An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) †

Literature Review on Pediatric Fluad® Influenza Vaccine Use in Children 6-72 Months of Age

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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EXECUTIVE SUMMARY

Despite the significant disease burden associated with influenza infections in children younger than 6 years of age, currently used inactivated unadjuvanted trivalent influenza vaccines (UTIVs) have limited effectiveness, especially after a single dose in unprimed children, during seasons with a mismatched strain and against Influenza B types. There are a limited number of studies on the effectiveness of UTIVs among children <2 years. Although FluMist®, a nasally administered live attenuated vaccine (LAIV), is reasonably effective among younger children, it is not recommended for children <2 years. New strategies are needed for effective influenza disease control in this age group.

Until recently, seasonal influenza vaccines approved for use in Canada did not include adjuvants. In 2011, Fluad®, an inactivated subunit adjuvanted trivalent influenza vaccine (ATIV), containing MF59™ as the adjuvant, was approved for use in older (≥ 65 years) adults for active immunization against influenza. Adjuvanted vaccines were used extensively during the 2009 H1N1 pandemic; a monovalent AS03 adjuvanted vaccine was used in Canada. However, the discussion of adjuvanted pandemic vaccines is beyond the scope of this review and has been excluded.

In anticipation of the availability of Fluad™ Pediatric vaccine, a systematic review of the literature was conducted to provide evidence to inform recommendations on using Fluad® for the prevention of influenza in children aged 6 to 72 months. On November 28, 2014, after completion of this review of the literature, Fluad® Pediatric Influenza Vaccine was approved for use in children 6 months to less than two years of age. The NACI review was not limited to children age 6 months to less than 2 years, as the product indications for Canada were not known when the review was being conducted, and there were some data available in the literature for children older than 24 months receiving ATIV.

A systematic review of the literature was conducted to provide evidence to inform recommendations on using ATIV for the prevention of influenza in children aged 6 to 72 months. Only 8 articles met all pre-specified inclusion criteria, of which 7 articles were from clinical trials that compared ATIV with a UTIV comparator and one from a study that looked at ATIV in healthy children compared to children with juvenile arthritis.

Based on this review, information on comparative efficacy is available only from a single trial suggesting a higher efficacy for ATIV (86% vs. 40% for comparator UTIV). The bulk of the data was obtained during one mild season that was dominated by influenza A/H3N2. The comparator vaccine induced a poorer immune response compared to equivalent UTIVs. There were also concerns raised by a European Medicine Agency inspection about the quality of diagnostic laboratory testing and validity of ascertainment of influenza cases.

There is limited but consistent evidence that ATIV is more immunogenic than comparable UTIVs against influenza A types. In particular, a single dose of ATIV is more immunogenic than a single UTIV dose. However, two doses of ATIV are still necessary to achieve satisfactory immune response against influenza B. As immunogenicity is an intermediate outcome, it is unclear what clinical protection is conferred.

ATIV was not compared directly to LAIV or to the quadrivalent influenza vaccine (QIV). One study using a dose-ranging factorial design with adjuvanted and unadjuvanted versions of seasonal TIV and QIV was identified, but a comparison of ATIV and QIV was not the primary objective of the study and the data were not grouped appropriately for such a comparison. Clinical trials comparing efficacy, immunogenicity, and safety of a single- and two-dose regimes of ATIV, LAIV and QIV are needed.

Safety data for ATIV in children is consistent with what is known about ATIV safety in adults. ATIV results in 10-15% more solicited local and systemic reactions compared to UTIV. However, most reactions are mild and tend to resolve quickly. Severe reactions are rare, but several of the reviewed studies were too small to detect clinically significant but rare adverse events. In particular, the safety information is limited for ATIV in children with immunodeficiencies and other chronic illnesses.

Taken together, the limited body of evidence identified in this review suggests that ATIV is likely both more immunogenic and more reactogenic than UTIV among children 6-72 months of age. There are insufficient data to assess whether ATIV is more effective than UTIV or LAIV in practice or to make an informed risk-benefit analysis.

INTRODUCTION

Influenza remains a significant cause of morbidity in children. Each year, 20-30% of children become infected with influenza.[1] Most of these infections are typically asymptomatic or associated with a mild self-limiting illness.[2] However, influenza can cause severe illness leading to hospitalization and death, especially among infants and children with underlying chronic conditions.[2,3]

The burden of pediatric influenza on the healthcare system is illustrated by the fact that up to 20% of pediatric acute care visits with fever or respiratory symptoms during influenza season are due to influenza.[4] In addition, children shed the virus for longer and more prolifically than adults, playing a major role in spreading influenza in their communities during annual influenza outbreaks.[5] Therefore, prevention of influenza infection among children can bring significant health benefits to both children and their communities.

Vaccination is the primary public health strategy for preventing influenza and reducing the impact of influenza epidemics.[6] Most provinces and territories in Canada offer universal influenza vaccination programs to all residents. Provinces without universal vaccination programs target groups at higher risk for infection including children.[7]

There are several seasonal influenza vaccine preparations currently authorized for pediatric use in Canada. The National Advisory Committee on Immunization (NACI) recommends that FluMist®, a nasally administered trivalent live attenuated influenza vaccine (LAIV), be used for healthy children and adolescents 2-17 years of age. There is evidence supporting preferential use in young children (<6 years of age), based on superior efficacy of LAIV compared to TIV, with weaker evidence in older children. It is anticipated that superior efficacy of LAIV extends beyond age 6 years, although the age at which efficacy between LAIV and TIV become equivalent is unknown. If LAIV is contraindicated or is unavailable, unadjuvanted trivalent inactivated vaccine (UTIV) should be used. For children 6–23 months of age, only UTIV is recommended. Use of currently available influenza vaccines is not recommended for infants <6 months of age, because of limited efficacy.[6]

Compared to UTIVs, LAIV, in children, induces a stronger systemic antibody response, as measured by serum levels of antibodies against hemagglutinin (HA) antigen of targeted strains, and a strong mucosal response, as measured by levels of nasal mucosal IgA antibodies.[8] However, LAIV is not currently recommended for children aged less than two years because of higher incidence of wheezing (4%) within 42 days of administration, compared to about 2% following UTIVs noted among children less than 12 months of age.[9] For the same reason, LAIV is not recommended for children with severe or unstable asthma. Because it contains a live virus, the vaccine is also contraindicated for children with immune compromising conditions.[6] There is also a theoretical risk of reassortment with wild type influenza and possible spread to immunocompromised individuals.[10]

The evidence for the effectiveness of the more commonly used conventional UTIVs (either inactivated split virus or subunit TIVs) is limited. Osterholm et al found no papers that met their strict inclusion criteria for UTIV effectiveness in children 2-17 years old.[11] The findings of other reviews with less stringent criteria are difficult to interpret because the reviewed studies varied significantly in terms of their methods, intensity of case finding, outcomes assessed, age ranges of participants, circulating strains etc.[10,12,13] In an extensive review of the literature

conducted as part of a recently published Cochrane review, Jefferson et al found, based on the analysis of 2 small clinical trials, that UTIVs were about 39% (95%CI: 0-66%) efficacious in preventing influenza among children younger than 6 years of age.[13] Corresponding estimates from observational studies varied by study design ranging from 37 to 55%. No usable evidence was identified for children younger than 2 years.[13] There was no evidence that UTIVs reduced the risk of lower respiratory tract disease or otitis media and weak evidence that UTIVs may reduce school absenteeism.[13] In addition, there is evidence that UTIVs perform particularly poorly among young children in seasons with significant strain mismatch.[10]

Prior to 2011, seasonal influenza vaccines approved for use in Canada did not include adjuvants. In 2011, Fluad®, an inactivated and MF59™ adjuvanted subunit TIV, was approved for use in older (≥ 65 years) adults for active immunization against influenza.[14] MF59™ refers to a group of squalene-in-water adjuvants manufactured by Novartis Vaccines and Diagnostics. The specific adjuvant used in Fluad® (MF59C.1) is an emulsion composed of squalene as the oil phase, stabilised with two non-ionic surfactants (polysorbate 80 and sorbitan trioleate), in a citrate buffer.[14] Squalene, a highly unsaturated hydrocarbon synthesized in the liver, is a precursor for all mammalian sterols, including cholesterol, steroid hormones and vitamin D, and principal hydrocarbon of human cell surface lipids.[15] Squalene used in the production of MF59C.1 is derived from shark liver oil. Squalene is also the primary ingredient of another adjuvant (AS03), manufactured by GSK, which was used in several monovalent 2009 pandemic influenza vaccines (e.g., Pandemrix® and Arepanrix®) as well as in candidate H5N1 vaccines.[16]

The adult formulation of Fluad® was first authorized in Italy in 1997 for use in the prevention of influenza in older adults and is now authorized in >30 countries for the same indication. The immunogenicity and safety of Fluad® was evaluated using clinical trials in different age populations, and there is considerable post-marketing experience with its use in adults (reviewed in a previous NACI statement[15]). NACI recommended that Fluad® can be used for the prevention of influenza in older (≥65) adults, but the evidence was insufficient to make a recommendation for its preferential use over other influenza vaccines available in Canada.[15]

This systematic review of the literature was conducted to provide evidence to inform recommendations on using Fluad® for the prevention of influenza in children aged 6 to 72 months. Fluad™ Pediatric received a Notice of Compliance from Health Canada on November 28, 2014, after the initiation of this review, for use in children 6 months to <2 years. Authorization for use in Canada was based on immunogenicity and safety data.

LITERATURE REVIEW METHODS

Search Strategy

The literature search was conducted in three primary electronic databases: Medline, Embase and Web of Science, employing a strategy based on using Medical Subject Headings (MeSH) for Medline, Emtree indexing for Embase, and keyword searching for all three databases. Specifically, the Ovid interface was used to search the following databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) 1946 to Present, Embase 1974 to 2014 and the Web of Science Core Collection.

The general search strategy was (Fluad®) OR (influenza vaccine AND adjuvant) AND (Pediatric), limited to human studies (See Appendix A or details of the search algorithm). All searches were limited to literature published between June 1st, 2004 and June 30th, 2014. The search strategy was applied to all 3 primary electronic databases on July 18th, 2014, yielding 1,529 articles.

Three additional databases were searched: clinicaltrials.gov, CINAHL and Cochrane Library. The general search terms for these databases consisted of "Fluad® OR MF59", with no additional restrictions to maximize yield from these small databases. This search was conducted July 21st, 2014 yielding 232 articles.

To capture a wider breadth of articles, particularly concerning the burden of disease, an additional search was conducted using the following general search strategy: "influenza" and "pediatric" and "Canada", limited to papers published after 2004. This search was applied to the same three primary databases: Medline, EMBASE and Web of Science. Various source of "grey literature" were also searched; these included the databases of the Canadian Agency for Drugs and Technologies in Health (CADTH), PHAC (e.g. FluWatch) and the WHO Tables on the Clinical Evaluation of Vaccines. In addition, forward (citing articles) and backward (cited articles) searching was performed to identify possible relevant articles. This was done by checking Google Scholar, Scopus and the citations of the included studies. Forward and backward searching yielded 1 additional study. One additional published poster was provided by the manufacturer through a project contact at the International Centre for Infectious Disease (ICID).

If possible, email alerts were set in databases to notify the literature review group of newly published citations which met the search strategy criteria set for each database. No relevant literature was identified by email alert. The total number of records identified through bibliographic database searching was 1,761 and 2 records were identified through other sources. After removing duplicates, 1,173 citations were identified for screening (Appendix B).

Eligibility Screening

Two independent reviewers screened all titles and abstracts for relevance based on the following predetermined eligibility criteria: (i) primary research studies, regardless of design, where the vaccine assessed is Fluad®; (ii) the population age range overlaps with the age group of interest (6 to 72 months); and (iii) publication date between June 1st, 2004 and June 30th, 2014. Case reports, case series, and opinion papers were excluded.

