over the 4-month period in which the Astra Zeneca vaccine was used.

The incidence of CVT in unselected populations is generally recognized to be 3–4 cases per million per year.[6] Thus, during the 4 months of vaccine administration, the expected incidence rate, at worst, would be **1.3 cases per million**, therefore almost half of the incidence rate recorded in the Astra-Zeneca vaccinated.

However, there are two important limits to be considered in the above comparison. The first is related to the high possibility of observational (detection) bias. The level of attention in the identification of cases of a most rare event, such as CVT, is not equally high when cases are sought, compared to cases recorded routinely in daily practice, also because, and this is the second limit, a disease of such a rarity can easily escape diagnosis during daily clinical observation. On this basis, a group of researchers from Adelaide, Australia,[7], identified all cases of CVT among 953 390 adults admitted to Adelaide hospitals in the period between 2005 and 2011, also using brain imaging techniques. The adjudicated cases of CVT were 105, after the exclusion of 63 doubtful cases. The reported incidence rate was 15.7 CVT cases per million people per year, which would correspond to an expected incidence rate of **5.2 cases per million** in 4 months, comparable to the period of use of ChAdOx1nCoV-19 vaccine, more than two-fold the observed incidence rate after vaccination (2.5 cases per million people). These results follow an even more extensive analysis, conducted on a population of over 3 million adults, in the Netherlands,[8] which had already reported a CVT incidence rate of 13.2 cases per million per year. Although both studies are potentially biased by the selection of patients admitted for different reasons to hospitals, therefore, not extracted from general population, they suggest that the expected incidence rate of CVT may be much higher than current estimates reported in ongoing vaccine surveillance studies. *Table 1* summarizes the reported numbers.

Based on these new epidemiological data, a group of Cameroonian researchers in collaboration with the School of Public Health of the XI University of Paris has launched a worldwide protocol with the ambition of collecting much more documentation to confirm the real incidence rate of CVT. This study is ongoing.

What appears not significant from the epidemiological perspective, gave rise to concerns due to the qualitative similarity of these cases, occurring in young people, mostly women, and possibly through autoimmune mechanisms (presence of antibodies against platelet factor 4).

In conclusion, the current epidemiologic evidence suggests that, among people vaccinated with Astra-Zeneca ChAdOx1nCoV-19 vaccine, the incidence rate of CVT is 2.5 cases per million people in the 4 months of administration, which seems to be within the expected incidence rates ranging between 1.3 and 5.2 cases per million in 4 months. In addition, it is now becoming evident that the risk of CVT is enormously higher in COVID-19 than in the worse, albeit still hypothetical, scenario associated with vaccination,[9] and that the efficacy of Astra-Zeneca vaccine is probably better than expected also for the UK variant.[10]

Table 1 Incidence rates of CVT

Condition	Cases of CVT/million/4 months
After ChAdOx1nCoV-19 vaccine	**2.5**
Initially reported incidence in general population	1.3
Reported incidence in Adelaide's hospital	5.2
Reported incidence in the Netherlands' hospitals	4.4

Conflict of interest: The authors do not have any conflict of interest to declare.

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