

Immunisation in the current management of cystic fibrosis patients

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Abstract

Although no special recommendations exist, clearly patients with cystic fibrosis (CF) can benefit from immunisation. We reviewed the literature regarding vaccination in CF and other chronic diseases. CF subjects should follow national immunisation programmes without delay to obtain optimal vaccination coverage. Indeed they may escape normal programmes due to frequent hospital admissions and school absenteeism and may be more at risk to get “vaccine-controlled” diseases at any age. There is no uniform European immunisation schedule for basic infant and childhood vaccines or for vaccines against hepatitis A (HAV) and B (HBV), varicella (VZ) and booster vaccinations. HAV and HBV vaccination is appropriate in CF as recommended in general for patients with chronic liver disease (CLD). Varicella (VZ) vaccination is not recommended in all European countries. There are no recent data about possible worsening of pulmonary status following VZ in CF, but it is known to cause pulmonary damage in non-CF adults and to be potentially fatal post transplantation and during steroid treatment. Therefore it is recommended at least for seronegative adolescents and transplant candidates. Influenza vaccine is recommended annually for CF patients aged ≥ 6 months. Pneumococcal vaccine is generally indicated for CF patients. RSV infection might play a role in the initial *Pseudomonas* colonization and the decline in pulmonary function. However no RSV vaccine is available at present. There are no recommendations for palivizumab in CF as an alternative but expensive prophylaxis. Anti-bacterial vaccinations protecting directly against *Pseudomonas aeruginosa* colonisation are promising for the future, potential candidates are currently being assessed in phase III clinical trials. More studies are needed to complete recommendations especially for CF adults and transplant candidates.

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Keywords: Vaccination; Viral infection; Prophylaxis; Surveillance; Adult CF care; Transplantation; Vaccine-preventable diseases

Abbreviations: BCG, Bacille Calmette-Guérin vaccine; CDC, Centers for Disease Control and Prevention; CLD, chronic liver disease; FI-RSV, formalin-inactivated alum precipitated Respiratory Syncytial Virus vaccine; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; IPV, intramuscular polio vaccine; LRTI, lower respiratory tract infection; MMR, measles mumps rubella; PRP, polyribosyl ribitol phosphate; RSV, Respiratory Syncytial Virus; RSVIG, Respiratory Syncytial Virus immunoglobulins; TB, tuberculosis; VZ, varicella-zoster; WHO, World Health Organization.

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1. Introduction

Forty years ago cystic fibrosis (CF) patients seldom survived beyond infancy and vaccination was far from being a priority. Although the introduction of better diagnostic techniques and refinements of therapeutic strategies has increased the median age of survival beyond 30 years [1,2], little attention has been paid to the contribution of vaccination to the current management of CF patients. A standard protocol on anti-viral and anti-bacterial vaccination could improve health care in CF, but until now there have been no specific recommendations for immunisation of CF children and adults as there are for other diseases [3–5]. Young CF children may easily escape normal national immunisation programmes, being more often absent from school and admitted to the hospital for treatment by specialists. Indeed, all children with a chronic disease run a higher risk of incomplete and delayed immunisation than healthy children [6]. Secondly, knowing that the adult population is greatly expanding, older children and adults with CF even despite being vaccinated correctly in infancy and childhood, might become susceptible to preventable diseases such as pertussis because for some diseases vaccine induced immunity wanes over time [7–11]. Little is known as to what extent, these diseases could cause pulmonary deterioration in CF. This must be a matter of concern in the adult care setting, which might be less involved in routine vaccination than paediatrics. Moreover, vaccination coverage has decreased due to ill-founded worries about vaccine safety [12] and the fact that most people no longer realise the severity of vaccine-preventable diseases because of the success of earlier immunisation programmes. The average coverage for “classic” vaccinations such as diphtheria, tetanus, pertussis and poliomyelitis in Europe is insufficient, with many countries attaining only low levels. Therefore vaccine-preventable diseases are not yet sufficiently controlled in Europe [13,14].

Current national vaccination schedules in the European countries differ widely, for instance for hepatitis A and B, and some booster vaccinations and we are far from a uniform European immunisation system [13,14]. This applies to both to different single vaccines as well as combinations. There is also considerable variation in legislation, the implementation systems and vaccination coverage in general. In some countries, vaccinations are centralised by the government, while other countries use decentralised private vaccination systems paid for by insurance companies [14]. Therefore data on vaccination coverage of CF patients are to our knowledge unavailable. For this reason also, data on the prevalence and complications of vaccine-preventable diseases in CF are lacking.

