

# Harnessing co-operative immune augmentation by contact allergens to enhance the efficacy of viral vaccines

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## Abstract

Although the development of successful vaccines against coronaviruses may be achieved, for some individuals the immune response that they stimulate may prove to be insufficient for effective host defence. The principle that a relatively strong contact allergen will have an enhancing effect on sensitization compared with a less potent contact allergen if they are co-administered, may not, at first, appear relevant to this issue. However, this augmentation effect is thought to be due to the sharing of common or complementary pathways. Here, we briefly consider aspects of the shared and complementary pathways between skin sensitization induced by exposure to a contact allergen and the immune response to viruses, with particular reference to COVID-19. The relationship leads us to explore whether this principle, which we name here as “co-operative immune augmentation” may be extended to include viral vaccination. We consider evidence that even relatively weak contact allergens, used in vaccines for other purposes, can show enhanced sensitization, which is in keeping with a co-operative augmentation principle. Finally, we consider how the potent contact allergen diphenylcyclopropanone could be employed safely as an enhancer of vaccine responses.

## KEYWORDS

adjuvant, contact allergens, co-operative immune augmentation, co-sensitization, COVID, diphenylcyclopropanone, vaccine

## 1 | INTRODUCTION

There is a global concerted effort underway to develop an effective vaccine against COVID-19. It is still relatively early in the process but, to date, attempts at finding a safe and effective vaccine against other coronaviruses have met with, at best, limited success.<sup>1,2</sup> Although this situation may change, there is merit in considering whether strategies exist that could be employed to enhance the effectiveness of an otherwise sub-optimal vaccine. In this paper, we review the principle of “co-operative immune augmentation”, observed when contact allergens of different potencies are administered, refer to the common and complementary immune pathways between contact allergens and

viruses, and outline the evidence to date for enhanced immunogenicity of contact sensitizers used as adjuvants/additives in viral vaccines. We attribute this effect to co-operative immune augmentation between the allergen and viral components, leading us to consider whether this principle could be applied for the purpose of augmenting the immunogenicity of viral vaccines via simultaneous administration of a safe but potent topical allergen.

## 2 | CO-OPERATIVE IMMUNE AUGMENTATION

A number of studies have explored the immunological effects of co-administration of contact allergens. Jowsey et al noted in a murine

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model that when low doses of two strong contact allergens (*p*-phenylenediamine and methyl dibromo glutaronitrile) were applied together the level of induction of sensitization was somewhat greater than would have been expected from the sum of the individual responses when applied alone.<sup>3</sup> More recently, it was reported that combinations of contact allergens induced a stronger elicitation reaction to a single contact allergen when compared with the reaction to the single contact allergen alone.<sup>4</sup> That is, the level of sensitization achieved with one contact allergen – as measured by the elicitation of challenge-induced skin reactions – was enhanced if at the time of sensitization it was co-administered with another contact allergen.

Bonefeld et al conducted some intriguing experiments in mice with fragrance chemicals.<sup>4,5</sup> The key observation was that topical co-administration of a mixture of contact allergens caused an increase in the level of sensitization to the individual allergens (as judged by subsequent challenge-induced increases in ear thickness) compared with levels of sensitization when administered alone. The conclusion drawn was that there is antigen-non-specific augmentation of specific skin sensitization to individual contact allergens when two or more contact allergens are co-administered.

This same group also conducted informative experiments in mice with cobalt and nickel.<sup>4,6</sup> Under the experimental conditions employed, it was found that co-administration of cobalt with nickel augmented the development of sensitization to cobalt, as witnessed by enhanced reactions following the subsequent ear challenge. In this case, nickel did not cause sensitization per se (mice do not develop skin sensitization to nickel<sup>7</sup>), but it was found to cause irritation. This provides an example of co-operative immune augmentation. The interpretation was that in these experiments, nickel is providing a stimulus that increases the effectiveness of sensitization to cobalt. Under these conditions it is speculated that nickel is facilitating enhanced sensitization to cobalt by generating increased levels of local danger signals that support enhanced responses to cobalt. This is feasible because it is known that local danger signals of various types are required for the elicitation of effective adaptive immune responses.<sup>8</sup> This concept is discussed more fully below.

The essential concept is that simultaneous exposure to a mixture of antigens may result in co-operative immune augmentation of adaptive immune responses to the weaker antigen. The argument is as follows. In such a mixture of two antigens, the more potent will be fully equipped to induce and sustain a vigorous adaptive immune response without the need of assistance from the second weaker antigen. Therefore, the immune response to the stronger antigen will be unaffected by the co-administration of the weaker antigen. The reverse is seen with responses to the weaker antigen. By definition, the weaker antigen is poorly equipped to mount a vigorous response, perhaps, for instance, because it lacks the ability to promote optimal danger-signal release. In this case, the weaker allergen will benefit from the co-administration of the stronger antigen (perhaps due to the greater release of danger signals by the latter), resulting in enhanced immunogenicity (so-called co-operative immune augmentation).

