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Adjuvants and Inactivated Polio Vaccine: A Systematic Review

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Abstract

Poliomyelitis is nearing universal eradication; in 2011, there were 650 cases reported globally. When wild polio is eradicated, global oral polio vaccine (OPV) cessation followed by universal use of inactivated polio vaccine (IPV) is believed to be the safest vaccination strategy as IPV does not mutate or run the risk of vaccine derived outbreaks that OPV does. However, IPV is significantly more expensive than OPV. One strategy to make IPV more affordable is to reduce the dose by adding adjuvants, compounds that augment the immune response to the vaccine. No adjuvants are currently utilized in stand-alone IPV; however, several have been explored over the past six decades. From aluminum, used in many licensed vaccines, to newer and more experimental adjuvants such as synthetic DNA, a diverse group of compounds has been assessed with varying strengths and weaknesses. This review summarizes the studies to date evaluating the efficacy and safety of adjuvants used with IPV.

Introduction

Poliomyelitis, once one of the most feared infectious diseases, is now nearing global eradication. Since 1988, when the World Health Organization's (WHO) Global Polio Eradication Initiative began, global annual cases have dropped from 350,000 to 650 in 2011 [1]. The last case of naturally-acquired wild poliovirus type 2 was reported in 1999, and only three countries (Nigeria, Pakistan, and Afghanistan) have never interrupted endemic transmission.

Poliovirus has several characteristics that make universal eradication feasible: it has an effective vaccine and no animal reservoir. . The two types of polio vaccines most widely used are inactivated polio vaccine (IPV), and the Sabin oral polio vaccine (OPV), a live attenuated vaccine. OPV is currently the vaccine recommended by the WHO for most of the developing world because it is simpler to administer, less expensive (fifteen to twenty cents per dose versus three dollars per dose of IPV) [2], and provides superior intestinal immunity [3].

However, OPV has several disadvantages that could be problematic after wild poliovirus eradication. OPV is shed in the stool of vaccinated children and can then spread to other people in the community. Although this increases immunity in the community [4], it can also allow OPV to replicate long enough to revert to a neurovirulent form. In approximately

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one out of 500,000 children receiving their first OPV dose, mutations that can be rapidly acquired during OPV replication in the gut lead to vaccine associated paralytic poliomyelitis (VAPP) [5]. When OPV is allowed to replicate for 6 months or more, it can revert to vaccine-derived poliovirus (VDPV) [6]. When this occurs through person-to-person spread in undervaccinated communities, it is called circulating VDPV (cVDPV). cVDPV has caused a number of poliomyelitis outbreaks with an attack rate and disease severity similar to outbreaks caused by wild poliovirus [7].

Several strategies have been considered for phasing out vaccines after wild poliovirus eradication. Global OPV cessation and change to universal IPV after wild poliovirus eradication is thought to be the safest strategy because IPV does not run the risk of VAPP or VDPV. IPV is a mixture of formalin-inactivated wild poliovirus serotypes 1, 2, and 3. Early IPV contained 20, 2 and 4 D units of type 1, 2, and 3 respectively, but was enhanced in 1987 to contain 40, 8, and 32 D Units. IPV in its current form may be prohibitively expensive in the developing world. Several measures being investigated to reduce the required dose, and thus the cost, of IPV include intradermal administration [8], [9], and administration with adjuvants.

Adjuvants are substances that are added to vaccines to augment their immunogenicity. Classes of adjuvants include mineral salts (such as aluminum and calcium), oil emulsions, microbial derivatives, and particulate formulations [10]. Individual adjuvants have wide-ranging strengths and weaknesses. This review explores the current knowledge of adjuvants used with IPV.

Methods

This systematic literature review primarily utilized the PubMed database. Our search terms were “IPV” and “adjuvant” or “polio” and “adjuvant”. We also used Plotkin’s *Vaccine* textbook chapters and their references on IPV [11], OPV [12], and adjuvants [13] in addition to references in papers found in PubMed and a Google search. We included both human and animal trials of IPV or IPV-derived peptides combined with adjuvants dating from 1950 to 2011. An exclusion criterion was using OPV as the adjuvanted test vaccine instead of IPV. To our knowledge, these studies are the extent of published trials assessing adjuvants with IPV.

Results

Twenty-one trials including 7 human and 14 animal studies were reviewed. The main findings are summarized in table 1. The 16 studies that included a nonadjuvanted comparator group are summarized in table 2.

Aluminum

The aluminum adjuvants include, among others, aluminum hydroxide, aluminum oxide, and aluminum phosphate. Millions of doses of aluminum-containing vaccines have been administered over the course of many decades. Aluminum is utilized in several licensed vaccines including diphtheria, tetanus, and acellular pertussis (DTaP), hepatitis B, and human papilloma virus vaccines.

In 1960, an Italian study observed higher antibody titers in guinea pigs inoculated with aluminum phosphate adsorbed IPV versus IPV alone, each given in two subcutaneous doses 14 days apart [14]. A German study the same year assessed antibody formation in infants after vaccination with aluminum hydroxide adjuvanted combination polio, diphtheria, pertussis, and tetanus vaccine. Vaccines were administered subcutaneously in three doses

given at four week intervals. The authors did not include a control group, but noted a 4–16 fold increase in median antibody titers to each serotype of poliovirus three months post vaccination [15].