A number of points need to be emphasised. First of all, it is important to underline that CF itself is not a contraindication to routine immunisation and that optimal coverage for routine vaccines against tetanus, diphtheria, pertus-

sis, poliomyelitis, measles, rubella, and mumps must be obtained [2]. Moreover, CF patients are candidates for extra vaccinations such as influenza, hepatitis, varicella, RSV [2,3,15] and perhaps most importantly *Pseudomonas aeruginosa* [16]. Some of these infections can be a contraindication to referral for transplantation. Since more than 90% of the mortality in CF is pulmonary, early immunisation are an important tool to prevent transplanted subjects being vulnerable to life-threatening vaccine-preventable infectious agents. Finally, CF patients have not been systematically studied to determine whether they make a normal response to all vaccines and the possibility of vaccine-failure is still an unanswered issue. Based on a review of the literature, we have attempted to establish recommendations for CF patients, independent of the countries’ national schedule and system. This document summarises information gathered by the authors, who are involved in immunisation programmes, in paediatric and adult CF care and in CF transplantation teams.

2. General recommendations

Although national vaccination schedules differ widely in the European countries, the obvious place to start is from the national recommendations and strategies of immunisation, and to apply them to all CF patients to obtain optimal coverage (Table 1). In CF patients, in children as well as in adults wheeze or cough are no reasons to withhold or delay vaccination, and the general practitioner can play a particularly important role in vaccine coverage [2]. New recommendations for conjugate pneumococcal and meningococcal C vaccines as well as for pertussis boosters in adolescent and adults should be implemented. With regard to BCG, national guidelines should be followed, although as with many recommendations, there are gaps in our knowledge as to how the CF patient will respond to immunisation. Although tuberculosis (TB) is rare in CF patients, there are obvious diagnostic difficulties, and since occult TB could be reactivated after transplantation, immunisation in accord with established local practice seems logical.

Vaccines should be withheld only under exceptional circumstances such as any recent or present treatment with oral prednisolone: doses of 2mg/kg/day or above may compromise the efficacy of any vaccines and may be a danger in live vaccines of contracting the disease [3]. Inhaled steroids, other in very high doses, are not a contraindications to vaccine administration.

In adolescence and when transplantation is considered, a vaccination check-up should be done, and any gaps in the vaccinations should be remedied (Table 2). There are no data on whether *Haemophilus influenzae* type b and pneumococcal vaccine immune response can be depressed in CF and that vaccination should be repeated. Specific antibody monitoring is helpful in determining the need for individual boosters.

Table 1
Childhood immunisation in European countries in 2004

Age → Vaccine ↓	2 months	3 months	4–6 months	12–13 months	15–18 months	4–6 years	10–12 years	13–18 years	Remarks
Poliomyelitis	X	X	X		X	X			IPV in 2001 WHO recommended booster schedules differ widely
Diphtheria, tetanus, pertussis	X	X	X		X	X		X	
Diphtheria, tetanus, pertussis <i>adult</i>									boosters recommended in some countries at 6 years, adolescents, adults
<i>Haemophilus influenzae</i> type b	X	X	X		X				
Hepatitis B	X	X	X		X	(xxx)	(xxx)		not in countries with low prevalence
Hepatitis A				(xx)					recommended in selected EU regions
Measles, mumps, rubella				X		(X)	(X)	(X)	booster recommended since 1995, age variable
Varicella				X				(xx)	recommended in some countries 2 doses >13 years
Meningococcal C									in some regions with increased prevalence, age cohort variable
Pneumococcal conj									recommended in some countries
Influenza virus									recommended in patients at risk
BCG (TB)	X								recommended at birth+booster at 6/12 years in some countries

Recommendations for vaccination of immunocompromised hosts after lung or liver transplantation are listed in Table 3. It is clear that live-attenuated vaccines such as varicella vaccine, oral poliomyelitis vaccine, measles-mumps-rubella and BCG cannot be administered in immunosuppressed subjects and that they should be scheduled before transplantation [3].

Depending on the country, national recommendations alone may be insufficient for CF patients. Vaccinations not recommended for healthy children in general or differently implemented in national vaccination schedules will be discussed separately in relation to CF in general and to CF lung transplant candidates.

3. Hepatitis A and B

Infection with the hepatitis A virus (HAV) results in a self-limited disease, which does not become chronic. When acquired in adulthood, more serious morbidity occurs and case-fatality rates of >1% have been reported. In industri-

alised countries, up to 50% of adults have detectable anti-HAV antibodies, although overall seropositivity rates due to natural infection are declining. A few reports have been published showing a higher case-fatality rate of hepatitis A infection in chronic liver disease patients (CLD) compared to non-CLD patients.