Upon applying these criteria, 1,116 records were excluded. Of the remaining 57 articles, 29 were Fluad®-related articles and were retrieved for full-text review. The rest (28) comprised articles on other MF59 adjuvanted influenza vaccines (e.g., the monovalent pandemic H1N1 vaccine).

Articles retrieved for full-text review were only excluded if they were assessed as ineligible by two independent reviewers. Any disagreements were resolved by consulting a third reviewer. Articles were excluded if, after reviewing the full text, they were deemed not to meet the inclusion criteria (outlined above). On this basis, 13 articles were excluded for the following reasons: age group outside range (n=1); intervention not Fluad® (3); no outcome of interest (1) and article was neither primary research nor a systematic review (8). Eight articles were included in the detailed review, of which 7 articles described controlled clinical trials that

compared Fluad® with one or more UTIV comparators and one from a uncontrolled trial that looked at Fluad® in healthy compared to arthritic children. All studies included at least one age group which overlapped with the 6-72 months of age criterion. In addition, several articles (relevant primary research, reviews etc.) were also retained to aid in writing the literature review but were not included in the summary tables (Appendix B).

Quality Assessment of Studies

Articles retained for review were critically appraised independently by two reviewers in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the design-specific criteria outlined in Harris et al.[17] On the basis of the information included in the articles, all included studies were rated “fair” or better and no studies were excluded due to poor quality.

Data Extraction

Two reviewers independently extracted data from the included articles using a common abstraction form designed to capture data for each of the outcomes of interest: vaccine efficacy, measures of immunogenic responses (e.g., seroconversion, seroprotection and geometric mean titre) and safety outcomes (solicited, unsolicited, and serious adverse events). The form also captured factors that might influence study findings such as different vaccine formulations, influenza seasons, participants’ age groups and inclusion criteria. Any disagreements or discrepancies between abstractors were resolved by discussion or by consulting a third reviewer.

FLUAD® IN PAEDIATRIC POPULATION (6-72 MONTHS)

Burden of influenza illness in children aged 6 to 72 months

The burden of disease due to influenza in young children is substantial, although rarely precisely known. Nair et al analyzed data from 43 population-based studies that collectively recruited more than 8 million children younger than 5 years from countries representing all WHO regions.[18] They estimated that about 90 million influenza infections, 20 million cases of influenza-associated acute lower respiratory infection (ALRI) and 1 million cases of severe ALRI occur worldwide each year among children <5 years of age.[18] They also estimated that influenza was responsible for about 13% of all ALRIs and 7% of all severe ALRIs in this age group.

Influenza incidence rates vary from year to year, depending on the circulating strain, population susceptibility and other environmental factors. In developed countries, the pooled incidence rate (95%CI) of influenza episodes was estimated by Nair et al to be around 550 (280-1000) per 10,000 children younger than 5 years per year, whereas the rates of ALRI and severe ALRI due to influenza were around 120 (70-180) and 10 (10-20) per 10,000 person-years, respectively.[18] These rates were approximately 2-3 times higher in developing countries. These figures likely underestimate the true burden of influenza, as most studies were based on passive hospital-based surveillance systems and employed relatively

insensitive rapid assays for influenza detection. The WHO estimates that during interpandemic seasons, 20-30% of children become infected with influenza.[1] In certain populations, e.g., daycare attendees, attack rates may exceed 50%.[19,20]

A child's age is a very important determinant of the risk of influenza infection. Evidence from seroprevalence studies suggests that most children would have been exposed to at least one influenza A virus by age 6.[19] By contrast, only a small percentage (20-30%) of 0-6 year-olds have influenza B virus-specific IgG antibodies,[21] supporting the notion that unvaccinated children accumulate natural immunity to influenza B more slowly than they do to influenza A.[22]

In Canada, and depending on the season (2003/04 through 2011/12), children under 4 years of age comprised between 10 and 33% of all laboratory confirmed influenza cases reported through the sentinel laboratory-based Respiratory Virus Detections Surveillance System (RVDSS), whereas those aged 5-9 years comprised between 5 and 12%. By age group, children under 4 years and children 5-9 years each comprise approximately 5-6% of the Canadian population. In addition to higher infection rates, these figures may also reflect increased utilization of acute care services and higher likelihood of laboratory testing among younger children. During influenza seasons, children under 4 years of age with ILI represent between 3 to 7% of all primary care visits made by patients to sentinel clinicians participating in the national FluWatch influenza surveillance program, reflecting the burden influenza (and other respiratory pathogens) imposes on the healthcare system. However, the high rates of laboratory confirmed influenza in young children observed in the RVDSS data are consistent with observations from active surveillance prospective studies conducted elsewhere.[18,19]

Young age is also an important risk factor for complications, serious illness and hospitalization among those infected with influenza. Generally, children younger than 2 years are at an increased risk of serious influenza illness although older (5-9 years) children are more likely to contract influenza.[1] For instance, in developed countries including Canada, estimates of the rates of hospitalizations attributed to influenza among infants ranged from 10 to over 100 per 10,000.[19,23-25] In one Canadian study, the highest rate of hospitalization due to influenza was among infants 6 to 11 months of age (20 per 10,000 infants per year), a rate that was comparable to the admission rate among 60-65 year-olds.[24] Nevertheless, respiratory syncytial virus and para-influenza infections were still more frequent among hospitalized infants than influenza, even during periods of peak influenza transmission.[24]

Complications of influenza, such as acute otitis media (25-75%), are very common especially among children younger than 2 years old.[19] Influenza can also cause croup and bronchiolitis and exacerbate asthma symptoms. More severe complications include bacterial co-infections, e.g., staphylococcal pneumonia, acute respiratory distress syndrome (ARDS), encephalitis and Guillain-Barre's syndrome.[19,25,26] Generally, rates of specific complications are not precisely known, but it is widely accepted that they are more common among very young children and those with underlying chronic diseases.[10,25,27]

Rates of severe respiratory illness due to influenza tend to decline with increasing age in children.[19] For instance, in the systematic review by Nair et al, the pooled rate of influenza-related severe ALRI was twice as high among infants (20/10,000) compared to all < 5 years-old.[18] In children above 5 years, the rate of hospitalization is only about 5/10,000 and a higher proportion of these children have underlying medical conditions. Over the period from 2003/04 to 2011/12, the number of influenza-associated pediatric hospitalizations, as reported by the Immunization Monitoring Program Active network (IMPACT) from participating Canadian centres ranged from 370 to 948 patients per season. Between 11-23% of all reported pediatric

hospitalizations were among 0-5 month-old infants, 8-32% were among 6-12 month-olds and a further 20 to 27% were reported for 2-4 year-olds. Overall, about 70-75% of all pediatric hospitalizations occurred among children under the age of 5, except during the 2009 pandemic where this age group represented less than 60% of all pediatric hospitalizations.

In the IMPACT data, the majority (60-99%) of pediatric hospitalizations were due to influenza A, except for the 2011/12 season when influenza B was identified in about 60% of pediatric hospitalizations. Consistently (excluding during the 2009 pandemic), about 50% of admitted children had an underlying medical condition. About 10-15% of all children admitted to hospital were also admitted to an Intensive Care Unit.

Excluding the pandemic year, the number of deaths attributed to influenza in Canadian children was small, ranging from 2-6 per season, and representing <0.8% of all children admitted with confirmed influenza-associated illness at participating IMPACT sites. About half of these deaths were among 6-23 month-olds, corresponding to about 1.5% of influenza hospitalizations in this age group. The average case fatality ratio (relative to all laboratory confirmed infection among children) is much smaller (<0.15%) and likely many folds smaller relative to all influenza infections. These figures are consistent with estimates from other developed countries where mortality rates were generally < 1 per 100,000 person-years and the pooled case fatality relative to influenza associated severe ALRI was 0.17% (95%CI 0.08-0,26%).[19] These figures are likely 10-20 fold higher in developing countries.[19]

In a country-wide surveillance study in the United States during the 2003/04 season, Bhat et al identified 153 influenza associated deaths among children. Mortality rates were highest among children < 6 months of age (about 9 per 100,000 children per year) and decreased with increasing age to about 0.11/100,000 among 5-17 year-olds.[26] About 50% of children had one or more underlying chronic conditions, most often respiratory or cardiac conditions. About 40% of fatalities occurred at home, in transit to hospital or in an emergency department, highlighting the sudden and unexpected nature of these deaths.[26] Only 16% of the children who died and had known vaccination status had received at least one dose of influenza vaccine during the 2003/04 season.

Efficacy and Effectiveness

A randomized control trial (Novartis identifier: V70P5) involving children aged 6 to 72 months conducted over two consecutive seasons (2007/08 and 2008/09) in Germany and Finland, was the only study that provided data on Fluad® (henceforth ATIV) efficacy against a disease (non-serological) endpoint (PCR-confirmed influenza).[28] Children (N=4707) were randomized 2:2:1 into those receiving 2 doses, 28 days apart, of either ATIV, an UTIV or a control non-influenza vaccine (a meningococcal C conjugate or encephalitis vaccine). The ATIV and UTIV used contained comparable doses of the WHO-recommended vaccine strains. For children aged 6 to < 36 months, a half dose (0.25mL) of either vaccine was administered, whereas a full dose (0.5mL) was administered for children aged 36 to < 72 months. The three study groups were comparable in demographic characteristics and attrition rates.

The attack rates of PCR-confirmed influenza among the control groups were relatively low in both seasons: 2.5% in 2007/08 and 5.2% in 2008/09. Vaccine efficacy (VE) estimates were calculated for the 2008/09 season which was dominated by a vaccine-matched A/H3N2 strain (90% of all isolates; 10% were lineage-mismatched B strains). VE was not calculated for 2007/08 due to a small case count. In the 2008/09 season, ATIV was 86% (95%CI: 73-92%)

effective (relative to the control non-influenza vaccines) against all strains compared to 40% (11-60%) for UTIV (relative to the control non-influenza vaccines). The efficacy of ATIV relative to UTIV was 76% (55-87%). ATIV had a lower VE (79%) in 6-36 month-olds compared to 92% in children 36 to 72 months of age. The corresponding values for UTIV were 40% and 45%.

VE estimates were very similar when data for both seasons were combined and when detection of vaccine-matched strains was the outcome. Because of the predominance of A/H3N2, the authors noted that no conclusions could be drawn with regard to VE against A/H1N1 or influenza B. Furthermore, UTIV used in 2008/09 was a split-virion product manufactured by GSK Biologicals, as opposed to the subunit UTIV manufactured by Novartis Vaccines that was used in the prior (non-contributory) season. The strain-specific antibody titres of the GSK UTIV formulation were shown to be 48-63% lower among children 6 to 35 months of age than a comparable Sanofi Pasteur formulation in an unrelated study conducted during the 2006/07 season.[30,31]

The European Medicines Agency (EMA) raised concerns regarding trial V70P5 during the regulatory approval process in 2011. Critical and major flaws in good clinical practice (GCP) were identified following an inspection of the sites of the main study.[31] Some of these flaws included:

- insufficient quality assurance system at the laboratory site in Germany,
- reliability of patient data collection (including recording of adverse events and tracking of suspected influenza cases) and data handling, and
- issues with sample storage and transport, including lack of temperature monitoring (some samples may have reached temperatures that resulted in sample degradation).

As evidenced in the product monograph, data from the efficacy trial was also not considered in granting product authorization in Canada. NACI considers the findings from the report of the EMA should be taken into account when assessing the results from the study.

