Vaccines for preventing herpes zoster in older adults

Update of 2012 Cochrane Systematic Review

Report for WHO, December 2013

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List of abbreviations

AE: adverse event

D: days

HZ: herpes zoster

IM: intramuscular

ITT: intention-to-treat

Mo: months

N: number

pfu: plaque-forming units

SAE: serious adverse event

SC: subcutaneous

SPS: Shingles Prevention Study

STPS: Short-Term Persistence Study.

vs: versus

VZV: varicella-zoster virus

y: year

ZV: zoster vaccine

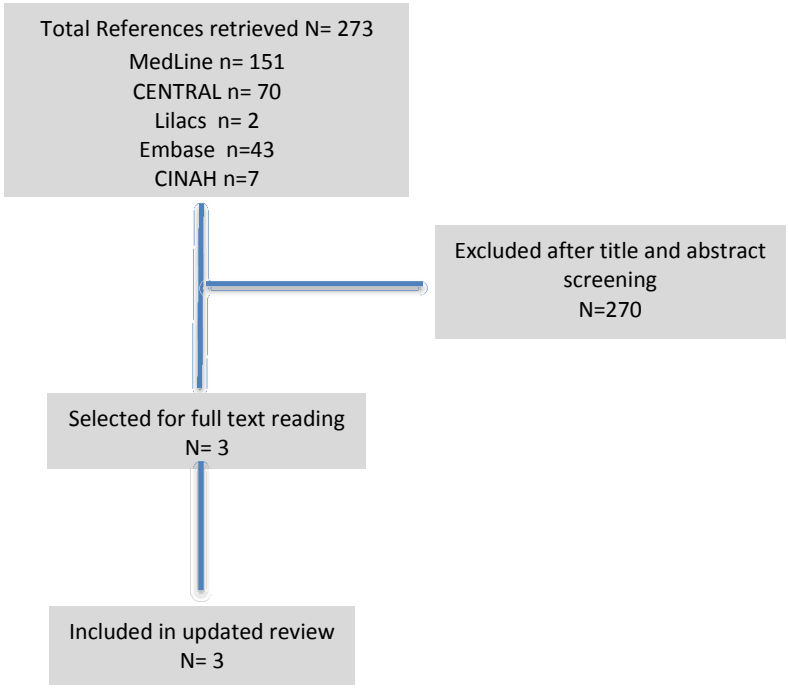
List of Figures

Contents

1. Identification and selection of new studies

We reran the original search strategy (available in Gagliardi et al., 2012) from 01/01/2012 to 08/31/2013 on the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) www.thecochranelibrary.com MEDLINE, EMBASE, LILACS and CINAHL. A total of 273 references were retrieved. After excluding duplicates, two independent reviewers (AG, BNGA) screened titles and abstracts for new, potentially relevant trials and selected 3 citations for full text reading (Leroux-Roels et al., 2012; Schmader et al., 2012 and Vesikari et al., 2013). Since the three studies fulfilled the previously described selection criteria (Gagliardi et al., 2012), they were included in the updated version of this review (Figure 1).

Figure 1. Process of identification and selection of studies



2. Main Characteristics of the newly included studies

Leroux-Roels 2012

Methods	Phase I/II, open-label, randomised, parallel-group trial with staggered enrolment, conducted at the Center for Vaccinology, Ghent University and Hospital, Belgium. Time of follow-up: 12 months after the last dose.
Participants	135 healthy older adults (50-70 years) not previously vaccinated for varicella zoster virus.
Interventions	1. N=45. Varicella zoster virus (Varilrix, approximately 10^4 plaque-forming units per dose of attenuated varicella zoster virus in 0.5 mL diluent) (OKA), subcutaneous injection. Two-doses schedule: second dose given 2 months after first dose 2. N=45. Recombinant adjuvanted vaccine, HZ/su (50 µg recombinant varicella zoster virus glycoprotein E antigen in 0.2 mL mixed with 0.5 mL of AS01B adjuvant) (HZ/su), intramuscular injection. Two-doses schedule: second dose given 2 months after first dose. 3. N=45. OKA and HZ/su were injected simultaneously into the deltoid areas of opposite arms of each participant. Two-doses schedule: second dose given 2 month after first dose.
Outcomes	Adverse events (AEs): -Local reactions (pain, redness, and swelling at injection site) and solicited general reactions (fatigue, fever, myalgia, gastrointestinal symptoms, and headache) were recorded by subjects on diary cards for up to 6 days after vaccination. -Investigators recorded all unsolicited AEs until 30 days after each vaccination and all severe adverse events (SAEs) for the duration of the study.
Purpose of the Study	Safety and immunogenicity of a recombinant adjuvanted vaccine, HZ/su in comparison with attenuated varicella zoster virus vaccine
Notes	20 young adults were also included in this study but we only used the data from the older adults. No vaccine-related SAEs and no deaths were reported in this study.

