Safety of varicella and MMRV vaccines: A systematic review

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ABSTRACT

The World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) established the Working Group on Varicella and Herpes Zoster Vaccines to review the evidence and formulate recommendations on use of varicella and herpes zoster vaccines. This systematic review utilized the PubMed database to extract publications on the safety of varicella and MMRV vaccines in immunocompetent and immunocompromised individuals. 244 articles, published before October 2013, were extracted and ultimately 84 were included in the review. RCTs, observational studies and post-licensure safety data were included. No increased incidence of serious adverse events following immunization was identified. MMRV, compared to MMR only or MMR+V, demonstrated a higher risk of adverse events and serious adverse events, including a higher risk of febrile seizures.

1. Introduction

The World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) established the Working Group on Varicella and Herpes Zoster Vaccines in May 2012. The Working Group was asked to review the evidence, identify the information gaps, and guide the work required to formulate proposed recommendations in preparation for a SAGE review of the use of varicella and herpes zoster vaccines. The ultimate goal is to update the current (1998) WHO varicella vaccine position paper. The Working Group was specifically asked to identify and review the safety and effectiveness profile of varicella and herpes zoster vaccines, including that of vaccine combinations such as MMRV, and to review the impact of varicella vaccination of immunocompromised individuals.

The Working Group formulated relevant research questions (PICO - Population, Intervention, Comparison, Outcome questions) and four of those questions are examined in this systematic review:

1. In immunocompetent individuals, what is the incidence of serious adverse events for any dose of varicella vaccination?
2. In immunocompetent individuals, what is the incidence of serious adverse events after vaccination with MMRV compared with MMR + V or V alone?
3. 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?
4. In immunocompromised individuals, what is the incidence of serious adverse events for any dose of varicella vaccination?

Safety of varicella vaccines have been previously evaluated in four published reviews of varicella and MMRV vaccines. In 2008 Galea et al. published a review of the safety profile of Varivax in the Journal of Infectious Diseases. Data derived from post-marketing surveillance and PCR analysis by the Varicella Zoster Virus Identification Program. Of the approx. 55.7 million doses distributed between 1995 and 2005 worldwide, 16,683 reports were voluntarily submitted. The reporting rate of adverse events was 3.4 per 10,000 doses distributed. Reports included rash, breakthrough varicella, herpes zoster, neurologic adverse events, and secondary transmission of the vaccine virus. Most frequently reported was rash 42 days after vaccination (19%). No primary neurological adverse events were associated with Varivax (Galea 2008).[1] Marin et al. published a review of varicella prevention in the United States in 2008. Post-licensure safety surveillance through the US Vaccine Adverse Event Reporting System (VAERS) and Merck's Worldwide Adverse Experience System found generalized rash, fever and injection site rash to account for two thirds of all reported adverse events (AE). Serious adverse events (SAE) accounted for five percent of reported received by VAERS (Marin).[2]

In 2009 Czajka et al. published a review of five clinical trials of Priorix-Tetra (GSK MMRV) that involved more than 3,000 subjects. The review noted a higher rate of low grade fever after the first dose and an increase in mild local reactions following the second dose for MMRV vaccinees compared to those who received MMR+V. Four SAEs were reported in the MMRV groups of the pooled studies; two febrile convulsions (one with tonsillitis), one urticarial allergic reaction and one prolonged fever. Following the first dose of Priorix-Tetra there were four febrile seizures, compared to none in the MMR+V group. After the second dose there were four in the MMRV group and two in the MMR+V group (Czajka 2009).[3] In August 2008 it was reported that research from the CDC showed an increased risk of febrile seizures for the combined MMRV vaccine compared to the MMR administered concomitantly with the varicella vaccine (Hamlin 2008).[4] Among children 12 to 23 months of age receiving a combination vaccine of MMRV, risk of febrile seizure was twice as high seven to ten days after vaccination compared to those who received MMR + V (Marin).[2]

The last available review of varicella vaccine use in immunocompromised individuals was published by Sartori in 2004. The literature review found that varicella vaccine had been studied extensively in children with acute lymphoblastic lymphoma (ALL) in remission but that studies in other immunocompromised children were rare. Japanese studies in children with ALL found higher rates of adverse events, particularly varicella-like illness, when compared to health children. Severe varicella like illness with visceral involvement was reported in leukemic children in four publications. Among bone marrow transplant recipients only one study with fifteen children was found and no AEs were observed. In kidney transplant recipients AEs were equivalent in observed rate and severity to immunocompetent children. The same was found to be true from four studies of children with steroid-sensitive nephrotic syndrome. As for HIV, at the time of publication there had only been one clinical in 41 HIV positive children with no or mild signs and symptoms (high CD4 count). Local reactions were observed in 20% following the first dose and systematic reactions in 37% (Sartori).[5]

This review aims to provide an update of the published literature to the afore mentioned reviews in order to adequately address the research questions formulated by the SAGE Working Group on Varicella and Herpes Zoster Vaccines.

2. Methods

2.1. Search Method

This literature review aims to summarize findings for four research questions concerning varicella vaccine safety: the safety of the varicella vaccine, the safety of the combined MMRV vaccine, the risk of febrile seizures following MMRV vaccination, and the safety of varicella vaccines in immunocompromised patients.

PubMed was used to search for relevant peer-reviewed literature (the search terms used are included in the appendix). Literature published up to October 2013 was included. In addition, reference lists were screened to identify further relevant studies. Studies done in any country and published in English language were included. The following study designs were included: RCT or quasi-randomized controlled trials as well as observational studies. Included were studies reporting on all registered varicella vaccines; either monovalent formulations or in combination with measles, mumps and rubella vaccine (MMRV, MMR+V and V only). Outcome measures were adverse events, serious adverse events and febrile seizures

Ecological studies, uncontrolled studies (i.e. case reports and case series studies) and studies including only individuals with the outcome of interest in the analyses ("case only" studies) were excluded. Additionally, animal studies were excluded.

