REVIEW

Influenza burden of illness, diagnosis, treatment, and prevention: what is the evidence in children and where are the gaps?

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Influenza is a disease of global public health significance. Traditionally the emphasis has been on adult disease because of the impact of influenza related mortality in the elderly and other high risk groups. However, it is becoming increasingly better recognised that young children suffer considerable morbidity from influenza.[1–6] There are also potential consequences for siblings, parents, other carers, and extended family members in terms of secondary infections and carer leave. Influenza infection in childhood could be effectively prevented through vaccination. However, the United States is the only industrialised country currently recommending universal influenza vaccination for young children (between the ages of 6 and 23 months), as opposed to vaccinating only those with high risk conditions.[7][8]

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This paper discusses the burden of influenza in children, its economic impact, the availability of diagnostic tests, and their place in clinical practice, along with the role of antiviral therapy. We describe current recommendations for influenza vaccination and highlight where more evidence would be helpful.

BIOLOGY OF INFLUENZA

Influenza viruses are classified as type A, B, or C.[9–11] Clinically, influenza A and B infections are not readily distinguishable, both producing seasonal epidemics, whereas influenza C produces a milder coryzal illness.[11] Type A influenza viruses are further divided into subtypes based on variation in haemagglutinin and neuraminidase surface antigens.[11] The nomenclature of influenza viruses describes type, geographical origin, strain number, year first isolated and subtype, for example A/New Caledonia/20/99 (H1N1).[12][13] So far only influenza A viruses containing H1, H2, or H3 and N1 or N2, and influenza B have caused widespread human disease.[10] Only influenza A has the propensity to cause pandemic influenza.[9][11]

BURDEN OF INFLUENZA IN CHILDREN

Attack rates of influenza are higher among preschool and school age children than in any other age group.[3][14][15] The likelihood of residual cross-immunity from previous influenza infection is directly proportional to age.[11] There is a growing body of evidence that influenza in children produces a heavy burden in terms of primary care consultations, hospitalisations, and the use of antibiotics and over-the-counter medications.[1][5][6] Relevant European data are also accumulating.[4][16–18] In contrast the elderly suffer by far the highest mortality from influenza, especially during inter-pandemic periods.[3][19] It is worthy of note, however, that mortality in those younger than 19 years of age has accounted for up to 12% of deaths due to pneumonia or influenza during some influenza epidemics.[20] During the 2003–04 influenza season there were 143 influenza related paediatric deaths documented in the USA; about 40% of these were younger than 2 years, highlighting the high vulnerability of this age group.[7] In addition, almost one half of victims aged 2–17 years did not have an underlying high risk condition.[7] Paediatric influenza related deaths were also widely reported in the media in the UK,[21] and at least 12 were confirmed.[22] Because day care attendance has risen considerably in recent times,[23] opportunities for exposure and transmission may be greater than ever before in preschool children. These children are at high risk of respiratory infection[24] and may account for substantial health expenditure.[25] They may also be among the first infected during a community influenza outbreak.[3]

ROLE OF CHILDREN IN THE TRANSMISSION OF INFLUENZA

Studies conducted over 25 years ago showed than influenza spreads within families with secondary attack rates of up to 30%. Preschool and school age children were major introducers of influenza infection into communities.[26–28] However, with increased use of day care,[23] preschool age children may have become an even more important source of community transmission. There is also growing evidence that influenza vaccination is effective in interrupting transmission within families and communities. A single blind randomised controlled trial found that school age household contacts of influenza vaccinated day care children had significantly fewer respiratory illnesses, less school absenteeism, fewer physician visits, and lower use of antibiotics and over-the-counter medications than did contacts of unvaccinated children.[29] Similar results were achieved in an open labelled study in Italy.[18] The community impact of childhood influenza vaccination was shown during the 1968–69 influenza season in

