

# Vaccine Adjuvant

Vaccine adjuvants are molecules or compounds that have intrinsic immunomodulatory properties and, when administered in conjunction with an antigen, effectively potentiate the host antigen-specific immune responses compared to responses raised when antigen is given alone.

From: [Mucosal Immunology \(Fourth Edition\), 2015](#)

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## Vaccines

In [Meyler's Side Effects of Drugs \(Sixteenth Edition\)](#), 2016

### Aluminium

A [vaccine adjuvant](#) is defined as an agent that increases specific immune responses to an antigen [200]. The only vaccine [adjuvants](#) currently licensed by the FDA are aluminium salts. All other adjuvants are considered experimental and must undergo special preclinical testing. Real and theoretical risks of [vaccine adjuvants](#) comprise various local acute or [chronic inflammation](#) with formation of [abscesses](#) and nodules; induction of [hypersensitivity](#) to the host's own tissues, producing autoimmune arthritis, [amyloidosis](#), [anterior uveitis](#); cross-reactions with human antigens, such as glomerular basement membranes or neurolemma, causing [glomerulonephritis](#) or meningoencephalomyelitis; sensitization to [tuberculin](#) or to other skin test antigens; [carcinogenesis](#); pyogenesis; [teratogenesis](#); abortion; and adverse pharmacological effects, such as [hypoglycemia](#).

Macrophagic myofasciitis is an uncommon inflammatory disorder of muscle, believed to be due to persistence of vaccine-derived [aluminium hydroxide](#) at the site of injection. The condition is characterized by diffuse [myalgia](#), [arthralgia](#), and fatigue. In one case of histologically confirmed macrophagic myofasciitis left chest and upper limb pain developed more than 10 years after immunization [201]. Treatment with [steroids](#) led to symptomatic improvement.

A meta-analysis has compared the reactogenicity of vaccines containing aluminium hydroxide versus vaccines without adjuvants in children aged up to 18 months, and vaccines containing different types of aluminium versus vaccines without adjuvants in children aged 10–16 years [202]. In young children, vaccines containing adjuvants caused significantly more [erythema](#) and induration than plain vaccines ( $OR = 1.87$ ; 95% CI = 1.57, 2.24) and significantly fewer reactions of all types ( $OR = 0.21$ ; 0.15, 0.28). In older children, there was no association between exposure to aluminium-containing vaccines and the onset of local reactions or a raised temperature, but there was an association with local pain lasting up to 14 days ( $OR = 2.05$ ; CI = 1.25, 3.38). The authors found no evidence that aluminium salts in vaccines cause any serious or long-lasting adverse reactions.

During trials in Gothenburg, Sweden, of aluminium-adsorbed diphtheria–tetanus/acellular [pertussis](#) vaccines from a single producer, persistent itching nodules at the immunization site were observed in an unexpectedly high frequency: in 645 children out of about 76 000 immunized (0.8%) after both subcutaneous and [intramuscular injection](#). The itching was intense and long-lasting. After a median of 4 years 75% still had

symptoms. There was [contact hypersensitivity](#) to aluminium in 77% of the children with itching nodules and in 8% of their symptomless siblings who had received the same vaccines [203]. The authors suspected that the high incidence of itching nodules was related to the injection technique used. [Post-marketing surveillance](#) data from other regions in Sweden, Denmark, and Norway have suggested that the incidence of itching nodules is low after correct intramuscular administration of aluminium-adsorbed vaccines manufactured by Statens Serum Institut in Copenhagen, Denmark [204].

The effect of reducing the aluminium content of a combined reduced-antigen-content Tdap vaccine on immunogenicity and safety has been evaluated in 647 healthy adolescents aged 10–18 years [205]. Of those enrolled, 224 (35%) received a Tdap formulation with aluminium 0.5 mg, 209 (32%) a formulation with aluminium 0.3 mg, and 214 (33%) a formulation with aluminium 0.133 mg. One month after administration of the booster dose, all the subjects were seroprotected against [diphtheria](#) and [tetanus toxoids](#). All were seropositive for anti-filamentous [hemagglutinin](#) and anti-pertactin antibodies, but 4% of those who were initially seronegative in both reduced aluminium groups did not seroconvert for anti-pertussis toxin. Booster responses did not differ significantly between the groups for any antibody, but geometric mean concentrations of anti-pertussis toxin after booster immunization differed significantly between groups and fell when vaccine aluminium content was reduced. There were no clear differences between the study groups in local or general adverse effects. The most frequently reported symptoms after immunization were [injection site pain](#) (90–91%), fatigue (42–47%) and headache (41–45%). This study showed that the aluminium content has a specific influence on the immunogenicity of this Tdap vaccine.