Aluminum oxide was assessed as an adjuvant for monovalent (Strain 1 Mahoney) IPV in a rhesus monkey model in 1962 [16]. The authors compared adjuvanted versus nonadjuvanted vaccine given either subcutaneously or intramuscularly with a variety of dosing schedules. Aluminum adjuvanted vaccine gave significantly higher geometric mean titers overall. After vaccination, monkeys were then challenged with three doses of live poliovirus injected intramuscularly along with two doses of immunosuppressive corticosteroids. In the adjuvanted vaccine group, 2/16 monkeys (12%) developed paralytic poliomyelitis whereas 15/19 monkeys (79%) in the non-adjuvanted group developed paralytic polio post challenge.

Similar experiments assessing the adjuvanticity of aluminum oxide with trivalent IPV in rhesus monkeys were carried out in 1967 with similar results [17]. Adjuvanted vaccines yielded higher geometric mean titers and conferred superior protection after intramuscular challenge with live virus of each of the three serotypes.

A 1985 study compared the adjuvanticity of aluminum hydroxide versus Freund's complete adjuvant on polio-derived peptides in rabbits, rats, and guinea pigs [18]. The authors did not include a nonadjuvant control group. The authors found that Freund's adjuvant induced higher levels of peptide-specific antibody titers than aluminum, but both adjuvants were similarly poor in induction of polio neutralizing antibodies.

Aluminum-based adjuvants are currently used in combination vaccines containing IPV and have been thoroughly assessed for safety and efficacy in humans. Three recent studies have compared standalone IPV to adjuvanted combination vaccines containing IPV. Diphtheriatetanus-acellular pertussis, hepatitis B and IPV (Pediarix®, GSK) containing aluminum hydroxide and aluminum phosphate was compared to standalone IPV in a 2001 pediatric study [19]. No significant difference in local reactions between combination and control groups was observed. Both combination and standalone IPV given in three doses at 2, 4, and 6 months of age gave protective levels of antibody titer in >98% of participants. Antibody titers were higher in the combination vaccine group to all 3 serotypes after three injections, but the difference was only statistically significant for serotypes 1 and 3.

A Chinese study compared the immunogenicity and safety of Pentaxim® (Sanofi Pasteur), diphtheria-tetanus-acellular pertussis, *Haemophilus influenza*, and IPV, adjuvanted with aluminum hydroxide, to standalone vaccines. When comparing combination vaccine and standalone IPV given at 3, 4, and 5 months, both groups showed seroconversion rates of >99% [20]. However, antibody titers were significantly higher in the combination vaccine group to all three serotypes. Erythema and swelling were seen more frequently in the combination vaccine group. Erythema was reported in 19.8–20.8% and swelling in 11.9–13.6% of combination vaccinees, compared to 8.9% and 4.3% in controls, respectively [20].

A similar study found seroprotective titers in 99.4–100% of toddlers immunized with either standalone IPV or Pentacel ® (Sanofi Pasteur), aluminum phosphate-containing diphtheriatetanus-acellular pertussis, *Haemophilus influenzae* and IPV (DTaP-IPV-Hib) [21]. Local reactions to combination vaccines were not significantly higher than to controls. Geometric mean antibody titers were roughly equivalent between combination and traditional groups for all three serotypes. However, in this trial, it was not stated whether the separate dose regimen injections were administered in separate limbs (as was stated in the Chinese study, [20]). Theoretically, if the standalone IPV was injected in close proximity to the DTaP, the aluminum in the DTaP could have increased the immune response against the

IPV, which could explain the different results in this study compared to the other 2 combination vaccine studies.

Despite aluminum's good efficacy as an adjuvant, it does have some weaknesses. It is less immunogenic than some other adjuvants, it has poor CD8 T-cell induction, and it can rarely generate local adverse reactions [22]. In spite of these shortcomings, it remains the most widely utilized adjuvant in the United States.

Calcium

Calcium phosphate is another mineral salt that has been used as an adjuvant for decades. It is licensed as an adjuvant in Europe and has been used in European DTP vaccines for many years. Field studies in the 1960s found calcium phosphate to be well tolerated in children and adults [23]. More recently, a 1994 study compared alum, calcium phosphate and stearyl tyrosine as adjuvants for tetanus toxoid, and found that calcium did not induce production of IgE antibodies [24]. Calcium phosphate demonstrated minimal reactogenicity at the site of administration in a trial as an adjuvant for Herpes Simplex Virus 2 (HSV-2) and Epstein-Barr Virus (EBV) vaccines. In the same trial, it was noted to have increased immunogenicity when compared to alum [25].

One study has specifically assessed calcium phosphate in IPV. A French trial in 1977 utilized calcium phosphate adjuvanted IPV and found 81% of infants seroconverted to all three serotypes of virus after two doses and 90% after a booster one year later [26]. The trial was a field study in the Central African Republic and lacked a nonadjuvanted control group. No local or general adverse reactions were observed. Calcium phosphate's immunogenicity and safety compared to aluminum warrants a modern trial to determine its adjuvanticity.