Immunogenicity

In all trials, the European Union (EU) Committee's for Medicinal Products for Human Use (CHMP) licensing criteria (CPMP/BWP/214/96) for interpandemic influenza vaccines (as set for 18-60 years-old adults) were used to benchmark observed immune responses. Regulators in Canada, the US and Europe accept immunologic data (HI antibody titers) as acceptable surrogates for clinical protection, and the same criteria are used for adults and children. An HI titre of ≥1:40 has been recognized as an immunologic correlate that corresponds to a 50% reduction in the risk of contracting influenza in adults (on the basis of a study by Hobson et al). [34] However, evidence is lacking on the HI titre required to confer the same level of protection in children. [35]

Recent evaluation of immunologic correlates of protection in children suggests that higher titers may be necessary to confer the same level of protection as in adults. Using data from the immunogenicity cohort of the V70P5 trial, Black et al estimated that an HI titre of ≥1:40 was associated with a risk reduction of only 22% in previously unvaccinated healthy 6-72 months-old children.[35] A much higher cutoff (1:110) was associated with 50% clinical protection rate, whereas titres of 1:330 and 1:629 were associated with 80% and 90% clinical protection, respectively. Similar to the Hobson study[34], the analysis by Black et al was based on protection against infection with a vaccine matched A/H3N2 strain. It is unclear whether the

findings would be applicable to protection against A/H1N1, B types or mismatched strains. It is also unclear whether these estimates are equally applicable to adjuvanted and unadjuvanted vaccines as there could be significant differences in the avidity of the generated antibodies or other aspects of the immune response due to the presence of the adjuvant. [35] Finally, the estimates were imprecise, with relatively wide confidence intervals, because they were based on a very small number of cases (n=22).

In addition to the abovementioned trial (V70P5),[28] two Phase 2 studies (V70P2[32] and V70P6[33]) assessed the immunogenicity of ATIV compared with UTIV in healthy previously unvaccinated children aged 6-36 months. V70P6 also provided data on children 36-59 months of age. In all three studies, two doses of vaccine were given 28 days apart. Children 6-35 months of age received 0.25mL of vaccine per dose and children 36-72 months of age received 0.5mL per dose. All studies used a hemagglutination inhibition (HI) assay to measure immune response before each dose (Day 1 and Day 29) and approximately 3 weeks after the second dose (Day 50).

Using the standard CHMP immunogenicity criteria set for adults 18-60 years of age, V70P5, V70P2 and V70P6 were consistent in showing that ATIV met at least two CHMP criteria for protection against Influenza A strains after a single dose but a second dose was necessary for a sufficient response to the B strain. Generally, ATIV induced a weaker HI response against B strains compared to A strains. However, ATIV induced a stronger immune response against B strains when compared with UTIVs. Similarly, ATIV induced a stronger response to heterologous A strains than to heterologous B strains, and in both cases, response was more robust than that observed for comparator vaccines.

A similar pattern was seen in a dose- and schedule-finding study that compared adjuvanted and unadjuvanted formulations of both trivalent and quadrivalent influenza vaccines (V70P6).[33] This study was conducted using a factorial design, with varying doses of both HA and the MF59 adjuvant. The study found that the addition of adjuvant conferred a clear increase in Geometric mean titres (GMT) with further small increases with increasing MF59 dose. Children receiving one dose of ATIV, or the quadrivalent equivalent, were well protected against influenza A strains, but few (17%) were seroprotected against B strains by day 29 (just before the second dose). Between 79-97% of children who received two doses of a vaccine that contained either 7.5 or 15µg HA (per strain) and 50% of the adult dose of the MF59 adjuvant were seroprotected against the B strains by day 50. By comparison, UTIV with 7.5 and 15µg of HA, did not meet the adult CHMP criteria for seroprotection for the B strains even after a second dose. The study also found that the addition of a second B strain did not affect the immunogenicity of the vaccine against other strains.

The extension study (V70P2E1[36]) assessed the immunogenicity of a third ("booster") dose of either ATIV or a split virus UTIV given in the following season, one year after the two priming doses given to the children participating in V70P2, who previously received MF59-adjuvanted TIV. In this small trial, both ATIV and UTIV induced 100% seroprotection (HI ≥1:40) against influenza A strains, but only ATIV induced 100% seroprotection against influenza B (compared to 68% for UTIV). Generally, ATIV induced higher GMTs than UTIV especially among younger children.

In a recently published phase 2 trial (V70_34)[37], Zedda et al, applying more stringent criteria of seroprotection (HI ≥1:330), reported a higher seroprotection rate for ATIV (80-92%), compared to UTIV (28-53%), against influenza A strains among healthy 6-36 month-olds receiving two 0.25ml doses four weeks apart. Comparable figures for B/Brisbane were much lower: 40% in

ATIV and 10% in UTIV. In addition, ATIV induced the expansion of CD4+ T cells specific for both homologous and heterologous strains, whereas UTIV induced a significant expansion of CD4+ T cells for homologous strains only. There was however no difference in the cytokine profile of influenza specific CD4+ T cells, which was dominated by the production of IL-2 and TNF-α for both vaccines.

One published poster describing a multi-site clinical trial (V70_29) conducted in Argentina, Australia, Chile, Philippines, and South Africa (n=6100) was provided by Novartis®.[38] The information provided included immunogenicity data comparing children who received a sub-unit type TIV (UTIV-1) or split-virion type TIV (UTIV-2) with children who received ATIV. Using more stringent seroprotection criteria (HI ≥1:330), a higher percentage of participants were seroprotected after a second dose (Day 50) against homologous influenza A/H1N1 strains if they received ATIV (91%) compared to UTIV-1 (56%) and UTIV-2 (61%). Comparable figures were reported for the homologous A/H3N2 (ATIV vs UTIV-1 vs UTIV-2: 95% vs 66% vs 74%) but the corresponding figures were much lower for B/Brisbane (56% vs 28% vs 25%) although still higher for ATIV than either UTIV. In addition, ATIV recipients maintained higher GMTs than UTIV-1 and UTIV-2 recipients against the three homologous strains on Day 209. This study was subsequently published after the literature review was conducted, and it was reported that re-defined non-inferiority criteria were met by ATIV for geometric mean titers (GMTs) and seroconversion rates when compared to UTIV-1 and UTIV-2 at Day 50. ATIV also met the superiority criteria compared to UTIV-1, but not compared to UTIV-2.[39]

Only one study investigated immunogenicity of ATIV in children and adolescents (mean age 9±5 years) with an autoimmune disease, juvenile idiopathic arthritis (JIA).[40] This study compared healthy boys with boys diagnosed with JIA being treated with anti-rheumatic drugs. The results indicate that immunogenicity of ATIV in JIA patients treated with Disease-Modifying Anti-Rheumatic Drugs (methotrexate or sulfasalazine) was not significantly different from that of healthy children of the same age. However, among those who received the TNFα antagonist etanercept alone or in combination with methotrexate, immunogenicity was good against influenza A strains (albeit with lower GMTs), but significantly impaired in the case of influenza B strains compared to children who were not on etanercept.

Safety

Clinical safety data were provided in all identified pediatric ATIV efficacy and immunogenicity trials. In addition, Black et al pooled safety data from several pediatric ATIV trials and other trials an MF95-adjuvanted influenza vaccine was used.[41] No observational studies were found. “Serious” adverse events (AEs) were rare and occurred at a similar rate among the recipients of ATIV and comparator vaccines. However, of the seven studies with safety data, five had fewer than 500 participants and limited power to detect rare but important AEs. There is no post-market experience with ATIV in children; however, there is considerable post-marketing experience with ATIV use in older adults (reviewed in a previous NACI statement[14]).

Across all pediatric ATIV trials, and regardless of age group or comparator vaccine type, additional 10-15% of ATIV recipients experienced solicited local and systemic reactions compared to UTIV recipients. Most reactions were described as “mild to moderate” in severity and self-resolved in 2-3 days. There was no significant difference in the incidence of local AEs following first or second vaccinations. On the other hand, the incidence of systemic AEs was

slightly lower following the second vaccination. Severe reactions were rare (<1%) in all vaccine groups.

Among 3-36 month-olds, the most frequently reported local reactions were: tenderness (range: 18-33% ATIV, 15-26% comparator) and erythema (15-25% ATIV, 11-22% comparator). Severe local reactions including severe ecchymosis, induration, erythema or tenderness, occurred in <1% of subjects regardless of vaccine group. There was no increased incidence of local reactions after a third dose given in the following year in the extension study (V70P2E1). Similar trends were reported for older (>36 months) children, although, as expected, pain at the injection site was the most frequently reported local reaction (36-48% ATIV; 27-35% comparator). Severe local reactions were slightly more frequent (1-3%) in this age group compared to younger children.

Among 3-36 month-olds, the most frequently reported systemic reaction was irritability (21-32% ATIV, 19-26% comparator). Unusual crying and changes in eating habits were also common (about 15-25% and slightly more common among ATIV recipients). Fever (≥38°C) was reported for 5-25% of children, regardless of vaccine group. Body temperature of ≥40°C was reported for <1% of children in V07P5 with similar incidence in each vaccine group. Among older children, the most frequently reported systemic reactions were: malaise (about 15% in all groups) and fatigue (21-33% ATIV, 17-20% comparator). Fever occurred at a comparable rate to that among younger children.

Incidence of unsolicited AEs was comparable between ATIV and active control vaccine groups, with most reported events representing the usual common childhood illnesses (e.g., cough, otitis media, rhinitis, URTI, diarrhea etc.). Incidence of unsolicited AEs deemed to be possibly or probably related to vaccination (e.g., fever, rash, etc.) was also similar (collectively about 10% within 3 weeks of vaccine administration in each vaccine group).

Severe AEs (AEs that prevent a person from performing normal daily activities) were infrequent in both vaccine groups and were very rarely (<1%) linked to vaccine administration. These include very few (1-2 each) cases of cyanosis, abnormal behaviour, asthma, autoimmune thyroiditis, ITP and epilepsy. In particular, there was no evidence of increased incidence of febrile or other convulsions in the ATIV group. One death occurred in the comparator group of trial V70P6 and was not related to vaccine administration.

Nolan et al provided safety data from the abovementioned multi-site trial (V70_29).[38,39] Solicited AEs possibly related to vaccination occurred with similar frequency in all three vaccine groups (5%-7% of subjects), with events occurring slightly more frequently following the first vaccination than the second. Rates of unsolicited AEs were very low and similar in the ATIV and subunit and split UTIV groups (<1% of subjects), and rates of serious AEs (fatal or life-threatening AEs or AEs resulting in hospitalization or prolongation of hospitalization or major disability) were similar across all three vaccine group (4-5% of subjects in each group). Rates of fever (≥38°C) in 24 to <72 month-olds were higher among ATIV recipients (25%) than UTIV recipients (13%), but were similar for all three vaccine groups in the younger age group 6 to <24 month-olds (19%-24%).

Only one study provided safety data on ATIV use in children with an underlying autoimmune disease.[40] Local reactions occurred in about 40% of the subjects, and systemic reactions in about 30%, with no significant difference between healthy children (n=30) and patients with juvenile idiopathic arthritis (JIA) (n=60). One serious but transient adverse event (fever and coxalgia) was reported in a 6-year-old JIA patient treated with Disease-Modifying Anti-

Rheumatic Drugs but resolved spontaneously. A follow up 3 months after vaccination determined that none of the JIA patients showed any significant clinical or laboratory changes in disease activity.

One study (V70P6) employed a dose-ranging factorial design and included both adjuvanted and unadjuvanted versions of seasonal TIV and QIV administered to children 6-36 months old.[33] Overall, there was no indication of an increasing risk of AEs associated with increasing MF59 dose, antigen dose, or the addition of a second B strain. However, reactogenicity of 15µg formulations were slightly higher for both adjuvanted and unadjuvanted vaccines compared to the corresponding 7.5µg formulations.

Evidence Gaps

Evidence on efficacy and effectiveness of ATIV in children aged 6 to <72 months is limited to a single clinical trial (V70P5) with concerns around the reliability of the results.

There is limited but consistent evidence that ATIV is more immunogenic than comparable UTIVs against influenza A types. However, the CHMP standard vaccine licensing criteria were used to benchmark vaccine immunogenicity in all these trials, and it is unclear whether these criteria are generalizable to young children, and the HI titre cutoff predictive of clinical risk reduction among children remains unknown. It is also unclear whether these criteria are applicable to protection against influenza B strains.

