

# **Varicella and Herpes Zoster vaccines: WHO position paper**

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**World Health  
Organization**

# Varicella disease

- Etiologic agent = varicella zoster virus (VZV), an  $\alpha$  herpesvirus
- Humans only reservoir of infection
- Primary infection: Varicella (chickenpox)
- Following infection, the virus remains latent in neural ganglia; upon subsequent reactivation, usually much later in adult life, VZV may cause herpes zoster (shingles), affecting mainly immunocompromised individuals and elderly people.
- Transmission from patients with varicella and herpes zoster primarily via respiratory route following aerosolization of infective viral particles from skin lesions, also direct contact.
- Incubation period 10-21 days.
- Highly infectious with secondary household attack rates of > 80% (range 61 – 100%) .
- Symptoms include febrile pruritic rash illness with macules, progressing to papules, vesicles and crusts. Lesions can be found in varying stages of development and resolution.
- Subclinical infection is uncommon.

# Varicella Epidemiology

- In most climates, strong seasonality with peak incidence in late spring in temperate climates or in the coolest/driest months in tropical climates.
- Because it is very contagious, in most populations, essentially all persons acquire varicella during their lifetime, most commonly during childhood.
- Differences in epidemiology described between temperate and tropical climates; later disease acquisition in some tropical settings.
- Factors affecting risk of exposure include area of residence (urban vs rural), childcare, school attendance and other.
- Disease burden depends on age-specific incidence, age-specific severe morbidity and mortality, and risk factors for severe disease in the population.

# Varicella Annual Disease Burden

## Developed Countries

- Incidence 16/1000/year or birth cohort equivalent
- Complications (3%)
- Hospitalizations (5‰)
- Congenital varicella syndrome
  - 1-2% first trimester affected pregnancies)
- Deaths (3/100,000 cases)

Iyun et al Geogr Med 1984, Valentim J et al Vaccine 2008, Jezek Z et al Ind J Pub Health 1978, Barss P Lancet 1983, Poulsen A et al PIDJ 2005

# Varicella Annual Disease Burden

Global annual minimum estimate

- Cases: 140 million
- Severe complications (hospitalization): 4.2 million
- Deaths: 4,200



# Varicella Vaccines

- Live, attenuated vaccine, developed in Japan by Dr Takahashi
- Oka VZV strain
- Refrigerator-stable and frozen vaccine formulations
- Vaccines
  - Monovalent vaccines: licensed on basis of efficacy and safety
  - Combination (MMRV): licensed on basis of safety and of non-inferior immunogenicity compared with MMR and Varicella vaccines
- Depending on the product, the vaccine may be administered either by subcutaneous or intramuscular injection



# Varicella Vaccines Efficacy

Four randomized controlled trials (RCTs) indicate that 1 dose of varicella vaccine is highly efficacious in preventing varicella disease in healthy children:

- One trial suggests 100% efficacy after 9 months and 98% after 2 years using a varicella vaccine with 17 000 PFU at release.
- Another trial assessed vaccine efficacy to be 88% after an average of 29 months using a 10 000 or 15 850 PFU vaccine. During the 7-year follow-up, 95% of these vaccine recipients were estimated to have remained free of varicella.
- Vaccine efficacy was 90.8% (95% CI: 88.7%–95%) after 12 months follow-up in a third clinical trial (with 10 000 PFU vaccine).
- In a recent RCT, 1 dose of a monovalent vaccine was 65.4% effective against varicella disease of any severity and 90.7% effective against moderate/severe varicella, while 2 doses of a combined vaccine were 94.9% effective against disease of any severity and 99.5% effective against severe/moderate disease.



# Varicella Vaccines Effectiveness

## Healthy children

- All disease  
Median ~ 82.5% (range 20%-100%)  
52 estimates
- Severe disease (clinical severity score,  
> 500 lesions complications/hospitalization)  
Median 100% (range 85-100%)
  - 18 estimates

## HIV+ children

- 82% (95% CI 24-100%)
- 1 study

No differences in vaccine effectiveness across vaccine manufacturers  
though number of studies are small for many vaccines

Seward JF et al, JID, 2008 (review); Bayer O et al Vaccine 2007, Son M et al, JID, 2010; SAGE WG background paper 2014, WHO systematic literature review of vaccine effectiveness