For the purpose of this review adverse events were defined to include all adverse events reported in publications as "adverse events" or "adverse reactions". For severe adverse events, febrile seizures were not included and are discussed in the separate section on the risk of febrile seizures associated with MMRV.

The studies identified in this review were assessed for risk of bias in trials using the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.[1] The GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE)[2], was used to assess the quality of evidence. Results will be summarized in GRADE tables.

3. Results

3.1. Literature Search

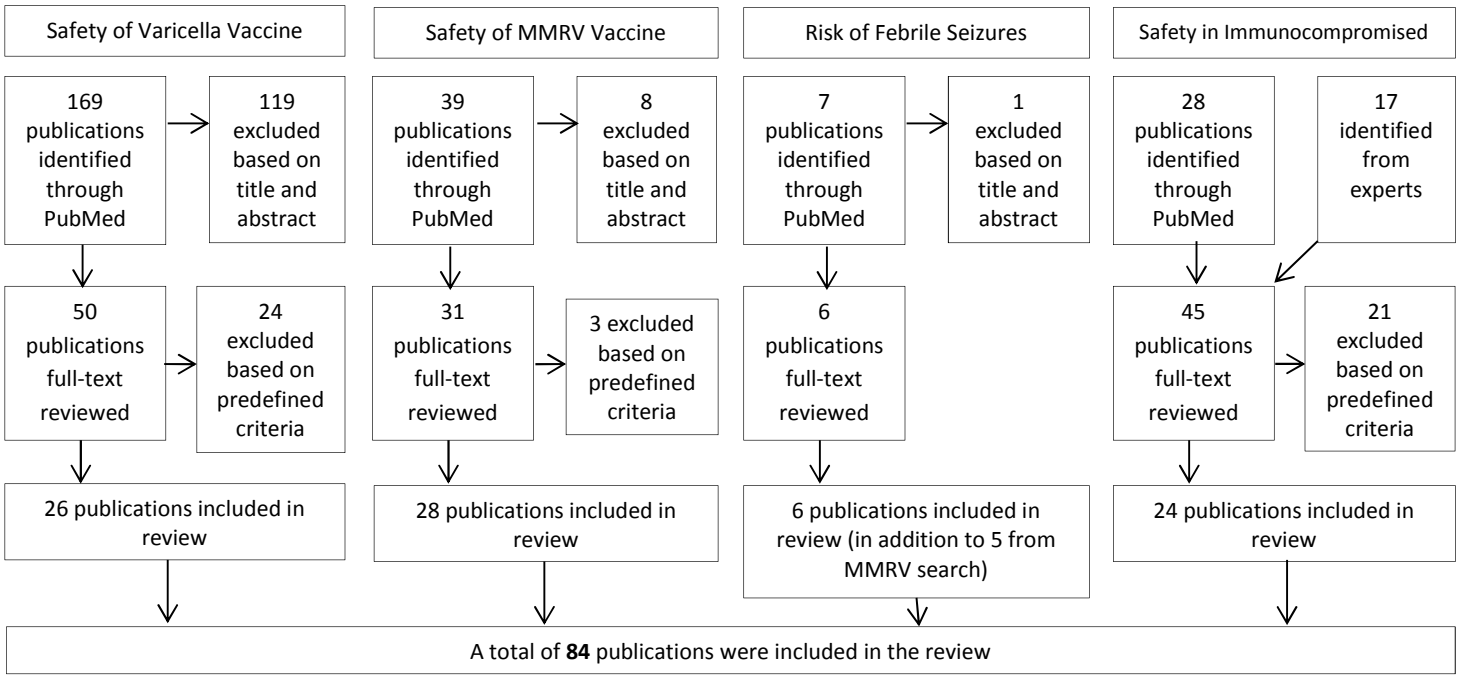
The search on the safety of varicella vaccine resulted in 169 publications. 50 of those publications were relevant and were selected for further review. 26 were included in the summary of varicella vaccine safety. The search on the safety of MMRV vaccine resulted in 39 publications. 31 of those publications were relevant and were selected for further review. 28 were included in the summary of MMRV vaccine safety. The search on the risk of febrile seizures resulted in seven publications. Six were included in the summary of the risk of febrile seizures. Several publications from the MMRV safety literature search contained reports on febrile seizures. Five of these studies were included in the section

[1] http://handbook.cochrane.org/

[2] Guidance for the development of evidence-based vaccine related recommendations. (http://www.who.int/entity/immunization/sage/Guidelines_development_recommendations.pdf)

on MMRV safety; in addition these studies were relevant to address the PICO question on risk of febrile seizures hence were selected for further review for that section. The search on the safety of varicella vaccine in immunocompromised patients resulted in 28 publications. Other publications were included from screening of reference lists of relevant literature. A total of 45 publications were selected for further review. 24 were included in the summary of varicella vaccine safety in immunocompromised patients. A total of 134 articles were reviewed and 84 were included in the following summary. Figure 1 displays the process of selection of articles for inclusion in this review.

Figure 1: Search Results Flow Diagram



3.2. Safety of varicella vaccine

Mild adverse events were the most frequently reported adverse events following immunization. This includes injection site reactions (pain, swelling or redness) following vaccination, which occurred in 21%[6], 19%[7], 28.3%[8], and 28.1%[9] of study participants. Rash, localized or generalized, was also found to be a common AE. Small clinical trials (<1,000 study participants) found 17%[10], 8.5%[11], 7%[6], and 3.2%[8] of study participants experienced a rash following vaccination. One small clinical trial (114 subjects) reported fever in 27.2% of vaccinees.[9]

Nine small clinical trials (<1,000 study participants) reported no vaccine related serious adverse events .[9, 12-18] In one small clinical trial of Varivax (507 participants) there was one possibly vaccine related SAE, idiopathic thrombocytopenic purpura.[8] A clinical trial of 200 participants reported 1 SAE, hospitalization for broncho-pneumonia.[11] Two moderately sized clinical trials (1,000 – 3,000 participants) reported no vaccine related SAEs.[19, 20] In a clinical trial of Varivax with 1,366 participants there was one SAE, pruritus (Diaz).