Risk of bias table Leroux-Roels 2012

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Blinding (performance bias and detection bias)	High risk	Open-label study
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study
Incomplete outcome data (attrition bias)	Low risk	Clear patient flow
Selective reporting (reporting bias)	Low risk	All data on adverse events that the authors proposed in their methodology were described in the results
Other bias	Unclear risk	Not described

Schmader 2012

Methods	Phase 3, Randomised, placebo-controlled, double-blind trial at 12 sites in the United States. Continuation of the Short-Term Persistence Study (STPS), described by Oxman 2005. Time of follow-up: 7 years of surveillance for Herpes zoster
Participants	14,270 participants (60 years or older) with history of varicella or who had resided in the continental United States for at least 30 years.
Interventions	1. N = 7,320. Zoster vaccine (frozen) (18,700 to 60,000 plaque-forming units per dose - pfu/dose); over 90% of vaccinated participants received 32,300 pfu or less), via subcutaneous injection 2. N = 6,950. Placebo, subcutaneous injection
Outcomes	Incidence of Herpes zoster,Incidence of postherpetic neuralgia, Adverse Events – Death, Withdrawals and Lost to follow-up
Purpose of the Study	'To assess the persistence of vaccine efficacy for the 3 study end points in the Short-Term Persistence Substudy population, the Shingles Prevention Study population, and the combined Shingles Prevention Study and Short-Term Persistence Substudy populations and to assess the persistence of vaccine efficacy for the 3 study end points for each year through year 7 after subjects received zoster vaccine or placebo in the Shingles Prevention Study."
Notes	'The Shingles Prevention Study (SPS) was a randomised, double-blind, placebo-controlled clinical trial initiated in November 1998 and reported initially by Oxman 2005. All vaccine and placebo recipients were actively followed for new cases of HZ through September 2003. There was a break in surveillance for cases of HZ of approximately 15 months between the completion of the SPS surveillance in September 2003 and resumption of follow-up in the STPS in December 2004. Beginning in October 2005, open-label zoster vaccine was offered without charge to SPS placebo recipients. Placebo recipients enrolled in the STPS completed the study upon receiving zoster vaccine, since they could then no longer serve as unvaccinated controls. The STPS subjects who were zoster vaccine recipients in the SPS continued to be followed until the initiation of the Long-Term Persistence Substudy in March 2006.' Time of follow-up of the zoster vaccine group: from December 2004 to March 2006, corresponding to 16 months Time of follow-up of the placebo group: from December 2004 to September 2005 (Beginning in October 2005, open-label zoster vaccine was offered to placebo recipients) corresponding to 10 months. We contacted the authors of this study asking for the data corresponding to the period from December 2004 to September 2005 (10 months) for both groups (vaccine and placebo). They replied to our email did not provide this information and suggested instead that we should 'assume a uniform rate of events and calculate the estimated number of cases from that'.

Risk of bias table Schmader 2012

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	'Each study site received randomly ordered vials of zoster vaccine and placebo in separate boxes for each age stratum'
Blinding (performance bias and detection bias)	Low risk	'All other study personnel were blinded to study treatment assignments'
Blinding of participants and personnel (performance bias)	Low risk	'Since the reconstituted zoster vaccine had a different appearance from the placebo, reconstitution and administration were performed by technicians who did not otherwise interact with participants, evaluate outcomes or adverse events, answer the telephone or enter study data.'
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Clear patient flow
Selective reporting (reporting bias)	Low risk	All data on effectiveness and Adverse Events that the authors proposed in their methodology were described in the results for both groups
Other bias	Unclear risk	Not described

Vesikari 2013

Methods	Phase III, open-label, randomised trial, multiple centers across the European Union (Finland, Germany, Italy, Spai, and the Netherlands). Randomised 1:1:1 ratio to receive either: a)one injection only (Single-dose schedule); b)two injections with 1 month between the doses (Two-doses, 1-month schedule) or c) two injections with 3 months between the doses (Two-doses,3 months schedule) Time of follow-up: 12 months after the last dose
Participants	759 older adults (≥ 70 years) with either a history of varicella or > 30 y residency in a country with endemic VZV infection were enrolled. 509 (67.2%) between 70-79 years and 248 (32.8%) > 80 years. Most (56%) were female. Individuals were excluded if they had: a history of HZ, previous varicella or HZ vaccination, exposure to varicella or HZ during the preceding 4 weeks, fever (oral temperature 38.3° C) during the preceding 72 hours, live-virus vaccination during the preceding 4 weeks, and inactivated vaccination during the preceding 2 weeks.
Interventions	1. N = 749, Live attenuated HZ vaccine. Single dose. 2. N = 232, Live attenuated HZ vaccine. Two-doses schedule: 1 month after first dose 3. N = 221, Live attenuated HZ vaccine. Two-doses schedule: 3 months after initial dose
Outcomes	AEs, immediate and not immediate, both at injection site and/or systemic: -Erythema, swelling and pain within 4 days of vaccination and other injection-site reactions were recorded by participants in a diary card -Other injection-site reaction and systemic AEs were recorded in the diary card for up to 28 days following each vaccination -Vaccine-related serious AEs, deaths, and occurrences of HZ, varicella, or zoster-like and varicella-like rashes were recorded by the investigators until the study was stopped (one year) -Varicella(-like) rash or HZ(-like) rash, any SAEs, vaccine-related AEs
Purpose of the Study	'The primary objective of the study was to demonstrate that a second dose of HZ vaccine, administered 1 mo or 3 mo after the first dose, elicits superior VZV antibody titres 4 weeks after vaccination compared with the first dose.' 'Secondary objectives of the study were to compare VZV antibody titres 12 mo after completion of each two-dose schedule with those 12 mo after a single dose, and to describe the safety profile of all three HZ vaccination schedules.
Notes	This was an immunogenicity study. For safety analyses, one patient randomised to the 1 mo between doses was analysed as receiving the 3 mo schedule. For the period of first vaccination, the data of the three groups were pooled.

