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Herpes zoster vaccine for the elderly: boosting immunity

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Abstract

Herpes zoster, also known as shingles, is a disease that results from the reactivation of a latent infection of the varicella zoster virus, which is usually encountered during early childhood. Aging is associated with an increased risk for herpes zoster and its complications. Boosting immunological memory is the key strategy for keeping the latent varicella zoster virus infection under control. A live attenuated virus vaccine is safe, effective and approved for use among healthy elderly adults aged 60 years or older. However, significant problems remain in the prevention of herpes zoster with the current vaccine. Future studies for improved vaccines and studies into the epidemiology of herpes zoster are required in order to address this significant public health burden.

Keywords

aging; immunity; shingles vaccine

Burden of shingles infections

Herpes zoster, more commonly known as shingles, is a disease that results from the reactivation of a latent varicella zoster virus (VZV) infection. The reactivation of the VZV usually results in a vesicular skin eruption that is localized to one, two or three dermatomes. The VZV may reside in dormancy for several years or even many decades in sensory ganglia, such as the dorsal root and cranial nerve ganglia, after the primary chickenpox (varicella) infection that occurred earlier in life. Before pediatric vaccination against varicella was introduced in the USA in 1995, varicella was highly endemic globally and nearly every person was naturally infected by adulthood. In the USA, nearly 99% of adults aged 40 years and older have serologic evidence of prior VZV infection and are therefore at risk for developing shingles during their lifetime [1]. Approximately a third of people who have experienced the primary VZV infection will develop shingles during their lifetime. As a result, approximately 1 million cases of herpes zoster occur in the USA each year [2].

The risk for herpes zoster and its complications rise with increasing age. As early as the 1960s, Hope-Simpson described the direct relationship between aging and the increasing annual incidence of herpes zoster [3]. He documented that the incidence of shingles was approximately two to three cases per 1000 persons before the age of 50 years [3]. However, among those aged

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50 years and older, a linear increase in the annual incidence rates of herpes zoster was observed, from five cases per 1000 persons at 50 years of age to ten cases per 1000 persons by 80 years of age [3]. At the age of 60 years and older there is an eight- to ten-times higher likelihood of developing herpes zoster compared with the younger population [4]. Among those aged 85 years or older, approximately 50% will have experienced one or more episodes or 'outbreaks' of shingles.

In addition to the increase in the incidence of herpes zoster observed with aging, an increase in the incidence of herpes zoster is observed in various conditions under which the immune system is compromised. When compared with the generally healthy population, herpes zoster occurs more frequently among patients receiving immunosuppressive therapy for underlying malignancies or who are on antirejection medications necessary for the successful maintenance of solid organ and bone marrow transplantation [5–9]. Reactivation with VZV is especially high among patients with HIV infection, leukemia and lymphoproliferative disorders [10,11]. It is worthy of note that there is not just an increase in the frequency of VZV reactivation events with immunocompromised individuals, but also an escalation in the rates of complication and death associated with VZV reactivation.

Herpes zoster and its complications have a considerable annual impact on the global population. The average herpes zoster hospitalization rate may be as high as 16.1 per 100,000 patient-years [12]. In 1996, this corresponded to an average cost of more than US$15,000 per hospital admission [12]. These estimates do not account for the indirect human costs, which are difficult to measure (e.g., lost productivity, quality of life and any other negative effects on a person's general wellbeing).

Varicella zoster virus & the role of varicella zoster virus-specific antibodies in herpes zoster

The VZV is a neurotropic enveloped DNA virus of the *Herpesviridae* family. Other medically relevant *Herpesviridae* viruses are herpes simplex viruses 1 and 2, Epstein–Barr virus and cytomegalovirus. An important characteristic of this family of viruses is their ability to establish latent infections. Similarly to its cousin viruses, VZV is a complex virus that is composed of a relatively large double-stranded, linear DNA genome that encodes more than a hundred genes. Encasing the genetic material of VZV is a protein-rich tegument and an outer lipid envelope, which incorporates numerous viral glycoproteins. These virus glycoproteins, designated as gB, gC, gE, gH, gI and gL, are expressed on the infected host cell membrane during viral replication. It is the highly conserved glycoprotein gB that plays a role in viral entry and is the target of neutralization and, therefore, protective antibodies (reviewed in [13]).