Although there is reasonable evidence regarding safety of the vaccine, no information is available on the long-term effects of repeated ATIV administration, and evidence on the safety (and effectiveness) among children with autoimmune diseases, cancer, organ transplant, or chronic medical conditions is limited.

No studies were found directly comparing trivalent ATIV to QIV or LAIV, which are the most relevant vaccine comparators for children <2 years of age and ≥ 2 years of age respectively. In most trials, children aged 6-36 months receive half a dose (0.25mL) as per regulatory guidelines. In Canada, the standard of care is a full dose (0.5mL) of unadjuvanted inactivated vaccine for all age groups including children 6 to <36 months of age, based on evidence of improved immunogenicity without increase in reactogenicity.[5] One study using a dose-ranging factorial design with adjuvanted and unadjuvanted versions of seasonal TIV and QIV was identified, but a comparison of ATIV and full dose QIV was not the primary objective of the study and the data were not grouped appropriately for such a comparison. Further trials that directly compare trivalent 0.5mL ATIV to 0.5mL dose of trivalent or quadrivalent influenza vaccine in children 6 to <36 months as is recommended in Canada would be beneficial.

All the identified primary clinical trials were sponsored and conducted by the manufacturer with the aim of obtaining licensure for pediatric use. No data provided by independent researchers were available for review.

DISCUSSION/SUMMARY

Information on the efficacy of ATIV versus UTIV is only available from a single trial. The bulk of the data was obtained during one mild season that was dominated by A/H3N2. The comparator vaccine induced a poorer immune response compared to equivalent UTIVs. There were also concerns raised by an EMA inspection about the quality of laboratory testing and validity of ascertainment of influenza cases especially at the main German site.

There is limited but consistent evidence that ATIV is more immunogenic than comparable UTIVs against influenza A types. In particular, a single dose of ATIV is more immunogenic than a single dose of UTIV. However, two doses of ATIV are still necessary to achieve a satisfactory immune response against influenza B. ATIV was not compared directly to LAIV in children ≥2 years of age, and it is unclear whether ATIV would generate a smaller, greater or equivalent immunogenic response than LAIV. Clinical trials comparing the immunogenicity and efficacy of a single- and two-dose regimes of ATIV and LAIV are needed.

It is unclear whether the stronger humoral immune response induced by ATIV translates into an appreciable advantage over UTIVs in terms of preventing influenza or its complications. Evidence is growing that the conventional CHMP adult immunogenicity criteria may not be applicable to young children, although it is far from clear what alternative criteria should be used for children.

Safety data in children are consistent with what is known about ATIV safety profile in adults. ATIV is more reactogenic than UTIV, with ATIV recipients experiencing 10-15% more solicited local and systemic reactions compared to UTIV recipients. However, most reactions were mild and resolved quickly. Severe reactions were rare, but all reviewed studies were too small to detect clinically significant but rare adverse events. Like all influenza vaccines, there are few data on safety and immunogenicity of ATIV in children with immunodeficiency and other chronic illnesses.

Taken together, ATIV is likely both more immunogenic and more reactogenic than UTIV among children 6-72 months of age. There are insufficient data to assess whether ATIV is more effective than UTIV or LAIV in practice or to make an informed risk-benefit analysis. More research is needed to inform these issues.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
AEs:	Adverse events
AQIV:	Adjuvanted quadrivalent influenza vaccine
ATIV:	Adjuvanted trivalent influenza vaccine
CHMP:	EU Committee for Medicinal Products for Human Use
CI:	Confidence Interval
DMARDS:	Disease-modifying anti-rheumatic drugs
GMT:	Geometric mean titre
HI:	Hemagglutination inhibition
IM:	Intramuscular
JIA:	Juvenile Idiopathic Arthritis
QIV:	Quadrivalent influenza vaccine
SAEs:	Serious adverse events
SD:	Standard Deviation
UTIV:	Unadjuvanted trivalent influenza vaccine

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Appendix A: Search Strategy

Table 1. Literature review search strategy for Medline (OVID) and search results.

#	Search terms	Search results as of July 18th 2014
1	(fluad* or MF59* or MF 59*).mp	402
2	exp Influenza Vaccines/ or influenza vaccin*.mp. or ((influenza or flu*) adj5 (vaccin* or immuni* or innoculat*)).mp.	23882
3	influenza.mp. or exp Influenza, Human/	80095
4	exp Vaccines/ or vaccin*.mp. or exp Viral Vaccines/ or immuni*.mp. or Vaccines, Subunit/ or Vaccines, Synthetic/	515705
5	3 and 4	29154
6	exp Adjuvants, Immunologic/ or adjuvant*.mp. or squalene*.mp. or Polysorbate*.mp. or Emulsion*.mp.	281852
7	(2 or 5) and 6	2791
8	1 or 7	2950
9[a]	(Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school* or prematur* or preterm*).mp.	3598447
10	8 and 9	571
11	Limit 10 to English	506
12	Limit 10 to French	4
13	11 or 12	510

[a] Leclercq, E., et al. (2013). *Validation of search filters for identifying pediatric studies in PubMed.* J Pediatr 162(3): 629-634.e622.

Table 2. Literature review search strategy for Embase (OVID) and search results.

#	Search terms	Search results as of July 18th 2014
1	(fluad* or MF59* or MF 59*).mp.	847
2	exp influenza vaccination/ or exp influenza vaccine/ or ((influenza or flu) adj5 (vaccin* or immuni* or innoculat*)).mp.	36448
3	influenza.mp.	107396
4	exp vaccine/ or vaccin*.mp. or exp vaccination/ or exp immunity/ or exp vaccination/ or exp immunization/ or immuni*.mp.	2071749
5	3 and 4	53534
6	exp adjuvant/ or adjuvant*.mp. or exp squalene/ or exp squalene derivative/ or squalene*.mp. or exp polysorbate/ or exp emulsifying agent/ or polysorbate*.mp. or exp lipid emulsion/ or exp emulsion/ or emuls*.mp.	271224
7	(2 or 5) and 6	3642
8	1 or 7	4013
9	(Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or school* or prematur* or preterm* or preschool*).mp.	3666539
10	8 and 9	606
11	Limit 10 to English and French Language	565
12	Limit 10 to French	6
13	11 or 12	570

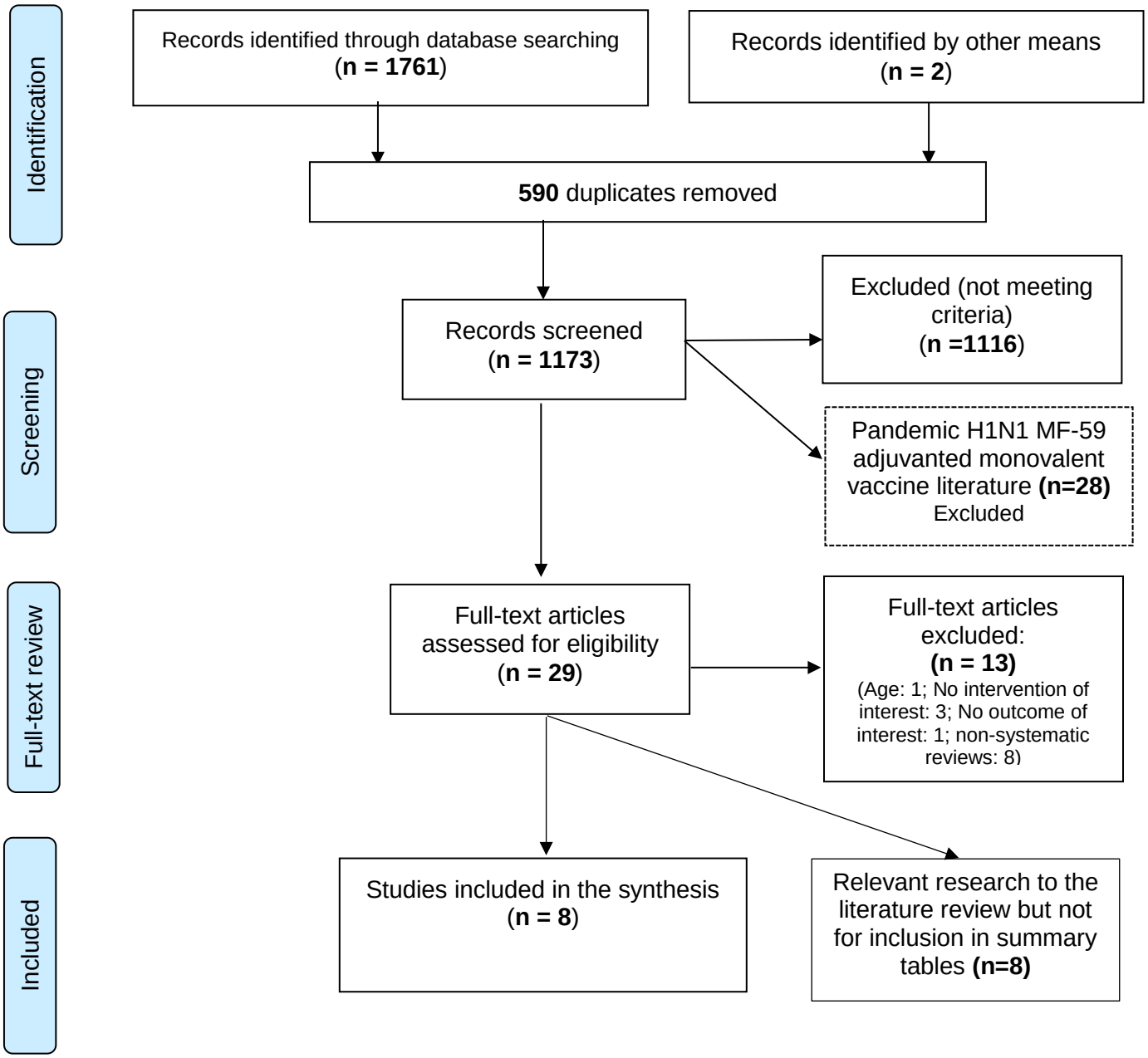
Table 3. Literature review search strategy for Web of Science and search results.

#	Search terms	Search results as of July 18th 2014
1	TS=(fluad* or MF59*)	513
2	TS=((influenza vaccin*) OR ((infuenza* or flu*) near/5 (vaccin* or immuni* or innoculat*)))	25630
3	TS=influenza*	94795
4	TS=(vaccin* or immuni*)	420579
5	#4 AND #3	31725
6	#5 OR #2	33889
7	TS=(adjuvant* or squalene* or polysorbate* or emuls*)	194102
8	#7 AND #6	2895
9	#8 OR #1	3028
10	TS=(Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or school* or prematur* or preterm* or preschool*)	2682208
11	#10 AND #9	457
12	#11 limited to English	443
13	#11 limited to French	6
14	#12 or #13	449

Table 4. Search results for clinicaltrials.gov, CINAHL and Cochrane Library

Database	Search Term(s)	Search results as of July 21st 2014
clinicaltrials.gov	“Fluad OR mf59”	89
CINAHL	“fluad OR mf 59”	32
Cochrane Library	“fluad” as well as “mf59”	111

Appendix B: Attrition Flow diagram



Appendix C: Summary of evidence related to the efficacy/effectiveness of Fluad in children 6 to 72 months of age