	Injection-site reactions were generally mild to moderate in intensity and resolved in 3-7 d. None of the serious AEs were considered by the investigators to be vaccine-related. No intention-to-treat analysis.

Risk of bias table, Vesikari 2013

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'blocks of randomisation, with stratification by age (70–79 y and ≥ 80 y) and country' were used, but the process used for random sequence generation was not reported
Allocation concealment (selection bias)	Low risk	'The allocation schedule was generated using balanced permuted blocks of randomisation, with stratification by age (70–79 y and ≥ 80 y) and country'
Blinding (performance bias and detection bias)	High risk	Open-label study
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study
Incomplete outcome data (attrition bias)	High risk	Not clear patient flow
Selective reporting (reporting bias)	Low risk	All data that the authors proposed in their methodology were described in the results
Other bias	Unclear risk	Not described

3. Assessment of the Risk of Bias of included studies

Figures 2 and 3 summarize the risk of bias of the three new studies.

Randomisation and Allocation concealment (selection bias)

Randomisation

The three trials (Leroux-Roels 2012, Schmader 2012 and Vesikari 2013) provided no details on the randomisation process and were therefore classified as having an unclear risk of bias in this domain.

Allocation concealment

We classified Schmader 2012 as low risk of bias because of adequate allocation concealment described by the authors.

Vesikari 2013 was also classified as low risk of bias because of the description provided by the authors.

Leroux-Roels 2012 report 'Staggered enrolment' but provided no information on allocation concealment. We therefore classified it as 'unclear' on this domain.

Blinding (performance bias and detection bias)

Only Schmader 2012 was double-blind and considered at 'low risk' for blinding bias because of the statement provided by the authors.

Leroux-Roels 2012 and Vesikari 2013 were open-label studies and therefore considered to be at high risk of bias for blinding.

Incomplete outcome data (attrition bias)

Leroux-Roels 2012 and Schmader 2012 provided a clear patient flow and were classified as 'low risk' for the attrition bias while Vesikari 2013 was considered at 'high risk' of bias for this domain for not having a clear patient flow.

Selective reporting (reporting bias)

We classified the three studies as 'low risk' in this domain because all data that the authors proposed in their methodology were described in the results.

Other potential sources of bias

There was no information on any significant aspects pertaining to this domain, in any of the three studies.

