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Review

Vaccination among the elderly: European state of art and the need for a culture shift

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Background: since the development of the first vaccine, immunization has been shown to be one of the most effective public health measures to prevent diseases. Vaccination policy is currently mainly focused on the young (aged below 18), to some extent the old (aged above 65) but, in contrast to childhood immunization programs, adult vaccination is not considered to be a routine health intervention.
Methods: a PubMed research was performed using elderly and vaccination policy as key words.
Conclusions: vaccination in adults remains an underused public health strategy in the promotion of healthy ageing, and adult vaccination rates are still far below the target. Influenza, pneumococcal pneumonia and pneumococcal invasive disease, pertussis and even HZV (because of a high incidence of post-herpetic neuralgia among the elderly) have been highlighted as the most important diseases for which is important to look after immunization strategies due to their burden related to deaths or disabilities. Investing € 1 in adult immunization can generate over € 4 of future economic revenue for government.

Key words: Public health, Herpes Zoster, Post-herpetic neuralgia, Pneumococcal vaccination, Influenza

BACKGROUND

Since the development of the first vaccine, immunization has been shown to be one of the most effective public health measures to prevent disease. Vaccination policy is currently mainly focused on the young (aged below 18), to some extent the old (aged above 65), especially for seasonal influenza, and those in at-risk groups (e.g. people with medical conditions that put them at increased risk of contracting certain infectious diseases). In contrast to childhood immunization programs, adult vaccination is not considered to be a routine health intervention. Hence, vaccination in adults remains an underused public health strategy in the promotion of healthy ageing, and adult vaccination rates are still far below the target [1] even for seasonal influenza vaccination rates remain limited among adults and in the specific high-priority groups [2 3]. This situation has the following consequences:

- vaccine uptake among adults remains low;
- there is a lack of coordinated programs for vaccination of adults [4];
- adults are not well protected [5].

Vaccination, as a prevention strategy, should be part of an age-based approach to health throughout all phases of life.

HIGHLIGHTS ON INFLUENZA

During the season 2012-2013 more than 3.5 million people were affected among the European countries. There were 724 serious cases requiring intensive care and at least 117 influenza deaths (ages ranged between 5 months and 97 years of age). Among the serious cases, only 11% were known to be vaccinated. Moreover, hospitalization rates peaked at 0.35 per 1000 during the pandemic year of 2009 [6]. Diaz Granados et al

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randomized nearly 32,000 adults age 65 and older to receive either the standard-dose or the high-dose vaccine. The primary end point was laboratory-confirmed influenza caused by any influenza viral type or subtype, in association with a protocol-defined influenza-like illness. The primary end point was reached in 1.4% of those with the high-dose vaccine and 1.9% of those with the standard-dose vaccine (relative efficacy 24.2%, 95% confidence interval 9.7-36.5). There was also a 26% reduction in respiratory illness regardless of laboratory confirmation. Mortality rates were similar and low (0.5%) in both groups. In those without laboratory confirmation of respiratory illness, there was a 26% lower rate of pneumonia but no statistical difference in rates of hospitalization, medication use, routine office visits, and emergency department visits [7]. These results can be interpreted as meaning that the high-dose vaccine prevented about a quarter of the laboratory-confirmed influenza cases that would have occurred with the standard-dose vaccine. However, due to the low rate of disease in those given the standard-dose vaccine, the number needed to treat to prevent one influenza infection was about 200 with the high-dose vs the standard dose vaccine; to prevent one case of pneumonia, more than 270 would need to be treated. Vaccination coverage rates (VCRs) among older age groups for the influenza season 2012-13 varied from 1% to 77.4% with the median VCR being 44.7%. The highest VCRs were reported by the Netherlands and the United Kingdom, which achieved, or almost achieved, the 75% EU target [8].

PNEUMOCOCCAL DISEASES: INVASIVE PNEUMOCOCCAL DISEASE (IPD) AND PNEUMONIA

Globally, an estimated 1.6 million people die of IPD annually [9]. Groups at high risk of contracting IPD include:

- children (1 million deaths annually);
- immunocompromised people (e.g. patients with chronic renal failure);
- the elderly (> 65 years of age).

