Influenza is an important cause of morbidity and mortality worldwide. Children exhibit the highest rates of influenza virus infection, whereas older adults have the highest mortality rates [1, 2]. However, half of all influenza-related deaths occur in groups with other risk factors [1, 2]. These risk factors include immune compromise, particularly in patients with cancer, because of both immune compromise from their disease and myelosuppressive chemotherapy. Within a given community, an influenza epidemic may last 3–6 weeks and may be associated with attack rates as high as 10%–20% in the general population; however, attack rates are higher among individuals with cancer [3–5].

In this issue of the Journal, Carr et al [6] from St. Jude Children’s Hospital report an open-label, single-site trial that compares the safety and immunogenicity of live attenuated influenza vaccine (LAIV) with trivalent inactivated vaccine (TIV) in mildly to moderately immunocompromised children with cancer. The authors enrolled 55 subjects with a mean age of 10.4 years; 28 subjects received LAIV, and 27 received TIV. This work builds upon prior investigations of influenza vaccines in immunocompromised children.

In 1977, Feldman et al [7] characterized the clinical features of laboratory-confirmed influenza in 20 children and young adults with cancer. Symptoms of influenza infection were typical but lasted twice as long as in the general population [7]. In addition, 16 patients had chemotherapy withheld for 4 days–3.5 weeks. In 1989, Kempe et al [4] reported a higher frequency of influenza infection among children with cancer (23 [32%] of 73 children), compared with community control subjects (10 [14%] of 70; \( P = .02 \)) in a prospective study of influenza among unimmunized, immunosuppressed children with cancer. A more recent study by Tasian et al [8] reported results from a 5-year retrospective review of children with cancer who had proven influenza A or B infection from 1 July 2000 through 30 June 2005. These investigators identified 27 clinical encounters in 24 oncology patients, with two-thirds of the patients hospitalized for a median duration of 7.4 days and 40% of them experiencing a delay in chemotherapy as result of influenza infection [8]. In addition, 15% of the subjects had concurrently diagnosed bacteremia. Others have reported severe and fatal complications due to influenza disease in this population, such as secondary bacterial infections and hemophagocytic syndromes [4, 7, 9, 10], including serious complications from the 2009 pandemic influenza A H1N1 virus [11]. In addition, immunosuppressed individuals can shed virus for prolonged periods, and this could lead to nosocomial outbreaks of influenza [12–14].

Yearly influenza vaccination is recommended for high-risk individuals, including children with cancer [15]. Most results indicate that, after immunization with inactivated influenza vaccines, hemagglutination inhibition assay titers in the range of 1:32 or 1:40 are required to confer 50% protection against infection [16], and higher titers are associated with higher degree of protection [17]. Studies published in the 1970s and 1980s investigated 2 doses of inactivated influenza vaccine in children with and children without cancer [18–20]. These discrepancies may be explained by the use of different influenza vaccines, different immunization schedules, different chemotherapeutic regimens, and most importantly, inadequate sample sizes in those studies in which a statistically significant difference was not observed between children with and children without cancer [20]. The majority of these earlier studies, however, reported that lower antibody titers were achieved in individuals with cancer, compared with antibody titers in healthy control subjects [20].

In addition, individuals who were receiving...
chemotherapy had significantly lower titers, compared with titers in those not receiving chemotherapy [20]. More recent influenza trials with the trivalent inactivated influenza vaccines revealed children with ALL did have an immune response [29–34]; however, these studies also confirmed lower titers and seroresponse rates to influenza vaccines in children with ALL compared to healthy controls and lower titers in those who received chemotherapy compared to those off chemotherapy [29, 30, 34].

A cold-adapted, Ann Arbor strain LAIV (MedImmune) is currently licensed for eligible individuals 2–49 years of age [35, 36]. Published studies indicate that LAIV is efficacious, especially in children and first-time vaccine recipients [37–40]. However, data regarding vaccine use in immunocompromised patients are limited. Previous studies have documented the safety and immunogenicity of this live vaccine in HIV-infected adults and children with mild to moderate immunodeficiency [41–43].