Figure 2. Risk of bias summary of included studies

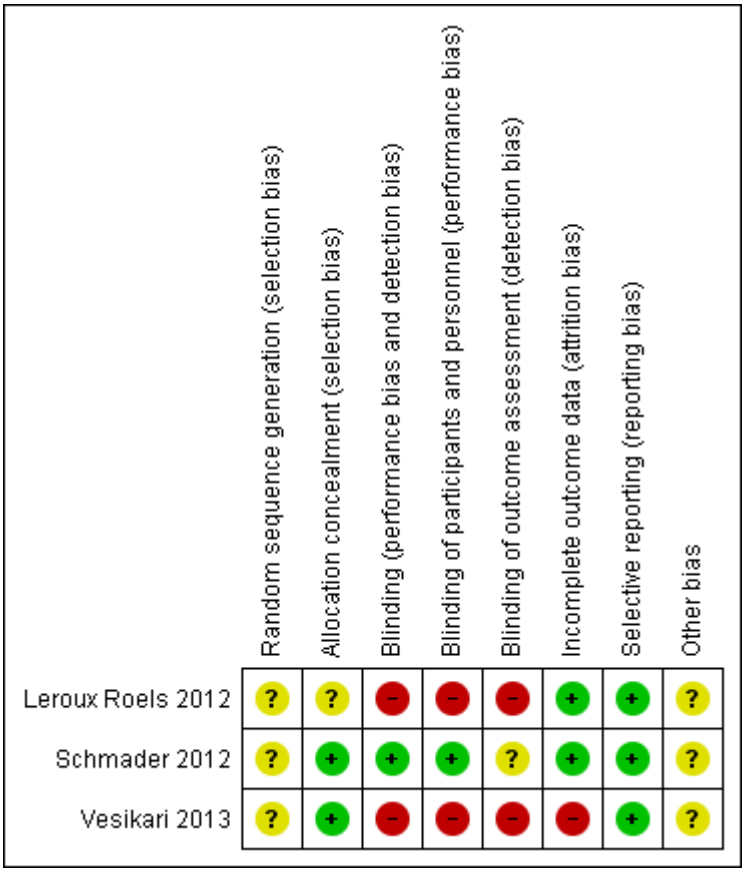
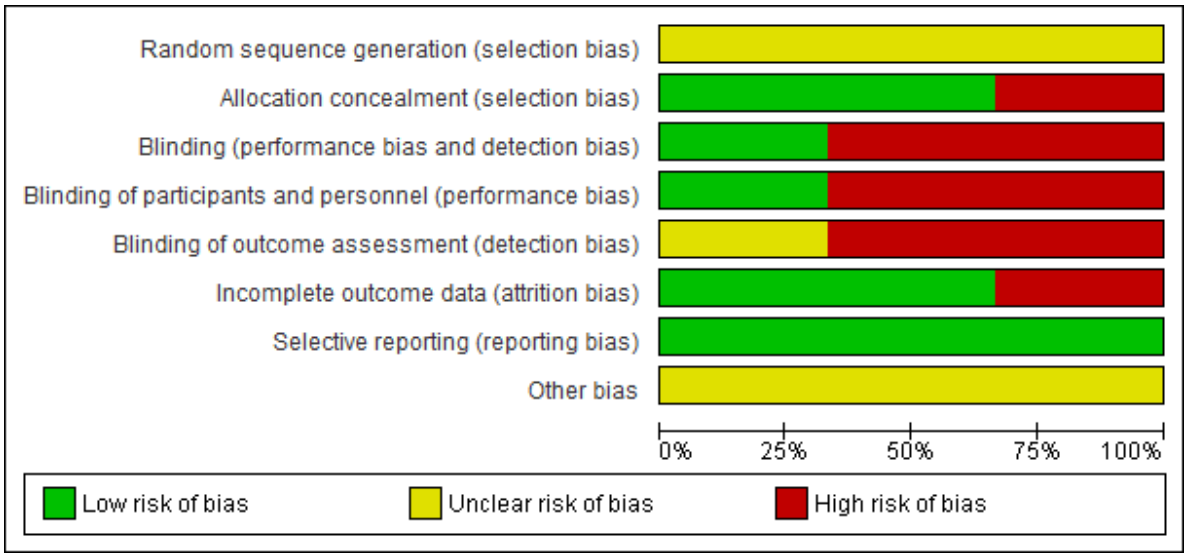


Figure 3. Risk of bias graph*



*Review authors' judgements about each risk of bias domain presented as percentages across all included studies

4. Data analyses

There was no data to compare zoster vaccine versus placebo subgroup analysis by age (60-69, 70+ years) for the following outcomes: cases of herpes zoster, post-herpetic neuralgia and serious adverse events (including deaths).

a. Zoster vaccine versus placebo

Schmader 2012 is a continuation of the Oxman 2005 study - Short-Term Persistence Study. The 2012 publication evaluated the effectiveness of the vaccine for up to 7 years after the participants had been vaccinated. However, the published data report different dates for the collection of outcomes in the intervention and in the placebo groups. The data from the zoster vaccine group are from December 2004 to March 2006 (16 months). In the placebo group, data are reported from December 2004 to September 2005 (10 months), since in October 2005, the zoster vaccine was also offered to participants in the placebo group, as stated by the authors: 'Beginning in October 2005, open-label zoster vaccine was offered without charge to Shingles Prevention Study placebo recipients.'

We contacted the authors of this study asking for the data corresponding to the period from December 2004 to September 2005 (10 months) for both groups (vaccine and placebo). They replied to our email but did not provide this information and suggested instead that we should 'assume a uniform rate of events and calculate the estimated number of cases from that'. According to their suggestion, we calculated that the inferred rate of events (HZ cases) would be 53 in the vaccine group at 10 months, as described below:

Time of follow up in the Zoster vaccine group: December 2004 (included) to March 2006, corresponding to 16 months

Time of follow up in the Placebo group: December 2004 (included) to September 2005, corresponding to 10 months

i. Outcome: Confirmed herpes zoster cases

Total number of events (confirmed HZ cases) in the vaccine group at 16 months: 84
Estimated number of events (confirmed HZ cases) in the vaccine group at 10 months: 53

