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Aluminum Adjuvants in Vaccines: Movement Towards Understanding Their Role and Mechanism of Action

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Abstract

Aluminum adjuvants have been used in vaccines for over 80 years in order to increase the immune response in vaccinated individuals. While the addition of aluminum adjuvants has been extremely successful, the success powered the adjuvants to be used in numerous vaccines without a proper understanding of their mechanisms of action. Advancements in medical understanding over the last 4-5 decades has resulted in researchers understanding the harsh reality of aluminum toxicity. Due to this,

researchers have begun to delve into the actions and mechanisms of these adjuvants in an effort to enhance understanding of how they work. This review will discuss the importance of understanding the history of vaccination, the use and incredible success of aluminum adjuvants in vaccines, proposed mechanisms of action for aluminum adjuvants, aluminum toxicity levels, and future issues to be discussed regarding the safety of addition of aluminum adjuvants.

Keywords

Vaccine, Adjuvant, vaccination, aluminum adjuvant

Introduction

The theory and practicality of vaccination has existed for centuries but has only recently come to full power near the turn of the 20th century. Vaccinations have been used to eradicate deadly infectious diseases such as smallpox and decrease overall mortality in the United States, “from 797 deaths per 100,000 in 1900 to 36 deaths per 100,000 in 1980” (Armstrong, Conn, & Pinner, 1999). However, in the 21st century, vaccination practices have come under attack due to a controversial article published in 1998 by Dr. Andrew Wakefield of the United Kingdom that proposed a link between the MMR (Measles, Mumps, and Rubella) vaccination and autism (Wakefield, et al., 1998). This article was picked up by media outlets across the globe, leading to a decrease in early childhood MMR vaccination in the United Kingdom, with rates decreasing from 90-95% in 1995-96, to roughly 80% in 2003-04 (Thompson, 2009). While 21 years have passed since the publication – during which Dr. Wakefield was removed from the United Kingdom Medical Register, the publication was recanted, and all the claims of the

publication were discredited – there remains an atmosphere of distrust involving vaccinations.

Many believed then and still do today that Wakefield's contains some truth, and the general media played an important role in swaying the public's mentality towards the dangers of vaccines. Due to this, the United Kingdom saw a decrease in the number of children getting MMR vaccinations, decreasing from 91.8% coverage in 1995-96 to 79.9% coverage in 2003-04 (Screening & Immunisations Team, NHS Digital, 2017) (Thompson, 2009). In recent years, researchers have become more interested in the mechanism of action for licensed aluminum-based adjuvants used in vaccines.

Despite the growing trend of "Anti-vaccination" throughout the United States, there appears to be gaps in the literature that indicate the true mechanism of action for aluminum vaccine adjuvants, which is coincidentally a major focal point of the anti-vaccination movement. There has been a great deal of literature published on aluminum adjuvants and their relative safety, but it seems that there is no agreement on the true mechanism of action for aluminum-based adjuvants. It is important that countries which strongly promote the use of vaccines understand the necessity of aluminum adjuvants and improve the quality and quantity of research regarding aluminum vaccine adjuvants.

In this review, the results of several studies regarding the proposed mechanisms of action of aluminum adjuvants, regulation of production for vaccines, the implications of declining numbers of vaccinated individuals, and the importance of the government's role in vaccination schedule requirements are discussed. This information is corroborated with data published by the United States government via the Centers for

Disease Control and Prevention. This discussion revolves around 4 key questions that will help to understand the importance and limitations of vaccinations: 1) what is the origin and history of vaccinations; 2) why are aluminum salts used as adjuvants in vaccines; 3) why are some individuals unable to be vaccinated; and 4) what is “herd immunity” and what role does it play in modern disease control. Identification of the true mechanism of action for aluminum salt adjuvants may increase vaccination rates, effectively reducing the recent outbreaks of communicable diseases such as measles (Centers for Disease Control and Prevention, 2019).

Deadly Smallpox and the Origin of Vaccination

The origins of disease traverse well beyond the time of written history. It is likely that humans have experienced infectious diseases since their delineation from their most recent common ancestor. One such infectious disease, estimated to be around since 10,000 B.C. is known as smallpox (Reidel, 2005). By the 18th century, smallpox was spreading to Europe, causing an estimated 6-10% of all deaths in London as reported by Davenport et al (Davenport et al, 2011). The first attempts at an early form of vaccination was called inoculation. Inoculation is the practice of introducing a live, infectious organism into a host in order to confer immunity upon contraction and after recovering from said infection. This practice was widely used throughout Europe in the late 18th century.

