

Clinical Commentary Review

Commonly Used Adjuvant Human Vaccines: Advantages and Side Effects

Raul Villarreal, MD, and Thomas B. Casale, MD Tampa, Fla

Vaccines are a cost-effective and successful means for preventing disease. Routine health vaccine administration begins in early childhood and extends into the elderly; however, there is evidence to suggest that the immunologic and protective response to vaccination is less potent in older individuals. In recent years, newer adjuvant vaccines have been developed to improve humoral and cell-mediated immune response after vaccination. Despite the use of adjuvants in vaccines for many decades, there is limited teaching in postgraduate medical education regarding the adjuvants found in human vaccines. We summarize the current literature cited in PubMed from January 1980 to December 2019. Studies examined included those supporting the use of adjuvants in human vaccines, the mechanisms via which they enhance the immunologic response, and the reported side effects that are associated with the use of adjuvant vaccines. Overall, the data show that newer adjuvant vaccines lead to improved humoral and cell-mediated immunity against infections in populations, including those with decreased response to typical vaccines without adjuvants. Side effects related to adjuvants in vaccines were reported. Research aimed at improving vaccine effectiveness and minimizing side effects continues to be underway. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Vaccine; Adjuvant; Innate immunity; Humoral immunity; Cell-mediated immunity

Vaccines are a cost-effective and efficient means for preventing disease and promoting wellness. The development of the first vaccine dates back to the time of Edward Jenner in the late 1700s with his vaccination efforts against smallpox. Since that time, the underlying goal of vaccination has remained the same, the creation of long-term protective immunity. However, it is now understood that individuals respond to vaccination differently with age, with the immunologic response to vaccination being less robust in older individuals. This is demonstrated by poor antibody production in response to

streptococcus pneumonia vaccines and low protection rates after influenza vaccines in the elderly.^{1,2} A better understanding of vaccines and vaccine immunogenicity is of clinical importance to improve health in an ever-increasing aging population.

Several strategies have been implemented to improve vaccine immunogenicity. One such method includes the use of live attenuated vaccines, which show improved long-term immunity. However, this method is not without limitation, as live attenuated viruses can revert to their virulent form and are contraindicated in immunocompromised individuals. A second and likely safer method for older individuals is to use adjuvant vaccines. The first adjuvanted vaccines were developed in the 1920s, with the addition of the distinct chemical compound potassium aluminum sulfate, or alum. For many decades, alum was the only approved adjuvant found in human vaccines. Today, alum is now largely substituted by aluminum salts, namely aluminum hydroxide and aluminum phosphate, via the technique of adsorption of vaccines to these salts. Aluminum salts can still be found in certain hepatitis B (Hep B) virus, human papillomavirus, diphtheria, and tetanus vaccines, and in allergen-specific immunotherapy. However, despite the widespread use of aluminum salts, the exact immunologic mechanisms of how they create a boosted cellular or humoral immune response remains debated. Studies using animal models have suggested that alum may activate the innate immune system via the NALP3 inflammasome and may upregulate the T-helper-2 response leading to improved antigen-specific antibody formation. These studies however have not been validated in humans.³

Between the 1920s and the 1990s, there was little progress with regard to new adjuvant vaccine development. This was partly due to limited understanding of innate immune signaling, which differs species to species. This made it difficult to develop effective human therapies using animal models. However, recent discoveries in human Toll-like receptor signaling and chemokine signaling have allowed for the development of new adjuvant vaccines. In the last 5 years, several new adjuvants have been found in human vaccines including AS01_B in the new shingles vaccine, CpG in the new Hep B vaccine, and MF59 in the adjuvant flu vaccine (Table I).

BASIC PRINCIPLES OF VACCINATION

To understand adjuvant vaccines, it is important to first understand the basic immunology of vaccine-mediated creation of memory B and T cells. The first step in generation of memory cells begins at the site of injection with vaccine-triggered activation of the innate immune system. This activation occurs via recognition of vaccine-related pathogen-associated molecular patterns by pattern recognition receptors on innate immune cells. An immune cascade then begins that leads to chemokine and cytokine upregulation. This upregulation creates a gradient that

Division of Allergy and Immunology, University of South Florida, Tampa, Fla

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 2, 2019; revised April 13, 2020; accepted for publication April 13, 2020.

