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Infants and the Seasonal Influenza Vaccine: safety, effectiveness & alternate forms of protection

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
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Abstract

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Seasonal influenza is a substantial cause of severe illness among infants under 6 months of age globally. There are multiple methods of vaccination against influenza, including inactivated and live vaccines that are approved and recommended for children and adults over 6 months of age, but there is no vaccine that protects against seasonal influenza for children <6 months of age. This group is at a high risk of severe illness and is associated with higher rates of hospitalization and mortality during the influenza season. In absence of an available vaccine, approaches protecting young infants from influenza must be taken seriously. These methods include vaccinating pregnant women for influenza as a method of protecting mothers and the fetus as well as vaccinating caregivers and close contacts of individuals in this age group.

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INTRODUCTION

Seasonal influenza is a significant cause of severe illness and hospitalization of infants. In many cases, the rate of hospitalization for children under the age of six months is three times that of children in the subsequent age group.[1] Mortality rates are highest for those ≥65 and among children <2 years, due to a lack of previous exposure.[2] A vaccine approved for children under the age of six months does not currently exist; nor do approved antiviral treatments exist for this age group. Preventing influenza infection in this vulnerable population is crucial in reducing severe illness and mortality.

BURDEN OF DISEASE

Children under 6 months of age are highly susceptible to infection with seasonal influenza, leading to severe illness and hospitalization. This might be a consequence of an absence of immunity among the population, due to a lack of previous exposure to influenza viruses or an immature immune system.[3],[4] Hospitalization rates in young children, even without underlying conditions, are at high during peaks in the influenza season, which occurs during the winter months in the northern hemisphere, and in tropical climates, year-round. Newborns have also been found to have more severe symptoms[1]. Children <6 months of age have a higher risk of death than children ≥6 months of age. In the 2004-2005 season in the United States, the influenza-associated mortality rate among infants <6 months was .88 per 100,000 (95% CI .52-1.39). The age group above, 6-11 months experienced a mortality rate of .59 per 100,000 (.30-1.02).[5] A population-based survey completed in the United States between 2000 and 2004 revealed an annual rate of hospitalization of .9 per 1000 children between 0 and 59 months of

age (95% CI: .8-1.1 per 1000). Among infants between 0-5 months of age, the rate was 4.5 per 1000 (3.4-5.5 per 1000).[6]

The global burden of disease due to influenza is difficult to determine, particularly in the developing world. It is challenging to evaluate the burden of influenza without laboratory capacity. It is also challenging to differentiate influenza from the numerous other prominent circulating febrile respiratory illnesses. In a meta-analysis of the global burden of disease among children in 2011 researchers found that a significant proportion of the disease burden of acute lower respiratory infection (ALRI) due to seasonal influenza is among infants. In an analysis of 43 studies, the authors found that globally, in 2008, an estimated 36% of influenza-associated severe ALRI in children <5 years of age were among children <1 year of age. 99% of the deaths associated with seasonal influenza among children <5 were in the developing world.[7]

In a nation-wide cross-sectional serological study completed in the Netherlands between 2006 and 2007 researchers sought to determine when influenza generally infects infants for the first time.[8] Taking samples of infants 1-12 months of age, they found serological evidence of a difference between the influenza types in infants 1-6 months of age and infants 7-12 months of age. The antibodies in the younger age group reflected older influenza strains. Authors also found that the antibody prevalence to these types of influenza decreased after 6 months of age. The hypothesis for this difference was the prevalence of maternally derived antibodies in the group 1-7 months of age, highlighted by the fact that vaccination of pregnant women in the Netherlands for influenza is not recommended.