By the late 18th century, a man by the name of Edward Jenner had published his own findings that suggested inoculation with cowpox – a common disease amongst dairy maids at the time – may confer immunity to smallpox. Jenner administered several

inoculations of cowpox excretions from infected individuals into healthy individuals. He found that these individuals would contract cowpox but would later recover. Once the individuals had recovered, Jenner would inoculate them with smallpox. Just as he suspected, these individuals had become immune to smallpox. Jenner named his technique *vaccination.* While his practices were met with controversy and distrust, years would pass, and Jenner's technique would eventually make its way back to Europe and the United States of America. Jenner became the first individual to recognize the scientific evidence behind vaccination, and his technique would be carried on for over a century, as scientists worked to develop new and safer vaccination techniques.

Louis Pasteur, a French scientist, would be one of the first to extend Jenner's work, creating the first attenuated vaccine. It was Pasteur who found that by growing a virulent strain of bacteria at an unusually high temperature would render the bacteria avirulent. He found that inoculating animals with the avirulent strain of the bacteria would result in the animal being immune to a virulent strain. This led to the development of the anthrax vaccine by Pasteur himself.

Years later, in the 1950s, a motion was set forward by the World Health Organization that promoted the use of vaccination against smallpox across the globe. By 1977, smallpox was eradicated completely from the world. While Jenner's experiments into vaccination may not have earned him copious recognition during his lifetime, it is now recognized that without his work, the world could very well still suffer from the epidemics caused by innumerable deadly diseases that are commonly vaccinated against today.

Antibody-Mediated Immunity Provides Long-Term Immunity

Adaptive immunity is that which is procured by introduction of an antigen to an organism. An antigen is defined as a foreign substance that induces an inflammatory response. Antigens may be bacterial DNA, lipopolysaccharides of bacterial cells, viral capsid proteins, or even foreign particles introduced to the body such as chemical compounds. In order to provide clarity and conciseness, a brief and basic summarization of basic adaptive immunity is as follows: Adaptive immunity is mediated by proteins called immunoglobulins, or antibodies, which are produced by B cells. Upon introduction of an antigen, antigen-processing cells called dendritic cells may phagocytize the antigen, use peptidases to fragment the antigen, and present the fragments of antigen attached to MHC class II receptor molecules on the cell surface.

Once presented on the cell surface, Helper T cells are presented with the antigen, and they in turn secrete cytokines that initiate maturation of naïve B cells. Upon maturation, B cells produce antibodies which attach themselves to the antigen, allowing the body to locate these antibodies and recognize the antigen as a foreign particle. Following secondary stimulation of B cells with the same antigen and cytokine secretion, the immune system will be able to quickly recognize a second encounter with the foreign particle and quickly remove it via phagocytosis and lysosomal fragmentation. This memory mechanism is likely related to the ability of T cells to signal B cells in exactly the same way as they had on the first encounter, therefore resulting in the same immune response and excretion of the same antibodies for the given antigen (Tizard, 2013).

Secondary immune responses typically result in a faster response and increased levels of antigen-specific antibodies, which are maintained in the bloodstream for a prolonged period of time. Due to this action, a secondary immunization is typical for most vaccines, because resultant blood-antibody levels will confer immunity for a longer period of time in humans and animals.

Aluminum Adjuvants in Vaccines Increases Immune Response

As previously discussed, Edward Jenner is considered to be the father of vaccination. His work provided insights into the actions of human humoral immunity, further progressing the understanding of immunology. While his practices may have prevented the deaths of hundreds of thousands of people, his technique still held an inherent risk of death to those who did not develop immunity to smallpox and to those who did not receive a second vaccination in their later years. Due to this, scientists began to delve into the science behind vaccination and the actions of the human immune system in order to develop vaccinations that ensured development of immunity.