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## Immunologic adjuvants

Frederick R. Vogel, Stanley L. Hem, in [Vaccines \(Fifth Edition\)](#), 2008

### Cytokine adjuvants

Several cytokines have been used as experimental vaccine adjuvants, including IL-2, IFN $\alpha$  and IFN $\gamma$ .<sup>62,62a,63</sup> IL-12 is an immunomodulatory cytokine that may play a pivotal role in the adjuvant activities of several microbial adjuvants. The adjuvant activity of IL-12 has been demonstrated in a [leishmania vaccine](#) in mice. Immunization of BALB/c mice with [Leishmania major](#) antigens and IL-12 induced leishmania-specific CD4 $^{+}$  Th1 cells and conferred protection against infection with *L. major*. Immunization of control animals with antigen alone elicited Th2 responses that were not protective.<sup>64</sup> However, the use of microbial adjuvants that induce the endogenous production of IL-12 may be preferable over the use of the preformed cytokine itself as an adjuvant for human prophylactic vaccines. A clinical study has shown that 1–4  $\mu$ g doses of recombinant IL-12 injected concomitantly with a pneumococcal [polysaccharide](#) vaccine induced dose-dependent fever and [flu-like symptoms](#) in human subjects.<sup>65</sup>

Cytokine mixtures, including [GM-CSF](#), [TNF- \$\alpha\$](#) , and IL-12 emulsified with [incomplete Freund's adjuvant](#) (IFA), have also been employed to 'steer' the immune response toward Th1 vs. Th2 responses.<sup>66</sup> In these studies, the investigators demonstrated that in BALB/c mice, GM-CSF acted in synergy with IL-12 to produce cytotoxic T cell (CTL) responses and the suppression of the Th2 cytokines IL-4 and IL-5 when delivered with HIV-1 (MN) peptide antigens in incomplete Freund's adjuvant (IFA).

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## MF59

S. Kommareddy, ... D.T. O'Hagan, in [Immunopotentiators in Modern Vaccines \(Second Edition\)](#), 2017

### MF59 Safety Profile

MF59 is a well-established, safe, and potent vaccine **adjuvant** that has been licensed in more than 30 countries, since its first approval in 1997. From the collective clinical trials and wide use during the 2009 pandemic, there is a large safety database available for the MF59 emulsion with the total number of administered doses reaching over ~200 million.<sup>28</sup>

A meta-analysis of the data from 20 clinical trials performed as a part of the MF59-adjuvanted vaccine registration in Europe showed that MF59 was well tolerated in the elderly with very mild local reactions.<sup>29</sup> Local reactions such as pain, temperature, erythema, and induration were observed to be higher in subjects who received MF59-containing **Fluad** than in subjects with comparator. However, all these reactions were rated as mild and were of short duration. The systemic reactions ranged from <1% to 8% for Fluad and from <1% to ~4% for comparator vaccines, of which myalgia was the most frequently reported and was rated as mild in 77% of the subjects. The combined results from all the 20 clinical trials demonstrated the safety of MF59-adjuvanted **influenza vaccine** in the elderly.<sup>29</sup>

A good safety profile of MF59-adjuvanted A/H1N1 pandemic influenza vaccine has been established by testing in clinical subjects aged 3–8 years ( $n = 194$ ) and 9–17 years ( $n = 160$ ) randomized to receive 3.75 µg of antigen with half dose of MF59, 7.5 µg of antigen with full dose of MF59, or 15 µg of nonadjuvanted antigen formulations.<sup>30</sup> Mild-to-moderate pain at the site of injection was the most common local reaction observed. Among the systemic reactions, myalgia and fatigue were the most commonly observed and none of the subjects experienced severe fever  $\geq 40^{\circ}\text{C}$  at any time during the study. The onset of new chronic diseases, serious adverse events, and adverse events leading to withdrawal were recorded for 18 months, with booster vaccination given at day 366, and none of the serious adverse events reported were associated with the vaccination in the study.<sup>30</sup> These clinical findings from this study together with other studies<sup>3,4,10,31–33</sup> support the good safety profile of MF59-adjuvanted pandemic influenza vaccine in children.