Findings from clinical trials were confirmed by post marketing surveillance. Post marketing licensure data of Varilvax (>11,000 vaccine recipients) reported pain at injection site for 19% of recipients, localized varicella like rash for 6% of subjects and 15% of subjects reported fever.[7] Ischemic stroke can be a complication of varicella disease but no association has been found between varicella vaccination and ischemic stroke or encephalitis.[21] Post marketing evaluation found no increased risk of cerebellar ataxia or encephalopathy.[22]

Surveillance for adverse events comes predominantly from the United States. The Vaccine Adverse Event Reporting System (VAERS) with 48 million doses of varicella vaccine distributed, reported 52.7 AEs per 100,000 doses and 2.6 severe adverse events (SAEs) per 100,000 doses as of 2008.[23] Further post-marketing surveillance found the rate of AEs to be 30 per 100,000 doses of varicella only (Oka vaccine). The rate of SAEs was just under four per 100,000 doses.[24] In summary, the most commonly reported AEs in post marketing surveillance and clinical trials are injection site reactions, rash (localized or generalized) and fever.[2]

Varicella vaccine was tested for concomitant administration with other childhood vaccines, included HibMenCY-TT, Influenza, Hib, and MMR, and was found to be safe.[14, 16, 17, 22, 25-29] Reactions at the injection site and general rash were increased slightly with concomitant administration with MMR vaccine.[26] In a study of concurrent administration of LAIV with MMR and varicella vaccines (1,245 study participants) there were four possibly vaccine related SAEs in the MMR+V group: two cases of croup, one case of pneumonia and one case of bronchiolitis.[28]

3.3. Safety of MMRV vaccine

Two small studies (<400 subjects) found no difference in the safety profile of MMRV compared with MMR+V.[30, 31] However, six clinical trials comparing MMRV to MMR+V (range of participants 240 to 5,833) found significantly higher rates of fever ($p<0.05$) after the first dose with MMRV. One study reported fever 15 days following the first dose to have occurred in 48.3% of MMRV recipients compared to 25.7% of MMR+V recipients. Fever was lower and comparable (20.3% and 22.1%) following the second dose.[32] A second study reported low grade fever in 67.7% of MMRV recipients compared to 48.8% in MMR+V recipients following the first dose and no difference following the second dose.[33] The rates of fever following the first dose (MMRV v. MMR+V) from four other trials were: 27.7% v. 18.7%[34], 59.5% v. 41.6% (0-14 days)[35], 39.1% v. 33.1%[36], 21.5% v. 14.9%[37]. Increase in local symptoms or rash following MMRV, compared to MMR+V, was found in three clinical trials.[34, 38, 39] Two small studies who reported increase in fever found no difference in local symptoms following MMRV vaccination.[33, 35] The safety of intramuscular versus subcutaneous administration of MMRV showed slightly less swelling 0-3 days after immunization in the IM group but no other reactogenicity differences.[40]

Ten small clinical trials (<1000 subjects) and one clinical trial of 1,620 subjects found no SAEs following MMRV administration.[30, 32-35, 38, 39, 41-44] A 326 subject trial of MMRV found two SAEs, anorexia and ataxia.[40] A 5,833 subject trial of ProQuad recorded six SAEs of fever, febrile seizure, cough and bronchiolitis.[37] In another moderately sized trial (3,927 subjects) one SAE, severe fever, was observed in the MMRV group.[36] Eight SAEs possibly related to MMRV vaccination were observed in a 3,388 subject

trial, including pyrexia, pneumonia, loss of consciousness, acute tonsillitis, gastroenteritis, viral infection, asthma and rash.[54]

Nine clinical trials studying concomitant administration of MMRV with other childhood vaccines (range of subjects from 294 to 1,915) found no SAEs.[45-53] Administration with DTP-IPV or DTPa-HBV-IPV/Hib or DTaP+Hib/HepB was found to be safe.[45, 49, 51, 53] Concomitant administration with MenACWY-CRM at 12 months of age was safe.[46] The same is true for concomitant administration of MMRV with ACWY-TT conjugate vaccine.[50] MMRV given concomitantly with PCV-7 or 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) both showed uncompromised safety profiles.[47, 51] MMRV given with hepatitis A vaccine was well tolerated.[55] Concomitant administration of MMRV with 4CMenB was associated with increased reactogenicity (higher rates of fever with 4CMenB dose).[47, 56]

3.4. Risk of febrile seizures

Clinical trials of MMRV of a range of sizes have reported febrile seizures. In a trial of 503 subjects two febrile seizures were reported, though multiple vaccines were given.[16, 57] A 300 subject trial comparing MMV to MMR+V reported one febrile seizure in the MMRV group.[32] A trial of 494 subjects reported one febrile convulsion in the MMRV group.[33] A 970 subject trial of MMRV reported one febrile convulsion.[43] A larger trial of 3,927 subjects reported four febrile seizures in the MMRV group, compared to one in the control group.[36] A second larger trial (3,388 subjects) reported eight vaccine related febrile seizures.[54]