By the early 1900s, tetanus and diphtheria toxins had become a subject of great concern when it was found that New York City alone averaged 14,000 cases of diphtheria and 1,290 deaths per year from the diphtheria toxin (Marrack, McKee, & Munks, 2009). Scientists began to formulate ways to increase the efficacy of vaccinations by adding antibodies and toxins together to form what was known as toxin-antitoxin vaccinations. These vaccinations were highly regarded due to their ability to initiate an immune response with greater protection and decreased adverse effects from the vaccination. By 1921, scientists had developed a new, heat-killed form of the

diphtheria toxin called the toxoid. By heating the toxin, it was found that it would be inactivated but would still initiate an immune response in the vaccinated individual. This proved to be the best defense against the toxins during the time period. In 1926, Alexander T. Glenny found that precipitating an antigen onto insoluble particles of aluminum potassium sulfate would result in an increased level of antibody response. This discovery would eventually lead to the worldwide use of aluminum salts in nearly all vaccines. When the practice of aluminum salt addition to vaccines first began, there was very little interest in the mechanisms of action for the longevity of immunity seen with these new adjuvants. In recent years, however, scientists have attempted to study the mechanism of action for licensed aluminum adjuvants, but there seems to be little agreement within the community about the true mechanism of action. These studies have helped to understand the actions of aluminum adjuvants and their role in increased immune response after vaccination, as well as defining the generalized mechanisms of the human immune system.

Proposed Mechanisms of Action for Aluminum Adjuvants

While still poorly understood, there have been several mechanisms of action proposed for aluminum adjuvants. The first example of a proposed mechanism is the depot effect, proposed by Glenny et al in 1926 (Gupta, Rost, Relyveld, & Siber, 1995). This mechanistic explanation purports that, due to its insoluble nature, the aluminum salts are maintained in the area of injection for a prolonged period of time, allowing for maximal contact with the antigen. This gives the immune system ample time to develop antibodies against the antigen and promote phagocytosis and lysosomal digestion.

A second proposed mechanism asserts that aluminum salts promote inflammation, resulting in an increased recruitment of immunocompetent cells to the site of injection, and ultimately the development of antibodies against the antigen.

A third mechanism that has been proposed is the “promotion of uptake of antigens by antigen-presenting cells” (Rambe, Giudice, Rossi, & Sanicas, 2015). This mechanism of action proposes that the aluminum salts induce a localized inflammatory response, resulting in increased uptake of antigen by antigen-presenting cells. This begins the series of events mentioned in the previous mechanism, ultimately resulting in conferred immunity.

While these three mechanisms have been researched extensively, there is still little to no agreement as to which is the true mechanism, and the possibility of these three mechanisms working synergistically still remains unmentioned in the literature.

Vaccine Regulation

Vaccines are heavily regulated and must undergo extreme scrutiny before they are able to be used on the general public. The governing bodies that oversee the regulations are a mixture of international bodies, as well as national and state governments. While the international and national governing bodies oversee the safety and efficacy of each and every vaccine, the state governing bodies dictate which vaccines are to be used within their specific area.

The United States federal government uses extreme scrutiny when studying the safety and efficacy of vaccinations. The Food and Drug Administration (FDA) is the primary body that oversees the trials of vaccines before they are approved and released

for use on the general public. According to the Centers for Disease Control and Prevention, there are 6 major steps that a vaccine must go through in order to be approved for full use in the United States. First the vaccine must go through the exploratory stage, where the researchers study multiple different antigens to find which may be used in a vaccine to control preventable diseases. This stage can last up to 4 years, during which the federal government funds the research. Once the research proves to have developed a proper antigen that can initiate an immune response, the vaccine moves on to the pre-clinical trials.

The pre-clinical trials consist of animal testing, as well as tissue and cell cultures to help understand the body's response to the given vaccine. During this phase, the researchers may adjust the concentration of antigen in the vaccine to ensure adequate dosage without increased risk of infection. Very few potential vaccines continue beyond this state due to their inadequacies. This stage is reported to last up to 2 years. Once approved beyond the pre-clinical phase of investigation, the vaccine will move on to privatized manufacturing.

During the period of privatized manufacturing, a company will adopt the vaccine and propose manufacturing methods to the FDA, which will either deny or approve the methods. These methods must pass through several review boards including a clinical review board, which must approve the proposed process for clinical trials, which are conducted at a specific institution. After the approval process is complete, the vaccine is then progressed to three testing phases which will dictate their safety and efficacy.

