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Effective influenza vaccines for children

A critical unmet medical need and a public health priority

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Seasonal influenza causes clinical illness and hospitalization in all age groups; however, conventional inactivated vaccines have only limited efficacy in young children. MF59®, an oil-in-water emulsion adjuvant, has been used since the 1990s to enhance the immunogenicity of influenza vaccines in the elderly, a population with waning immune function due to immunosenescence.

Clinical trials now provide information to support a favorable immunogenicity and safety profile of MF59-adjuvanted influenza vaccine in young children. Published data indicate that Fluad®, a trivalent seasonal influenza vaccine with MF59, was immunogenic and well tolerated in young children, with a benefit/risk ratio that supports routine clinical use. A recent clinical trial also shows that Fluad provides high efficacy against PCR-confirmed influenza. Based on the results of clinical studies in children, the use of MF59-adjuvanted vaccine offers the potential to enhance efficacy and make vaccination a viable prevention and control strategy in this population.

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Introduction

Children have the highest attack rates of influenza and an increased risk of influenza-related hospitalizations due to their naive immune systems. Putting aside the matter of community transmission and herd effects conveyed to the entire population that are achievable by vaccination of children, direct protection of all children with vaccines that are efficacious in the pediatric population remains an unmet medical need and a public health priority. Increasingly, countries around the world are following the lead of the US and implementing influenza vaccination recommendations for young children. However, conventional trivalent inactivated influenza vaccines based on split virions or subunits of the influenza virus work poorly in young children.[1] Highlighting this point, recent data from the US Centers for Disease Control and Prevention (CDC) reveal that during the 2010–2011 influenza season, 115 US children died from influenza, including 56 children with no high risk condition.[2] Moreover, of the 115 pediatric influenza deaths, 17 of these children were fully vaccinated in accordance with the ACIP recommendations, calling out the tragically inadequate efficacy of current pediatric influenza vaccines. Clearly pediatric influenza remains an unsolved public health problem and an area of unmet medical need. Live attenuated influenza vaccine (LAIV), while more efficacious in young children than inactivated vaccines, is of limited utility due to its safety profile in the pediatric population under two years of age. Adjuvanted vaccines such as an MF59-adjuvanted influenza vaccine (Fluad, Novartis Vaccines) may provide the most promising option for protecting young children from influenza.

Burden of Influenza in Children

Approximately 20% of children contract influenza each year; however, as most cases are self-limiting and medical care is not always sought, the prevalence of mild illness is difficult to measure accurately.[3] Incidence estimates based on outpatient visits vary by country (**Table 1**).[4-15]

Table 1. Summary of burden of influenza among children in Europe

Country	Outpatient incidence[a] (age 0–4 y)	N/rate of hospitalizations	Number of deaths	Influenza vaccine recommendations
England	354 per 100,000 (2002–2008) [Paget et al., 2010][2]	144 per 100,000; age < 6 y (2001–2002) [Nicholson et al., 2006][5]	n = 70; age < 18 y (June 2009–March 2010) [Sachedina and Donaldson, 2010][6]	Children aged ≥ 6 mo with underlying medical conditions
France	NR	n = 226; age < 14 y (July–November 2009) [Fuhrman et al., 2010][7]	n = 5; age < 15 y (July–November 2009) [Fuhrman et al., 2010][7]	Children aged ≥ 6 mo with underlying medical conditions
Germany	NR	123 per 100,000; age 0–3 y (1999–2001) [Forster et al., 2004][8]	n = 4; age < 15 y (2009) [Federal Health Monitoring, 2010b][9]	Children aged ≥ 6 mo with underlying medical conditions
Italy	9,229 per 100,000 (2002–2008) [Paget et al., 2010][2]	n = 63; age ≤ 15 y (August–December 2009) [Calitri et al., 2010][10]	NR	Children aged ≥ 6 mo with underlying medical conditions
The Netherlands	925 per 100,000 (2002–2008) [Paget et al., 2010][2]	62.7 per 100,000 (non-ICU); age 0–5 y (June–December 2009) [van't Klooster et al., 2010][11]	n = 14; age 0–14 y (Jun–Dec, 2009) [van't Klooster et al., 2010][11]	Children aged ≥ 6 mo with underlying medical conditions
Spain	2,156 per 100,000 (2002–2008) [Paget et al., 2010][2]	4.1 per 1000; < 6 mo (2001–2004) [Montes et al., 2005][12]	n = 41; age 5–14 y (weeks 46–48, 2009) [Leon-Gomez et al., 2010][13]	Children aged ≥ 6 mo with underlying medical conditions
Finland	179 per 1000[b] age 0–3 y (2000–2002) [Heikkinen et al., 2004][14]	276 per 100,000; age < 6 mo; 173 per 100,000; age 6–11 mo (1988–2004) [Silvennoinen et al., 2011][15]	n = 2; age ≤ 16 y (1998–2004) [Silvennoinen et al., 2011][15]	All children aged 1–3 y