Oil Emulsions

Early formulations of oil emulsification adjuvants such as Freund's complete and incomplete adjuvant were found to be highly effective immunostimulators. Complete Freund's adjuvant (CFA) differs from incomplete Freund's adjuvant (IFA) in that it contains a strain of killed mycobacteria while IFA does not. A Russian trial in 1977 found CFA a strong adjuvant when combined with type 1 polio in rabbits, significantly so when injected directly into the popliteal lymph node [27]. However, this formulation is not used in humans due to excessive reactogenicity.

A rhesus monkey trial in 1950 assessed adjuvanticity of live virus combined with paraffin oil with or without killed *Mycobacteria butyricum*. Neutralizing antibody titers were ten times higher in groups receiving adjuvanted virus [28]. One year later, Salk and colleagues utilized adjuvants in an attempt to classify types of polioviruses. Lansing strain (type 2) poliovirus either alone or combined with IFA was injected intramuscularly into rhesus monkeys. The adjuvanted virus produced higher antibody titers when diluted one hundred fold compared to undiluted nonadjuvanted virus, and still produced measurable neutralizing antibodies when diluted one thousand fold [29]. A 1963 study compared IPV with or without IFA given intramuscularly to rhesus monkeys [30]. Two doses of adjuvanted vaccine each containing one tenth the normal antigen dose resulted in approximately equal titers to three doses of undiluted nonadjuvanted vaccine.

These data led to a second study, this time in infants [31]. Ninety-six infants were randomized to receive either separate DPT plus IFA-adjuvanted IPV, separate DPT plus nonadjuvanted IPV, or a combined DPT-IPV (Tetravax). Non-adjuvanted and combination vaccine were given in three doses at the standard dose. Adjuvanted vaccine was administered in two doses with one-tenth the standard IPV dose. All three groups were vaccinated one month apart with a booster of the same vaccine nine months after initial

dose. No local reactions were noted. Geometric mean titers and seroconversion rates were uniformly lower in the adjuvanted one-tenth dose group. Seropositivity was 90%, 80%, and 87% to types 1, 2, and 3 respectively in the adjuvant group compared to 100%, 96% and 100% in the non-adjuvanted group after the booster dose. The authors attributed the lower titers to the fewer doses and lower antigen dose.

In 1962, a non-controlled trial assessed adverse reactions encountered when using mineral oil as an IPV adjuvant in humans, this time in a community-wide immunization program. No serum samples were taken during this study to measure immune response. Out of 12,479 patients immunized once, 65 individuals reported pain in limb injected, 7 had local induration that resolved within 4–6 months, and 7 had nodule formation that diminished but did not resolve in six weeks. Two patients had granulomas diagnosed via biopsy over six weeks after injection [32].

Modern oil emulsion adjuvants such as MF59, AF03, and AS03 contain less oil and have increased purity and biocompatibility compared to formulations in the 1960s. A very recent study evaluated the effectiveness of an oil-in-water emulsion based on the composition of MF59 when combined with IPV administered intramuscularly in rats [33]. After one injection, the vaccine with oil-in-water emulsion generated higher neutralizing antibody titers versus nonadjuvanted vaccine, although this only achieved statistical significance for serotype 2. In the two dose protocol, vaccinations were given one month apart. Rats were given diluted vaccine alone or adjuvanted with either aluminum or one of two different oil-in-water emulsions. There were higher titers for all three serotypes in the emulsion groups compared to the alum and nonadjuvanted groups. Furthermore, two doses of adjuvanted vaccines with 1/30 the antigen dose produced higher antibody titers than two doses of nonadjuvanted undiluted vaccine. One rat died during the study which the authors attribute to a sore which developed post anesthesia. All other rats gained weight and had no adverse effects observed.

MF59 was specifically developed for the elderly but has been used in all age groups with a large base of safety data [34]. It is licensed for use in 20 countries and was utilized during the 2009 influenza pandemic. Despite some initial problems with oil emulsions used in the mid-20th century, modern oil emulsions like M59 could prove a viable option to adjuvant IPV.

Chitosan

Chitosan is a nontoxic, biodegradable polymer that is a potent activator of the innate immune system [35]. Chitosan has been explored as an intramuscular adjuvant in polio as well as influenza vaccines in rodent studies [36, 37]. The polio study used two formulations of 85% deacetylated chitosan: a nanoparticle emulsion (hypothesized to potentially increase bioavailability) [38] and a solution in glutamate. The chitosan formulations were added to either traditional or Sabin strains of trivalent inactivated poliovaccine and injected intramuscularly in mice and rats. Chitosan glutamate and nanoparticles elicited a significantly higher antibody titer than control after two vaccine doses of inactivated Sabin strains with 4 to 32-fold higher neutralizing antibody titers compared to nonadjuvanted vaccine. Adjuvanted vaccine could be diluted fourfold with a two dose schedule to elicit equal antibody titers as two doses of undiluted nonadjuvanted vaccine. When combined with traditional trivalent IPV, both formulations of chitosan evoked elevated antibody titers compared to control, however, chitosan nanoparticles showed higher levels for each type of virus. It was noted that the Sabin strains elicited a higher immune response than comparable doses of traditional IPV, which the authors hypothesized was because the neutralization assays used Sabin strains [37].