A phase I, multicenter, randomized, double-blind trial comparing LAIV with placebo in mild to moderately immunocompromised children with cancer was recently reported [44]. Twenty subjects were enrolled (LAIV, 10 subjects; placebo, 10 subjects), with a mean age of 12.2 years. Ten subjects had hematologic malignancy (LAIV, 4 subjects; placebo, 6 subjects); 10 subjects had solid tumors (LAIV, 6 subjects; placebo, 4 subjects). The authors found that LAIV resulted in an increased incidence of runny nose or nasal congestion occurring in all LAIV recipients, but no related serious adverse events related to the vaccine were observed. Four of 10 LAIV recipients shed vaccine virus, with none exceeding 7–10 days duration. LAIV demonstrated modest immunogenicity by hemagglutination inhibition (≥4-fold increase for any strain, 33%) and microneutralization assays (≥4-fold increase for any strain, 44%) [44]. These previous trials generated initial safety data regarding LAIV in children with cancer and provided a foundation for the current study.

In the report by Carr et al [6], the group also assessed the incidence and duration of viral replication after vaccination with LAIV. The authors confirmed the earlier safety findings of LAIV in this population and also documented shedding of virus limited to 7 days [44]. In contrast to a previous study that compared LAIV with placebo [44], rhinorrhea was equal in both groups, with over a third of both groups reporting this symptom. Two serious adverse events were considered to be possibly related to the vaccine, with 1 adverse event in each group.

Unexpectedly, the authors discovered that TIV was significantly more immunogenic for influenza A antigens, but no differences were noted for influenza B responses. Data were available for 52 subjects (26 in each group). When comparing the postvaccination geometric mean titers, TIV induced greater responses, compared with LAIV, against both A/H1N1 virus (89 vs 17; P < .001) and A/H3N2 virus (228 vs 126; P < .001). TIV also elicited a higher percentage of seroconversion against A/H3N2 antigens (46.1% vs 7.6%; P = .004), and a higher percentage of subjects who received TIV achieved protective titers (>1:40) for A/H1N1 virus (73% vs 34.6%; P = .01). The authors suggested that, because both groups had high percentages of preexisting antibodies (80.7% for the TIV group and 84% for the LAIV group), this could explain why no differences were noted in the percentage of subjects who achieved seroprotection against A/H3N2 virus.

Of note, antibody responses to all 3 influenza antigens were lower in the study cohort than in healthy children. This has been shown previously in numerous influenza vaccines trials conducted in cohorts of children with cancer, with healthy control subjects achieving higher antibody titers. The authors noted that individuals with higher immunoglobulin (Ig) G levels were more likely to achieve higher seroprotection against A/H1N1 in both vaccine groups, compared with those with lower IgG levels. However, the authors did not identify a difference in vaccine response based on the total number of circulating lymphocytes or neutrophils, which was possibly attributable to small sample sizes. Moreover, T-cell responses as measured by enzyme-linked immunospot assay were also variable between groups, presumably because of the underlying immune compromise in these patients.

Even though the study by Carr et al [6] was not powered for efficacy, 2 children in the TIV group and 1 child in the LAIV group had documented laboratory-confirmed influenza A infection after vaccination. In previous efficacy trials that compared LAIV to TIV in children, 2 studies demonstrated higher efficacy in the LAIV group, one in a cohort of healthy children [39] and the other in a cohort of children with asthma [45]. However, the opposite has been reported in LAIV versus TIV comparisons among adults, with TIV reported as more efficacious at preventing laboratory-confirmed symptomatic influenza A disease [46–48] and more efficacious against laboratory-confirmed influenza among highly immunized military service members [38]. The exact explanation for age-specific differences in efficacy is a matter of speculation. Previous reports have suggested that the apparent increase in efficacy of TIV in adults is attributable to the inability of the live attenuated viruses to infect some adults because of their past exposure to similar strains [46]; the same phenomenon may explain the enhanced immune response to TIV in this highly vaccinated cohort of children. Conversely, previous data also suggest that LAIV may be just as effective as TIV among vaccine-naive military personnel [38]. Thus, further studies to understand the correlates of protection of LAIV in this population are needed.

Influenza is an important cause of morbidity and mortality among
children with cancer, and optimizing the best influenza prevention strategies in this population is important, especially given the emergence of oseltamivir-resistant influenza viral strains [49, 50]. Therefore, the "old" way of preventing influenza disease in high-risk immunocompromised individuals with TIV may be the best strategy, given the current data. However, other "new" vaccine strategies, such as higher antigen doses and/or adjuvanted influenza vaccines, could prove valuable in this vulnerable population, because vaccine responses in this population are less than optimal, especially when compared with those in healthy individuals.

Notes

Financial support. This work was supported by Sanofi Pasteur, Novartis, UBS Optimus Foundation and Pfizer, and MedImmune.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


