Vaccine trials with no serious adverse reactions – estimation of upper 95% confidence intervals for likelihood of such events

Dear Editor,

COVID-19 remains a pandemic at the time of writing (July 2021) and the ultimate solution appears to be global vaccination. In trials, vaccines did not demonstrate serious side effects and only manifested transient symptoms such as fever and malaise, as well as local reactions such as pain and tenderness at the injection site, effects that continue to be observed even with ongoing mass vaccination. However, it is still possible to have serious rare side effects as millions and even billions are vaccinated. This paper will demonstrate a simple way to estimate such risks based on actual trial data and the on ongoing vaccination.

The trial considered in this study is AstraZeneca's AZD1222 Phase 3. AZD1222 utilizes a non-replicating chimpanzee adenovirus, which delivers SARS-CoV-2 spike protein so as to induce an immune response, and is administered in two doses at eight to ten weeks apart. The ratio of placebo to the vaccine in the trial was 1:2 with 20,000 volunteers in the vaccine arm.[1]

Had rare and serious side effects occurred, the equations of Fleiss [shown in Figure 1] could have been used to calculate upper and lower 95% confidence intervals for the proportion.[2] Had no such effects been observed, an upper 95% confidence interval based on a zero numerator could still have been estimated from the denominator (n) using the formula 3/n. This is known as the 'rule of threes' and the result coincides with the upper limit of a one-tailed 95% confidence interval from the Poisson distribution.[3]

$$\text{Upper CI} = \frac{(2np + z^2 + 1) + z\sqrt{z^2 + (2 - 1/n) + 4p(nq - 1)}}{2(n + z^2)}$$

$$\text{Lower CI} = \frac{(2np + z^2 - 1) - z\sqrt{z^2 - (2 + 1/n) + 4p(nq + 1)}}{2(n + z^2)}$$

Figure 1: The equations of Fleiss based on the so-called binomial methods should be used for the calculation of confidence intervals when the proportion is ≤0.3 or ≥0.7.[2]

Table 1: Upper 95% confidence intervals and rates per 10,000 for zero events with increasing denominator values

n	Denominator	Upper 95% CI	Per 10,000
0	20,000	0.000150000	1.500000
0	200,000	0.000015000	0.150000
0	2,000,000	0.000001500	0.015000
0	20,000,000	0.000000150	0.001500
0	200,000,000	0.000000015	0.000150
0	2,000,000,000	0.000000002	0.000015

No serious side effects were reported. Using the 'rule of threes' yields an upper 95% confidence interval of 0.015% [first row of Table 1]. The larger the denominator, the smaller the range of the confidence interval [rest of Table 1].

Despite the end of phase 3 trials for extant COVID-19 vaccines, as vaccine rollouts continue, it is universally expected that any serious and rare side effects should be registered with the Vaccine Adverse Event Reporting System (https://vaers.hhs.gov).

Due to the global and mass nature of ongoing vaccination, and the sometimes idiosyncratic nature of adverse reactions, very rare and serious side effects are being observed.[4] However, COVID-19 vaccines are generally safe in the short term, and the benefits of vaccination far outweigh the risks.[5]

Vaccine hesitancy is a non-trivial phenomenon and may adversely impact or delay the attainment of herd immunity. In the future, even in the absence of serious adverse effects following clinical trials, it may be worth being more transparent with the public and acknowledging the possibility of rare side effects up front as this may mitigate vaccine hesitancy. This may be done by educating the public on the concept of risk versus benefit.

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Conflicts of interest

There are no conflicts of interest.

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