Chitosan has a good safety profile. Intramuscular inoculation does not produce chitosan-specific IgE, IgG, or IgM antibodies in rats [37]. Chitosan has demonstrated oral safety in humans and is sold as an anti hypercholesterolemic agent [39]. As a molecule for intramuscular human use it has not been extensively studied. However, a 2006 phase IIb clinical trial in South Korea utilized holmium-166/chitosan complex injection therapy as local ablation for hepatocellular carcinoma. Chitosan was well tolerated by the subjects and the therapy demonstrated potent anti-tumor capabilities [40]. Despite its ubiquity in commonly used products, as an intramuscular delivery route for humans it requires further assessment.

Vitamin D

1,25-Dihydroxyvitamin D3, the active form of vitamin D, is a steroid hormone with known immunomodulatory abilities [41]. It has been tried as an adjuvant in combination with influenza vaccine, where it increased humoral immunity in mice but failed to do so in human trials. [42].

Vitamin D in fractionated triglyceride of coconut oil has been tested as an adjuvant in combination with IPV in mice [43]. Monovalent IPV with or without the Vitamin D was injected intraperitoneally for 2 to 3 doses at 2 week intervals, and blood and saliva samples were assessed for levels of polio-specific IgA, IgG, and neutralizing antibodies 4 weeks post inoculation. For all three serotypes of IPV, Vitamin D significantly increased neutralizing antibody titers. Serotypes 1 and 3 showed significant increases in IgA titers in saliva and serotype 2 showed a significant increase in serum IgG levels. The authors note a known disparity between IgG ELISAs and neutralizing antibody titers (the more functional test) which may have caused the discrepancy between the serum IgG levels and neutralizing titers. As one drawback of IPV versus oral polio vaccine is its inferior mucosal immunity, the rise in saliva IgA titers (felt to be a marker for mucosal immunity) is of particular interest. Oil in water emulsions are also utilized as vaccine adjuvants, so it is not clear whether the use of coconut oil with the Vitamin D may have altered the immune response.

In humans, Vitamin D has an excellent established safety profile. High dose therapy of Vitamin D3 in treatment of deficiency has been assessed in humans and is well tolerated [44]. Kriesel et al. found that Vitamin D adjuvanted influenza vaccines caused more pain at the injection site than non adjuvanted vaccines but noted no other adverse reactions [42]. The observed discrepancy between immunogenicity of Vitamin D in mice and humans necessitates a human trial to determine Vitamin D’s safety and effectiveness in human use IPV.

CpG Oligodeoxynucleotides

Synthetic oligodeoxynucleotides with unmethylated CpG motifs (CpG-ODN) have comparable immunogenic properties to bacterial DNA [45] and have been assessed as adjuvants in a wide array of preclinical and clinical vaccine trials [46].

In 2009, CpG-ODN was compared to aluminum and non-adjuvanted IPV in mice [47]. The authors used a CpG-ODN sequence found to be immunogenic and well tolerated in both mice and human clinical trials [48]. Mice were immunized intramuscularly with serotype 2 Sabin strain IPV adjuvanted with CpG-ODN, alum, or CpG-ODN with alum and compared to nonadjuvanted vaccine as a control. The authors focused on inactivated Sabin strain serotype 2 due to its lower immunogenicity than other Sabin serotypes. Alum and CpG-ODN evoked approximately four-fold higher titers of antigen-specific IgG than vaccine alone as a control. Together, the two showed ten-fold increase in IgG titer. The authors also assessed neutralizing antibody titers in mice after intramuscular injections of undiluted,

four-fold, and sixteen-fold dilutions of inactivated Sabin strains of all three serotypes. Combined, alum and CpG-ODN allowed for antigen sparing of 4-fold, 16-fold, and 16-fold in types 1, 2, and 3 respectively compared to nonadjuvanted control.

CpG-ODN have been utilized in a variety of human vaccine trials. CpG-ODN are generally well tolerated, however in a pneumococcal polysaccharide vaccine trial with HIV-infected patients, a CpG adjuvanted version of the vaccine resulted in a statistically significant increase in influenza-like side effects [49]. Some studies note increased frequency of mild local reactions compared to non-adjuvanted vaccines [46]. Despite its apparent increased reactogenicity, further testing is warranted due to its promising antigen sparing ability.

Stearyl Tyrosine

Stearyl tyrosine or octadecyl tyrosine was explored as an adjuvant for various vaccine formulations in the 1980s and 1990s, but not significantly since. It has been called an organic equivalent to alum. Yet, when compared to alum, it was shown to be an equally effective adjuvant for bacterial vaccines, but a more potent immunostimulator of viral vaccines [50].

A 1986 study on cynomolgus monkeys analyzed the adjuvanticity of stearyl tyrosine on IPV [51]. Monkeys were vaccinated twice intramuscularly with vaccine, vaccine adjuvanted with stearyl tyrosine, vaccine diluted 1:4, or diluted vaccine with stearyl tyrosine. The authors utilized metabolic inhibition tests to assess the levels of neutralizing titers produced at varying time points over the course of 168 days. Neutralizing antibody titers were uniformly higher in the adjuvanted vaccine groups versus non-adjuvanted controls. Diluted adjuvanted vaccine elicited higher levels of titers than nondiluted adjuvanted vaccine at most time points. Both adjuvanted vaccines resulted in longer durations of antibody elevation, with persisting high titers at the close of the experiment, 168 days after first injection.

Stearyl tyrosine has good reported safety data. There is no evidence of local reaction or granuloma formation in published data [50]. However, a lack of recent studies on the compound limits its application to modern vaccines.

