Background Paper on Varicella Vaccine

SAGE Working Group on Varicella and Herpes Zoster Vaccines

Contents

Introduction

Varicella or chickenpox is an acute, highly contagious viral disease with worldwide distribution. It is characterized by a generalized, pruritic maculopapular vesicular rash that appears in successive crops and that rapidly progresses to develop crusts and scabs [1]. Although varicella is usually a self-limited illness of childhood, it can cause significant morbidity and mortality in otherwise healthy children and adults and may assume greater relative importance in preventable disease burden as other diseases are prevented through vaccination. Morbidity and mortality are higher in immunocompetent infants and adults as well as in immunocompromised persons compared to healthy children[1]. Nonetheless, due the ubiquitous nature of varicella infection, the majority of severe disease burden occurs in healthy persons, primarily children[2, 3]. Varicella is the manifestation of the primary infection caused by the varicella-zoster virus (VZV). Following the primary infection, the virus remains latent in neural and intestinal ganglia and may reactivate years or decades later to cause herpes zoster (HZ) or shingles[4]. HZ develops primarily in healthy adults after the age of 50 and in immunocompromised persons of all ages. In its full clinical expression, HZ causes pain which is followed by a pruritic vesicular rash usually restricted to one or more dermatomes that closely overlap the segmental distribution of the nerve cells in which latent VZV resided[4]. Rash can disseminate beyond the initial dermatome in immunocompromised patients.

Varicella can be treated with antiviral drugs[5]. However, considering the minimal clinical benefit in healthy persons and the cost of the treatment, antiviral treatment is recommended for persons at high risk for severe varicella. Varicella-zoster immune globulins are effective as post-exposure prophylaxis to reduce disease severity in persons at high risk for severe varicella but they are also costly and not widely available worldwide[5]. Control of varicella can be achieved only by vaccination. A varicella vaccine based on attenuated live VZV virus (Oka strain) was developed approximately four decades ago and some countries started introducing vaccination into the childhood immunization programs after more widespread global licensure that followed licensure in the United States in 1995. Currently there are several formulations of live attenuated varicella vaccines. While these vaccines are licensed and available throughout the world they are recommended for routine use only in a small number of countries, primarily industrialized countries (i.e., Unites States, Canada, Australia, Germany, Greece, Latvia, Israel, Uruguay, Costa Rica, United Arab Emirates, Saudi Arabia, Quatar, Taiwan, various regions in Spain and Italy). Where high coverage rates have been attained, vaccination has resulted in important declines in varicella-related incidence, morbidity and mortality[6-9].

Objectives

The SAGE Working group on varicella and herpes zoster vaccines (established in May 2012) was tasked with reviewing the evidence, identifying information gaps, and guiding the work to formulate proposed

recommendations related to the use of varicella vaccine to update the 1998 varicella vaccine WHO position paper for SAGE review. This report reviews the evidence related to the main topics considered by the working group, including:

1. Varicella epidemiology: the global incidence and burden of disease caused by varicella according to country development status
2. Safety and effectiveness profile of varicella vaccine and duration of protection following immunization, including those of combination vaccines such as MMRV
3. Country experiences with introduction and use of varicella vaccines
4. Changes in the epidemiology of varicella with the introduction of the childhood varicella vaccination
   a. In population groups who received the vaccine
   b. Potential for shift in the age at infection and increase burden of varicella
5. Changes in the epidemiology of herpes zoster with the introduction of the childhood varicella vaccination
   a. In population groups who received the vaccine
   b. Potential impact of the varicella vaccination program to increase the incidence of herpes zoster
6. Evidence on the cost-effectiveness of varicella vaccination, in particular in low and low-middle income countries
7. Varicella disease and vaccination in immunocompromised individuals

Methods

To update the 1998 WHO position paper on varicella vaccine, the SAGE working group for varicella and herpes zoster vaccination considered several key issues (outlined above). To address these issues and review available data on varicella disease and varicella vaccines, the working group first met in June 2012 conducted monthly teleconferences through February 2014 and had a face-to-face meeting in June 2013. Published, peer-reviewed studies were the primary source of data used. They were identified by leading experts in the field of varicella and varicella vaccines based on their expertise and by literature search in preparation for the presentations during teleconferences. In addition, a systematic review of literature available in the electronic databases (the Cochrane Library and Pubmed) was performed by the WHO secretariat on varicella vaccine effectiveness, duration of protection and safety from the beginning of each candidate database through November, 2013. Included were studies reporting on vaccination with varicella vaccine alone, MMR and varicella, or MMRV. The electronic search was completed by a manual search examining bibliographies of relevant previous reviews and the reference lists of selected articles to identify studies not identified through the databases listed above. The summary of the reviews is included in the present document and the detailed reports are posted on the web for SAGE members. The working group discussed the quality of evidence (study design, risk of bias, results) and the results were summarized by WHO secretariat in GRADE tables. The Global Advisory Committee on Vaccine Safety reviewed the varicella vaccine safety data during a dedicated call.

Because published data are sparse on the burden of varicella disease in low and middle income countries, and especially from the African continent for which only one seroprevalence study was identified[10], WHO funded two studies to inform discussions:

- a serologic study to test specimens from one African country to gain insight on VZV serology and distribution of varicella by age groups
- a modeling study to assess the potential impact of one dose varicella vaccination on shifts in the age at infection and morbidity in low and middle income countries

Results

Pathogen and transmission

The causal agent of varicella and zoster is varicella-zoster virus (VZV), a double-stranded DNA virus belonging to the herpesvirus family[11] that naturally infects only humans. VZV is transmitted from person to person by direct contact with rash, inhalation of aerosols from vesicular fluid of skin lesions of patients with varicella or herpes zoster, or from infected respiratory tract secretions of patients with varicella that might also be aerosolized. The virus enters the host through the upper-respiratory tract or the conjunctiva. After primary infection as varicella, the virus remains dormant in the sensory-nerve ganglia and can reactivate at a later time, causing herpes zoster. The period of communicability of infected varicella patients is estimated to begin 1-2 days before the onset of rash and to end when all lesions are crusted, typically 5-6 days after rash onset in immunocompetent people, but this period may be longer in immunocompromised people[1]. Herpes zoster patients are less contagious than patients with varicella and are considered infectious while they have active lesions (usually 7–10 days). In utero infection can occur during the first two trimesters of gestation as a result of transplacental passage of virus during maternal varicella infection. Varicella infection usually confers immunity for life; second attacks of varicella are rare in immunocompetent persons but have been documented[12, 13]; subclinical reinfection is common[14].

Clinical description of varicella

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10 to 21 days[1]. The incubation period may be shorter in immunocompromised patients. Subclinical varicella is rare. Before smallpox eradication, especially in adults, varicella was the most common disease confused with smallpox. Prodromal symptoms may be present, particularly in older children and adults. Fever (usually moderate, 100-102^{0}F or 37.7-38.8^{0}C) malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hours before the rash appears and usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk[1]. The initial exanthem consists of pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles, superficially located in the dermis layer. Subsequent crusting of the lesions occurs in 24-48 hr. While the initial lesions are crusting, new crops form for about 5 to 7 days; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella and distinguishes it from smallpox. The distribution of the rash is predominantly central or centripetal with the greatest concentration on the trunk and proximally on the extremities. The average number of lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older healthy children and adults, more lesions usually occur. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

Because one dose of varicella vaccine is not 100% effective, some vaccinated persons will develop varicella. Varicella occurring in vaccinated persons more than 42 days after vaccination (also referred to as "breakthrough disease") is always due to wild-type VZV. The clinical presentation is highly modified in the majority of patients (~70%) with mildly elevated or no fever and frequently an atypical rash with <50 lesions that are predominantly maculopapular[15, 16]. Lesions may be so few in number that they escape observation and present challenges for confirming the diagnosis. Among 2-dose vaccine recipients, disease may be even further attenuated. About 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella; recipients of 2 doses of varicella vaccine are less likely to have breakthrough disease than those who received one dose[17].

Though varicella is usually self-limited in immunocompetent persons it may be associated with severe complications, mediated by either VZV or bacteria[1]. Groups at higher risk for severe complications are infants, adults, newborns and immunocompromised persons. The most common complications are secondary bacterial infections, mainly caused by group A ß-haemolytic streptococci or *Staphylococcus aureus* which affect primarily the skin and underlying soft tissue. Invasive infections (pneumonia, arthritis, osteomyelitis, necrotizing fasciitis or sepsis) can be life threatening. Pneumonia, commonly viral, is the most common complication in adults; it is

often severe, fatality was reported in 10%-50% of adults with pneumonia in the pre-antiviral era[18]. Complications of the central nervous system range from cerebellar ataxia (1 in ~4,000 cases[19]) where the prognosis is usually good to encephalitis (1 in 33,000-50,000 cases[19]) or meningoencephalitis where prognosis is less favorable. Hemorrhagic varicella with multi-organ system failure is rare in healthy children but is frequently fatal. Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after seven days, is a severe complication of primary VZV infection with the highest risk in patients with congenital cellular immune deficiency disorders and those with malignancy. Rarely (about 1 case in 40,000[2]), these complications may result in death, especially among immunocompromised persons. The complication rates above were reported in studies from developed countries.

Congenital varicella syndrome occurs in 0.4%-2% children born to mothers with varicella during the first 20 weeks of gestation[20, 21]. It is characterized by cicatricial skin scarring in a zoster-like distribution, limb hypoplasia, and neurologic (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis with scarring, microphthalmia, and cataracts), and autonomic nervous system abnormalities (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia); low birth weight is common. Affected infants are developmentally retarded and their prognosis is poor. Infants whose mothers had varicella in pregnancy have a higher risk of zoster in the first years of life[22].

Varicella epidemiology

Methodological issues

Surveillance data to monitor varicella incidence and age distribution are reported predominantly from developed countries, more frequently those who have included varicella vaccination into the routine childhood immunization schedule. Even in these countries, the methods used to determine the number of cases differ, impacting completeness and ascertainment. Sources of data included household, healthcare provider and passive reporting systems. Seroprevalence data can also be used to estimate age specific incidence. Increasingly more VZV seroprevalence data are available, including from middle/lower-income countries. However, use of seroprevalence data to estimate varicella incidence is complicated by differences in the method for sample selection (nationally or regionally representative, convenience sampling) and laboratory tests which may vary in sensitivity and specificity and also may not be directly comparable over long periods of time. Methodological issues should also be considered when comparing surveillance data for severe disease outcomes. Severe disease is commonly described by hospitalization and deaths but use of these data sources can bias the comparison because of differences in access to medical care, available treatment (antiviral therapy, antibiotics), or validity of a varicella code on hospital discharge or death records from country to country.

Incidence

Varicella is a highly contagious disease that occurs worldwide and, in the absence of a vaccination program, generally affects nearly every person by mid-adulthood. Secondary attack rates are usually around 85% (range 61% and 100%)[23-25] for susceptible household contacts (all secondary attack rates were described from developed countries with temperate climate); in a community setting, where the contact is more casual, the attack rates are lower. The epidemiology of the disease differs between temperate and tropical climates[26-30]. The reasons for the differences are poorly understood and may relate to properties of VZV (known to be heat labile), climate, population density and risk of exposure (e.g., attendance at childcare or school or number of siblings in the household). Additionally, use of the varicella vaccine has changed the epidemiology of varicella in countries where the vaccine is routinely recommended.

In temperate climates the highest incidence of varicella occurs among pre-school aged children (1-4 years of age) or children in early elementary school (5-9 years of age) leading to >90% of people being infected before adolescence and <5% of adults being susceptible (fig. 1)[28]. Studies with complete ascertainment have shown that disease incidence in the total population is in the range of 13-16 cases per 1,000 persons per year, with substantial year to year variation[28, 31]. Based on seroprevalence and surveillance data, it was estimated that in developed countries with temperate climates, on average, the number of infections that occur annually

approximates the birth cohort[27, 28]. Varicella shows a strong seasonality, with peak incidence during winter and spring[26]. Periodic large outbreaks may occur with an inter-epidemic cycle of 2 to 5 years. Outbreaks occur in settings where children congregate such as childcare centers and schools but have also been described in hospitals, facilities for institutionalized children and adults, refugee camps and in adult settings including among healthcare workers, military personnel and correctional facilities.
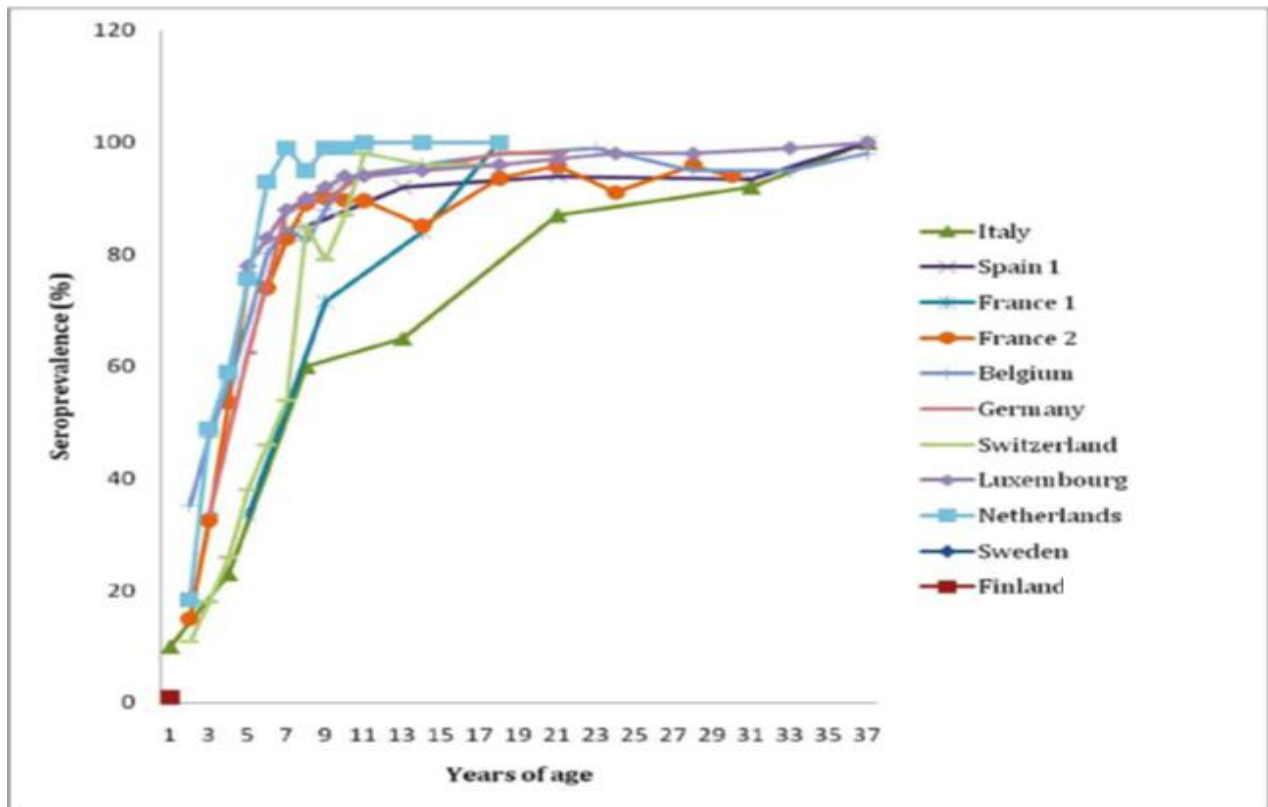

