# COMPARING THE SAFETY OF COVID-19 VACCINES: A GEOMETRICAL APPROACH

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Abstract. The prompt development of multiple vaccines for the immunization against the world-wide spread of the COVID-19 infection has raised the issue of comparison of their efficacy and of symptomatic effects on the population treated. The different trial reports, made available from the vaccine producers and from the regulatory authorities, analyze some selected systemic reactions reported from patients after the doses received, these are given in a graded scale. In this contribute we propose a geometric way to compare frequency distributions of categorical variables by introducing a distance measure from the best possible scenario in this repartition. The measure proposed is suitable for a direct comparison among the vaccines in terms of the severity of symptomatic reactions.

## 1. Introduction

The disastrous impact of the global widespread of the COVID 2019 pandemic has requested a huge effort from the medical community for a rapid development and experimentation of vaccines to help in the immunization programs. Several vaccines have been already evaluated and approved from the regulatory authorities and many others will be available for the use in the population within a short time period. One of the consequences of the distribution of multiple vaccines in the population is the need of a system for their comparison, both in terms of general efficacy against severe disease, but also in terms of possible side effects and degree of adverse events caused. While the efficacy is always numerically quantified the same cannot be said for the safety and tolerability of each vaccine. Clinical studies usually report about the appearance of systemic reactions with the specification of a level of its severity. The availability of this information in the form of frequency distributions in ordered levels, for each vaccine and for each adverse event, makes possible a direct comparison between vaccines. In this research we propose to assign a numerical index that quantify the tolerability of a vaccine. For each adverse event, such index is defined in terms of a geometrical distance of each observed repartition in terms of frequencies from the ideal best possible scenario in which none of the patients reported adverse events.

## 2. The indicator for the evaluation of ordered distributions

Let start considering a *standard $n$-simplex*

$$\Delta_n := \left\{ (x_1, x_2, \dots, x_{n+1}) \in \mathbb{R}^{n+1} \colon x_i \geq 0 \text{ for all } i = 1, \dots, n+1 \text{ and } \sum_{i=1}^{n+1} x_i = 1 \right\}$$

geometrically we have that $\Delta_0$ represents the point $1 \in \mathbb{R}$, $\Delta_1$ the line segment in $\mathbb{R}^2$ joining $P_1 = (1, 0)$ to $P_2 = (0, 1)$, $\Delta_2$ the equilateral triangle in $\mathbb{R}^3$ whose vertices are $P_1 = (1, 0, 0)$, $P_2 = (0, 1, 0)$, $P_3 = (0, 0, 1)$, and $\Delta_3$ the regular tetrahedron in $\mathbb{R}^4$ with vertices $P_1 = (1, 0, 0, 0)$, $P_2 = (0, 1, 0, 0)$, $P_3 = (0, 0, 1, 0)$, $P_4 = (0, 0, 0, 1)$.

If we consider a categorical variable with $n + 1$ ordered classes we can represent it as a point in the simplex . If $x_i$ is the relative frequency of observations belonging to the category $i$, then,

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since for each $i \in \{1, \dots, n+1\}$ $x_i \geq 0$ and $\sum_{i=1}^{n+1} x_i = 1$, each point $P_0 = (x_1^0, \dots, x_{n+1}^0)$ in the $n-$dimensional symplex $\Delta_n$ represents a specific distribution of frequencies.

The best scenario is represented in the simplex by the point $P_1 = (1, 0, \dots, 0)$, corresponding to the ideal situation in which all the observations fall in the highest class. The remaining points in $\Delta_n$ represent intermediate situations, so that we range from $(P_1)$, the best possible scenario, until $(P_{n+1})$ which represents the worst situation. This ordering is reflected in the simplex so that the positioning of each distribution in classes must be evaluated relatively to the ordered vertices. Geometrically the evaluation of the positioning of each $P_0$ repartition in classes can be assessed by measuring its distance in the simplex from the best scenario $P_1$.

Such a distance between points should take into account and respect the order of importance between vertices, for doing so we construct a path from the point $P_o$ to $P_1$ in a way that the evaluation changes continuously through this path as slow as possible.