# Varicella Vaccine Safety

## Pre- and Post-licensure

- Placebo-controlled trials: small risk rash, fever, injection site reactions in appropriate time windows
- Post-licensure safety monitoring mainly from the US
  - Rare/extremely rare confirmed serious adverse events:
    - Rash, hepatitis, pneumonia, herpes zoster, meningitis, encephalitis, secondary transmission
    - 2 vaccine strain VZV deaths, one immunocompromised and one with significant medical history suggestive of being immunocompromised
    - Ataxia, thrombocytopenic purpura
- Increased risk of febrile seizure in 5-12 day window following first dose MMRV vaccine in children 12-23 months
  - One additional febrile seizure for every 2,500 children vaccinated with MMRV vaccine compared with MMR+V vaccines

Wiebel R et al NEJM 1984, Dos Chaves SS et al JID 2008 (review), Galea SA et al JID 2008 (review), Klein NP et al Pediatrics 2010, Jacobsen S et al Vaccine 2009 IOM Report: Adverse Effects of Vaccines: Evidence and Causality, August 2011, Schrauder et al Lancet 2007, Leung et al Human Vaccines 2014, Goulleret N Vaccine 2010 (review)

# WHO position

## Varicella Vaccines

- Although the burden of severe disease and mortality due to varicella and herpes zoster is substantially lower than that of other currently vaccine-preventable disease such as measles, pertussis, rotavirus or invasive pneumococcal disease prior to vaccine introduction, the public health value of varicella vaccination in lowering morbidity and mortality due to VZV, particularly in vulnerable population groups, is well established.

# WHO position

## Varicella Vaccines

- Before countries decide on the introduction of varicella vaccine into routine childhood immunization programmes, they should have set up adequate disease surveillance to assess the disease burden caused by varicella, with provision of continued surveillance after introduction of vaccination.
- Countries where varicella is an important public health burden could consider introducing varicella vaccination in the routine childhood immunization programme.
- Resources should be sufficient to ensure reaching and sustaining vaccine coverage  $\geq 80\%$ . Vaccine coverage that remains  $< 80\%$  over the long term is expected to shift varicella infection to older ages in some settings, which may result in an increase of morbidity and mortality despite reduction in total numbers of cases. Decision-making on childhood varicella vaccination should also include consideration of the possible impact on herpes zoster.

# WHO position

## Varicella Vaccines

- Countries which decide to introduce routine childhood varicella immunization should administer the first dose at 12–18 months of age.
- The number of doses recommended is dependent on the goal of the vaccination programme:
  - One dose is sufficient to reduce mortality and severe morbidity from varicella but not to prevent limited virus circulation and outbreaks.
  - Two doses have higher effectiveness and should therefore be recommended in countries where the programmatic goal is, in addition to decreasing mortality and severe morbidity, to further reduce the number of cases and outbreaks. The minimum interval between the 2 doses should be as recommended by the manufacturer, ranging from 4 weeks to 4–6 weeks.
- Countries with a high average age ( $\geq 15$  years of age) of acquisition of infection, indicating a high proportion of susceptible persons in the population, could consider alternative vaccination strategies such as vaccination of adolescents and adults without evidence of varicella immunity. This strategy requires a 2-dose schedule.

# WHO position

## Varicella Vaccines- choice of vaccines

- Countries could use either monovalent or combination MMRV vaccines, taking into consideration the safety and effectiveness profiles, including a higher risk of febrile seizures after the first dose, but not after the second dose, when MMRV vaccine is used for the first dose at 12–18 months.

# WHO position

## Varicella Vaccines-special populations

- Varicella vaccine is usually contraindicated in persons with congenital or acquired immune deficiencies. However, due to the increased severity of varicella in certain groups of immunocompromised persons, varicella vaccination (2 doses) may be considered in these groups.
- Use of monovalent vaccine in these populations should only be considered in health-care settings where specific antiviral therapy against varicella is readily available and physicians have expertise with the vaccine in these patients.
- MMRV has not been tested and is contraindicated in immunocompromised persons.
- The use of varicella vaccine (2 doses administered 3 months apart) may be considered in clinically stable HIV-infected children or adults with CD4+ T-cell levels  $\geq 15\%$ , including those receiving highly active antiretroviral therapy (HAART). HIV testing is not a prerequisite for varicella vaccination. The vaccine has not been studied in individuals with CD4+ T-cell counts  $< 15\%$  or in those who are not clinically and immunologically stable, and should not be used in such cases.