Fig. 1. Age specific incidence of VZV in European countries (from Sengupta and Brewer, Current Pediatric Reviews, 2009)

In tropical climates, the majority of studies have described later acquisition of varicella in childhood with a higher proportion of cases and higher susceptibility among adults (fig. 2)[26-30]. These features lead to a higher overall mean age at varicella infection compared with temperate climates and associated higher morbidity. A 2013 analysis of surveillance data from Sri Lanka found that in 2011 and 2012 most of the cases were reported in the 20-29 years age group (33% and 29% of all cases, respectively), with ~40% of cases occurring in persons age 30 years or older (unpublished data, Palihawadana P, personal communication, 2013). Crowding in densely populated urban cities or in household may overcome VZV's diminished ability to spread in tropical climates[29]. Population-based epidemiology data is less complete for countries in tropical climates but the highest incidence was described from a number of countries in the driest, coolest months[32, 33]. A study examining risk factors for susceptibility among newly arrived migrants in Canada found the highest varicella susceptibility among those originating from climates with the highest temperature and the most months of humidity per year (tropical rainforest)[29]. VZV seroprevalence from several tropical countries almost uniformly confirm higher adult susceptibility compared with adults in temperate countries[30, 34-38]. The lowest population seroprevalence has been reported from a single study conducted in St. Lucia, West Indies in the 1980s[39] (10%-20% among adolescents and young adults), with intermediate seroprevalence in Singapore[35] (41% among 15-24 year-olds and >86% for those age 25 years or older) and higher levels noted in large community surveys conducted during the 1990s in Thailand[37] (~70% among 10-14 year-olds and 96% for 30-39 year-olds), and Manila, Philippines[34] (57% among 10-14 year-olds and 96% for >30 year-olds). Studies in adult subgroups have demonstrated levels of seronegativity among healthcare workers ranging from 11% - 16% in Malaysia and Saudi Arabia, 22% or

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higher in Thailand to as high as 51% among first year medical and engineering students in Sri Lanka[40-42]. Studies among women of child bearing age demonstrated 27% lacked VZV antibodies in Iran and 56% in Sri Lanka[36, 43]. 24% of Singapore military recruits were VZV seronegative[44]. In island populations that may not have sufficient size to support continuous endemic transmission seroprevalence can also vary with the timing of the last epidemic year in relation to the serologic study.
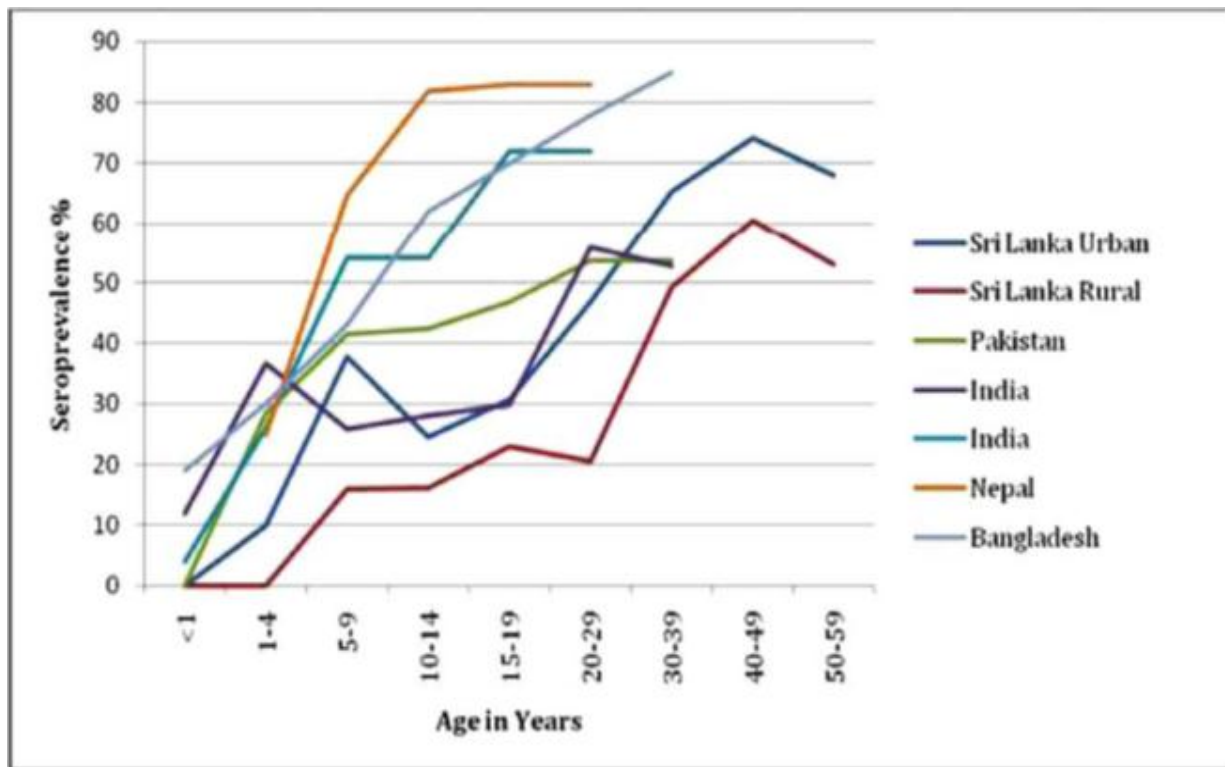

Fig. 2. Age specific incidence of VZV in different countries in the Indian subcontinent (from Sengupta and Brewer, Current Pediatric Reviews, 2009)

Severe disease burden

As presented in the Clinical description, varicella usually is a self-limited disease but can result in serious complications and sometimes death. The rates of serious complications may be described by the mortality rates but in developed countries, additionally, admission to hospital for varicella could be used as a reasonable surrogate measure for severe morbidity. However, when comparing results across countries, differences in methods that may affect ascertainment of hospitalization and cases and access to care must be considered.

Crude rates of admission to hospital with varicella in developed countries range from about 2 to 6 per 100,000 population-year[28, 31]. Most of these admissions (56%-67%) were children, which is consistent with the fact that 90% of varicella cases occur in this age group. For all ages combined, hospitalization rates have ranged from 2.2 to 4.7 per 1,000 varicella cases in studies in France, USA and UK[3, 45, 46]. In developed countries, average crude varicella mortality rates range from 0.3 to 0.5 per million population-year, and overall case fatality ratios are about 2-4 per 100,000 cases[28, 31]. Since most cases of varicella occur in healthy persons, most cases of severe morbidity and mortality also occur in healthy persons: 70% of all varicella deaths in France (1990-1997) occurred in people with no underlying high-risk medical disorders[3]; similarly, in the USA in the prevaccine era (1970-1994) 89% and 75% of varicella deaths in children and adults, respectively, occurred in otherwise healthy persons[2]. Almost 90% of persons admitted to hospital with varicella are described as healthy or immunocompetent[45, 47].

Population-based data for severe disease burden from developing countries and from those with tropical climates are sparse. A household study in Guinea-Bissau in 2000–2001, which identified 1,539 cases of varicella, reported that two cases died thus the case fatality rate in this small series was 130/100,000 cases[48]. With the caution that this is a small study and the confidence intervals are likely wide, the case fatality in this study was approximately 50 times higher than in the U.S. One study of all patients admitted to the main infectious disease hospital in Sri Lanka during 2000–2001 demonstrated that 58% of the total 1,690 hospitalizations were due to varicella[49]. Varicella was the most common disease treated at the infectious disease hospital and a significant cause of morbidity and mortality among adults. In India in late 1970s enhanced rash illness surveillance post smallpox eradication reported 433 deaths/862,155 reported cases; 80% deaths were adults[50]. The case fatality rate was 52/100,000 cases, 20 times higher than US/UK in the 1980s and 90s.

Risk factors for severe disease

Varicella is a more serious disease in infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children[2, 3, 51, 52]. The risk of dying from varicella is highest at the extreme of age (fig 3); in the US, in adults the risk of death was 23-29 times higher, and in infants 4 times higher than in children in whom case fatality ratios were about 1 per 100,000[2]. Similarly, the risk of hospital admissions is higher for infants and adults than for children[3, 45]. Immunocompromised persons at high risk for severe varicella include those with deficiencies in cell mediated immunity due to illness (e.g., severe combined immunodeficiency syndrome, leukemia, lymphoma, HIV, etc.) or therapy (e.g., chemotherapy, radiotherapy, high dose of steroids). Leukemic children especially had a reported incidence of viscerally disseminated disease of 30% with a 10% fatality rate in the absence of antiviral treatment[53] and this burden of severe disease prompted vaccine development for this high risk group. Although severe varicella has occurred in children with HIV infection, the risk for death is not as great as for leukemic children[54, 55].

Data from case reports and case series suggest that varicella in pregnant women is more severe than in non-pregnant women but population-based studies are needed to confirm this finding. In utero transmission of VZV can occur. When pregnant women contract varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. However, clinically apparent congenital disease in the infant occurs less commonly, the congenital varicella syndrome (that has poor prognosis) occurs in approximately 0.4%-2% of infants born to women who have varicella during the first 20 weeks of pregnancy[20, 21]. The incidence of varicella during pregnancy varies according to the susceptibility of women of childbearing age and the rate of exposure to the virus. Severe infection can also occur among newborns who lack maternal antibodies and who were transplacentally infected[56]. These newborns are at greatest risk for severe or fatal illness if the mother's rash occurs within 5 days prior to delivery to 2 days postpartum. The risk of death for these newborn is ~30% without treatment[57].

There are few data on severe varicella disease burden in low and middle income countries, in countries with high HIV seroprevalence and in countries with tropical climates where the average age at infection is higher. In these situations, varicella morbidity and mortality may be higher than described in developed countries.
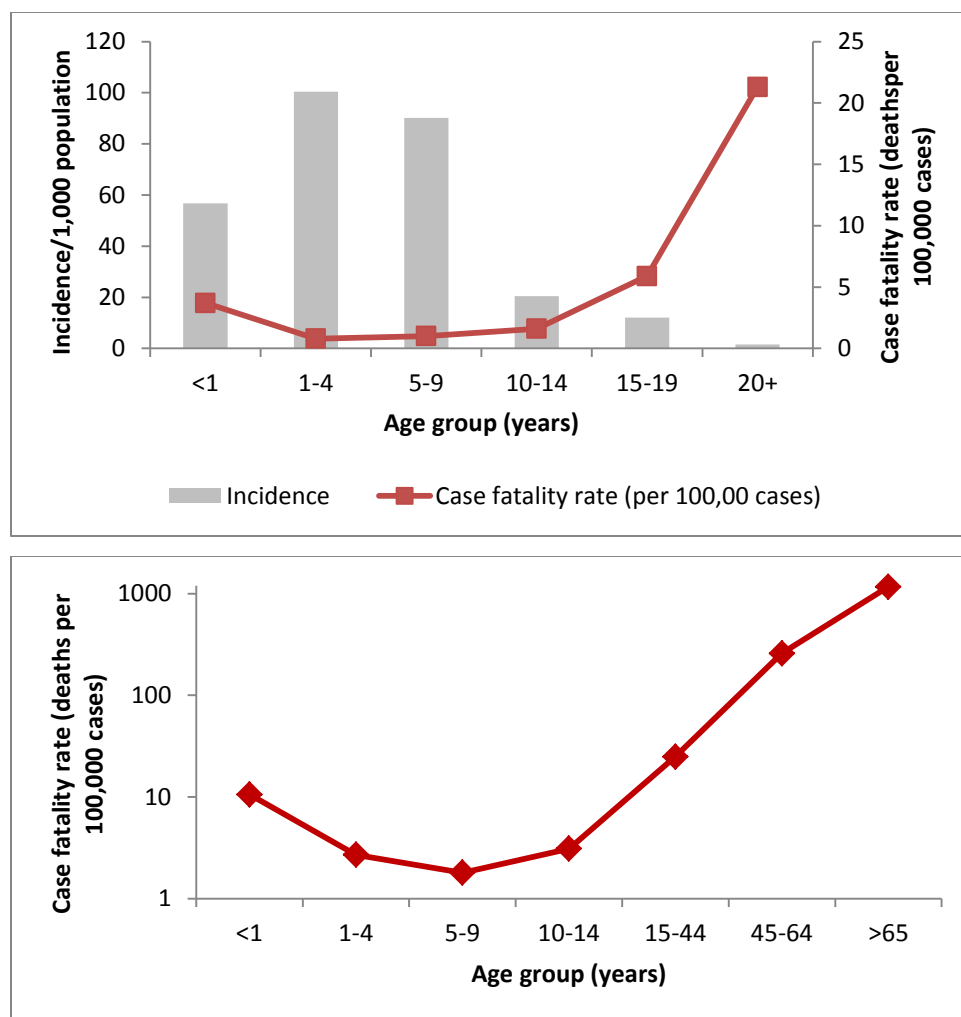
Fig. 3. Top graph: Varicella case fatality rate and incidence by age group, United States, 1990-1994 (pre-vaccine) (ref: Meyer et al, JID, 2000). Bottom graph: Varicella case fatality rate by age group, Brazil, 2001-2003 (logarithmic scale) (ref: Valentim et al, Vaccine 2008)

Epidemiology of varicella in the vaccine era

Countries that introduced varicella vaccination have experienced substantial reductions in varicella morbidity and mortality (figs. 4-6). In the United States, where a one dose childhood vaccination program was introduced in 1995, overall disease incidence declined > 70% within 5 years in communities where vaccine coverage among children age 19 to 35 months had reached ~ 80%[58]. Declines in incidence were apparent earlier in preschool aged children. By 2005, when vaccine coverage had reached approximately 90%, varicella incidence declined 90% or more[6]. The greatest declines (>90%) occurred in children aged 1 to 9 years but declines occurred in every age groups including infants (80%) not eligible for vaccination and adults (60%-80%) indicating considerable community protection effects (also referred to as herd immunity) outside of age groups targeted for vaccination. The peak age of varicella infection increased from 3-6 years in 1995, to 9-11 years in 2005 and the proportion of cases that were vaccinated increased from < 1% to 60% over the same time period but varicella incidence declined in all age groups. From 1995 to 2005, the declines in incidence were mirrored by declines in the number, size and duration of varicella outbreaks in childcare centers and schools[59]. In Veneto region, Italy, varicella incidence rates decreased significantly 2.5 years after the universal vaccination program was introduced and >70% vaccine coverage reached[60]. In Germany, where a one dose national vaccination program

was implemented in 2004, comparing varicella seasons in 2005 and 2009, a 63% decline in cases and 81% decline in varicella complications was observed using data from physician based sentinel surveillance[8].

