Vaccine efficacy and iron deficiency: an intertwined pair?

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Vaccines are the most effective measure to prevent deaths and illness from infectious diseases. Nevertheless, the efficacy of several paediatric vaccines is lower in low-income and middle-income countries (LMICs), where mortality from vaccine-preventable infections remains high. Vaccine efficacy can also be decreased in adults in the context of some common comorbidities. Identifying and correcting the specific causes of impaired vaccine efficacy is of substantial value to global health. Iron deficiency is the most common micronutrient deficiency worldwide, affecting more than 2 billion people, and its prevalence in LMICs could increase as food security is threatened by the COVID-19 pandemic. In this Viewpoint, we highlight evidence showing that iron deficiency limits adaptive immunity and responses to vaccines, representing an under-appreciated additional disadvantage to iron deficient populations. We propose a framework for urgent detailed studies of iron–vaccine interactions to investigate and clarify the issue. This framework includes retrospective analysis of newly available datasets derived from trials of COVID-19 and other vaccines, and prospective testing of whether nutritional iron interventions, commonly used worldwide to combat anaemia, improve vaccine performance.

Introduction

As the COVID-19 vaccine rollout proceeds worldwide, attention is increasingly being paid to vaccination of patient groups with underlying ailments that can affect vaccine efficacy. In February, 2021, The European Hematology Association (EHA) issued a series of expert opinions on vaccination in individuals with haematological conditions. One states the following: "Data on the COVID-19 vaccine in the context of chronic iron deficiency is still scarce. However, it is advisable to correct the iron deficiency before administration of the COVID-19 vaccine."[1] This short comment points to advances in basic and global health research on the role of iron in immunity, indicates an important and plausible area of concern, and illuminates a knowledge gap that pertains not only to COVID-19 but to vaccination programmes in general.

Iron is a nutrient required for immunity

Iron deficiency and iron deficiency anaemia are highly prevalent worldwide.[2] Studies over the previous decades have suggested a potential association between iron deficiency and decreased immunity and poorer response to some vaccines.[3–5] In 2016, a rare mutation impairing the ability of cells to take up iron was found to cause severe immunodeficiency rather than iron deficiency anaemia, revealing the unsuspected sensitivity of adaptive immune responses to iron deprivation.[6] Subsequent preclinical work has clearly shown that low serum iron and iron deficiency, both of which decrease the availability of iron to cells, can impair immune responses to vaccination and infection.[7,8] Studies in African children have indicated the effects of anaemia on immune development,[9] and people with a rare inherited form of iron deficiency anaemia have lower concentrations of some vaccine-inducible antibodies than people without this condition.[7] Together these studies suggest that the iron status of individuals can affect responses to immunisation.

Iron deficiency and reduced efficacy of vaccines

The effect that iron status has on responses to vaccines was brought into sharper focus by analyses in Kenyan children. In this cohort, anaemia and iron deficiency at time of vaccination were strong predictors of decreased responses to diphtheria, pertussis, and pneumococcal vaccines.[10] Moreover, in a randomised trial of Kenyan infants who were iron deficient, iron-containing micronutrient powders given at time of vaccination increased anti-measles antibody avidity and seroconversion after primary measles vaccination, again suggesting that iron availability is a limiting factor affecting vaccine efficacy in this population.[10]

Notwithstanding the huge benefits vaccination programmes have brought to global health, some vaccines have variable efficacy in different populations, age groups, and in the context of particular underlying conditions. The reasons for this variable efficacy remain unclear. Although many factors have been shown to influence vaccine efficacy,[11] we have noted an unappreciated epidemiological overlap between lower vaccine efficacy and higher prevalence of iron deficiency and anaemia. For example, rotavirus vaccines and live attenuated influenza vaccines in infant populations in low-income and middle-income countries (LMICs),[12,13] hepatitis B vaccines in patients with chronic kidney disease or coeliac disease,[14,15] and influenza vaccines in older people,[16,17] all represent instances where lower efficacy has been reported and where iron deficiency is common.

Iron deficiency anaemia is a leading global cause of years lived with disability, especially affecting LMIC populations.[18] A stated aim of WHO is to decrease the prevalence of anaemia in women of reproductive age by 50% by 2025.[19] However, projected increases in atmospheric CO_2 are predicted to increase the prevalence of nutritional iron deficiency through effects on iron content of food crops.[20] Furthermore, the ongoing COVID-19 pandemic has increased food insecurity in

LMICs,[21] potentially exacerbating iron deficiency in the shorter term. Therefore, if iron deficiency also impairs the efficacy of some vaccines in addition to the recognised contributions to anaemia and cognitive impairment,[2] then the existing and future impact of iron deficiency on global health might be underestimated. From this perspective we consider investigation of further effects of iron deficiency and iron supplementation on vaccines to be both timely and necessary.