In the simplest situation in which we have only two categories, the simplex degenerates into the segment from the point $P_1$ to $P_2$. Given a point $P_0 = (x_1^0, x_2^0) = (x_1^0, 1 - x_1^0)$ of the segment, a measurement $\delta(P_0)$ of the distance from $P_o$ to the best possible scenario $P_1$ is simply the length of the segment from $P_0$ to $P_1$, that is (see Figure 1 (left))

$$\delta(P_0) = \sqrt{2}(1 - x_1^0).$$

In the 2-dimensional case, in which there are 3 possible scenarios (the "best", the "intermediate" and the "worst") there is no natural order relation which can be used. We suggest that, a natural path is to move first from $P_0$ along the line parallel to $P_2 - P_3$ until the intersection $(P_0')$ of that line with the edge of the simplex through the points $P_1$ and $P_2$ (see Figure 1(right)), and then from the intersection point $P_0'$ to $P_1$. In this way we obtain the distance

$$\delta(P_0) = \|P_0' - P_0\| + \|P_1 - P_0'\| = \sqrt{2}x_3^0 + \sqrt{2}(1 - x_1^0) = \sqrt{2}\left(2 - 2x_1^0 - x_2^0\right),$$

where $\|\cdot\|$ denotes the Euclidean norm. The construction can be generalized to the case of $n+1$ categories, so that the distance from the point $P_0 = (x_1^0, \dots, x_{n+1}^0)$ to $P_1$ is given by the following formula ( for more details see [1])

$$\delta(P_0) = \sqrt{2}\left(n - nx_1^0 - (n-1)x_2^0 - \cdots - 2x_{n-1}^0 - x_n^0\right) \tag{1}$$

## 3. Comparing vaccines systemic reactions

We apply the indicator defined to compare the systemic responses to the injection of vaccines using the data publicily available (see [2, 3, 4]) for the three vaccines: ChAdOx1 nCoV-19 (AZD1222) (Astrazeneca), mRNA-1273 (Moderna) and BNT162b2 mRNA (Pfizer-Biontech). In all the studies considered the presence of eventual systemic adverse events was reported within 7 days after the injection of each dose. Two delayed doses are recommended to develop an overall immunogenicity and protection, the time interval between the doses is specific for each

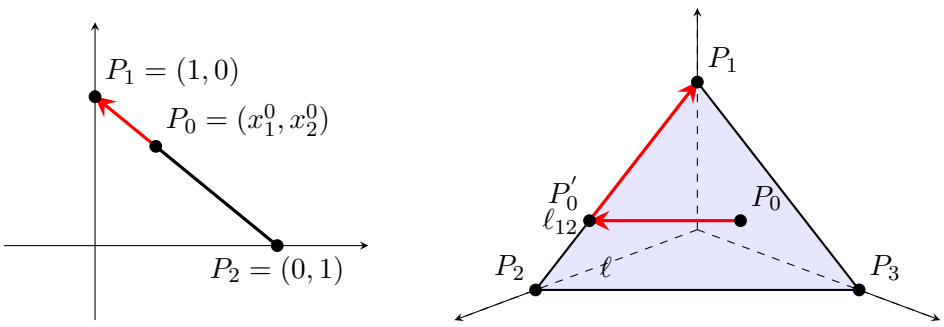


FIGURE 1. On the left the 1-dimensional case: the length of the red segment is $\delta(P_0)$. On the right the 2-dimensional case: $\delta(P_0)$ is the sum of the length of the two red segments.

vaccine. Common systemic reactions registered in the three studies were: fever, headache, fatigue, chills. The severity of each solicited reaction was registered according to four increasing levels: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and grade 4, emergency department visit or hospitalization. The clinical reports and publications associated to Moderna and Astrazeneca made available also an overall distribution of relative frequencies across the severity levels (see Table 1), considering the number of individuals reporting at least one adverse reaction. These overall distributions considere also other adverse events, not necessarily common to the two vaccines, that are not analyzed in the description of results here reported. The comparison between vaccines reactions looking directly at the entire distribution in classes could not be an easy task.

Following the description in Section 2 we, therefore, propose to calculate for each of the three vaccines the $\delta$ measure in (1) by considering as best possible scenario (the $P_1$ vertex in the simplex) the one in which none of the patients receiving the dose reported a systemic reaction.

For each vaccine and for each adverse event an ordered variable with $n + 1 = 5$ categories is considered where the first category corresponds to no-adverse events and the other ones to the severity levels reported. Considering that the maximum value of $\delta$ corresponds to the worst situation in which the whole set of of observations belong to the last class (here corresponding to Grade 4), the value of the index can vary between 0 and $4\sqrt{2} = 5.657$.