CURRENT INFLUENZA VACCINES

Although there are different manufacturers of the inactivated influenza vaccine, most inactivated vaccines are grown in embryonated hens' eggs, and some now use mammalian cell lines. The monovalent antigens are combined to trivalent or quadrivalent vaccines. Because of the yearly change in influenza virus strain and therefor vaccine composition, and waning immunity year-to-year, annual influenza immunization is recommended. Children <9 years old are recommended to receive two doses of vaccine for adequate immunity against influenza.[1]

The inactivated influenza vaccine has been used United States since 1945 and since the 1960s in Europe.[9] The inactivated influenza vaccine is recommended annually for everyone ≥6 months of age in the United States.[2] The World Health Organization recommends annual vaccination, prioritizing high risk groups including pregnant women, children under <5 years of age, the elderly, and those with underlying health conditions.[10] The effectiveness of the vaccine changes each year, as the composition of the vaccine is changed and the prediction of which influenza viruses will be most prominent that year is not perfect.[2] Different studies have yielded estimations of effectiveness of the inactivated influenza vaccine against laboratory/culture confirmed influenza illness between 59-65%.[11]

The Live Attenuated Intranasal Vaccine (LAIV) is a vaccine that was put on the market in 2003 and updated every year like the inactivated vaccine that is produced in hen's eggs and is preservative-free.[1] The vaccine is recommended for healthy children and non-pregnant adults between 2 and 49 years of age, and between 2 years and 17 years of age in Europe.[9] A range of

effectiveness for the LAIV in preventing laboratory/culture confirmed influenza illness has been found to be between 72-82%.[11]

INFLUENZA VACCINE IN YOUNG INFANTS

Evidence demonstrating that seasonal influenza vaccine would be effective in infants is lacking, and variable in even the youngest age group for which the vaccine is recommended (>6months of age). Randomized controlled trials of children aged 6-24 months have demonstrated vaccine efficacies for inactivated influenza vaccine (IIV) between -7 and 66%. The efficacy live attenuated influenza vaccine (LAIV) in children 6 months to 7 years old have been found to be between 57-93% from 1998 to 2010.[12] Because these vaccines are not made for use in children <6 months, data on efficacy or effectiveness of the vaccine in this age group is sparse.

One four-year study completed in Colorado in the 1990s showed that giving IIV to high-risk infants between 3 and 6 months of age months does not pose safety concerns. However, the seroconversion rates among the children 3-6 months of age compared to children 6-18 months of age was low, with exception to the A/Mississippi (H3N2) antigen, which was associated with a higher seroconversion rate among all age groups in the study.[13]

A prospective, phase I, open-label study sought to evaluate the safety and immunogenicity of the 0.25mL dose Fluzone® trivalent inactivated influenza vaccine (IIV) among 50 children 10-22 weeks of age at the Vanderbilt University Medical Center between 2004 and 2006. Two doses of the vaccine were given between 28 and 42 days apart. Non-severe adverse reactions after 2 doses of IIV included local reactions, elevated temperature in 7% and 1 case of otitis media

among the 42 infants enrolled. The seroconversion rates for the influenza B virus were low among all subjects, and slightly higher for H3N2 antigen compared to the other two, similar to the previously mentioned study from Colorado.[13],[14] Additionally, the infants in the study that showed evidence of having maternal antibodies previous to vaccination were less likely to show signs of immunity for H1N1 or H3N2 after two doses of vaccine. This could potentially be due to memory responses from influenza specific T-cells in these infants but could not be confirmed with the testing methods used in the study. Overall, this study yielded results that verified the safety of IIV in young infants, but showed overall low post-vaccination titers.[14],[15]

A randomized control study to assess the safety and immunogenicity of IIV in 1096 infants 6-12 weeks of age demonstrated that no difference in vaccine safety between the group receiving IIV and the group receiving the placebo.[16],[17] Infants were randomized to receive two doses of IIV with one month in between each dose, with the first dose alongside routine childhood immunizations. 90.2% of infants in the IIV group demonstrated titers $\geq$1:40, compared with only 16.4% of those in the placebo group. Researchers also found that administering IIV did not have an affect on the responses to routine immunizations given concurrently. Adverse events were mild and did not significantly differ between groups, demonstrating the safety of IIV in this age group. This study established a case for further evaluation of efficacy of influenza vaccine in young infants.[16]

A proof of concept study was completed to assess the difference in safety and immunogenicity of the pediatric formulation of the 2004-2005 IIV Fluzone® given between 6 and 12 weeks and 24 to 36 weeks in a group of 394 subjects. The vaccine was more immunogenic in infants aged 24

to 36 weeks than in infants aged 6 to 12 weeks. Among children in the younger age group, 54% experienced any solicited injection site reactions, compared to 47% of the children in the older age group.[18]

