

Herpes Zoster and Postherpetic Neuralgia: Prevention and Management

JULIA FASHNER, MD, *Saint Joseph Family Medicine Residency Program, South Bend, Indiana*

AMANDA L. BELL, MD, *Wright State University Boonshoft School of Medicine, Dayton, Ohio*

Herpes zoster (shingles) is diagnosed clinically by recognition of the distinctive, painful vesicular rash appearing in a unilateral, dermatomal distribution. An estimated 1 million cases occur in the United States each year, and increasing age is the primary risk factor. Laboratory testing, including polymerase chain reaction, can confirm atypical cases. Treatment with acyclovir, famciclovir, or valacyclovir decreases the duration of the rash. Adjunct medications, including opioid analgesics, tricyclic antidepressants, or corticosteroids, may relieve the pain associated with acute herpes zoster. There is conflicting evidence that antiviral therapy during the acute phase prevents postherpetic neuralgia. Postherpetic neuralgia in the cutaneous nerve distribution may last from 30 days to more than six months after the lesions have healed. Evidence supports treating postherpetic neuralgia with tricyclic antidepressants, gabapentin, pregabalin, long-acting opioids, or tramadol; moderate evidence supports the use of capsaicin cream or a lidocaine patch as a second-line agent. Immunization to prevent herpes zoster and postherpetic neuralgia is recommended for most adults 60 years and older. (*Am Fam Physician.* 2011;83(12):1432-1437. Copyright © 2011 American Academy of Family Physicians.)

► Patient information:

A handout on shingles, written by the authors of this article, is provided on page 1438.

Herpes zoster (shingles) presents as a painful vesicular rash and is caused by reactivation of the varicella-zoster virus within the dorsal root or cranial nerve ganglia. Approximately 1 million cases occur in the United States each year,¹ with an incidence of 3.2 cases per 1,000 person-years.² Increasing age is the primary risk factor for herpes zoster. The disease usually occurs between 50 and 79 years of age, and approximately 60 percent of cases occur in women.² Other risk factors include human immunodeficiency virus infection, neoplastic diseases, organ transplantation, use of immunosuppressive drugs, and other conditions that cause a decline in cell-mediated immunity.³

Clinical Presentation

Prodromal symptoms include malaise, headache, photophobia, abnormal skin sensations, and occasionally fever. These symptoms may occur one to five days before the appearance of the rash.⁴ Abnormal skin sensations range from itching and burning to hyperesthesia and severe pain. The intensity of the pain may lead to a misdiagnosis, such as renal colic or myocardial infarction, depending on location.

The rash (*Figure 1*) begins as maculopapular lesions in a unilateral, dermatomal distribution that rarely crosses the midline.



Figure 1. Herpes zoster. (A) The rash begins as maculopapular lesions in a unilateral, dermatomal distribution. (B) The lesions progress to clear vesicles before crusting and healing.

Copyright © Logical Images, Inc.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Antiviral therapy should be initiated within 72 hours of onset of the rash in patients with acute herpes zoster to increase the rate of healing and decrease pain.	A	10-12
Based on individual patient characteristics, a tricyclic antidepressant, tramadol (Ultram), long-acting opioid, or anticonvulsant (i.e., gabapentin [Neurontin] or pregabalin [Lyrica]) should be selected to decrease the pain of postherpetic neuralgia.	A	7, 19-21
If topical therapy is indicated, capsaicin cream (Zostrix) or a lidocaine patch (Lidoderm) may decrease pain in patients with postherpetic neuralgia.	B	7, 19, 20, 22
Herpes zoster vaccine (Zostavax) should be given to most persons 60 years and older to prevent herpes zoster and postherpetic neuralgia.	B	25, 27

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

Lesions progress to clear vesicles that become cloudy within three to five days, then crust and heal within two to four weeks. Scarring and changes in pigmentation may occur. Dermatomes of the back and face are most often affected, although multiple dermatome involvement is possible.

Diagnosis

The diagnosis of herpes zoster is usually clinical, based on recognition of the distinctive presentation and rash. Cases of herpes zoster without a rash (zoster sine herpete) are difficult to diagnose and require laboratory confirmation of varicella-zoster virus reactivation.⁵ Fluid obtained from vesicles may be evaluated with polymerase chain reaction testing, viral culture, or direct immunofluorescent antigen staining.⁶ Table 1 lists the accuracy of diagnostic testing for herpes zoster.⁶