# WHO position

## Varicella Vaccines-special populations

- Susceptible individuals with a history of acute lymphocytic leukaemia (ALL) and patients with certain solid tumours who have successfully completed chemotherapy and are unlikely to relapse can receive vaccine at least 3 months after all chemotherapy has been completed.
- Protocols defining the timing of vaccination in terms of time in remission on maintenance chemotherapy, when to interrupt that chemotherapy, including corticosteroids, before and after vaccination, and minimal acceptable lymphocyte and platelet counts at the time of vaccination should be followed.
- Consideration of vaccination in other populations of patients who are receiving or have received medications that may be immunosuppressive, should be discussed with specialists with expertise in this area.
- Vaccine can be safely given to patients with isolated defects in antibody production (hypogammaglobulinaemia or agammaglobulinaemia).
- It should not be given to those with conditions in which defects in antibody production are part of a complex immunodeficiency that includes defects in cellular immunity (e.g. severe combined immunodeficiency) or any condition characterized by defects in cellular immunity, except as described above for HIV, ALL and certain solid tumours.



# WHO position

## Varicella Vaccines-household contacts of immunocompromised patients

- Susceptible household contacts of immunocompromised patients at high risk of severe disease (e.g. premature infants or children with leukaemia or solid cancer) should be considered for vaccination with 2 doses of varicella vaccine spaced according to the minimum interval recommended by the manufacturer in countries that have introduced routine VZV vaccination.
- Two doses are recommended for household contacts of immunocompromised persons for higher effectiveness even if the country has a routine 1-dose childhood programme.





# WHO position

## Varicella Vaccines- post exposure prophylaxis

- Vaccination as soon as possible, within 3–5 days post-exposure, can be effective in preventing disease and should be considered in settings where routine varicella vaccination is implemented within the regular schedule.



# WHO position

## Varicella Vaccines-pregnancy

- Varicella vaccine is contraindicated during pregnancy and pregnancy should be delayed for 4 weeks after vaccination.
- Limited data from infants born to women who had been inadvertently vaccinated during pregnancy have not revealed any cases of congenital varicella syndrome.
- Termination of pregnancy is not indicated if vaccination was carried out inadvertently during pregnancy.
- Routine laboratory documentation of pregnancy status prior to vaccination is not recommended.
- In countries where varicella vaccination has been included in the routine programme, efforts should be made to counsel and vaccinate women without evidence of immunity, either prior to pregnancy or post-partum, in order to prevent infection during subsequent pregnancies.

# WHO position

## Varicella Vaccines-health care workers

- Countries should consider vaccination of potentially susceptible health-care workers (i.e. unvaccinated and with no history of varicella) with 2 doses of varicella vaccine, even if it is not included in the routine immunization schedule, in settings where the risk of severe varicella in the population in direct contact with the health-care workers is high.
- Where financial constraints prohibit vaccination of all susceptible health-care workers, priority should be given to vaccination of those in close contact with persons at high risk of serious varicella complications such as severely immunocompromised patients and premature infants born <28 weeks' gestation or weighing <1000 grams.
- This indication should be defined at the regional/country level, given the marked influence of local factors on varicella epidemiology.

# WHO position

## Varicella Vaccines- co-administration with other vaccines

- Varicella vaccine can be administered concomitantly with other vaccines included in the routine childhood immunization programme.
- Unless given together with other live viral vaccines (measles, MR, MMR), it should be administered at a minimum interval of 28 days.