Significant declines in varicella-related deaths, hospitalizations, ambulatory visits and health expenditures were also noted within 5-6 years of program implementation in the United States. Considering varicella as the underlying cause of death, pre-vaccine era deaths averaged 105/year. By 1999–2001, compared with the 5 years preceding the vaccination program (1990–1994), mortality rates declined 92% in children 1–4 years, and 74%–89% in infants < 1 year and persons 5 to 49 years[61]. By 2005-2007, which primarily reflected impact of the decade long one dose vaccination program in children, deaths averaged 15/year and the average age-adjusted mortality rate due to varicella as an underlying cause of death declined 88% to 0.05 per million population-year from 0.41 per million in 1990-1994[9]; during the same period, the age-specific mortality rates declined 97% among children and adolescents aged <20 years, 90% among adults aged 20-49 years, and 67% among adults aged ≥50 years (an age group in whom the validity of varicella as a cause of death on death certificates is lower). Varicella hospitalizations have declined significantly as well. By 2002, compared with 1994–1995, US hospitalizations for varicella declined by 88% and ambulatory visits by 59%, with > 90% declines in children < 10 years and adolescents 10–19 years old[62]. Direct medical expenditures for varicella hospitalizations and ambulatory visits decreased by 74%[62]. Updated analyses showed continued declines in varicella hospitalizations in all age groups from 2000 to 2006, with a 98% reduction in varicella hospitalizations by 2006, among patients 0-4 years old[63].

In Canada, where the varicella vaccination program was recommended in 1999, declines of 81%-88% in the number of hospitalized varicella cases were reported between 2000-2008, with effects of the vaccination program being noted beginning 1 to 2 years after the start of the program; indirect protection of persons outside the vaccinated cohorts was also documented[7]. Vaccination coverage were available for a few provinces and ranged from 74%-91% in 2007-2008. The impact of a one dose vaccination program on varicella and its severe morbidity has also been described from Taiwan, Uruguay, Sicily and Australia[64-67]. Additionally, several studies indicated the indirect protection afforded by vaccination, with declines in populations that are not directly targeted to receive the varicella vaccine (e.g., decline in incidence, hospitalization and deaths in infants and adults in the US mentioned above). Similarly, a study in Australia described 100% and >85% decline in congenital varicella syndrome and neonatal varicella following introduction of universal varicella vaccination[68].

A one dose program led to considerable successes in control of varicella disease and its severe complications. However, as experience demonstrated, cases and varicella outbreaks (although less in number, smaller in size, and of shorter duration) might continue to occur in highly vaccinated one dose populations[6, 59]. This, coupled with the evidence that two doses induce higher effectiveness[17], resulted in adoption of a routine 2 dose policy for children in the United States in 2006. During the first 5 years after introduction of the two dose program the reported varicella incidence was the lowest since the start of the vaccine program (with decline ~70% during the two dose program), with fewer outbreaks and milder disease[69].
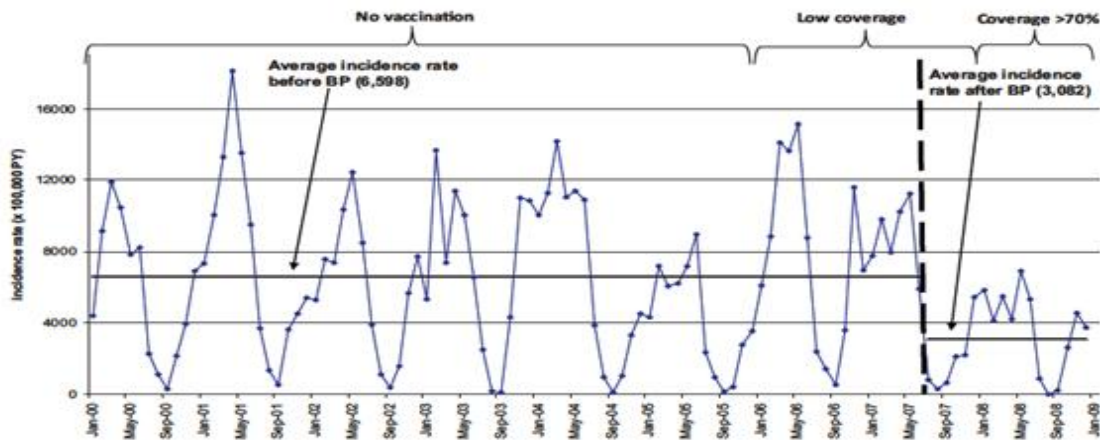
Fig. 4. Monthly incidence rates of varicella and change in the temporal trend in Veneto region, Italy; data from the sentinel surveillance based on a sample of pediatricians, 2000-2008 (from Pozza et al, Vaccine 2011)
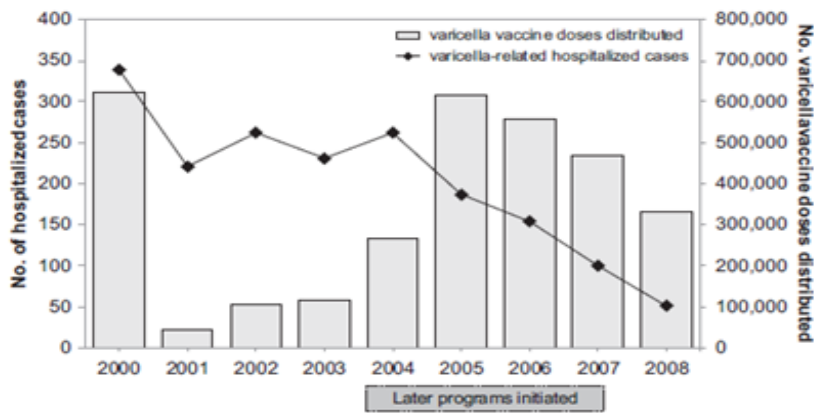
Fig. 5. Trend in varicella related-hospitalized cases, 8 Canadian provinces/territories (comprising 86% of the Canadian population), 2000-2008 (from Tan et al PIDJ, 2012). The bars show the combined number of vaccine doses (Varivax and Varilrix) distributed each year in these 8 settings.
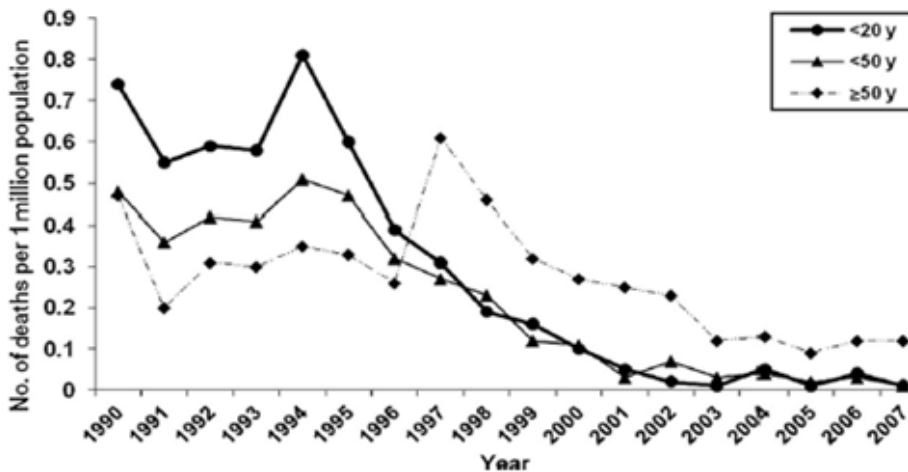
Fig. 6. Annual age-specific mortality rates for varicella listed as the underlying cause of death, United States, 1990-2007 (from Marin et al, Pediatrics, 2011)

Varicella vaccines

All available varicella vaccines are live attenuated vaccines and all but one formulation are based on the Oka strain of VZV isolated in Japan by Takahashi[11]. The vaccine licensed in Korea was developed from a different isolate (Korean)[70]. Currently, varicella vaccine is licensed as monovalent vaccine or combination measles, mumps, rubella varicella vaccine (MMRV). The monovalent varicella vaccine was first licensed in Japan in 1987, while the combination MMRV vaccine was first licensed in the US in 2005. Monovalent vaccine is produced in the United States (VARIVAX; Merck & Co., Inc), Belgium (Varilrix; GlaxoSmithKline [GSK]) Japan (OKAVAX; Biken, distributed by Sanofi Pasteur), South Korea (Green Cross), and China (4 manufacturers: Shanghai Institute of Biologic Products, Changchun Keygen Biological Products Co., Ltd., Changchun BCHT Biotechnology Co, [Baike], Changchun Changsheng Life Sciences Ltd.). MMRV is produced in the United States (ProQuad; Merck & Co., Inc) and Belgium (Priorix-tetra; GSK). The vaccine is marketed in a lyophilized form to improve stability. Varicella vaccine is stored at refrigerator temperatures (2^0C-8^0C or 36^0F-46^0F) or at freezer temperature (<-15^0C or <5^0F), according to the manufacturer's instructions. Monovalent varicella vaccines are licensed and available throughout the world for the prevention of varicella in healthy children, adolescents and adults. Combination MMRV vaccines which are licensed for prevention of varicella in children through 12 years of age are available in fewer countries. The minimum age for both types is either 9 or 12 months, depending on the manufacturer.

Varicella vaccines are contraindicated if there is a history of anaphylactic reaction to any component of the vaccine (including neomycin), during pregnancy (due to theoretical risk to the fetus) and in primary or acquired immunodeficiency states[71-74]. Pregnancy should also be avoided for 4 weeks following vaccination. Two vaccines allow use in immunocompromised patients in certain conditions: Okavax (Sanofi Pasteur) is licensed for use in leukemic patients who meet certain criteria (e.g. lymphocyte count, suspension of chemotherapy, etc.) and for one of the vaccines used in China, use is cautioned in leukemic and immunodeficient patients. However, vaccine may be recommended by certain vaccine advisory groups for specific groups of immunocompromised patients (e.g., the US Advisory Committee on Immunization Practices recommends vaccination for persons with impaired humoral immunity, HIV-infected children with CD4+ T-lymphocyte percentage ≥15%, or patients with leukemia, lymphoma, or other malignancies whose disease is in remission and whose chemotherapy has been terminated for at least 3 months[75]).

An estimated annual average number of 31 million varicella vaccine doses were distributed worldwide between 2007 and 2011, with approximately half of the doses in the WHO region of the Americas. From data that the working group could obtain, the price of the monovalent vaccine per dose ranges from $13 (Pan American Health Organization revolving fund) to $94 (United States). MMRV price is ~$148-$157 per dose.

Measure of vaccine protection

The Working Group focused its evaluation of varicella vaccine performance on effectiveness data that assess the performance of the licensed formulation vaccines in conditions of everyday clinical practice. Several factors were considered for this decision: 1) pre-licensure and post-licensure studies of immunogenicity and efficacy of varicella vaccine used varying concentrations of the Oka strain therefore comparisons across studies and inference of results to licensed vaccine formulations are difficult; 2) different serological tests have been used to assess immunogenicity including neutralization, FAMA, gpELISA and other IFA tests; 3) cutoff levels to define seroconversion with the gpELISA test have varied with initial studies using >0.6 gpElisa units/ml and more recent studies using a higher cutoff level or serologic response rate of ≥5 units/mL; 4) vaccine performance may be different under conditions of real world use; and 5) immune correlates of protection against varicella have been studied but need further clarification and development. A gpELISA titer of ≥5 units/mL or greater 6 weeks after vaccination is reported to be an 'approximate correlate of protection for individual vaccine recipients' but this cutoff was used in latter studies only; a positive FAMA titer (>1:4) at the time of exposure to the virus correlates with protection but few studies used FAMA to determine seroconversion. Nonetheless, prelicensure clinical trial data were reviewed and are presented briefly below. Immunogenicity data were reviewed and considered when effectiveness data were not available.

Pre-licensure vaccine efficacy

Three double-blind, placebo-controlled one dose efficacy studies have been carried out in healthy children. The first was conducted in the US in the early 1980s using Merck's vaccine among VZV seronegative children age 12 months to 14 years (mean age 4.7 years); 468 children were immunized and 446 were given placebo[76]. After 9 months of follow up, the vaccine was found to be 100% efficacious; after 2 years, efficacy was 98% overall and 92% after household exposure. During a 7-year follow-up, 95% of these vaccine recipients were estimated to have remained free of varicella[77]. These data cannot be directly compared with those of subsequent studies in the US, however, because these children received the highest dose of vaccine used in the US as a monovalent vaccine (17,430 plaque forming units (PFU) vs. a minimum of 1,350 PFU in the licensed vaccine).

A second double blind placebo controlled study was performed in Finland in the early 1990s, using vaccine produced by SmithKline Beecham (now GSK)[78]. This study included 513 healthy seronegative children ages 10 to 30 months who were divided into three groups to receive a high dose vaccine (10,000 or 15,850 PFU), a low dose vaccine (630 or 1,260 PFU) and placebo. After an average 29 months of follow up the efficacy was 88% for the high dose vaccine and 55% for the low dose vaccine.

The third double blind placebo controlled study was conducted more recently in China using the vaccine (10,000 PFU) manufactured by Changchun Keygen Biological Products Co., Ltd[79]. This study included 5,000 children aged 3-7 years with no history of varicella or varicella vaccine. Mumps vaccine was the placebo; the follow-up period was 12 months and vaccine efficacy was 90.8% (95% CI 88.7%-95%).

For the two dose vaccine efficacy, a 10 year follow up (1993-2003) of 2,216 healthy children aged 1 to 12 years (with a negative history of varicella) randomized to receive 1 or 2 doses of varicella vaccine (five different lots of vaccine ranging from 2,900 to 9,000 PFUs) 3 months apart yielded an estimated vaccine efficacy of 2 dose and 1 dose of varicella vaccine of 98.3% versus 94.4% (P <0.001)[17]. Following household exposures, efficacy was 96.4% for 2 doses and 90.2% for one dose (P = 0.112).

Formal studies to evaluate clinical efficacy of MMRV vaccine have not been performed. MMRV vaccines were licensed on the basis of non-inferior immunogenicity of the antigenic components compared with simultaneous administration of MMR and varicella vaccines[72, 74]. Anti-varicella antibodies were tested using gpELisa (Merck vaccine) and indirect immune fluorescence assay (GSK vaccine).

Post-licensure vaccine effectiveness

To assess vaccine effectiveness (VE), 40 studies were identified by systematically searching the literature[80-119]. In addition, a meta-analysis[120] and a systematic review for VARIVAX[121] were identified. A variety of methods have been used to study the postlicensure effectiveness of varicella vaccine, including prospective and retrospective cohort, case-control, and secondary attack rate (household contact) studies. The populations studied have included children in different settings, such as child care centers and schools, clinical practices in the community, managed care organizations, and households. Most studies assessed protection against clinically diagnosed varicella. The definitions used for the severity of varicella differed between studies (table 1).

One dose vaccine effectiveness

For one dose VE, most of the estimates were for VARIVAX (Merck), fewer for Varilrix (GSK), and one each for the other vaccines; several studies either did not specify the vaccine or more than one type of vaccine was used in the country. Table 1 presents the summary finding of the review of the post licensure VE estimates for one dose for monovalent varicella vaccine by disease severity. Available evidence on vaccine effectiveness is for within the first decade after vaccination.