Review of MMRV safety indicated that the risk of febrile seizures for children 12-23 months receiving MMRV vaccine was 7-9 per 10,000 children, compared to 3-4 per 10,000 for the children receiving separate MMR and varicella vaccines. This risk peaked 5 to 12 days after vaccination.[4, 58-61] A retrospective cohort study assessed the relative risk 5 to 12 days after vaccination to be significantly higher for MMRV recipients (2.20 (95% CI, 1.04-4.65)). This risk was no longer elevated 30 days post immunization (RR=1.10, 95% CI=0.72-1.69).[59] Additionally, it was reported from post marketing surveillance and a large retrospective cohort that there was no increased risk for children 4-6 years old receiving MMRV.[58, 61] The relative risk of febrile seizures after vaccination with MMRV compared to MMR+V was 1.96 (95% CI: 1.43–2.73) for children 12-23 months. This increased risk amounts to one additional febrile seizures for every 2,300 doses of MMRV.[60]

3.5. Safety of varicella vaccine in Immunocompromised

Only small scale trials have been conducted to study the safety of varicella vaccination for immunocompromised individuals. Multiple studies have been conducted with cancer patients, particularly children with leukemia. A trial of 548 subjects found a significantly increased incidence of adverse events in the six weeks following varicella vaccination in children with leukemia compared to healthy children. Of children with leukemia receiving chemotherapy, 50% developed a rash, compared to only 5% of children no longer receiving chemotherapy.[62] In another study of 437 subjects 40% of vaccinated children in remission from leukemia developed a rash, almost exclusively following the first dose of varicella vaccine.[63] Among 29 children in remission for various cancers there were no SAEs,

though some children experienced mild to moderate rash following vaccination.[64] In a very small study of 17 children with cancer there were no local injection site reactions or SAEs. One child had a fever with generalized skin lesions.[65] In a second small study of 19 pediatric leukemic or non-Hodgkin lymphoma patients rash occurred in seven of the children following vaccination.[66] Researchers have published recommendations for use of varicella vaccine in pediatric leukemia patients who are in remission or during an interrupted period of maintenance chemotherapy.[63, 64, 67]

Many studies have been conducted on varicella vaccination of pediatric HIV patients. In a study of only ten HIV + children with category 1 or 2 immunosuppression (mild or moderate immunosuppression)[3], three had low grade fever following immunization, no SAEs were reported.[68] Another small study (15 HIV+ children with lymphocyte count above 700 cells/µl) found no clinical symptoms or SAEs following vaccination.[69] Two injection site reactions and no SAEs were observed in a study of 46 HIV+ children ($CD4^+$ 15-25%) with previous varicella.[70] A 112 subject study (category 1 and 2 immunosupression[3]) found low rates of injection site reactions (6-21%) and systemic adverse events (12-28%) following the first dose and one possibly vaccine related febrile seizure.[71] No SAEs were observed in a 60 subject study of HIV+ children (CD4 T lymphocyte >=15% or >=200 cell/mm^3) in which 15% had local reactions, 5% had systemic reactions and 5% had fever after the first dose.[72]

One of the other major groups of immunosuppressed patients to be evaluated for the safety of varicella vaccine is transplant recipients. A Cochrane review of eight clinical trials and a total of 305 adult stem cell transplant recipients vaccinated local AEs were frequent but overall the vaccine was safe.[73] In a randomized clinical trial 59 hematopoietic-cell transplants recipients received varicella vaccine and AEs were observed in 10%.[74] Three mild-moderate AEs and no SAEs were observed among 68 pediatric recipients of hematopoietic stem cell transplants.[75] Varicella vaccination was also shown to be safe for bone marrow transplant recipients in a study where 36 patients received a three dose regimen with no SAEs.[76] For organ transplants (kidney, liver and intestine have been studied) varicella vaccination was safe.[77-79] No SAEs were observed in a review of six studies and two case reports (a total of 179 doses).[77] A study of 77 pediatric liver transplant recipients reported localized AEs in 54.8%, systemic AEs in 64.5% with a decrease in the rate of AEs following the second and third doses.[78] Sixteen pediatric liver and intestine transplant recipients were studied and 31% developed mild local AEs, 25% fever, and 25% non-injection site rashes following vaccination with Varivax.[79]

The safety of varicella vaccine in pediatric and juvenile patients with chronic autoimmune diseases has also been demonstrated. Use of varicella vaccine has been shown to be safe in 54 children and adolescents with systemic lupus erythematous (Barbosa).[80] No SAEs were observed among 50 children with chronic renal failure.[81] No local reactions, no vaccine related SAEs and four reports of fever and respiratory symptoms were observed among 29 children with chronic liver disease.[82] A clinical trial of 133 children with atopic dermatitis observed local symptoms in 17.1%, fever in 10.3%, exanthema in 16.2% and no SAEs.[83] No SAEs were observed among 25 patients with juvenile rheumatic diseases.[84]

[3]1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age. *MMWR,* 43(12):1-10 http://wonder.cdc.gov/wonder/help/AIDS/MMWR-09-30-1994.html

4. Discussion

This review of RCTs, observational studies and post-licensure safety of varicella vaccine identified no increased incidence of serious adverse events following immunization. Combined measles, mumps, rubella, varicella vaccine (MMRV) compared to MMR only or MMR+V demonstrate a higher risk of adverse events and serious adverse events. In addition, a higher risk of febrile seizures was identified with use of MMRV vaccine.

These findings are in line with the WHO review of varicella vaccine of the Global Advisory Committee on Vaccine Safety and confirm the safety of currently licensed monovalent varicella vaccines yet underline the risk of febrile seizures after vaccination among children aged 12–23 months receiving MMRV vaccination, compared with children receiving separate MMR and varicella vaccination.