### 3 | THE IMMUNOLOGICAL RESPONSES TO CONTACT ALLERGENS AND VIRUSES: COMPLEMENTARY IMMUNE PATHWAYS

It is likely that co-operative immune augmentation extends beyond apparently synergistic effects between different contact allergens. There are commonalities between immune responses involved in the acquisition of skin sensitization and those that are induced by pathogenic microorganisms.<sup>8-10</sup> This begs the question of whether immune responses to microbial antigens and those induced by contact allergens could display co-operative effects, and if so, whether this could be exploited as a mechanism for enhancing the immunogenicity of viral vaccines. This could be through different pathways that augment each other, or directly shared common pathways.

Directly shared pathways include natural killer (NK) cell activity and perforin expression, which appear to be crucial for both the response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in the innate and memory response in contact sensitization.<sup>9-12</sup> Another example of a “common” pathway between responses to a respiratory virus and contact allergens is NLRP3 activation.<sup>13,14</sup>

Danger signals can take a variety of forms, but it is convenient to distinguish between pathogen associated molecular patterns (PAMPs) that are elicited during infection with a pathogenic microorganism, and danger associated molecular patterns (DAMPs) that are danger signals generated following cell and tissue damage or death.<sup>8</sup> The question is whether PAMPs, associated with microorganisms, and DAMPs, induced by skin trauma associated with exposure to contact allergens, co-operate to augment adaptive immune responses.

### 4 | IMMUNE RESPONSE TO CONTACT ALLERGENS CONTAINED WITHIN VACCINES

During the history of vaccine development several agents have been used as co-formulants that display some potential to induce skin sensitization, although their inclusion within vaccines has not been specifically for this property. These include adjuvants, antibacterial substances and preservatives. The definition of adjuvant activity is broad, usually relating to the enhancement/modulation of the immune response to an unrelated antigen, but many of these agents have not been added (yet) specifically for their contact allergy sensitizing properties. Sensitizing agents found in vaccine formulations have only weak sensitizing activity. If, as described above, the weaker antigen in a mixture is the more likely to be associated with enhanced responses and immunological memory, then in a vaccine it would be expected that the sensitizing response of these weak allergens would be augmented.

Aluminium salts have been used as adjuvants in virus vaccines for decades. Bergfors et al described cases of contact sensitization to aluminium salt (aluminium hydroxide and aluminium phosphate) from diphtheria-tetanus-pertussis-polio (DTP)-Haemophilus influenza type B vaccine, usually manifesting as granulomas at the original site of injection, to occur on average 3 months after injection.<sup>15</sup> Twenty-nine

of 34 children (age 3–12 months, just under 1% of children receiving this vaccine) with this clinical presentation had a positive patch test to a 2% aluminium chloride patch test. In all but three there were ++ to ++ + reactions. Additionally, in a study where 20 subjects had both documented allergic contact dermatitis to aluminium and a + or stronger reaction to an aluminium patch test, two of four who had ++ or +++ to a 2% aluminium chloride 2% patch test, provided a history of local reactions to immunotherapy/vaccination as the potential sensitizing exposure to aluminium. These strong reactions are unexpected as aluminium exposure through other sources (deodorants, ear drops, antiseptics, sun creams/lotions, tattoos, patch test chambers) only rarely leads to sensitization. Furthermore, 2% aluminium chloride has often been adjudged to be too weak for patch testing purposes.<sup>16</sup> Therefore, when aluminium salts are used as adjuvants, the immune response to the usually weak sensitizer, aluminium, appears to be augmented.

The use of mercury/thimerosal in vaccines was extensive in the past, but has decreased in the last 20 years because of toxicity concerns. Marked allergic contact reactions to mercury/thimerosal from vaccines have also been described.<sup>17</sup> A 3-year-old girl developed an acute eczematous eruption 6 months after DTP vaccination. Patch testing to mercury agents, ie thimerosal 0.1%, phenylmercuric nitrate 0.05%, ammoniated mercury 1%, and organic mercury 0.5%, all gave + to +++ reactions, increasing in strength between 48 and 96 hour readings.<sup>18</sup> Osawa et al showed that guinea pigs sensitized with the DTP vaccine containing thimerosal gave stronger challenge reactions to thimerosal compared to guinea pigs sensitized with thimerosal alone. They concluded that the high rate of mercury allergy amongst patients in Finland (over 10% in ages 10–59 years) was a reflection of vaccinations containing mercury.<sup>19</sup>