Study Details					*Summary*
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings Using Text or Data***	***Quality and level of evidence***
Timo Vesikari, Markus Knuf et al. Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children. New England Journal of Medicine (2011) 365:1406-16 Study ID#: **V70P5** Trial #: NCT00644059	**Name**: Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines **Admin:** 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Comparator Vaccines:** **Study Year 1 (07/08) TIV:** Agrippal® S1, non-adjuvanted subunit TIV **Manufacturer:** Novartis Vaccines **Details**: 15ug HA/strain in 0.5mL of: A/Solomon Islands/3/2006 (H1N1); A/Wisconsin/67/2005 (H3N2); B/Malaysia/2506/2004 **Study Year 2 TIV (08/09):** Influsplit SSW®, non-adjuvanted split-virion TIV **Manufacturer**: GlaxoSmithKline Biologicals **Details**: 15ug HA/strain in 0.5mL A/Brisbane/59/2007 (H1N1); A/Brisbane/10/2007 (H3N2);	Phase III, Multicenter, randomized controlled trial	**Age**: 6 to <72 months **Countries**: Germany Finland **Number of participants**: **2007/08:** Germany: 654 **2008/09:** Germany: 2104 Finland: 1949 **Inclusion Criteria:** Healthy children who have not previously received influenza vaccine and had no contraindications to vaccination.	**Outcome:** Efficacy of ATIV, TIV, and control (non-influenza) vaccines against PCR-confirmed influenza over two seasons: 2007–2008 and 2008–2009 **Efficacy against all strains** # of confirmed influenza cases/# participants; % vaccine efficacy (95% CI) Age 6 to <72 months ATIV vs. control: 13/1937 vs. 47/993; 86 (74 to 93) UTIV vs. control:50/1772 vs. 47/993; 43 (15 to 61) ATIV vs. UTIV: 13/1937 vs. 50/1772; 75 (55 to 87) Age 36 to <72 months ATIV vs. control:4/834 vs. 25/427; 92 (77 to 97) UTIV vs. control:25/777 vs. 25/427; 45 (6 to 68) ATIV vs. UTIV: 4/834 vs. 25/777; 86 (59 to 95) Age 6 to <36 months ATIV vs. control: 9/1103 vs. 22/566; 79 (55 to 90) UTIV vs. control: 25/995 vs. 22/566; 40 (−6 to 66) ATIV vs. UTIV: 9/1103 vs. 25/995; 64 (23	I-Fair *Note: This grading does not take into considerati on the issues identified by the European Medicines Agency with the execution of the clinical trial.*

Study Details					*Summary*
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings Using Text or Data***	***Quality and level of evidence***
	B/Florida/4/2006 **Placebo vaccines:** **Name:** Menjugate®, meningococcal C conjugate vaccine **Admin:** 2 doses, IM **Dose:** Age 6 to < 12: 0.25mL **Manufacturer:** Novartis Vaccines **Name:** Encepur® Children, tick borne encephalitis vaccine **Admin:** 2 doses, IM **Dose:** Age 12 to < 72 months: 0.5mL **Manufacturer:** Novartis Vaccines			to 83) **Efficacy against vaccine-matched strains** Age 6 to <72 months ATIV vs. control: 9/1937 vs. 41/993; 89 (78 to 95) UTIV vs. control: 44/1772 vs. 41/993; 45 (16 to 64) ATIV vs. UTIV: 9/1937 vs. 44/1772; 80 (59 to 90) Age 36 to <72 months ATIV vs. control: 2/834 vs. 22/427; 96 (81 to 99) UTIV vs. control: 22/777 vs. 22/427; 48 (8 to 71) ATIV vs. UTIV: 2/834 vs. 22/777; 91 (63 to 98) Age 6 to <36 months ATIV vs. control: 7/1103 vs. 19/566; 81 (49 to 93) UTIV vs. control: 22/995 vs. 19/566; 41 (−9 to 68) ATIV vs. UTIV: 7/1103 vs. 22/995; 68 (27 to 86)	

Abbreviations:
CI: Confidence Interval
DMARDS: Disease-modifying anti-rheumatic drugs
IM: Intramuscular
SD: Standard Deviation
TIV: Adjuvanted trivalent influenza vaccine
UTIV: Unadjuvanted trivalent influenza vaccine

Appendix D: Summary of evidence related to the immunogenicity of Fluad in children 6 to 72 months of age

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Della Cioppa G, Vesikari T et al. Trivalent and quadrivalent MF59®-adjuvanted influenza vaccine in young children: A dose- and schedule-finding study Vaccine (2011) 29: 8696-8704 Study ID#: **V70P6** ClinicalTrials.gov Identifier: NCT00848887	**Name**: Egg derived sub-unit ATIV and AQIV **Manufacturer**: Novartis Vaccines and Diagnostics **Other vaccine**: split-virion TIV **Manufacturer**: Sanofi Pasteur **Admin**: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL 17 (A-P) study groups defined by factorial combinations of 7.5µg or 15µg doses of each TIV strain and 0%, 12.5%, 25%, 50%, or 100% of the MF59 adjuvant dose. In the QIV groups, 7.5µg or 15µg of a second influenza B strain were added. Groups A–N received 2 doses 4 weeks apart, on Days 1 and 29, whereas groups O and P (100% MF59) received 1 dose on Day 1 only.	Observer blind, randomized, multicenter, dose-ranging factorial design clinical trial	**Age**: 6 to < 36 months **Mean (SD)**: 16.8 (8.5) months **Sex** (% male) =50.5 **Countries**: Finland and Belgium **Number of participants**: 410 enrolled. **Immunogenicity analyses on:** 395 at baseline 322 at day 29 282 at day 50 **Inclusion Criteria:** Healthy children, no influenza vaccine or infection within 6 months of enrollment.	**Outcome:** Antibody response measured by HIA on Day 29 and Day 50. -Prevaccination: low levels of antibodies against Flu A, 1 dose of any adjuvanted formulation was non-inferior to 2 doses of the unadjuvanted comparator. For B strains only 50% or 100% MF59 were non-inferior after 1 dose. -After 2 doses, all 3 CHMP criteria were met for the 3 TIV strains by all adjuvanted formulations. None of the unadjuvanted formulations met all CHMP criteria after either first or second vaccination. - The addition of a second B strain did not significantly impact the antibody responses against other strains. - Linear regression analysis (data was not shown): higher MF59 dose was associated with higher antibody titre and response was consistently greater for the 15µg formulation compared to the 7.5µg formulations. However, increments were small above 25% MF59 formulation. -Authors' conclusion: "The combination of the 7.5- µg antigen and 50% MF59 appears	I-Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
	Group Q: comparator marketed unadjuvanted TIV (Vaxigrip pediatric) **Season**: 2009-2010, NH **Details**: 15ug HA/strain in 0.5mL **TIV:** A/Brisbane/59/2007 (A/H1N1) A/Brisbane/10/2007 (A/H3N2) B/Florida/4/2006 (B/Yamagata lineage) **QIV = *TIV + a second B strain:*** B/Malaysia/2506/2004 (B/Victoria lineage)			to offer the best balance between significantly improved immunogenicity and good tolerability".	
Timo Vesikari, Markus Knuf et al. Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children. New England Journal of Medicine (2011) 365:1406-16 Study ID#: **V70P5** Trial #: NCT00644059	**Name**: Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines **Comparator Vaccines:** **Study Year 1 TIV:** Agrippal® S1, non-adjuvanted subunit TIV **Manufacturer:** Novartis Vaccines **Admin:** 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Season**: 2007–2008, NH **Details**: 15ug HA/strain in 0.5mL A/Solomon Islands/3/2006	Phase III, Multicenter, randomized controlled trial	**Age**: 6 to <72 months **Countries**: Germany Finland **Number of participants**: 783 children completed the study and were included in the immunogenicity analysis: 319 in ATIV group, 316 in TIV group, 158 in placebo group **Inclusion Criteria:** Healthy children who	**Outcome:** Antibody response measured by HIA on Day 29 and Day 50. **% seroprotected (≥40) for ATIV vs TIV, 6 to <36 & 36 to <72 months:** Homologous A/H1N1 Day 29: 92 vs 20 & 100 vs 63 Day 50: 100 vs 38 & 100 vs 80 Day 181: 98 vs 25 & 98 vs 75 Homologous A/H3N2 Day 29: 95 vs 12 & 97 vs 60 Day 50: 100 vs 45 & 98 vs 88 Day 181: 100 vs 45 & 98 vs 88 Homologous B virus Day 29: 10 vs 10 & 45 vs 40 Day 50: 88 vs 19 & 99 vs 60	I Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
	(H1N1); A/Wisconsin/67/2005 (H3N2); B/Malaysia/2506/2004 **Study Year 2 TIV:** Influsplit SSW®, non-adjuvanted split-virion TIV **Manufacturer**: GlaxoSmithKline Biologicals **Admin:** 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Season:** 2008-2009, NH **Details**: 15ug HA/strain in 0.5mL A/Brisbane/59/2007 (H1N1) A/Brisbane/10/2007 (H3N2) B/Florida/4/2006 **Placebo Control vaccines:** **Name:** Menjugate®, meningococcal C conjugate vaccine Admin: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 12 months: 0.25mL **Manufacturer:** Novartis Vaccines **Name:** Encepur® Children, tick borne encephalitis vaccine **Admin:** 2 doses, 28 days apart,		had not previously received influenza vaccine and had no contraindications to vaccination	Day 181: 40 vs 13 & 64 vs 33 - % seroprotected (≥40) against heterologous H1N1 and H3N2 after 2 doses of ATIV was >95%. - % seroprotected (≥40) against mismatched B strain after 2 doses of ATIV was <15%.	

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
	IM **Dose:** Age 12 < 72 months: 0.5mL **Manufacturer:** Novartis Vaccines				
Nolen T, Bravo L, Ceballos A, et al. Enhanced and Persistent Immune Response Against Homologous and Heterologous Strains Elicited by an MF59-Adjuvanted Influenza Vaccine in Infants and Young Children. (Published Poster) (2013) Title in Clinicaltrials.gov: Safety, Tolerability, and Immunogenicity of the Adjuvanted Trivalent Subunit Influenza Vaccine and the Non-Adjuvanted Trivalent Subunit Influenza Vaccine Compared to the Non-Adjuvanted	**Name:** Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines & Diagnostics **Comparator TIV-1:** Agriflu®, non-adjuvanted, sub-unit TIV **Manufacturer** Novartis Vaccines & Diagnostics, Siena, Italy **Comparator TIV-2:** Fluzone®, non-adjuvanted, split particle TIV **Manufacturer** Sanofi Pasteur, Inc. **Admin**: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Season:** 2011-2012, SH **Details:**15ug HA/strain **Homologous strains**: A/California/7/2009 (H1N1)-like; A/Perth/16/2009 (H3N2)-like; B/Brisbane/60/2008-like	Phase III, observer blind, randomized multi-center clinical trial	**Age**: 6 to < 72 months **Mean (SD)**:33.7 (18.1) **Countries**: Argentina (8), Australia (5), Chile (2), Philippines (12) and South Africa (5). **Number of participants**: 6100 **Inclusion Criteria:** Healthy children.	**Outcome:** Antibody response measured by HIA on Day 29, Day 50 and Day 209. **% seroprotected on Day 29 (1:40)** **H1N1 H3N2 B** **ATIV** 90 99 69 **TIV-1** 58 94 46 **TIV-2** 55 95 48 **% seroprotected on Day 50:** **≥1:40 ≥1:110 ≥1:330** **A (H1N1)** ATIV 99 99 91 TIV-1 88 82 56 TIV-2 91 86 61 **A (H3N2)** ATIV 100 99 95 TIV-1 99 94 66 TIV-2 100 97 74 **B** ATIV 99 94 56 TIV-1 86 56 28 TIV-2 89 62 25 **Ratio of GMTs** **ATIV:TIV1 ATIV:TIV 2** **A (H1N1)**	I Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Trivalent Split Influenza Vaccine in Children 6 to < 72 Months of Age. Study ID#: **V70_29** Trial #: NCT01346592	**Heterologous strains:** A/New Jersey/8/1976 (H1N1) A/Uruguay/716/2007 (H3N2) B/Malaysia/2506/2004			Day 1 1.06 1.17 Day 50 **3.2** **2.44** **A (H3N2)** Day 1 0.92 0.96 Day 50 **2.38** **1.89** **B Strain** Day 1 0.98 0.97 Day 50 **3.14** **3.07**	
Nolan T, Bravo L, Ceballos A, et al. Enhanced and persistent immune response against homologous and heterologous strains elicited by a MF59®-adjuvanted influenza vaccine in infants and young children. Vaccine. 2014;32(46):6146-56. Study ID#: **V70_29** Trial #: NCT01346592	**Name:** Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines & Diagnostics **Comparator TIV-1:** Agriflu®, non-adjuvanted, sub-unit TIV **Manufacturer** Novartis Vaccines & Diagnostics, Siena, Italy **Comparator TIV-2:** Fluzone®, non-adjuvanted, split particle TIV **Manufacturer** Sanofi Pasteur, Inc. **Admin**: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Season:** 2011-2012, SH	Phase III, observer blind, randomized multi-center clinical trial	**Age**: 6 to < 72 months **Mean age in months (SD)**: ATIV: 37.1 (18.6) TIV-1: 30.2 (16.9) TIV-2: 30.0 (16.9) **Countries**: Argentina (8), Australia (5), Chile (2), Philippines (12) and South Africa (5). **Total participants**: 6104 Participants for immunogenicity: 2655 Participants for safety:	**Immunogenicity** **Outcome:** Antibody response measured by HIA on Day 29, Day 50 and Day 209. **% seroconverted on Day 50:** (HI titers ≥40 seronegative at baseline, or 4-fold increase if seropositive at baseline) **GMT ratios** **ATIV:TIV1** **ATIV:TIV2** **A (H1N1)** Day 1 1.07 (.87, 1.30) 1.18 (.97, 1.44) Day 29 **3.82 (3.14, 4.64)** **4.07 (3.34, 4.95)** Day 50 **3.21 (2.79, 3.71)** **2.38 (2.07, 2.75)** Day **2.58 (2.19,** **2.84 (2.41,**	I Good