84 HZ cases ----------16 months

X ----------10 months

X = 52,5 = 53 cases of HZ

Figure 4. Risk Ratio for Confirmed HZ cases: Zoster vaccine vs Placebo

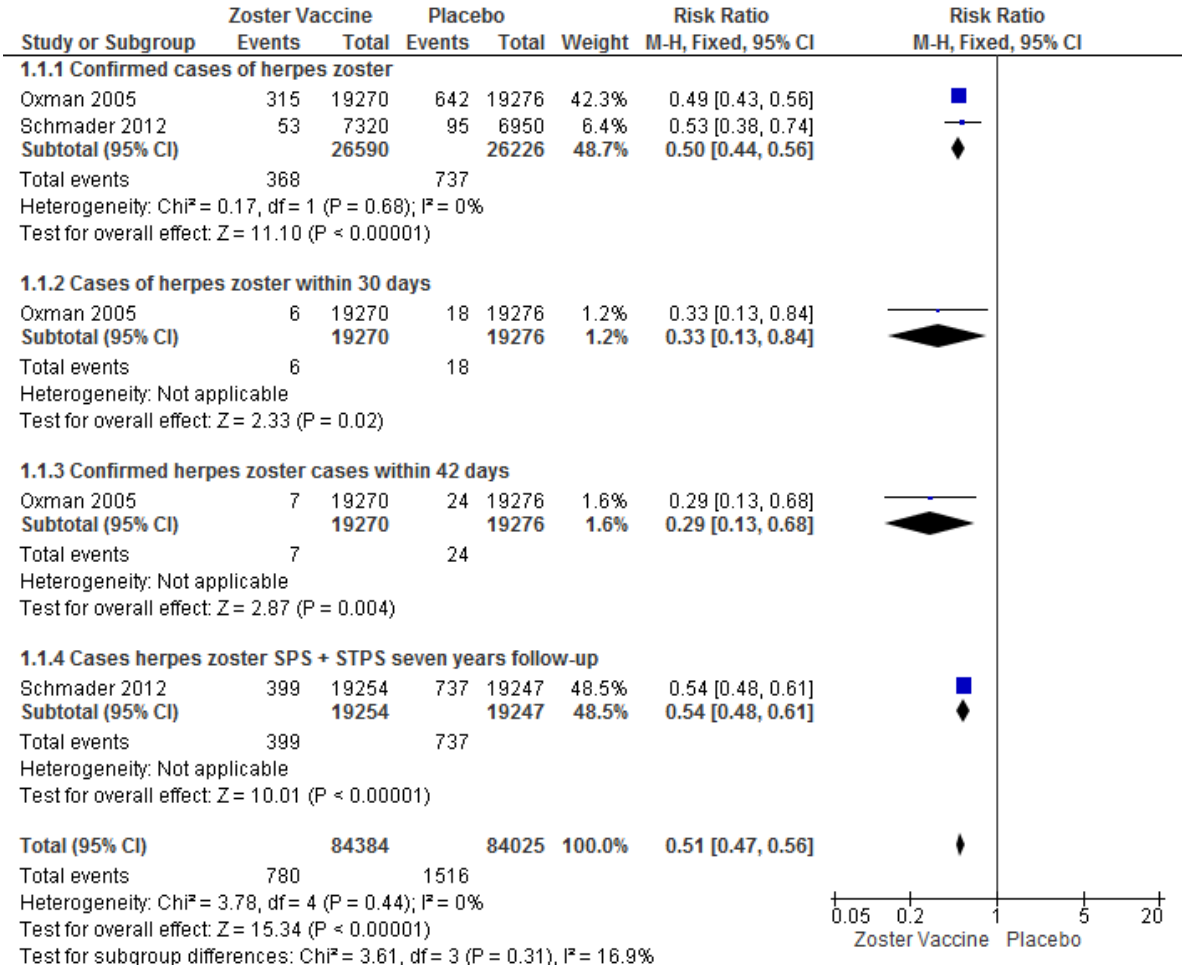
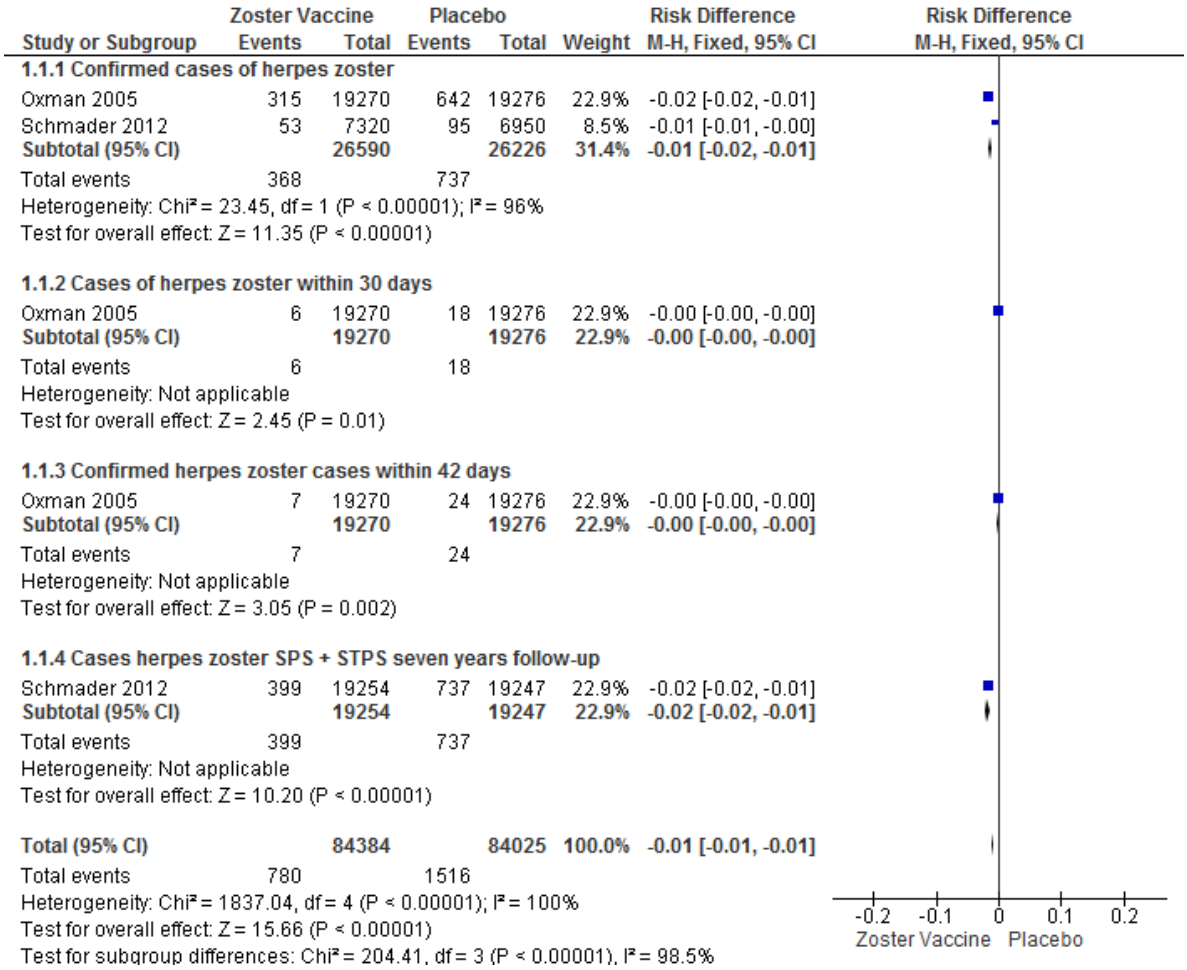