Table 1. One dose varicella vaccine effectiveness estimates by type of vaccine and varicella severity (monovalent vaccine)

Vaccine	Prevention of all varicella			Prevention of combined moderate and severe varicella[a]			Prevention of severe varicella		
	No. estimates	Median	Mean/ range	No. estimates	Median	Mean/ Range	No. estimates	Median	Mean/ Range
Varivax	28	83%	81% (44%-100%)	18	96.5%	96% (86%-100%)	11	100%	99% (97%-100%)
Varilrix	8	76%	70% (20%-92%)	5	95.0%	93% (80[b]%-100%)	3	100%	100%
Okavax	1	90%	90%	1	100%	100%	1	100%	100%
Shanghai	1	93%	93%	-			-		
Keygen/ Changchun	1	77%	77%						
Changsheng	2	80%	80%	-			-		
Baike	1	91%	91%	-			-		
Unspecified/ >1 vaccine used	10	80%	79% (60%-100%)	3	99.5%	96% (86%-100%)	3	100%	95% (85%-100%)

Note: 1) Data presented in the table are from 40 papers. However, the number of vaccine effectiveness estimates does not total 40 for several reasons: several papers presented more than one vaccine effectiveness estimate for the same outcome (e.g., investigation in 2 schools and estimates against all varicella presented separately by school); in the same paper vaccine effectiveness estimates are presented for more than one outcome (e.g., for prevention of all varicella, for prevention of moderate and severe varicella, or prevention of severe varicella)

2) Available evidence is on vaccine effectiveness within the first decade after vaccination

3) Two of the vaccine effectiveness estimates reported were below 50% (i.e., 20% and 44%). They were calculated during investigations of outbreaks that tend to underestimate the performance vaccines. While there are no definitive explanations for the low effectiveness, it is possible that vaccine effectiveness lies within a range and by chance a lower value could be identified. This emphasizes that to accurately assess vaccine effectiveness more than a few estimates are needed.

[a]Moderate: 50-500 lesions, no complications; Severe: 1) >500 lesions or a complication requiring physician visit, or any complication; 2) any hospitalization regardless of the number of lesions; 3) two studies defined severe disease as >250 and >200 lesions; 4) disease severity scale used in clinical trials: # lesions, fever, systemic signs and subjective assessment of illness

[b]80% is for prevention of moderate disease only

Only one study compared directly the effectiveness of one dose of VARIVAX and Varilrix and found lower effectiveness for Varilrix (49% vs. 83%) but the overlapping confidence intervals suggest that the values were not significantly different[110]. The same study provided the only estimate on VE for one dose of MMRV (62%) which was on the lower end of the range reported for monovalent vaccines but with wide confidence intervals that overlapped those of the monovalent vaccines. In summary, available data to date support similar performance of the various one dose monovalent varicella vaccines in preventing varicella. One dose varicella vaccine is moderately effective (~80%) for preventing all varicella and highly effective (>95%) for preventing moderate and severe varicella. The moderate effectiveness in prevention of all varicella supports the immunogenicity findings from the United States that primary vaccine failure occurs in 9%-14% of children after one dose of vaccine[17, 122]. A small study found that 24% of infants lacked VZV antibody measured by FAMA a median of 4 months after vaccination[123].

A number of potential risk factors for vaccine failure after one dose have been studied, including younger age at vaccination, time since vaccination, asthma, eczema, receipt of varicella vaccine within 28 days of MMR and problems with storage and handling[121]. Most studied were age at vaccination (variously defined as <14 months to ≤18 months) and time since vaccination (using a cut-off of 3 years or 5 years). The results did not show consistent findings but the sample sizes were usually not sufficient to assess the independent effect of each factor. Among studies that controlled for other risk factors, Chaves et al used cases clinically diagnosed and found that the risk and severity of breakthrough disease increased with time since vaccination[124] while Vazquez et al used laboratory confirmed cases and described a decline in vaccine effectiveness between years 1 and 2 after vaccination but not subsequently (up to 7 years of follow up)[117]; Verstraeten et al used a large retrospective cohort and found that children vaccinated at <15 months of age have a slightly higher risk for breakthrough disease[125] while Vazquez et al found that vaccination at age <15 months was associated with a higher risk for breakthrough within the first year after vaccination[117]. An increased risk for breakthrough disease was also found during the 3 months after prescription of an oral steroid and when varicella vaccine was administered within 28 days of MMR vaccination[125].

One-dose varicella vaccine administered within 3-5 days of exposure is highly effective for prevention of moderate or severe disease (79%-100%) but estimates varied for prevention of any disease (9%-93%)[126-129].

Two dose vaccine effectiveness

Fewer studies (5 with 6 estimates) assessed vaccine effectiveness after two doses of monovalent varicella vaccine in children, all for Varivax (table 2)[84, 90, 102, 108, 112]. Overall (mean =93%, median=95%) 2 doses of vaccine provided better protection than one dose, however, two of the estimates, both from outbreak investigations, were <90%. Additionally, one study reported 94% vaccine effectiveness of two doses of any varicella-containing vaccine used in the country (Varilrix, Varivax, or MMRV/GSK)[99] and one reported 93% vaccine effectiveness for two-doses of MMRV (GSK)[110]. Considering the vaccine effectiveness estimates, the immunologic findings of an improved humoral and cell mediated immune response after the second dose and the observed further decline in the incidence of varicella in the US following implementation of the 2nd dose recommendation for children[69, 130], 2 doses of varicella in children improve the performance of varicella vaccine for prevention of all varicella.

Table 2. Two dose varicella vaccine effectiveness (monovalent vaccine[a])

Author	Country	Prevention of all varicella	Setting/Design
Gould[90]	USA	88.1% (95% CI=82.2%-92.1%)	School outbreak retro/prospective cohort
Nguyen[112]	USA	95%[b]	School outbreak retro/prospective cohort
Shapiro[108]	USA	98.3% (95% CI=83.5%-100%)	Case-control study
Mahamud[102]	USA	84.2%[c] (95% CI=74.2%-90.3%); 94.7%[c] (95% CI=89.2%-97.4%)	School outbreaks retro/prospective cohort
Cenoz[84]	Spain	97% (95% CI=80%-100%)	Case-control study

[a] All estimates are for Varivax
[b] Not presented in the article but calculated based on the raw data presented in the article
[c] The investigation took place in two schools and the authors reported vaccine effectiveness by school
Data are for within the first 5 years after the second dose

Estimates of vaccine efficacy or effectiveness for persons 13 years or older are lacking. However, using data reported during open trials (i.e., without a control group) on attack rates among adult vaccine recipients of two doses administered 4-8 weeks apart (17%[71] and 26%[11]) and an 85% historical attack rate for wild-type varicella following household exposure to varicella among unvaccinated children, the efficacy can be estimated in the range of 70%-80%. Most adults who developed varicella after vaccination experienced a mild form. These efficacy estimates are backed by immunogenicity data that also support the need for 2 doses routinely in this age group. In prelicensure clinical trials in the United States using VARIVAX it was noted that the seroconversion measured by gpELISA in adolescents aged 13-17 years was only 79% after one dose; moreover, their GMT was half the levels seen in healthy children[131]. Likewise, immunogenicity studies in adults have indicated that adults require two doses of vaccine to achieve a seroconversion rate by gpELISA of >90%[132]. A study in Australia where 2 doses of Varilrix were administered to susceptible health care workers, found that 95% of subjects had detectable antibodies using a commercial immunoassay 2 months after the first dose and 100% of vaccines had antibodies 6 weeks after the second dose[133]. Additionally, the cell-mediated immune responses of adults to varicella vaccine are lower than those observed in children[134].

The quality of evidence was graded for following research questions:

- What is the scientific evidence of the effectiveness of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing all grades of severity of varicella (evidence available for the first 10 years after vaccination) (GRADE table 1)
- What is the scientific evidence of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing severe varicella (evidence available for the first 10 years after vaccination) (GRADE table 2)
- What is the scientific evidence of the effectiveness of two doses of varicella vaccination (versus placebo/no vaccination) against all grades of severity of varicella disease in immunocompetent individuals (evidence available for the first 5 years after the second dose) (GRADE table 3)

GRADE Table 1. Effectiveness of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing all grades of severity of varicella (evidence available for within the first 10 years after vaccination)

Population : Immunocompetent children (9 month to 12 years of age)
Intervention: One-dose varicella vaccination
Comparison: Placebo/ No vaccination
Outcome   : All grades of severity of varicella disease

			Rating	Adjustment to rating
What is the scientific evidence of the effectiveness of one dose of varicella vaccination (versus placebo/no vaccination) in preventing all grades of severity of varicella in immunocompetent children (9 months to 12 years of age)?				
Quality Assessment	No. of studies/starting rating		40/ Observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect[2]	Applicable	+2
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**A single dose of varicella vaccination is effective to protect children of 9 months to 12 years against all grades of severity of varicella disease. Single dose varicella VE against all grades of disease severity ranged from 20 – 100%, with an approximate mean VE of 80% against all grades of disease severity, irrespective of vaccine type.**

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[1] Two systematic reviews (Seward et al.; Bayer et al.) and a syst. rev. done by WHO of the current literature (through October 2013) identified 40 observational studies. Single dose varicella VE against all grades of disease severity ranged from 20 – 100%, with an approximate mean VE of 80% against all grades of disease severity, irrespective of vaccine type. Only one study demonstrated vaccine effectiveness against all varicella to be 20% (95%CI 0%-40%).
[2] Upgraded by two levels as strong evidence from observational studies of a vaccine effectiveness of 80% or higher with no major residual confounders. In addition to effectiveness on an individual level, decline in incidence in all age groups over time, not only age-group targeted by vaccination program, suggests induction of community protection (Marin et al 2008, Marin et al 2011, Lopez et al 2011, Guris et al 2008).

GRADE Table 2. Effectiveness of one dose varicella vaccination in immunocompetent children (9 months to 12 years of age) in preventing severe varicella (evidence available for within the first 10 years after vaccination)

Population: Immunocompetent children (9 month to 12 years of age)
Intervention: One dose varicella vaccination
Comparison: Placebo
Outcome: Severe varicella (mostly defined as >500 lesions, complication requiring physician visit, hospitalization, death); two studies defined severe disease as >250 and >200 lesions and two defined severity in accordance with a modified disease severity score from clinical trials

			Rating	Adjustment to rating
What is the scientific evidence of the effectiveness of one dose of varicella vaccination (versus placebo/no vaccination) in preventing severe varicella disease (≥500 lesions) in immunocompetent children (9 month to 12 years of age)?				
Quality Assessment	No. of studies/starting rating		29/ Observational[3]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[4]	+2
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**A single dose of varicella vaccination is highly effective to protect children of 9 months to 12 years against severe varicella disease, with vaccine effectiveness (VE) of 95% for preventing moderate-severe disease and VE of 99% for preventing severe disease only.**

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[3] Two systematic reviews (Seward et al. 2008; Bayer et al. 2007) and a syst. rev. done by WHO on the current literature (through October 2013) identified 25 relevant observational studies. Included studies provided vaccine effectiveness data on the predefined outcome of severe varicella or on moderate-severe varicella. Studies that did not specifically report a VE value reported that no cases of hospitalization or severe complications were observed. Single dose varicella VE against moderate and severe disease ranged from 78 – 100%, with an approximate mean VE of 95%, irrespective of vaccine type. Of the sixteen studies reporting a VE value against severe varicella, fifteen reported a VE of 100% and only one study (Huang, 2011) reported a VE of 85%.

[4] Upgraded by two levels as strong evidence from observational studies of a vaccine effectiveness of 80% or higher with no major residual confounders. Vaccine effectiveness against severe varicella was 100% in 15/16 studies. In addition to effectiveness on an individual level, decline in incidence in all age groups over time, not only age-group targeted by vaccination program, suggests induction of community protection (Marin et al 2008, Marin et al 2011, Lopez et al 2011, Guris et al 2008).

GRADE Table 3. Effectiveness of two doses of varicella vaccination in immunocompetent individuals in preventing all grades of severity of varicella (evidence available for within the first 5 years after the second dose)

Population : Immunocompetent individuals
Intervention: Two doses varicella vaccination
Comparison: Placebo/ No vaccination
Outcome   : All grades of severity of varicella disease

			Rating	Adjustment to rating
What is the scientific evidence of the effectiveness of two doses of varicella vaccination (versus placebo/no vaccination) against all grades of severity of varicella disease in immunocompetent individuals?				
Quality Assessment	No. of studies/starting rating		7/observational[5]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[6]	+2
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**We are very confident that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**Two doses of varicella vaccination are effective to protect against all grades of severity of varicella disease. Two-dose varicella VE against all grades of disease severity ranged from 84 – 98%, with an approximate mean VE of 93%, irrespective of vaccine type.**

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[5] Vaccine effectiveness of 2 doses of varicella vaccination was assessed in 7 observational studies identified by systematic review of the evidence with seven studies providing nine VE estimates of combined and non-combined varicella vaccine against all grades of disease severity. Cenoz et al. assessed VE against all varicella to be 97%. Gould et al as 88%, Liese et al as 94.3% (95%CI: 76.4 – 98.6%). Mahamud et al. estimated VE in two different settings as 95% and 84% respectively. Shapiro et al assess 98% VE. Spackova et al. provided two VE estimates for different types of vaccines as 93% (95%CI: 71 – 98%) and 95% (95%CI: 79 – 99%) against all grades of disease severity. Nguyen, 2010 estimated VE of two doses to be 95%.

[6] Quality rating was upgraded by two levels for strong evidence from observational studies of VE of 80% or higher

Duration of vaccine protection

Persistence of antibody in children after one dose of varicella vaccine was demonstrated in several studies[17, 135-137]. However, most studies were done while wild type VZV was still circulating in the community and could have provided external boosting.

Some epidemiologic evidence suggests waning of vaccine-induced immunity after one dose of vaccine while others do not. One large study which examined 10 years of active surveillance data (1995-2004) from a sentinel population of 350,000 subjects in California suggested that breakthrough varicella was twice as likely to be moderate/severe (defined as >50 skin lesions) in children who developed varicella more than 5 years after vaccination compared with those who became ill less <5 years after vaccination (Odds Ratio=2.6, 95%CI: 1.2-5.8)[124]. This study also found an increase incidence of breakthrough varicella with time since vaccination after controlling for likelihood of exposure and age although the rate of breakthrough disease was still low. A metaanalysis concluded waning immunity (based on 4 studies which all showed a decrease in vaccine effectiveness with time since vaccination) but changing varicella epidemiology and risk of exposure/force of infection were not considered[120]. Two recent studies reported lower effectiveness >3 years after vaccination compared with the first post-vaccination year[84, 99]. In contrast, a case control study in which cases were laboratory confirmed, found that vaccine effectiveness against all varicella decreased from 97% in the first year after vaccination to 85% in the second year post-vaccination but with no further drop during the subsequent 6 years of follow up[117]. An analysis evaluating vaccine effectiveness of one and two doses found one dose vaccine effectiveness 86% after a mean 8.5 years since dose one[108]. In the two dose clinical trial study over a 10 year follow up neither the incidence nor the severity of breakthrough disease increased over time[17]. Notably, no severe cases (≥300 lesions) of varicella were reported among breakthrough cases in this study in either one or two dose vaccine recipients. A second long term follow up study of a cohort of >7,300 vaccinated children reported a decline in the annual rates of varicella over 14 years[138]. This study reported occurrence of severe breakthrough varicella (defined as >300 lesions) in 2% of all breakthrough cases but no increase in severity of breakthrough over time. When interpreting the results of these last two studies consideration should be given to the fact that they did not adjust for likelihood of exposure or force of infection which declined over time.