Available online ■■

Corresponding author: Thomas B. Casale, MD, Division of Allergy and Immunology, University of South Florida, 12901 Bruce B Downs Blvd, MDC 19, Tampa, FL 33612. E-mail: tbcasale@usf.edu.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.04.045>

Abbreviations used

APC- Antigen-presenting cell
 Hep B- Hepatitis B
 MPL- Monophosphoryl lipid A
 NF- κ B- Nuclear factor- κ B

recruits antigen-presenting cells (APCs) to the area where vaccine antigens were delivered on vaccination. APCs then uptake the vaccine antigens and migrate to secondary lymphoid tissues where they present the antigens to naïve CD4+ and naïve CD8+ T cells. The interaction between APCs and T cells causes naïve T cells to then become effector T cells. Certain effector CD4+ T-helper cells, designated follicular T-helper cells, can then interact with B cells in germinal centers within the secondary lymphoid tissues. Activation of B cells by follicular T-helper cells leads to vaccine antigen-specific antibody production by B cells. Initially, the immune response consists of short-lived effector B cells secreting low-affinity IgM antibodies. After a lag phase and clonal B-cell expansion, activated B cells may differentiate into memory cells or into plasma cells that produce high-affinity IgG, or other Ig isotypes. A subset of plasma cells and long-lived memory B cells are able to migrate to the bone marrow and can remain there indefinitely, where they remain ready to respond robustly on future exposure to specific antigens. These long-lived memory and plasma cells are a key component of the adaptive immune system and form the basis for long-term humoral immunity^{4,5} (Figure 1).

THE NEWER ADJUVANT VACCINES**Adjuvant flu vaccine**

The adjuvanted influenza vaccine is currently marketed as FLUAD and is indicated for adults who are 65 years and older.

This vaccine is composed of conventional subunit influenza antigens and is combined with the adjuvant MF59. The influenza antigens are selected according to strains designated by the World Health Organization each year. The adjuvant MF59 is an oil-in-water adjuvant emulsion that is made up of 5% v/v squalene, 0.5 v/v polysorbate 80, and 0.5% v/v sorbitan trioleate.⁶ Influenza vaccines containing MF59 were developed after studies showed that improved humoral and cellular response with MF59 enhanced HSV and HIV vaccines.⁶

MF59 promotes immunogenicity through the creation of a transient “immunocompetent” environment at the site of vaccine injection. This environment is driven by a chemokine gradient produced by MF59 on local innate immune cells, which in turn promotes recruitment factors for APCs.⁷ This is supported by studies that show a higher influx of macrophages, monocytes, and granulocytes and an improved differentiation toward dendritic cells in a C-C chemokine ligand 2-dependent manner.⁸

The adjuvanted flu vaccine is beneficial in reducing hospitalization rates and reduces the incidence of laboratory confirmed influenza compared with the nonadjuvant influenza vaccine.⁹ Case control studies show a reduced risk of acute coronary syndromes with the adjuvanted vaccine compared with no influenza vaccination.¹⁰ Seroconversion rates for both primary and subsequent immunizations are superior with the adjuvant influenza vaccine compared with the nonadjuvant vaccine, which supports yearly administration.¹¹

Overall, the adjuvanted flu vaccine containing MF59 is generally well tolerated. Meta-analyses show that solicited local and systemic reactions, such as myalgia, headache, fatigue, and malaise, are more common in the overall population after receiving the adjuvant flu vaccines compared with traditional flu vaccines (470 vs 284 local reaction; 302 vs 196 severe reaction, n [per 1000]). However, the same study also shows lower rates of unsolicited adverse events with the adjuvant MF59 vaccine