	ATIV	TIV-1	TIV-2
A (H1N1)	95.5	77.8	85.1
A (H3N2)	98.1	92.5	95.6
B	98.1	79.3	85.4

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
	Details:15ug HA/strain **Homologous strains**: A/California/7/2009 (H1N1)-like; A/Perth/16/2009 (H3N2)-like; B/Brisbane/60/2008-like **Heterologous strains:** A/New Jersey/8/1976 (H1N1) A/Uruguay/716/2007 (H3N2) B/Malaysia/2506/2004		6100 **Inclusion Criteria:** Healthy children.	209 **3.04)** **3.34)** **A (H3N2)** Day 1 0.95 (0.78, 1.16) 0.97 (0.80, 1.19) Day 29 **2.40 (2.15, 2.68)** **1.95 (1.74, 2.18)** Day 50 **2.40 (2.19, 2.62)** **1.88 (1.72, 2.06)** Day 209 **1.91 (1.69, 2.16)** **1.67 (1.48, 1.89)** **B Strain** Day 1 0.99 (0.88, 1.11) 0.97 (0.87, 1.09) Day 29 **1.95 (1.65, 2.29)** **2.03 (1.73, 2.39)** Day 50 **3.08 (2.73, 3.47)** **2.93 (2.60, 3.30)** Day 209 **2.05 (1.81, 2.32)** **2.17 (1.92, 2.46)**	
Zedda L, Forleo-Neto E, Vertruyen A et al. Dissecting the Immune-Response to MF59®-Adjuvanted and Non-Adjuvanted Seasonal Influenza Vaccines in Children Less Than Three Years of Age. *Pediatric Infectious Disease, 2014 (in press).*	**Name:** MF59®-Adjuvanted, trivalent inactivated influenza vaccine (ATIV) **Comparator Vaccine:** trivalent inactivated influenza vaccine (TIV) **Both Vaccines:** **Manufacturer:** Novartis Vaccines **Admin:** IM, 28 days apart **Dose:** 2 doses of 0.25 mL, **Details:** 7.5ug HA/strain A/California/7/2009 (H1N1)	Phase II, randomized, multicenter clinical trial	**Age:** 6 to < 36 months **Mean Age:** TIV group: 21.4 months ATIV group: 20.2 months **Sex (% male):** TIV group: 66% ATIV group: 53% **Country:** Siena, Italy **Number of**	**Outcome:** Antibody response measured by HIA on Day 50. **% seroprotected at Day 50** ≥ 1:40 (U A) ≥ 1:110 (U A) ≥ 1:330 (U A) Homologous A/H1N1 93 100 80 96 53 80 A/H3N2 97 100 80 100 23 92 B 57 100 33 68 10 40 Heterologous A/H3N2 10 32 3 8 0 0	I Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Study ID#: **V70_34** Trial #: NCT01342796	A/Perth/16/2009 (H3N2) B/Brisbane/60/2008		**participants:** 84 TIV group: n= 41 ATIV group: n = 43 **Inclusion criteria:** Healthy children who had not previously received influenza vaccine. **Exclusion criteria:** Impairment of the immune system, any serious medical condition or recent infectious disease, immunization with licensed vaccines within 2 weeks (for inactivated vaccines) or 4 weeks (for live vaccines) or any other agent within 30 days prior to enrollment, any history of hypersensitivity to any component of the study vaccine.	B 27 68 0 24 0 0 **Ratio of GMTs (Day 50/Day 1)** UTIV vs ATIV (95% CI) Homologous A/H1N1 10(5.9-17) vs 41(23-74) A/H3N2 35(24-51) vs 199(130-303) B/Brisbane 5.6(3.8-8.29) vs 34(22-52) Heterologous A/H3N2 1.4 (0.9-2.1) vs 3.35 (2.11-5.3) B/Malaysia 2.3 (1.4-3.7) vs 6.49 (3.8-11)	

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Vesikari T, Pellegrini M, Karvonen A, et al. Enhanced Immunogenicity of Seasonal Influenza Vaccines in Young Children Using MF59 Adjuvant. Pediatric Infectious Disease Journal (2009) 28.7: 563-571. Study ID#: **V70P2** Trial #: NCT00408395	**Name:** Fluad®**,** MF59-adjuvanted subunit TIV **Manufacturer:** Novartis **Comparator vaccine:** Vaxigrip®, non-adjuvanted, split-virion TIV **Manufacturer:** Sanofi Pasteur **Admin:** 2 doses, 28 days apart, IM, booster dose approximately 1 year after the Dose 1 **Dose:** Age 6 to <36 months: 0.25mL Age >36 months: 0.5mL **Details**: 9.75mg of MF59 per 0.5mL and 15µg of HA/strain: A/New Caledonia/20/99 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 A/H1N1 changed for booster to A/Solomon Islands/3/2006 **Season:** Dose 1 and 2: 2006/2007, NH Booster dose: 2007–2008, NH Note: see Vesikari, Groth et al study for details on extension study with booster (Dose 3) results.	Phase II, observer-blind, randomized, multicenter clinical trial	**Age:** 6 to <36 months **Mean Age (SD):** ATIV: 20.8 (8.6) months TIV group: 21.2 (8.9) months **Country:** Finland **Number of participants:** 222: ATIV: n=104 TIV: n=118 **Inclusion criteria:** Healthy children. **Exclusion Criteria:** Known allergy to any vaccine component, known or suspected neurologic reactions following influenza vaccination, any acute infectious or respiratory disease requiring treatment up to 30 days before the study or lab-confirmed influenza disease in the previous 6 months.	**Outcome:** Antibody response measured by HIA on Day 50. **% seroprotected (≥40) at Day 50** ATIV vs. UTIV A/H1N1: 100 (97-100) vs. 86 (79-92) A/H3N2: 100 (97-100) vs. 99 (95-100) B: 99 (95-100) vs. 33 (25-42) **Ratio of GMTs, Day 50/Day1 (95CI):** A/H1N1: 33 (28-38) vs. 14 (12-17) A H3N2: 61 (50-75) vs. 22 (18-27) B: 19 (16-23) vs. 4.0 (3.4-4.6)	I Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Vesikari T, Groth N, Karvonen A, Borkowski A, Pellegrini M. MF59-adjuvanted influenza vaccine (FLUAD) in children: safety and immunogenicity following a second year seasonal vaccination. Vaccine (2009) 27:6291-6295. Study ID#: **V70P2E1** Trial #: NCT00644540	**Name:** Fluad®, MF59-adjuvanted, subunit vaccine **Manufacturer:** Novartis **Admin:** 1 dose, IM, booster **Dose:** Age < 36 months: 0.25mL Age ≥ 36 months: 0.5mL **Season:** 2007/08 NH **Details:** 15ug/strain A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 **Comparator Vaccine:** **Name:** Vaxigrip®, split vaccine **Manufacturer:** Sanofi Pasteur **Admin:** 1 dose, IM, booster **Dose:** Age <36 months: 0.25mL Age ≥36 months: 0.5mL **Season:** 2007/08 NH **Details:** 15ug/strain A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	Observer-blind, extension study to V70P2	**Age:** 16 to <48 months **Mean Age (SD):** ATIV group: 33.5 (8.8) months TIV group: 33.9 (8.1) months **Sex (% female):** Sub/MF59:44% Split:46% **Country:** Finland **Number of participants:** 81 ATIV: n= 41 TIV: n= 40 **Inclusion criteria:** Children primed (2-dose) with FLUAD® or Vaxigrip® (2006/07 NH) in V70P2.	**Outcome:** Antibody response measured by HIA on Day 22. **% seroprotected (≥40) at Day 1** ATIV vs. UTIV A/H1N1: 15 (6- 29) vs 5 (1- 17) A/H3N2: 88 (74- 96) vs 40 (25- 57) B: 10 (3–23) vs 0 (0- 9) **% seroprotected (≥40) at Day 22** A/H1N1: 100 (91-100) vs. 100 (91-100) A/H3N2: 100 (91-100) vs. 100 (91-100) B: 100 (91-100) vs. 68 (51-81) **Ratio of GMTs, Day 22/Day1 (95CI)** A/H1N1: 91 (59- 140) vs 52 (35- 79) A/H3N2: 17 (12- 24) vs 12 (8.1- 18) B: 18(14- 24) vs 8.14 (5.7- 12)	II-1 Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Dell'era L, Corona F, Daleno C et al. Immunogenicity, safety and tolerability of MF59-adjuvanted seasonal influenza vaccine in children with juvenile idiopathic arthritis. Vaccine (2012) 30:93640.	**Name:** Fluad, MF59-adjuvanted seasonal influenza vaccine **Manufacturer:** Novartis **Season**: 2010-2011, NH **Admin:** 1 dose, IM **Dose:** 0.5mL **Details:** 15 ug HA /strain A/California/7/2009 H1N1-like virus; A/Perth/16/2009 H3N2-like virus; B/Brisbane/60/2008-like virus; **No comparator.**	Non-randomized non-controlled clinical trial of children and adolescents comparing JIA patients on DMARD (Group A) with JIA patients on etanercept (Group B) and healthy controls (Group C)	**Mean Age (SD):** Group A: 8.43 (4.55) Group B: 9.50 (5.69) Group C: 9.11 (5.01) **Sex (%Males):** Group A: 46.7% Group B: 53.3% Group C: 50.0% **Country:** Italy **Number of participants:** 90 Group A: n=30 Group B: n=30 Group C: n=30 **Inclusion criteria:** Children/adolescents with stable JIA treated with DMARDs or etanercept. JIA patients had been receiving the same drug treatment for at least 6 months and none of them had received corticosteroids for at least 1 year.	**Outcome:** Antibody response measured by HIA on Day 28 and Day 90. Group A vs Group B vs Group C **% seroprotected (≥40) at Day 28** A/H1N1: 100 vs 100 vs 100 A/H3N2: 100 vs 100 vs 100 B: 83 vs 30 vs 93 **% seroprotected (≥40) at Day 90** A/H1N1: 100 vs 96.7 vs 100 A/H3N2: 100 vs 96.7 vs 100 B: 83.3 vs 10.0 vs 90.0 **Ratio of GMTs (Day 28/Day 1)** A/H1N1: 32 vs 16 vs 34 A/H3N2: 29 vs 20 vs 24 B: 16 vs 10 vs 13 **Ratio of GMTs (Day 90/Day 1)** A/H1N1: 19 vs 10 vs 27 A/H3N2: 17 vs 8 vs 15 B: 14 vs 6 vs 12	II-1 Fair