5. References

1. Galea SA, Sweet A, Beninger P et al. The Safety Profile of Varicella Vaccine: A 10-Year Review. Journal of Infectious Diseases 2008;197(Supplement 2):S165-S169.
2. Marin M, Meissner HC, Seward JF. Varicella Prevention in the United States: A Review of Successes and Challenges. Pediatrics 2008;122(3):e744-e751.
3. Czajka H, Schuster V, Zepp F, Esposito S, Douha M, Willems P. A combined measles, mumps, rubella and varicella vaccine (Priorix-TetraGäó): Immunogenicity and safety profile. Vaccine 2009;27(47):6504-6511.
4. Hamlin J, Senthilnathan S, Bernstein HH. Update on universal childhood immunizations. Current Opinion in Pediatrics 2008;20(4).
5. Sartori AMC. A review of the varicella vaccine in immunocompromised individuals. International Journal of Infectious Diseases 2004;8(5):259-270.
6. Dennehy PH, Reisinger KS, Blatter MM, Veloudis BA. Immunogenicity of Subcutaneous Versus Intramuscular Oka/Merck Varicella Vaccination in Healthy Children. Pediatrics 1991;88(3):604.
7. Krause PR, Klinman DM. Efficacy, immunogenicity, safety, and use of live attenuated chickenpox vaccine. The Journal of Pediatrics 1995;127(4):518-525.
8. Ferrera G, Gajdos V, Thomas Sp, Tran Cm, Fiquet A. Safety of a refrigerator-stable varicella vaccine (VARIVAX-«) in healthy 12- to 15-month-old children: a randomized, double-blind, cross-over study. Human Vaccines 2009;5(7):455-460.
9. Kanra G, Ceyhan M, Ozmert E. Safety and immunogenicity of live attenuated varicella vaccine in 9-month-old children. Pediatrics International 2000;42(6):674-677.
10. Ozaki T, Nishimura N, Kajita Y. Experience with live attenuated varicella vaccine (Oka strain) in healthy Japanese subjects; 10-year survey at pediatric clinic. Vaccine 2000;18(22):2375-2380.
11. Ramkissoon A et al. Immunogenicity and safety of a live attenuated varicella vaccine in healthy Indian children aged 9-24 months. South African Medical Journal 1995;85(12):1295-1298.
12. Fridman D, Monti A, Bonnet MC, Armoni J, Stamboulian D. Safety of a second dose of varicella vaccine administered at 4 to 6 years of age in healthy children in Argentina. Human Vaccines 2011;7(10):1066-1071.
13. Hadinegoro SRH, Hindra IS, Han HH, Gatchalian S, Bock HL. Reactogenicity and immunogenicity of a live-attenuated refrigerator-stable varicella vaccine (oka strain) in healthy seronegative subjects age

10 months to 12 years. Southeast Asian Journal of Tropical Medicine and Public Health 2009;40(5):991-999.
14. Klein NP, Weston WM, Kuriyakose S et al. An open-label, randomized, multi-center study of the immunogenicity and safety of DTaPGÇôIPV (Kinrix) co-administered with MMR vaccine with or without varicella vaccine in healthy pre-school age children. Vaccine 2012;30(3):668-674.
15. Lau YL, Vessey SJR, Chan ISF et al. A comparison of safety, tolerability and immunogenicity of Oka/Merck varicella vaccine and VARILRIX in healthy children. Vaccine 2002;20(23GÇô24):2942-2949.
16. Parment PA, Svahn A, Rud+¬n U et al. Immunogenicity and Reactogenicity of a Single Dose of Live Attenuated Varicella Vaccine and a Booster Dose of Measles-Mumps-Rubella Vaccine Given Concomitantly at 12 years of Age. Scandinavian Journal of Infectious Diseases 2003;35(10):736.
17. SHINEFIELD HR, Black SB, Staehle BO et al. Vaccination with measles, mumps and rubella vaccine and varicella vaccine: safety, tolerability, immunogenicity, persistence of antibody and duration of protection against varicella in healthy children. The Pediatric Infectious Disease Journal 2002;21(6).
18. Watson B, Rothstein E, Bernstein H et al. Safety and Cellular and Humoral Immune Responses of a Booster Dose of Varicella Vaccine 6 Years after Primary Immunization. The Journal of Infectious Diseases 1995;172(1):217-219.
19. Meurice F, Bouver JLD, Vandevoorde D, Woods S, Bogaerts H. Immunogenicity And Safety Of A Live Attenuated Varicella Vaccine (Oka/Sb Bio) In Healthy Children. Journal of Infectious Diseases 1996;174(Supplement 3):S324-S329.
20. NGAI AL, Staehle BO, Kuter BJ et al. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. The Pediatric Infectious Disease Journal 1996;15(1).
21. Donahue JG, Kieke BA, Yih WK et al. Varicella Vaccination and Ischemic Stroke in Children: Is There an Association? Pediatrics 2009;123(2):e228-e234.
22. Black SB, Cimino CO, Hansen J et al. Immunogenicity and Safety of Measles-Mumps-Rubella, Varicella and Haemophilus influenzae Type b Vaccines Administered Concurrently With a Fourth Dose of Heptavalent Pneumococcal Conjugate Vaccine Compared With the Vaccines Administered Without Heptavalent Pneumococcal Conjugate Vaccine. The Pediatric Infectious Disease Journal 2006;25(4).
23. Chaves SS, Haber P, Walton K et al. Safety of Varicella Vaccine after Licensure in the United States: Experience from Reports to the Vaccine Adverse Event Reporting System, 1995GÇô2005. Journal of Infectious Diseases 2008;197(Supplement 2):S170-S177.
24. Goulleret N, Mauvisseau E, Essevaz-Roulet M+, Quinlivan M, Breuer J. Safety profile of live varicella virus vaccine (Oka/Merck): Five-year results of the European Varicella Zoster Virus Identification Program (EU VZVIP). Vaccine 2010;28(36):5878-5882.
25. Bryant KA, McVernon J, Marchant CD et al. Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: A pooled analysis of randomized trials. Human Vaccines & Immunotherapeutics 2012;8(8):1036-1041.
26. Gatchalian S, Tabora C, Bermal N, Leboulleux D, Desauziers E. Immunogenicity and safety of a varicella vaccine (okavax) and a trivalent measles, mumps, and rubella vaccine (trimovax) administered concomitantly in healthy Filipino children 12gçô24 months old. The American Journal of Tropical Medicine and Hygiene 2004;70(3):273-277.
27. Hesley TM, Reisinger KS, Sullivan BJ et al. Concomitant administration of a bivalent Haemophilus influenzae type b-hepatitis B vaccine, measles-mumps-rubella vaccine and varicella vaccine: safety, tolerability and immunogenicity. The Pediatric Infectious Disease Journal 2004;23(3).
28. Nolan T, Bernstein DI, Block SL et al. Safety and Immunogenicity of Concurrent Administration of Live Attenuated Influenza Vaccine With Measles-Mumps-Rubella and Varicella Vaccines to Infants 12 to 15 Months of Age. Pediatrics 2008;121(3):508-516.

