

syndrome (SBS) before the date when the authors supposed first description in 2011.² Clinical and statistical analysis showed a coincidental onset of autoimmune processes triggered by the sick building and a parallel absence of definitive score for SBS in people without immune problems.^{2,3} The discussion was raised to the arena in response to the statement that ASIA presents without autoantibodies,⁴ which had to be admitted. Although overlooked, evidence from those studies allows us to support that SBS, and possibly another ASIA, translates an immune susceptibility for autoimmune diseases or other immune phenomena⁵ triggered by adjuvants or environmental components. Problems with ASIA, as SBS, are the oddity of their presentation, which defies the medical explanation. For example, SBS investigations have focused on the effects of the buildings, but clinical individual assessment has been neglected and surveys are usually run by no experts. In conclusion, refutation of existence of ASIA is a strong statement without enough base.

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Reply to Crépeaux et al and Blasco



To the Editor:

We thank Crépeaux et al¹ and Blasco² for their responses to our article refuting the existence of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA).³

The evidence for the existence of ASIA is based on the diagnostic criteria published by its creators (Fig 1).⁴ As shown in our review, the symptoms of ASIA such as pyrexia, arthralgias, and irritable bowel syndrome are nonspecific and are commonly experienced in the community. The criteria for ASIA could include the entire community. This alone refutes the existence of such a syndrome as a clinically useful diagnosis.

The second scientific question we addressed was whether aluminum salts cause autoimmunity. The causes of most

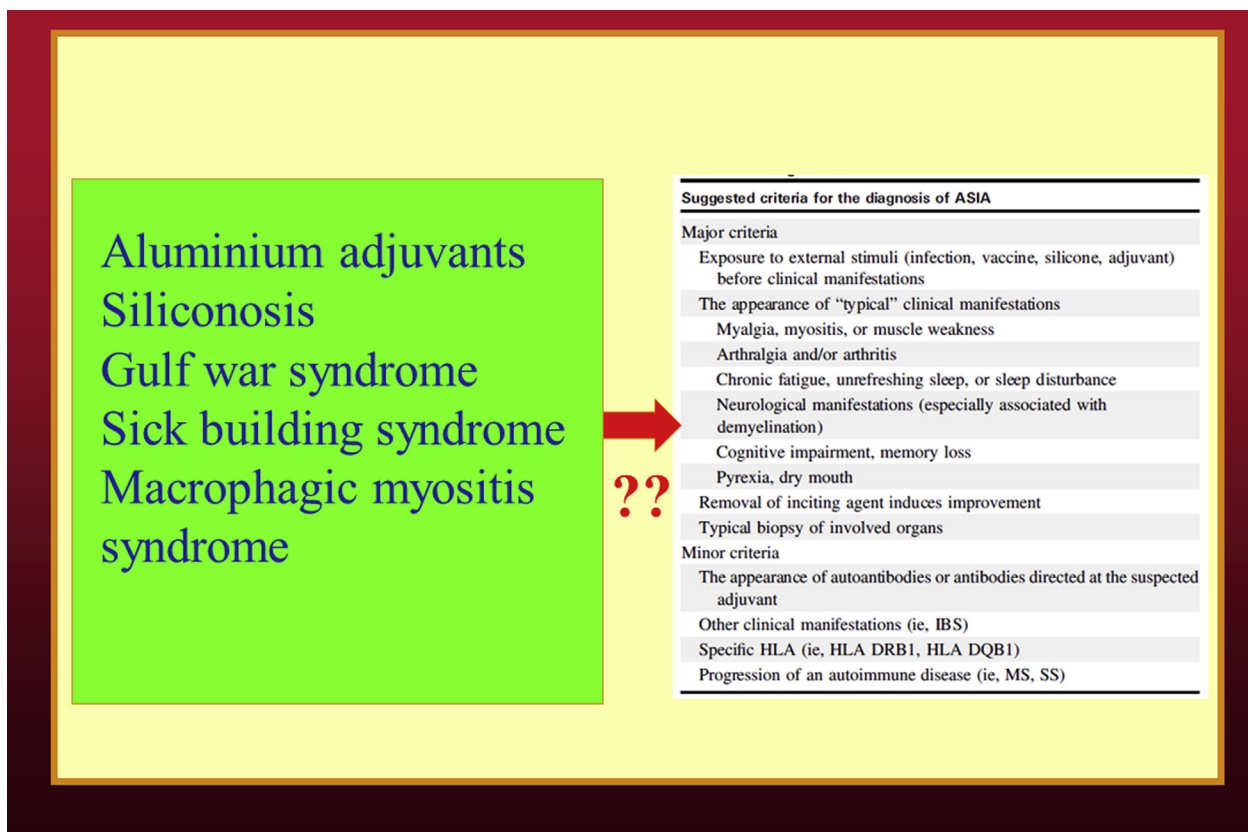


FIGURE 1. Causes and manifestations of the ASIA syndrome. A range of conditions are stated to cause a large number of nonspecific symptoms. The symbol ?? represents the unproven link between the exposure (vaccine adjuvants, silicone, etc.) and outcomes (ASIA).

autoimmune disorders are currently unknown. In this situation, epidemiological studies are required to support causality. As shown in Table I, there is little support for a causal link between aluminum-containing adjuvants and systemic autoimmunity. This is the second scientific reason for refuting the existence of ASIA as defined by its creators.