Although specific antibodies against VZV confer protection against the primary exogenous VSV infection (i.e., chickenpox), they appear to play little to no role in the host resistance against reactivation of the latent infection (i.e., the development of herpes zoster). The magnitude of neutralizing VZV-specific antibodies remains constant, even though increasing age; however, episodes of shingles may occur even when these antibody levels remain elevated [14,15]. Furthermore, herpes zoster may occur even during circumstances in which the level of VZV-specific antibody is maintained by intravenous immunoglobulin; for example, in patients shortly after bone marrow transplantation [7,9].

Herpes zoster: pathogenesis & post-herpetic neuralgia

The primary chickenpox infection is believed to originate after exposure and entry of the virus through inoculation of the respiratory tract by infectious respiratory droplets or direct contact

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with a mucosal surface, such as the conjunctiva. Therefore, the most appropriate mode of infection control during the primary VZV infection is respiratory isolation. The VZV quickly replicates in mononuclear cells of regional lymph nodes and viremia occurs within 4–6 days, resulting in systemic dissemination of the virus. Further replication occurs in these visceral organs and a secondary viremia, resulting in the classic skin manifestation of a generalized highly pruritic vesicular rash, typically occurs 10–21 days after the initial exposure. There is a substantial amount of infectious virus that is in the vesicular fluid of the rash. The infection is communicable from 1–2 days before the onset of the rash and until all skin lesions have formed crusts. At some point during the primary infection, some viruses enter the sensory nerve endings in the skin and travel in a retrograde fashion up the sensory nerve axon to the neuronal cell body at the dorsal root and cranial sensory (trigeminal) ganglia. Within these clusters of nerve cells, VZV may remain throughout the lifespan in the nuclei of the cell [16] and evades elimination by the immune system by limiting the expression of viral proteins.

Ultimately, this latent viral infection can lead to reactivation of the virus for some individuals. Reactivated VZV multiplies and disseminates within the sensory ganglion, resulting in intense inflammation and subsequent neuronal destruction. The virus descends along the neuronal axon producing the pathognomonic dermatomal rash observed during a shingles outbreak (i.e., unilateral vesicular eruption in a dermatomal distribution). These vesicular lesions contain high concentrations of infectious viruses, which make contact precautions the most appropriate mode of infection control until the lesions are encrusted. However, most US medical centers adopt a combination of both contact and respiratory isolation precautions for patients with herpes zoster.

Owing to the fact that VZV usually begins with intense replication within the neuronal ganglion before spreading to the skin, this explains the reason why herpes zoster usually begins with severe localized pain that precedes the appearance of the rash by several days. The skin eruption appears in crops of erythematous papules that rapidly evolve into discrete intraepithelial vesicles. The skin lesions last for 1–2 weeks before crusting. Although healing of the skin is almost always completed within 4 weeks of the onset of the rash [17], pain may persist and develop into the chronic syndrome known as post-herpetic neuralgia (PHN).

Post-herpetic neuralgia is partly a consequence of neuronal loss and subsequent scar formation in the part of the sensory ganglion and dorsal horn of the spinal cord that has been damaged by the viral reactivation. However, the neuropathic disease experienced by each individual is very heterogeneous and is the result of complex mechanisms of action that are yet to be completely understood. Nonetheless, abnormal nociceptive afferent signaling and central processing, such as pathologic hyperexcitability, are important in the pathogenesis of PHN [18–20]. PHN affects up to 20% of patients who develop herpes zoster and the risk for this complication is increased among the elderly population [21,22]. In fact, PHN develops in 73% of adults aged 70 years and older, an incidence that is triple that observed among adults aged 55 years and older [17]. The clinical spectrum of PHN is vast. It can present as mild discomfort that lasts for a few months to a severe debilitating pain that may persist throughout the remainder of a patient's lifetime. The pain may be so severe that it disrupts sleep, work and activities of daily living. Importantly, PHN is very difficult to treat once present, making prevention of shingles the paramount strategy.