Figure 5. Risk Difference for Confirmed HZ cases: Zoster vaccine vs Placebo

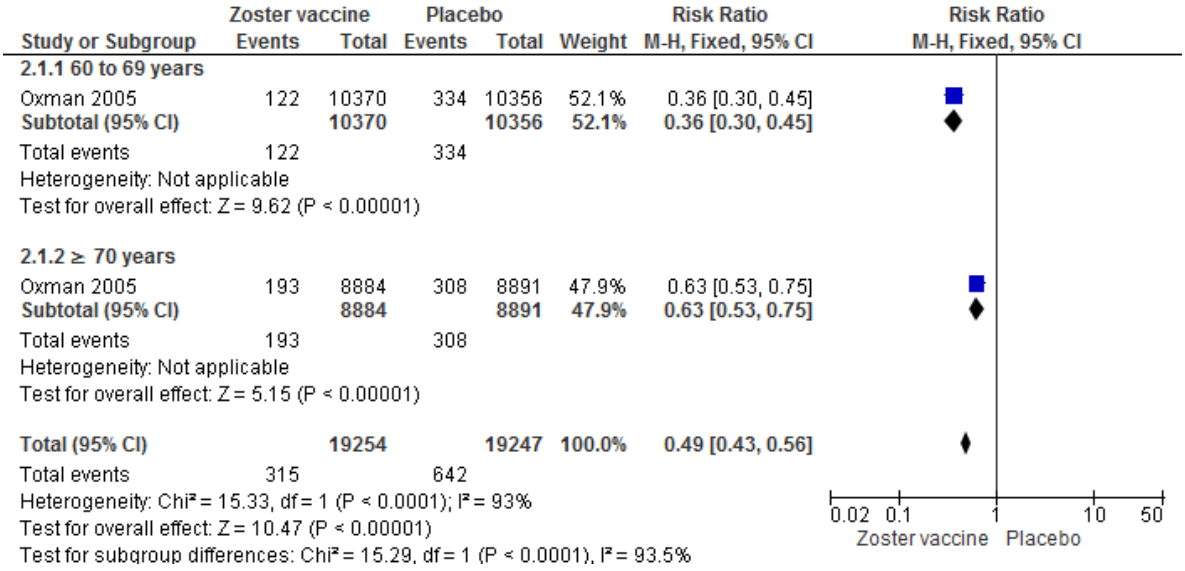


Risk Difference= 0.02 or 2%.

Number needed to treat for an additional beneficial outcome (NNTB) =50.

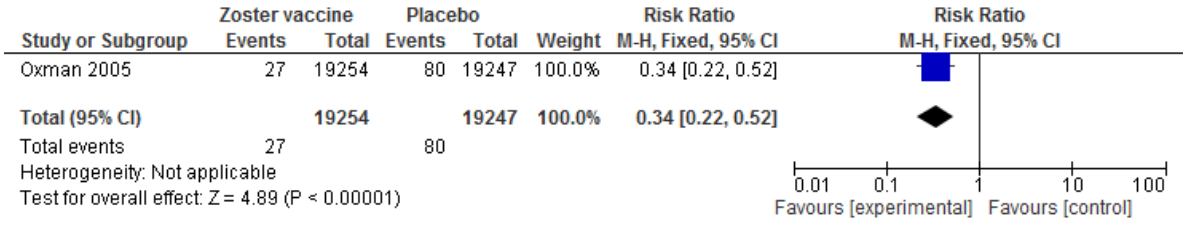
It was the same data found before the update of the review.