TABLE I. Common adjuvant vaccines in clinical practice

Vaccine	Adjuvant	Disease target	Pathway	Benefits	Side effect profile
TDAP, HAV, HBV, HPV	Aluminum salts	Diphtheria, tetanus, hepatitis A, hepatitis B, human papilloma virus	Conflicting theories. Possibly NALP3 inflammasome activation	Improved Th2 response	Rare systemic reaction. Pyrexia usually not seen
FLUAD	MF59	Influenza virus	“Immunocompetent” environment. Chemokine ligand 2-dependent manner	Reduced hospitalization rates and reduced risk of acute coronary syndromes compared with nonadjuvant flu vaccine	Myalgia, headache, fatigue, malaise commonly reported
Shingrex	AS01B	Varicella zoster virus	TLR4 activation by MPL	>90% protection against HZ (compared with 38% if older than 70 with Zostavax)	Myalgia reported by close to half of recipients. Malaise, rigors, chills, fever, lethargy also commonly reported
Heplisav-B	CpG-ODN	Hepatitis B virus	Caspase-1 and MyD88 upregulation by QS-21 TLR9 found in plasmacytoid dendritic cells	>90% protection rates compared with >70% with Engerix	Similar rates of injection site reactions, fever, and malaise compared with alum-adjuvant vaccine

CpG-ODN, Cytosine-phosphate-guanosine oligodeoxynucleotide motifs; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; HPV, human papilloma virus vaccine; HZ, herpes zoster; MPL, monophosphoryl lipid A; MyD88, myeloid differentiation primary response 88; NALP3, NACHT, LRR, and PYD domains containing protein; QS-21, a saponin molecule from *Quillaja saponaria*; TDAP, adult tetanus, diphtheria, pertussis vaccine; Th2, T-helper-2; TLR4, Toll-like receptor 4; TLR9, Toll-like receptor 9.