Control of herpes zoster: a function of cell-mediated immunity & the effects of aging

Control of the latent VZV infection primarily involves the host's cell-mediated immunity (CMI). Humoral immunity or antibodies play almost no role in controlling the latent infection [15]. The presence of a robust VZV-specific CMI response prevents reactivation from

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occurring. Several conditions have been demonstrated to influence the host's ability to contain the virus. One of the most important factors is aging. As individuals age, the highly coordinated homeostatic balance of the immune system becomes increasingly dysregulated. This phenomenon, known as immunosenescence, is the reason why older individuals are less able to fight off infection compared with young adults, as demonstrated by older adult's increased susceptibility and their greater morbidity and mortality associated with certain infections. Immunosenescence is also the explanation for the poor protective responses (i.e., less than optimal protection) observed after vaccination (reviewed in [23]) and the higher risks for diseases caused by the reactivation of latent viral and bacterial (e.g., tuberculosis) infections. With advancing age, all components of the immune system may become dysfunctional. The innate immune system is affected since the phagocytic and killing ability of neutrophils and macrophages are reduced and the cytotoxicity of natural killer cells is diminished. However, the impact of aging on the adaptive immune system is most pronounced; the differentiation potential and function of T cells and B cells is blunted [24,25]. As prime examples of the effects of immunosenescence, the lack of expression of the costimulatory molecule CD28 and the loss of telomerase activity has been associated with significant cell senescence and clinical disease [26]. Therefore, it should be no surprise that the control of a latent viral infection may wane during aging.

Apart from aging, other conditions can affect CMI thereby influencing the control of latent VZV infection and so predispose a person to reactivation and herpes zoster flare-up. Active hematologic malignancies significantly increase the risk for herpes zoster; for example, Hodgkin's lymphoma is associated with a 20% cumulative increase in risk [27]. The first year following allogeneic hematopoietic stem cell transplantation is associated with a 15–50% cumulative increase in risk [28]. Solid cancers can also increase the risk for herpes zoster, and this increase is related to the level of immunosuppressive chemotherapy received [29]. Solid organ transplantation is also associated with chronic use of potent immunosuppressive medications in order to prevent graft rejection, and therefore leads to a 5–15% increase in incidence of herpes zoster [5]. HIV infection and the decline in $CD4^+$ T-cell counts is associated with a tenfold higher risk for herpes zoster compared with the general population [30]. Additional medical comorbidities can also affect CMI and the risk for herpes zoster. These conditions include: rheumatologic diseases, such as rheumatoid arthritis, systemic lupus erythematosus and Wegener's granulomatosis; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; and severe diabetes mellitus.

The main agents of CMI that are involved in keeping VZV reactivation under control are believed to be VZV-specific T cells. The decline in number of VZV-specific IFN-γ-producing T cells is associated with an increase in the incidence of herpes zoster [31–33]. In addition, VZV-specific T-cell proliferation defects and a lack of generation of MHC class I VZV-specific cytotoxic T cells were associated with an increased herpes zoster risk (reviewed in [34]). Therefore, if the loss of general T-cell function is an inevitability of aging, how might one defend oneself against herpes zoster?

Natural immunity: the road to a herpes zoster vaccine

A classic study conducted by Hope-Simpson during a 16-year observational study demonstrated that individuals rarely experience a second episode of shingles, even among the elderly [3]. It has been confirmed that even among healthy adults, the incidence of herpes zoster recurrence is quite low – less than 1.5% [35]. The relative infrequency of a second herpes zoster episode was postulated to be a natural phenomenon of ‘boosting’ VZV-specific CMI.

The establishment of a latent infection by VZV results in a lifelong immune response, which limits the ability of the latent virus to reactivate. When this level of immunity is disrupted (e.g.,

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the decay in cellular immunity that occurs with aging), a threshold may be reached that will allow VZV replication to occur unchecked, thus resulting in a herpes zoster episode [3,36]; this represents the concept of defective immune surveillance. However, the reactivation event leads to re-exposure of the immune system to VZV antigens, resulting in a significant boosting effect to the VZV-specific CMI and the boosting of memory T cells that are effective in fending off subsequent reactivations [3,36]. Therefore, a shingles episode essentially reimmunizes an individual via endogenous boosting of the immune system.