Appendix E: Summary of evidence related to the safety of Fluad in children 6 to 72 months of age

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Della Cioppa G, Vesikari T et al. Trivalent and quadrivalent MF59®-adjuvanted influenza vaccine in young children: A dose- and schedule-finding study Vaccine (2011) 29: 8696-8704 Study ID#: **V70P6** ClinicalTrials.gov Identifier: NCT00848887	**Name**: Egg derived sub-unit ATIV and AQIV **Manufacturer**: Novartis Vaccines and Diagnostics **Other vaccine**: split-virion TIV **Manufacturer**: Sanofi Pasteur **Admin**: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL 17 (A-P) study groups defined by factorial combinations of 7.5µg or 15µg doses of each TIV strain and 0%, 12.5%, 25%, 50%, or 100% of the MF59 adjuvant dose. In the QIV groups, 7.5µg or 15µg of a second influenza B strain were added. Groups A–N received 2 doses 4 weeks apart, on Days 1 and 29, whereas groups O and P (100% MF59) received 1 dose on Day 1 only.	Observer blind, randomized, multicenter, dose-ranging factorial design clinical trial	**Age**: 6 to < 36 months **Mean (SD)**: 16.8 (8.5) months **Sex** (% male) =50.5 **Countries**: Finland and Belgium **Number of participants**: 410 enrolled. **Immunogenicity analyses on:** 395 at baseline 322 at day 29 282 at day 50 **Inclusion Criteria:** Healthy children, no influenza vaccine or infection within 6 months of enrollment.	**Follow up:** 7 days after the 1st and 2nd dose of vaccinations for the solicited local and systemic adverse events (AEs). **Most common local reactions across 17 comparison groups:** Erythema: 12 - 44% Tenderness: 5 – 42% Reactions were mild to moderate resolving within 4 days. **Most frequent systemic reaction across the groups:** Irritability: 12 – 43% **Spontaneously reported AEs:** 58- 96%; Possibly related to vaccination: 4- 36%. **Serious AEs (SAEs):** Lymphadenitis in a recipient of 0% MF59 7.5µg QIV Gastroenteritis in a recipient of 0% MF59 15µg QIV Pyelonephritis in a recipient of 12.5% MF59 7.5µg TIV Pneumonia in a recipient of 25% MF59 15µg QIV Lymphadenitis and gastroenteritis in a recipient of 50% MF59 15µg TIV Gastroenteritis in a recipient of 50%	I- Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
	Group Q: comparator marketed unadjuvanted TIV (Vaxigrip pediatric) **Season**: 2009-2010, NH **Details**: 15ug HA/strain in 0.5mL **TIV:** A/Brisbane/59/2007 (A/H1N1) A/Brisbane/10/2007 (A/H3N2) B/Florida/4/2006 (B/Yamagata lineage) **QIV = *TIV + a second B strain:*** B/Malaysia/2506/2004 (B/Victoria lineage)			MF59 7.5µg QIV Gastroenteritis rotavirus in a recipient of 50% MF59 15µg QIV Gastroenteritis rotavirus in a recipient of 0% MF59 7.5µg licensed TIV comparator None of the SAEs were considered to be related to the study vaccine.	
Timo Vesikari, Markus Knuf et al. Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children. New England Journal of Medicine (2011) 365:1406-16 Study ID#: **V70P5** Trial #: NCT00644059	**Name**: Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines **Admin:** 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Comparator Vaccines:** **Study Year 1 (07/08) TIV:** Agrippal® S1, non-adjuvanted subunit TIV **Manufacturer:** Novartis Vaccines **Details**: 15ug HA/strain in	Phase III, Multicenter, randomized controlled trial	**Age**: 6 to <72 months **Countries**: Germany Finland **Number of participants**: **2007/08:** Germany: 654 **2008/09:** Germany: 2104 Finland: 1949 **Inclusion Criteria:** Healthy children who	**Follow up:** Not stated % with AEs among ATIV; TIV and Control groups ***Solicited*** **Age 6 to <36 months** Local: 54%; 46% and 52% Systematic: 68%; 66% and 61% Serious: 8%; 10% and 11% **Age 36 to <72 months** Local: 68%; 60% and 55% Systematic: 63%; 44% and 50% Serious: 4%; 8% and 11% 13 children withdrawn from the study due to SAEs; 2 children in each group	I-Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
	0.5mL of: A/Solomon Islands/3/2006 (H1N1); A/Wisconsin/67/2005 (H3N2); B/Malaysia/2506/2004 **Study Year 2 TIV (08/09):** Influsplit SSW®, non-adjuvanted split-virion TIV **Manufacturer**: GlaxoSmithKline Biologicals **Details**: 15ug HA/strain in 0.5mL A/Brisbane/59/2007 (H1N1); A/Brisbane/10/2007 (H3N2); B/Florida/4/2006 **Placebo vaccines:** **Name:** Menjugate®, meningococcal C conjugate vaccine **Admin:** 2 doses, IM **Dose:** Age 6 to < 12: 0.25mL **Manufacturer:** Novartis Vaccines **Name:** Encepur® Children, tick borne encephalitis vaccine **Admin:** 2 doses, IM **Dose:** Age 12 to < 72 months: 0.5mL **Manufacturer:** Novartis Vaccines		have not previously received influenza vaccine and had no contraindications to vaccination.	had SAE that were judged as possibly related to the vaccines.	

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Nolen T, Bravo L, Ceballos A, et al. Enhanced and Persistent Immune Response Against Homologous and Heterologous Strains Elicited by an MF59-Adjuvanted Influenza Vaccine in Infants and Young Children. (Published Poster) (2013) Title in Clinicaltrials.gov: Safety, Tolerability, and Immunogenicity of the Adjuvanted Trivalent Subunit Influenza Vaccine and the Non-Adjuvanted Trivalent Subunit Influenza Vaccine Compared to the Non-Adjuvanted Trivalent Split Influenza Vaccine in Children 6 to < 72	**Name:** Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines & Diagnostics **Comparator TIV-1:** Agriflu®, non-adjuvanted, sub-unit TIV **Manufacturer** Novartis Vaccines & Diagnostics, Siena, Italy **Comparator TIV-2:** Fluzone®, non-adjuvanted, split particle TIV **Manufacturer** Sanofi Pasteur, Inc. **Admin**: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Season:** 2011-2012, SH **Details:**15ug HA/strain **Homologous strains**: A/California/7/2009 (H1N1)-like;	Phase III, observer blind, randomized multi-center clinical trial	**Age**: 6 to < 72 months **Mean (SD)**:33.7 (18.1) **Countries**: Argentina (8), Australia (5), Chile (2), Philippines (12) and South Africa (5). **Number of participants**: 6100 **Inclusion Criteria:** Healthy children.	**Follow up**: 29 and 50 days % with solicited local and systemic AEs ATIV vs TIV1 vs TIV2 **Local** Any local: 35; 20; 21 Ecchymosis: 6; 5; 6 Erythema: 10; 8; 5 Induration: 8; 4; 5 Tenderness: 5; 5; 5 Site swelling: 7; 99; 99 Site pain: 51; 29; 30 **Systemic** Any systemic: 48; 42; 39 Chills: 5; 2; 1 Myalgia: 7; 3; 1 Arthralgia: 4; 1; 1 Headache: 9; 3; 3 Fatigue: 7; 3; 2 Eating habit: 14; 13; 14 Diarrhea: 14; 16; 15 Irritability: 9; 11; 13 Crying: 6; 7; 8 Sleepiness: 7; 10; 11 Vomiting: 8; 7; 7 Fever: 24; 16; 15 Any other: 34; 21; 22 Any AEs (Day 1-50): 49; 58; 55	I- Fair

Study Details					Summary
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Months of Age. Study ID#: **V70_29** Trial #: NCT01346592	A/Perth/16/2009 (H3N2)-like; B/Brisbane/60/2008-like **Heterologous strains:** A/New Jersey/8/1976 (H1N1) A/Uruguay/716/2007 (H3N2) B/Malaysia/2506/2004			Probably related (Day 1-50): 5; 5; 6 Any SAEs: 4; 4; 5 Probably related: 0; 0; 0	
Nolan T, Bravo L, Ceballos A, et al. Enhanced and persistent immune response against homologous and heterologous strains elicited by a MF59®-adjuvanted influenza vaccine in infants and young children. Vaccine. 2014;32(46):6146-56. Study ID#: V70_29 Trial #: NCT01346592	**Name:** Fluad®, MF59-adjuvanted TIV **Manufacturer**: Novartis Vaccines & Diagnostics **Comparator TIV-1:** Agriflu®, non-adjuvanted, sub-unit TIV **Manufacturer** Novartis Vaccines & Diagnostics, Siena, Italy **Comparator TIV-2:** Fluzone®, non-adjuvanted, split particle TIV **Manufacturer** Sanofi Pasteur, Inc. **Admin**: 2 doses, 28 days apart, IM **Dose:** Age 6 to < 36 months: 0.25mL Age 36 to < 72 months: 0.5mL **Season:** 2011-2012, SH **Details:**15ug HA/strain	Phase III, observer blind, randomized multi-center clinical trial	**Age**: 6 to < 72 months **Mean age in months (SD)**: ATIV: 37.1 (18.6) TIV-1: 30.2 (16.9) TIV-2: 30.0 (16.9) **Countries**: Argentina (8), Australia (5), Chile (2), Philippines (12) and South Africa (5). **Total participants**: 6104 Participants for immunogenicity: 2655 Participants for safety: 6100 **Inclusion Criteria:** Healthy children.	**<u>Safety</u>** Follow up: immediate (within 30 mins), solicited up to day 7, unsolicited up day 50 % with mild to moderate solicited reactions 6h-7days after vaccination, ATIV vs TIV1 vs TIV2 **Local** **After 1st vaccination (n=2991, 1430, 1422)** Ecchymosis: 4; 3; 4 Erythema: 6; 5; 3 Induration: 5; 3; 3 Swelling: 3, 2, 2 Tenderness: 7, 5, 6, Site pain: 33, 17, 20 **After 2nd vaccination (n=3018, 1426, 1408)** Ecchymosis: 3, 2, 3 Erythema: 6, 4, 3 Induration: 5, 2, 2 Swelling: 5, 1, 1 Tenderness: 5; 3; 3 Site pain: 27, 15, 16	I Good

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	Homologous strains: A/California/7/2009 (H1N1)-like; A/Perth/16/2009 (H3N2)-like; B/Brisbane/60/2008-like **Heterologous strains:** A/New Jersey/8/1976 (H1N1) A/Uruguay/716/2007 (H3N2) B/Malaysia/2506/2004			**Systemic** **After 1st vaccination (n=3074, 1451, 1443)** Chills: 7; 2; 2 Myalgia: 10, 5, 4 Arthralgia: 5, 2, 2 Headache: 13, 5, 6 Fatigue: 10, 7, 5 Eating habit: 11, 9, 10 Diarrhea: 10, 11, 11 Irritability: 14, 12, 13 Crying: 10, 7, 9 Sleepiness: 12, 11, 12 Vomiting: 6, 4, 5 Fever: 15, 8, 9 **After 2nd vaccination (n=3016, 1427, 1407)** Chills: 5, 4, 2; 1 Myalgia: 7, 6, 4 Arthralgia: 4, 3, 3 Headache: 8, 6, 5 Fatigue: 6, 5, 4 Eating habit: 6, 6, 7 Diarrhea: 6, 8, 7 Irritability: 9, 7, 8 Crying: 5, 5, 6 Sleepiness: 6, 6, 6 Vomiting: 3, 3, 3 Fever: 14, 9, 8 % with unsolicited reactions up to day 50, ATIV vs TIV1 vs TIV2 (n=2123,	