29. Shinefield HR, Black SB, Staehle BO et al. Safety, tolerability and immunogenicity of concomitant injections in separate locations of M-M-R II, VARIVAX and TETRAMUNE in healthy children vs. concomitant injections of M-M-R II and TETRAMUNE followed six weeks later by VARIVAX. The Pediatric Infectious Disease Journal 1998;17(11).
30. Halperin SA, Ferrera G, Scheifele D et al. Safety and immunogenicity of a measles-mumps-rubella-varicella vaccine given as a second dose in children up to six years of age. Vaccine 2009;27(20):2701-2706.
31. Watson BM, Laufer DS, Kuter BJ, Staehle B, White CJ. Safety and Immunogenicity of a Combined Live Attenuated Measles, Mumps, Rubella, and Varicella Vaccine (MMRIIV) in Healthy Children. Journal of Infectious Diseases 1996;173(3):731-734.
32. Goh P, Lim FS, Han HH, Willems P. Safety and Immunogenicity of Early Vaccination with Two Doses of Tetravalent Measles-Mumps-Rubella-Varicella (MMRV) Vaccine in Healthy Children from 9 Months of Age. Infection 2007;35(5):326-333.
33. Knuf MM, Habermehl PM, Zepp FM et al. Immunogenicity and Safety of Two Doses of Tetravalent Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children. The Pediatric Infectious Disease Journal 2006;25(1):12-18.
34. Shinefield H, Black S, Digilio L et al. Evaluation of a Quadrivalent Measles, Mumps, Rubella and Varicella Vaccine in Healthy Children. The Pediatric Infectious Disease Journal 2005;24(8).
35. Nolan T, McIntyre P, Roberton D, Descamps D. Reactogenicity and immunogenicity of a live attenuated tetravalent measles-mumps-rubella-varicella (MMRV) vaccine. Vaccine 2002;21(3-4):281-289.
36. Lieberman JMM, et al. The Safety and Immunogenicity of a Quadrivalent Measles, Mumps, Rubella and Varicella Vaccine in Healthy Children: A Study of Manufacturing Consistency and Persistence of Antibody. The Pediatric Infectious Disease Journal 2006;615-622.
37. Kuter BJ, Hoffman Brown ML, Hartzel J et al. Safety and Immunogenicity of a Combination: Measles, Mumps, Rubella and Varicella Vaccine (ProQuad). Vaccines 2006;2(5):205-214.
38. Gillet Y, Steri GC, Behre U et al. Immunogenicity and safety of measles-mumps-rubella-varicella (MMRV) vaccine followed by one dose of varicella vaccine in children aged 15 months -2 years or 2-6 years primed with measles-mumps-rubella (MMR) vaccine. Vaccine 2009;27(3):446-453.
39. Vesikari TM, Baer MM, Willems PM. Immunogenicity and Safety of a Second Dose of Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children Aged 5 to 6 Years. The Pediatric Infectious Disease Journal 2007;26(2):153-158.
40. Knuf M, Zepp F, Meyer C et al. Safety, immunogenicity and immediate pain of intramuscular versus subcutaneous administration of a measles-mumps-rubella-varicella vaccine to children aged 11-21 months. Eur J Pediatr 2010;169(8):925-933.
41. Reisinger KS, Hoffman Brown ML, Xu J et al. A Combination Measles, Mumps, Rubella, and Varicella Vaccine (ProQuad) Given to 4- to 6-Year-Old Healthy Children Vaccinated Previously With M-M-RII and Varivax. Pediatrics 2006;117(2):265-272.
42. Rumke HC, Loch HP, Hoppenbrouwers K et al. Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. Vaccine 2011;29(22):3842-3849.
43. Schuster VM, Otto WM, Maurer LM et al. Immunogenicity and Safety Assessments After One and Two Doses of a Refrigerator-Stable Tetravalent Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children During the Second Year of Life. The Pediatric Infectious Disease Journal 2008;27(8):724-730.
44. Vesikari T, Becker T, Gajdos V et al. Immunogenicity and safety of a two-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad) in infants from 9 months of age. Vaccine 2012;30(20):3082-3089.