In a retrospective study from the Centers for Disease Control and Prevention (CDC), the hepatitis A case-fatality rate is 4.6% in patients with pre-existing CLD, approximately 23-fold higher than for patients without pre-existing liver disease [17]. Four cases of fulminate hepatic failure and death secondary to acute hepatitis A infection in patients with intravenous drug abuse and alcoholic liver disease have been reported by Akriavidis [18]. A large survey conducted by Williams [19] has shown that HAV superinfection of patients with CLD

Table 2
Recommended strategies pre-transplantation

Routine	influenza vaccination annually
To check	1. booster poliomyelitis (inactivated)-diphtheria-tetanus-pertussis 2. vaccination against hepatitis A and B 3. antibody level against varicella-measles-mumps-rubella-pneumococci and if insufficient→complete vaccination
To consider	pneumococcal/ <i>Haemophilus influenzae</i> b/meningococcal C vaccination

Table 3
Immunisation in immunosuppressed patients (including high dose steroid treatment)

Vaccine	Authorised	Remarks
Poliomyelitis	X	only inactivated intramuscular vaccine authorised
Diphtheria, tetanus, pertussis	X	
Diphtheria, tetanus, pertussis <i>adult</i>	X	
<i>Haemophilus influenzae</i> type b	X	response may be decreased
Hepatitis B	X	
Hepatitis A	X	
Measles, mumps, rubella	NO	live attenuated vaccine
Varicella	NO	live attenuated vaccine
Meningococcal C	X	response may be decreased
Pneumococcal 23-valent	X	response may be decreased
Pneumococcal conjugated	X	response may be decreased
Influenza virus	X	response may be decreased
BCG (TB)	NO	live attenuated vaccine

increases mortality to 27.5% compared with 3.4% in non-CLD patients.

Two vaccine studies have investigated the safety and immunogenicity of inactivated hepatitis A vaccine in patients with CLD [20–22]. It can be concluded from these studies that the vaccine is safe and well tolerated, with lower but satisfactory geometric mean titres compared to healthy individuals.

Hepatitis B virus (HBV) infection, in contrast to the rather benign character of HAV, can result in a chronic carrier state in 5–10% of adult patients, and in >30% of infected children. It is estimated that there are approximately 367 million chronic carriers of hepatitis B virus worldwide. About 25% of these carriers will develop serious chronic liver disease, including chronic hepatitis, liver cirrhosis and primary hepatocellular carcinoma. Limited data are available on the outcome of hepatitis B infection in patients with CLD [23]. Generally, hepatitis B vaccination is implemented in national schedules except in some countries with a low prevalence. WHO recommends the inclusion of hepatitis B vaccination into all national immunisation programmes [14,24,25].

CF patients are predisposed to liver disease because of lack of a functional CF transmembrane conductance regulator protein on the biliary epithelium. Although longitudinal data describing and quantifying the liver abnormalities [26] are still not available in the literature, chronic liver disease accounts for virtually all non-pulmonary causes of mortality in CF patients. Therefore, along with lung disease and nutritional status, liver disease is an important predictor of the outcome of CF [27]. Cross sectional studies have described a prevalence of CF liver disease of 1.4–7% when diagnosed as hepatosplenomegaly on clinical examination. However a far greater prevalence is suggested by abnormal liver ultrasonography and biochemical tests [26,28], and in a recent study over 4 years Ling [26] found some evidence of liver abnormality in 92% of children under the age of 14 years. With increasing survival of CF patients, some authors predict an increasing predisposition to cancer. In a study including more than 38,000 North American and European CF patients, an excess of digestive cancers including liver cancer was shown. Many of these patients were only in their third decade at the time of their cancer diagnosis [29].

Inactivated hepatitis A vaccine and recombinant hepatitis B vaccine have been extensively studied and shown to be safe and efficacious in preventing infection [30,31]. In recent years, several studies have investigated the outcome of HAV or HBV infection of patients with chronic liver disease (CLD) and discussed the rationale of vaccinating these patients against HAV and HBV, including in countries with a low risk of hepatitis where these immunisations are not included in the routine national programme [5,20–22]. Up to now CF has not been specifically considered. Data on hepatitis A and B prevalence or vaccination coverage of CF patients are lacking. As some evidence of liver abnormality

can be found in up to 92% of CF patients, CF patients are expected to run a higher probability of fatal hepatitis A and B infection when exposed to these viruses. Most CF patients do not have identifiable risk factors. For this reason, CF patients should be considered as a target group for vaccination. An appropriate time to vaccinate them is the time point of diagnosis of CLD [22] or preferably at the time of CF diagnosis. This is in line with reports from the World Health Organisation and from CDC, recommending vaccination for persons with CLD caused by viral hepatitis or other aetiologies [24,32].