Tecumseh, Michigan. A high vaccination rate among schoolchildren (about 85%) was associated with a threefold decrease in respiratory illnesses in the wider community compared with the rate in an unvaccinated community nearby.[30] In addition, population based findings from Japan suggest that a statutory programme of influenza vaccination of schoolchildren (from the 1960s through to the early 1990s) led to a significant decrease in winter season pneumonia and influenza and all-cause mortality, especially in the elderly. When the programme was subsequently discontinued, winter seasonal mortality increased.[31] However, an increase in the elderly population may have confounded these findings.[32] Our understanding of the direct and indirect effects of childhood influenza vaccination should be improved. Modelling would be helpful, as would a cluster randomised double blind controlled trial among day care children and their families.[33] If the vaccination of day care children is shown to substantially benefit both vaccinees and their close contacts, through reducing transmission and the incidence of influenza-like illness, this could form part of the justification for universal vaccination of preschool aged children against influenza.

ECONOMIC BURDEN OF CHILDHOOD INFLUENZA INFECTION

Influenza is associated with considerable economic costs to families, healthcare services, and society. When a child is symptomatic with influenza, costs may be incurred in terms of physician visits, medications, and parental absence from work. Transmission of influenza in the household may lead to parental time off work or parental illness that produces onward transmission in the workplace and in turn reduced productivity. Influenza vaccination of working adults and the elderly against influenza is both clinically and cost effective.[34] Vaccination of children is efficacious[35–37] and may well be cost effective.[34 38] No large scale randomised trial has yet evaluated the wider impact of routinely vaccinating children in terms of healthcare and other economic costs. Broadening the scope of influenza vaccination to include children would have the secondary benefit of increasing annual inter-pandemic usage, thereby increasing manufacturing capacity which would be needed in the event of a future pandemic.[39]

DIAGNOSTIC TESTS

Having an influenza-like illness has low specificity. Consequently specific tests performed in the laboratory are helpful. Recommended clinical samples include a nasal aspirate, nasal wash, and a nose or throat swab.[40 41] Direct and indirect fluorescent antibody testing (DFA and IFA) are both widely available and have high specificity, albeit with lower sensitivity. In comparison with viral culture, studies of the sensitivity of DFA for influenza A showed a median sensitivity of 62%.[42] The addition of polymerase chain reaction facilitates more sensitive diagnosis of influenza but requires specialised skills and is expensive. Presently it takes 1–2 days.[43] In contrast, rapid diagnostic, or near patient testing is clinically available and can produce a diagnosis within 30 minutes. Some kits also allow differentiation of influenza A from influenza B.[40 42] Rapid tests have been evaluated in both children and adults. Again the specificity is high with varying but generally moderate sensitivity.[40 42] The results of rapid diagnostic tests should always be interpreted against the background of clinical symptoms, the level of influenza activity in the community (epidemiological and virological surveillance data), and the presence of any high risk conditions in the patient. The use of near-patient tests has been associated with a reduction in investigations ordered and antibiotics prescribed in the emergency department setting.[44 45] They are most useful in the investigation of

outbreaks of respiratory disease or guiding decisions as to whether to commence antiviral therapy,[11] especially in severely ill children. In the clinical setting, a positive DFA, IFA, or rapid diagnostic test will have the highest positive predictive value when influenza activity in the surrounding community is high.[42] However, it should be noted that a positive diagnostic test for influenza does not exclude bacterial co-infection; and influenza may predispose to serious secondary bacterial pneumonia.[46 47]

ANTIVIRAL TREATMENT

In the absence of routine vaccination in children, antiviral treatment deserves consideration both for its therapeutic effect and its impact on disease transmission. During the 2003–04 northern hemisphere influenza season the combination of a clinically significant drift variant and shortages in vaccine supply, for example in the USA[48] threw into sharp relief the role of antivirals. They may be useful when there is a vaccine shortage during an inter-pandemic period and are likely to be of use in the first wave of a pandemic to contain spread from initial cases, and to protect healthcare workers when vaccine is either unavailable or in extremely short supply. Antivirals for influenza include two neuraminidase inhibitors (NAIs), oseltamivir and zanamivir (inhaled drug not recommended in children <12 years), and two M2 inhibitors, amantadine (not licensed in children <10 years in the UK) and rimantadine (not licensed in UK).[49]