Liposomes

Liposomes are artificially generated lipid bilayer vesicles that have been explored as drug carriers and vaccine adjuvants. Several different liposome-based systems exist and are generated from varying constituents. Traditional liposomes are generally neutral lipids such as cholesterol or phosphatidylcholine with an immunomodulator as they are weakly immunogenic alone. Virosomes are highly immunogenic vesicles derived from influenza cell membranes and are currently sold as part of influenza and hepatitis A vaccines. As drug carriers and in vaccines, they have been found to be safe, well-tolerated, biodegradable, and versatile [52].

A 1991 study combined small unilamellar liposomes generated from egg phosphatidylcholine and cholesterol with poliovirus peptide VP2 of strains 1 and 3 [53]. Peptides were either surface linked or internally trapped within the liposome. Mice were injected intramuscularly with free, surface linked, or internally trapped peptide and then boosted four weeks later with the same. Sera were analyzed for specific anti-peptide IgG by ELISA. Ten days after booster, mice had uniformly higher levels to liposome associated peptide than free peptide alone. For both type 1 and type 3, surface linked peptides showed stronger antibody response after primary injection with a drop in titer by day 38. After booster injection, surface linked peptide showed an initial elevation but a sharp drop by day 48. Entrapped peptide had a more vigorous response to booster in type 3, but no anamnestic response was seen in type 1. Type 1 was generally less immunogenic.

This study was limited by small size (five mice per group) and use of subunit vaccine rather than whole IPV. Further, the antibody response may have been weak due to the use of a traditional liposome without an immunomodulator. Liposomes or potentially virosomes could be a promising adjuvant for IPV, but require a modern, larger study.

Discussion

Now that global polio eradication is nearing reality, it is becoming increasingly important to develop strategies to make IPV affordable for the developing world. To prevent vaccine-derived polioviruses after eradication, there will need to be global cessation of oral polio vaccine use. IPV will be the only option for countries wanting to maintain community immunity against poliovirus. As such, there is renewed interest in using adjuvants to reduce the required dose, and thus the cost, of IPV. A recent position paper written by PATH (the Program for Appropriate Technology in Health) estimated that aluminum-based adjuvants could enable a three- to four-fold dose reduction of IPV, and that oil-in-water adjuvants could enable a ten-fold dose reduction of IPV [2].

Although the current commercial forms of IPV do not contain adjuvants (with the exception of some IPV-containing combination vaccines), animal and human trials of adjuvants with IPV date back to Jonas Salk's studies in the 1950s. A wide variety of adjuvants have been shown to increase the immunogenicity of IPV in animal studies (Table 1 and Table 2). Only aluminum, oil emulsions, and calcium have been tested as adjuvants with IPV in human studies. However, many of these human studies contained no control group [15, 26, 32], assessed safety but not immunogenicity [32], occurred prior to the development of enhanced IPV [15, 26, 31, 32], or had somewhat conflicting results [19, 20, 21]. Further, these studies focus on serologic antibody titers, though an important indicator of community IPV protectivity lies in mucosal immunity. Of the trials discussed, only the Vitamin D study specifically assessed mucosal immunity, and it did so by evaluating IgA titers, not by evaluating stool shedding duration following a challenge of OPV [43].

Adjuvants have been shown to be efficacious and safe for a variety of vaccines, and the studies reviewed here suggest that adjuvants could be efficacious and safe for IPV as well. Further studies are needed to assess the potential of adjuvants in humans to allow for a reduced dose of IPV.

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Highlights

- Adjuvants are an option to reduce the cost and improve the immunogenicity of IPV
- Since the 1950s, several adjuvants have been explored with IPV
- No adjuvants are currently used in standalone IPV
- This review compares published data on different adjuvants and their effectiveness

Table 1

Adjuvants studied with IPV. Studies described are indicated by footnotes. Increased immunogenicity refers to a trial that includes a quantitative measure of adjuvanted vaccine with increased immune response relative to control, measured for example by antibody titers or challenge with live virus.

Adjuvant	Species	Increased Immunogenicity In Animals	Increased Immunogenicity In Humans	Safety Data (human studies: IPV with adjuvant)	Safety Data (human studies: adjuvant without IPV)
Aluminum					
Aluminum oxide	Rhesus monkey[16, 17]	Yes	Not studied	Not studied	Regarded as very safe rare adverse reactions[22]
Aluminum hydroxide	Guinea pig, rabbit, rat[18], human[15, 20]	Unclear	Yes	Increased erythema and swelling in Pentaxim® trial	Regarded as very safe rare adverse reactions[22]
Aluminum phosphate	Guinea pig[14], human[19,21]	Yes	Mixed	No increased local reactions in Pediarix® or Pentacel®	Regarded as very safe rare adverse reactions[22]
Calcium Phosphate	Human[26]	Not studied	Unclear	No local or generalized adverse reactions seen	Minimal reactogenicity, does not induce IgE Antibodies[24, 25]
Oil Emulsions					
CFA	Rabbit[27]	Yes	Not studied	Not studied, too reactogenic	Excessively reactogenic in humans, not used
IFA	Rhesus monkey[28, 29, 30] human[31]	Yes	Unclear	No increased local reactions seen	Older formulations were too reactogenic
Mineral Oil	Human[32]	Not studied	Not studied	Increased induration, edema, and granuloma formation	Older formulations were too reactogenic
MF59-based emulsion	Rat[33]	Yes	Not studied	Not studied	Newer formulations are more biocompatible[34]
Chitosan	Rat, mouse[37]	Yes	Not studied	Not studied	Excellent oral safety and biocompatibility[39] Well tolerated in chemotherapy trial[40]
Vitamin D	Mouse[43]	Yes	Not studied	Not studied	Excellent safety data for injection therapy[44] Increased pain at injection site in one study[42]
CpG ODN	Mouse[47]	Yes	Not studied	Not studied	Increased mild local reactions[46]. HIV/PPV trial had significant increase in influenza-like side effects[49]
Stearyl Tyrosine	Cynomolgus monkey[51]	Yes	Not studied	Not studied	No local reaction or granuloma formation[50]
Liposomes	Mouse[53]	Yes	Not studied	Not studied	Used as drug carriers and vaccine delivery systems Well tolerated[52]