The Live Attenuated Influenza Vaccine (LAIV) has been found to address the problem of IIV being less immunogenic in young children and the elderly, which are two of the most vulnerable populations to severe influenza infection. However, LAIV is not recommended for children <2 years of age.[19]Because cold-adapted, live attenuated vaccines are associated with longer-lasting immunity, only one dose might suffice in young children, which could have positive implications in efficiency during a pandemic or in general cost-effectiveness for protecting populations.[20] Different studies have demonstrated that LAIV was more effective than IIV in preventing laboratory-confirmed influenza, specifically in influenza A strains in healthy children 6-59 months old. Further evaluation of the safety of LAIV in young children has recently completed, or has been taking place currently (Table 1).[21, 22]

In 1995 Karron et al[23] sought to test a live, cold-adapted influenza A (specifically H1N1) vaccine given by nose drops in infants >6 months of age. Infants were given two doses of the vaccine either with other routine childhood vaccines or separately. The authors found that when the cold adapted vaccine was given in conjunction with other immunizations, only 20% of children had protective HAI antibody titers, as opposed to 83% of the infants who received the vaccine by itself. They also found that age (receiving the first vaccine at 2 months rather than 4 months of age) was also a predictor of immunogenicity of the vaccine independently of maternally acquired antibodies, race and breastfeeding.[23]

In 1997, a randomized control trial was done to examine the effect of a live attenuated bivalent influenza A vaccine in children aged 2 months to 3 years of age. Children ≤ 6 months were found to have antibody responses to H3N2 and H1N1 less frequently than older children. While the vaccine was proven safe in this younger age group, there was a lack of adequate serologic response in this group.[24]

A Phase II randomized control clinical trial was completed in Bangladesh in 2013 explored the Safety and Immunogenicity of 1 dose of the intranasal trivalent LAIV in children 24 to 59 months old, for which the results are not yet available.[21] An ongoing Phase III randomized, controlled trial is taking place in Bangladesh on the efficacy and safety of LAIV in children aged 24 through 59 months. This is the first time the LAIV has been investigated in a low-income setting.[22] This study could induce further investment in further investigation of different existing vaccines in young infants.

[19][20][21, 22]

Among the general population, the seasonal influenza vaccine is not as effective as many other vaccines, with a mean efficacy in adults of about 60%, and the immunity is reduced within months.[25] Using adjuvants have the potential to augment the length and strength of immunity induced by the vaccine, but potential safety concerns prevent clinical trials and approval of many adjuvants. MF59, an oil-in-water emulsion adjuvant is found to enhance immunogenicity and used in influenza vaccines made for the elderly.[26] Clinical trials in Finland and Germany have demonstrated that MF59 also enhances immunity to seasonal in children 6 to 72 months old. In

Finland, the attack rate for children in the group who received trivalent inactivated influenza vaccine (IIV) with MF59 adjuvant was .7%, and in the group who received the IIV without adjuvant, the attack rate was 2.8%. Adverse events in both groups were similar and the adjuvanted vaccine was described to be as safe as the IIV without adjuvant in this group.[27] Virosome adjuvants are approved in one vaccine in the United States (Inflexal V), and two adjuvants, AS03 and Aluminum phosphate are used in pandemic influenza vaccines in Europe.[25] A Phase II clinical trial was completed in 2012 to explore the immunogenicity and safety of MF59C.1-adjuvanted influenza vaccine (currently used in the elderly population) in infants aged 6 to 36 months in Belgium.[28],[29]

There are several adjuvants being investigated for potential use in seasonal influenza vaccines to be used for different age groups, including the use of liposomes as adjuvants in virosomal vaccines.[30] Because young infants are at an elevated risk for influenza-related complications. Studies that demonstrate efficacy of adjuvants in children ≥6 months cannot necessarily be extrapolated to children <6 months due to the frequent changes in immune responses in early life. Adjuvants are potential solutions to inducing the protective response in infants[25], but the widespread fear of adverse events from adjuvants that persist in popular media may be a hindrance for vaccine acceptance even if it is approved.[31]