Data collected in Germany during the 2008/2009 and 2009/2010 seasons indicate that influenza was from 1.5 to 3 times more common in children ≤ 4 y of age than in those from 5 to 15 y of age.[16,17]

Hospitalizations due to laboratory-confirmed influenza affected 123 per 100,000 children in Germany between 1999 and 2001,[8] and in those below 4 y of age, from 300 to 3,500 such hospitalizations occurred annually between 2002 and 2010.[17] In the US during the 2009/2010 influenza season, the hospitalization rate for children aged 0 to 4 y was 6.7 per 10,000, for children aged 5 to 17 y was 2.5 per 10,000 and for adults was 2.8 per 10,000.[18] Although a significant number of deaths were reported during the A/H1N1 pandemic in 2009, influenza mortality is generally low in European children.[6,7,9,11]

The economic burden of influenza in children is largely driven by hospitalizations, emergency department visits, and missed work by parents. A study considering 2000/2001 through 2003/2004 seasons in the US found that the average direct medical costs for children below 5 y of age with laboratory-confirmed influenza were $5,402 per hospitalization, or $44–163 million per annum, and $512 per emergency department visit, or $62–279 million per annum.[19] The average length of stay was 2.1 d for children not admitted to intensive care and 6.1 d for children requiring intensive care. Significantly higher medical costs were associated with intensive care treatment ($22,580 vs. $3,668; $p < 0.001$). High-risk conditions, respiratory syncytial virus coinfection, and pneumonia were also associated with higher cost, as consistent with earlier findings.[20] In Germany, influenza hospitalizations for children under 15 y of age cost €14 million in 2008, and hospitalizations for children up to 3 y of age in an earlier season were €7.5 million.[21,22]

A population-based study found that 14.2% of UK children aged 1 to 14 y developed complications following influenza infection.[23] In a US study, the respective rates of acute otitis media or pneumonia within 30 d of influenza in children 6 mo to 17 y of age were 10.9% and 2.5% during the 2009 influenza A/H1N1 pandemic, 12.6% and 1.5% during the 2008/2009 H1N1 season, and 22.0% and 2.0% during the 2007/2008 H3N2 season.[24] The risk of developing otitis media or other respiratory complications is highest in children aged below 2 y, but remains significant throughout childhood.[25] Decreased health-related quality of life was estimated at 9.36 d for children who developed otitis media and 7.89 d for those who had respiratory complications.[26]

Medical Need for an Improved Influenza Vaccine for Children

Children have an increased susceptibility to infection and play an active role in the spread of influenza, serving as the main vector for household infection.[27] Children also have a longer duration of virus shedding than adults, are less likely to observe cough and sneeze precautions, and are more often found in close proximity to other children, family members and caregivers.[28,29]

Vaccination is the most important strategy for preventing and controlling influenza. Conventional trivalent inactivated influenza vaccines are not very effective in producing protective antibodies in young unprimed children. Antibody production during early life differs from that seen during adulthood; immunoglobulin G (IgG) and IgA antibody responses to pathogens are relatively weak and short-lived, and the antibodies produced have low avidity. One systematic analysis

revealed a disappointing 59% efficacy in preventing confirmed influenza and 36% effectiveness in preventing influenza-like illness in children aged below 2 y but efficacy similar to that of placebo in younger (immunologically unprimed) children.[1] Notably, the CDC data revealed that, of the 115 US children who died from influenza or influenza-related complications during the 2010–2011 influenza season, 23% were vaccinated.[2]

Thus far, a universal immunization strategy for children has not been implemented in most countries in Europe. In the Americas, the trend over the past decade has been toward an increased focus on pediatric influenza vaccination (**Table 2**). The rationale for this policy shift has primarily centered on the need for direct protection of children as an at risk population, but also on the benefits of indirect protection, or herd effects. The use of an adjuvant, such as MF59, offers a potential strategy for enhancing vaccine immunogenicity and effectiveness without the need to increase the antigen content of a single vaccine dose.