CFA = complete Freund's adjuvant, CpG ODN = synthetic oligodeoxynucleotides with unmethylated CpG motifs, IFA = incomplete Freund's adjuvant, IPV = inactive polio vaccine, Pentaxim® = diphtheria-tetanus-acellular pertussis, *Haemophilus influenza*, and IPV, adjuvanted with aluminum hydroxide, Pediarix® = aluminum phosphate and hydroxide adjuvanted diphtheria-tetanus-acellular pertussis, hepatitis B and IPV, Pentacel® = aluminum phosphate-containing diphtheria-tetanus-acellular pertussis, *Haemophillus influenza* and IPV, PPV = pneumococcal polysaccharide vaccine.

Table 2

Studies assessing adjuvanted IPV with a non-adjuvanted comparator group.

Study	Year	Species	Adjuvant	Antigen	Methods	Results
14	1960	Guinea pig	Aluminum phosphate	IPV	Two SQ injections given 14 days apart of either adjuvanted IPV (14 guinea pigs) or non-adjuvanted IPV (12 guinea pigs), repeated with both lower dose and higher dose IPV.	Significantly higher polio neutralizing antibody GMTs for serotypes 1 and 2 in the adjuvanted group when low dose IPV used (5, 32, and 10.8 vs 2, 14.2, and 3.2 for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups). Nonsignificant trend towards higher GMTs for all serotypes in the adjuvanted group when high dose IPV used (50.8, 101.6, and 40.3 vs 18, 45.2, and 35.9 for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups).
16	1962	Rhesus monkey	Aluminum oxide	Monovalent (Type 1 Mahoney) IPV	Eight groups of six monkeys each given either adjuvanted or nonadjuvanted IPV, either IM or SQ, as either a 2 dose schedule (on days 0 and 42) or a 3 dose schedule (on days 0, 28, and 60)	Polio neutralizing antibody GMT of combined adjuvanted groups was significantly higher than the GMT of combined nonadjuvanted groups after all vaccine doses (33.5 vs 4.5). Monkeys were challenged with three IM injections of active serotype 1 poliovirus + steroids. After challenge, 2/16 (12.5%) of the monkeys vaccinated with adjuvanted IPV vs 15/19 (78.9%) of the monkeys vaccinated with nonadjuvanted IPV vs 9/10 monkeys (90%) from an unvaccinated control group developed paralytic poliomyelitis. On histologic examination, 3/16 (18.7%) of the adjuvanted group vs 18/19 (94.7%) of the nonadjuvanted group had central nervous system lesions.
17	1967	Rhesus monkey	Aluminum oxide	Monovalent types 1 or 2 or trivalent IPV	Sixteen groups with between 5 and 12 animals were given IM injections of either 2 or 3 doses (40 days between dose 1 and 2, at least 60 days between dose 2 and 3) of either adjuvanted or nonadjuvanted IPV.	Significantly higher polio neutralizing antibody GMTs for the vaccine serotype(s) after all vaccine doses in the adjuvanted groups (~2–8X higher GMT in the adjuvanted groups). Monkeys were challenged with three IM injections of active poliovirus + steroids. After poliovirus type 1 challenge, 11.1–20% vs 77.7-88.8% of monkeys from the adjuvanted vs nonadjuvanted group developed paralytic polio. After poliovirus type 2 challenge, 25% vs 75% of monkeys from the adjuvanted vs nonadjuvanted group developed paralytic polio. After poliovirus type 3 challenge, 0% vs 16.6% of monkeys from the adjuvanted vs nonadjuvanted group developed paralytic polio.
19	2001	Human	Combined aluminum hydroxide and aluminum phosphate	eIPV	Two groups of 100 infants each, given Pediarix® (DTaP, HBV, and IPV--containing aluminum adjuvant) vs standalone constituents, all IM in 3 doses at 2, 4, and 6 months.	Significantly higher polio neutralizing antibody GMTs for serotypes 1 and 3 for adjuvanted group (415, 514, and 1729 vs 213, 329, and 432 for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups). Similar seroconversion rates in all groups (100%, 98.8%, and 100% vs 100%, 100%, and 100% for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups).
20	2011	Human	Aluminum hydroxide	eIPV	Two groups of 264 infants each, given Pentaxim® (DTaP, Hib, and IPV--containing aluminum adjuvant) vs standalone constituents, all IM in 3	Significantly higher polio neutralizing antibody GMTs for all serotypes for adjuvanted group (299.2, 160.1, and 525.5, vs 130.1, 78.8, and 222.6 for serotypes 1, 2, and 3 respectively in adjuvanted vs