The M2 inhibitors are not effective against influenza B.[50 51] In addition, when used for treatment and prophylaxis in the same setting they are likely to lead to the rapid emergence of resistant viruses which are transmissible person-to-person.[52 53] NAIs can reduce the chances of developing influenza by 70–90% in adults.[54] However, there is currently judged to be insufficient evidence for using an NAI for prophylaxis in children.[54] When used in treatment, NAIs reduce the duration of symptoms by up to two days.[42 54 55] The use of oseltamivir in children has also been associated with a reduction in the use of antibiotics,[56] but evidence for a reduction in hospitalisation has so far been obtained only in adults.[57] When used for treatment or prophylaxis, both M2 inhibitors and NAIs should be started within 48 hours after the onset of illness or exposure, respectively.[42 49 50 58 59] The NAIs have a considerably better adverse event profile than the M2 inhibitors,[10 50] although oseltamivir is sometimes associated with vomiting.[56] Guidelines have been set out by the Centers for Disease Control (CDC) in the USA and the National Institute for Clinical Excellence (NICE) in the UK (boxes 1 and 2).[49 51 58 59]

The cost effectiveness of antiviral therapy is less clear than for vaccination.[38] In addition, delivering timely treatment to a large number of children during the 8–12 week period of an influenza epidemic presents obvious logistic challenges. The problem for clinicians in deciding how best to use antivirals in the context of official guidelines is made more difficult by the lack of controlled trials of antiviral therapy in children less than 1 year old, immunocompromised children, and those with serious influenza related complications.[42] However there is a consensus that, during periods of known community influenza activity, antivirals should be considered for the treatment of high risk children with influenza-like illness providing treatment can be started within 48 hours of the onset of symptoms,[49] and for seriously ill children in hospital.[58]

INFLUENZA VACCINES

While inactivated and cold adapted, live attenuated influenza vaccines are both regarded as safe and effective,[35 36 60] only inactivated vaccines are currently licensed in the UK.[61] Inactivated influenza vaccines comprise either split virion

Box 1: Guidelines on the use of antivirals in the treatment of influenza

NICE: When influenza is circulating, patient is high risk, has an influenza-like illness, and can start within 48 hours of the onset of symptoms[49]

- Zanamivir: ≥12 years old
- Oseltamivir: child (lower age limit not specified)
- Amantadine is not recommended for treatment of influenza

CDC[51 58]

- Zanamivir if age ≥7 years
- Oseltamivir if age ≥1 year
- Amantadine for influenza A if age ≥1 year
- Rimantadine for influenza A in adults only

In institutions or other closed communities with many high risk individuals, should be used for treating persons who have been ill with influenza for <48 hours

Antiviral drugs should also be considered for the treatment of:

- High risk persons aged ≥1 year with influenza infection <48 hours after the onset of illness
- Seriously ill influenza infected hospital patients
- Family members of high risk individuals during local community influenza activity
- Low risk influenza infected individuals if adequate antiviral drug supplies

Box 2: Guidelines for the use of antivirals for prophylaxis against influenza

NICE: When influenza is circulating, patient is high risk, has an influenza-like illness, and can start within 48 hours of the onset of symptoms[59]

Oseltamivir:

- Age ≥13 years, and
- Exposed to an individual with an influenza-like illness, and
- Either (a) Not effectively protected by vaccination, that is
  - Not vaccinated, or
  - Vaccination yet to take effect, or
  - Vaccine strain not well matched to the circulating strain

or (b) Lives in residential care, regardless of vaccination status

Amantadine not recommended for prophylaxis

CDC[51 58]

- Oseltamivir: if patient ≥13 years
- Zanamivir not approved for prophylaxis
- Amantadine and rimantadine approved for prophylaxis of influenza A if age ≥1 year

These should be used for outbreaks in institutions or other closed communities with many high risk individuals for prophylaxis for both residents/patients and unvaccinated employees who are contacts during the outbreak.