Using the intradermal route rather than the intramuscular route with current vaccine formulations in infants under six months of age could possibly induce a sufficient immune response as opposed to the intramuscular route. Studies exploring this in adults have showed that a reduced dose produced a similar effect as a full dose given intramuscularly. [32] In 1961, researchers

investigated the immune response of the influenza vaccine given to infants and children between 2 months and 5 years old given intradermally and subcutaneously and found no difference in immune response between the two groups. Additionally, subjects given the vaccine intradermally had febrile reactions after the vaccine than the group given the vaccine subcutaneously.[33] A randomized control trial in Hong Kong with 126 infants published in 2009 compared intradermal to intramuscular vaccination in infants 2-3 months of age with the inactivated trivalent influenza vaccine. Two doses of the vaccine were given four weeks apart. Both groups of subjects tolerated the vaccine well, and no differences in mild adverse events was found except for more redness at the injection site in the group who received the vaccine with the intradermal route. No difference was found between the groups in fold-rise of HAI titers, indicating that influenza vaccination using the intradermal route of vaccination did not induce a superior immune response compared to the intramuscular route. Almost all infants in the study demonstrated immunity prior to vaccination with maternal antibodies.[34] Studies in France on adults showed higher immunogenicity when influenza vaccine was delivered through the Imule® jet injector compared to a syringe.[35] There was a recent trial to investigate the effect of using a needle-free jet injector to administer a reduced dose of IIV in children between 6 and 24 months old in the Dominican Republic, for which the results are not yet available.[36]

Sub-groups of the pediatric population do not have a desired immune response to IIV such as children with immune-compromising illnesses. High-dose vaccines, which are also recommended in the elderly population has been investigated to see if it would be a solution to the decreased immune-response in children with Acute Lymphoblastic Leukemia and no difference between the high-dose and regular dose vaccine was found.[37] There are clinical

trials being conducted on the safety and immunogenicity of high-dose influenza vaccine on special groups such as immunocompromised individuals, but not on infants <6 months of age.[38] Further exploration into whether or not this would be a potential solution for inducing an immune response in young infants is necessary.

PREVENTION OF INFLUENZA IN CHILDREN <6 MONTHS

While there is competing evidence of the safety and immunogenicity of the influenza vaccine in young infants, other forms of protecting this group have been tested and recommended. There is strong evidence to suggest that vaccinating a pregnant woman for influenza will induce immunity in the newborn through the transport of IgG antibody through the umbilical cord and breast milk.[39] In a randomized control trial in Bangladesh, pregnant women were to receive either influenza vaccine or 23-valent pneumococcal polysaccharide vaccine as the control group. Vaccine effectiveness among infants <6 months born to mothers who received the influenza vaccine was 63% (95%CI: 5-85). A reduction in clinic visits due to respiratory illness was also found.[40]

Immunizing pregnant women against influenza can also prevent additional unwanted pregnancy outcomes. Researchers assessed birth weight and premature birth in the Bangladesh study. During the influenza season, there was a significant reduction in infants born small for the gestational age and that birth weight was on average higher among infants born to mothers who received the influenza vaccine[41]. A retrospective cohort study with data from the Pregnancy Risk Assessment Monitoring System (PRAMS) in the state of Georgia demonstrated a significant protective effect of inactivated influenza vaccine on preterm birth and low birth

weight for live births during the influenza season. The odds of premature birth among infants born during the influenza season to mothers vaccinated during any trimester of pregnancy were 40% lower relative to the odds of babies born during the same season to unvaccinated mothers (95% CI, .38-.94).[42] These data show that in addition to protecting newborns from becoming ill with influenza, that health outcomes with potentially adverse long-term effects aside from influenza itself can be prevented with maternal vaccination during pregnancy.