Subclinical boosting of the immune system also appears to occur throughout the lifespan [3]. Latent VZV may intermittently attempt to reactivate itself, but is kept under control by the intact CMI response. These subclinical events may be either entirely asymptomatic – fully contained – or may result in dermatomal pain without any rash (i.e., *zoster sine herpete*) – partial containment. Under any circumstances, these aborted reactivation events result in enhanced VZV-specific immunity [3,36]. By the same virtue, there appears to be a protective role in natural exposure to individuals with VZV or herpes zoster in terms of potentially boosting the immune system (i.e., CMI) and reducing the risk for herpes zoster [37,38]. Therefore, exogenous boosting of the immune system (i.e., vaccination) should be a viable strategy for preventing herpes zoster and its associated complications.

Vaccines against varicella zoster virus

The development of an attenuated varicella virus, known as the Oka strain, by Takahashi and colleagues in the 1970s was a milestone in VZV vaccine research [39]. The Oka strain virus was isolated from a healthy child in Japan with varicella, and the virus was serially passaged *in vitro* into human cell cultures, resulting in an attenuated or weakened virus. Immunization of VZV-naive children and young adults with a vaccine containing the live attenuated Oka strain virus was successful in dramatically reducing the incidence of primary VZV infection by as much as 98% [40–43]. The vaccine's efficacy in children is durable and has been demonstrated to persist even after 10 years of observation [40,42].

Although the Oka strain-based vaccine was successful in preventing primary VZV infection, the question arose: would this vaccine work against VZV reactivation? Oka strain-based vaccines successfully demonstrated that vaccination could induce a substantial boost in both humoral and cell-mediated VZV-specific immunity in immunocompetent elderly subjects [32,44,45]. Importantly, these trials demonstrated that the live attenuated Oka strain vaccine was safe and well tolerated.

Owing to the fact that live attenuated vaccines are generally contraindicated for immunosuppressed individuals, a heat-inactivated version of the Oka strain-based vaccine was studied among hematopoietic stem cell transplant recipients. When this vaccine was administered before and during the first 90 days of transplantation, there was a significant reduction in the risk for herpes zoster [46]. Moreover, vaccine recipients who developed symptomatic VZV reactivation experienced a significantly less severe disease compared with control subjects who were unvaccinated [47]. The vaccine-induced protection correlated with the reconstitution of VZV-specific $CD4^+$ T-cell mediated immune responses [46,47].

The Shingle Prevention Study: a landmark vaccine strategy for the elderly

Licensure of the sole vaccine currently available for shingles, composed of the live attenuated Oka strain virus, was based on a seminal Phase III study named the Shingles Prevention Study (SPS) [48]. This was a randomized, double-blind, placebo-controlled trial among 38,546 healthy adults aged 60 years or older at 22 sites. Over the 3 years of observation, 957 episodes of herpes zoster occurred; 315 among vaccine recipients and 642 among placebo recipients. In addition, there were 107 cases of PHN; 27 among vaccine recipients and 80 among placebo

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recipients. This resulted in a vaccine efficacy or a reduction in the burden of illness of herpes zoster and PHN of 51 and 66%, respectively [49]. However, vaccine response may be significantly affected by age, as demonstrated by the reduced vaccine efficacy observed in the older age cohorts; for subjects who were 80 years of age or older, there was only an 18% reduction in herpes zoster and a 39% reduction in PHN.

Under an ancillary immunological study, 1395 subjects who participated in the parent study were evaluated for their VZV-specific CMI responses by IFN-γ production and $CD4^+$ memory T-cell proliferation assays [49]. The vaccine induced an increase in VZV-specific CMI, which persisted throughout the 3-year follow-up period, although these levels waned over time. The magnitude of VZV immune responses were greater in the younger subjects (aged 60–69 years) compared with the older subjects (of age ≥70 years). In addition, there was an inverse correlation between VZV-specific CMI and the likelihood for developing herpes zoster [49].