# WHO position

## Varicella Vaccines- travellers

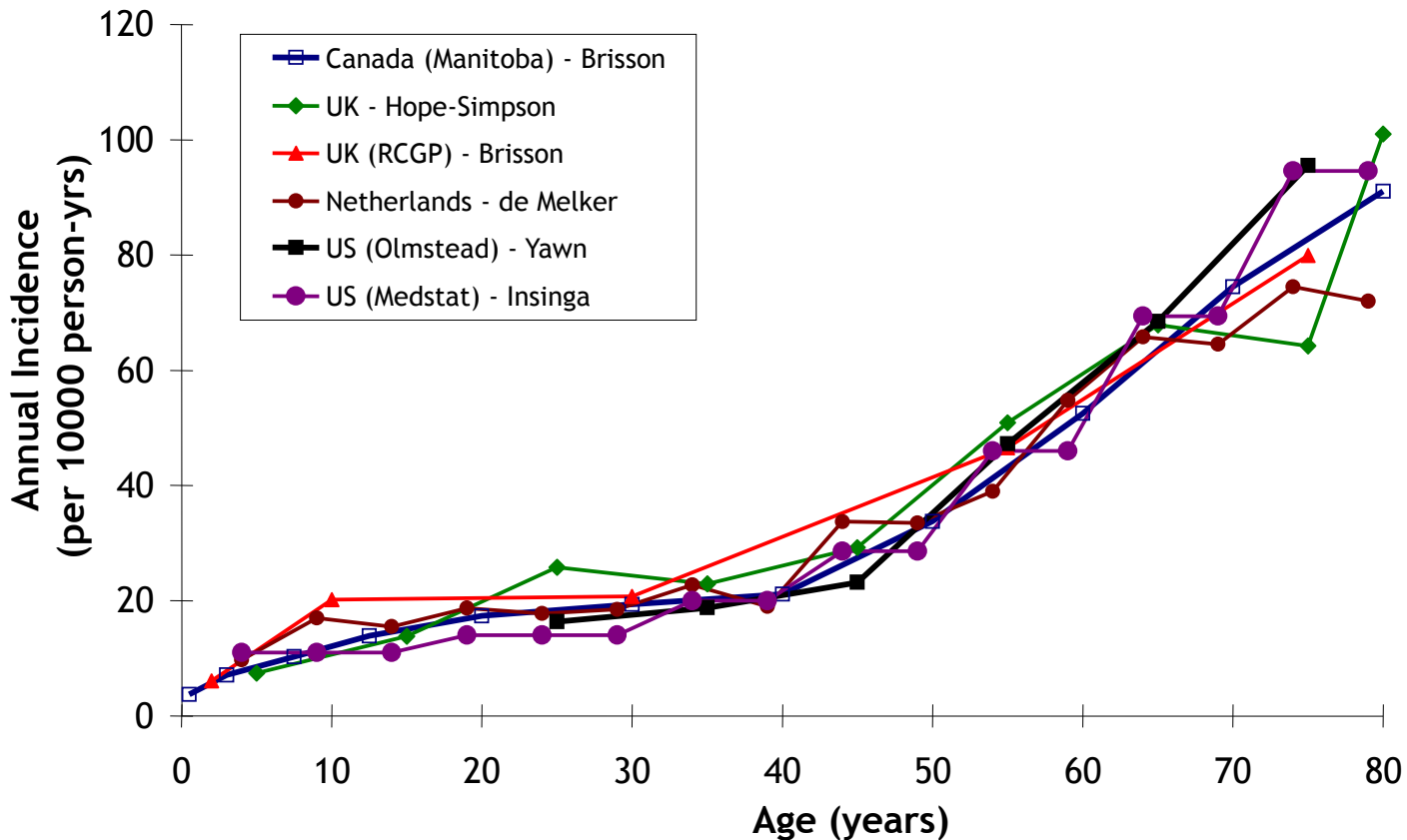
- Travellers are not at increased risk of acquiring or transmitting varicella or herpes zoster compared to the general population. Vaccinating travellers against varicella and/or herpes zoster is not specifically recommended, though travellers (children and adults) should have completed routine vaccination (varicella and/or herpes zoster vaccination) according to their national schedule.

# Herpes Zoster Disease

- Reactivation of VZV: Herpes zoster (shingles)
- Symptoms included rash with dermatomal distribution along with severe pain.
- Complications include:
  - Post-Herpetic Neuralgia (PHN) in 22% (8-26%) of herpes zoster patients: Pain persisting more than 90 days after rash onset
  - Herpes zoster Ophthalmicus: Ophthalmic division of trigeminal nerve ~15% of cases (If untreated, 50-70% develop acute ocular complications chronic complications, reduced vision, even blindness)
  - Neurologic: Invasion by VZV of vascular or neurologic structures can lead to Encephalitis, myelitis, optic neuritis, palsies, stroke syndromes, hearing impairment, vertigo, loss of taste sensation
  - Deaths mostly occur among the immunocompromised (0.25-0.51 per 1 million population; 7-25 per 100,000 cases)