Study	Year	Species	Adjuvant	Antigen	Methods	Results
					doses at 3, 4, and 5 months of age.	nonadjuvanted groups). Similar seroconversion rates in all groups (100%, 100%, and 99.6% vs 100%, 99.6%, and 99.6% for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups).
21	2009	Human	Aluminum phosphate	eIPV	Two groups of 485 infants each given Pentacel® (DTaP, Hib and IPV--containing aluminum adjuvant) vs standalone constituents, all IM in 3 doses at 2, 4, and 6 months of age.	Similar polio neutralizing antibody GMTs (398.13, 1032, and 969.82 vs 463.49, 913.35, and 902.12 for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups). Similar seroconversion rates in all groups (99.4%, 100%, and 100% vs 100%, 100%, and 100% for serotypes 1, 2, and 3 respectively in adjuvanted vs nonadjuvanted groups)
28	1950	Rhesus monkey	IFA with or without *M. butyricum*	Live virus (Type 2 Lansing strain)	Three groups of 6 monkeys each given either IM nonadjuvanted poliovirus or poliovirus with paraffin oil with or without *M. butyricum*, in 3 doses, 5 weeks and 11 weeks apart.	Mean neutralizing antibody titers were 1.9, 3.1, and 3.3 one month after the first injection, 3.1, 3.9, and 4.2 two weeks after the second injection, and 3.4, 4.3, and 3.7 one week after the third injection, in the nonadjuvanted, oil, and oil + *M. butyricum* groups respectively. Of note, 4 of the 6 monkeys in the oil + *M. butyricum* group died of fatal allergic encephalitis, two before the first blood draw.
29	1951	Rhesus monkey	IFA	Live virus (Type 2 Lansing strain)	Five groups of 6 monkeys each, one IM dose, 4 dilutions with adjuvant vs nonadjuvant control.	Marked adjuvant effect with adjuvanted vaccines producing antibody titers of 1:3200, 1:120, 1:5, and 0 in the 10, 100, 1000, and 10000 fold diluted virus, compared to 1:16 in the nonadjuvanted 10 fold diluted virus.
30	1963	Rhesus monkey	IFA	IPV	Nine groups of 12 monkeys each, receiving IM vaccine in 1 or 2 doses (28 days apart) of either adjuvanted or nonadjuvanted vaccine diluted 1/10 or 1/4, plus a control group receiving 3 doses of nonadjuvanted nondiluted vaccine.	Markedly higher polio neutralizing antibody GMTs and seroconversion rates for all three serotypes for the adjuvanted vaccine. GMTs approximately 20 fold higher in adjuvanted groups with same dose vaccine, and similar between two adjuvanted 1/10 doses IPV vs three nonadjuvanted full doses IPV (315, 440, and 104 vs 330, 294, and 157 for serotypes 1 (Mahoney), 2, and 3 respectively). Seroconversion rates of 100%, 100%, and 100% vs 50%, 100%, and 10% for adjvuanted vs nonadjuvanted two 1/10 doses IPV for serotypes 1, 2, and 3 respectively. Seroconversion rates of 100%, 100%, and 100% vs 42%, 92%, and 17% for adjuvanted vs nonadjuvanted two 1/4 doses IPV for serotypes 1, 2, and 3 respectively. Seroconversion rates for 3 doses nondiluted nonadjuvanted vaccine 100% for all 3 serotypes.
31	1963	Human	IFA	IPV	Three groups receiving IM doses one month apart: 31 infants given 3 doses nonadjuvanted IPV, 34 given 2 doses adjuvanted 1/10 dose IPV, 31 infants given DPT-Salk (different IPV composition than other 2 arms). All groups received booster dose at 9	Lower polio neutralizing GMTs after booster dose in 2 adjuvanted 1/10 IPV doses group vs 3 nonadjuvanted full IPV doses group: 50, 50, and 120 vs 220, 110, and 320 in serotypes 1, 2, and 3 respectively. Lower seroconversion rates after booster dose in 2 adjuvanted 1/10 IPV doses group vs 3 nonadjuvanted full IPV doses group: 100%, 96%, and 100% vs 90%, 80%, and 87% for serotypes 1, 2, and 3 respectively. Lower seroconversion rates before booster dose in 2 adjuvanted 1/10 IPV doses group