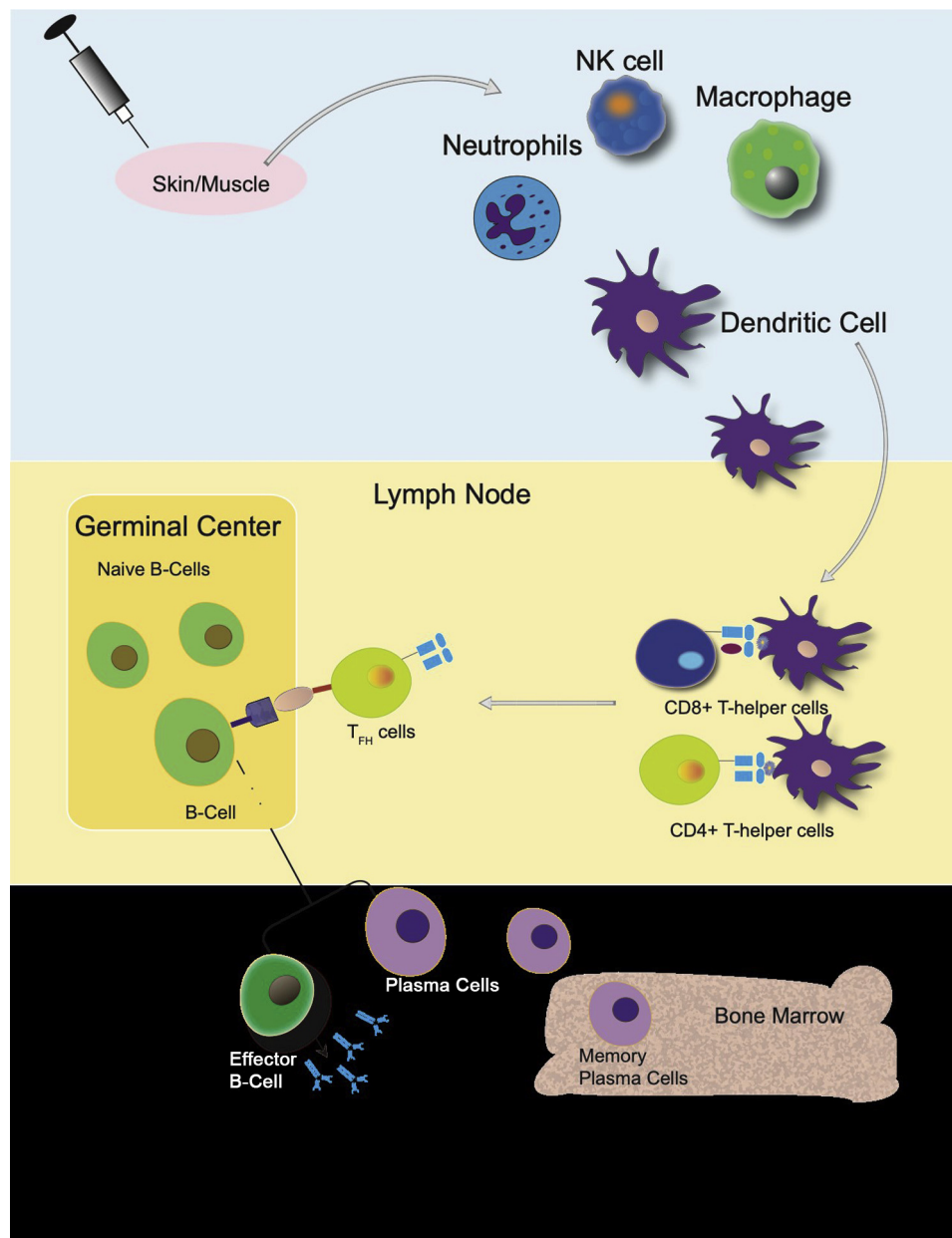


FIGURE 1. Production of antibodies after vaccination. Initially, vaccine antigens and paired adjuvant are delivered subcutaneously or intramuscularly. Innate immune cells, consisting of neutrophils, NK cells, and macrophages recognize PAMPS via Toll-like receptors and pattern recognition receptors and subsequently upregulate cytokines. Antigen-presenting cells, including dendritic cells, are recruited to the site of injection and uptake the vaccine antigens locally. Dendritic cells then migrate to secondary lymphoid tissue, most commonly regional lymph nodes, where they meet and prime naïve T cells into effector T-helper-1 and T-helper-2 cells (Th2). In the germinal centers, a subset of Th2 cells, designated as T-follicular cells (TFH cells), interact with B cells. Activation of B cells by TFH cells causes B-cell proliferation. A subset of B cells, designated effector B cells, begin producing antibodies. The other subset of B cells become long-lived plasma cells or memory cells, some of which migrate to the bone marrow and are ready to fight future infections on re-exposure to specific antigens. *NK*, Natural killer; *PAMPS*, pathogen-associated molecular pattern.

compared with nonadjuvanted influenza vaccines.¹² Given the overall improved immunologic protection afforded by the MF59-containing adjuvant flu vaccine, these data showed no evidence that adverse reactions are serious enough not to recommend this adjuvant vaccine for patients at risk of poor response to the conventional flu vaccine.

Adjuvant zoster vaccine

A new adjuvant zoster vaccine, with the trade name of Shingrex, is recommended to prevent herpes zoster and post-herpetic neuralgia. Both disorders are caused by the varicella zoster virus.^{13,14} Shingrex is approved for adults 50 years and older. The recommended schedule is to administer 2 separate