Antiviral chemoprophylaxis should also be considered for:

- High risk persons ≥1 year of age during outbreaks in closed communities or even in the wider community
- Unvaccinated healthcare workers in close contact with influenza infected patients
- Seriously ill influenza infected hospital patients
- Family members of high risk individuals during local community influenza activity
- Low risk influenza infected individuals if adequate antiviral supplies

(virus particles disrupted by detergent treatment), subunit (haemagglutinin and neuraminidase surface antigens), or virosomal (surface antigens combined with phospholipids to produce virosomes) formulations.[12 62–64] There is no established preference as to which type should be administered in children, although thiomersal-free formulations are clearly desirable.[7 62] Meta-analysis has shown that the inactivated and live vaccines are of comparable efficacy in children,[37] although, if anything, the inactivated is slightly better. Despite evidence of safety from clinical trials, some experts have expressed theoretical concerns that the live intranasal vaccine could genetically reassort in the presence of co-infection to a more virulent strain.[37] The efficacy of influenza immunisation depends on a number of factors including the age of the vaccinee and the antigenic match between vaccine and circulating strains.[35] Achieving the latter is not always a straightforward process. For example, the circulating influenza A(H3N2) strain in the winter of 2003–04 was an A/Fujian/411/2002/like drift variant,[65] but it could not be grown readily in embryonated eggs in time to use as a seed virus in vaccine manufacture.[13] Since virological studies had shown that the Fujian-like strain was antigenically related to A/Panama/2007/99,[66] which was widely used in the 2002–03 northern hemisphere season, the latter was used again in 2003–04, even though it was not regarded as an ideal match. For the southern hemisphere winter of 2004 a Fujian-like drift variant was developed,[13] and this has also been incorporated into the northern hemisphere 2004–05 winter vaccine (H1N1: A/New Caledonia/20/99-like; H3N2: A/Fujian/411/2002-like; influenza B: B/Shanghai/361/2002-like).[67]

RECOMMENDATIONS FOR USE OF INFLUENZA VACCINES

When children who have not been previously exposed to influenza receive the influenza vaccine for the first time, they are immunologically naïve and immunogenicity is suboptimal. This mainly holds true for young children and is the reason why children under 13 years who are being vaccinated for the first time should receive two doses separated by 4–6 weeks.[68] Annual influenza vaccination is recommended for certain risk groups in many countries of the world, for example by the Advisory Committee on Immunization Practices (ACIP) in the USA and the Department of Health in the UK. These recommendations include persons aged 65 years and over, persons with chronic conditions of the lungs, heart, or kidneys, diabetes mellitus, immunosuppression, and anyone living in long term residential accommodation. Children with high risk conditions are included,[7 62] but

uptake is poor, especially where physicians do not proactively recommend the injection.[69] With effect from autumn 2002, annual influenza immunisation for children in the USA between 6 and 23 months of age was ''encouraged when feasible'' by ACIP.[11] This advice was recently upgraded for the 2004–05 winter season to a full ACIP recommendation.[7] In contrast, healthy European children and their household contacts are not currently recommended for immunisation,[70] although the subject is under investigation in some countries. More needs to be known about likely parental acceptance of annual influenza vaccination for children in Europe if policy were to change.

CONCLUSION

Children suffer substantial morbidity from influenza. However, most of the evidence is from the USA and more needs to be understood regarding the burden of disease in European countries and elsewhere in the world. Rapid diagnostic tests may be useful in detecting outbreaks or when deciding to whether to start antiviral drugs in high risk patients. During known periods of community influenza activity, antiviral therapy should be given to high risk children suffering an influenza-like illness, within 48 hours of the onset of symptoms, even without laboratory confirmation, and should be considered in any child who is seriously ill with an influenza-like illness. The inactivated vaccine is safe and effective. Universal infant influenza vaccination has been recommended in the USA but not yet elsewhere. More needs to be known about the likely parental acceptance of annual vaccination of children and stronger evidence needs to be generated for the clinical and cost effectiveness of vaccination, for children in terms of direct benefit, and indirectly regarding effects on the wider community. If so, a case might be established for other developed countries to emulate the ACIP recommendation.

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