In summary, duration of protection after one dose is not fully understood or studied, especially in a setting of low varicella incidence. The relative roles of waning immunity after an initial response and of a primary immunologic failure rate of 9%-14% (possibly 24% according to one study)[17, 122, 123] in the inability of a one dose of vaccine to provide complete protection is not known and there is still debate about whether breakthrough is primarily due to primary failure, waning of protection, or both. To date, there is no evidence of increased severe outcomes (death or hospitalization rates) at population level with time since vaccination[9, 63].

A routine two-dose schedule among children was only recently recommended in some countries therefore data on duration of protection of the two dose regimen are limited. In the clinical trial in the US comparing one and two doses VARIVAX, over 10 years, the efficacy of two doses in prevention all varicella was 98.3% after community exposure and 96.4% after household exposure (higher than after one dose)[17]. In this study, in years 7 to 10 after vaccination no breakthrough cases occurred in recipients of two doses while cases continued to occur in recipients of one dose. The two dose regimen also was 100% effective against severe disease. In a clinical trial of two doses of MMRV (Priorix-tetra) versus separate injections of MMR (Priorix) and varicella (Varilrix) vaccines, immunogenicity of the varicella component was sustained 3 years post-vaccination (>97% subjects in each arm had antibodies measured by immunofluorescence); no severe varicella cases (≥150 lesions) after one or two- doses varicella vaccination were reported[139]. A postlicensure study reported two dose vaccine effectiveness of 98.3% a median of 12 months (range 0-50 months) after receipt of the second dose with no varicella cases occurring among two dose recipients[108].

Data available for adults who received two doses of varicella vaccine show that 25%-31% of adult vaccine recipients who seroconverted after VARIVAX lost detectable antibodies (by FAMA) at multiple intervals (range: 1-11years) after vaccination[140, 141]; ~10% developed mild varicella after exposure (21% after household exposure)

however, severity of illness or attack rates did not increase over time[142]. A follow up of health care workers who received 2 doses of GSK varicella vaccine showed that 4% who had sera tested 12 months after the 2nd dose had lost detectable antibody[133].

The quality of evidence was graded for following research question:

- In immunocompetent individuals, is protection against severe varicella reduced ≥5 years after one dose of varicella vaccine compared to <5 years after vaccination? (GRADE table 4)
- In immunocompetent children (9 months to 12 years of age), what is the evidence for duration of protection against severe varicella with a two-dose versus a one-dose schedule? (GRADE table 5)

GRADE Table 4. Duration of protection of one dose varicella vaccination against severe varicella in regard to time since vaccination in immunocompetent individuals

Population: Immunocompetent individuals who have received one dose of varicella vaccine
Intervention: One dose varicella vaccination < 5 years
Comparison: One dose varicella vaccination ≥ 5 years
Outcome: Severe varicella (>300 lesions (or >500 lesions), complication requiring physician visit, hospitalization, death)

			Rating	Adjustment to rating
In immunocompetent individuals is protection against severe varicella reduced ≥5 years after one dose of varicella vaccine compared to <5 years after vaccination?				
Quality Assessment	No. of studies/starting rating		3/ observational[7]	2
	Factors decreasing Confidence	Limitation in study design	None serious	0
		Inconsistency	Serious[8]	-1
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**We have very little confidence in the estimate of the effect on the health outcome**
	Conclusion			**In two large studies with more than 11 000 children, no higher annual rate of severe breakthrough cases was seen ≥5 years after vaccination than <5 years after vaccination. One large study which examined 10 years of active surveillance data (1995 to 2004) from a sentinel population of 350,000 subjects suggests the number of moderate to severe breakthrough cases is significantly higher ≥5 years after vaccination, than <5 years after vaccination.**

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7 Observational study (Kuter et al. 2004), active surveillance (Chaves et al. 2007) and prospective cohort study (Baxter et al. 2013) and case-control study (Vasquez et al. 2004) with follow-up time of 10, 10 ,14 and 8 years respectively.

[8] Kuter et al.: No severe case (≥300 lesions) of varicella was reported among break-through cases. Baxter et al.: 13 severe (≥300 lesions) cases <5 years after vaccination (annual rate of severe varicella in break-through cases per 1000person years for one dose varicella ranges from 0.3 (95%CI: 0.1-1.2) to 0.6 (95%CI: 0.2-1.7)). 15 severe cases ≥5 years after vaccination (annual rate of severe varicella in break-through cases ranges from 0.0 (95%CI: 0.0-0.8) to 0.7 (95%CI: 0.2-1.8)). Chaves et al. 2007 suggests that number of moderate to severe breakthrough cases ≥5 years after vaccination was significantly higher than <5 years after vaccination (odds ratio: 2.6, 95%CI:12.-5.8). Vaccine effectiveness against all grades of severity of varicella disease decreased from 97% (p-value: <.001; 95%CI:91-99) in the first year after vaccination to 81% (p-value: .005; 95%CI:40-94%) in year 7-8 years in case-control study with 339 cases suggesting a non-linear decrease in vaccine effectiveness (Vazquez et al 2004).

GRADE Table 5. Duration of protection in immunocompetent children (9 months to 13 years of age) after two- dose varicella vaccination

Population: Immunocompetent children (9months-13years)
Intervention: Two dose varicella vaccination
Comparison: One dose varicella vaccination
Outcome: Duration of decreased severe varicella (>500 lesions, complication requiring physician visit, hospitalization, death)

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ observational[9]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited.**
	Conclusion			**Studies do not demonstrate increased duration of protection against severe varicella for two doses of varicella vaccination compared to a single dose varicella vaccination in immunocompetent children. No study reported cases of severe varicella after two doses.**

The header row above the table reads:

In immunocompetent children (9 months to 12 years of age), what is the evidence for duration of protection against severe varicella with a two-dose versus a one-dose schedule?

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[9] RCT (Knuf et al. 2012), observational study (Kuter et al. 2004) and case-control study (Shaprio et al. 2011) follow-up 10, 3, and 2.5 years respectively. Kuter et al.: No severe varicella cases (>300 lesions) after single (MMR and MMR+V) vs. two- doses varicella vaccination (2x MMRV). Knuf et al: No severe varicella cases (≥150 lesions) after single vs. two- doses varicella vaccination. Shapiro et al. 2011: The matched odds ratio for 2 doses versus 1 dose of the vaccine was 0.053 (95% CI: 0.002–0.320; P < 0.001), no varicella cases after 2nd dose. No severe cases of varicella were reported in either of the studies.

Vaccine safety

Monovalent varicella vaccine

Monovalent varicella vaccine was well tolerated when administered to >11,000 healthy children, adolescents and adults during prelicensure clinical trials: overall, 19% of subjects reported pain at injection site, 6% localized varicella like rash and 15% of subjects reported fever[143]. However, local injection site reactions, fever and even rash are not uncommon in young children so the placebo-controlled trials are the best methodology for studying vaccine safety and attribution. Examining data from two placebo-controlled studies, the most common adverse events reported after varicella vaccination of healthy children were minor and included mild tenderness and redness at the injection site, and mild rash[76, 78]. In the US trial, pain and redness at the injection site were reported by 26.4% and 5% of vaccine recipients versus 17.5% and 2.5% of placebo recipients, respectively (P < 0.05)[76]. In a study comparing the safety of one dose of monovalent varicella vaccine with that of two doses administered 3 months apart, no serious adverse events related to vaccination were reported among approximately 2,000 healthy subjects ages 12 months to 12 years[144]. The safety profile of the two dose regimen was comparable to that of the one dose regimen. Incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (21%) (p=0.015). Incidence of systemic clinical complaints was lower after dose 2; fever incidence from days 7-21 post-vaccination was 7% after dose 1 and 4% after dose 2 (p=0.009), and varicelliform rash incidence after dose 1 was 3%, compared with 1% after dose 2 (p=0.008), with peak occurrence 8-21 days post-vaccination. Among persons ≥13 years of age, a higher percentage of injection site complaints was reported after both one and two doses of vaccine: 24.4% and 32.5%, respectively[71]. Varicella-like rash at the injection site occurred in 3% of 1 dose vaccine recipients and 1% of 2 dose recipients. A non-localized rash occurred in 5.5% of vaccine recipients after the first injection and in 0.9% of vaccine recipients after the second, at a peak of 7-21 and 0-23 days post-vaccination, respectively. There was no comparison group who received a placebo injection.

Postlicensure data have confirmed that the varicella vaccine is safe and well tolerated when administered to healthy persons. Considering approximately 48 million vaccine doses distributed in the US from 1995 to 2005, there were 25,306 adverse events reported (52.7/100,000 doses distributed) to the Vaccine Adverse Event Reporting System; 5.0% were classified as serious (2.6/100,000 doses distributed)[145]. The most common adverse events, accounting for 67% of all reports, have consistently been rash, fever and injection site reactions. Similarly, post-marketing surveillance over the first 5 years of Varivax use in Europe (~3.3 million doses distributed) found that most (88%) adverse events reported after vaccination were non-serious and the rate of reporting was 30 reports/100,000 doses[146]. By collecting information on a large number of persons (millions) who received the vaccine, post-marketing surveillance can also detect rare, serious adverse events. Serious adverse events that have been reported as temporally related to varicella vaccination include urticaria including some cases of recurrent papular urticaria, ataxia, thrombocytopenia, pneumonia, anaphylaxis, encephalitis, erythema multiforme, stroke, transverse myelitis, and death[11, 145, 147]. Most of these events were not found to be caused by the vaccine virus.

For reported adverse events following vaccination, laboratory testing of submitted specimens for VZV strain identification is critical. Rare complications that have been confirmed to be caused by VZV Oka strain include pneumonia, hepatitis, HZ meningitis, recurrent herpes zoster, severe rash and secondary transmission[145, 147-151]. Most of these patients were immunocompromised or had other serious medical conditions that were undiagnosed at the time of vaccination, but some were healthy. Some adverse events such are ataxia are biologically plausible and would be very challenging to confirm through laboratory testing. An Institute of Medicine systematic review of the epidemiologic, clinical, and biological evidence for adverse events associated with varicella vaccines through 2010 concluded that evidence supports causality in 5 adverse events[152]: 1) disseminated vaccine strain virus without organ involvement (e.g., varicella-like rash extending to dermatomes beyond the initial injection), 2) disseminated vaccine strain virus with organ involvement (e.g. pneumonia, meningitis, etc.) in individuals with demonstrated immunodeficiencies, 3) vaccine strain reactivation (HZ)

without organ involvement, 4) vaccine strain reactivation (HZ) with organ involvement, and 5) anaphylaxis. A follow up review of the evidence from the end of the IOM report through 2012 identified evidence consistent with the IOM report (F. Barash, presentation to the Global Advisory Committee on Vaccine Safety, December 2012). Several post-marketing studies examined the association between varicella vaccination and specific adverse outcomes: one study did not find an association with ischemic stroke[153], another found no increased risk of cerebellar ataxia or encephalopathy[154], while a third found an elevated risk for immune thrombocytopenic purpura among 11-17 year olds[155]. The results of this last study were based on only 1 case occurring in the first 42 days post-vaccination and the authors concluded that additional studies are needed to better explore this possible association. Two deaths confirmed to be due to the vaccine strain VZV have been reported to date, one in a 4 year old child from Germany[156] who received Varilrix while in remission from acute lymphoblastic leukemia and another one in a 15 month old child from the US who received VARIVAX and who did not have a known immunocompromising condition but did have a medical history (failure to thrive and repeated hospitalizations early in life for presumed infections and respiratory compromise treated with corticosteroids) that could suggest a primary or acquired immune deficiency[157].

A review of data reported after 16 years of pregnancy registry for VZV-containing vaccines that follows up pregnancy outcomes in women who inadvertently received Merck varicella vaccine during pregnancy showed no congenital varicella syndrome among 157 live born infants of seronegative women (Rate=0 per 100, 95% CI 0.0, 2.4) or in the overall registry (735 live births)[158]. However, the numbers of exposures are not sufficient to rule out a maximal theoretical risk for congenital varicella syndrome lower than 4% among seronegative women exposed during the high risk period (compared with ~2% risk after infection with wild-type VZV).

MMRV

In prelicensure clinical trials of Merck MMRV, fever and measles-like rash were reported at a significantly greater rate 0-42 days post-vaccination in children age 12-23 months who received a first dose of ProQuad than in children who received first doses of MMR and varicella vaccine: fever, reported as abnormal of elevated ≥102F (39C), 21.5% vs. 14.9% and measles-like rash, 3% vs. 2.1%[72]. Both of these adverse events were reported to occur more frequently 5-12 days post-vaccination and typically resolved without sequelae. Similarly, following the administration of the first dose of GSK MMRV, higher incidences of fever (approximately 1.5 fold) within 42 days postvaccination were observed when compared to the concomitant administration of MMR and varicella vaccines as separate injection to children age 9-27 months[74]. No differences in systemic reactions, including fever, occurring within 42 days of vaccination were observed when MMRV was administered as a second dose to children in the second year of life[159] or at age 4-6 years[160].

Because of the higher rate of fever seen in pre-licensure studies following the first dose of MMRV vaccine compared with MMR and varicella vaccines administered separately at the same visit, postlicensure studies to evaluate the risk for febrile seizures were conducted with a larger number of subjects. Compared to separate MMR and monovalent varicella vaccines administered simultaneously at the same visit, studies with Merck MMRV (>60.000 children received MMRV and ~400,000 received simultaneous MMR and varicella vaccines) demonstrated a doubled incidence of febrile seizures in vaccinated children 12-23 months of age, 5-12 or 7-10 days after the first dose of MMRV (RR 2.0; 95% CI 1.4 – 2.9, and RR 2.2; 95% CI 1.0 – 4.7), amounting to one extra febrile seizure for every 2,300-2,500 children vaccinated[161, 162]. A retrospective database analysis of the first dose GSK MMRV administered to children age 9 to 30 months reported a 2.4-fold increased risk for febrile seizures for the risk period of 5 to 12 days post-vaccination in the group who received MMRV compared with the group who received MMR and varicella vaccines separately (>82,000 children in each comparison arm) and one extra febrile seizure for every ~2,700 children vaccinated with MMRV instead of separate MMR and varicella vaccines, suggesting a class effect for these quadrivalent vaccines[74]. Postlicensure data did not find that children age 4-6 years who received MMRV as a second dose had an increased risk for febrile seizures after vaccination compared with children who received a second dose of MMR and varicella vaccine at the same visit[163].