During the 2009 **H1N1** influenza pandemic, two MF59-adjuvanted vaccines were licensed and used safely in all age groups (down to 6 months of age) including pregnant women. An observational study conducted following vaccination indicated that there was no significant difference in the rates of preeclampsia, spontaneous abortion, still birth, low birth weight, neonatal death, or congenital malformation in pregnant women receiving MF59-adjuvanted vaccine versus unvaccinated pregnant women.<sup>34</sup> Postlicensure of the adjuvanted influenza vaccine, monitoring of the pharmacovigilance data indicated that there was no increased risk of narcolepsy,<sup>35</sup> demyelinating disease, **anaphylaxis**, **Guillain–Barré syndrome**, **immune thrombocytopenic purpura**, and **vasculitis**.<sup>36</sup>

Studies have also shown that MF59-adjuvanted vaccines do not elicit any antibodies against squalene. For this purpose, sensitive assays have been developed at the Walter Reed Institute of Research, USA.<sup>37,38</sup> Analysis showed that there were very low levels of IgG and **IgM antibodies** against squalene even before immunization with MF59-adjuvanted vaccines and that the adjuvanted vaccine did not induce any changes in the levels of antisqualene

antibodies.<sup>39</sup>

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# Absorption of Aluminum from Antiperspirants and Vaccine Adjuvants

Richard Flarend, in [Aluminium and Alzheimer's Disease](#), 2001

## Sources of Aluminum

In order to understand the potential impact from the exposure to aluminum from antiperspirants and vaccine adjuvants, one must also consider the daily exposure to aluminum from other common sources.

The intake of aluminum from the diet has been studied by the FDA in an ongoing total diet study (TDS). The results of the TDS have been published in 1989 (Pennington & Jones, 1989) and more recently in 1995 (Pennington & Schoen, 1995). Both of these publications give the [aluminum content](#) of many varieties of food and also a breakdown of aluminum intake by age and gender. The typical amount of aluminum ingested by adult males is about 10 mg Al/day, 7 mg Al/day for adult females and children, and 0.7 mg Al/day for 6–11 month infants (Pennington & Schoen, 1995). A study of newborn and premature infants found that the intake from milk and formulas for preterm infants is about 0.03 mg Al/day and about 0.04 mg Al/day respectively (Bougle et al., 1992). Table 1 contains typical values of aluminum intake for various age groups.

Table 1. Aluminum intake by age group

Age group	Mean aluminum intake
Premature infants	0.03 mg Al/day
0–3 months	0.04 mg
6–11 months	0.7 mg
Children (2 years old)	5 mg
Children (6 + years)	7 mg
Adult females	7 mg
Adult males	10 mg

The aluminum content of foods vary greatly, but only 7% of the foods studied by Pennington & Schoen contained greater than 1 mg Al/serving. Of these 7%, most were over 1 mg Al/serving due to aluminum-containing [food additives](#) such as baking powder, emulsifying agents, and anti-caking agents (Pennington & Schoen, 1995).

Drinking water can contain a large range of aluminum, from less than 0.014 mg Al/L to 2.7 mg Al/L, although the median amount is about 0.02–0.03 mg Al/L based on the locale (Miller et al., 1984). Thus, even in the rare locality with the highest aluminum concentration, drinking water would account for just 1/3 of the aluminum absorbed

from food and water. In localities with a median concentration of aluminum in water, the water adds a negligible amount of aluminum to the diet. To date, the [bioavailability](#) or metabolism of aluminum from food has not been compared to that from water.

