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EDITORIAL

Efficacy and effectiveness of covid-19 vaccine - absolute vs. relative risk reduction

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Over the last few months, there has been a passionate debate within the scientific community on the risks and the benefits of the vaccines against COVID-19 disease. Reporting relative risk reduction (RRR), as usually done in phase 3 studies, does not consider the background risk of being infected and becoming ill with COVID-19, which varies between population and over time. For this reason, several researchers argued that the absolute risk reduction (ARR), namely the difference between attack rates with and without the vaccine, should also be reported [1,2]. The two indices, being conceptually different, are of different order of magnitude (Table 1) [3–10]; for example, the 95% RRR for BNT162b2 (Pfizer-BioNTech) vaccine [3] corresponds to 0.85% ARR [1]. Using one of the two measures to estimate the risk/benefit ratio would lead to different conclusions. We need to examine some points to use these indicators in an optimal way.

Comparison with vaccines against other respiratory-borne viruses is likely to be of little use in interpreting these data. As an example, efficacy and effectiveness of influenza vaccines are estimated on studies lasting the whole influenza season (5–6 months), considerably longer than COVID-19 vaccine studies [11], and are tested in a completely different background situation, with no or limited use of mitigation procedures at population level (social distancing, use of face-masks). Both these elements, as we will see shortly, can substantially influence the effectiveness of vaccines as estimated by phase 3 trials.

Actually, ARR and its derivative number needed to vaccinate to prevent a disease (NNV) are time-dependent parameters, affected by follow-up duration (Figure 1) [12]. The above mentioned fall of risk reduction indices of BNT162b2 vaccine could therefore be, at least in part, correlated to the very short duration of the study [3] (median value 2 months). A pivotal question is: how effective is a vaccine with 95% RRR in preventing COVID-19 in next years in a large population exposed to a long-lasting risk of infection? It may be useful to compare data of COVID-19 vaccines with those of other primary prevention studies in different fields of preventive medicine. Polypill (fixed doses of aspirin, statin and antihypertensive drugs given to large populations) is a strategy used to reduce cardiovascular disease burden in primary prevention, appointed of a number needed to treat (NNT) of 36–57 to prevent an acute cardiovascular event in 5 years [13], a period 30 times longer than phase 3 studies on COVID-19 vaccines. Since survival event-free curves showed an approximately constant slope, we could therefore estimate that polypill had, in the first months of treatment, a NNT roughly around 1000, considerably higher than the NNV calculated for BNT162b2 vaccine during the phase 3 study (119) [3]. Needless to say that this is an oversimplified model and that many factors (in the case of vaccines, progressive reduction in the number of vulnerable subjects after vaccination or natural infection, immunity decline and emerging of new variants able to escape the vaccine) can modify the effectiveness of vaccine over time. Nevertheless, very recent papers reporting five to six-months update on BNT162b2 and mRNA1273 (Moderna-NIH) vaccines [14,15], actually gives the measure of the dependence of ARR on the time of observation, showing an increase of ARR up to 3.7% and 4.9%, respectively (corresponding to NNVs of 27 and 21, respectively).

Another relevant point is that ARR, unlike RRR, is not an intrinsic property of a drug or a vaccine, but it's rather a predictor of the effectiveness of an intervention during the translation in the 'real world,' being the result of the interaction between that drug or vaccine (with its own efficacy expressed by RRR) and the baseline population risk. The relationship between the effectiveness of a preventive action and the baseline risk is well-known. For example, in the early 2000s the Seven Countries Study [16] showed that the relationship between blood pressure values and mortality for coronary heart disease had different slopes in different populations. In other words, the relationship between risk factor (hypertension) and the relative risk of death for ischemic heart disease was similar while the relationship with absolute risk was different across the populations studied. For that reason, the same intervention (blood pressure reduction of a given value) will give a different number of prevented events in different population, being the effectiveness higher the higher the slope of the relationship and, hence, baseline cardiovascular risk. The same is expected for vaccination against an infectious disease: the higher the viral circulation in the population (i.e. the infection rate), the higher the effectiveness (ARR) (Figure 1). In this regard, we have to take into account that the effect of COVID-19 vaccines has been evaluated over a background of strict preventive measures at population level (social distancing, hand hygiene, mask wearing) that reduced significantly the

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Table 1. Absolute risk reduction, relative risk reduction and number needed to vaccinate for COVID-19 vaccines. Data from phase 3 studies.