With the availability of a combined hepatitis A and B vaccine, which has shown to be safe, well tolerated and highly immunogenic, it is worth considering using this combined vaccine in CF patients. It offers dual protection in a simple schedule (0, 1, 6 months) [33].

4. Measles-mumps-rubella

The symptoms of measles include cough, coryza, general irritation of the respiratory tract with complications of the ears (otitis) and the lungs (bronchopneumonia). These particular symptoms and complications may add an extra burden on the respiratory system of CF patients. Although data on the epidemiology of vaccine-preventable diseases in Europe are incomplete, it is clear that measles is not yet controlled in most European countries [14,34]. An important aspect is the unsuccessful achievement of high population vaccine coverage in some European regions, due to ill-founded public fears, resulting in regional measles outbreaks [14,34]. The epidemiology of measles morbidity has changed in the last 3 decades and hence the extent of exposure to the wild virus in immunised individuals is unknown. It has, however been suggested that about 1% of immunised persons per year may lose protection [35].

Measles vaccine combined with rubella and mumps (MMR) vaccines have been included in all basic vaccination schedules since the early eighties. The age recommended for primary immunisation is 12–15 months (Table 1). Antibodies develop in approximately 95% of children immunised at 12 months and 98% of those immunised at 15 months of age. Recommendations for a booster at 4, 6 or 12 years have been implemented in the mid-nineties after school-based outbreaks, to prolong immunity and possibly eradicate measles [13,36,37]. More than 99% of individuals who receive 2 doses of measles vaccine (separated by at least 1 month) after the age of 1 year, develop serologic evidence of measles immunity [37]. Protection conferred by immunisation is long lasting in most people. A small percentage may lose protection after several years. In countries with high immunisation coverage, population immunity and elimination of the virus ensure continued protection.

A specific recommendation should be made that CF patients ensure they are immune to measles. In most

countries, CF adults may have been immunised with only one dose of measles vaccine in the early eighties, before the later recommendations for the booster at school age, so that a cohort of young CF adults are currently incompletely immunised. Measles vaccination is recommended to all CF adults who do not have a valid documentation of a history of measles disease or a documented correct complete vaccination administered after the age of 12 months, consisting of 2 doses separated by at least 4 weeks.

5. Varicella

Varicella-zoster (VZ) virus predominantly affects young children and is generally perceived as benign. However in a recent 13-month survey of severe complications of VZ in hospitalised children less than 16 years of age, 78% complications were seen in children younger than 4 years. Bacteraemia, pneumonia, encephalitis and ataxia were most frequently reported [38–41]. After adolescence the risk for severe pulmonary complications rises, and varicella may be particularly harmful for CF adults, although recent data on specific effects in CF are almost completely lacking [38,42,43]. In adults, pneumonia is the most serious complication in terms of morbidity and mortality and may be life-threatening [44–47]. An upward shift in the age distribution of VZ was described 10 years ago in the UK as well as in the USA before the implementation of the vaccination, resulting in an increased risk of infection in pregnant women, health care workers and vulnerable chronic patients [48]. Moreover, VZ is a serious, life-threatening disease in immunocompromised hosts, such as patients on steroids and transplanted subjects [15,49,50].

Varicella vaccine has been introduced in the universal vaccination schedule of the USA in the nineties [51] and recently in some European countries, implementing one dose of VZ vaccine for the immunisation of all immunocompetent children at age 12–18 months. Catch-up immunisation of subjects aged 19 months to 13 years is recommended in those who do not have a reliable history of chickenpox. The vaccine has been found to be safe and immunogenic in adults and elderly [52]. To control VZ disease, a coverage rate of over 85% of the population is required, which may be difficult to obtain in Europe [40,53]. Experience concerning the effects of inefficient vaccination coverage of the population is limited in VZ and the time needed to obtain the target level of 85% coverage cannot be predicted. As immunisation will be gradually introduced in vaccination schedules, a further switch of morbidity to older ages is at risk of occurring. In an American report [54], VZ vaccine is stated to give protection against disease 7 years after vaccination, in a population with 20% vaccine coverage, and has not led to the earlier described age-shift of the disease. Re-exposure to the wild type virus could have contributed to maintain VZ antibody responses and long-term protection in those vaccinated people living in a

population with a low vaccine coverage. When coverage rises, re-exposure of vaccines with of waning immunity to VZ will decrease. For the moment there are no recommendations for the introduction of booster vaccinations to prevent people from becoming more susceptible to VZ in later life [52].