[Ingestion](#) of aluminum by infants from human breast milk is very small as it contains 0.02 mg Al/L (about the same as typical drinking water). Formulas based on cow's milk contain around 0.2 mg Al/L, and soya-based formulas for [lactose](#) intolerance are fairly high in aluminum at 0.5 to 1 mg Al/L (Coni et al., 1993; Fernandez-Lorenzo et al., 1999).

Some common oral pharmaceutical products contain aluminum such as some calcium supplements (12 mg Al/day), buffered aspirin (10–20 mg Al/tablet), and aluminum-containing antacids (50 mg Al/tablet) (Greger & Sutherland, 1997; Pennington & Schoen, 1995). Much effort is being taken to reduce the aluminum content of the above products or to switch to alternative products which contain less aluminum.

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## A Framework for Evaluating Nonclinical Safety of Novel Adjuvants and Adjuvanted Preventive Vaccines

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P.E. Boucher, in [Immunopotentiators in Modern Vaccines \(Second Edition\)](#), 2017

### Abstract

For certain nonadjuvanted vaccines targeting infectious diseases such as tuberculosis, [human immunodeficiency virus](#), and malaria, purified protein antigens are insufficient to achieve the requisite immune responses required for achieving durable clinical efficacy. Novel [vaccine adjuvants](#) such as the [Toll-like receptor agonists](#) offer the possibility of tailoring appropriate immune responses required for protection against these and other emerging infectious diseases. To ensure the relative safety of new-generation adjuvanted vaccines before they enter into clinical studies, we discuss herein the elements and principles behind a rationally designed preclinical safety program. We suggest that a preclinical safety package based on a scientifically sound justification for the inclusion of an [adjuvant](#) (with particular attention to the adjuvant mode of action), concise product characterization documentation, adequate and relevant preclinical toxicity studies, and available supplemental analyses should facilitate regulatory acceptance. We summarize the current status of relevant, global regulatory guidance and initiatives related to the regulatory review of vaccines and also focus on the perceived link between vaccination and autoimmunity.

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## Adjuvants Targeting the DNA Sensing Pathways – Cyclic-di-GMP and other Cyclic-Dinucleotides

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Rebecca Schmidt, Laurel L. Lenz, in [Biological DNA Sensor](#), 2014

### Comparisons of c-di-NMPs and Conventional Adjuvants

Ideally, [vaccine adjuvants](#) should increase the efficacy of vaccination – presumably by increasing [immune stimulation](#) – while minimizing toxicity [80]. It appears that c-di-GMP is non-toxic, at least in mice. In addition, this compound is stable in human serum [60], suggesting that it may have prolonged immune stimulatory effects. However, no detailed [pharmacokinetics](#) have been published for systemically or mucosally administered c-di-NMPs in rodents and/or humans. Future work in this area may provide insight on the differing *in vivo* efficacies of

different NMPs and further guide development of vaccination regimens using these **adjuvants**.

Another major outstanding question is whether c-di-GMP or other c-di-NMPs are more safe and effective than adjuvants currently in use. Only a few studies thus far have directly compared the **adjuvant** properties of c-di-NMPs with adjuvants in clinical use, such as TLR **agonists** or alum. Thus, the jury is still out on this question. However, the available results are quite promising. One study, discussed in detail above, found that immunization of mice with pneumococcal antigens plus c-di-GMP was significantly better than antigens plus alum at increasing survival following subsequent challenge with live *S. pneumoniae*[63]. In another study, the efficacy of c-di-GMP for immunizing responses to *S. aureus* was found to be similar to that of alum with regard to reducing bacterial numbers [76]. However, the mice immunized with c-di-GMP showed substantially stronger **antibody responses** to the immunizing antigens. Thus, in these studies c-di-GMP appears to be at least as effective (and by some measures more effective) as alum at immunizing anti-bacterial immune responses.