The shingles vaccine was granted licensure by the US FDA on 25 May 2006. It is a similar vaccine to the pediatric chickenpox vaccine but is of a higher potency; it contains approximately 14-times more virus than the pediatric vaccine. Therefore, the pediatric vaccine is not a substitute for the shingles vaccine.

The shingles vaccine can significantly reduce the burden of herpes zoster among the elderly and its introduction has demonstrated cost–effectiveness [50,51]. The direct healthcare utilization costs of an episode of herpes zoster in an average outpatient is estimated to range from US$112 to US$287 and the cost of hospitalization is estimated to range from US$3221 to US$7206 [2,52,53]. However, the indirect costs of reduced quality of life owing to pain, suffering and disability, and the effects of loss in productivity, are impossible to calculate but are believed to be considerable. Therefore, a safe and effective shingles vaccine should be made available to the highest risk groups within the population.

Current recommendations for shingles vaccine from the Advisory Committee on Immunization Practices

The 2008 Advisory Committee on Immunization Practices (ACIP) recommendations advocate for the routine vaccination of all persons aged 60 years or older with one dose of shingles vaccine. Although vaccination is not recommended in order to treat acute herpes zoster, to prevent persons with acute zoster from developing PHN or to treat individuals with ongoing PHN who report a previous episode of herpes zoster, and patients with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis and chronic pulmonary disease) can be vaccinated, unless those conditions are contraindications or precautions. Shingles vaccination is contraindicated for those with anaphylactic reactions to any component of the vaccine, pregnant women and those individuals with primary or acquired immunodeficiencies (e.g., active hematologic malignancy, HIV with AIDS and a CD4 count of ≤200 cells per mm^3, recent hematopoietic stem cell transplantation and patients receiving immunosuppressive therapy or immunomodulatory therapy). Although there is no published experience with the shingles vaccine among HIV-infected adults, there is currently an ongoing study of the safety, tolerability and immunogenicity of the shingles vaccines in HIV patients with CD4 counts of greater than or equal to 200 cells per mm^3 (NCT00851786). Under circumstances in which an individual is anticipating the introduction of immunosuppressive medications, it is recommended that shingles vaccination should be administered at least 14 days prior to the initiation of therapy; however, other experts advise allowing 1 month prior to initiation. The shingles vaccine is not licensed for persons aged younger than 60 years. The shingles vaccine can be administered with other indicated inactivated vaccines (e.g., tetanus and pneumococcal polysaccharide vaccines) but should be given at different anatomical sites. Individuals receiving anti-VZV medications, including acyclovir, famciclovir and

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valacyclovir, should delay vaccination for at least 24 h after discontinuing these medications and should not resume these medications for at least 14 days in order to enable optimum vaccine efficacy.

Pitfalls of the current shingles vaccine

The current live attenuated virus shingles vaccine is not approved for certain groups of patients who might benefit from a shingles vaccine. The live attenuated shingles vaccine is not approved for use in individuals who received the varicella vaccine at any age. However, varicella vaccination only commenced in 1995 and very few adults aged 40 years or older have received this vaccine. Since the vaccine is composed of a live attenuated virus, there is a theoretical risk for overwhelming viremia among those who are severely immunocompromised; however, this phenomenon has never been documented in a shingles vaccine recipient. By contrast, the severely immunocompromised represent a substantial proportion of the population who are at risk for herpes zoster and its complications. Therefore, early and aggressive antiviral therapy of vesicular lesions or cutaneous pain syndromes, which are consistent with VZV reactivation, form the standard of care for the approach to herpes zoster in the severely immunocompromised. A rare yet known adverse effect of vaccination is the development of a mild varicella-like rash, which is usually limited to less than 25 vesicles. There is a possibility for the transmission of the live attenuated virus from vesicular fluid; therefore, individuals with close household or occupational contact with at-risk persons who are susceptible for severe varicella should adopt contact precautions until the lesions have crusted.