CF patients should be considered as a target group for VZ vaccination for multiple reasons: VZ infection can cause pulmonary deterioration and a proportion of the CF population will receive steroids or be immunosuppressed after transplantation [43,48–50]. The most appropriate time for children to be vaccinated, is preferably, as soon as the diagnosis of CF is made (1 dose at age 1–13 years). Adolescents past their 13th birthday and young adults, without a history of VZ, should be immunised by administration of 2 doses of vaccine 4–8 weeks apart. Longer intervals between doses do not necessitate a third dose [55]. All patients who do not have a valid documentation of a history of VZ disease or a documented correct complete vaccination should at least be vaccinated before being put on the transplant waiting list.

6. Influenza

Influenza virus infection is a cause of substantial morbidity and mortality, particularly in vulnerable populations. Recent data report that infants with CF acquiring respiratory virus infection show lung function deterioration, which may persist for months after the acute illness [56]. Although recent studies on influenza virus infection as a trigger for the onset of bacterial pulmonary infections in CF children are lacking, the role of influenza was highlighted in several older studies [57–59]. Influenza significantly increases the incidence of hospitalisation and of respiratory illness in children with CF. Influenza virus infection is shown to be one of the main mediators of the onset of chronic *P. aeruginosa* infection in CF [57]. Even though reports have documented that school-age patients with CF are not more susceptible to viral infections than their healthy siblings [60], recent studies have identified healthy non-CF children as a risk group for their CF peers [61]. These studies stress the impact of influenza on hospitalisation and pulmonary exacerbations in young children in general, so that vaccination is strongly encouraged from the age of 6 months. Annual vaccination is considered the best means of protection against influenza infection. Vaccination is now strongly recommended annually for anyone aged ≥ 6 months who, because of age or medical condition, has a higher risk of complications of influenza [62]. The immunisation of their family members is also recommended [62,63]. The indications particularly include (but are not limited to) patients with chronic diseases affecting the respiratory tract, cardiovascular disorders, asthma, metabolic diseases (diabetes mellitus), sickle cell disease, HIV, renal dysfunction and their household members [62–65].

Most CF doctors agree that all their patients would benefit from influenza vaccination, not merely the adult population [2,66]. However, because vaccines are currently not approved for children <6 months of age, and the majority are poorly immunogenic in young children in general, vaccination is often postponed. Children aged 6–35 months need 2 (half) doses with a 1-month interval. Children between 3 and 8 years who are receiving influenza vaccine for the 1st time should receive 2 doses separated by at least 4 weeks, but for the succeeding seasons a single dose is sufficient in this age group as in adults. However, note that a uniform vaccination schedule is not agreed, and some advise 2 doses at the 1st seasonal vaccination until the age of 12 years. The immunogenic effect of influenza vaccines in CF children is comparable to that of healthy individuals [67] and several studies have demonstrated the safety of influenza vaccinations in children with CF [68]. One study has compared a virosome adjuvant vaccine with a subunit vaccine in paediatric CF patients detailing their strong efficacy and tolerability [69]. The coming live attenuated intranasal vaccines will offer an alternative more suitable for children and reduce the number of injections.

Finally, new antiviral drugs belonging to the class of neuramidase inhibitors were developed for the treatment and the chemoprophylaxis of influenza. However, maximum time to treatment is mostly within 24–48 h necessitating rapid bedside tests for identifying influenza viruses. Paediatric experience is almost totally lacking. Studies are needed concerning the clinical potential of these antiviral drugs. Prevention by appropriate use of vaccines remains the best choice [70].

7. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*

Infection with the gram-positive coccus *S. pneumoniae* is the most common cause of otitis media, community-acquired bacterial pneumonia and bacterial meningitis. The incidence of invasive pneumococcal disease is estimated at 100–250 cases of pneumonia, 15–25 cases of septicaemia and 1–2.5 cases of meningitis per 100,000 persons per year. At the present time, pneumococcal disease remains a major health problem, both with regard to morbidity and mortality [71,72]. There is a clear relationship between age and susceptibility to pneumococcal invasive disease. The incidence of invasive disease is high in infants up to 2 years of age, low in teenage children and young adults, and increases in elderly. Most clinical isolates contain an external capsule made of repeating oligosaccharides. More than 90 serotypes of *S. pneumoniae* have been identified based on antigenic differences in these capsular polysaccharides. In patients with CF, the prevalence of *S. pneumoniae* in the respiratory tract may be underestimated, as *S. pneumoniae* is difficult to isolate from sputa often heavily infected

with other organisms. Moreover patients who are immunocompromised may be more susceptible to invasive disease [72–74].