Key unknowns and how to address them

It is not understood which vaccines in which populations are impaired by iron deficiency. For example, although indicators of iron deficiency anaemia were strong predictors of poor response to diphtheria and pertussis in Kenyan infants, in the same children there was no such association between iron deficiency anaemia and response to tetanus or Hib vaccines.[10] The basis of this selectivity of effect is unclear but might reside in quantitative and qualitative effects of iron on immunity. Another unknown is the degree of iron deficiency that is required to affect immune responses to vaccines, or whether other nutritional deficiencies, or inflammatory conditions, can exacerbate the effects of iron deficiency. Moreover, it is not known which of the different branches of the immune system are most sensitive to iron deficiency, or how the development and maintenance of immune memory is affected by iron.

Iron deficiency not only arises from a lack of dietary iron, but also during inflammation (eg, from bacterial infection or chronic kidney disease), which drives iron retention in myeloid immune cells, eventually causing functional iron deficiency and anaemia of inflammation.[22] Other causes of iron deficiency and anaemia can be hip fracture or colon neoplasia.[2] Given the variable underlying pathophysiology, these types of iron deficiency resulting from different causes could have distinct effects on adaptive immunity and responses to vaccination.

Considerable progress in these areas could be made by retrospective analyses of samples from the many vaccine trials that take place in LMICs and high-income countries each year, to assess links between iron status and vaccine efficacy at individual and population level. Key iron-associated parameters to measure should include transferrin saturation and serum iron, which reflect the circulating iron compartment (the source of iron for the responding immune system); ferritin, which reflects iron stores; and soluble transferrin receptor, which indicates erythropoiesis. Markers of inflammation should also be assessed, because inflammation suppresses serum iron, through induction of hepcidin, and increases ferritin. Conversely, immunological endpoints (eg, vaccine-induced antibody responses) could be added to clinical trials investigating iron interventions. Successful exploitation of datasets will require cross-disciplinary collaboration between nutritionists, immunologists, vaccinologists, haematologists, and global health practitioners.

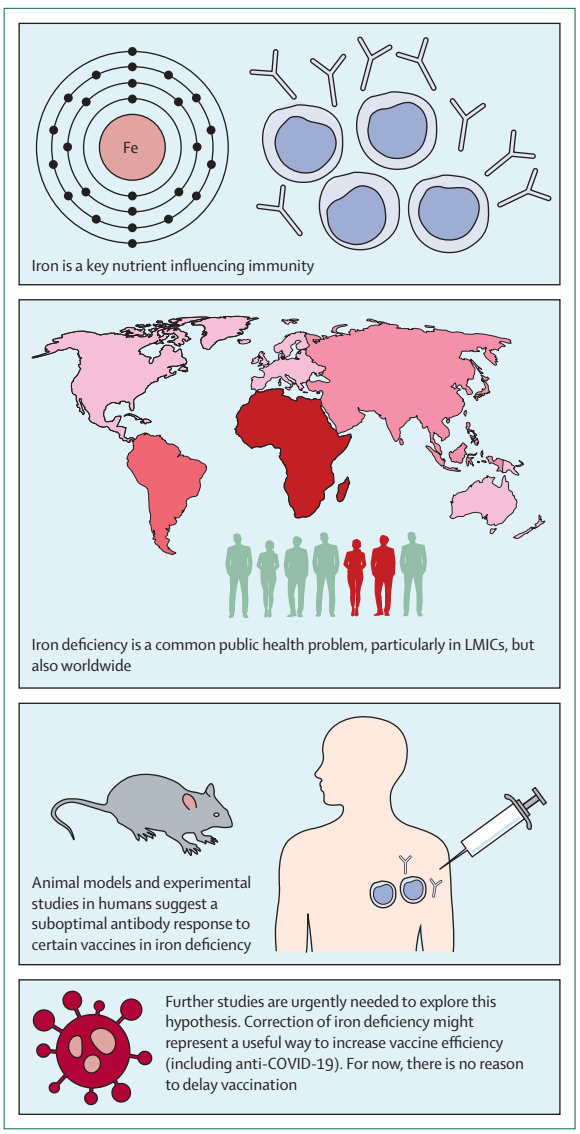

Figure: **Infographic summarising the key issues of this Viewpoint**
LMICs=low-income and middle-income countries. In the world map (second panel), darker shading represents higher prevalence of iron deficiency.