Complications

Postherpetic neuralgia is the most common complication

of herpes zoster. It occurs in approximately 30 percent of patients older than 80 years and in approximately 20 percent of patients 60 to 65 years; it is rare in patients younger than 50 years.⁷ Replication of the varicella-zoster virus in the basal ganglia destroys the nerves, leading to pain in the affected dermatome. Postherpetic pain may take several forms, including allodynia (nonpainful stimulus perceived as painful), hyperpathia (slightly painful stimulus perceived as very painful), and dysesthesia (abnormal sensation with no stimuli).⁸

Women are at greater risk of postherpetic neuralgia. Additional risk factors include older age, moderate to severe rash, moderate to severe acute pain during the rash, ophthalmic involvement, and history of prodromal pain.^{8,9} Postherpetic neuralgia may persist from 30 days to more than six months after the lesions have healed, and most cases resolve spontaneously.⁷

Herpes zoster ophthalmicus (ophthalmic zoster) occurs in 5 to 10 percent of patients with herpes zoster and may lead to permanent vision loss and cranial nerve palsies.⁸ Urgent ophthalmology referral is recommended in these patients. Superimposed bacterial skin infections with streptococci and staphylococci should be treated with appropriate oral antibiotics. Encephalitis, meningitis, myelitis, and disseminated cutaneous and visceral disease may occur in patients with severe immunosuppression.

Management of Acute Herpes Zoster

Antiviral therapy is first-line treatment and should be initiated within 72 hours of rash onset to increase the rate of healing and decrease pain.¹⁰⁻¹² No study has investigated the effectiveness of later initiation of antiviral therapy, but it is believed to benefit patients with active vesicle eruptions.³

Table 1. Diagnostic Testing for Herpes Zoster

<i>Test</i>	<i>Sensitivity (%)</i>	<i>Specificity (%)</i>
Polymerase chain reaction	95	99
Direct immunofluorescent antigen staining	82	76
Virus culture	20	99

NOTE: Diagnosis of herpes zoster is usually clinical, and testing is limited to atypical cases. Tests should evaluate fluid from vesicles.

Information from reference 6.

Herpes Zoster

Acyclovir (Zovirax), famciclovir (Famvir), and valacyclovir (Valtrex) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute herpes zoster. These agents are considered safe and are well tolerated with minimal adverse effects (e.g., headache, nausea). All three drugs are available in a generic form, although acyclovir is significantly less expensive than famciclovir or valacyclovir¹³ (Table 2). These antiviral agents decrease the severity and duration of acute herpes zoster. In one randomized controlled trial, valacyclovir led to complete pain resolution sooner than acyclovir (44 versus 51 days) and required less frequent dosing.¹⁴ Famciclovir has shown similar effectiveness to valacyclovir.¹⁰ Topical antiviral agents are not effective.³

Although antiviral medications slow the production of the virus and decrease the viral load in the dorsal root ganglia, evidence showing that these medications alter the incidence and course of postherpetic neuralgia is inconsistent. Some studies suggest that no antiviral agent prevents postherpetic neuralgia,^{8,15} whereas others report reduced duration of symptoms.^{4,7,16} Famciclovir and valacyclovir are associated with better outcomes than placebo or acyclovir.^{11,14}

Antivirals alone are usually insufficient to relieve the often debilitating pain of acute herpes zoster. Mild to moderate pain may be controlled with acetaminophen or nonsteroidal anti-inflammatory drugs, alone or in combination with a weak opioid or tramadol (Ultram).³ Moderate to severe pain requires scheduled opioids (e.g., oxycodone, morphine).³ The intensity of pain during the acute attack is an important predictor for the development of postherpetic neuralgia, and medications given during this phase may influence the outcome of later interventions for postherpetic neuralgia.¹⁷

If pain does not rapidly respond to opioid analgesics or if opioids are not tolerated, the prompt addition of an adjunctive therapy should be considered.³ Nortriptyline (Pamelor), gabapentin (Neurontin), and pregabalin (Lyrica) have been recommended, but they have not been extensively studied for pain relief in patients with acute herpes zoster.³

The addition of corticosteroids to acyclovir decreases the pain of acute herpes zoster¹⁷ and speeds lesion healing and return to daily activities. Combination therapy with corticosteroids and antivirals should be considered in older patients with no contraindications.¹⁷ Although corticosteroids have anti-inflammatory effects that could be expected to decrease nerve damage and the risk

Table 2. Antiviral Medications for Herpes Zoster

Medication	Dosage	Cost of generic (brand)*
Acyclovir (Zovirax)	800 mg five times daily for seven to 10 days	\$29 to \$41 (\$392 to \$560)
Famciclovir (Famvir)	500 mg three times daily for seven days	\$228 (\$281)
Valacyclovir (Valtrex)	1,000 mg three times daily for seven days	\$221 (\$273)