Figure 6. Risk Ratio for Confirmed HZ cases: Zoster vaccine vs Placebo subgroup analyses by age



ii. Outcome: post-herpetic neuralgia

Figure 7. Risk Ratio for post-herpetic neuralgia: Zoster vaccine vs Placebo



In the 2012 publication (long-term follow-up), the data for this outcome are presented in cases/1000 Person-years. We contacted the authors asking for raw data to perform the analyses for this outcome but they did not respond to this request.

iii. Outcome: Deaths

Inferred number of deaths estimated from available data:

103 deaths --------- 16 months $\boxed{Y = 64.4 = 64}$

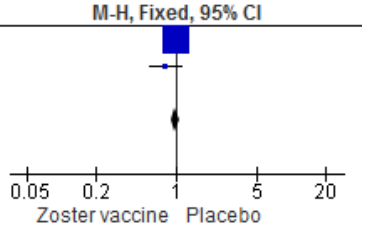
Y ------- 10 months

Figure 8. Risk Ratio of deaths: Zoster vaccine vs Placebo

Study or Subgroup	Zoster vaccine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oxman 2005	793	19254	795	19247	91.1%	1.00 [0.91, 1.10]
Schmader 2012	64	7320	76	6950	8.9%	0.80 [0.57, 1.11]
Total (95% CI)		**26574**		**26197**	**100.0%**	**0.98 [0.89, 1.07]**
Total events	857		871			

Heterogeneity: Chi² = 1.58, df = 1 (P = 0.21); I² = 37%

Test for overall effect: Z = 0.44 (P = 0.66)



iv. Outcome: Adverse events

According to the authors, there were 'No serious adverse events occurred during the Short-Term Persistence Substudy that were judged possibly, probably, or definitely related to the vaccination.' Therefore, we could not calculate risk ratios for this outcome.

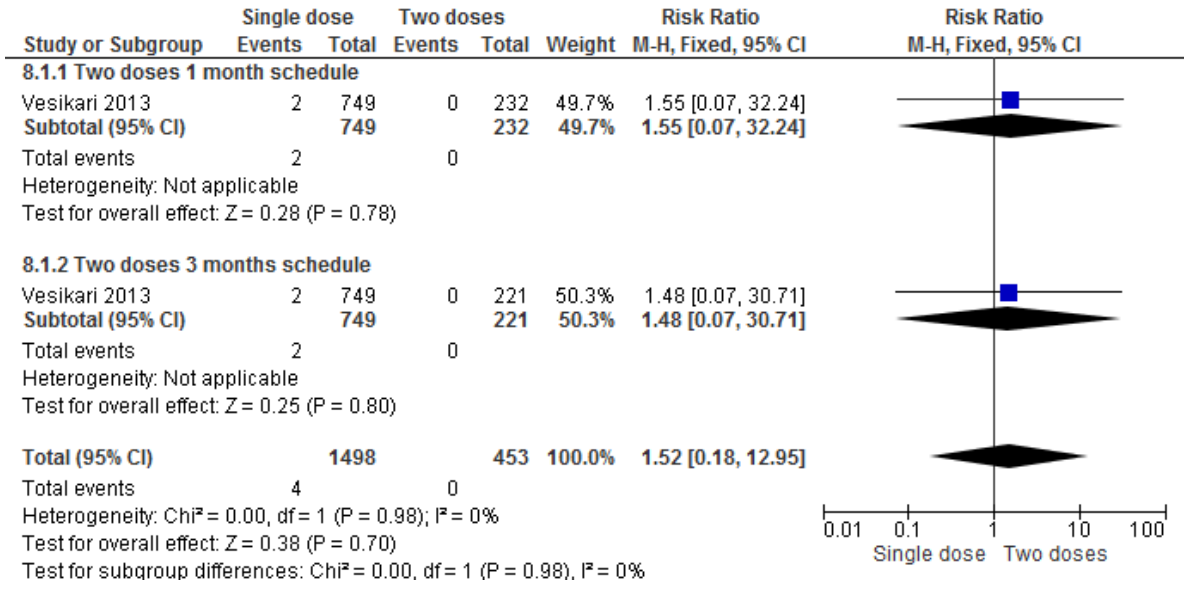
b. Single dose of zoster vaccine versus two different 2-doses schedules

Vesikari et al., 2013 was a randomized trial that assessed zoster vaccine in elderly people. However, authors reported results only for immunogenicity and safety of the vaccine, comparing a single dose of zoster vaccine versus two different 2-doses schedules, i.e. either after one or two months after the original dose.

i. Outcome: Herpes zoster/zoster-like rash

There was no significant difference in the incidence of herpes zoster/zoster-like rash in the the groups that received a single dose versus two doses of the vaccine, regardless of the time between doses.