A 4-year-old boy complained of persistent nodules at a vaccination site (site not reported). He had positive patch tests to aluminium, neomycin, and formaldehyde.<sup>20</sup> Sensitization to neomycin from its use as an antibacterial agent in vaccines is again surprising. Neomycin-containing vaccines typically contain less than 150 µg per dose (often 25 µg). Of note, the TRUE Test, an epicutaneous patch test, contains 190 µg of neomycin sulfate per patch. Neomycin is an extremely weak contact allergen. Despite millions of people being patch tested to neomycin (usually 20% pet. or at TRUE Test dose above) there have been no reports of active sensitization to neomycin from patch testing. Among 50 patients with contact allergy to thimerosal, Cox et al noted eight (16%) were also allergic to neomycin.<sup>18</sup> While this may be due to coexistence among agents in such products as eyedrops, the alternative explanation would be co-operative augmentation from vaccines. In summary, as described above, weak contact allergens used as part of a vaccine for different purposes have been observed to cause surprisingly strong contact sensitization.

## 5 | CAN THE CO-SENSITIZING PRINCIPLE BE USED TO ENHANCE VIRUS VACCINATION?

If, as expected, the augmentation principle applies to virus vaccine then administration of a potent (but safe) contact allergen at the same

time as vaccination, and at a site that will likely drain into the same lymphatic system, might be expected to augment the viral antigenic signal and resultant protective immunity. This could, potentially, be of significant benefit in enhancing the effectiveness of the vaccination per se, but of particular value in those individuals where there is reason to believe that the adaptive immune responses may be sub-optimal.

It would be inappropriate to use contact allergens that may be encountered in everyday life; this leaves few options. Furthermore, preclinical experience with vaccines for earlier coronaviruses causing severe respiratory disease (SARS1 and Middle East respiratory syndrome) raised concern about exacerbating lung disease, either directly or through antibody enhancement.<sup>21</sup> Lurie et al suggest that if an adjuvant response is required in order to generate a sufficient immune response, that (as well as giving a neutralizing antibody response) delivering a type 1 T helper (Th1) response rather than a Th2 response, is theoretically more likely to be protective and avoid the risk of immunopathology.<sup>21</sup>

Diphenylcyclopropenone (DPCP), a potent topical sensitizer, delivers a dominantly Th1 response and has been in use as immunotherapy for decades, usually in the treatment of alopecia areata.<sup>22</sup> It has also been used in the treatment of recalcitrant verrucae. In a study of 27 patients who were first sensitized with DPCP (0.5%–1% concentrations applied to the arm) and the verrucae then treated by immunotherapy (1%–2% DPCP), eliciting DPCP skin reactions appeared to eliminate the verrucae.<sup>23</sup> Four patients had temporary itching during the sensitization phase (relieved by antihistamines), but no serious adverse effects were reported. In a study of 108 children sensitized by 2% DPCP, 21% had “marked” sensitization reactions at the initial application site, such as oedema, vesicles, desquamation, or local urticaria.<sup>24</sup> However, in most patients the sensitization phase manifested clinically as 2–4 days of erythema. Lower primary concentrations of DPCP such as 0.1% instead of 2% can also have immunological effects without adverse effects being reported.<sup>22</sup>

## 6 | CONCLUSION

For safety reasons, a trend in vaccination has been to replace inactivated organisms with antigenic proteins. Whilst making the vaccine safer this can sometimes reduce the immune response, hence the importance of co-administration of adjuvants. Here we have reviewed the potential for strong experimental contact allergens to be used in special circumstances, ie where there has been an ineffective response to the original viral vaccine. One such agent could be DPCP, which, even when applied at a marginally lower dose than the usual sensitizing dose of 2% to reduce allergic skin reactions, may still be expected to give a strong immune reaction.<sup>22</sup> The proposal is that topical exposure to an appropriate dose of DPCP, at the time of vaccination, and at an adjacent anatomical location draining into the same lymphatic bed, could boost the immunogenicity of viral vaccines significantly and improve host resistance to infection.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

**Louise Cunningham:** Data curation; software; writing-original draft; writing-review and editing. **John McFadden:** Conceptualization; data curation; supervision; writing-original draft; writing-review and editing. **David Basketter:** Supervision; writing-review and editing. **Felicity Ferguson:** Writing-review and editing. **Ian White:** Writing-review and editing. **Ian Kimber:** Supervision; writing-review and editing.

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