Another potential advantage of c-di-GMP as an adjuvant is its demonstrated efficacy in stimulation of **mucosal immune responses** [61–64,66,76–78]. Presumably, the ability to vaccinate for strong **mucosal immunity** to a given pathogen is advantageous as **mucosal tissues** are typically the points of pathogen entry [3]. Currently available mucosal vaccines in humans are exclusively live attenuated pathogens [4]. Such attenuated pathogens often exert some toxicity and in addition have the potential for reversion to **pathogenicity**. Development of adjuvants that induce mucosal immune activation to purified antigens, rather than tolerance, could thus be a huge advance in vaccinology. As mentioned above, studies in mice thus far suggest that c-di-GMP is an effective mucosal adjuvant in conjunction with **influenza vaccines** [77,78]. Furthermore, the c-di-NMPs as a group induced greater mucosal adjuvant effects compared to the widely used model mucosal adjuvant CTB [61,62]. The finding that both c-di-IMP and c-di-AMP showed more potent adjuvant effects than c-di-GMP [61,62] suggest that these or other modified c-di-NMPs might prove to be even more efficacious mucosal adjuvants than c-di-GMP.

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## Flagellins as Adjuvants of Vaccines

M. Rumbo, ... J.C. Sirard, in [Immunopotentiators in Modern Vaccines \(Second Edition\)](#), 2017

### Flagellin Potentiates Innate Antiinfectious and Tissue Repair Immune Effectors

Besides its role as **vaccine adjuvant**, flagellin has displayed innate protective capacities in experimental models of lethal radiation, chemical-induced **colitis**, or xenogenic colon cancer transplantation.<sup>69–71</sup> However, it is especially in the field of infectious diseases that flagellin has demonstrated strong innate protective activity. Mucosal or systemic administration of stand-alone flagellin protects animals against intestinal, respiratory, cutaneous, or urinary tract infections in mice models. **Flagellin** has a protective effect against gram-negative (*Salmonella*, *P. aeruginosa*, *Burkholderia cepacia*) and gram-positive (*Enterococcus faecalis*, *C. difficile*, or *Streptococcus pneumoniae*) bacteria, virus (rotavirus, cytomegalovirus), and fungi (*Candida albicans*).<sup>70,72–80</sup> We showed that flagellin administration improves the therapeutic index of antibiotics for the treatment of pneumonia.<sup>81</sup> The mechanisms of protection are multifactorial and based in part on the production of antimicrobial molecules by epithelial cells and recruitment of **effectors cells** (natural killer cells, **neutrophils**, or ILCs). For instance, flagellin triggers a massive production of **chemokines** (CXCL8, CXCL1, and CXCL2) and the recruitment of neutrophils in the respiratory tract and to a certain extent in the gut.<sup>23,76,82,83</sup> This process is strongly induced by **TLR5** signaling in

the epithelial compartment.<sup>27,55</sup> Flagellin was found to promote the production of IL-22 by ILC3 in a process that requires TLR5-dependent activation of DCs and the subsequent production of IL-23.<sup>35,56,60</sup> Interestingly, IL-22 is an important mucosal **cytokine** that drives epithelial production of antimicrobial molecules and **cell repair** factors, thereby contributing to the maintenance of epithelial **homeostasis**.

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## Vaccines

Alan R. Shaw, Mark B. Feinberg, in [Clinical Immunology \(Fourth Edition\)](#), 2013

### Toll-receptor agonists

Of the defined TLR **agonists** being explored as vaccine **adjuvants**, LPS and its partially detoxified form, MPL, which activate TLR 4, have been most thoroughly explored in clinical trials. With evidence of enhanced ability to increase the percentage of individuals responding with protective antibody levels to hepatitis B as compared to a standard **hepatitis B vaccine**, one hepatitis B vaccine that employs an **adjuvant** formulation (termed AS04) consisting of a combination of alum and MPL<sup>135</sup> has been licensed for use in high-risk individuals, and one of the two licensed **HPV vaccines** (HPV2) also includes this adjuvant formulation.

