Current developments and trends in childhood immunization

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Abstract

In this paper we highlight several instances in which there is potential for novel utilization in the near future of relatively recently licenced vaccines, vaccines approaching licensure or vaccines already in established use. Specifically we discuss the potential for universal seasonal influenza immunization and the arrival of live attenuated intranasal vaccine which was licenced for use in children aged 2—17 years in Europe in 2010, the potential use of live oral rotavirus vaccines for infants, two of which have been available in Europe since 2006, pertussis, which despite availability and widespread use throughout Europe of acellular vaccines for many years is causing, if anything, worsening problems in many countries so that novel strategies and solutions are needed and finally endemic meningococcal disease, for which in Europe, conjugate group C vaccines have been in use for 10 years but may now require revised schedules. Novel protein-based vaccines designed to prevent much of this disease caused by the main remaining European serogroup, namely B, are expected to be licenced and available for use imminently.

Keywords catch up programmes; duration of immunity; herd protection; influenza-related morbidity; intussusception; LAIV (live attenuated influenza vaccine); MenB vaccine; meningococcal vaccines; pertussis; rotavirus vaccine

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Introduction

The prevention of childhood infections has been the main driving force behind the development of vaccines for many years. The general use of vaccines globally in early life has proven to be one of the most valuable and cost-effective tools in modern medicine and has already saved millions of lives while their potential impact continues to grow. Over time, developments in microbiology and manufacturing techniques combined with a massive clinical trials effort have permitted steady growth in the list of infections against which effective vaccines are available. More recently improvements in the understanding of immunology and genetics have opened new doors in vaccine development and in the near future new approaches to administration of vaccines and implementation of a range of new adjuvants which amplify immune responses will also lead to further significant advances.

In terms of vaccine utilization, two important new trends have emerged in the last decade, one in resource-poor countries and the other in the wealthier nations. In the former, important recent global funding and policy initiatives have driven both higher uptake rates in established programmes with improved disease control notably of polio and measles. Development, evaluation and implementation of new vaccines have also progressed in these regions, including some also in use in the West, like conjugate Hib and pneumococcal vaccines and rotavirus vaccines. Work testing and implementing other vaccines specifically intended for poorer countries like malaria vaccines and conjugate meningococcal group A vaccine are also moving forwards rapidly.

The new and emerging implementation trend in many well-resourced countries, particularly in Europe, is a widening gap between the number of vaccines recommended and in routine use and the number licenced and available, with the latter number rising noticeably faster than the former. With widely heterogeneous policy making, purchasing and delivery mechanisms in different countries, the factors which drive this trend are complex but, in essence, they are all related to evaluation of the balance between the cost and benefit derived from specific novel vaccines, decisions either made centrally by governmental health policy agencies or by the individual clinician or parent. The net result is that a substantial proportion of current vaccine-preventable illness is not being prevented and this issue needs now to be confronted by all the relevant parties (including, amongst others, both purchasers and manufacturers) who need jointly to re-formulate their strategies in order to address it, recognizing the need for distinct business cases for different economic and policy environments.

Last but not least, there is a growing recognition that the single most important potential limiting factor for effective deployment of paediatric vaccines in coming years is likely neither to be availability of safe and effective vaccines nor their cost, but rather their acceptance by parents. Vaccine scares are now commonplace and, in the context of the rarity in wealthy countries of severe or fatal infectious deaths in childhood, both because of immunization itself and improved hygiene and nutrition, the need for more accurate and effective communication concerning immunization is becoming critical. As so many new communication tools have recently become widely available and used throughout the world, the need to exploit them to promote public health through vaccination is now urgent if not overdue.

Live attenuated intranasal vaccine against influenza

It is estimated that epidemics of influenza cause up to 5 million cases of severe illness and up to a half a million excess deaths each year. Young children are especially likely to be hospitalized and admission rates are comparable to the elderly, reaching 103.8 per 10,000 children under 6 months old. Complications following influenza infection are well known even in the paediatric population and more importantly over 50% of the paediatric deaths related to influenza are observed in previously healthy children not eligible for vaccine in programmes targeted only at high risk groups. Children have higher rates of infection and are ill and secrete the virus for longer than adults so, as a group, they not only bear a significant part of influenza morbidity but may also be important drivers of influenza epidemics. Close contact with their parents, siblings and other children at day care centres and schools further facilitates the transmission of the virus. Thus primary prevention of influenza in children by universal immunization could have both important direct and indirect effects. Although mortality rates among children are low in influenza epidemics, the considerable overall morbidity causes significant burden on healthcare systems as well as societal costs when parents are forced to take time off work. Since 2008, the Advisory Committee on Immunization Practices (ACIP) in the US have recommended that all children aged 6 months to 18 years be vaccinated every year, and some European countries have also issued recommendations on childhood influenza vaccinations. However, to date, such initiatives have not achieved consistently high uptake rates.