45. Ferrera G et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: A randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. Human Vaccines & Immunotherapeutics 2012;8:355-362.
46. Klein NP, Shepard J, Bedell L, Odrljin T, Dull P. Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in healthy toddlers. Vaccine 2012;30(26):3929-3936.
47. Leonardi M, Bromberg K, Baxter R et al. Immunogenicity and Safety of MMRV and PCV-7 Administered Concomitantly in Healthy Children. Pediatrics 2011;128(6):e1387-e1394.
48. Reuman P, Sawyer M, Kuter B, Matthews H, The MMRV Study Group. Safety and immunogenicity of concurrent administration of measles-mumps-rubellavaricella vaccine and PedvaxHIB® vaccines in healthy children twelve to eighteen months old. The Pediatric Infectious Disease Journal 1997;16(7):662-667.
49. Shinefield HM, et al. Safety and Immunogenicity of a Measles, Mumps, Rubella and Varicella Vaccine Given With Combined Haemophilus influenzae Type b Conjugate/Hepatitis B Vaccines and Combined Diphtheria-Tetanus-Acellular Pertussis Vaccines. The Pediatric Infectious Disease Journal 2006;25(4):287-292.
50. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. Vaccine 2011;29(25):4274-4284.
51. Vesikari TM, Karvonen AM, Lindblad NM et al. Safety and Immunogenicity of a Booster Dose of the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D Conjugate Vaccine Coadministered With Measles-Mumps-Rubella-Varicella Vaccine in Children Aged 12 to 16 Months. The Pediatric Infectious Disease Journal 2010;29(6):47-56.
52. White CJ, Stinson D, Staehle B et al. Measles, Mumps, Rubella, and Varicella Combination Vaccine: Safety and Immunogenicity Alone and in Combination with Other Vaccines Given to Children. Clinical Infectious Diseases 1997;24(5):925-931.
53. Zepp F, Behre U, Kindler K et al. Immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine co-administered with a booster dose of a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine in healthy children aged 12-23 months. Eur J Pediatr 2007;166(8):857-864.
54. Rüger G et al. Safety of a 2-dose regimen of a combined measles, mumps, rubella and varicella live vaccine manufactured with recombinant human albumin. Pediatr Infect Dis J 12 A.D.;31(11):1166-1172.
55. Rinderknecht S et al. Immunogenicity and safety of an inactivated hepatitis A vaccine when coadministered with measles-mumps-rubella and varicella vaccines in children less than 2 years of age. Pediatr Infect Dis J 2011;179-185.
56. Vesikari T, Esposito S, Prymula R et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. The Lancet 2009;381(9869):825-835.
57. Guerra FA, Gress J, Werzberger A et al. Safety, Tolerability and Immunogenicity of VAQTA Given Concomitantly versus Nonconcomitantly With Other Pediatric Vaccines in Healthy 12-Month-Old Children. The Pediatric Infectious Disease Journal 2006;25(10).
58. Committee on Infectious Diseases. Prevention of Varicella: Update of Recommendations for Use of Quadrivalent and Monovalent Varicella Vaccines in Children. Pediatrics 2011;128(3):630-632.

59. Jacobsen SJ, Ackerson BK, Sy LS et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009;27(34):4656-4661.
60. Klein NP, Fireman B, Yih WK et al. Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures. Pediatrics 2010;126(1):e1-e8.
61. Klein NP, Lewis E, Baxter R et al. Measles-Containing Vaccines and Febrile Seizures in Children Age 4 to 6 Years. Pediatrics 2012;129(5):809-814.
62. Breuer J. Vaccination to prevent varicella and shingles. J Clin Pathol 2001;54(10):743-747.
63. Gershon AA, Steinberg SP. Persistence of Immunity to Varicella in Children with Leukemia Immunized with Live Attenuated Varicella Vaccine. N Engl J Med 1989;320(14):892-897.
64. Ecevit Z, Kanra G+, Sevinir B, Ueda S. Oka Strain Live Varicella Vaccine in Children With Cancer. The Pediatric Infectious Disease Journal 1996;15(2).
65. Leung TF, Li CK, Hung ECW et al. Immunogenicity of a two-dose regime of varicella vaccine in children with cancers. European Journal of Haematology 2004;72(5):353-357.
66. Yeung CY. Varicella Vaccine in Children with Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma. Pediatr Hematol Oncol 1992;9(1):29-34.
67. Gershon AA, LaRussa P, Steinberg S. CLINICAL TRIALS IN IMMUNOCOMPROMISED INDIVIDUALS. Infectious Disease Clinics of North America 1996;10(3):583-594.
68. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and Immunogenicity of Live Varicella Virus Vaccine in Children With Human Immunodeficiency Virus Type 1. The Pediatric Infectious Disease Journal 2006;25(4).
69. Bekker V, Westerlaken GH, Scherpbier Ht et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. AIDS 2006;20(18).
70. Gershon AA, Levin MJ, Weinberg A et al. A Phase I-II Study of Live Attenuated Varicella-Zoster Virus Vaccine to Boost Immunity in Human Immunodeficiency Virus-Infected Children With Previous Varicella. The Pediatric Infectious Disease Journal 2009;28(7).
71. Levin MJ, Gershon AA, Weinberg A, Song LY, Fentin T, Pediatric AIDS Clinical Trials Group. Administration of Live Varicella Vaccine to HIV-Infected Children with Current or Past Significant Depression of CD4+ T Cells. Journal of Infectious Diseases 2006;194(2):247-255.
72. Taweesith W, Puthanakit T, Kowitdamrong E et al. The Immunogenicity and Safety of Live Attenuated Varicella-zoster Virus Vaccine in Human Immunodeficiency Virus-infected Children. The Pediatric Infectious Disease Journal 2011;30(4).
73. Cheuk DKL CALTCGHS. Vaccines for prophylaxis of viral infections in patients with hematological malignancies. Cochrane Database of Systematic Reviews 2011;(3).
74. Hata A, Asanuma H, Rinki M et al. Use of an Inactivated Varicella Vaccine in Recipients of Hematopoietic-Cell Transplants. N Engl J Med 2002;347(1):26-34.
75. Kussmaul SC, Horn BN, Dvorak CC, Abramovitz L, Cowan MJ, Weintrub PS. Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. Bone Marrow Transplant 2010;45(11):1602-1606.
76. Redman RL, Nader S, Zerboni L et al. Early Reconstitution of Immunity and Decreased Severity of Herpes Zoster in Bone Marrow Transplant Recipients Immunized with Inactivated Varicella Vaccine. Journal of Infectious Diseases 1997;176(3):578-585.
77. Danerseau A, Robinson J. Efficacy and safety of measles, mumps, rubella and varicella live viral vaccines in transplant recipients receiving immunosuppressive drugs. World J Pediatr 2008;4(4):254-258.
78. Posfay-Barbe KM, Pittet LF, Sottas C et al. Varicella-Zoster Immunization in Pediatric Liver Transplant Recipients: Safe and Immunogenic. American Journal of Transplantation 2012;12(11):2974-2985.

