Herpes zoster vaccine: a shot to maintain wellbeing

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The current era is full of contradictory vaccine issues. The emerging Ebola pandemic stimulates the world's citizens who are calling for the urgent development of vaccine to prevent the disease [1]. They seem to be suddenly remembering that vaccines represent a major advancement in public health [2]. While the complete eradication of polio, neonatal tetanus, congenital rubella, and measles are still the main targets in less developed countries [3], inhabitants of high-resource countries are focusing on rare adverse effects of vaccines to discredit the efficacy and effectiveness of vaccination. As a result, there is an increase in vaccine-preventable diseases in both children and adults. Indeed, it has been estimated that ten times more adults (40 to 50 thousand) die than children in the USA annually from potentially vaccine-preventable diseases [4].

In this controversial context, alongside vaccines for life-threatening diseases, there have emerged new vaccines to prevent the occurrence of diseases and their complications. Herpes zoster (HZ) vaccine [5–7], is the best example of such quality improvement vaccines. In this issue, Stefania Maggi and collaborators present a comprehensive and up-to-date review of how the HZ vaccine improves healthy ageing [8]. This paper raises some questions concerning the global epidemiology of the disease, improved knowledge of HZ risk factors, the well-known and more surprising consequences of the disease, as well as the increasing dilemma about age and the new indications for the currently available vaccine.

The incidence rate (IR) of HZ in Italy, at 6.3 per thousand person-years [8, 9], is higher than the mean incidence rate of 3–5 per thousand person-years reported in an analysis of 130 studies conducted in 26 countries in North America, Europe, and Asia-Pacific [10]. This could be related to a temporal increase in the incidence of HZ, often occurring before the introduction of varicella vaccination programmes [11], as in Finland [11] and Germany [12]. In the United Kingdom, one study reported that the median age at HZ diagnosis was 62 years (interquartile range 48–73) [13]. The IR was more or less stable between the ages of 10 and 44 years (at around 2.4 per thousand person-years), but increased more than threefold, to reach 15 in the 80–84 year old age group [12]. In the same study population, the IR was 36 % higher in females than in males [12]. Prodromic pain was experienced by 69.5 % of South Korean patients, of whom 95.1 % had moderate-to-severe pain [14]. In Italy, postherpetic neuralgia (PHN) occurred in 20.6 and 9.2 % of HZ patients older than 50 years after 3 and 6 months respectively [8, 15], which corresponds to the mean 6-month PHN risk reported in the world literature [16].

The risk factors for HZ have recently been better identified, and Maggi's paper describes them in detail [8]. However, it is important to insist on a few of these factors. In a study cohort of 144,959 adults diagnosed with herpes zoster between 2000 and 2011, severely immunosuppressive conditions represented the main risk (with odds ratios between 1.78 and 13.46), followed by systemic lupus erythematosus, rheumatoid arthritis and chronic pulmonary disease (increased risk over 30 %) [13]. In the same study, it appeared that asthma, chronic kidney disease, and depression increased the risk of HZ by 10 %, while no association was found with diabetes [13]. Stress and stressful life events were also found to be antecedents to

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outbreaks of HZ [17]. Similarly, the development of PHN has been associated with the psychological antecedents of somatization, nonspecific personality psychopathology, hypochondriasis, and somatic symptoms [17]. However, explicit psychiatric diagnoses, mood, and anxiety disorders have rarely been examined, except for depression, with HZ reported to be an independent risk factor for major depression and depressive disorders in a large prospective study [18]. In general, the relative effects of these risk factors for HZ onset decreased with increasing age [13].

Interestingly, recent studies have reported that chronic cytomegalovirus (CMV) infection may stimulate increasing HZ virus reactivation with age [19], and that there is a significant increase in chronic fatigue after HZ, with incidence increasing over time [20]. It is impossible not to pose the critical question of whether chronic activation of inflammatory pathways plays a role in the pathogenesis of frailty [21]. Indeed, the relationship between chronic CMV infection and HZ may compound the risk frailty [22]. Moreover, HZ and its complications may impair physical, social, and mood function, frequently provoking functional decline [23]. This in turn leads to a decrease in general or usual activity and self-care, associated with mobility disturbances, reduced mood and enjoyment [18], as well as disturbed sleep and relations with others [24, 25]. The repercussions on daily life of HZ, and even more so of PHN, negatively impact on patients and their family members, who express feelings of helplessness, frustration, sadness, and anger [26].