The rate of elderly patients affected has increased from 9.84 in 2009 to 14.4 in 2010. Diagnosis and treatment can be difficult because diagnosis must be confirmed by laboratory analysis of blood, cerebrospinal fluid, pleural fluid, or peritoneal fluid [10] and multidrug resistance (resistance to three or more antibiotic classes) can occur [9]. Pneumococcal pneumonia is responsible for 2% of hospitalizations in the EU-27, with an average stay of 10 days in 2005 and an average hospitalization rate of 3.3 per 1000 population, with the highest rates in Finland, Lithuania and [6]. To understand the real extension of the problem, it is recommended to take a look at pneumonia related death: In England and Wales in 2011, 25,696 people died of pneumonia (5.3% of all deaths), compared to 109 with influenza and 316 with pandemic influenza and wide variations in mortality rates are seen between some countries. Mortality could be over 30% in patients requiring intensive care. Also, in all countries the elderly, disabled and those with healthcare-associated pneumonia are at increased risk of multidrug resistance mortality [11]. The aforementioned data is impressive especially because a 23-valent polysaccharide vaccine has been available since 1983 and is recommended in the United States for all adults age 65 and over. It costs 72 $ per dose. A recent Cochrane Collaboration analysis of 11 randomized trials involving 36,489 participants 16 years or older concluded that PPSV23 was 74% (95% CI, 55-86%) effective against invasive pneumococcal disease and 74% (95% CI, 54-85%) effective against confirmed pneumococcal pneumonia. However, PPSV23 is far from perfect. There have yet to be any high-quality randomized trials focusing on PPSV23 in elderly individuals, and the available data on the elderly population are at times conflicting (although overall, lower-quality observational data suggest 68% [95% CI, 53-78%] effectiveness against invasive pneumococcal disease in elderly individuals) [12]. Furthermore, a 13-valent pneumococcal-diphtheria conjugate vaccine (PCV13) has been available since 2010. It costs 152 $ per dose and it also contains the conjugated protein which gives a more robust immune response. Up until recent times, the conjugate vaccine was recommended for children; the only adults for whom it was recommended were those age 19 and over who either were immunocompromised or had a cochlear implant, asplenia (anatomic and/or functional, i.e. coeliac disease), a cerebral spinal fluid leak, or renal failure [12]. The CAPiTA (*Community Acquired Pneumonia Immunization Trial in Adults*) trial randomized nearly 85,000 people (most 65 and older, and some children) in the Netherlands to receive either the conjugate vaccine or placebo. It found a 46% reduction in community-acquired pneumonia ($p = .0006$), a 45% reduction in nonbacteremic nonvaccine-type community-acquired pneumonia ($p = .0067$), and a 75% reduction in vaccine-type invasive pneumococcal disease ($p = .0005$) [10 11]. The ACIP correctly points out that PCV13 induces higher antibody levels than PPSV23 in people with weakened immunity, such as individuals 65 years or older. In addition, the clinical efficacy of PPSV23 in that age group is not well established. Nonetheless, this reasoning does not obviate the need for compelling clinical data demonstrating the value of giving PCV13 in addition to PPSV23 [15]. Anyway, rapid uptake and improved PCV13 coverage

among adults might help to close the immunity gap in the short term [16].

PERTUSSIS: A TOUGHER DISEASE THAN EXPECTED

The global incidence of pertussis is estimated at 48.5 million cases a year with 295,000 deaths [17]. In the US, pertussis has the greatest incidence and mortality of all vaccine-preventable diseases [18] and it continues to be a public health concern, even in countries with high vaccination coverage [9]. The main reasons are that adults may be unaware of having the disease so they may infect vulnerable infants who are not yet vaccinated [9]. As most severe cases and deaths occur in infants [9] policy makers need to reconsider regular pertussis booster vaccinations in adolescents and adults as well as in healthcare workers and pregnant women to reduce the overall incidence and indirectly protect susceptible infants which are called "Cocoon Strategy" [19]. The incidence of pertussis varies widely in Europe due to differences in vaccination policies, levels of awareness, and surveillance procedures. In 2010, confirmed cases were low overall (3.87 per 100,000 population), with the highest rates reported in Estonia and Norway (95.44 and 73.28 per 100,000, respectively) [9]. There is a considerable gap between number of confirmed cases reported in the EU in 2010 (14,000) when compared to epidemiological evidence from the US showing infection rates of 1-6% (800,000 to 1 million cases) during non-epidemic periods [20]. A review [21] indicated 4 different US state-specific studies (in Colorado [22], Michigan [23], New York [24] and California [25], all demonstrated that schools and communities with high vaccine exemption rates also had higher rates of pertussis. The risk for acquiring pertussis was higher even for those who were appropriately vaccinated.