There are currently two approaches to pneumococcal vaccination: capsular polysaccharide vaccines and polysaccharide-protein conjugate vaccines.

Capsular polysaccharide vaccines have been available for more than 15 years. The present 23-valent vaccines include 25 µg purified capsular polysaccharide antigens from each of the 23 serotypes that represent approximately 90% of all serotypes that cause invasive pneumococcal disease. It has been recommended by the American Academy of Pediatrics that all CF patients who are older than 2 years, receive the 23-valent polysaccharide vaccine [72,75]. Vaccination results in antibody formation against an average of about three-quarters of the antigens present in the vaccine. The immune response to polysaccharide antigens is T-lymphocyte independent. Therefore, vaccination with polysaccharide vaccines will confer immunity only transiently. Thereafter, revaccination must be considered to maintain protective immunity. The optimal timing for revaccination is not well established at the present time. In general, revaccination is recommended every 5–7 years in otherwise healthy patients and every 3–5 years in patients, who may have a more rapid decline of antibody titres and who have an increased risk for invasive disease. Vaccination with polysaccharide vaccines does not lead to the generation of memory cells and results only in a weak booster effect after revaccination. At best after revaccination, immunoglobulins G levels return to the same range of the original post-vaccination antibodies titres [76–78]. The existing polysaccharide vaccines have two major drawbacks. Firstly, they are not effective in children younger than 2 years because the immature immune system is unable to respond to polysaccharide antigens; similarly, they are not fully effective in the elderly [79]. Secondly, they confer protective immunity against invasive disease to immunocompetent adults [80–82], but their protective efficacy against pneumonia has not been established beyond doubt.

A novel generation of polysaccharide-protein conjugate vaccines is now available. The protein component of these vaccines triggers a T cell-dependent immune response with production of high levels of antibodies and generation of memory cells, even when administered during the first months of life. Infants and non-responders to the polysaccharide vaccines will benefit from these new conjugate vaccines [83]. However, until now a maximum of 9–11 serotypes could be included in these vaccines. The results of the 7-valent vaccine show a protective efficacy mainly for the prevention of invasive disease, but also for the prevention of radiologically confirmed pneumonia and otitis media [84] so that pneumococcal conjugate vaccines are used in vaccination programs in North America and in some European countries. The 7-valent vaccine is recommended for all children aged 2–23 months and for certain children at risk aged 24–59 months.

There are no data in the literature indicating an increased risk of CF patients regarding invasive pneumococcal disease. Moreover, CF patients show a wide range of pneumococcal polysaccharide antibody levels comparable to a normal immunocompetent population [72,85]. Therefore, universal indiscriminate vaccination with the actual 23-valent polysaccharide vaccines becomes an issue in CF patients if pre-immunisation antibody levels are unknown. Vaccination could lead to a heightened inflammatory reaction and additional lung damage in those with high antibody levels and should therefore only be considered in CF patients without protective antibodies. The latter is particularly true when lung transplantation is considered as transplant recipients might be at an increased risk of pneumococcal infection [73,74,86]. CF lung transplant recipients may also be vaccinated after transplantation. However, as has been observed in other transplant recipients, their post-vaccine antibody levels will probably be lower and decline more rapidly than in other individuals and they will probably require revaccination sooner than normal subjects to maintain protective immunity [76].

With regard to the pneumococcal conjugate vaccines, national recommendations should be followed [13,87]. More evidence is needed before recommending conjugate pneumococcal vaccine to all CF infants in countries without national implementation of the vaccine and to confirm whether they offer a better alternative for CF lung transplant recipients as compared to the classic 23-valent vaccines.

H. influenzae is part of the normal colonising flora of the upper respiratory tract. Most *H. influenzae* strains are not encapsulated, 6 strains (a–f), however, do have a capsule, *H. influenzae* type b being the most virulent strain, responsible for invasive disease, bacterial meningitis, pneumonia, otitis media, epiglottitis, cellulitis and osteo-arthritis in children under the age of 5 years and especially under 18 months. The capsule contains a specific polysaccharide called polyribosyl ribitol phosphate (PRP). Antibodies against PRP confer protective immunity. Most of the population is colonised by some non-encapsulated strain of *H. influenzae*, including the strains recovered often in sputa and nasopharyngeal swabs of CF patients. Only 1–5% of non-immunised persons are colonised by *H. influenzae* type b, mostly young children.