The prospective study of patients with systemic lupus erythematosus (SLE) ($n = 28$) who received the hepatitis B vaccine is important evidence that aluminum-containing adjuvants do not trigger autoimmunity in such highly susceptible individuals.⁶ Even more powerful evidence for causality would have emerged if these patients with SLE developed a different autoimmune disorder: neither outcome occurred.

Most importantly, the very large population-based study in Denmark is very strong evidence that aluminum *significantly reduced* the risk of autoimmunity.⁷ This is precisely the *opposite outcome* that would have been predicted from cases series of ASIA. As calculated in our article, patients undergoing allergen-specific immunotherapy (IT) ($n = 18,841$) receive between 100 and 500 times the amount of aluminum contained in 3 hepatitis B vaccines and yet they have a *significantly lower* incidence of autoimmunity. In this study, patients receiving nasal steroids and antihistamines ($n = 428,484$) were the controls for those undergoing IT. If there are significant unexplained discrepancies as seen in this high-quality study, a causal relationship is very unlikely between exposure (vaccines) and outcome (ASIA).

Crépeaux et al state that lower doses of aluminum may be more likely to cause neurotoxicity than higher doses. Because allergen

IT is administered over 3 to 5 years, patients begin with lower doses of aluminum-containing allergens. We would have expected patients to suffer the symptoms claimed by Crépeaux et al at the start of IT. There is no evidence for this in humans. If the authors are claiming that less Al is more likely to cause neurotoxicity or ASIA than higher doses, we would expect more evidence than the data from a small number of mice in their own study.⁸

In their letter, Crépeaux et al also raise the issue of macrophagic myositis syndrome and chronic fatigue syndrome (systemic exertional intolerance syndrome, SEID), being part of ASIA. Our primary focus was autoimmunity caused by aluminum-containing adjuvants. It is however surprising that the macrophagic myositis syndrome seems to be mostly confined to French adults in spite of being described almost 2 decades ago. Most publications on this condition have originated from one center. We find this geographic restriction difficult to explain. Similarly, we have found no published data that patients undergoing allergen IT are unduly susceptible to SEID.

In his letter, Blasco raises the issue of the sick building syndrome (SBS), which has been stated to be another cause of ASIA (Fig 1).⁹ We certainly accept that poor-quality buildings could harbor environmental allergens including mold and dust mites leading to allergies. Similarly, exposure to toxic chemicals such as asbestos could cause illness. The main difficulty is explaining how poor-quality buildings can cause such a broad range of ailments (Fig 1).

Of the 379 possible cases in 3 papers presented by Blasco in his letter, only 8 cases demonstrated the presence of autoantibodies. In none of these cases was the appearance of autoantibodies demonstrated to be caused by SBS, and no follow-up has been undertaken. Blasco himself concludes: “a direct link cannot be confirmed by this observation.” In none of the studies cited were controls used, and as such, at best, these cases are part of a case series.

We respectfully suggest to both correspondents, that case series, no matter how large, are no more than anecdotal evidence when inferring causality. Case series are likely to be the result of random events, and the association with systemic autoimmunity is likely to be spurious.

We have previously acknowledged that it is biologically plausible that there could be a link between vaccine adjuvants and autoimmunity, but the evidence is precisely the *opposite*.¹⁰ When reviewing ASIA as an entity however, it seems implausible that such a disparate range of triggers including aluminum, silicone, chemicals in the Gulf war, and poor-quality buildings could all cause such a large range of nonspecific clinical disorders (Fig 1).

We have acknowledged that all vaccines carry a very small risk of a serious adverse event. The benefits of vaccines far outweigh these small risks. As stated in our review, we are concerned that fear of ASIA and other so-called autoimmune disorders are reducing vaccine uptake rates and placing large numbers of women at risk of death or disease from vaccine preventable disorders including cervical cancer. We are in agreement with Crépeaux et al in asking for an independent expert panel to evaluate the existence of ASIA and the specificity of its diagnostic criteria. This should be done under the aegis of the World Health Organization and International Union of Immunological Societies.

TABLE I. Application of Sir Austin Bradford Hill's criteria for causality to ASIA

Bradford Hill criterion	Comment
Strength of association	Poor: ASIA is a rare event
Consistency	Poor: the study of patients with SLE and the study from Denmark contradict case series of ASIA
Specificity	Poor: multiple triggers are claimed to cause multiple disorders. We accept that specificity is a relatively weak criterion as smoking can cause multiple disorders
Temporality	Poor: ASIA can occur from days to over 2 decades. This makes it very difficult to design randomized studies
Biological gradient.	Poor: large amount of aluminum is associated with a significantly lower incidence of autoimmunity
Plausibility	Yes: a potentially attractive hypothesis but unproven
Coherence	Poor: the causes of most cases of autoimmunity are unknown and the SLE study and the Denmark study indicate potentially the opposite conclusion
Experiment	Poor: animal models suffer from numerous flaws ⁵ and a randomized study may take decades
Analogy	This may be similar to electromagnetic fields where many health hazards have been claimed, but remain unproven

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