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Commentary

Covid-19 vaccine trials: Ethnic diversity and immunogenicity

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1. Introduction

In recent years it has become increasingly recognised that immunogenicity of vaccines can vary significantly between individuals, with age, comorbidities and medication use being some of the key factors determining immune response [1]. Responses can differ further with ethnic groups from the same location demonstrating varied vaccine responses and differing antibody decline rates, suggesting a genetic influence [1]. Furthermore, twin studies estimate a 36–90% and 39–90% degree of heritability for humoral responses and cellular responses, respectively, depending on the vaccine [1].

There is evidence to suggest that Covid-19 affects individuals from black and South Asian ancestries disproportionately, with higher rates of hospitalisation and increased mortality compared to Caucasian counterparts [2]. In a UK study, after age, sex and geography were accounted for, death rates for individuals of black African descent were 3.5 times higher than for Caucasians, compared to 2.7 and 1.7 times higher for those of Pakistani or black Caribbean descent [2]. Similar data was reported in studies from the United States, with significantly increased death rates among black/African-American and Hispanic/Latino people compared to those from Caucasian or Asian descent (92.3, 74.3, 45.2 and 34.5 deaths per 100,000 population, respectively) [2]. Furthermore, the severity of Covid-19 in different ethnic populations could be further exacerbated by the under-representation of recruits from ethnically diverse backgrounds for interventional treatment trials [3,4]. The success of candidate interventions could be statistically proven or dismissed for one population but not the other.

As such it is important that phase III clinical trials, in particular, assessing vaccine efficacy and safety include a diverse mix of ethnicities and that such sub-analyses are included in trial data. This is especially pertinent for candidate vaccines against diseases with either a higher prevalence or increased risk of morbidity and/or mortality in ethnic minority groups such as Covid-19 in order for vaccine efficacy data to be applicable to these individuals. Furthermore the paucity of ethnic diversity in vaccine trials means efficacy may differ between countries, resulting in health disparities.

This commentary assesses clinical trial data of the three Covid-19 vaccines: BNT162b2 (Pfizer/BioNtech/Fosun Pharma), AZD1222 (Oxford/Astra Zeneca) and mRNA-173 (Moderna) currently approved for use by the UK Medicines and Healthcare products Regulatory Agency, and asks whether the results provide sufficient evidence of efficacy in the whole population.

2. Covid-19 vaccine trials and ethnic diversity

As of 20th April 2021 the World Health Organization (WHO) reported 91 and 184 Covid-19 vaccines in clinical and pre-clinical development, respectively [5]. The majority of candidate vaccines in the clinical phase constitute Covid-19 viral protein subunits, with other common vaccines containing non-replicating viral vectors, DNA, RNA and inactivated Covid-19 virus [5].

In a recent UK report, the National Institute of Health Research analysed ethnicity data provided by a total of 622,978 participants in Covid-19 vaccine studies nationally and identified that only 5.72% (1,509 participants) came from ethnic minority backgrounds [6]. The protocol for the Oxford vaccine Phase 2/3 UK study (COV002), for example, had no mention of ethnicity and out of a total of 560 participants in Phase 2 only 28 (5%) individuals were from ethnic minority backgrounds [7]. This reflects a significant underrepresentation of such groups, which constitute 13.8% of the UK population [6]; although sub-analyses of vaccine efficacy can be performed depending on ethnicity, low numbers from minority groups may reduce the statistical significance of this data and thereby render the results less accurate. An interim report of the Phase 3 trials in UK & Brazil showed that participation from ethnic minority backgrounds had marginally increased to 8.6% in the UK, and significantly (33.4%) in Brazil (Table 1) [8].

Some of the US-based studies placed a conscious effort into recruiting a diverse participant cohort. mRNA-173 by Moderna Therapeutics contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilised spike glycoprotein of SARS-CoV-2 virus [8]. Participants were recruited from the United States, Brazil and Argentina and phase 1, 2a and 3 studies included 120, 600 and 30,418 participants, respectively [8]. As part of the study sub-analysis 36.5% of participants were from ethnic minority

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Table 1
Overview of participation from ethnic minority groups in three phase 3 trials.

	UK Cov002 LD/SD		UK Cov002 SD/SD		Brazil SD/SD	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Black	6	2	17	14	230	210
Asian	76	59	137	138	54	53
Mixed	19	22	48	42	410	386
Other	9	13	22	22	12	10
Total BME	206	440	1365			
Total	2741		4807		4088	
BME	7.5%		9.2%		33.4%	

backgrounds (20% Hispanic/Latino, 9.7% African-American, 4.7% Asian, and <3% from other racial groups) [8]. Interim analysis of the primary efficacy endpoint demonstrated vaccine efficacy of 94.5% for all participants, with subgroup analysis demonstrating 93.4% efficacy in participants aged 18–64 years old and 100% efficacy in those 65 years and older [8]. Sub-group analysis was also reviewed for gender and ethnicity. Although there was no significant difference between vaccine efficacy between genders (93.5% female, 95.5% male), the difference between ethnicities was more marked [8]. Interestingly when reviewing sub-analyses 14 days after the second vaccine dose, efficacy was 100% in the African-American, Hispanic/Latino and Asian populations compared to 93.8% efficacy in participants from white backgrounds [8].