The inactivated influenza vaccine has had a good safety record in pregnant women as demonstrated by several research studies. Neither vaccine-related adverse events nor negative outcomes for the young infants have been found to be due to receipt of the influenza vaccine during pregnancy. While the safety and immunogenicity of the vaccine in pregnant women and their children have been demonstrated, vaccine hesitancy in this group is common and effective communication strategies are necessary to effectively protect young infants with this method. [43]

In addition to vaccinating expecting mothers with inactivated influenza vaccine, vaccinating infants with pneumococcal conjugate vaccine can reduce the risk of upper respiratory infections in young infants. In a randomized, blinded, controlled trial in Dhaka, Bangladesh, it was found that the combined efficacy of IIV given to pregnant and 7-valent pneumococcal conjugate vaccine given to their infants was higher than the effects of either IIV or pneumococcal conjugate vaccine by themselves in protecting infants from febrile respiratory illness. The implications of this study are important for developing countries and suggest that maternal influenza immunization can enhance the impact of infant pneumococcal vaccine.[44]

The American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) recommend "cocooning" as a method to prevent seasonal influenza in young infants.[33, 45] Cocooning is a strategy to protect those who are at high-risk for severe disease who are not able to be immunized by immunizing close contacts of those individuals.[46],[47] If close contacts of the infant are protected from influenza, then that reduces the chance of being infected with influenza in those that are not recommended to receive the vaccine. The underlying assumption for this technique is that most infants contract influenza from caregivers or other close contacts.[48] Some hospitals around the country are implementing programs to provide free or reduced influenza or Tdap vaccines to close contacts of either ill pediatric patients or infants <6 months of age in order to increase the use of this technique. The integration of cocooning in family-care and in hospitals treating high-risk patients is a way to protect individuals from illness. The providing of the vaccine to adults in the pediatric care setting has yielded high vaccine acceptance rates among caregivers.[48][46]

DISCUSSION

Research to find a safe and immunogenic influenza vaccine for children <6 months is hindered by biologic, ethical and political factors. Studies to explore methods of vaccinating young infants are often *in vitro* studies using human cord, infant peripheral blood, or blood-derived leukosites, or *in vivo* with newborn mice or adult humans. Because of the unique nature of the immune responses of a young infant, these studies are not sufficient to determine the response of a young child to a new vaccine. The situation is likely more complicated, particularly by maternal antibodies that persist in infancy.[49]

[50, 51]

There are several clinical trials currently under way to add to the body of evidence regarding maternal immunization against seasonal influenza as a method of protecting young infants in a variety of settings globally. Three of these trials are sponsored by the Bill and Melinda Gates Foundation, including the previously mentioned controlled trial of LAIV in Bangladesh.[22] [52] In Mali, where influenza vaccine is recommended for pregnant women but not accessible, investigators are conducting a randomized controlled trial to assess the immunogenicity and safety of TIV in mothers and their young infants.[53] Investigators in a rural area of southern Nepal are conducting a field trial to measure the efficacy of the influenza vaccine on mothers during pregnancy and their infants.[54] These studies are ongoing.

There are several ongoing or recently compelted studies for which the results are not yet available, including a study in Utah to compare influenza titers in infants to mothers who received IIV in early pregnancy to mothers who received the vaccine in late pregnancy.[55] Investigators in Bangladesh conducted a placebo controlled clinical trial to explore the potential effect of vitamin A supplements on the immune response to IIV in both mothers and.[52] There is also an continuing randomized control trial in South Africa looking at IIV in HIV-negative pregnant women.[56] A study based in the United States compared LAIV to TIV IIV in breastfeeding mothers on the immunogenicity on mothers and young infants.[57]

A study was recently completed to assess the safety and immunogenicity of the 2010-2011 IIV in pregnant women and their infants. Three vaccines were given to groups of pregnant and non-

pregnant women (N=232). Investigators looked at outcomes including serious and non-serious vaccine-related adverse events, complications during pregnancy, labor, and delivery, neonatal complications, and immune response to the vaccine. All pregnant women enrolled in the study resulted in live-births, and 49 of the infants are enrolled in a 6-week follow up study. No vaccine-related serious adverse events have been found. A final report on this trial, including data on immunogenicity is pending.[58] [59] The results of these trials will possibly inform further policy and support for implementing influenza vaccine programs to protect mothers and young infants globally. (Table 1)