In Table 2 are reported the values of the $\delta$ scores observed for the three vaccines after each of the two doses. A specific score was calculated for the four common adverse events. For the two vaccines from Astrazeneca and Moderna we were able to calculate an overall measure of assessment which considers the occurrence of at least one adverse event in each category. We observe that smallest values of the score are associated with less aggressive reactions. The results arising from the application of the method give evidence of the fact that it is possible to build a classification in terms of post reactions. In particular is registered an inversion in the classification when passing from the first to the second dose injected. When looking for Dose 1 to the four adverse events independently, the strongest reactions are observed as a consequence to the injection of the Astrazeneca vaccine, followed by Pfizer-Biontech and then Moderna (the last two had very similar results). Things look reversed after Dose 2 where Astrazeneca provides better results. The delay of second dose vaccinations for AstraZeneca (from 4 to 26 weeks instead of the originally intended 4 to 12 weeks interval, see [2]), that was not registered for the other two vaccines here analyzed, could have influenced in some way this lowering in strongness of reactions.

More accurate classifications could have been considered if instead of the repartition in severity classes was possible to distinguish between patients according to the number of adverse events jointly reported. Unfortunately at the moment that level of disaggregate information is not available, but this could be a suggestion for researchers having access to the full datasets.

The $\delta$ score could be normalized with respect to its maximum value attainable to obtain a measure of the safety of vaccines in the range of a proportion. If $\bar{\delta} = \delta/max(\delta)$ then taking $1 - \bar{\delta}$ gives the tolerability of the vaccine. Values closer to 1 indicate a higher level of tolerability. In Table 3 are reported such values for the overall $\delta$ measures in the comparison between AstraZeneca and Moderna.

TABLE 1. Ordinal frequency distribution of the number of patients reporting at least one adverse event after the injection of the first and the second dose of vaccine. AstraZeneca and Moderna vaccines are considered.

| | DOSE 1 | | | | | DOSE 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NONE | MILD | MODERATE | SEVERE | GRADE 4 | NONE | MILD | MODERATE | SEVERE | GRADE 4 |
| AstraZeneca | 0.2096 | 0.4048 | 0.2985 | 0.0871 | 0 | 0.4403 | 0.4141 | 0.1277 | 0.0179 | 0 |
| Moderna | 0.4515 | 0.3542 | 0.1645 | 0.0295 | 0.0003 | 0.2061 | 0.2537 | 0.3809 | 0.1584 | 0.0009 |

TABLE 2. $\delta$ score values of the systemic reactions calculated for three vaccines. Four different syptoms are considered. According to the information available from the EMA reports and from [5] an overall measure is reported for Astrazeneca and Moderna

| | DOSE 1 | | | | | DOSE 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Fever | Headache | Fatigue | Chills | Any | Fever | Headache | Fatigue | Chills | Any |
| AstraZeneca | 0.188 | 0.750 | 1.194 | 0.709 | 1.786 | 0.013 | 0.548 | 0.679 | 0.093 | 1.023 |
| Moderna | 0.016 | 0.580 | 0.729 | 0.148 | 1.093 | 0.329 | 1.258 | 1.653 | 0.988 | 2.113 |
| Pfizer Biontech | 0.050 | 0.656 | 0.863 | 0.196 | - | 0.279 | 0.985 | 1.344 | 0.958 | - |

TABLE 3. Tolerability levels to the appearance of at least one adverse event after each dose of Astrazeneca and Moderna vaccines.

| | DOSE 1 | DOSE 2 |
|---|---|---|
| AstraZeneca | 0.684 | 0.819 |
| Moderna | 0.807 | 0.627 |

## 4. Conclusions

The method presented allows a direct comparison and ranking of ordered frequency distributions avoiding possible ambiguous situations in which is not straightforward to define an order in the grading. The score proposed is simple in its interpretation and at the same time has a rigorous geometrical definition. The use of such a geometric score in the comparison of vaccines effects is an insightful way of communicating important information in a simple and clear way. More and more vaccines will, hopefully, be soon available to respond to the emergency ongoing and the availability of valid tools for comparison can be an important resource. The same methods can be used to compare two or more homogeneous situations where ordinal qualitative evaluations are considered.

## References

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