*—Estimated retail price based on information obtained at <http://www.drugstore.com> (accessed February 16, 2011). Generic price listed first; brand price listed in parentheses.

of postherpetic neuralgia, a Cochrane review found no significant difference between corticosteroids and placebo in preventing postherpetic neuralgia six months after onset of the rash.¹⁸

Management of Postherpetic Neuralgia

Theoretical models suggest that reducing pain during the acute phase of herpes zoster may stop the initiation of the mechanisms that cause chronic pain, thus reducing the risk of postherpetic neuralgia.⁴ If the condition develops, treatment focuses on preventing a chronic pain syndrome. Several medications have proved effective for postherpetic neuralgia (Table 3¹⁹) and should be selected based on individual patient characteristics.^{7,19-22} Many of these medications require dosing adjustment in older patients and in those with reduced creatinine clearance.

Tricyclic antidepressants, such as amitriptyline, desipramine (Norpramin), and nortriptyline, have pain-modulating effects in neuropathic and other chronic pain states. They are the mainstay of treatment for postherpetic neuralgia, and evidence supports their effectiveness.²⁰ In older patients, tricyclic antidepressants should be started at lower doses given at bedtime, and the patient should be monitored for adverse effects, including interactions with other medications.

Opioid medications have analgesic effects and are helpful for postherpetic neuralgia. Studies have shown that patients taking oxycodone, morphine, or methadone have better pain relief than those taking placebo.⁷ Opioids should be carefully adjusted in all patients for clinical response. Oxycodone is of special concern because of a 50 percent higher serum concentration when creatinine clearance is less than 60 mL per minute per 1.73 m² (1.00 mL per second per m²).²³ Morphine and methadone have been shown to provide better pain relief than tricyclic antidepressants.^{7,20} A Cochrane review of seven trials

Table 3. Medications to Treat Postherpetic Neuralgia

Class	Medication	Dosage	Cost of generic (brand)*	NNT	Adverse effects
Anticonvulsants	Gabapentin (Neurontin)	1,800 to 3,600 mg per day	\$93 to \$186 (\$365 to \$729)	2.8-5.3	Somnolence, dizziness, edema, dry mouth
	Pregabalin (Lyrica)	150 to 600 mg per day	NA (\$95 to \$190)	4.9	
Opioids	Controlled-release oxycodone (Oxycontin)	Variable	NA (\$209, 15-mg 12-hour tablets)	2.7	Constipation, nausea, vomiting, sedation, dizziness, dependence
	Long-acting morphine	Variable	\$64 (\$84), 15-mg 12-hour tablets	2.7	
	Tramadol (Ultram)	100 to 400 mg per day	\$34 (\$140), 100 mg per day	4.8	Dependence
Topical agents	Capsaicin 0.075% cream (Zostrix)	Applied three or four times per day	NA (\$19 to \$25, 2 oz)	3.3	Burning skin
	Lidocaine 5% patch (Lidoderm)	Maximum three patches per day	NA (\$217, 30 patches)	2.0	Mild skin reaction
Tricyclic antidepressants	Amitriptyline†	Up to 150 mg per day	\$17 (NA)	2.6	Sedation, dry mouth, blurred vision, constipation, urinary retention
	Desipramine (Norpramin)	Up to 150 mg per day	\$140 (\$180)		
	Nortriptyline (Pamelor)†	Up to 150 mg per day	\$19 (\$1,082)		

NA = not applicable; NNT = number needed to treat.

*—Estimated retail price based on information obtained at <http://www.drugstore.com> (accessed February 16, 2011). Generic price listed first; brand price listed in parentheses.

†—May be available at discounted prices (\$10 or less for one month's treatment) at one or more national retail chains.

Adapted with permission from Garroway N, Chhabra S, Landis S, Skolnik DC. Clinical inquiries: what measures relieve postherpetic neuralgia? *J Fam Pract.* 2009;58(7):384d-f.

found tramadol to be effective for neuropathic pain, including postherpetic neuralgia.²¹

Studies involving anticonvulsants showed that gabapentin and pregabalin reduce pain from postherpetic neuralgia by approximately 50 percent.^{7,19,20} Another study comparing the maximum tolerated dosages of gabapentin and nortriptyline found that both reduced pain scores, but gabapentin was associated with fewer adverse effects.⁷

