Letter to the Editor

Optimising COVID-19 vaccine efficacy by ensuring nutritional adequacy

Dear Editor

Now that a number of COVID-19 vaccines are being employed to control the current pandemic, we are concerned about the likelihood of a poor response in the frail or malnourished elderly which would reduce the effectiveness of the vaccination campaigns.

Older people have a weakened immune response[1,2] and are known to respond less well than middle-aged adults to many vaccines including the seasonal influenza vaccine[3,4]. We note that the Oxford Vaccine trial recruited older participants with "few comorbidities, [who] might not be representative of the general older population, including those living in residential care settings or older than 80 years"[5]. Both the 56-69 and $\geq$ 70 year-old groups showed a lower IgG response and lower neutralising antibody titres to a single dose of the Oxford vaccine than did the 18-55 year-olds[5]. Hence, in the real-world setting, weaker older people may not gain the desired clinical protection from the vaccine and resource may be wasted. Poor vaccination responses in older people are related not only to frailty[6] which cannot be easily remedied, but also to deficiencies in micronutrients, which can be addressed.

An effective immune response requires an adequate host nutritional status[7]. In recognising this, the European Food Safety Authority has authorised nutrient function health-claims for vitamins A (including β-carotene), B6, B9 (folate), B12, C and D, and the minerals zinc, selenium, iron and copper based on scientific assessment of their contributions to the normal functioning of the immune system[8]. Each of these micronutrients, as well as vitamin E, has been shown to have multiple key roles in supporting the immune system and reducing the risk of infections. This is detailed in recent comprehensive reviews that attest the importance of individual micronutrients to the immune response and explain the multiple mechanisms of action involved[9,10]. Human studies, particularly in the elderly, have associated impairments in immune markers to low status of micronutrients such as vitamin B6, vitamin C,

zinc and iron (see [7,9,10] for references). Such immune impairments have been linked to poor vaccine responses. For example, a systematic review and meta-analysis of nine studies involving 2,367 individuals found lower seroprotection rates to influenza A virus subtype H3N2 and to influenza B virus in those who were vitamin D deficient[11]. By contrast, randomised controlled trials of supplemental micronutrients (e.g., vitamin B6, vitamin E, zinc and selenium) in older people report enhancements in many of the immune biomarkers measured (see [9,10] for references). In surveying the literature in this field, it appears that vitamins C, D and E together with zinc and selenium are needed by the immune system in excess of amounts that can usually be achieved through diet alone[9,10]. As an example, selenium status above that required for optimal selenoprotein function has been associated with better cure-rate from COVID-19[12].

A cause and effect relationship between micronutrient status and vaccination responses has been demonstrated through randomised, controlled trials. Such trials in older people have shown better responses to vaccination after an intervention. For example, a randomised controlled trial of $\geq$5 servings of fruits and vegetables per day compared with $\leq$2 servings in people aged 65 to 85 years reported a better response to pneumococcal vaccination in the group consuming the higher amount of fruits and vegetables[13]. A study of vitamin E demonstrated improvement in response to some vaccines in individuals aged over 65 years given 60 or 200 mg vitamin E/day compared to those in the placebo group[14]. Selenium supplementation (50 or 100 μg/day) in adults in the UK with low selenium status improved some aspects of their immune response to a poliovirus vaccine and also reduced the emergence of mutant viral strains[15].

Nutritional deficiency and malnutrition are common in the elderly. In a systematic review of intake and deficiency of eight trace elements in adults ≥ 60 years in seven Western countries, consistent nutritional insufficiency was found for selenium, zinc, iodine and copper[16]. Notably, zinc deficiency was observed in 31% and 49% of community-based women and men, respectively, and in 50% and 66% of women and men in institutional care [16]. Selenium intake was similarly compromised with deficiency found in 49% of women and 37% of men in the community and in 44% of women and 27% of men in institutions[16]. Significant proportions of both populations showed insufficiency for iron, iodine and

copper[16]. Specific to the UK, the 2019 National Diet and Nutrition Survey showed "a sustained worsening of the dietary intakes and chronic shortages of several of the nutrients involved in supporting the normal immune functions"; these included vitamins A, B12, C and D and the trace minerals zinc, selenium and copper[17]. Such micronutrient deficiencies may limit the effectiveness of the COVID vaccines.

We propose that a nutritional supplement (e.g. containing vitamins A, B6, B9, B12, C, D and E and the minerals zinc, copper, selenium and iron) should be provided free of charge to all those aged over 70 years for a period of weeks before and after they receive the vaccine. The additional cost of providing a supplement of those nutrients important to immune function that are likely to be deficient in the elderly would be small investment to better assure a robust vaccine response. It is possible to buy a multi-vitamin and mineral supplement, retail, for around £1.50 (US$2) per 45 tablets. A 45-day supply of the supplement, purchased wholesale, would provide great potential gain and would add only a modest cost to any vaccination programme: the US Government negotiated price of the Pfrizer vaccine is US$20 per dose (i.e. US$40 per full treatment), the Moderna vaccine is costed at US$10 to $50 per dose with the European Union negotiating a cost of up to US$25 per dose (i.e. US$50 per full treatment), while the cost of the Astra Zeneca vaccine to the US Government is US$4 per dose (i.e. US$8 per full treatment)[18].

Yours sincerely

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