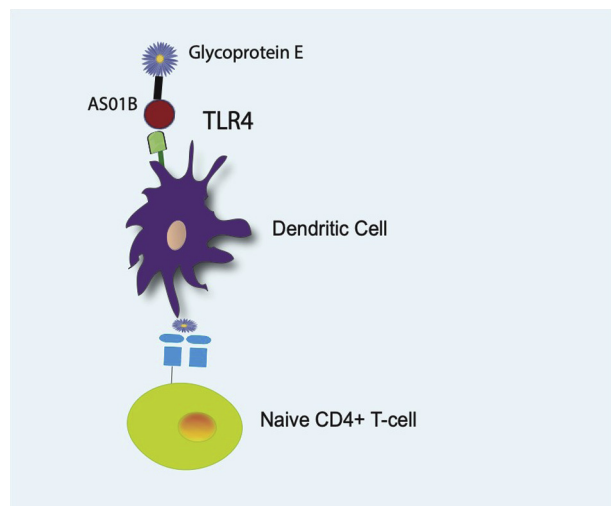


FIGURE 2. Components of the new zoster vaccine that includes the adjuvant AS01_B paired with glycoprotein E of the varicella zoster virus. Monophosphoryl lipid A, a lipopolysaccharide derived from *Salmonella minnesota*, is one of the 2 major components of AS01_B and promotes strong CD4⁺ T cell and humoral immune response via Toll-like receptor 4 (TLR4) agonist activity.

doses that are between 2 and 6 months apart. This adjuvant vaccine has been shown to be effective in upwards of 90% of recipients among all age groups. This is notable because protection rates with the nonadjuvanted zoster vaccine are much lower. It is expected that only approximately 70% of adults of ages between 50 and 59 and only 38% of those older than 70 years of age receive protection from the previously available zoster vaccine.¹³

The adjuvant zoster vaccine contains varicella zoster virus glycoprotein E and the adjuvant AS01_B. Glycoprotein E is an antigen of the varicella zoster virus that is essential for viral replication and cell-to-cell spread. Antibody formation against this antigen leads to humoral immunity and protection against future zoster infections. AS01_B is a combination of monophosphoryl lipid A (MPL) and QS-21, a saponin molecule from the bark of a South American tree *Quillaja saponaria Molina*.

MPL is a lipopolysaccharide derived from *Salmonella minnesota*. This portion of the adjuvant is expected to promote strong CD4⁺ T-cell and humoral immune response via Toll-like receptor 4 agonist activity. It is also thought to cause dendritic cells to produce inflammatory cytokines, upregulate costimulatory molecules, and increase transcriptional activity of nuclear factor- κ B (NF- κ B) (Figure 2). Of note, MPL, like aluminum salts, is also used in some allergen-specific immunotherapy products.

QS-21, on the other hand, is thought to accumulate in the resident macrophages of lymph nodes and subsequently upregulate innate cell recruitment through activation and maturation of dendritic cells. The mechanism by which QS-21 causes recruitment and activation of dendritic cells is less well understood but is thought to culminate with the upregulation of caspase-1 and MyD88 pathways.^{15,16}

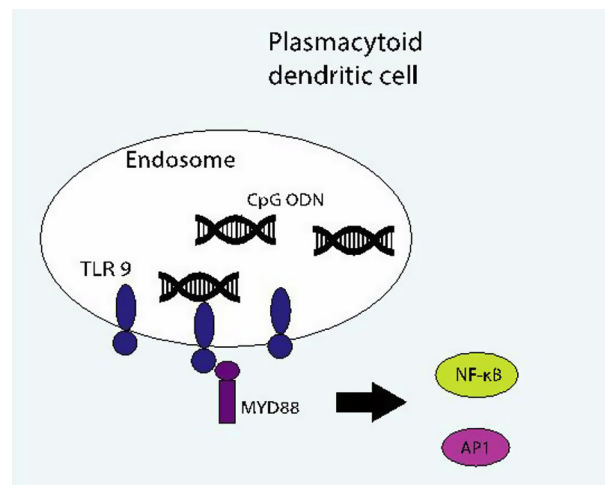


FIGURE 3. Synthetic cytosine-phosphate-guanosine oligodeoxynucleotide motifs (CpG-ODN), also known as adjuvant 1018, from the new recombinant adjuvant hepatitis vaccine binding to Toll-like receptor 9 (TLR9) found in the endosome of plasmacytoid dendritic cells. This leads to activation of the innate immune system and downstream proinflammatory gene expression, initially via MYD88, and ultimately culminates in the upregulation of activating protein 1 (AP1) and nuclear factor- κ B (NF- κ B) transcription factors.