The FDA has approved two topical medications for treatment of postherpetic neuralgia. A Cochrane review that included a few small studies of topical lidocaine patches (Lidoderm) reported benefit in some patients, but found insufficient evidence to recommend them as first-line therapy.²² Based on poor-quality studies, capsaicin cream (Zostrix), which is derived from peppers, provides limited reduction in postherpetic neuralgia.^{7,19,20} Topical antiviral agents, such as idoxuridine (not available in the United States), may reduce the prevalence of postherpetic neuralgia in immunocompetent patients, but the evidence is low-quality.⁷ Intrathecal preservative-free methylprednisolone (not

available in the United States) is effective for intractable postherpetic neuralgia. However, it should be used only if other agents have been ineffective.²⁰

Other treatments for postherpetic neuralgia have been investigated, but not all are effective. Aspirin cream has been helpful in a few small studies, but the benefit is not considered significant.²⁰ No recommendations can be made for the anticonvulsants valproate (Depakote)¹⁹ and carbamazepine (Tegretol)²⁰ because of limited data. Anesthetic agents such as *N*-methyl-D-aspartate receptor antagonists play a role in processing pain signals and could potentially benefit patients with postherpetic neuralgia. Ketamine (Ketalar), dextromethorphan, and memantine (Namenda) have not been shown to improve pain compared with placebo.²⁰

Prevention

Herpes zoster and postherpetic neuralgia are preventable conditions. The Centers for Disease Control and Prevention recommends one dose of the herpes zoster vaccine (Zostavax) for persons 60 years and older.^{24,25}

Table 4. Special Considerations for Herpes Zoster Virus Vaccination (Zostavax)

<i>Special consideration</i>	<i>Recommendations</i>
Anticipating immunosuppression	Recommended; administer two to four weeks before initiating immunosuppressive therapy
History of herpes zoster	Recommended; administer as soon as rash and pain resolve
Age younger than 60 years	Recently approved by the U.S. Food and Drug Administration for patients 50 to 59 years of age; awaiting recommendation from the Advisory Committee on Immunization Practices
History of varicella vaccination	Not labeled for this indication; however, few adults 40 years and older have received the vaccine
AIDS	Contraindicated, including in persons with clinical manifestations of human immunodeficiency virus or a CD4 cell count of 200 mm ³ (0.20 × 10 ⁹ per L) or less
Anaphylaxis to gelatin or neomycin	Contraindicated; contact dermatitis from neomycin is not a contraindication
Blood cancers	Contraindicated; may vaccinate patients with leukemia if in remission and no chemotherapy or radiation therapy for three months
High-dose steroid therapy (greater than 20 mg per day for at least two weeks)	Contraindicated; defer vaccination for one month after discontinuation of steroid
Pregnancy	Contraindicated

Information from references 9, 24, and 26.

The FDA recently approved the herpes zoster vaccine for healthy patients between 50 and 59 years of age, and the Advisory Committee on Immunization Practices is expected to vote on recommending the vaccine for this population in late 2011.²⁶ Patients may be immunized without serologic testing and regardless of any history of varicella virus infection or herpes zoster.^{24,25} Coadministration with other inactivated vaccines common in this age group is considered safe.²⁴ Special considerations for herpes zoster vaccination are presented in *Table 4*.^{9,24,26}

The Shingles Prevention Study found the herpes zoster vaccine to be 51.3 percent effective in preventing herpes zoster and 66.5 percent effective in preventing postherpetic neuralgia (when defined as pain rated as at least a 3 out of 10 on a severity scale that persisted for at least 90 days after rash onset).²⁷ Vaccination has also been shown to reduce the incidence of postherpetic neuralgia by 39 percent among patients who develop herpes zoster.²⁴ The number needed to treat to prevent one case over three years is 58 for herpes zoster and 364 for postherpetic neuralgia.⁹

Fewer than 10 percent of eligible persons receive the herpes zoster vaccine.²⁸ Patient surveys show that many do not know about it or believe it is not needed.²⁹ Cost is a significant issue with the vaccine. The average wholesale cost of Zostavax is \$194 per dose,¹³ and many insurance

plans do not cover it. Another concern is storage. The vaccine must be frozen, and in-office administration requires a monitored, temperature-controlled freezer. Patients may be referred to a pharmacy for immunization or given a prescription for the vaccine, which must be kept cold and administered within 30 minutes.⁸ Physicians can play a key role in overcoming these barriers and should encourage vaccination to prevent herpes zoster and postherpetic neuralgia.

Data Sources: We received two evidence summaries from *AFP*. The first, PubMed "clinical queries search for herpes+zoster," yielded meta-analyses and systematic reviews. The second, "evidence report for herpes zoster," included InfoPOEMs, Cochrane reviews, and practice guidelines. We also used primeanswers.org to search PubMed for postherpetic neuralgia within ACP Journal Club, Clinical Evidence, Cochrane Database of Systematic Reviews, FPIN Clinical Inquiries, NEJM Clinical Practice, and U.S. Preventive Services Task Force. In addition, we searched Dynamed for herpes zoster and postherpetic neuralgia. Search dates: *AFP*'s searches, May 10, 2010; our searches, May 12, 2010.