Transmission of vaccine virus

Accumulated data from pre and postlicensure studies and surveillance suggest that transmission of vaccine strain VZV from healthy persons to susceptible contacts is very rare. In the postlicensure period with >130 million doses distributed, transmission of vaccine strain virus from healthy vaccine recipients to susceptible contacts has been documented by PCR analysis in 11 instances from 9 vaccine recipients (2 vaccinated persons transmitted virus to two contacts) most commonly following household exposure but also in institutional and school settings[146, 147, 164-168]. Transmission occurred only when the vaccine recipient had a rash (including 4 cases from herpes zoster caused by the vaccine strain) with one possible exception[169]: neonatal varicella with vaccine-strain VZV was diagnosed 22 days after maternal postpartum vaccination; the mother did not have a rash but the newborn was in the room when the mother was vaccinated and the most plausible mode of transmission was deemed aerosolization when the vaccine-filed syringe was cleared of air bubbles rather than transmission from the mother. Additionally, in prelicensure trials of leukemic recipients of varicella vaccine, only those with skin lesions as a side effect of varicella vaccination spread vaccine strain virus to varicella-susceptible close contacts (incidence of spread 10%-17%)[170, 171].

Herpes zoster after vaccination

The Oka strain, like wild-type VZV, may cause latent infection, and can reactivate from latency to cause HZ. In vaccinated children, HZ can also be caused by reactivation of latent wild-type VZV acquired either from unrecognized infection before or after vaccination or from breakthrough varicella. Some evidence suggested that HZ tends to be milder in vaccinated than in unvaccinated children[172, 173] however, determination of the causal agent (i.e. vaccine vs. wild-type strain) cannot be made on clinical grounds and attribution requires laboratory confirmation and genotyping. Some vaccine strain HZ cases have required hospitalization and few reported HZ cases had concurrent meningitis or encephalitis confirmed to be vaccine strain VZV[145]. Importantly, studies have documented that both immunocompetent and immunocompromised children vaccinated with varicella vaccines are at reduced risk for vaccine strain VZV HZ as compared with the risk for HZ from wild-type VZV in children with a history of varicella. Among immunocompromised children, one study indicated that varicella vaccine was 100% highly effective in preventing HZ among HIV-infected children[174] and a prelicensure study found the risk for HZ was approximately 65% less among leukemic children who had received the varicella vaccine compared with those with previous wild-type varicella infection[175]. In population-based studies of healthy vaccine recipients, Civen et al. described a 4 to 12-times lower risk of HZ among vaccinated children aged <10 years compared to children with a history of varicella and Weinmann et al. found that among children age <18 years HZ incidence was 79% lower among vaccinated than among unvaccinated and that wild-type virus caused half of HZ cases among vaccinated children[172, 173]. The risk for HZ in children after two doses of varicella vaccine and whether the reduced HZ risk documented in children after one dose is maintained as they become adults remain to be studied.

The quality of evidence was graded for following research questions:

- In immunocompetent individuals, what is the incidence of serious adverse events following the first dose of varicella vaccination (monovalent vaccine)? (GRADE table 6)
- In immunocompetent individuals, what is the incidence of serious adverse events (febrile seizures excluded) after vaccination with MMR and varicella or varicella alone? (GRADE table 7)
- In immunocompetent children (9 months to 12 years of age), what is the evidence for the increase in febrile seizures risk in those receiving one dose varicella vaccination with MMRV versus separate MMR and varicella simultaneously? (GRADE table 8)
- In immunocompetent children (9 months to 12 years of age), what is the risk of febrile seizures in those receiving two doses varicella vaccination with MMRV versus separate MMR and varicella simultaneously? (GRADE table 9)

GRADE Table 6. Vaccine safety of varicella vaccination in immunocompetent individuals (monovalent vaccine)

Population: Immunocompetent individuals
Intervention: Varicella vaccination (one dose)
Comparison: Placebo/no vaccination
Outcome: Serious adverse events

			Rating	Adjustment to rating
In immunocompetent individuals, what is the incidence of serious adverse events following any dose of varicella vaccination?				
Quality Assessment	No. of studies/starting rating		9/ RCT[10]	4
	Factors decreasing confidence	Limitation in study design	Serious[11]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect**
	Conclusion			**Our confidence in the estimate of the effect is moderate that incidence of serious adverse events following one or two doses of varicella vaccination is low. Overall few reports and low incidence of serious adverse events in RCTs, observational studies and post-marketing surveillance data. Despite overall low incidence of serious adverse events, incidence after first dose of vaccination is higher than after second dose.**

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[10] 6 RCTs Ferrera et al. 2009 ; Gatchalian et al.2004 ; Lau et al. 2004 ; Parment et al. 2003 ; Ramkissoon et al. 1995 ; Shinefeld et al. 2002), 3 observational studies (Black et al. 1999 ; Chaves et al. 2009 ; Ozaki et al. 2000) assess the vaccine safety of one dose of varicella vaccination. Consistent findings across studies, overall low incidence of serious adverse events

[11] Small number of study participants to assess very rare serious events

GRADE Table 7. Vaccine safety of varicella vaccination in immunocompetent individuals (MMRV vaccine)

Population: Immunocompetent individuals
Intervention: MMRV (one or two doses)
Comparison: MMR + V or V alone (one or two doses)
Outcome: Serious adverse events (febrile seizures excluded)

In immunocompetent individuals, what is the incidence of serious adverse events (febrile seizures excluded) after vaccination with MMRV compared with MMR + V or V alone?

			Rating	Adjustment to rating
Quality Assessment		No. of studies/starting rating	8/ RCT[12]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[13]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			3
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.**
	Conclusion			**The risk of serious adverse events (febrile seizures excluded) in immunocompetent individuals is low, both after having received MMRV vaccination and MMR+V or V alone. The reported events resolved without sequelae.**

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[12] 8 RCTs evaluate the risk of serious adverse events of MMRV compared to MMR+V or varicella vaccine alone. Observed serious adverse events comparing MMRV vs MMR+V are low: Czajka et al. 2009: 2/2206 vs 0/574; Goh et al.2007: 0/153 vs 0/146; Halperin et al. 2008 : 0/195 vs 0/195; Knuf et al.2006: 0/311 vs 0/108; Reisinger et al. 2006: 0/399 vs 0/195; Schuster et al. 2008: 7/732 vs 3/238; Watson et al. 1996: 0/57 vs 0/54; White et al 1996: 0/239 vs 0/239.

[13] Number of study participants is very small, difficult to identify rare serious adverse events.

GRADE Table 8. Risk of febrile seizures after first dose of MMRV in immunocompetent children (9months to 12 years)

Population: Immunocompetent children (9 months to 12 years)
Intervention: MMRV (one dose)
Comparison: MMR + V (one dose)
Outcome: Febrile seizures

			Rating	Adjustment to rating
In immunocompetent children (9 months to 12 years of age), what is the evidence for the extent (RR or attributable risk) of febrile seizures in those receiving varicella vaccination with MMRV versus MMR + V?				
Quality Assessment	No. of studies/starting rating		2/ observational[14]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**The risk of febrile seizures 5-12 days after the first dose of combined measles, mumps, rubella, varicella (MMRV) vaccination in immunocompetent children is 2 fold higher than using non-combined vaccination (MMR+V). This higher risk was documented in studies among children 12 (9) to 23 months of age.**

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[14] 2 observational studies indicate an elevated risk of febrile seizures 7-10 days (age 12-23 months) (RR: 1.98; 95% CI :1.43-2.73) and 5-12 days (age 12-60months) (RR: 2.2; 95% CI: 1.04-4.65) following the first dose of immunization with MMRV compared to MMR+V (Klein et al. 2010; Jacobsen et al. 2009).

GRADE Table 9. Risk of febrile seizures after second dose of MMRV in immunocompetent children

Population: Immunocompetent children
Intervention: MMRV (two doses)
Comparison: MMR + V (two doses)
Outcome: Febrile seizures

			Rating	Adjustment to rating
In immunocompetent children, what is the evidence for the extent (RR or attributable risk) of febrile seizures in those receiving two doses of varicella vaccination with MMRV versus MMR + V?				
Quality Assessment	No. of studies/starting rating		1/ observational[15]	2
	Factors decreasing confidence	Limitation in study design	None Serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**The risk of febrile seizures 7-10 days after vaccination with the second dose of combined measles, mumps, rubella, varicella (MMRV) vaccination in immunocompetent children was no different from non-combined vaccination (MMR+V).**

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[15] One observational study (Klein et al. 2012) found no elevated risk of confirmed febrile seizures in children (age 4-6 years) of MMRV compared to MMR+V 7-10 days after immunization (Incidence: 1.2/100 000doses; 95% CI:0.03-6.4)

Co-administration of monovalent varicella vaccine and MMRV with other childhood vaccines

Varicella vaccine was tested for concomitant administration with other childhood vaccines, included DTaP, DTaP-IPV, HibMenCY-TT, Influenza (LAIV), Hib, Comvax (Hib/HepB), and MMR[71, 73]. It was found to be safe (type, frequency and severity of adverse events reported were similar to those seen when each vaccine was given alone) with non-inferior immunogenicity. The co-administration of MMRV with other childhood vaccines was tested as well[72, 74]. Administration with DTP-IPV or DTPa-HBV-IPV/Hib or DTaP+Hib/HepB or hepatitis A vaccine was found to be safe with non-inferior immunogenicity. Co-administration with MenACWY-CRM at 12 months of age or meningococcal ACWY-TT conjugate vaccine was safe. MMRV given concomitantly with PCV-7 or 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) both showed uncompromised safety profiles. Concomitant administration of MMRV with 4CMenB was immunogenic but associated with increased reactogenicity (higher rates of fever with 4CMenB dose)[176].

In summary, simultaneous administration of the majority of widely used live and inactivated vaccines has produced seroconversion rates and rates of adverse events similar to those observed when the vaccines were administered separately. Monovalent varicella vaccine and MMRV may be administered simultaneously with other childhood vaccines. If not administered at the same time with other live vaccines the interval between administration of varicella vaccine or MMRV and other live vaccines (e.g., MMR, live attenuated influenza vaccine, yellow fever) should be at least 28 days.

Modeling the potential impact of a childhood varicella vaccination program on varicella and adult herpes zoster epidemiology

Potential for shift in the age at infection and increase burden of varicella

Prior to the introduction of the varicella vaccination program in the developed countries concerns were raised that widespread vaccination of children could decrease exposure to VZV in the population, resulting in an older age distribution of the remaining cases. Since complication rates in adults are higher than those in children there was concern that a shift in the age distribution of cases could increase overall morbidity, even though the total number of cases would be reduced[177]. In the United States, the average age at infection increased over the first ten years of the program from 3-6 years in 1995, to 9-11 years in 2005 but the age specific incidence decreased in all age groups[6]. A model developed to assess the effect of the varicella vaccination program on morbidity found that the total number of cases was more sensitive to the level of coverage than to variations in vaccine assumptions (effectiveness, duration of immunity)[178] and the United States achieved within a decade high coverage with the varicella vaccine among young children with important catch-up occurring. In addition, modeling results suggest that greater shifts in the age at infection are predicted when vaccine efficacy is high. However, according to model predictions, it is too early to see the effects of shift in the age at infection due to community protection effects.

Modeling performed to inform the working group deliberations to address the question of the shift in the age at infection indicated that for high income countries, at vaccine coverage levels of <30% and ≥80% very little risk exists of increased morbidity due to shifts in the age of infection (Brisson et al. The potential impact of varicella vaccination in low to middle income countries: A feasibility modeling study. Report to the SAGE working group on varicella and herpes zoster vaccines, unpublished, 2013). However, at moderate coverage levels (30%-70%), there may be a risk of increased morbidity due to shifts in the age at infection. The risk of increase in morbidity due to shifts in the age at infection increases with: higher vaccine efficacy (e.g., 2-dose vaccination), higher contact rates between children and adults and when severity/morbidity increases significantly with age (e.g., mortality). Based on findings from modeling using high income country data it was hypothesized that low/middle income countries may be at greater risk for shifts in the age at infection and increased morbidity after varicella vaccination due to higher risk for moderate coverage, less assortative mixing patterns and greater morbidity and case-fatality in older ages. In the absence of comprehensive data, for low/middle income countries, modeling was performed for countries representing a range of seroprevalence from different world regions: South Asia (India, urban and rural Sri Lanka), East Asia and Pacific (Thailand, Malaysia, Singapore), Latin

America and Caribbean (Brazil, Bolivia, St. Lucia) and Africa (Nigeria, Kenya). The analysis concluded that for low/middle income countries with medium/high seropositivity (most countries) there is a high risk of shifts in the age at infection when one-dose vaccination coverage is between 20% and 80% and this scenario can lead to increased mortality following varicella vaccination (fig. 6) (Brisson, unpublished, 2013). A coverage of at least 60% is required for substantial reductions in mortality. Low/middle income countries with very low seropositivity (e.g., Sri Lanka: less than 20%-30% in 20 year-olds) may see important reduction in mortality and morbidity, even with low vaccine coverage. There remain important data gaps for low/middle income countries: better seroprevalence data and morbidity outcomes to inform potential vaccination programs.

### Potential impact on adult herpes zoster epidemiology

A number of studies have either directly or indirectly examined the role of exposures to varicella on the risk of HZ in both immunocompromised and healthy populations[179]. Exposure to varicella disease has been shown to boost VZV specific immunity[14]; whether ongoing exposures throughout life is needed to maintain immunity to VZV through external boosting, especially as the population ages, is not certain though some studies support this hypothesis (e.g., persons with >3 exposures to varicella have 1/5th risk of HZ compared to unexposed[180], adults living with children have higher exposure to varicella and significantly lower HZ incidence[181]) while others do not[182]. Under the assumption that external boosting is important, mathematical models predicted that widespread varicella vaccination, by reducing varicella infection, will lead to an increase in HZ incidence over short and medium term (over 10–40 years in one study and up to 70 years in another)[177, 183, 184]. Some countries have postponed universal varicella vaccination, at least partially based on this prediction. However, on long term a decrease in HZ incidence is expected as the cohorts infected with wild-type VZV will be replaced by those who have received vaccine virus and assuming that its lower reactivation rate is maintained on long term[177, 184].

Experience has now been gained with observing HZ epidemiology in countries implementing varicella vaccine programs as well as in countries without a varicella vaccination program. Multiple studies examining overall population rates of HZ were conducted in many developed countries (US, UK, Canada, Spain, Japan, Australia) and the majority show evidence of increasing incidence trends in HZ[46, 185-191]. In countries with a vaccination program, increases in HZ incidence had started years before use of varicella vaccine therefore it is difficult to attribute the increase to varicella vaccination. Further studies are needed to understand factors that may explain these increases including methodological issues, changes in access to healthcare or health seeking behaviors, demographic/societal changes common to all high income countries, and risk factors for HZ that have not been well described to date including chronic medical conditions like diabetes, stress, and possible immune compromising effects of new immune modulating medications (e.g., monoclonal antibodies used to treat rheumatologic diseases).

A 2013 systematic multidisciplinary review of herpes zoster risk reduction through exposure to varicella patients analyzed the peer-review publications on exogenous boosting studies: 13 observational studies on herpes zoster incidence after widespread varicella vaccination, 4 longitudinal studies on VZV immunity after re-exposure, 9 epidemiological risk factors studies, 7 mathematical modeling studies, 7 and other studies[179]. The authors concluded that exogenous boosting exists, although not for all persons, nor in all situations and that its magnitude is yet to be determined adequately in any field study.