H. influenzae polysaccharide-protein conjugate vaccines were introduced in the early nineties and are actually part of the general vaccination recommendations for infants and children, including CF patients. Since the start of a mass vaccination programme in Finland invasive *H. influenzae* type b infection decreased successfully [88]. Vaccination however did not influence the presence of non-encapsulated or non-b strains in the respiratory tract of non-CF children [89]. Moreover rare cases of invasive capsulated *H. influenzae* type b infection were recently reported in children who failed to mount a good antibody response to

immunisation and assay of anticapsular antibody is required if immune status is in doubt; the rare possibility of vaccine failure should not be forgotten [90,91]. Data on vaccine failure in general however, are scarce in CF.

Finally vaccination against serogroup C *N. meningitidis* will be applicable to CF patients as for non CF subjects in regions with increased prevalence [13,92].

8. Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the most important cause of viral lower respiratory tract infection (LRTI) in infants and children worldwide [93,94]. RSV consists of two major antigenic groups, A and B strains, the A strains being found predominantly in the community [93,95]. In the United States, the risk of primary infection in infants younger than 12 months of age ranges from 50% to 70%, and although not all infected infants will acquire LRTI, the latter will nevertheless reach 30–40% of the total infant population. By the time infants reach 2 years of age, nearly all have had a primary RSV infection and the risk of LRTI remains high with reinfection due to lack of persistent immunity [95]. Infants who are premature or have chronic lung disease or congenital heart disease are at particular risk for severe RSV disease. RSV infection can also have long-term consequences. Approximately 50% of infants with RSV LRTI will have recurrent episodes of wheezing during early childhood [93,96]. After RSV bronchiolitis in infancy an excess of respiratory symptoms for at least 10 years has been reported [97]. Although traditionally regarded as a paediatric pathogen, RSV can also cause life-threatening pulmonary disease in adults with chronic obstructive pulmonary disease or congestive heart failure [93,98], bone-marrow transplant recipients and the elderly [93,94].

In CF adults and children, acute pulmonary exacerbations and acute worsening of airway obstruction may result from viral infection [56,99,100]. As with influenza, limited recent studies are available. Data support the hypothesis that RSV infection in CF, although self-limited, is accompanied by airway inflammatory changes and plays a role in the initial infection of the airway with *P. aeruginosa* [56,57,101–104].

Data demonstrate that infants with CF and normal controls have the same number of RSV respiratory illnesses over a single season. However, RSV infection in CF infants may cause significant pulmonary morbidity, a prolonged hospitalisation and complications such as mechanical ventilation, persistent hypoxemia and decreased lung function for several months after LRTI [56,105]. Some authors advice long-term prophylaxis with inhaled antibiotics in infants with risk situations such as RSV infection [104]. Most authors conclude that children with CF should be considered prime candidates for RSV prevention trials using RSV intravenous immunoglobulin, RSV monoclonal antibodies, and RSV subunit vaccines. However, the relative

roles of the humoral and cellular components contributing to RSV immunity in protection and pathogenesis are still debated, resulting in difficulties of developing an effective vaccine [93].

Passive immunoprophylaxis with specific hyperimmune immunoglobulin (RSVIG) [106] or humanised monoclonal antibody (palivizumab) [107] is restricted at present to a small number of high risk infants, such as those born at less than 35 weeks gestation and children with bronchopulmonary dysplasia. The humanised monoclonal antibody has to be administered in a dose of 15 mg/kg body weight, once a month during the RSV season (from September to May, maximum 5 injections/season). No data on the effect of palivizumab on the morbidity of CF children are available. Clinical trials on the safety and tolerance of palivizumab in CF patients <2 years are in progress.

Although the importance of RSV as a respiratory pathogen has been recognised for over 30 years, a vaccine is not yet available because of several problems inherent to RSV vaccine development. As serious RSV disease can occur in high-risk individuals who have experienced previous RSV infection, as well as in RSV naïve infants, it is also likely that more than one type of RSV vaccine will be needed for immunising all those in whom protection is mandatory [94].