MF59 Adjuvant

MF59 is an oil-in-water emulsion of small and stable microvesicles of squalene, a naturally-occurring biodegradable, biocompatible compound.[30] The squalene is surrounded by a monolayer of nonionic surfactants [polysorbate 80 (Tween 80) and sorbitan trioleate (Span 85)] found in many foods and pharmaceutical products, with citrate buffer to stabilize pH. MF59 acts only in the presence of antigen by inducing a local immunostimulatory environment that enhances antigen uptake by monocytes, promotes their maturation into dendritic cells, then facilitates migration of the dendritic cells to lymph nodes where they can stimulate a specific immune response. This process results in the production of more effective antibodies, resulting in improved virus neutralization and inducing broader cross-reactivity. In addition, MF59 is rapidly cleared from the injection site.[30]

The MF59-adjuvanted influenza vaccine (Fluad) is currently licensed for use in older adults from 65 y. Fluad is an inactivated surface antigen influenza vaccine based on the egg-derived conventional vaccine, Agrippal® (Novartis Vaccines) and is formulated for seasonal influenza vaccination based on the WHO recommended strains. For the 2011/2012 season, these strains include an A/California/7/2009 (H1N1)-like virus, an A/Perth/16/2009 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. Each vaccine dose contains 15 μg of each recommended surface antigen in 0.5 mL, which is produced in eggs and adjuvanted with MF59.

MF59 was first approved for human use in Europe in 1997 as an adjuvant in a seasonal influenza subunit vaccine for older adults, a population in which it produced higher hemagglutination inhibition (HI) titers than conventional comparator influenza vaccines, particularly in persons with underlying chronic disease.[31] An integrated safety analysis of 64 clinical trials showed that those who received the MF59-adjuvanted vaccine had no increased risk for important adverse events, such as cardiovascular diseases, autoimmune diseases, new onset of chronic diseases, and death compared with subjects who received non-adjuvanted vaccines. Mild, transient postimmunization reactions were more common in subjects receiving the adjuvanted vaccine and are generally attributable to the local pro-inflammatory response induced by the adjuvant.[32] No cases of narcolepsy or increase in sleep-related adverse events were found in recipients of MF59-adjuvanted influenza vaccines.[33]

A pharmacoeconomic evaluation of the MF59-adjuvanted vaccine in the elderly population of Italy[34] showed that a vaccine coverage rate of 65.6% would reduce the number of influenza-like disease cases by 26.9% with a conventional vaccine or 35.8% with MF59-adjuvanted vaccine. The projected increased cost savings with MF59-adjuvanted vaccine largely reflected decreased hospital admissions.

MF59-Adjuvanted Influenza Vaccine in Children

The immunogenicity and safety of the MF59-adjuvanted vaccine were first evaluated in children during the 2006/2007 season in Finland. In this study, 269 unprimed healthy children 6 to 36 mo of age received two doses, four weeks apart, of the MF59-adjuvanted vaccine or a licensed non-adjuvanted split virion vaccine (Vaxigrip®, Sanofi pasteur). The

Table 2. National recommendations for seasonal influenza vaccination by age group, 2008/09/10

	Children	Chronically ill	Older Adults
North America	USA (6 mo +)	USA	USA
North America	Canada (2–4 y)	Canada	Canada
Europe	Austria, Estonia, Slovakia (6 mo–18 y) Finland (6–35 min) Latvia, Slovenia (6–24 min) Russia (2–11 y, attending pre/school)	EU 27 Russia	EU 27 (65+) Germany, Greece, Hungary, Russia (60+) Poland (55+) Austria (50+)
Latin America	Mexico (6 mo–5 y) Chile (6–4 y) Argentina, Brazil, Colombia (6–23 min) Venezuela (6–23 min)	Argentina, Brazil, Chile Colombia, Mexico Venezuela	Argentina, Brazil, Chile, Colombia (65+) Mexico, Venezuela (65+)
Asia	India (6 min–9 y) Thailand (6 mo–12 y) China, S. Korea (< 59 min)	China, Turkey S. Korea, Thailand	Australia, India, Turkey (65+) Thailand, S. Korea (65+) China (60+)