Recent convincing evidence appears to associate HZ infection, particularly HZ ophthalmicus, with an increased risk of stroke within 6 months [27]. A retrospective study of 106,601 HZ cases and 213,202 age- and gender-matched controls demonstrated that HZ is an independent risk factor for vascular diseases in the UK population [28]. Adjusted hazard ratios [95 % confidence intervals] reached 1.15 [1.09–1.21] for transient ischemic attack (TIA), and 1.10 [1.05–1.16] for myocardial infarction. The risk of TIA, stroke, and myocardial infarction increased significantly if HZ occurred in patients less than 40 years of age. In older subjects, better ascertainment of vascular risk factors and early intervention may explain the reduction in risk of stroke after HZ [28]. The so-called “varicella zoster virus (VZV) vasculopathy” is probably directly linked to VZV infection and replication within arterial walls, provoking vascular damage and disruption of vascular flow [29]. According to Nagel et al. [30] “VZV vasculopathy” could lead to transient ischemic attacks and ischemic and haemorrhagic stroke, but also temporal artery infection mimicking giant cell arteritis, extra cranial vasculopathy, aneurysm with and without subarachnoid haemorrhage, as well as spinal cord infarction and peripheral thrombotic disease.

All the possible consequences of HZ mentioned above adequately explain the results of a large prospective study proving that major depression and depressive symptoms occur more in HZ patients than in controls (respectively, 2.2 vs. 1.4 % and 4.3 vs. 3.2 %) [18].

Despite its established efficacy against HZ and PHN, well summarized in Maggi’s paper (HZ vaccine effectiveness is 48 % for HZ and 59 % for PHN at 3 months [27]), the uptake of HZ vaccine remains extremely low, at only 3.9 % of eligible subjects according to Langan et al. [27], and only 16 % in 2011 [31] and 20 % in 2012 for US adults over 60 years of age [32].

However, the most surprising of all these considerations is that the patients at greatest risk (i.e. those with severely immunosuppressive conditions and individuals below the age of 40 years at risk of vascular events) are not currently eligible to receive the vaccine [13].

Due to the increased severity of varicella in immunocompromised subjects, and in light of a recent prospective study demonstrating that HZ vaccine prior to chemotherapy reduced HZ incidence by half [33], Oxman et al. [34] purport that it may be time to reconsider the use of HZ vaccine in selected populations of immunocompromised patients. Updated HZ recommendations published by the Strategic Advisory Group of Experts (SAGE) in May 2014 have already widened the HZ recommendations to cover: (a) clinically stable HIV-infected children or adults with CD4 + T cell determinations above 15 %, including those receiving highly active antiretroviral therapy (HAART); (b) non-immunocompromised individuals with a history of acute lymphocytic leukaemia; and (c) patients with certain solid tumours who have successfully completed chemotherapy and are unlikely to relapse can receive the vaccine at least 3 months after all chemotherapy is completed. Furthermore, the vaccine can safely be given to subjects with isolated defects in antibody production and those with immunodeficiency conditions that include defects in cell-mediated immunity [35]. Indeed, it is also recommended that HZ vaccination of health care workers in contact with these immunocompromised patients be included in the routine immunization schedule [36].

Nonetheless, as also stressed by Oxman, specific vaccine recommendations should not divert attention from the urgent need to increase the currently inadequate uptake of HZ vaccine by adults [34]. The debate about the age at which adults should get the HZ vaccine is still wide open. In the UK, 45 % of HZ cases occurred before the age of 60 and 65 % in those under 70 [13]. Moreover, as the risk of developing HZ vasculopathy was proven to be major for subjects under 40 of age [28], the role of HZ vaccine in younger individuals could be promoted, as well as universal childhood varicella vaccination [37].

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