A wide variety of TLR9-specific agonists consisting of **oligodeoxynucleotides** containing unmethylated CpG motifs (CpG-ODN) are being evaluated in **preclinical studies**. These CpG-ODNs resemble **bacterial DNA**, modified to include a **phosphorothioate** backbone to increase their stability. Two **CpG-ODN** adjuvants have been evaluated in recent phase I and II trials and shown to increase the timing and magnitude of induction of protective antibody levels, as well as the proportion of responding individuals, to recombinant HBSAg vaccine.<sup>136</sup> One of these CpG-ODN adjuvants also elicits protective **antibody responses** in immunized HIV-infected individuals who had previously failed to respond to the hepatitis B vaccine. This approach is now being studied as a way of inducing protective immune responses to hepatitis B earlier after initiation of the vaccination regimen or with fewer doses of the vaccine, and in individuals who would be predicted, as a result of specific chronic medical conditions (such as renal failure) to respond poorly to standard hepatitis B vaccines.

In addition to the CpG-ODN-based **TLR9** adjuvants described above, small chemical compounds with structures that resemble **nucleic acid bases** have been identified that activate **TLR7** (e.g., imiquimod) or both **TLR7** and **8** (e.g., resiquimod). These compounds are being evaluated as vaccine adjuvants in preclinical studies. Flagellin, a **TLR5** agonist, is also being explored as an adjuvant.

Recently, attention has also been focused on coupling TLR agonists to antigens, rather than merely mixing them together before injection. CpG **oligonucleotides** conjugated to antigens have been tested in preclinical studies of hepatitis B vaccines<sup>137</sup> and in human clinical trials for treatment of allergy.<sup>138</sup> Ligands for TLR7/8 have been coupled to **HIV antigens**,<sup>139</sup> and the ligand for TLR5 (flagellin) has been fused to a variety of antigens.<sup>140,141</sup> In some instances, coupling a TLR ligand to an antigen resulted in a substantial improvement of the immune response compared to mixtures—potentially the result of enabling the antigen and the TLR ligand to co-locate in the same DC compartments.

Numerous preclinical studies have confirmed that many natural and synthetic TLR agonists possess adjuvant activity. Importantly, early human clinical trials of TLR-predicated adjuvants have supported the promise of this approach to mechanism-based strategies to augment vaccine **immunogenicity**. An important challenge is to

define the most potent and best-tolerated variants, and to define rules by which activation of specific TLR pathways might translate into predictable augmentation of desired types of immune responses. It is hoped that general rules will emerge to suggest which of an increasing number of novel adjuvants in development performs best with which type of vaccine immunogen, and if results obtained with a specific type of immunogen–adjuvant combination can be extrapolated to predict the likelihood of enhanced immunogenicity with other vaccines.

However, important challenges remain. A primary challenge for next-generation adjuvant development is finding a combination that retains immunopotentiating action while minimizing vaccine-associated adverse experiences. Short-term adverse experiences, such as local [injection site reactions](#), represent undesirable side effects that may disqualify candidate adjuvants early in clinical development. But given that vaccines are administered to healthy people to prevent potential future infectious diseases, the potential for rarer adverse experiences (such as autoimmunity), which may only be manifest with much longer latency from the time of vaccine adjuvant administration, will undoubtedly be important considerations for use in prophylactic vaccines.

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## Toll-Like Receptor 7 and 8 Agonists for Vaccine Adjuvant Use

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M.A. Tomai, J.P. Vasilakos, in [Immunopotentiators in Modern Vaccines \(Second Edition\)](#), 2017

### Use of Toll-Like Receptor 7/8 Agonists in Combination With Other Adjuvants

The aforementioned approaches clearly show that TLR 7/8 [agonists](#) can be optimized for vaccine [adjuvant](#) use. Despite this fact, there may be reasons to combine [adjuvants](#) to obtain even more effective vaccines. Indeed, Pulendran et al. showed that optimal protection with [yellow fever virus](#) vaccine occurred due to adjuvant effects mediated by [TLR4](#), [TLR7](#), and [TLR9](#).<sup>74</sup> Studies by Kedl et al. showed that combining TLR 7/8 agonists with [CD40 ligands](#) in mice enhanced [CD8](#) responses dramatically, and showed the importance of type I IFN and the costimulatory molecule [CD70](#) in this synergy.<sup>61</sup> Further studies in primates showed that this combination also enhanced CD8 responses, but the enhancement was localized to the mucosa.<sup>75</sup>