Study	Year	Species	Adjuvant	Antigen	Methods	Results
					months.	vs 3 nonadjuvanted full IPV doses group: 83%, 55%, and 84% vs 52%, 42%, and 48% for serotypes 1, 2, and 3 respectively. 3 doses Salk-DPT vaccine had comparable seroconversion rates to 2 adjuvanted 1/10 IPV doses group, but lower GMTs after booster (25, 25, and 50 for Salk-DPT group for serotypes 1, 2, and 3 respectively).
33	2011	Rat	MF59-based emulsion, stable oil emulsion, or aluminum	IPV	Multiple groups of 4–10 rats each receiving 1–2 IM doses (1 month apart) of various dilutions of IPV with or without one of the three adjuvants.	Higher polio neutralizing antibody titers with adjuvanted vaccines compared to nonadjuvanted vaccine after one dose that only reached significance for serotype 2 with oil-based adjuvants. Higher polio neutralizing antibodies with adjuvanted vaccines compared to nonadjuvanted vaccine after two doses that reached significance for stable oil emulsion for serotype 1 (3 fold dose sparing) and all adjuvants for serotypes 2 and 3 (MF59-like adjuvant induced 15-fold higher titers for serotype 2, and both oil-based adjuvants induced 30-fold higher titers for serotype 3 vs nonadjuvanted vaccine).
37	2011	Rat & mouse	Chitosan (nanoparticles and glutamate solution)	IPV and inactivated monovalent Sabin strains	Multiple groups of 4–6 mice receiving 2–3 IM doses at days 0, 21, +/− 31 of undiluted or diluted vaccine with or without adjuvant. Multiple groups of 5 rats receiving one IM dose of undiluted or diluted vaccine with or without adjuvant.	At least 16-fold higher neutralizing antibody titers after 2 adjuvanted inactivated Sabin doses vs nonadjuvanted control for all 3 serotypes in mice. For inactivated Sabin type 1, 2 doses of adjuvanted 4-fold diluted vaccine produced equivalent titers to 2 doses nonadjuvanted undiluted vaccine. After 2 doses in mice, adjuvanted IPV produced 5- to 16-fold higher titers than nonadjuvanted IPV, with nanoparticles producing highest titers. In rat experiments, chitosan nanoparticles appeared to increase immunogenicity of IPV ~100-fold (for all 3 serotypes, adjuvanted IPV diluted 100-fold produced similar antibody titers to nonadjuvanted undiluted IPV).
43	2006	Mouse	Vitamin D (DHVD3) in fractionated triglyceride of coconut oil	Monovalent IPV (all serotypes)	Multiple groups of 8–18 mice each, intraperitoneal injections 2 or 3 doses, 2 week intervals, of IPV with or without adjuvant.	A significant increase in the adjuvanted group vs the nonadjuvanted group was seen for saliva IgA serotypes 1 and 3 (percentage mice with detectable IgA in saliva was 43%, 92%, and 33% vs 7%, 76%, and 16% for serotypes 1, 2, and 3 respectively in the adjuvanted vs nonadjuvanted groups), serum IgG serotype 2, and serum polio neutralizing antibodies for all 3 serotypes (>400%, >500%, and >800% higher for serotypes 1, 2, and 3 respectively in the adjuvanted group).
47	2009	Mouse	Aluminum or CpG oligodeoxynucleotides	Inactivated monovalent Sabin strains	Multiple groups of 8 mice each injected IM with 1 or 2 doses (28 days apart) of diluted or undiluted vaccine adjuvanted with CpG-ODN, aluminum, both, or neither.	For serotype 2: neutralizing antibody titers of 120, 91, 223, and 33.5 for vaccine adjuvanted with CpG-ODN, aluminum, both, or neither; dose sparing of 4-fold with either adjuvant alone and >16-fold with both adjuvants combined. For serotype 1: dose sparing of 4-fold with both adjuvants combined. For serotype 3: dose sparing of >16 fold with both adjuvants combined. For each adjuvant alone, neutralizing titers only consistently higher for serotype 2.

Study	Year	Species	Adjuvant	Antigen	Methods	Results
51	1986	Cynomolgus monkey	Stearyl Tyrosine	IPV	Four groups of 4 monkeys each, 3 IM injections at 0, 28 and 168 days, with IPV diluted 1:1 or 1:4 with or without adjuvant.	Ratio of antibody titers to reference serum markedly higher in adjuvanted groups (six days after 3rd dose: 33.81, 49.16, and 125.31 vs 7.36, 34.76, and 35.99 for serotypes 1, 2, and 3 respectively in the 1:1 diluted adjuvanted vs nonadjuvanted groups; 7.89, 21.4, and 58.46 vs 0.26, 0.03, and 0.46 for serotypes 1, 2, and 3 respectively in the 1:4 diluted adjuvanted vs nonadjuvanted groups).
53	1991	Mouse	Liposomes (with peptide either surface-linked or entrapped)	Poliovirus serotype 1 or 3 VP2 peptides	Six groups of 5 mice each injected IM- 2 doses, 1 month apart - with serotypes 1 and 3 VP2 either free, liposome surface-linked, or liposome entrapped.	Antibody responses (measured by ELISA read spectrophotometrically at 492 nm) were approximately 0.8, 0.25, and 0.1 one month after the first dose and 0.5, 0.5, and 0.1 10 days after the second dose of serotype 3 peptide in surface-linked, entrapped, and free vaccine respectively. Antibody responses were approximately 1.0, 0.1, and 0 one month after the first dose and 0.25, 0.1, and 0 10 days after the second dose of serotype 1 peptide in surface-linked, entrapped, and free vaccine respectively.

CpG-ODN = oligodeoxynucleotides with unmethylated CpG motifs, DTaP = diphtheria, tetanus, acellular pertussis vaccine, DPT = diphtheria, tetanus, pertussis vaccine, eIPV = enhanced IPV, GMT = geometric mean titer, HBV = hepatitis B vaccine, Hib = *Haemophilus influenzae b* vaccine, IFA = incomplete Freund's adjuvant, IPV = inactivated polio vaccine, IM = intramuscular, SQ = subcutaneous