The authors thank Emmanuel Evangelista, PharmD candidate, and Sue Rytel, MA, for their assistance in the preparation of the manuscript.

The Authors

JULIA FASHNER, MD, FAAFP, is an associate director at the Saint Joseph Family Medicine Residency Program in South Bend, Ind.

AMANDA L. BELL, MD, is an assistant professor of family medicine at Wright State University Boonshoft School of Medicine in Dayton, Ohio.

Address correspondence to Julia Fashner, MD, FAAFP, Saint Joseph Family Medicine Residency Program, 837 E. Cedar St., Ste. 125, South Bend, IN 46617 (e-mail: fashnerj@sjrhc.com). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. CDC. About shingles (herpes zoster). <http://www.cdc.gov/vaccines/vpd-vac/shingles/dis-faqs.htm>. Accessed July 29, 2010.
2. Insinga RP, Itzler RF, Pellissier JM, et al. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med*. 2005; 20(8):748-753.
3. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44(suppl 1):S1-S26.
4. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med*. 2002;347(5):340-346.
5. Dworkin RH, Gnann JW Jr, Oaklander AL, et al. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain*. 2008;9(1 suppl 1):S37-S44.
6. Sauerbrei A, Eichhorn U, Schacke M, et al. Laboratory diagnosis of herpes zoster. *J Clin Virol*. 1999;14(1):31-36.
7. Watson P. Postherpetic neuralgia (updated). *Clin Evid (Online)*. October 8, 2010. <http://clinicalevidence.bmj.com/ceweb/conditions/ind/0905/0905.jsp>. Accessed February 7, 2011.
8. High KP. Preventing herpes zoster and postherpetic neuralgia through vaccination. *J Fam Pract*. 2007;56(10 suppl A):51A-57A.
9. Lang PO, Hasso Y, Michel JP. Stop shingles in its tracks. *J Fam Pract*. 2009;58(10):531-534.
10. Tyring SK, Beutner KR, Tucker BA, et al. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med*. 2000;9(9):863-869.
11. Tyring S, Barbarash RA, Nahlik JE, et al.; Collaborative Famciclovir Herpes Zoster Study Group. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. *Ann Intern Med*. 1995;123(2):89-96.
12. Wood MJ, Kay R, Dworkin RH, et al. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis*. 1996;22(2):341-347.
13. *Red Book*. Montvale, N.J.: Medical Economics Data; 2010.
14. Beutner KR, Friedman DJ, Forszpaniak C, et al. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother*. 1995;39(7):1546-1553.
15. Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2009;(2):CD006866.
16. Alper BS, Lewis PR. Does treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? *J Fam Pract*. 2000;49(3):255-264.
17. Wareham DW, Breuer J. Herpes zoster. *BMJ*. 2007;334(7605):1211-1215.
18. Chen N, Yang M, He L, et al. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2010;(12):CD005582.
19. Garroway N, Chhabra S, Landis S, Skolnik DC. Clinical inquiries: what measures relieve postherpetic neuralgia? *J Fam Pract*. 2009;58(7):384d-f.
20. Dubinsky RM, Kabbani H, El-Chami Z, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;63(6):959-965.
21. Hollingshead J, Dühmke RM, Cornblath DR. Tramadol for neuropathic pain. *Cochrane Database Syst Rev*. 2006;3:CD003726.
22. Khaliq W, Alam S, Puri N. Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database Syst Rev*. 2007;(2):CD004846.
23. Gold standard/Elsevier. Clinical pharmacology. Oxycodone. <http://www.clinicalpharmacology.com/Forms/drugoptions.aspx?cpnum=457&n=Oxycodone> (subscription required). Accessed November 12, 2010.
24. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1-30.
25. CDC. Adult immunization schedule. Immunization recommendations, United States—2011. <http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm>. Accessed February 5, 2011.
26. FDA approves Zostavax vaccine to prevent shingles in individuals 50 to 59 years of age. U.S. Food and Drug Administration; March 24, 2011. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm248390.htm>. Accessed April 5, 2011.
27. Oxman MN, Levin MJ, Johnson GR, et al.; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352(22):2271-2284.
28. Hurlley LP, Lindley MC, Harpaz R, et al. Barriers to the use of herpes zoster vaccine. *Ann Intern Med*. 2010;152(9):555-560.
29. Lu PJ, Euler GL, Jumaan AO, et al. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007. *Vaccine*. 2009;27(6):882-887.