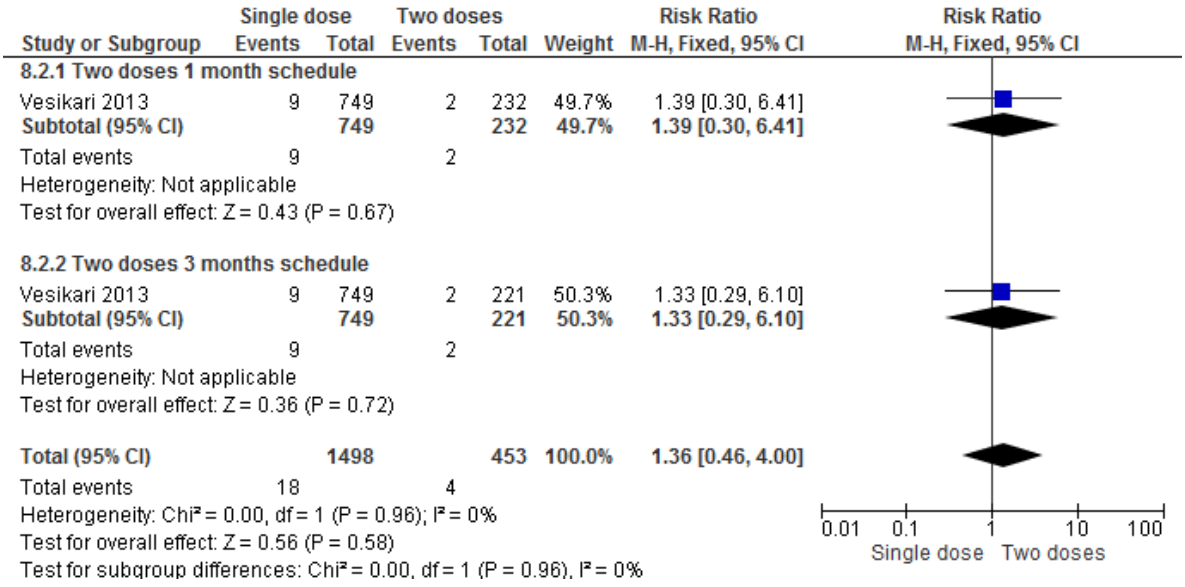
Figure 9. Risk Ratio for HZ cases: Single dose vs Two doses of vaccine



ii. Outcome: Serious adverse events

There was no significant difference in the incidence of serious adverse events in the the groups that received a single dose versus two doses of the vaccine, regardless of the time between doses.

Figure 10. Risk Ratio for Serious AE: Single dose vs Two doses of vaccine



c. Zoster vaccine versus recombinant adjuvanted vaccine

Leroux-Roels 2012 was a phase I/II, open-label, randomised, parallel-group trial that evaluated the safety and immunogenicity of a recombinant adjuvanted vaccine(HZ/su) in comparison with attenuated varicella zoster virus vaccine (OKA). There were no reports of vaccine-related serious adverse events and no deaths.

5. Summary of findings tables after inclusion of studies published 2012-2013

1. Zoster vaccine versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Cases of herpes zoster	2	168409	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.01, -0.01]
1.1.1 Confirmed cases of herpes zoster	2	52816	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.02, -0.01]
1.1.2 Cases of herpes zoster within 30 days	1	38546	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.00, -0.00]
1.1.3 Confirmed herpes zoster cases within 42 days	1	38546	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.00, -0.00]
1.1.4 Cases herpes zoster SPS + STPS seven years follow-up	1	38501	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.02, -0.01]
1.2 Post-herpetic neuralgia	1	38501	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.22, 0.52]
1.3 Deaths	2	52771	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.07]

2. Zoster vaccine versus placebo subgroup analysis by age

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Confirmed cases of herpes zoster	1	38501	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.43, 0.56]
2.1.1 60 to 69 years	1	20726	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.30, 0.45]
2.1.2 ≥ 70 years	1	17775	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.53, 0.75]

3. Single versus two doses zoster vaccine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Herpes zoster/zoster-like rash	1	1951	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.18, 12.95]
3.1.1 Two doses 1 month schedule	1	981	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.07, 32.24]
3.1.2 Two doses 3 months schedule	1	970	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.07, 30.71]
3.2 Serious adverse events	1	1951	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.46, 4.00]
3.2.1 Two doses 1 month schedule	1	981	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.30, 6.41]
3.2.2 Two doses 3 months schedule	1	970	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.29, 6.10]

4. Zoster vaccine versus recombinant adjuvanted vaccine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Vaccine-related serious adverse events	1	90	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

6. Authors' conclusions

The evidence gathered including the most recently published studies suggests that there is benefit in vaccinating elderly people with the herpes zoster vaccine, with no major safety/tolerability concerns. The available data suggest that the vaccine works for up to 7 years to prevent herpes zoster in individuals over 60 years of age.

There were no statistically significant differences in terms of safety of the herpes zoster vaccine when comparing one versus different two-dose schedules.

The recombinant adjuvanted vaccine, HZ/su (50 µg recombinant varicella zoster virus glycoprotein E antigen in 0.2 mL mixed with 0.5 mL of AS01B adjuvant) (HZ/su) proved to be safe with respect to serious adverse events (including death) when compared with the live attenuated vaccine.

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