Future perspective

The newly licensed shingles vaccine represents a useful means to significantly reduce the burden of a disease that afflicts the elderly. However, there are future directions for vaccine development that should be addressed in upcoming studies. First, the age of vaccination is currently limited to those aged 60 years or older. As detailed previously, the slow decline of the immune system (immunosenescence) is one of the primary reasons for the increased incidence of herpes zoster among the elderly; why not initiate vaccination at earlier ages when the immune system is ‘intact’? This question is partially being addressed with a Phase III trial of the shingles vaccine evaluated in adults aged 50–59 years (NCT00534248; completion anticipated for May 2010). A second direction should address the gap in high-risk segments of the population who are immunocompromised. An inactivated or nonreplicating vaccine may successfully be administered to the severely immunocompromised and yield protection. A heat-inactivated version of the Oka strain vaccine is under testing in persons with hematologic malignancies, recent hematopoietic stem cell transplants, solid organ cancers and HIV with CD4 counts of less than or equal to 200 cells per mm^3 (NCT00535236).

A third concern is the durability of protection with vaccination. The seminal licensure trial demonstrated protection from herpes zoster for as long as 3 years after vaccination. However, the questions regarding how much longer protection will persist for and whether another dose of vaccine should be recommended at a later time still remain. At present, a single 10-year observational study is being conducted in order to determine whether vaccine effectiveness may wane over time. A fourth concern relates to the immunologic correlates of protection. For tetanus, antibody titers can easily be measured and the achievement of a certain level of antibody is known to correlate with protection from infection. However, with herpes zoster (and varicella) antibodies do not afford protection. It is known that some markers of T-cell immunity become enhanced subsequent to vaccination (or natural infection); however, standardized clinical laboratory methods and prospectively validated cut-offs are yet to be established.

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There is considerable controversy regarding the long-term effects of using VZV vaccines owing to the potential adverse effects on the future epidemiology of shingles. Since there will be less exogenous and natural exposure to VZV, there may be an increase in adult VZV or an increase in the incidence and costs associated with herpes zoster in the coming decades [20, 54,55]. Some countries have not adopted routine childhood VZV vaccination for fear of increasing the burden of this disease on middle-aged and elderly adults. Furthermore, it may be unrealistic to expect the complete extinction of VZV with any vaccination strategy, given that this would require the global elimination of a latent virus from all infected individuals. This potential detrimental consequence highlights the importance of continued close surveillance of VZV and shingles activity in both adults and children from countries that either have or have not adopted vaccination.

Additional issues continue to impede the progress of shingles prevention. The current vaccine demonstrated an approximately 51% reduction in the incidence of herpes zoster; next-generation vaccines might attempt to improve the reduction in incidence of herpes zoster. There are likely to be future trials on the efficacy of shingles vaccine among prior recipients of the pediatric varicella vaccine. Since only one vaccine is currently licensed (Zostavax™, Merck, NJ, USA), additional vaccine manufacturers are likely to seek licensure of their own shingles vaccines; at present, GlaxoSmithKline is conducting early testing of a herpes zoster vaccine (NCT00802464 and NCT00434577). Ongoing and future epidemiological trials should be conducted in order to determine whether significant changes will occur with the introduction of the pediatric varicella vaccine. Will the occurrence of shingles begin at earlier ages owing to a lack in the robustness of the immune response against VZV reactivation compared with the immune response against a natural infection? With the global eradication of smallpox in 1979 and the elimination of poliovirus in most parts of the world, a final but more realistic destination for shingles and VZV may be the prevention of serious disease but not complete elimination of the virus. However, this final goal will not be possible without continuous development, licensure and use of additional and next-generation vaccines against VZV.

Executive summary

Burden of shingles & pathogenesis

- Herpes zoster represents a significant healthcare burden among the elderly, even among the healthy elderly.
- Herpes zoster and its complications are a result of reactivation of a latent infection, usually first encountered in early life.
- Aging is associated with the slow decay of the immune system, which may eventually compromise the ability of the body to keep the latent varicella zoster virus infection under check.

Herpes zoster vaccine

- Memory T-cell mediated immunity can be ‘boosted’ in order to prevent varicella zoster virus reactivation.
- A safe and cost-effective shingles vaccine is licensed for use among adults aged 60 years or older.
- Since the vaccine is composed of a live attenuated virus, there are important contraindications to its use that limit the scope of protection, especially among the highest risk segments of the population.

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- Ongoing and future studies are planned in order to address the current gaps in knowledge and the use of shingles vaccines.

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