Like the adjuvanted flu vaccine, the adjuvanted zoster vaccine has been well studied with regard to safety. However, systemic symptoms after receiving the adjuvant zoster vaccine have been reported. Studies show that approximately 17% of adjuvant zoster vaccine recipients experience symptoms that prevent normal everyday activity. The median duration of these symptoms is reported as 1 day, though the duration may range from 1 to 3 days. Myalgia is the most common systemic side effect reported in 46% of adjuvant vaccine recipients. In addition, injection site reactions are commonly reported in solicited recipients of the vaccine containing the adjuvant AS01_B (81.5% of recipients in one study). Head-to-head comparison of the side effects of Zostavax (live-attenuated) versus the adjuvant Shingrex has not been done.¹³

Recombinant adjuvant hepatitis B vaccine

As previously mentioned, aluminum salts have been included in Hep B vaccines for many years, and can still be found in the currently available Engerix-B. However, despite the availability and use of this vaccine, there remains a high incidence of new cases of Hep B infections in the United States. The rise in Hep B is postulated to be due to the increase in intravenous opioid use and as a result of low protection rates in adults who are most susceptible to Hep B, such as dialysis patients and patients with HIV. To combat this rising endemic disease, a newer adjuvant Hep B vaccine, marketed as Heplisav-B, was approved by the Food and Drug Administration in November 2017.

This newer recombinant adjuvant vaccine is a combination of a single antigen Hep B vaccine with a novel immunostimulatory sequence adjuvant. The single antigen is made of yeast-derived recombinant Hep B surface antigen and is then combined with synthetic cytosine-phosphate-guanosine oligodeoxynucleotide

motifs, also known as adjuvant 1018. These motifs bind to Toll-like receptor 9 found in the endosome of plasmacytoid dendritic cells and lead to activation of the innate immune system and downstream proinflammatory gene expression via MYD88, and ultimately culminate in upregulation of activating protein 1 and NF- κ B transcription factors^{17,18} (Figure 3).

Seroprotection rates with newer recombinant adjuvant Hep B vaccine are improved compared with rates reported with the previously available aluminum salts containing vaccine, 90% to 100% versus 70% to 90%, respectively. Safety-wise, similar rates of mild, serious, and cardiovascular events are seen with Heplisav-B compared with the aluminum salt-containing Hep B vaccine (45.6, 5.4, 0.27 vs 45.7, 6.3, and 0.14, respectively).¹⁹

Heplisav-B is recommended to be administered as 2 doses that are 1 month apart. This schedule differs from the traditional 3-dose schedule over 6 months of the previously available aluminum salt-containing Hep B vaccine. Testing to evaluate for seroprotection is also recommended 1 to 2 months after the final dose of Heplisav-B in certain populations. These populations include hemodialysis patients, HIV-infected individuals, health care personnel, immunocompromised persons, and partners of HBsAg-positive persons. Administration of more than 2 complete series is not recommended except for hemodialysis patients.²⁰

SPECIAL POPULATIONS

Vaccination schedules of immunocompromised individuals vary depending on the underlying immune defect. As a general principal, live vaccines should not be administered to patients with combined (humoral and cellular) immunodeficiencies nor to patients on high levels of immunosuppression (such as those treated with TNF- α antagonists, anti-B lymphocyte monoclonal antibodies, or cancer chemotherapy). Special attention should also be paid to patients with antibody deficiency or combined immunodeficiency who receive immunoglobulin therapy, as there is concern that IgG replacement may interfere with the immune response after vaccination. Such interference has been reported for live vaccines such as measles, rubella, and varicella vaccines that are inactivated by circulating IgG from the replacement therapy.²⁰

Fluad, Shingrex, and Hepsilav however are all inactivated adjuvant vaccines and are considered safe in patients with most immunodeficiencies. Patients on immunoglobulin replacement therapy who have primarily a humoral defect may still benefit from these vaccines through the induction of T-cell-mediated cellular immunity.

CONCLUSION

Overall, large human studies show improved seroprotection rates after vaccination with newer adjuvant vaccines compared with previously available alternative vaccines. Side effects related to adjuvants in vaccines are not uncommonly reported; however, overall safety evaluations show them to be safe. The primary mechanisms of actions of the newer adjuvants involve enhancement of the innate immune system typically via local environmental upregulation of cytokines and recruitment of APCs to the injection site.