With respect to COVID-19 vaccines, evidence is that vaccine efficacy is remarkably high,[23–25] even among premenopausal women and older populations in whom iron deficiency and anaemia are relatively common. These efficacy data suggest that the aforementioned EHA guideline, recommending correction of iron deficiency before COVID-19 vaccination, might (in the context of a rapidly spreading virus) be overly cautious. Nevertheless, immune responses to COVID-19 vaccines appear to be slower to develop in older people. Moreover, with the emergence of relatively vaccine-resistant SARS-CoV-2 variants, characterising the speed and duration of response to COVID-19 vaccines in different

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Search strategy and selection criteria

We searched PubMed with the terms "iron and immunity", "iron and vaccine", and "iron and immune response", without applying any date or language restrictions. The last search was done on April 15, 2021. We used previous reviews of older studies on iron–immunity interactions and focused on the most recent primary literature advancing knowledge of how iron affects immune responses. We integrated key background information summarising the causes and prevalence of iron deficiency and iron deficiency anaemia with several studies highlighting examples of variable efficacy of some vaccines in different population types.

contexts, including iron deficiency, is necessary to model expected benefits of the vaccination rollout.[26] Clinical trials on immune responses to COVID-19 vaccines have provided rich data, which could be interrogated to test for signals of the effects of iron deficiency on the immunogenicity of the vaccines.

Iron supplements in oral or intravenous form are commonly used to restore haemoglobin concentrations and counteract systemic iron deficiency. Timing and dosages of iron interventions are continually being optimised,[27,28] providing an excellent knowledge base from which to launch prospective tests on how iron affects response to different vaccines across different types of iron-deficient populations. If successful, this has great promise, because even small increases in vaccine efficacy, driven by inexpensive iron supplements and fortificants, could translate to substantial improvement in mortality at a global scale, potentially altering the overall risk–benefit and cost–benefit considerations for these interventions.[29] The type and amount of iron given will necessarily vary depending on the target population—eg, infants receiving vaccines as part of the Expanded Programme on Immunization, patients with chronic kidney disease receiving hepatitis B vaccines, or older people receiving influenza vaccines. Condition-specific scenarios must be taken into account; for example, iron is given to alleviate anaemia in chronic kidney disease, but is often co-administered with erythropoietin, which might divert iron to the erythron and away from the immune system.

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Conclusions

Iron is a key nutrient affecting immunity, and iron deficiency and iron deficiency anaemia remain major global health problems (figure). Vaccine efficacy could be compromised in the many population groups who have iron deficiency and anaemia, further affecting their health. Emerging data support this concept, urgently calling for further investigation to delineate and quantify this hitherto under-recognised effect of iron deficiency. Potential effects of iron deficiency on the quality, magnitude, and duration of the immune response to COVID-19 vaccines should be investigated, although the high efficacy of these vaccines argues against delaying vaccination in order to correct iron deficiency. Prospective trials of iron supplementation in iron deficient populations receiving vaccines that are known to have variable efficacy are recommended. We encourage a concerted cross-disciplinary effort and open sharing of data to make rapid progress and improve defences against infectious diseases.

Contributors

HD, CH, IC, and PK were responsible for the conceptualisation of the study. HD did the literature search and wrote the original draft of the manuscript. HD, CH, IC, MUM, EN, CC, NS, S-RP, MBZ, GW, PK, and DG reviewed and edited the manuscript. DG made the figure. All authors critically reviewed the Viewpoint and approved the final version for submission.

Declaration of interests

IC was the President of BioIron from 2018 to 2019. EN reports consulting fees from Ionis Pharmaceuticals, Disc Medicine, Vifor Pharma, Protagonist Therapeutics, Shield Therapeutics, and AstraZeneza/FibroGen, and stock in Intrinsic LifeSciences and Silarus Therapeutics. PK served on an advisory board with Vifor Pharma. DG reports co-funding from Vifor Pharma (along with the Italian Ministry of Health) for a research project on Perioperative Anemia in Cancer Patients, as well as honoraria from Vifor Pharma. S-RP reports a fellowship grant and project grants from the National Health and Medical Research Council; project grants from the Bill & Melinda Gates Foundation; consulting fees from Keros Therapeutics and Merck; and serving on guideline development committees for WHO and as Lead for the WHO Collaborating Centre for Anaemia Detection and Control. CC reports royalties from UpToDate and Wolters Kluwer, and honoraria from Vifor Pharma. GW reports grants from the Austrian Science Fund (FWF), European Union, and Christian Doppler Laboratory. HD reports grants from the UK Medical Research Council and National Institute for Health Research Biomedical Research Centre; consulting fees from Keros Therapeutics; speaker honoraria from Pharmacosmos; and serving on an advisory board for Vifor Pharma. MBZ reports consulting fees from Nestlé, Danone, Nutricia, Procter & Gamble, and DSM, and serving on advisory boards for Vifor Pharma and Procter & Gamble. All other authors declare no competing interests.

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