Available influenza vaccines

The currently available influenza vaccines are the trivalent inactivated influenza vaccines (TIV) which are licenced for all age groups from 6 months of age and the live attenuated influenza vaccine (LAIV) which is given as an intranasal spray and in Europe licenced for children 2–17 years of age. The idea of paediatric influenza vaccination programmes for all children has been in the spotlight lately and a recent meta-analysis suggests that adequate evidence for efficacy of inactivated injected trivalent influenza vaccine in the paediatric population is lacking, especially in children younger than 2 years old. The pooled efficacy of TIV from eight randomized controlled studies of healthy adults was 59% (CI: 51–67) whereas only one study exclusively studied children 6–24 months old over two influenza seasons found 66% efficacy in the first season but a −7% in the second one. Like other seasonal influenza vaccines, LAIV currently contains three strains (A/H1N1, A/H3N2 and one type B strain), (although quadrivalent versions of both vaccine types containing both of the divergent B strains now circulating are expected to be available soon) but the strains are weakened during the manufacturing process so that an attenuated phenotype emerges which can only replicate in the respiratory mucosa and not at temperatures higher than 20 °C. The vaccine is administered through a nasal spray using a delivery device (Accuspray, Becton Dickinson, Franklin Lakes, NJ, USA) and, like TIV is given as two doses 1 month apart if the child is younger than 9 years of age and has never been previously vaccinated against influenza. Other children are considered likely to be primed (either through vaccine administration or exposure to wild type viruses in previous years) and are given one dose. The vaccine was first licenced in 2003 in the US for healthy individuals aged 2–49 years old. In six randomized placebo controlled studies done in children 6 months–7 years old, over eight influenza seasons, the pooled efficacy was 83% (CI: 69–91) and the vaccine was significantly better than placebo in all seasons. In a randomized, double blind head to head study of almost 8000 healthy children, LAIV was found to be approximately twice as effective in preventing virologically proven influenza as TIV (153 vs 338 cases, $p < 0.001$) with similar side effect rates, although TIV recipients complained more of sore arms while LAIV recipients had more nasal congestion. In this study, children aged 6–11 months who received LAIV had significantly higher rates of all-cause hospital admission during the 180 days following enrolment ($p = 0.002$) and previously unvaccinated 6–23-month-olds had more episodes of wheezing during the 42 days after the first dose although the difference did not reach statistical significance ($p = 0.076$). Another placebo controlled study also showed increased rates of wheezing in children aged 18–35 months although no associated increase in hospitalization was observed. Several randomized controlled studies failed to show such increase in wheezing episodes or hospitalizations as reviewed by Osterholm et al. As a consequence of these observations, the vaccine is not currently licenced for children younger than 2 years of age. Although it is recommended that children with severe asthma (BTS sign step 4) in the preceding months or active wheezing at the time of vaccination should not receive LAIV, widespread use of the vaccine in children in the US, many of whom have histories of asthma or wheezing, has not been associated with significant problems. Based on the available data, LAIV appears to be consistently more effective in protecting against RT-PCR or viral culture confirmed influenza, especially in children aged 2–7 years old.

Herd protection and influenza immunization

The likely role in propagation of influenza infections by children means that effective widespread immunization might indirectly prevent influenza-related morbidity in others including children and adults at high risk. There are data demonstrating herd protection effects resulting from immunizing children against influenza. A Canadian cluster-randomized study of TIV in isolated communities found that a mean coverage rate of 83% in children aged 3–15 years resulted in a protective effectiveness of 61% among non-vaccinated individuals of all age groups and results of one of two published non-randomized school-based cluster studies of LAIV both of which achieved approximately 50% coverage showed evidence of indirect protective effects among unimmunized pupils.

Estimating cost-benefit

Increasingly efforts are made objectively to evaluate the potential cost-benefit of proposed health interventions competing for health budgets and universal influenza immunization is no exception. Such projects are usually based on mathematical transmission models which attempt to predict the more complex heterogeneity of real life and which can include allowances for indirect effects. One such study predicts that influenza vaccination of children in England and Wales aged 2–18 years at 50% coverage would lead to the prevention of up to 95% of