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
				1477,1474) URTI: 14, 16,17 Nasopharyngitis: 9, 10, 12 Gasteroenteritis: 4, 5, 6 Viral infection: 3, 4, 3 Pyrexia: 2, 3, 4 Rhinitis: 3, 4, 3 Bronchitis: 2, 3, 3	
Zedda L, Forleo-Neto E, Vertruyen A et al. Dissecting the Immune-Response to MF59®-Adjuvanted and Non-Adjuvanted Seasonal Influenza Vaccines in Children Less Than Three Years of Age. Pediatric Infectious Disease, 2014 (in press). Study ID#: **V70_34** Trial #: NCT01342796	**Name:** MF59®-Adjuvanted, trivalent inactivated influenza vaccine (ATIV) **Comparator Vaccine:** trivalent inactivated influenza vaccine (TIV) **Both Vaccines:** **Manufacturer:** Novartis Vaccines **Admin:** IM, 28 days apart **Dose:** 2 doses of 0.25 mL, **Details:** 7.5ug HA/strain A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008	Phase II, randomized, multicenter clinical trial	**Age:** 6 to < 36 months **Mean Age:** TIV group: 21.4 months ATIV group: 20.2 months **Sex (% male):** TIV group: 66% ATIV group: 53% **Country:** Siena, Italy **Number of participants:** 84 TIV group: n= 41 ATIV group: n = 43 **Inclusion criteria:** Healthy children who had not previously received influenza vaccine.	**Follow-up:** 7 days post-vaccine: active; 8–50 days post-vaccine:passive. % with AEs: TIV vs ATIV, dose 1 & dose 2 **Solicited Local AE:** Any: 26% vs 42% & 18% vs 26% Erythema: 0% vs 17% & 5% vs 10% Ecchymosis: 0% vs 10% & 3% vs 0% Induration: 5% vs 5% & 5% vs 8% Swelling: 0% vs 2% & 3% vs 3% Tenderness: 23% vs 24% & 13% vs 13% **Solicited Systemic AE:** Any: 56% vs 56% & 42% vs 49% Change in eating habits: 21% vs 21% & 13% vs 21% Sleepiness: 21% vs 21% & 18% vs 18% Unusual Crying: 8% vs 7% & 11% vs 15% Irritability: 10% vs 19% & 16% vs 15% Vomiting: 10% vs 7% & 0% vs 5% Shivering: 3% vs 5% & 0% vs 0% Diarrhea: 21% vs 19% & 8% vs 13%	I- Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
			Exclusion criteria: Impairment of the immune system, any serious medical condition or recent infectious disease, immunization with licensed vaccines within 2 weeks (for inactivated vaccines) or 4 weeks (for live vaccines) or any other agent within 30 days prior to enrollment, any history of hypersensitivity to any component of the study vaccine.	Fever: 23% vs 26% & 13% vs 28% Stayed home due to AE: 5% vs 19% & 3% vs 13% Analgesic or Antipyretic used: 21% vs 19% & 8% vs 23% Related or possibly related SAE (unsolicited) reported after 7 days: Injection Site Swelling/Induration/: 2 cases in ATIV group Pyrexia: 1 case in TIV group Somnolence: 1 case in TIV group % with Any AEs TIV vs ATIV (dose 2): All: 44% vs 47%	
Vesikari T, Pellegrini M, Karvonen A, et al. Enhanced Immunogenicity of Seasonal Influenza Vaccines in Young Children Using MF59 Adjuvant. Pediatric Infectious Disease Journal (2009) 28.7: 563-571. Study ID#: **V70P2**	**Name:** Fluad®**,** MF59-adjuvanted subunit TIV **Manufacturer:** Novartis **Comparator vaccine:** Vaxigrip®, non-adjuvanted, split-virion TIV **Manufacturer:** Sanofi Pasteur **Admin:** 2 doses, 28 days apart, IM, booster dose approximately 1 year after the Dose 1 **Dose:** Age 6 to <36 months: 0.25mL	Phase II, observer-blind, randomized, multicenter clinical trial	**Age:** 6 to <36 months **Mean Age (SD):** ATIV: 20.8 (8.6) months TIV group: 21.2 (8.9) months **Country:** Finland **Number of participants:** 222: ATIV: n=104 TIV: n=118	**Follow-up**: 7 days: solicited AEs after each vaccination. Study start up to 3 weeks after the last vaccination: all AEs and SAEs % with AEs: Fluad vs. Vaxigrip **Local reactions, number (%)** **Tenderness:** After 1st dose: 43 (33) vs. 36 (26) After 2nd dose: 34 (29) vs. 28 (22) Overall: 58 (45) vs. 47 (34) **Erythema:** After 1st dose:32 (25) vs. 30 (22) After 2nd dose: 29 (25) vs. 22 (17)	I-Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Trial #: NCT00408395	Age >36 months: 0.5mL **Details**: 9.75mg of MF59 per 0.5mL and 15µg of HA/strain: A/New Caledonia/20/99 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 A/H1N1 changed for booster to A/Solomon Islands/3/2006 **Season:** Dose 1 and 2: 2006/2007, NH Booster dose: 2007–2008, NH Note: see Vesikari, Groth et al study for details on extension study with booster (Dose 3) results.		**Inclusion criteria:** Healthy children. **Exclusion Criteria:** Known allergy to any vaccine component, known or suspected neurologic reactions following influenza vaccination, any acute infectious or respiratory disease requiring treatment up to 30 days before the study or lab-confirmed influenza disease in the previous 6 months.	Overall: 46 (35) vs. 38 (27) **Induration:** After 1st dose: 10 (8) vs. 13 (9) After 2nd dose: 12 (10) vs. 11 (9) Overall: 21 (16) vs. 20 (14) **Swelling:** After 1st dose: 10 (8)* vs. 3 (2) After 2nddose: 8 (7) vs. 5 (4) Overall: 16 (12) vs. † 7 (5) **Ecchymosis:** After 1st dose: 11 (8) vs. 13 (9) After 2nd dose: 9 (8) vs. 8 (6) Overall: 18 (14) vs. 19 (14) **Systemic reactions, number (%)** **Fever:** After 1st dose: 38°C 9 (7) vs. 6 (4) After 2nd dose: 7 (6) vs. 8 (6) Overall: 16 (12) vs. 13 (9) **Analgesic/antipyretic use:** After 1st dose: 23 (18) vs. 17 (12) After 2nd dose: 18 (15) vs. 17 (13) Overall: 34 (26) vs. 32 (23) **Irritability:** After 1st dose: 41 (32) vs. 36 (26) After 2nd dose: 29 (25) vs. 24 (19) Overall: 53 (41) vs. 46 (33) **Unusual crying:** After 1st dose: 15 (12) vs. 11 (8) After 2nd dose: 13 (11) vs. 11 (9) Overall: 24 (18) vs. 19 (14) **Sleepiness:** After 1st dose: 24 (18) vs. 19 (14) After 2nd dose: 17 (15) vs. 13 (10)	

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				Overall: 35 (27) vs. 26 (19) **Change in eating habits:** After 1st dose: 23 (18) vs. 24 (17) After 2nd dose: 14 (12) vs. 9 (7) Overall: 32 (25) vs. 30 (22) *P _ 0.034. †P _ 0.033 vs. split vaccine. All others not statistically significant at P <0.05 **SAEs:** No vaccine-related SAE; 21 children in each group had SAEs assessed as possibly or probably vaccine-related.	
Vesikari T, Groth N, Karvonen A, Borkowski A, Pellegrini M. MF59-adjuvanted influenza vaccine (FLUAD) in children: safety and immunogenicity following a second year seasonal vaccination. Vaccine (2009) 27:6291-6295. Study ID#: **V70P2E1**	**Name:** Fluad®, MF59-adjuvanted, subunit vaccine **Manufacturer:** Novartis **Admin:** 1 dose, IM, booster **Dose:** Age < 36 months: 0.25mL Age ≥ 36 months: 0.5mL **Season:** 2007/08 NH **Details:** 15ug/strain A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004 **Comparator Vaccine:** **Name:** Vaxigrip®, split vaccine **Manufacturer:** Sanofi Pasteur **Admin:** 1 dose, IM, booster	Observer-blind, extension study to V70P2	**Age:** 16 to <48 months **Mean Age (SD):** ATIV group: 33.5 (8.8) months TIV group: 33.9 (8.1) months **Sex (% female):** Sub/MF59:44% Split:46% **Country:** Finland **Number of participants:** 81 ATIV: n= 41 TIV: n= 40	**Follow-up:** 6 months post-third injection No (%) with AEs: Sub/MF59 vs Split Any reaction: 34 (79%) vs 27 (59%) Local: 30 (70%) vs 21 (46%) Systemic: 18 (42%) vs 17 (37%) Other (body temp, analgesic, antipyretic use.): 9 (21%) vs 4 (9%) Any AE: 30 (70%) vs 35 (76%) Fever: 1 (2%) vs 0 Cough: 2 (5%) vs 0 Injection site pruritus: 1 (2%) vs 1 (2%) Induration: 1 (2%) vs 0 Irritability: 1 (2%) vs 1 (2%)	II-1 Fair

Study Details					Summary
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Quality and level of evidence**
Trial #: NCT00644540	**Dose:** Age <36 months: 0.25mL Age ≥36 months: 0.5mL **Season:** 2007/08 NH **Details:** 15ug/strain A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004		**Inclusion criteria:** Children primed (2-dose) with FLUAD® or Vaxigrip® (2006/07 NH) in V70P2.	Nasopharingitis: 1 (2%) vs 0 Respiratory tract infection: 3 (7%) vs 0 Rhinitis: 2 (5%) vs 1 (2%) **SAE**: 0 vs 0	
Dell'era L, Corona F, Daleno C et al. Immunogenicity, safety and tolerability of MF59-adjuvanted seasonal influenza vaccine in children with juvenile idiopathic arthritis. Vaccine (2012) 30:93640.	**Name:** Fluad®, MF59-adjuvanted seasonal influenza vaccine **Manufacturer:** Novartis **Season**: 2010-2011, NH **Admin:** 1 dose, IM **Dose:** 0.5mL **Details:** 15 ug HA /strain A/California/7/2009 H1N1-like virus; A/Perth/16/2009 H3N2-like virus; B/Brisbane/60/2008-like virus; **No comparator.**	Non-randomized non-controlled clinical trial of children and adolescents comparing JIA patients on DMARD (Group A) with JIA patients on etanercept (Group B) and healthy controls (Group A)	**Mean Age (SD):** Group A: 8.43 (4.55) Group B: 9.50 (5.69) Group C: 9.11 (5.01) **Sex (%Males):** Group A: 46.7% Group B: 53.3% Group C: 50.0% **Country:** Italy **Number of participants:** 90 Group A: n=30 Group B: n=30 Group C: n=30 **Inclusion criteria:** Children/adolescents with stable JIA treated with DMARDs or etanercept. JIA patients had been receiving the	**Follow-up:** 14 days following vaccination Group A vs Group B vs Group C **Local reactions** Erythema: 6.7% vs 10.0% vs 10.0% Swelling/induration: 40.0% vs 36.7% vs 36.7% Pain: 43.3% vs 36.7% vs 40.0% Any local event: 43.3% vs 36.7% vs 40.0% **Systemic reactions** Fever≥38◦C: 23.3% vs 13.3% vs 16.7% Rhinitis: 30.0% vs 26.7% vs 23.3% Malaise: 20.0% vs 26.7% vs 26.7% Sleepiness: 20.0% vs 13.3% vs 16.7% Changed eating habits: 26.7% vs 13.3% vs 16.7% Vomiting: 6.7% vs 6.7% vs 3.3% Diarrhea: 6.7% vs 3.3% vs 6.7% Any systemic event: 30.0% vs 26.7% vs 26.7%	II-1 Fair

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			same drug treatment for at least 6 months and none of them had received corticosteroids for at least 1 year.	Any local or systemic event: 30.0% vs 36.7% vs 40.0% Required drugs for treatment of event: 13.3% vs 10.0% vs 16.7% SAE: 3.3% vs 3.3% vs 0.0%	