Until additional evidence becomes available, countries will have to consider the impact of varicella vaccination on adult HZ as being uncertain on short and medium term and ranging from no impact to increase associated with increases in morbidity and health care costs and decide on use of varicella vaccine in light of this uncertainty. In low/middle income countries the incidence of HZ is unknown and no modeling work on the impact of varicella vaccination on HZ incidence in these countries has been performed.

Figure 5. Predicted incidence of a) natural varicella, b) breakthrough varicella, c) varicella-related deaths and d) morbidity at post- equilibrium by country and vaccination coverage. 1-dose base case vaccine efficacy, Equilibrium=80 years post-vaccination, Morbidity=Inpatient days, Seroprevalence/force of infection estimated using the Farrington function. (from Brisson et al. The potential impact of varicella vaccination in low to middle income countries: A feasibility modeling study. Report to the SAGE working group on varicella and herpes zoster vaccines, unpublished, 2013)
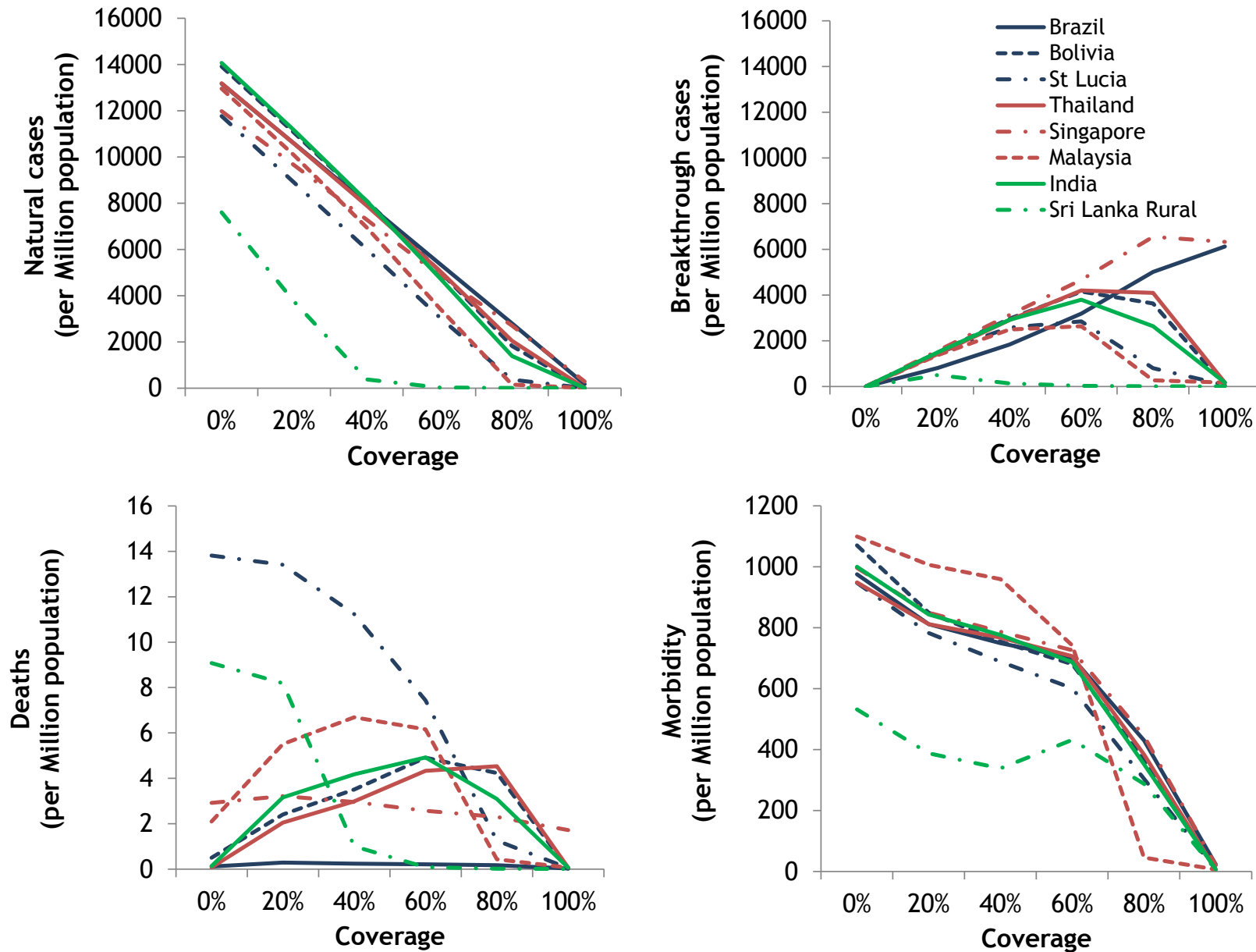
Cost effectiveness of varicella vaccination

A review of the literature found 41 studies that addressed the cost-effectiveness of childhood varicella vaccination, including two reviews[192, 193]. Most of the cost effectiveness studies were from Europe and North America (UK, Spain, Germany, Switzerland, US), two studies from Taiwan, and one each from Israel and Singapore. The study quality varied greatly. Most studies did not include dynamic models that account for community protection effects (only 9 studies used dynamic models) and likely underestimate the impact of varicella vaccination. However, the findings were highly consistent: studies found a childhood varicella vaccination program to be cost saving under the societal perspective, cost-effective under the health payer perspective when excluding any potential impact on HZ incidence and not cost-effective when including HZ natural history; this last approach predicts that the varicella vaccination program will increase morbidity on short term by increasing HZ incidence and that will counterbalance the benefits of varicella vaccination. In terms of magnitude of effect, most studies showed vaccinating children to be highly cost-effective or cost-ineffective depending on assumptions about HZ incidence. The evidence on these studies was indirect as they were based on modeling studies to account for community protection after varicella vaccination, uncertainties on duration of vaccine protection and impact of varicella vaccination on HZ incidence.

There appears to be agreement among models that over the long term (>50 years after childhood vaccination is initiated) the varicella vaccination program is likely to reduce HZ. This is the period when the incidence of HZ is expected to decline as the vaccinated cohorts enter the age groups when they are at greatest risk of developing zoster (with models assuming that the lower HZ risk seen among vaccinated children vs. those infected with wild-type VZV will be maintained into older ages). Increasing our understanding on the impact of varicella vaccination on zoster epidemiology was identified as a key issue that would help with refining the cost-effectiveness estimates. Data on cost-effectiveness from low and middle income countries is currently not available. Additionally, an accurate statement on what the cost-effectiveness would be in these countries cannot be made based on published studies because many of the parameters included in the modeling analyses are from high income countries and unknown for low and middle income countries (e.g., underlying epidemiology, mixing between ages, vaccine cost, health care costs).

Immunocompromised populations

Varicella in immunocompromised populations

Varicella causes much greater severity and mortality in populations who have compromised cellular immune function due to medical conditions or immunosuppressive therapy[1]. Persons with congenital deficits in cell-mediated immunity and those receiving chemotherapy, radiotherapy (or both), high doses of steroids, (e.g., severe asthma) are at greatest risk to develop varicella with dissemination of VZV throughout their organs and association with coagulopathy, severe hemorrhage, and continued vesicular lesion development after seven days (progressive varicella). Several studies have highlighted the severity of varicella among children with cancer/acute lymphoblastic leukemia (ALL), especially in those receiving chemotherapy[53, 194-197]. The risk for severe disease was particularly high if chemotherapy, and especially corticosteroids, was given during the incubation period[194, 195] and the absolute lymphocyte count was <500 cells/mm3[53]. In a study of 60 children with cancer who were still receiving chemotherapy when they developed varicella, 19 (32%) had disseminated disease and 4 (7%) died[194]. All four children who died had pneumonia and 3 also had encephalitis. There were no complications in the 17 children who had completed chemotherapy at least 2 months prior to onset of varicella. Further analyses on a larger number of immunocompromised children from the same center described that among 91 leukemic children on chemotherapy when they developed varicella and who were not treated with antivirals, 29 (32%) developed pneumonia and 9 (10%) died; the severity among leukemic children was greater than among children with other malignancies in which pneumonia occurred in 19% and no deaths were reported[53]. Mortality was much less (<1%) in the modern era (after 1984) when all patients received prompt antiviral treatment[198]. Nonetheless, clinical experience indicates that in settings with inadequate infrastructure and supplies for prevention, diagnosis and treatment VZV infection is an important cause of

morbidity and mortality among immunocompromised patients[198]. Children with ALL are also at a higher risk for HZ than healthy children.

Varicella also causes greater morbidity and mortality in HIV-infected persons than among the general population however, the risk of severe varicella and death is not as great as for leukemic children; while the illness is more extensive and lasts longer than in healthy children, fatalities and severe complications from varicella were unusual[54, 55]. Severely immunocompromised HIV-infected children can have persistent chronic infection, with continued appearance of new lesions for >1 month after primary infection[55, 199] and with atypical lesions (non-healing ulcers or necrotic, hyperkeratotic verrucous lesions). Chronic infection was reported in 14% of HIV-infected children with VZV in the pre-HAART era but it is uncommon in the HAART era[200]. An important burden of VZV infections among HIV-infected children is represented by HZ for which the risk of occurrence is >10-25 times higher than in the general population[201]. The CD4 count at the time of varicella correlates with the subsequent risk of developing HZ, 70% of HIV-infected children with <15% CD4-lymphocytes at the time of varicella developed zoster[202]. Ophthalmic complications due to VZV (either acute retinal necrosis or progressive outer retinal necrosis) associated with a high rate of visual loss have also been described in HIV-infected persons[201]. Since most individuals develop varicella by the age of 10 years, primary varicella in HIV-infected adults is rare. In the few reported cases, the clinical presentation and outcome were similar to those seen in HIV-infected children[203].

Varicella vaccine in imunocompromised populations

Because diseases caused by wild type VZV are more severe and fatal in persons with defects in cell mediated immunity, varicella vaccine (various regimens but mostly 2 doses administered 3 months apart) has been studied for safety and efficacy in select immunocompromised populations. Children with acute lymphoblastic leukemia (ALL) have been the most extensively studied immunocompromised group, >1,200 children with ALL received the vaccine in open-label trials[204]. The largest clinical trial in leukemic children was conducted in the United States and included children with acute lymphoblastic leukemia in remission (n=575) who were no longer receiving chemotherapy or had their chemotherapy suspended for at least one week before and one week after vaccination[205]. The most common adverse event was rash resembling mild varicella about 1 month after vaccination that occurred mostly after the 1st dose in 5% of leukemic children no longer receiving chemotherapy and in about 50% of those still receiving maintenance chemotherapy. 40% of those on chemotherapy developed a rash severe enough (>50 skin lesions) to require high dose acyclovir, for some administered intravenously (if >200 lesions). Rashes were less common after the second dose, occurring in only 10% of children still receiving maintenance chemotherapy. Seroconversion to VZV, measured by FAMA, occurred in 82% of leukemic children after one dose of vaccine and in 95% after two doses. In general, about 80% of vaccine recipients tested developed positive cell-mediated immune responses after one dose of vaccine and 90% after two doses, mirroring the experience with humoral immune responses. Over 11 years, 13% of vaccine recipients who originally seroconverted become seronegative[206]. Many were exposed to varicella but did not become ill. Prospective cohort studies also showed that children with leukemia who received varicella vaccine were 3 times less likely to develop HZ than those who had natural VZV infection (8 vs. 25 per 1000 person-years)[175].

Very few children with malignancies other than ALL were included in trials. Among children with lymphosarcoma an increased likelihood of severe rash was determined and these children were no longer included in future studies. Children with solid tumors who were given the vaccine did not have a greater frequency or severity of adverse events compared with leukemic children but further studies involving patients with solid tumors are needed[204].

One of the other major groups of immunocompromised patients evaluated for the safety of varicella vaccine was transplant recipients. In one small study, the live vaccine was administered to hematopoietic stem cell transplant patients with demonstrable immune reconstitution; 4% of vaccine recipients experienced mild-to-moderate symptoms potentially attributable to vaccination and there were no severe reactions[207]. Three studies with <100 subjects total examined varicella vaccine given to organ transplant recipients (kidney, liver) on

immunosuppressive therapy[208-210]. They concluded that the vaccine caused mostly local reactions, rash and fever. However, some of the rashes were severe and disseminated and required treatment with acyclovir.

Several studies have been conducted in approximately 220 VZV-seronegative HIV positive children[211-215]. For the most part these were 2 dose regimens with the second dose typically given after 3 months. Studies were done in those who had progressively more immunosuppression, however, none were in severely immunosuppressed (CD4+T-lymphocyte percentage <15%). In the two studies conducted by Levin et al. that account for >50% of all HIV positive subjects studied, local reactions were reported in 5%-20% of participants after dose 1 and 3%-12% after dose 2[212, 213]. Fever and rash also occurred and for the most part were mild and transient. Two cases of pneumonia and one of seizure were reported but these were found to be related to other causes. Regardless of immunologic category, at least one measure of VZV-specific immunity (antibody and/or cell mediated immunity) was present in at least at least 83% of vaccine recipients after 2 doses[216]. The percentage of children with detectable VZV antibody declined at one year post-vaccination but was similar to that found in a comparator group of HIV-infected children who had natural varicella in the prior year. No serious adverse events were reported from other trials. There were no studies of varicella vaccine conducted among HIV positive adults who were VZV seronegative.

The safety of varicella vaccine in pediatric and juvenile patients with a range of chronic and autoimmune diseases has also been demonstrated[217-221]. Use of varicella vaccine has been shown to be safe with no serious adverse events reported among children and adolescents with systemic lupus erythematous, juvenile rheumatic diseases (both groups also on immunossupressive medication), chronic renal failure, chronic liver disease, or atopic dermatitis. In general these were small studies, with all but one including less than 60 subjects; .

Data on vaccine efficacy/effectiveness of 2 doses varicella vaccination in immunocompromised children was gathered in a few studies. The vaccine was found to be 86% effective among leukemic children, 73% effective post renal transplant (children received the vaccine before transplantation) and, among HIV-infected children, 85% effective in protection against any varicella and 100% effective in preventing zoster[11]. Varicella that occurred in vaccinated children was generally a modified disease, less severe than in unvaccinated children with similar immunocompromising conditions.

All studies in immunocompromised populations were small and in very controlled settings with close follow up and monitoring, hence, results may not be generalizable. HIV status and CD4 count status of children in routine vaccination programs are typically not known. All but one of these studies were from developed countries. Compared to healthy children, varicella vaccine is associated with higher risk of adverse events, some severe, in selected subpopulations of children with deficiencies in cell mediated immunity. Available data suggest that the vaccine can prevent most cases of severe varicella in these populations.