# Herpes Zoster incidence by age

Highly consistent findings between high income countries, no data from low and low-middle income countries



Lifetime risk=20-35%, steep increase in incidence with age

# Herpes Zoster Vaccine

- Currently available – Oka VZV vaccine
- Licensed in over 60 countries
- Indicated in immunocompetent individuals aged  $\geq 50$  years
- Live vaccine – contraindicated in immunosuppressed
- Administered as a single subcutaneous injection
- Formulated with a minimal potency of 19 400 PFU
- Lyophilized refrigerator-stable and frozen formulations licensed





# Herpes Zoster Vaccine

## Efficacy and Effectiveness

Vaccine efficacy within clinical trials (short term) <sup>[1,2]</sup>

	Incidence of HZ			Burden of illness			Incidence of PHN		
	V	P	VE (95% CI)	V	P	VE (95% CI)	V	P	VE (95% CI)
Age									
50-59 yrs	2.0	6.6	70 (54-81)	0.1	0.5	73 (53-85)	NA	NA	NA
60-69 yrs	3.9	10.8	64 (56-71)	1.5	4.3	66 (52-76)	0.3	0.7	66 (20-87)
≥ 70yrs	7.2	11.5	38 (28-52)	3.5	7.8	55 (40-67)	0.7	2.1	67 (43-81)

V: Vaccine group; P: Placebo group; VE: Vaccine efficacy; Burden of illness score is a composite measure of HZ incidence, severity and duration of pain

### Vaccine effectiveness US post-licensure studies (≥60 years):

- Herpes zoster = 55%<sup>[3]</sup> and 48%<sup>[4]</sup>
- Ophthalmic herpes zoster = 63%<sup>[3]</sup>
- Hospitalizations coded as herpes zoster = 65%<sup>[3]</sup>
- PHN = 59%<sup>[4]</sup>
- Immunosuppressed = 37% (95%CI: 6-58)<sup>[4]</sup>

Ref: 1. Oxman *NEJM* 2005; 2. Schmader *CID* 2012; 3. Tseng *JAMA* 2011; 4. Langan *PlosMed* 2013



# Herpes Zoster Vaccine Safety

Immunocompetent adults  $\geq 50$  years

- The vaccine was well-tolerated in the Shingles Prevention Study<sup>[1,2]</sup>
  - Similar proportions (1.4%) of participants who received the vaccine (n=19,270) or the placebo (n=19,276) reported serious adverse events
  - Varicella-like rash at the site of injection was the only adverse event statistically more frequent among vaccinated
- Safety of the vaccine was confirmed in the RCT among younger subjects (50-59 years) <sup>[3]</sup>
  - 0.6% and 0.5% of participants who received the vaccine (n=11,211) or the placebo (n=11,228) reported serious adverse events
- Vaccine safety has been demonstrated in post-licensure studies<sup>[4-7]</sup>

Ref: 1. Oxman *NEJM* 2005; 2. Simberkoff *Ann Int Med* 2010; 3. Schmader *CID* 2012; 4. Tseng *J Intern Med* 2012; 5. Baxter *Vaccine* 2012; 6. Leroux-Roels *J Infect Dis* 2012.

# WHO position

## Herpes Zoster Vaccines

- Due to the unknown burden of herpes zoster in most countries and insufficient data concerning the use of this relatively new vaccine, WHO does not offer any recommendation concerning the routine use of HZ vaccine at this time.

# WHO position

## Herpes Zoster Vaccines

- Currently, data on the duration of protection provided by HZ vaccination are insufficient and there is initial evidence of waning of protection over time, as well as uncertainty regarding the optimal age for vaccination and the potential role of a booster dose.
- However, countries, especially those with an aging population and demographic shift towards older ages, may decide to introduce routine herpes zoster vaccination if they have an important burden of disease and consider the programme beneficial.
- For those countries deciding to proceed with a herpes zoster vaccination programme, the optimal age and dosing schedule of HZ vaccination should take into consideration the age-dependent burden of disease, vaccine effectiveness, duration of protection, and cost-effectiveness.

**For more information on the WHO  
Varicella and Herpes Zoster position  
paper, please visit the WHO website:**

**[www.who.int/immunization/documents/  
positionpapers](http://www.who.int/immunization/documents/positionpapers)**



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