Physicians now have more options to choose from when recommending vaccines, but knowledge about their appropriate

use and adverse effects is essential to make therapeutic recommendations.

Acknowledgment

We thank Dr. Farnaz Tabatabaian for her help with our illustrations.

REFERENCES

1. Cadeddu C, De Waure C, Gualano MR, Di Nardo F, Ricciardi W. 23-valent pneumococcal polysaccharide vaccine (PPV23) for the prevention of invasive pneumococcal diseases (IPDs) in the elderly: is it really effective? *J Prev Med Hyg* 2012;53:101-3.
2. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12:36-44.
3. Del Giudice G, Rappuoli R, Didierlaurent AM. Correlates of adjuvanticity: a review on adjuvants in licensed vaccines. *Semin Immunol* 2018;39:14-21.
4. Fox CB. Vaccine adjuvants. *Methods Mol Biol* 2017;1494:13-6.
5. Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology. Philadelphia, PA: Elsevier; 2017:608.
6. Fang J-H, Hora M. The adjuvant MF59: a 10-year perspective. In: Ott G, Radhakrishnan R, editors. Vaccine adjuvants. Methods in molecular medicine. Totowa, NJ: Humana Press; 2000. p. 211-28.
7. O'Hagan DT, Ott GS, De Gregorio E, Seubert A. The mechanism of action of MF59—an innately attractive adjuvant formulation. *Vaccine* 2012;30:4341-8.
8. Seubert A, Monaci E, Pizza M, O'Hagan DT, Wack A. The adjuvants aluminum hydroxide and MF59 induce monocyte and granulocyte chemoattractants and enhance monocyte differentiation toward dendritic cells. *J Immunol* 2008;180:5402.
9. Domnich A, Arata L, Amicizia D, Puig-Barbera J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. *Vaccine* 2017;35:513-20.
10. Puig-Barberà J, Díez-Domingo J, Varea AB, Chavarri GS, Rodrigo JAL, Hoyos SP, et al. Effectiveness of MF59TM-adjuvanted subunit influenza vaccine in preventing hospitalisations for cardiovascular disease, cerebrovascular disease and pneumonia in the elderly. *Vaccine* 2007;25:7313-21.
11. Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. *Vaccine* 2001;19:2673-80.
12. Pellegrini M, Nicolay U, Lindert K, Groth N, Della Cioppa G. MF59-adjuvanted versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database. *Vaccine* 2009;27:6959-65.
13. Lal H, Cunningham AL, Godeaux O, Chlibek R, Díez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015;372:2087-96.
14. Centers for Disease Control and Prevention. Vaccines and preventable diseases. What everyone should know about Zostavax. Available from: <https://www.cdc.gov/vaccines/vpd/shingles/public/zostavax/index.html>. Accessed August 10, 2019.
15. Didierlaurent AM, Collignon C, Bourguignon P, Wouters S, Fierens K, Fochesato M, et al. Enhancement of adaptive immunity by the human vaccine adjuvant AS01 depends on activated dendritic cells. *J Immunol* 2014;193:1920-30.
16. McElrath MJ. Adjuvants: tailoring humoral immune responses. *Curr Opin HIV AIDS* 2017;12:278-84.
17. Jackson S, Lentino J, Kopp J, Murray L, Ellison W, Rhee M, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. *Vaccine* 2018;36:668-74.
18. Klinman DM. Immunotherapeutic uses of CpG oligodeoxynucleotides. *Nat Rev Immunol* 2004;4:249-58.
19. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the advisory committee on immunization practices for use of a hepatitis B vaccine with a novel adjuvant. *MMWR Morb Mortal Wkly Rep* 2018;67:455-8.
20. Sobh A, Bonilla FA. Vaccination in primary immunodeficiency disorders. *J Allergy Clin Immunol Pract* 2016;4:1066-75.