The quality of evidence was graded for following research questions:

- What is the scientific evidence of the effectiveness of varicella vaccination against all grades of severity of varicella disease in HIV-infected individuals (with CD4+ ⩾15%)? (GRADE table 10)
- In HIV-infected individuals (with CD4+ ⩾15%), what is the (attributable) incidence of serious adverse events for any dose of varicella vaccination? (GRADE table 11)

GRADE Table 10. Vaccine effectiveness of varicella vaccination in HIV infected individuals (CD4+ ≥15%)

Population: HIV infected individuals (CD4+ ≥15%)
Intervention: Varicella vaccination (one or two doses)
Comparison: Placebo/no vaccination
Outcome : All grades of severity of varicella disease

			Rating	Adjustment to rating
What is the scientific evidence of the effectiveness of varicella vaccination (versus placebo/no vaccination) against all grades of severity of varicella disease in individuals with HIV (CD4+ ≥15%)?				
Quality Assessment	No. of studies/starting rating		4/ observational[16]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the health outcome is limited**
	Conclusion			**Varicella vaccination demonstrates to be effective in protecting individuals with HIV infection (CD4+ ≥15%) against all grades of severity of varicella disease.**

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[16] Four studies evaluated the effectiveness or immunogenicity of varicella vaccination in children with HIV (Son et al. 2010 , Armenian et al. 2006, Taweesith et al. 2011, and Levin et al. 2006). Vaccine effectiveness in 72 children having received one (46%) or two doses (54%) was 82% (95%CI: 25%-99%; p=0.01) (Son et al. 2010). Among 34 children (57%) who were VZV seronegative at baseline, 11.8% (95% CI, 3.3%-27.5%) and 79.4% (95% CI, 62.1%-91.3%) were VZV seroconverted after first and second dose of vaccine, respectively (Taweesith et al. 2011). Seroconversion rates ranged from 11.8%-72% after the second dose and from 43%-65% one year after vaccination depending on the level of immunosuppression (Levin et al.2006). Varicella-zoster virus-specific lymphocyte proliferative responses were detected 100% (n=10) subjects 90% one year after vaccination (Armenian et al. 2006).

GRADE Table 11. Vaccine safety of varicella vaccination in HIV infected individuals (CD4+ ≥15%)

Population: HIV infected individuals (CD4+ ≥15%)
Intervention: Varicella vaccination (one or two doses)
Comparison: Placebo/no vaccination
Outcome : Serious adverse events

In individuals with HIV (CD4+ ≥15%), what is the (attributable) incidence of serious adverse events for any dose of varicella vaccination?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		6/ RCT[17]	4
	Factors decreasing confidence	Limitation in study design	Serious[18]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect**
	Conclusion			**Reports of serious adverse events following one or two doses of varicella vaccination in individuals with HIV (CD4+ ≥15%) is low, yet the evaluated studies are conducted in controlled settings with a limited number of participants.**

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[17] Levin et al.2001: N=41, Levin et al. 2006 :n = 97, Bekker et al. 2006. N =15, Armenian et al. 2006 : n=10, Taweesith et al. 2011, n= 60, Weinberg et al. : n= 82. Except Weinberg, all studies evaluated the safety in children. 5/6 studies reported no serious adverse events, only one report of report of seizure 19 days post vaccine (Levin et al. 2006).
[18] All studies reviewed were small and in very controlled settings with close follow up and monitoring

Varicella in healthcare settings

Nosocomial transmission of VZV is a well recognized medical and public health problem[222-233]. Sources of nosocomial exposure that have resulted in transmission in health-care settings have included patients, health-care personnel and visitors with either varicella or HZ. Due to generally close contact with their patients, health-care personnel are at higher risk of being exposed to VZV, and may become infected if they are not immune. On the other hand, health-care workers with incubating or clinical varicella are at risk to transmit VZV to their patients. Of special concern are certain groups of susceptible patients (e.g., neonates, premature, pregnant women, immunocompromised hosts due to immunosuppressive therapy or malignant diseases) who are at increased risk for severe varicella with complications[1]. Most of the patients at high risk of serious complications are ineligible for varicella vaccine therefore protection from exposure is important.

Nosocomial transmission has been attributed to delays in the diagnosis or reporting of varicella or HZ and in failures to implement appropriate control measures promptly. The recognition of patients and staff who represent a source for VZV is difficult because the infectious period for patients with varicella starts before rash (1-2 days) and also the diagnosis may be missed in the early stages. Additionally, airborne transmission of VZV from patients with either varicella or HZ has resulted in varicella among staff and patients who had no direct contact with the index case-patient[223, 224, 234].

VZV exposures among patients and health-care personnel can be disruptive to patient care, time-consuming, and costly even when they do not result in transmission[227, 233, 235, 236]. Identification of susceptible patients and staff, reassignment of staff until proof of immunity becomes available, medical management of susceptible exposed patients at risk for complications of varicella and furlough of susceptible personnel 8-21 days post-exposure all place a burden on health-care facilities.

The VZV immune status of health-care personnel is expected to mirror the immune status of adults in the respective country. Most adults in temperate regions are immune to varicella and outbreaks in health-care personnel are uncommon, more common are exposures that do not lead to transmission. A review of nosocomial outbreaks associated with VZV in the United States before introduction of varicella vaccination found that following nosocomial exposure to VZV, 2% to 16% of susceptible staff has developed clinical varicella[229]. From February 1996 to May 1999, 9 hospitals in the US National surveillance system for health care workers reported 72 exposures to VZV, affecting a total of 1111 staff and resulting in 113 lost work-days recorded; 36 patients, 26 staff and 7 visitors were identified as the sources of exposure; 6 staff developed disease following VZV exposure[237]. Therefore, a small but significant risk exists for nosocomial varicella when susceptible health care personnel are exposed to VZV. Because varicella among adults is more common in tropical regions, health-care personnel from the tropics may be at high risk for varicella.

Conclusions and recommendations

Use of varicella vaccine in the general population
Context

- Varicella-zoster virus causes varicella as an acute disease; the virus remains latent and can reactivate causing herpes zoster, usually later in life

- Varicella is a highly communicable viral disease with worldwide distribution that most persons acquire during their lifetime. It is considered to be transmitted primarily by inhalation of aerosols from vesicular fluid of skin lesions, and also by direct contact and possibly by infected respiratory tract secretions.

- In countries where the burden of disease is well described, the severe disease burden in children is much lower than for measles, rotavirus or pneumococcal disease

- In temperate climates, varicella exhibits strong seasonality with peak incidence in the period from late winter to early spring. Most cases occur before 10 years of age, hence the majority of adults are seropositive when tested. In tropical areas, varicella may show a seasonal distribution related to temperature and rainfall, but, a larger proportion of adults, especially in low population density areas, are seronegative.

Safety and effectiveness of varicella vaccination:
- There is strong scientific evidence that varicella vaccine is safe and effective in preventing varicella related morbidity and mortality in immuncompetent individuals.

Factors to be considered for vaccine policy decisions:
Burden of disease:
- Fewer data are available on burden of disease from low and middle income countries. However, considering access to care, specialized treatment options, acquired immune deficiency states such as HIV and, in tropical climates greater disease burden in adults due to later acquisition of varicella, it is likely that varicella-related morbidity and mortality would be higher than in developed countries.
- The relationship between the acute (varicella) and reactivated (zoster) phases of the infection in individuals and on a population level. Though concerns have been raised through mathematical models that herpes zoster incidence may increase over the short and medium term due to a varicella vaccine program, epidemiological studies have not confirmed that increases herpes zoster incidence that have been observed in many countries globally are attributable to varicella vaccine.
- Varicella causes higher morbidity and mortality in immunocompromised populations, especially those with defects in cell-mediated immunity and in non-immune young infants and adults including pregnant women.
- There are differences in the epidemiology of varicella between temperate and tropical climates. Other risk factors that affect seroprevalence in populations include area of residence, population density, attendance at childcare and school and number of siblings in the household.
- Due to the high incidence of varicella in children and low susceptibility among adolescents and adults, the impact of a vaccination program aimed at adolescents and adults is expected to be minimal (except in countries with a high average age at infection)
- The experience of countries that introduced universal childhood varicella vaccination indicates an important impact on varicella cases, hospitalizations and deaths

Coverage:
- A routine childhood vaccination program with coverage of <80% in children could result in an increase in morbidity and mortality due to a shift of varicella burden to older age groups
- Private market use of the varicella vaccine, in the absence of a routine immunization program, may reach coverage levels high enough to have a detrimental effect of increasing the median age of varicella disease and the burden of varicella but not sufficiently high to ensure protection at country level (it is estimated that an undesired effect occurs at coverage levels between 20% and 80%).

Cost-effectiveness:

- Cost-effectiveness is dependent on vaccine cost, safety and effectiveness and the impact of the vaccine in reducing overall direct medical and societal costs of varicella morbidity and mortality in a country.
- Cost-effectiveness studies and models on the impact of vaccination can further assist countries considering introduction.
- Cost-effectiveness results will be subject to the uncertainty that currently exists regarding the boosting effect of circulating varicella on the incidence of herpes zoster later in adulthood.

Resources:

- Countries need to consider the impact of varicella vaccination versus other important public health interventions.
- Countries should assess whether adequate resources can be allocated to implement and sustain varicella vaccination in a routine immunization schedule to achieve and <u>maintain</u> high coverage levels and/or to support recommendations for high-risk populations such as healthcare workers.

Recommendations for the general population:

- Routine childhood immunization against varicella (generally at 12-18 months of age) should be considered in countries where this disease is an important public health and socioeconomic problem. In countries where the vaccine is licensed for persons <12 months of age, vaccination can be considered at an earlier age. For countries considering a two dose program, a decision on the age at the second dose can consider the childhood vaccination schedule and vaccine licensure as well as scientific evidence on vaccine immune response and efficacy. Resources need to be sufficient to support a vaccination program so that sustained vaccine coverage ≥80% can be achieved and maintained.
- Countries in which coverage levels from use of varicella vaccine in the private sector reach between 20%-80% should give a higher priority to considering implementing a routine vaccination program to reach the coverage ≥80% due to the likelihood that the incidence of disease that occurs in adults would otherwise increase.
- Implementation of a one or two dose varicella vaccine schedule is dependent on the goal of the vaccination program: If the country focus is to reduce mortality and severe morbidity from varicella, a one dose schedule could be implemented into routine immunization. Two doses induce 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 which might continue to occur with a one dose schedule.
- Countries with a high average age (≥15 years of age) of infection, could take into consideration alternate vaccination strategies such as vaccination of susceptible adolescents and adults. This strategy requires a two dose schedule.

Special groups/risk groups

Health care workers

Context:

- Due to close contact with patients, health-care workers are at higher risk of exposure and consequently transmission of the varicella-zoster virus to patients at high risk for serious complications.
- Nosocomial transmission and outbreaks may cause higher mortality and serious morbidity if they affect immunocompromised and other high-risk patients. Additionally, outbreaks are costly, and disruptive in healthcare settings.

Recommendations:

- Countries should consider vaccination of susceptible health care workers with two doses of varicella vaccine even in absence of varicella vaccination in the routine immunization schedule.
- In settings where financial constraints prohibit vaccination of all susceptible health care workers, priority should be given to vaccination of health care workers in close contact with persons at high risk of serious varicella complications such as immunocompromised individuals, neonates and pregnant women.

Immunocompromised patients

Context

- Varicella causes higher morbidity and mortality in immunocompromised populations, especially those with defects in cell-mediated immunity
- Varicella vaccine has been studied selectively, under strict protocols, in children with acute lymphocytic leukemia and HIV
- The label for varicella vaccines contraindicates their administration to persons with congenital or acquired immune deficiencies. However, the vaccine may be used in selected immunocompromised populations. Nevertheless, because of the risk of severe vaccine-related complications, use of the vaccine in these specific populations should only be considered in health care settings where specific antiviral therapy is readily available and physicians have expertise with the vaccine in these populations.
- MMRV vaccine has not been studied in these populations and should not be used for vaccination of immunocompromised patients.

Recommendations:

HIV

- Varicella vaccine has been shown to be safe, immunogenic, and effective in HIV-infected children with CD4 ≥15%. The use of the vaccine (2 doses administered 3 months apart) should be considered in clinically stable HIV-infected children including those receiving highly active antiretroviral therapy (HAART) with CD4 determinations ≥15%. The vaccine has not been studied in individuals with CD4 <15% or in those who are not clinically and immunologically stable, and should not be used in these situations.
  Malignancies
- The vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia (ALL) and certain solid tumors, on maintenance chemotherapy in remission. Protocols defining 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.
- Expert opinion varies, but in general, children who have successfully completed chemotherapy and remain in remission and are unlikely to relapse can receive vaccine approximately 3-6 months after all chemotherapy is completed.
  Other types of immunodeficiencies
- Consideration of vaccine 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 subjects with isolated defects in antibody production (i.e. hypo- or agammaglobulinemia). It should not be given to those with conditions where defects in antibody production are part of an immunodeficiency condition that includes defects in cellular immunity (i.e. severe combined immunodeficiency, etc.) or on any condition characterized by defects in cellular immunodeficiency, except as described above for HIV, ALL and certain solid tumors.

Household contacts of immunocompromised patients
Context:
- Varicella vaccine can be safely used in household contacts of immunocompromised patients. The risk of transmission from a vaccinated person to the patient or their household contacts is very low.

Vaccination of household contacts provides protection for immunocompromised persons by decreasing the likelihood of exposure to wild-type varicella-zoster virus.

Recommendation:

- Susceptible household contacts of immunocompromised patients should be considered for vaccination with two doses of varicella vaccine spaced according to the minimum interval recommended by the manufacturer.
- Two doses are recommended for household contacts of immunocompromised persons to offer greater protection to household contacts even if the country has a routine one dose childhood program

Pregnant women

- Infection with wild varicella-zoster virus during the first 2 trimesters of pregnancy can result in congenital varicella syndrome (scarring on the skin, abnormalities in limbs, brain, and eyes, and low birth weight) in 1-2% of the offspring. Varicella vaccine is contraindicated during pregnancy
- Limited data from a pregnancy registry which followed the birth outcomes of pregnant women who had inadvertently received varicella vaccine has not detected any cases of congenital varicella syndrome in their offspring however the sample size has precluded exclusion of the 1-2% risk of congenital varicella syndrome associated with wild VZV infection during pregnancy; the maximal theoretical risk ruled out by the pregnancy registry data is 4% among seronegative women exposed during the high risk period. Nonetheless, the data are reassuring on the low risk for congenital varicella syndrome after varicella vaccination
- According to expert opinion, the risk of congenital infection is likely to be lower from an attenuated vaccine virus than wild virus and termination of pregnancy is not recommended if a pregnant woman was inadvertently vaccinated
- Routine laboratory documentation of pregnancy status prior to vaccination is not recommended
- Given implementation of varicella vaccination in the routine program, efforts should be made to counsel and vaccinate susceptible women post-partum in order to prevent infections during subsequent pregnancies

High priority research questions

Burden of varicella and age-specific varicella incidence, severe morbidity and mortality especially in low and middle income countries, including those with high prevalence of HIV

Long-term duration of protection for both 1 and 2 doses of varicella vaccine

More data to understand the effect of varicella vaccination on herpes zoster, both through observational studies and modeling

More evidence to examine how different varicella vaccine coverage levels would change varicella epidemiology

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