Other studies have shown that combining other TLR agonists with TLR 7/8 agonists can also lead to enhanced immune responses. Combining TLR 7/8 agonists with TLR4 agonists led to enhanced IL-12 production in *in vitro* models<sup>76</sup> and memory CD8 T-cell responses to a peptide cancer antigen.<sup>77</sup> Studies by Moody et al. demonstrated that in nonhuman primates, combining TLR 7/8 agonists like [resiquimod](#) with TLR9 agonists induces the highest titers of binding, neutralizing, and ADCC-mediating antibodies against the protein immunogen HIV-1 envelope gp140.<sup>78</sup> Finally, combining [imiquimod](#) and the TLR4 [agonist](#) glucopyranosyl lipid adjuvant (GLA) in an anionic liposome enhances IFN-γ responses while inhibiting Th2 immune responses such as IL-5 production.<sup>49</sup> These results demonstrate that combining different TLR agonists has the potential to work synergistically to enhance immune responses.

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# Vaccine additives and manufacturing residuals in United States-licensed vaccines

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Theresa M. Finn, William Egan, in [Vaccines \(Fifth Edition\)](#), 2008

## Adjuvants

Adjuvants are materials that enhance and direct the immune response. They are discussed in detail in Chapter 5. Vaccine adjuvants are not licensed separately; rather, the adjuvant is a constituent of the licensed vaccine and it is the vaccine formulation, *in toto*, that is tested in clinical trials and is licensed. As a consequence, an adjuvant cannot be added or removed, or the amount in a licensed vaccine changed, without submitting a supplement to the vaccine license and obtaining approval from the FDA. At present, only the various aluminum salts [aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts] are utilized in U.S.-licensed vaccines. Despite their worldwide use for over 50 years, surprisingly little is known about the mechanism whereby the aluminum salts function as adjuvants (see, e.g., HogenEsch<sup>22</sup>). There is no *a priori* reason why other vaccine adjuvants could not be used in future U.S.-licensed vaccines; indeed, a number of non-aluminum-based adjuvants are included in various vaccines being studied under the Investigational New Drug process. In Europe and elsewhere, an MF-59 adjuvanted inactivated influenza vaccine, FluAd® (Chiron), is marketed for use in persons over 65 years of age. Two vaccines marketed by GlaxoSmithKline, Fendrix®, a hepatitis B vaccine marketed in Europe for use in patients with renal insufficiency and Cervarix, an HPV vaccine marketed in Australia for use in females 10–45 years of age, include an MPL® (monophosphoryl Lipid A) containing adjuvant. For US-licensure, data supporting the need for an adjuvant, and the safety of the vaccine containing the new adjuvant, are needed.

The specific aluminum salt (hydroxide, phosphate, sulfate, or mixed) and the quantity of aluminum that is contained in a number of commonly used vaccines are presented in Table 6-1. (The aluminum content that is listed for some vaccines noted in Table 6-1 represents the upper limit of the specification; the vaccine may routinely contain less aluminum.) Currently, live vaccines do not contain an adjuvant. By regulation (21 CFR § 610.15(a)), the aluminum content of a vaccine cannot exceed 0.85 mg of aluminum per dose if the amount is assayed, or 1.14 mg/dose if determined by calculation based on the amount of the aluminum compound that is added. To harmonize with WHO recommendations, this regulation was amended in 1981 to permit up to 1.25 mg of aluminum per dose. However, the higher amount was permitted only ‘provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research’ (21 CFR § 610.15(a)).

Concerns have been raised in recent years about the use of aluminum in vaccines and potential [adverse outcomes](#) that may be associated with its use at the levels that exist in individual vaccines and through the additive effects of multiple vaccinations. These concerns about the use of aluminum in vaccines prompted a workshop that was sponsored by the National Vaccine Program Office (NVPO) in May 2000. The general use of aluminum salts in vaccines<sup>23</sup> and aluminum toxicokinetics<sup>24</sup> were reviewed during the workshop. In their overall summary of the workshop, Eickhoff and Meyers<sup>25</sup> noted that ‘Based on 70 years of experience, the use of salts of aluminum as adjuvants in vaccines has proven safe and effective.’

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