79. Weinberg A, Horslen SP, Kaufman SS et al. Safety and Immunogenicity of Varicella-Zoster Virus Vaccine in Pediatric Liver and Intestine Transplant Recipients. American Journal of Transplantation 2006;6(3):565-568.
80. Barbosa CM, Terreri MT, Ros+írio PO, de Moraes-Pinto MI, Silva CA, Hil+írio MO. Immune response and tolerability of varicella vaccine in children and adolescents with systemic lupus erythematosus previously exposed to varicella-zoster virus. Clin Exp Rheumatol 2012;30(5):791-798.
81. Furth S, Hogg R, Tarver J, Moulton L, Chan C, Fivush B. Varicella vaccination in children with chronic renal failure. Pediatr Nephrol 2003;18(1):33-38.
82. Nithichaiyo C, Chongsrisawat V, Hutagalung Y, Bock HL, Poovorawan Y. Immunogenicity and Adverse Effects of Live Attenuated Varicella Vaccine (Oka Strain) in Children with Chronic Liver Disease. Asian Pacific Journal of Allergy and Immunology 2001;19:101-105.
83. Kienast AK, Kreth HW, H+¦ger PH. Varicella vaccination in children with atopic eczema. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2007;5(10):875-880.
84. Pileggi GS, de Souza CBS, Ferriani VnPL. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res 2010;62(7):1034-1039.

6. Appendix

6.1. Search terms used in PubMed

All searched completed with filters for publications on humans and in English only

1. Safety of Varicella vaccine
    a. Search terms: ("Chickenpox Vaccine"[Mesh] OR “Chickenpox Vaccine”[tiab] OR “Chickenpox Vaccines”[tiab] OR “Varicella Vaccine”[tiab] OR "measles, mumps, rubella, varicella vaccine" [Supplementary Concept]) AND (safety[tiab] OR “adverse events” [tiab] OR “adverse event” [tiab] OR "drug toxicity"[MeSH Terms] OR SEA[tiab] OR AE[tiab] or AEFI[tiab] OR "drug toxicity"[MeSH Terms]) NOT "Herpes Zoster Vaccine"[Mesh] NOT "Immunocompromised Host"[Mesh]
    b. No. of results: 169

2. Safety of MMRV
    a. Search terms: ("measles, mumps, rubella, varicella vaccine" [Supplementary Concept] OR "Priorix-Tetra vaccine" [Supplementary Concept] OR ProQuad[tiab] OR MMRV[tiab]) AND (safety[tiab] OR “adverse events” [tiab] OR “adverse event” [tiab] OR SEA[tiab] OR AE[tiab] or AEFI[tiab] OR "drug toxicity"[MeSH Terms]) NOT "Herpes Zoster Vaccine"[Mesh] NOT "Immunocompromised Host"[Mesh]
    b. No. of results: 39

3. Risk of febrile seizures
    a. Search terms: ("Chickenpox Vaccine"[Mesh] OR “Chickenpox Vaccine”[tiab] OR “Chickenpox Vaccines”[tiab] OR “Varicella Vaccine”[tiab] OR "measles, mumps, rubella,

varicella vaccine" [Supplementary Concept] OR "Priorix-Tetra vaccine" [Supplementary Concept] OR ProQuad[tiab] OR MMRV[tiab] OR “MMR+V”[tiab] OR "herpesvirus 3, human"[MeSH Terms]) AND "Seizures, Febrile"[Mesh]

b. No. of results: 7

4. Safety of varicella vaccine in immunocompromised:
    a. Search terms: (("Chickenpox Vaccine"[Mesh] OR “Chickenpox Vaccine”[tiab] OR “Chickenpox Vaccines”[tiab] OR “Varicella Vaccine”[tiab] OR "measles, mumps, rubella, varicella vaccine" [Supplementary Concept]) OR ("measles, mumps, rubella, varicella vaccine" [Supplementary Concept] OR "Priorix-Tetra vaccine" [Supplementary Concept] OR ProQuad[tiab] OR MMRV[tiab])) AND (safety[tiab] OR “adverse events” [tiab] OR “adverse event” [tiab] OR "drug toxicity"[MeSH Terms] OR SEA[tiab] OR AE[tiab] or AEFI[tiab]) AND ("Immunocompromised Host"[Mesh] or Immunocompromised)
    b. No. of results: 28

6.2. List of Reviews Not Included

Safety of Varicella Vaccine

Author	Title	Date	Journal
-	American Academy of Pediatrics. Committee on Infectious Diseases. Varicella vaccine update.	2000 Jan	Pediatrics
Sharrar RG	The postmarketing safety profile of varicella vaccine.	2000 Nov 22	Vaccine
White CJ	Clinical trials of varicella vaccine in healthy children.	1996 Sep	Infect Dis Clin North Am.

Safety in Immunocompromised

Author	Title	Date	Journal
Sparks L	The new varicella vaccine: efficacy, safety, and administration.	1998 Apr	J Pediatr Nurs