For BNT162b2, a lipid nanoparticle-formulated, nucleoside-modified RNA encoding the SARS-CoV-2 full-length spike, modified by two proline mutations [9], patients were recruited from the United States, Argentina, Brazil, South Africa, Germany and Turkey. Similar to the Moderna study, sub-analyses between ethnic groups demonstrated 100% vaccine efficacy in African-American participants at least seven days after the second vaccine dose; efficacy in other ethnic groups, however, was slightly lower (95.2%, 94.4% and 89.3% in white, Hispanic/Latino and other ethnic minority groups, respectively) [9]. The overall study population included 83%, 28%, 9% and 4.3% from white, Hispanic/Latino, black/African-American, Hispanic/Latino and Asian backgrounds, respectively [9].

In the above two studies, although the significant proportion of Hispanic/Latino participants in the trials reflects the high proportion of such individuals in the United States such numbers are disproportionate when considering national populations in other continents such as Europe, Asia and Africa. Furthermore, the above studies have very few participants from Asian origins, and clarification regarding whether such individuals are from South Asian or East Asian decent is required to enable local health authorities to review whether trial data is applicable nationally. These comments also apply for the AZD1222 vaccine, despite trials in Brazil including a large cohort of local ethnic groups, the statistical power remains poor for those ethnically from East and South Asia. The producers of the AZD1222 have lauded the vaccine as advantageous to developing nations, especially those without ubiquitous freezer storage, yet Phase 3 trials have yet to begin in South (India) or East Asia (Japan), and no detailed participation data was provided for their South African trial [8].

3. Ethnicity and immunogenicity

Although the immunogenicity to vaccinations is likely to be dependent on multiple factors, for example vaccine composition, it is likely that there will be some variability to each of the candidate vaccines depending on race. One mechanism that produces variations in vaccine response are polymorphisms in major histocompatibility complex (MHC) genes, though polymorphisms in pattern recognition receptors (PRRs) or single-nucleotide polymorphisms (SNPs) have also been shown to be associated with variations in immunogenicity [1]. In recent years, multiple studies reviewing immunogenicity to influenza A vaccines have demonstrated this and, in particular, polymorphisms in the IGHV1-69 gene have been demonstrated to modulate anti-influenza antibody repertoires [10]. This is one of the genes responsible for antibody production and it exists in 14 variations, with certain polymorphisms being more effective at mounting a response to the influenza A virus compared to others; ethnicity dramatically varied the frequency of various polymorphisms, with those from African, Asian and European descent showing marked differences [10]. Furthermore there are variations in immune response to the 2007 H5N1 influenza virus itself depending on which polymorphisms in the IGHV1-69 gene were present, as well as how many copies of the genes were present.

Other gene polymorphisms that vary between ethnicities are also likely to play a part. A study by Kurupati et al. (2016), for example, demonstrated that gene expression profiling arrays revealed marked differences in 1,368 probes at baseline between Caucasians and African-Americans [11]; furthermore genes expressed differently between these two ethnicities irrespective of age were enriched for myeloid genes, whereas those that differed between younger participants were enriched for those specific for B-cells [11].

Although we are still in the early stages of studies reviewing immunogenicity of candidate vaccines against Covid-19, it is key that clinical trials take the potential differences between ethnicities into account during study development as well as during post-study data analysis. This will not only allow local authorities to be better informed regarding the potential effects of the vaccine on their local population, but this may also guide which vaccines may be more appropriate for different patient cohorts. Indeed, the Phase 3 protocols for the three approved UK vaccines did not propose to analyse the immune response of individuals from different ethnicities separately in subgroups. However, Moderna did add a sentence to describe their intention to enrol a representative sample of racial and ethnic minority participants [12]. Analysis of ClinicalTrials.gov for the three vaccines suggest AZD1222 and BNT162b2 trials are planned in countries outside of Europe and North America, but not for mRNA-173 [13–15]. Despite this, as of 15th April 2021: BNT162b2 has already been approved by local authorities for vaccination for not just the UK, US and European Union (EU), but in regions before the vaccine has been trialled: e.g. East Asia (Hong Kong, Japan, Mongolia, Philippines, South Korea, Singapore) and North & Central Africa (Rwanda, Tunisia). Likewise AZD1222 has already been approved by authorities in many countries in East & South Asia, North & Central Africa, Central America but not by the US FDA. mRNA-173 has been authorised for wider vaccination by the UK, US, EU; but also in countries with little relevant demographic trial data such as Mongolia and Vietnam [16].

One limitation to consider with ethnic diversity in clinical trials, however, is social and cultural behaviours that may differ globally irrespective of underlying race, as it is likely that the complex

interactions between host, pathogen and environmental factors are key. For example, a Western diet of African-American participants in clinical trials may affect immunogenicity compared to individuals native to Africa and factors such as smoking habits, use of herbal remedies and levels of stress between countries may also differ between populations of the same ethnic group. As such, future data is required not only on ethnicity and immunogenicity to medicinal products such as vaccinations but also on different population groups internationally. Certain genetic mutations within geographic populations may also, for example, impact immunogenicity, highlighting the importance of both ethnicity as well as geographic distribution of trial participants [10,17].

Continued evaluation of vaccine efficacy on an international level is pertinent, as modernisation of third world countries are likely to lead to changes in environmental factors, for example diet, which may impact factors relating to immunogenicity. Future trials in vaccines could consider obtaining genetic and ethnicity data / environmental data and linking with immunogenicity.

All authors declare no conflicts of interest in the preparation of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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