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Commentary

When is it reasonable to extrapolate during a pandemic?: The case of broad UK labeling for AstraZeneca COVID-19 vaccine

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Amid an unprecedented surge of COVID-19 cases in the UK, with an increasing number due to a novel more infectious SARS-CoV-2 variant, [1] the UK regulatory agency (MHRA) granted emergency approval to the AstraZeneca COVID-19 vaccine on 30 December 2020. The target population includes adults and elderly. The posology consisting of two separate doses given 4-12 weeks apart. Almost simultaneously, the UK health authorities recommended a dose interval of 12 weeks for both COVID-19 authorized vaccines (Pfizer/BioNTech; AstraZeneca), due to the shortage of doses and to vaccinate the highest number of citizens.

The MHRA decision was based on the efficacy results of two trials conducted in the UK (phase 2/3) and Brazil (phase 3) that included 5,807 and 5,829 vaccine and placebo recipients, respectively. Two additional phase 1/2 trials run in the UK and South Africa reported data on immunogenicity and safety. Phase 3 trials were originally planned to investigate a single dose regimen but, in the light of early immunogenicity results, the protocols were amended to investigate a two-dose regimen: lower (LD) and standard doses (SD) given as the priming (first) dose; SD administered as the booster (second) dose. This resulted in two dosing regimens: LD/SD (N=2741) and SD/SD (N=8895). Interestingly, the vaccine efficacy of LD/SD was 90%, but only 62% with SD/SD. The second dose was given 4-26 weeks post-priming dose [2,3]. Since the MHRA authorized only the SD/SD schedule, it would be prudent to consider only the data supporting it. From the scrutiny of the publicly available information on the authorization, two issues regarding the vaccine efficacy deserve reflection.

First, the analysis of immunogenicity results in the SD/SD cohorts showed that longer interval periods provided higher geometric mean titers (GMTs): the 106 and 154 participants that got the booster dose 9-11 and ≥12 weeks after the priming dose had around 1.5- and 2.8-times higher SARS-CoV-2 S-binding antibody levels, respectively, than the 443 volunteers who received the booster dose with <6-week interval. While the longer dosing intervals in the immunogenicity analysis were 9-11 and ≥12 weeks, those of the efficacy analysis, as shown below, were 8-11 and >11 weeks [3].

Voysey et al [2] found that there was no statistically significant difference in vaccine efficacy between those participants (age 18-55 years) that received the second dose in <6-week interval (53%) and those receiving it with ≥6-week interval (65%). However, in an analysis with different interval grouping, those receiving the second dose at 8-11 weeks and >11 weeks post-priming had a vaccine efficacy of 73% and 82%, respectively [3].

The information issued by the MHRA state —without providing any further data/analysis— that efficacy was demonstrated with more certainty for dose intervals from 8-12 weeks [3,4]. The 12-week period appears here without precedent, considering that the longer dose interval assessed in the efficacy analysis was 11 weeks. The inconsistency between the dosing intervals used in the immunogenicity and clinical efficacy analyses raises concerns, as it may be open to bias due to the small number of participants in each stratum. The rationale for choosing 12-weeks as maximum limit of the interval for administration of the

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second dose can only be understood by assessing the immunogenicity and efficacy data of participants who received the booster dose 12-week post-priming. However, these data are not publicly available.

The second issue refers to the efficacy data supporting the vaccine administration in elderly individuals (≥65-year-old). Healthcare professionals are informed that efficacy (and safety) data are currently "limited" in the elderly [4]. This information, however, is not included in the document issued for vaccine recipients [5]. Although 100% seroconversion rate was observed in elderly participants after the second dose, GMTs for S-binding antibodies were lower in the elderly group (N=52; GMT=109.212) than in the 18-64-year-old group (N=497; GMT=173.708) [3]. This finding was partially explained by the observation that most elderly had a dose interval <6 weeks [3,4]. There were only two COVID-19 cases in a total of 660 elderly participants in both vaccine and placebo groups, too few to draw any conclusion on efficacy [4]. However, the MHRA reports there is nothing "to suggest lack of protection" in this higher risk population [3]. Extrapolating immunogenicity data from a limited number of individuals to infer vaccine efficacy, as the MHRA seems to have done, should be clearly stated in the information issued to healthcare professionals and disclosed to vaccine recipients. The investigators were much more prudent in the published article. They acknowledged that the vaccine efficacy in the older age groups (≥56-year-old) could not be assessed but will be determined as more cases are accrued in the future [2]. Aligned with this, commentators believe that from the data published by Voysey et al, it cannot be inferred efficacy in older adult [6].

Thus, the MHRA has made two potentially questionable technical decisions driven, we believe, by the understandable public health and societal need during a situation derived from the surge of COVID-19 cases in the UK in December 2020. Otherwise, it could have been more prudent. The approval in the elderly, for instance, could have been delayed until collecting more COVID-19 cases —something that is likely to happen— that would provide enough efficacy data in this population group. The fact that the Public Health England's "COVID-19 vaccination programme", dated 31 December 2020 —one day after the MHRA granted approval for the AstaZeneca vaccine—, stated that the recommended interval for the two vaccine doses was 4 weeks, [7] suggests a last-minute change in the lengthening of the dosing interval to up to 12 weeks to facilitate the deployment of the vaccines by the UK health authorities. This has also happened in India where the application stated two doses to be administered 4 weeks apart, [8] but the approved schedule allows for a 4-12-week interval [9]. On the one hand there is the technical regulatory decision, on the other what advisory committees [10] and professional scientific societies [11] could advice and health authorities decide when facing an unprecedent grave pandemic situation.

The decision taken by the MHRA will have widespread implications. First, large countries like Argentina, Bangladesh, Brazil, Mexico, Pakistan, South Africa, and Thailand, have also granted emergency authorizations with likely identical labeling to that of the UK. Second, this vaccine could be rolled out in low- and middle-income countries before being approved by their own national regulatory agencies [12]. The EMA has recommended granting a conditional approval for this vaccine in the EU aligned with the MHRA approved label, but acknowledging the lack of enough data for individuals ≥56-year-old, and expecting protection due to the immune response observed [13]. Meanwhile, the US FDA [14] and Health Canada [15] will likely delay any eventual emergency use authorization until AstraZeneca submits data from the phase 3 placebo-controlled trial (NCT04516746) that is on-going in the USA.

Emergency authorizations offer a suitable regulatory tool to grant indications strictly based on the evidence on safety, efficacy and quality, but open to rapid revisions as soon as further data affecting the benefit-risk profile become available. Regulatory decisions are one fundamental aspect of public health decisions and should be fully driven by evidence; they cannot ignore this unprecedented grave pandemic situation but not to the extent to let unduly influence the product label. Other factors, that involve political responsibility and require full transparency to be reliable, legitimately contribute to complex health decisions, as those that must be taken in the emergency situations.

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Declaration of Competing Interest

none to declare.

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