The first phase of vaccine trials takes place with a small group of less than 100 adults. The goal of phase I trials is to assess the vaccine's viability in initiating an

immune response, and the length of time that the immune response is instigated. If the vaccine instigates a proper response, the researchers may attempt to infect some of the individuals with the disease under close monitoring and control. Upon completion of phase I, the vaccine will be evaluated and will either progress to phase II or be removed from testing.

During phase II trials, the vaccine is given to individuals who are at risk for developing the disease that the vaccine is meant to prevent. In these trials, a placebo group is used to estimate the true efficacy of the vaccine. This phase also gives the researchers insight into the effects of the vaccine when given to a participant who is at risk for acquiring the disease. During phase II, several other factors are proposed, including the dosage of the vaccine, the method of delivery for the vaccine, and the proper immunization schedule for the vaccine. Upon successful completion and evaluation, the candidate vaccine will move on to Phase III trials.

Phase III trials involve administration of the vaccine to thousands of people. These trials test the vaccine against a placebo. Due to the large population involved in this phase, the adverse effects of the vaccine may also be studied as well. This gives the researchers insight into their product's safety on a large scale, and it also helps to define the efficacy of the vaccine. This phase also shows any low-risk adverse effects on individuals. Upon completion of phase III testing, the manufacture must submit a license application to be approved by the FDA. After approval, the vaccine's production is continuously inspected and monitored by the FDA, including data analysis, safety analysis, and facility inspections.

The entire process of vaccine approval and use on the general public may take a decade or longer, which emphasizes the United States' role in regulating vaccine production. The safety of a vaccine is taken very seriously and any proven implication that the vaccine may incur serious adverse effects could result in its removal from the vaccination schedule. Beyond the federal government's involvement in vaccine regulation, the states also have the decision to require certain vaccines before enrolling in an educational institution so long as these requirements do not overreach the federal government's standards. This may include requiring all children above a certain age to have acquired all necessary and/or recommended vaccines pertaining to that age group before they enroll into the institution. States may also opt out of requiring certain vaccines before enrollment, so long as these do not overstep the requirements of the federal government.

Importance of Vaccination Schedule

While vaccination in itself is important in preventing a large majority of communicable diseases, it is equally important to pursue proper vaccination schedule. As stated previously, vaccines are not 100% effective, and several require two, three, and even four administrations in order to elicit maximal immunity. According to the CDC, the current 2019 schedule recommends that children aged from birth to 5 months receive 3 doses of the Hepatitis B vaccine, 2 doses of the Rotavirus vaccine, 4 doses of the DTaP vaccine, 3-4 doses of *Haemophilus influenzae* type b, 4 doses of Pneumococcal conjugate, 3 doses of Inactivated Poliovirus, and 1-2 doses annually of the influenza vaccine. These specific vaccines only confer maximal immunity upon administration of the final dose of each vaccine. Consequently, some variations of

several of the previously-mentioned vaccines contain aluminum adjuvants. While there may currently be a distrust of vaccines containing additives such as aluminum salts, it is strongly recommended that children are vaccinated against these diseases, as they can prove fatal if contracted.

A proper vaccination schedule also helps to prevent the transmission of communicable diseases to those who are unable to be vaccinated due to health risks associated with infection and compromised immunity. Recently, this has come to be known as “herd immunity,” and has proved successful over the last several decades. Herd immunity occurs when a large enough number of individuals are vaccinated against a given disease, therefore preventing the disease from spreading person-to-person. With such a large amount of people who are unable to contract the disease, those individuals who are unable to be vaccinated due to health concerns are also considered immune because they are at a decreased risk of coming into contact with someone who has the disease.

Summary

While there has been an abundance of advancements in understanding the mechanisms of aluminum adjuvants and their biological fates, there is still a great deal of research to be done on them. As reported in this review, there has been a drastic decline in vaccinations in the United Kingdom, as well as a developed anti-vaccination movement found in the United States. The development of this movement is likely the result of declining trust in vaccinations due to poor understanding of mechanism of action of aluminum adjuvant constituents. In future studies, researchers should focus on

a singular proposed mechanism of action and report findings that either demonstrate truth of a single mechanism or falsify another mechanism. By increasing our understanding of these adjuvants, we can further the great success of vaccination by providing the media, the public, and medical professionals with a genuine knowledge of the true mechanism of action of vaccines containing aluminum adjuvants.

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