Sources: EU: Mereckiene et al., EuroSurveill. 2010; CENSIA; S. Korea Ministry of Health; US CDC

MF59-adjuvanted vaccine produced significantly higher postvaccination immune responses, measured as geometric mean titers (GMTs) and geometric mean ratios (GMRs) against haemagglutinin when compared with the non-adjuvanted split vaccine ($p < 0.001$ for each strain tested). Both vaccines yielded high seroprotection rates for A/H3N2 (100 vs. 99%), but the MF59-adjuvanted vaccine gave significantly higher rates for A/H1N1 (100 vs. 86%; $p < 0.001$) and influenza B (99 vs. 33%; $p < 0.001$). More recipients of the adjuvanted vaccine had evidence of seroprotection against A/H3N2 (91 vs. 49%) and A/H1N1 (51 vs. 18%) after the first dose of vaccine (both $p < 0.001$). A similar pattern was observed for seroconversion rates. Antibody titers declined over time, but remained higher with the adjuvanted vaccine when measured 6 and 12 mo postvaccination. In addition, the adjuvanted vaccine induced higher seroprotection rates against mismatched strains of A/H1N1, A/H3N2 and B.[33] Of note, two doses of the MF59-adjuvanted trivalent influenza vaccine were sufficient to meet all Committee for Medicinal Products for Human Use (CHMP) assessment criteria for all strains tested, whereas two doses of the non-adjuvanted split vaccine were sufficient to meet all criteria for the A strains but not the B strain.

During the 7 d postvaccination, solicited injection site and systemic reactions were typically mild or moderate and subsided within 2 to 3 d. More injection-site swelling was observed with the adjuvanted vaccine consistent with its mechanism of action; however, in other respects reactogenicity was similar among children receiving either vaccine. In general, both local and systemic reactions occurred at lower rates after the second dose than after the first dose with both vaccines. Other adverse events from the start of the study until the end of the 6-mo follow-up were comparable between vaccine groups.[35]

Eighty-nine children who completed the clinical study were enrolled in an extension study and received a booster dose formulated for the 2007/2008 season. GMTs measured three weeks after booster vaccination were significantly higher with the MF59-adjuvanted vaccine than with the non-adjuvanted vaccine. All participants had evidence of seroprotection against the influenza A strains; for influenza B 100% of adjuvanted vaccine recipients and 68% of non-adjuvanted vaccine recipients had evidence of seroprotection. Among children under 3 y of age at the time of the booster dose, the MF59-adjuvanted vaccine was more likely to impart protective immunity against influenza strains than the non-adjuvanted vaccine. As in the earlier study, injection site reactions were more common with the MF59-adjuvanted vaccine.[36]

A randomized, observer-blind, controlled study was conducted over two consecutive influenza seasons (2007/2008 and 2008/2009) in Finland and Germany to investigate the efficacy of the MF59-adjuvanted vaccine in the pediatric population. Approximately 4900 healthy children aged 6 to 72 mo of age received the MF59-adjuvanted seasonal influenza vaccine, or a conventional seasonal trivalent inactivated influenza vaccine (in the first season: Agrippal, Novartis Vaccines; in the second season: Fluarix/Influsplit SSW, GlaxoSmithKline), or comparator non-influenza vaccines (a meningococcal C conjugate vaccine, Menjugate®, or a tick-borne encephalitis vaccine, Encepur® Children). The primary outcome was the incidence of PCR-confirmed influenza. The vaccine efficacy of the MF59-adjuvanted vaccine vs. non-influenza vaccine against vaccine matched strains was 89% while the conventional seasonal trivalent inactivated influenza vaccine had an efficacy of 45%. Age specific relative efficacies of the MF59-adjuvanted vaccine over conventional trivalent inactivated influenza vaccine for 6–24, 6–36 and 36– < 72 mo old children were 75%, 68% and 91%.[37]

Conclusion

Influenza causes a substantial clinical and socioeconomic burden in children, particularly in younger children who are at high risk of influenza-related hospitalizations. Although vaccination is an effective strategy for preventing and controlling influenza infection, conventional non-adjuvanted vaccines have limited immunogenicity and efficacy in younger children owing to the functional immaturity and naivety of their immune system. The MF59-adjuvanted influenza vaccine enhances immunogenicity and efficacy, and thereby may offer a more effective vaccine strategy for preventing and controlling influenza in the pediatric population.

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