CONCLUSIONS

Serious illness due to seasonal influenza is a significant concern for young infants and there is currently no vaccine recommended to protect infants <6 months of age against an illness associated with high rates of illness and hospitalization. Some studies have shown that there is potential for a safe and immunogenic vaccine for infants <6 months old, but the vaccines recommended for those ≥6 months of age have not shown to have the same effect on young infants as they do on children and adults. Currently, it is recommended that pregnant women are immunized against seasonal influenza to protect themselves and their newborns from influenza as well from adverse birth outcomes such as low birth weight and preterm birth. Although the recommendation is in place, the rate of immunization among pregnant women is extremely low. This recommendation is inadequate without effective communication to pregnant women about

the safety and effectiveness of the vaccine in protecting their unborn children, and investment in strategies to deliver vaccines to pregnant women in low-resource settings.[51, 60]

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Table 1: Current clinical trials relevant to protecting young infants from seasonal influenza (clinicaltrials.gov)

Title	Intervention Type	Population	Location
The Role of Immunizing Pregnant Women In Protecting Young Infants Against Influenza	Trivalent Inactivated Influenza Vaccine	Healthy pregnant women & their infants	Salt Lake City, Utah, United States
Effect of Maternal Vitamin A Supplementation on Maternal Immune Response to Inactivated Influenza Vaccination, and on Passive Protection of Infants	Vitamin A Supplement Trivalent Inactivated Influenza Vaccine	Pregnant Women & their infants	Dhaka, Bangladesh
Prospective, Randomized, Controlled, Observer-Blind Trial to Measure the Efficacy, Safety and Immunogenicity of Trivalent Inactivated Influenza Vaccine and the Safety and Immunogenicity of Quadrivalent Meningococcal Polysaccharide Diphtheria Conjugate Vaccine in Pregnant Malian Women and Their Infants up to 6 Months of Age	Trivalent Inactivated Influenza Vaccine Meningococcal Polysaccharide Diphtheria Conjugate Vaccine	Pregnant women & their infants	Bamako, Mali
A Randomized, Double-Blind Trial, Comparing the Safety in Mothers and Their Infants and Immunogenicity in Mothers of Live Attenuated Influenza Vaccine (LAIV) to Inactivated Trivalent Influenza Vaccine (TIV) When Administered to Breast Feeding Women	Live Attenuated Influenza Vaccine Trivalent Inactivated Influenza Vaccine	Breast feeding women & their infants	Washington, DC Atlanta, GA Saint Louis, MO Durham, NC Cincinnati, OH Seattle, WA (United States)
Vaccination of HIV-	Trivalent	HIV-negative	Soweto,

uninfected Pregnant Women With Trivalent Influenza Vaccine in the Prevention of Influenza Illness During Early Infancy and in Mothers: Randomized Controlled Phase III Trial Evaluating Safety, Immunogenicity and Efficacy	Inactivated Influenza Vaccine	pregnant women & their infants	Johannesburg, Gauteng, South Africa
Field Trial of Maternal Influenza Immunization in Asia	Influenza Vaccine	Pregnant women & their infants Family members of study women	Sarlahi District, Southern Nepal
A Randomized, Double-Blind Trial on the Safety and Immunogenicity of Seasonal 2010-2011 Inactivated Trivalent Influenza Vaccine in Pregnant Women	Trivalent Inactivated Influenza Vaccine	Pregnant women	Saint Louis, MO Durham, NC Nashville, TN Houston, TX Seattle, WA (United States)
Prospective Pilot Safety Study Administering Two Doses of Inactivated Influenza Vaccine to Infants 10-22 Weeks of Age	Trivalent Inactivated Influenza Vaccine	Healthy infants aged 10 to 22 weeks	Cincinnati, OH Nashville, TN (United States)
Safety and Immunogenicity of Fluzone Influenza Virus Vaccine (2005-2006 Formulation) Among Healthy Children 6 to 12 Weeks of Age	Trivalent Inactivated Influenza Vaccine	Healthy infants 6 to 12 weeks of age	Seattle, WA (United States)
Prevention of Influenza in Infants by Immunization of Their Contacts in the Household	Cocooning (Trivalent Influenza Vaccine)	Newborns & Household contacts of newborns	Durham, NC, United States
Proof of Concept Study of the Safety and Immunogenicity of Influenza Virus Vaccine	Inactivated influenza vaccine	Infants 2 months of age Infants 6 months	Little Rock, AK Marietta, GA Durham, NC Akron, OH