	Reference	*ARR* (%)	*RRR* (%)	*NNV*
BNT162b2 (Pfizer-BioNtech)	[3]	0.84	95.0	119
mRNA1273 (Moderna-NIH)	[4]	1.24	94.1	81
ChAdOx1nCoV19 (Astra Zeneca – Oxford)	[5]	1.11	72.8	90
Ad26CoV2S (Johnson & Johnson)	[6]	1.19	66.9	84
GamCovidVac (Gamaleya)	[7]	0.93	91.0	86
NVX-CoV2373 (Novavax)	[8]	1.23	89.7	82
CORONAVAC (Sinovac)	[9]	0.76	83.5	131
WIBP-CorV (Wuhan – Sinopharm)	[10]	0.54	72.8	185
BBIBP-CorV (Beijing – Sinopharm)	[10]	0.58	78.1	172

ARR = Absolute Risk Reduction; NNV = Number Needed to Vaccinate; RRR = Relative Risk Reduction.

background incidence rate and, hence, a steep increase in NNV. We can easily speculate about the reduction of baseline cardiovascular risk, and consequently the increase in NNT, if all participants to cardiovascular prevention studies stopped smoking, exercised and had a healthy diet. The unusual conditions under which COVID-19 vaccines have been tested (in particular social distancing, that cannot be maintained for a long time), possibly makes ARR an unreliable 'effectiveness predictor' of vaccination at population level.

In conclusion, reporting results both in terms of ARR and RRR would be undoubtedly more complete, allowing both an estimate of the intrinsic preventive efficacy of vaccines and (with some caution) of their effectiveness during translation in the real world through vaccination campaigns. Nevertheless, what we primarily need to know during this unprecedented pandemic is that vaccines are safe and that mass vaccination will curb viral circulation in the population or, as recently seen after diffusion of Delta and Omicron variants, will reduce severe COVID-19 cases, preventing health services overload. The latter are better predicted by RRR of contracting COVID-19 (any degree of severity or severe disease, respectively), crudely expressing the proportion of vaccinated subjects that will be protected, rather than by ARR, that could be profitably used by decision makers to estimate and to compare the effectiveness of vaccination in different countries with different attack rates, in order to plan health policies.

A final reflection concerns the wide diffusion that the subject matter of the present commentary has had in non-specialized media and in the web. In this delicate moment for the whole humankind, news on scientific research is awaited with great apprehension all around the world, and researchers are probably not prepared to communicate their results in an adequate way to such a state of tension. As an example, in a paper here commented is said that 'ARRs tend to be ignored because they give a much less impressive effect … ' [1], suggesting a sort of data picking, highlighting the most impressive and concealing the less appealing ones. Perhaps for this reason, the paper has been used, distorting its comprehensive meaning, to support conspiracy theories and to foster vaccine hesitancy.

We should be aware that specific knowledge and skills are essential for a complete understanding of such a technical matter and that, in this particular moment, both results of studies and discussion among experts should be communicated and divulged with great caution, carefully avoiding the risk of manipulation.

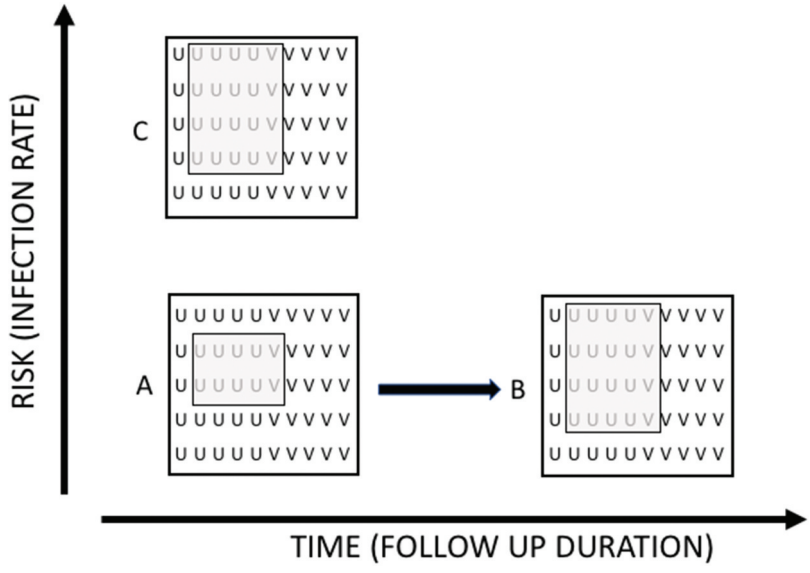

Figure 1. Schematic representation of the influences of baseline risk and follow up duration on ARR in a hypothetical study on the effects of a vaccine with a 75% RRR. A: Population at low risk and short observation. RRR 75% corresponds to an ARR of 12% (16% of cases in unvaccinated subjects vs. 4% in vaccinated subjects). B: Extending follow up in the same sample and at steady risk will increase the number of infected subjects (32% in unvaccinated subjects vs. 8% in vaccinated subjects). RRR 75% will therefore correspond to an ARR of 24%. C: Population at higher risk and short observation. RRR 75% corresponds to an ARR of 24%. (32% of cases in unvaccinated subjects vs. 8% in vaccinated subjects).

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