The first vaccine, a formalin-inactivated alum-precipitated (FI-RSV) preparation given intramuscularly did not protect infants and children from infection in the early 1960s. Moreover, the illness in the vaccinated group following subsequent infection was unusually severe, with some deaths and a high rate of hospitalisation [108]. Several strategies for the development of a live attenuated RSV vaccine were explored. In recent years new vaccine candidates derived by chemical mutagenesis of an incompletely attenuated cold-passaged RSV mutant have generated a promising vaccine candidate for seronegative infants [109]. Naked DNA and RNA vaccines show also considerable results. Finally subunit RSV F and G (this glycoprotein predominantly distinguishes A and B strains) vaccines, containing the viral glycoproteins, which induce neutralizing and protective antibodies, have been evaluated as potential vaccines. A variety of vaccine strategies are being evaluated that target different groups: these include immunisation of breast-feeding women with the hope of protecting neonates from RSV infection during the critical few months of life [110], immunisation of neonates and infants, and immunisation of high risk groups [95].

Studies have shown that RSV infection in CF infants, as well as in older patients can lead to a higher morbidity and hospitalisation rate. Therefore RSV vaccination of CF patients seems reasonable, as soon as an RSV vaccine is available on the market. However, more studies are needed to clarify the role of RSV infection in the morbidity of children and adults with CF (with or without chronic *P. aeruginosa* infection) and in their pulmonary exacerbations.

9. *Pseudomonas aeruginosa*

P. aeruginosa is an opportunistic gram-negative bacterial pathogen that produces various immunomodulatory products that enable it to survive in the lung and to cause significant morbidity and mortality. Particularly at risk are patients with compromised respiratory function, such as burn patients and those with CF [111]. The development of a *P. aeruginosa* mucoid phenotype and subsequent chronic pulmonary infection is directly associated with the deterioration of lung function in patients with CF. This chronic infection produces an immunologically conditioned destruction of the pulmonary tissue, and can lead to fatal bronchiectasis. The general deterioration in lung function has a direct bearing on the quality of life of patients with CF. Limited exercise capacity, frequent hospital admissions for treatment of acute pulmonary exacerbation, and an association with lowered life expectancy are all associated with a deterioration of lung function. Its preservation should therefore be one of the main goals in the management of these patients. Once chronic infection of the airways by *P. aeruginosa* has become established, it is virtually impossible to eradicate the organism in the lower respiratory tract. This is despite considerable progress in antibiotic treatments. In addition, innate and increasing resistance of *P. aeruginosa* to antibiotic therapy emphasises the need for effective prophylaxis against *P. aeruginosa* infection through active vaccination.

P. aeruginosa is occasionally detected in throat swabs of CF patients in infancy, but there is generally a period of several years when prophylactic measures, which potentially would include vaccination, may delay or even prevent infection [112]. This window of opportunity provides a reasonable time frame for the vaccination of CF patients at a very early age, which may prevent *P. aeruginosa* infection in the lower respiratory tract, leading to an improved prognosis.

There have been many approaches in the development of vaccines for the prevention of *P. aeruginosa* infection but earlier trials produced disappointing results [113]. Despite several attempts at prophylactic vaccine development, a recent publication investigating the effectiveness of vaccination against *P. aeruginosa* in patients with CF revealed that there was very little information available concerning multi-centred, randomised controlled trials that are adequately-powered to evaluate potential *P. aeruginosa* vaccines [114]. A more recent publication has shown that regular vaccination for a period of 10 years with a polyvalent conjugate vaccine, reduced the incidence of chronic infection with *P. aeruginosa* and was associated with better preservation of lung function, particularly in older patients [16]. Prospective, randomised, multicenter, double blind, controlled trials are currently being conducted in order to confirm the preliminary data already gathered.

Although *P. aeruginosa* infection alone is not sufficient to serve as a prognostic criterion for life expectancy in CF

patients, the prevention of airway infection by *P. aeruginosa* is fundamental in the preservation of the patients' quality of life. Effective prophylaxis by immunisation against *P. aeruginosa* infection in CF patients, complementing current antibiotic therapies, remains an 'unmet medical need'.

10. Conclusions and future considerations

The recommendations embodied in this paper are intended to serve as a call for special attention to achieve correct immunisation and antiviral strategies in CF children, adolescents and adults. They focus on the importance of linking correct immunisation to the general care of CF patients, who experience multiple barriers to vaccine administration, such as cough and wheezing, school absenteeism, hospital admissions and their complicated multidisciplinary care. Therefore the general practitioner or paediatrician plays an important role in coordinating this aspect of management. This paper also calls for the diagnosis and reporting of the effect of vaccine-preventable diseases in CF patients at any age. In the future, new coming antiviral vaccines will certainly be interesting for CF patients such as Respiratory Syncytial Virus or Cytomegalovirus vaccines. There is also hope that antibacterial vaccines against *Pseudomonas* might prevent fatal pulmonary infection.

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