Fluzone® 2004-2005 Among Healthy Children 2 Months vs 6 Months of Age		of age	Dayton, OH Pittsburgh, PA Norfolk, VA Seattle, WA (United States)
A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety and Tolerability of Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold Adapted (CAIV-T) in Healthy Infants	Live, Cold-Adapted Trivalent Influenza Vaccine	Healthy Infants 6 weeks to 24 weeks of age	Tampere, Finland
Clinical Trial of Safety (Reactogenicity) and Immunogenicity of Needle-free Jet Injection of Reduced-dose, Intradermal Influenza Vaccine (INF) Administered to >= 6 to < 24 Month-old Infants and Toddlers in the Dominican Republic	Inactivated influenza vaccine	Infants 6 to 24 months old	Santo Domingo, Distrito Nactional, Dominican Republic
A Single-centered, Open-labeled, Phase 4 Study of 2012-2013 Trivalent Seasonal Influenza Vaccine	Inactivated influenza vaccine	Individuals 6 months to 85 years	Zhengzhou, Henan, China
Evaluation of Safety and Immunogenicity Among Different Age-groups Receiving Different Split Influenza Vaccines	Evaluated vaccine, imported compared vaccine, domestic compared vaccine	Children between 6 and 36 months Children between 6 and 12 years old Adults above or equal to 60 years old	Langfang, Hebei, China Baotou, Inner Mongolia, China
A Multi-centre, Phase II, Open Labelled	Trivalent Inactivated	Children aged 14 months to 26	Oxford, Oxfordshire,

Randomised Control Trial to Describe Immune & Transcriptomic Responses to Trivalent Inactivated Vaccine (TIV) & MF59 Adjuvanted Influenza Vaccine (ATIV) in 14 -26 Month Healthy Children	Influenza Vaccine Trivalent Inactivated Influenza Vaccine with MF59 Adjuvant	months	United Kingdom
A Randomized, Double-Blind, Placebo-Controlled Trial on the Clinical Efficacy and Safety of a Single Dose of Trivalent Seasonal Live-Attenuated Influenza Vaccine(LAIV) Among Children Aged 24 Through 59 Months in Bangladesh	Trivalent Live-Attenuated Influenza Vaccine	Children aged 24 through 59 months of age	Dhaka, Bangladesh Matlab, Bangladesh
Assessment of the Safety and Immunogenicity of a Single Dose of Intranasal Seasonal Trivalent Live-Attenuated Influenza Vaccine Among Children Aged 24 Through 59 Months in Bangladesh	Trivalent Live-Attenuated Influenza Vaccine	Children aged 24 through 59 months of age	Dhaka, Bangladesh
A Randomized, Double-Blind, Phase I Study Comparing an Increased Dose(s) (0.5 ml) of Trivalent Inactivated Influenza Vaccine (TIV) With Standard Dose(s) (0.25 ml) TIV in Children 6-35 Months of Age	Trivalent Inactivated Influenza Vaccine .5mL v .25mL doses	Children between 6 and 35 months of age	Atlanta, GA Iowa City, IA Baltimore, MD Saint Louis, MO Cincinnati, OH Nashville, TN (United States)
A Phase II, Randomized, Controlled, Observer-Blind, Clinical Study to Evaluate the Humoral and Cell Mediated Immunity and Safety of Two Intramuscular Doses of MF59C.1-adjuvanted	MF59C.1 adjuvanted subunit influenza vaccine Inactivated subunit influenza vaccine	Healthy children between 6 and 36 months	Sint Vincentiusstraat 20, Antwerpen, Belgium Stadsomvaart 5, Hasselt, Belgium

Subunit Influenza Vaccine or Conventional Subunit Influenza Vaccine in Previously Unvaccinated Healthy Subjects Aged 6 to <36 Months