HIGHLIGHTS ON HERPES ZOSTER: AN OLD NEW PROBLEM FOR WHICH THERE IS A SOLUTION

Herpes zoster, commonly referred to as "shingles", is a serious disease in older people and in the immunocompromised. In the absence of antiviral therapy, up to 45% of patients over 60 years of age experience considerable pain due to post-herpetic neuralgia for 6-12 months [26 27], severely affecting their quality of life [28]. Herpes Zoster is common in people ≥ 50 years of age and they account for 70% of the estimated 1 million new cases per year [29]. The incidence in people > 60 years of age is 10 cases per 1000 population per year [30]. Lifetime risk of developing shingles is approximately 1 in 3 [31 32] and, by the age of 85 years, 50% of people will have had shingles [33]. Shingles is considerably less contagious than Chickenpox but can be transmitted to non-immune people, resulting in a primary varicella infection [34]. Post-herpetic neuralgia is the most common complication of shingles, even though a variety of other complications can occur and could involve nervous system, eyes, skin and even gut [31]. Acute complications such as pneumonia and encephalitis rarely occur, but may lead to persistent complications or even death and hospitalization rates are very low [6]. In 2010 the mortality rates had fallen to an average of 0.03 per 100,000 [11]. It is difficult to eradicate Varicella-Zoster because of its ability to establish latency (i.e. the virus can lie dormant). In the US, universal varicella vaccination was adopted for children in 1995. The vaccination program produced a 90-95% decline in chicken pox in children aged 1-9 and reduced the incidence of zoster in children aged 10 years by 55%. Live attenuated Varicella-Zoster vaccination is recommended for healthy adults aged 60 or more and at risk groups [US children and adult schedules 2012]. Otherwise, in Europe, recommendations suggest vaccinating people aged over 50. There is plenty of evidence in favor of vaccinating against HZV [35]. Schmader 2012 [36] is a continuation of the Oxman 2005 study – Short-Term Persistence Study [37]. The 2012 publication evaluated the effectiveness of the vaccine for up to 7 years after the time of vaccination. Number needed to treat for an additional beneficial outcome (NNTB) = 50. It was the same data found before the update of the review. Since 2006 a live, attenuated varicella zoster virus vaccine, that contains VZV Oka strain, was licensed for the prevention of HZ and PHN in adults aged ≥ 60 years. Since 2011, the licensure has been extended to adults between 50 and 59 years. Leroux-Roels 2012 was a phase I/II, open-label, randomized, parallel-group trial that evaluated the safety and immunogenicity of a recombinant adjuvanted vaccine (HZ/su) in comparison with attenuated varicella zoster virus vaccine (OKA). The recombinant adjuvanted vaccine, HZ/su (50 µg recombinant varicella zoster virus glycoprotein E antigen in 0.2 mL mixed with 0.5 mL of AS01B adjuvant) (HZ/su) proved to be safe with respect to serious adverse events (including death) when compared with the live attenuated vaccine. There were no reports of vaccine-related serious adverse events and no deaths [38]. The evidence gathered including the most recently published studies suggests that there is benefit in vaccinating elderly people with the herpes zoster vaccine, with no major safety/tolerability concerns [36 37 39]. The available data suggest that the vaccine works for up to 7 years to prevent

herpes zoster in individuals over 60 years of age. There were no statistically significant differences in terms of safety of the herpes zoster vaccine when comparing one versus different two-dose schedules. Anyway, all the aforementioned studies received funding from the pharmaceutical industry.

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness evidence of immunization for adults aged 50 years or over in EU Member States was found for at least four of the seven most important vaccine-preventable diseases examined in this report: herpes zoster, seasonal influenza, IPD and pneumococcal pneumonia. These studies showed that immunization is likely to provide a cost-effective strategy for adults aged 50 years or over. Hence, immunization strategies can be recommended for specific age groups:

- Herpes Zoster: the general consensus across studies which compared a vaccination strategy versus no vaccination strategies was that vaccination is a cost-saving or a cost-effective intervention. Existing evidence indicated that if immunization was not cost-effective in the short-term, it did not imply cost-ineffectiveness in the long run [40]. There is evidence that adult vaccination is a valuable preventive option when targeting populations aged 50-54 years [41] and that vaccinating older cohorts (70+) is less cost-effective than vaccinating younger cohorts [42]. In Italy, the annual costs related to the HZ and PHN disease accounted to 41.2 million euros, of which 28.2 million related to direct costs (21.5 million for treatment of acute HZ) and 13 million associated to indirect costs (12.2 in lost productivity related to acute episode of HZ) [43]. A pharmaco-economic evaluation performed in Italy confirmed that vaccination program against HZ and PHN within subjects aged 60-79 years is cost-effective from both societal and third-payer standpoints in the Italian scenario [44]. Related to that, some Italian regions, such as Liguria and Puglia, established to introduce HZ vaccination in the regional immunization plan by the active and free offer of the vaccine to specific age-group;
- IPD: a study [45] conducted a multi-country analysis across 10 EU countries to analyze the cost-effectiveness of pneumococcal vaccination for IPD across those aged > 65 years. The study observed substantial variation in the Incremental Cost-Effectiveness Ratios (ICERs) across the countries, with older populations generally having higher ICERs. A UK based study [46] recommended routine vaccination of all populations aged ≥ 65 years. It was estimated to be the best strategy, with lower cost per life year gained compared to vaccinating high-risk groups only;
- Pneumococcal pneumonia: a study conducted in the Netherlands concluded that vaccination with pneumococcal conjugate vaccine to be cost-effective when compared with no vaccination [47] for both the general population and high risk populations aged ≥ 65 years;
- Seasonal influenza: the results of the multi-country analysis [48 49] found vaccination for influenza to be cost-effective across all the countries of interest. An Italian study [50] concluded that the economic advantage of extending influenza vaccination to healthy adult workers aged 50-64 years mainly relate to indirect costs such as costs associated with productivity loss.

Investing € 1 in adult immunization can generate over € 4 of future economic revenue for government (case study in the Netherlands). The budget needed for vaccinating a cohort of individuals aged 50 in the year 2012 was estimated to be € 136 million, which includes annual costs for influenza vaccination for the remainder of life. In return, the adult immunization program for the seven main infectious diseases in the Netherlands was projected to:

- prevent 34,528 infectious disease cases over the remaining life span;
- prevent roughly 5,782 premature deaths from infections;
- reduce the number of lost work days by 127,480 days with an estimate of 29 fewer disability cases over the remaining number working years for those vaccinated at 50-years of age;
- generate health cost savings reaching € 6.6 million and an additional € 4.2 million in social insurance savings paid towards disability and sick day payments to workers;
- generate future lifetime tax contributions from implementing adult vaccination, which would result in a revenue gain of € 537 million over the remaining life years of the cohort.

CONCLUSIONS: POLICY GAPS IN ADULT IMMUNIZATION

Despite the wide spreading of antivaccine movements [51], vaccination still remains one of the most important public health policy in order to prevent potentially deadly diseases. Moreover, thanks to the development of new policies aimed towards the elderly, there is the possibility to prevent not only life-threatening (e.g. pneumococcal pneumonia) diseases but also the ones which could badly affect quality of life (e.g. HZV).

Another very interesting and important aspect related to the previously stated succeed the cost-effectiveness analysis. There is a strong need to plan international public-health recommendations and also to create awareness about the importance of adult immunization, among the public and the health care professionals. Even though the value of adult vaccination programs is becoming more and more well-known, various critical points have to be solved:

- age-based recommendations, which allow individuals to assess their own status with regards to vaccination, are not applied to all diseases. When they are, the age of recommended vaccination varies across countries, despite an overall consensus towards influenza, pneumococcal and Herpes Zoster vaccinations;
- adult immunization is severely undervalued by the public and by providers [52 53];
- additionally, significant misinformation, much perpetuated by the anti-vaccine movement, exist surrounding vaccines and vaccination [51];
- natural boosting of immunity may be decreased because of less frequent exposure to pathogens that cause VPDs and because of immunosenescence due to the decreasing immunization given by the childhood vaccination;
- the failure of primary vaccine series and boosters, may have indirect consequences on certain fragile populations, such as the newborns, infants, immunosuppressed and the elderly;
- the lack of implementation of these recommendations may be linked to limited vaccination reimbursement systems and access to vaccines;
- coupled with limited awareness and promotion of adult vaccination schedules by healthcare professionals and health authorities, this may result in low and inconsistent uptake. According to the data from VENICEII Survey Report, only six countries have a comprehensive summary document or schedule describing all vaccines which are recommended for adults [54]. The Adult Vaccination Campaign in Europe (ADVICE) was developed with an aim to raise awareness for adult vaccination and to understand the dynamics of the vaccination practices and the possible barriers against achieving targeted vaccination rates in Europe [1].

Eventually, it appears clear that to achieve the worthy success of adult vaccination programs, there needs to be a cultural shift in public health policies.

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